



LIGHTHOUSE

TRAINING MANUAL IN HIV AND TB MEDICINE

Tom Heller, MD

Lighthouse Training Manual in HIV and TB Medicine

Tom Heller, MD

Specialist in Internal Medicine and Infectious Diseases (Germany)

Clinical Advisor

Lighthouse Clinic

Lilongwe, Malawi

To Claudia:

*'Dalla sua pace la mia dipende;
quel che a lei piace vita mi rende'*

from *Don Giovanni*
Wolfgang Amadeus Mozart
Libretto: Lorenzo da Ponte

Disclaimer

Every attempt has been made to ensure that the information in this casebook is accurate and correct. The author and publishers accept no responsibility for any loss or damage that may arise out of the reliance of any person upon any of the information provided in the book, nor is responsibility accepted for any loss or damage sustained as a result of the use of the information contained herein.

When in doubt, seek the assistance of a more senior colleague, or, when further information is required concerning drug indications or dosage, consult the National Drug Formulary, the current pharmaceutical package inserts, or the relevant pharmaceutical company.

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Foreword

Malawi continues to make progress in its national response to HIV and AIDS. The HIV prevalence among women and men aged 15–49 decreased between 2010 and 2015–16, from 10.6% to 8.8%. The national HIV incidence for both women and men aged 15–49 is 0.32%. Malawi is a global pioneer of the Option B+ programme, which automatically puts HIV+ pregnant and breast-feeding women on lifelong antiretroviral therapy (ART). Malawi aims to achieve the 90-90-90 targets; as of 2016, it is estimated that 72.7% of people aged 15–64 living with HIV know their status, 88.6% are on ART, and 90.8% of those on ART are virally suppressed.

Malawi has registered significant progress in the prevention, control, and management of TB over the last five years. Strategies put in place to strengthen TB/HIV collaboration are further enhancing efforts in the control and management of TB. Approximately 80% of HIV-infected TB patients are receiving ART. However, results from the national TB Prevalence Survey conducted in 2014 indicate that there is still a high TB burden in Malawi, with an estimated prevalence of 451/100 000 among the adult population, with an adjusted prevalence for all age groups at 334/100 000. This is slightly more than twice the 2014 WHO case detection target of 140/100 000.

To ensure quality of care in this amazing rollout, qualified clinicians are key. The *Lighthouse Training Manual in HIV and TB Medicine* is therefore written for the medical doctors, clinical officers, medical assistants, nurses, and midwives working at the Lighthouse and its supported sites. However, it is expected that similar cadres of staff working in public and private sector health facilities in Malawi would also use it. The manual is designed to be a practical guide for implementation of integrated TB/HIV services.

The author of this manual, Dr Tom Heller, is a Lighthouse Clinical Advisor. Dr Heller has a lot of experience and passion in comprehensive clinical care, as well as in teaching both undergraduate and post-graduate health care providers.

I would like to thank German Corporation for International Cooperation (GIZ) GmbH for technical support provided to the Lighthouse under the Integrated Experts Scheme (via the Ministry of Health), through which the author of this manual is supported.

I would also like to acknowledge the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which provided support to both the International Training and Education Center for Health (I-TECH) at the University of Washington (UW) in Seattle and the Lighthouse Trust in Lilongwe for the production of this manual, through cooperative agreements with the Centers for Disease Control and Prevention (CDC)

With this book, we hope to support and enhance clinical care for HIV and TB patients. We hope it will serve health care workers as a valuable tool and knowledge resource.

Prof. Sam Phiri
Executive Director
Lighthouse Clinic Trust

Preface

ART in Sub-Saharan Africa is an amazing success story. It has led to increased life expectancy in many countries, and, along the way, changed the face of the epidemic from a fatal, hopeless disease to a chronic condition that needs to be treated adequately but can be managed. The Global Burden of Disease study published in *The Lancet* in October 2016 showed an increase in life expectancy for Malawi of 13.7 years for females and 10.5 years for males between 2005 and 2015. Approximately 8.5 of the gained years for females, and 7.0 years for males, can be attributed to reduced HIV/AIDS and tuberculosis mortality.

Over the years, the integration of HIV and TB treatment has changed the parallel management of these diseases to a more unified approach. In more recent times, there is additional effort to address such non-communicable conditions as hypertension, diabetes, and cancers affecting HIV patients in maturing cohorts via integrated care models to make use of the successes.

The enormous effort to find patients, link them to antiretroviral treatment, and achieve viral suppression (summarized under the WHO 90-90-90 goals) are admirable; we are on a promising path to achieve our goals. In Malawi, the early and committed efforts by the Department of HIV, in a pragmatic public health approach to HIV care, are key to this success story.

Nevertheless, as much as the public health approach saves big numbers of lives, in the end, the patient is not a number, but a human individual. The programmatic approach is successful, but it treats all patients with the same approach. It resembles a swimming pool with only a single depth; unfortunately, not all our patients are equally good swimmers.

Differentiated care models and *differentiated service delivery* are buzzwords; regrettably, these differentiation models often favour stable patients, and lean towards seeing less of patients. Differentiated care models must equally ensure to take care of patients with advanced disease, late presentations, and unstable disease courses.

Recent changes in guidelines have seen a move towards people starting ART earlier, at higher CD4 counts. The *test-and-treat strategy* (treating all HIV-positive individuals irrespective of their CD4 count) carries the optimism that ‘sick patients’ can be prevented. Unfortunately, this is not happening (yet). Still, we see a substantial proportion of people who do not get diagnosed or initiated on ART until their CD4 counts are very low; approximately 25% of the patients starting ART at Lighthouse have CD4 counts of 100 and below. As much as these patients profit from early ART, careful examination and history-taking to assess for opportunistic infections in general, and for TB in particular, help to prevent—or at least foresee—complications like IRIS. Even in times of ‘test and treat’, it still needs to be ‘test—think—and treat’.

Increasingly, we have POC tests available that allow us to get a lot of information and diagnostic clues about our patients in a very timely manner. These tests seem to be an ‘easy’ answer, thanks to technology; nevertheless, we have to remember that a test result is *not* equal to diagnosis, and that test results need to be interpreted in light of the history and clinical picture of the patient. This requires knowledge and experience on the part of the health care worker.

Today we have a far broader—and, luckily, less toxic—selection of drugs available to adapt ART regimens, even in resource-poor(er) settings, than we had few years ago. When patient characteristics require it, or side effects develop, we have options to offer. As much as this makes ART more tolerable, it also makes it more complicated. We need to be able to assess and monitor laboratory values, like renal and liver function, or haematological parameters. As easy as this sounds, basic laboratory values may be more complicated to obtain than complex molecular tests, because general health systems receive far less attention (and funding) than HIV services. And again, results are one thing—interpretation of those results is another. Training for HCW is essential—as is the ability to refer patients to, or seek advice from, more specialized and experienced staff at referral centre(s).

HIV-infected patients live in the face of a disease that causes various changes to their bodies, requires lifelong treatment, and causes a great amount of fear and insecurity. They have to adapt their lives, cope with their situation, and re-adjust their plans and life projects. Although the somatic side is only one part in this, to allow their lives to be as normal as they deserve, patients need clinicians trained in recognising and treating their bodily problems using the limited resources available.

Acknowledgments

Compiling the pages of a clinical medical book is ultimately always a learning process for the author. I am deeply indebted to, and would like to thank, the numerous colleagues who taught me, formally and informally over the years, through advice, discussions and disputes, and, of course, through referral of cases.

The idea to write the *Hlabisa Case Book of HIV and TB Medicine*, the predecessor to (and basis of) this manual, was born out of the experiences of myself and my colleagues in KwaZulu-Natal facing new conditions in an environment with different pathologies, and with different diagnostic and therapeutic possibilities. For their cooperation with that book, I would like to thank my KZN colleagues and co-authors: Drs Houlinan, Seigel, Buckley, Copelyn, and Lessels. Drs Dedicoat, Johansson, and Mayat contributed images and advice.

The main drive to update, expand, adapt, and re-write the cases for this manual came from my current colleagues, the clinical officers at the Lighthouse clinics, who welcomed the old version enthusiastically (even as it became outdated). All of them participate actively in our case discussions in the Lighthouse ART and TB Smart Saturday meetings; many of the new cases originate from these meetings, and from the lively discussions in the Lighthouse WhatsApp group. As *pars pro toto*, I want to mention Joe Gumulira, focal person for clinical training, who was invaluable in finding and following patients; in all the stress, he maintains the human, caring face I see as characteristic of the Lighthouse team.

Many of our patients are seen in collaboration with our colleagues at Kamuzu Central Hospital. In particular, I would like to thank Dr Lilian Chunda and B. Armando for their great cooperation with the inpatient care of HIV and TB patients; and Drs Huson and Hoel, who contributed cases to this book. To the following colleagues, I am grateful for their input and cooperation in their areas of speciality: Drs Tamiwe Tomoka and Dungel Bal from pathology, Dr Satish Gopal from oncology, Drs Suzgo Msumara and Joekes (Liverpool) from radiology, Drs Rajab and Pope from gynaecology, Dr Nyaka from ophthalmology, Dr L. Levin from Right to Care (on resistance testing), and many others. Further, I would like to thank Kevin J. O'Conner of Alarm Cat Design in Seattle for his great work on layout of the manual, and the I-TECH staff for their help with layout and printing.

I would especially like to thank my wife, Dr Claudia Wallrauch, in the Department of Medicine, for clinical cooperation, academic discussions, and simply for always being supportive of all my 'strange ideas'.

Finally, I want to acknowledge the patients whose cases are presented in this book. They clearly know the urgent need for well-trained clinicians to treat them well.

I hope that this book may be of help to all who practice HIV and TB medicine, both in Malawi, and in Sub-Saharan Africa.

Tom Heller

How to Use This Book

The *Lighthouse Training Manual in HIV and TB Medicine* uses a case-based learning approach. Each case starts with a small description of the key points in the patient's history and physical exam; it may also contain laboratory values, x-rays, or other clinical information needed to assess the patient. Please read these carefully, look at the questions, and then pause to think about your answers—about the approaches that you would take, about differential diagnoses you would consider. Maybe even try to search first, ask around—'Dr Google' and others may have an opinion. Only after you have finished doing this, turn the page and look at the solutions we suggest.

The results page contains the diagnosis, model answers to the questions, and comments with other potentially relevant information. Additional images may be included here. Most cases end with a key point to remember, as well as suggestions for further reading for those who want to delve deeper.

The case-question-riddle format has one main purpose—learning should be fun. So do not overdo it; try to crack as many riddles as you feel fit, and then put the book away for another day. Each case is a stand-alone problem; you can open and start the book on whichever page you like. If you want to use the manual as a tool to refresh you on a certain condition or special treatment, you may use the index in the back to find the relevant case.

The cases are organized in three sections—green, yellow and red. The **green** section contains more basic cases that may be encountered more frequently, and which are more important to everyday work. The **yellow** section presents more advanced cases. The **red** section contains some unusual cases and complex differential diagnoses for those with more experience in ART and TB treatment. Obviously, this grading is subjective; what one finds difficult may seem obvious to somebody else. Nothing prevents you from using the book to go from green to red, or from red to green. Everything can be easy when you know it—as Goethe wrote: 'we see only what we know.'

Lighthouse: A Centre of Excellence for Integrated HIV Prevention, Treatment, and Care

The Lighthouse was established in 2001 as a public trust to provide a centre of excellence, as well as leverage and leadership, in the provision of integrated HIV prevention, treatment, and care services in Malawi. To achieve this, it works in close collaboration with the Ministry of Health and the Lilongwe District Health Office. Lighthouse Trust acknowledges the UNAIDS targets of ensuring that 90% of all people living with HIV (PLHIV) know their HIV status; 90% are on HIV treatment (ART); and 90% of current ART patients have attained viral suppression. In doing so, Lighthouse promotes a public health approach to the provision of high quality, efficient, and effective care for PLHIV, and serves as a tertiary level referral ART centre, providing clinical oversight and care for complicated cases.

As of June 2017, Lighthouse operates two large integrated HIV testing, treatment, and care clinics in Lilongwe, where many of the patients in this case book were seen.

One clinic is based on the campus of Kamuzu Central Hospital (KCH), the major tertiary hospital in Malawi's capital, Lilongwe, and the Central Region. Beside its role as a major ART outpatient clinic on the hospital grounds, treating a cohort of 11 000 ART patients, Lighthouse works closely with KCH staff in the care of HIV- and TB-infected inpatients in the internal medicine wards.

The second Lighthouse clinic, the Martin-Preuss Centre (MPC), is located at Bwaila Hospital, in the centre of Lilongwe's Old Town. MPC is home to the largest treatment cohort in Malawi, seeing more than 22 000 ART patients. At the same time, it hosts the largest TB program in the country, registering approximately 1 000 patients per year. Lighthouse staff also support treatment, particularly of re-treatment patients and patients too sick for ambulatory treatment (outpatient care), in the TB inpatient ward, also located at Bwaila. The volume of patients at KCH and Bwaila Hospital clinics continues to increase, with an average of more than 15 000 patient visits per month at MPC alone—equal to over 700 consultations per day.

From the beginning of 2018, Lighthouse will operate high-quality referral clinics for integrated HIV care at Queen Elizabeth Central Hospital (Umodzi Clinic) in Blantyre in the Southern Region, and at Mzuzu Central Hospital (Rainbow Clinic) in the Northern Region, in order to enhance advanced HIV care in Malawi.

The Lighthouse Trust has three operational arms that integrate HIV prevention, treatment, care, and support programs: facility- and community-based HIV testing and counselling services (HTS), facility-based clinical care (Clinic), and community health services (CHS). These operational arms operate under three technical approaches:

Service Delivery

Enhance high-quality, integrated HIV prevention, treatment, care, and support services for adults and children.

Innovation

Develop, pilot, evaluate, and disseminate innovative programs and policies across the continuum of HIV prevention, treatment, care, and support.

Capacity Building

Build and strengthen health care capacity for high-quality HIV prevention, treatment, care, and support services.

One of the mainstays of the Lighthouse approach to clinical care is integration of a wide spectrum of health services as part of HIV care. To this end, it offers integrated reproductive health services, including family planning and STI treatment. Cervical cancer screening and treatment with cryotherapy are available directly to eligible female patients in the clinics. Screening and treatment of non-communicable diseases (NCDs)—in particular hypertension, but also diabetes and epilepsy—are also available. Both clinics are registered TB treatment points, seamlessly integrating HIV and TB services. Combination chemotherapy for Kaposi sarcoma for outpatients is provided at both clinics; treatment for other HIV-related cancers is available through the oncology department at KCH.

At the same time, differentiated care models of HIV treatment play a central role in the Lighthouse philosophy. Based on the principle that one size does not fit all, a variety of models are used in treating patients: fast-track pharmacy visits for stable patients; the Nurse-led Community Art Programme (N-CAP) for patients using community ART services; the Tiwale Teen Club for adolescent patients; and models for advanced, late(-stage), or unstable patients (ALUP). The goal is to find the optimal treatment option for each patient within the limited resources available.

In recognition of Malawi's plans to move towards the test-and-treat strategy, Lighthouse has increasingly supported decentralisation of high-quality services, through initiatives that replicate elements of the Lighthouse prototype in other health facilities in the Lilongwe District—including clinics in Kawale, Area 18, Area 25, Lumbadzi, Chitedze, Chileka, Nathenje, Mitundu, and the MACRO Lilongwe clinic.

For many years, Lighthouse has been involved in capacity building in the form of pre- and in-service trainings for Ministry of Health staff throughout Malawi, as well as for significant numbers of staff from other non-governmental organisations. In the first wave of Malawi's national ART scale-up, more 70% of ART providers were trained at Lighthouse. Lighthouse continues to provide and support new and refresher trainings for HIV testing counsellors, nurses, and clinical officers in support of the national HIV response. This manual may be seen as part of this effort to train staff and enhance capacity for care of HIV patients, both at Lighthouse and beyond.

Cases

Case 1

Presentation

A 24-year-old man tested HIV positive yesterday. The patient decided to get tested because a community testing event was organized in his area, and it made him wonder about his HIV status. He had no symptoms, and felt well otherwise. A confirmatory HIV test was done, and he attended ART training sessions with the HIV counsellors. He was referred for ART initiation.



Questions

- 1) What is shown in the picture? What is the recommended HIV testing strategy in high-prevalence countries?
- 2) Which examinations and investigations do you need before starting ART?
- 3) Which drugs can you prescribe? What are the main side effects?

Diagnosis

Asymptomatic HIV-1 infection

Answers

1) Rapid HIV tests, which use spot capillary blood, are shown in the photo above. From top to bottom: negative Determine® test, positive Determine® test, positive Unigold® test (confirmatory test).

In high-prevalence settings (areas with HIV prevalence >10%, as per WHO criteria), a positive test result has to be confirmed with a second test; another rapid test from a different company is usually used. If this is positive, the patient is considered to be HIV positive. If the tests are discordant, both tests are repeated. If the results are still discordant, a blood sample can be sent to the reference lab to clarify the individual's HIV status.

2) The patient needs to be asked about symptoms of TB (cough, weight loss, night sweats), as well as other symptoms in general. It might be useful to ask the patient about symptoms of peripheral polyneuropathy and headache (suggesting meningitis). You want to examine the patient physically for skin changes (do not forget legs and groins for Kaposi sarcoma), mucosal changes (gingivitis, KS on the palate), chest auscultation, and abdominal palpation for organomegaly.

In Malawi, patients can be started on treatment without further lab tests. However, you may want to check and document the patient's CD4 count to help assess the initial degree of immune suppression (although, in the 'test-and-treat' approach, a CD4 count is not needed for treatment initiation). Routine chemistry monitoring is not required, but ALT and creatinine may be helpful in determining baseline values to help you in case side effects develop at a later stage.

3) The patient should receive Cotrimoxazole (CTX) 1 tab od as prophylaxis for PCP and other infections—e.g., salmonellosis and malaria (CPT, or CTX preventive therapy). Additionally, multivitamins 1 tab od have been shown to delay disease progression, and could be given as adjunctive treatment when available.

First-line ARV treatment in Malawi includes the following drugs:

- a) **TDF 300 mg od**—Nucleoside reverse transcriptase inhibitor (NRTI)—*Side effects*: Generally, TDF is very well tolerated. The main side effect is renal impairment, and even renal failure. Additionally, it can cause Fanconi syndrome, which is characterized by hypophosphatemia, proteinuria, and normoglycemic glucosuria. TDF may allow glucose, phosphate, and amino acids to be excreted into the urine. Additionally, reduced bone density has been described.
- b) **3TC 300 mg od**—NRTI—*Side effects*: diarrhoea, pancreatitis; generally, 3TC is a very well tolerated drug, with rare side effects.
- c) **EFV 600 mg od nocte**—Non-nucleoside reverse transcriptase inhibitor (NNRTI)—*Side effects*: CNS disturbances (dysphoria, vivid dreams, and distractedness). To avoid the CNS symptoms from interfering with the daily life of the patient, the drug is given in the evening. Patients working night shifts might prefer to take the drug in the morning. Skin rash (mild initial skin rash, usually resolves by itself). Lipomastia (breast enlargement in men and children, on one or both sides). Known psychiatric diseases are a contraindication.

Outcome and Follow-up

The patient's CD4 count was found to be 306 cells/mm³; he was started on TDF/3TC/EFV plus CPT. He was further treated and monitored by the nurse.

Comments

Rapid HIV tests are high in both sensitivity (>99%) and specificity (99%). In a setting with high prevalence of HIV, confirmatory tests—such as ELISA, western blots, or PCR—are needed only when results are ambiguous.

Suggested Reading

Department of HIV and AIDS; Ministry of Health, Malawi. Clinical management of HIV in children and adults: Malawi integrated guidelines and standard operating procedures for providing HIV services. 3rd ed. Lilongwe (Malawi): Ministry of Health, Malawi; 2016.

Key Learning Point

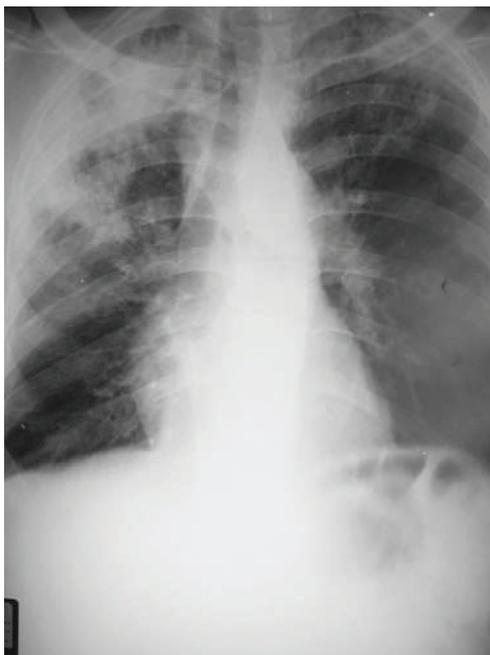
HIV is often asymptomatic. Therefore, expansion of HIV testing is important to achieve the goal of 90% of those infected with HIV knowing their status.

Case 2

Presentation

A 25-year old man came to the TB clinic at the hospital. He had been seen at his PHC clinic with a history of three weeks of cough, weight loss, and drenching night sweats. The patient had never previously been treated for TB, and reported no household TB contact. Sputum was sent for AFB, which was negative. At the PHC clinic, he had received amoxicillin 500 mg tds and erythromycin 500 mg tds for one week, without improvement of his symptoms.

As the patient's HIV status was unknown, he was referred for HTC, and tested HIV positive. A CXR was taken.



Questions

- 1) Comment on the value of acid-fast staining of sputum in diagnosing TB.
- 2) Which further diagnostic steps could be indicated?
- 3) Which treatment should be given?
- 4) Is it a useful step to send the patient for HIV testing? Why?

Diagnosis

Smear-negative pulmonary tuberculosis

Answers

- 1) Direct smear staining of sputum and examination by Ziehl-Neelsen or fluorescent staining is one of the quickest and most reliable ways of making a diagnosis of TB. In high-prevalence settings, a positive stain can be considered diagnostic, as mycobacteria other than tuberculosis (MOTT) are relatively rare. Unfortunately, the number of AFBs in sputum needs to be high (5 000–10 000 organisms/mL). Under program conditions, 35% of PTB cases are smear-negative; in HIV patients, the rate of smear-positive cases is even lower. In summary, a positive AFB smear is very helpful for diagnosing TB; however, a negative smear can never rule it out.
- 2) MTB/RIF GeneXpert would be the next step. It is a PCR method that can detect lower concentrations of mycobacteria, and is particularly helpful in HIV-positive patients with lower bacterial loads. Additionally, it screens at the same time for resistance against rifampicin.

Sputum TB culture is a possible next diagnostic step. However, due to the long time (3–6 weeks) required for the culture to become positive, and to the logistical problems involved (transport to a central lab, finding the patient once the result returns, etc.), it is often no help in guiding the therapeutic decision. The clear advantage is the possibility of obtaining a resistance profile of the TB strain, which is of particular importance in retreatment cases, and in cases with RIF resistance in the GeneXpert result. Invasive diagnostic steps, such as bronchoscopy, are rarely possible, and seldom indicated in our setting.

- 3) Standard TB treatment consists of two months of a four-drug combination (rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E)), preferably in a fixed drug combination (intensive phase). This is followed by four months of RH (consolidation phase). Pyridoxine 25 mg (vitamin B6) should be given simultaneously with isoniazid to prevent haematological and neurological side effects.
- 4) TB and HIV infections are often found in the same patient. To screen TB patients for HIV is therefore an effective way to identify HIV-infected individuals. The radiological appearance of TB may be different in HIV patients; it is helpful to know the patient's immune status when interpreting the CXR. This patient's x-ray shows a 'typical' TB upper lobe infiltrate with cavitation, which might suggest his CD4 count was not very low.

Outcome and Follow-up

The patient was started on RHZE. Additionally, pyridoxine 25 mg od, multivitamin tablets, and CPT were prescribed on the same day. ART (TDF/3TC/EFV) was initiated after the patient had tolerated TB treatment well for two weeks.

Comments

It has been shown that multivitamins slow the progression of HIV disease in the setting of a nutritionally deficient population. CPT is indicated for all patients, particularly those with advanced immunodeficiency; most guidelines recommend it for WHO Stage 3 and 4 disease, and in patients with low CD4 counts. All HIV-positive patients with PTB should receive CPT.

Key Learning Point

All TB patients should be tested for HIV, and all HIV patients should be tested for TB.

Suggested Reading

Ministry of Health, Malawi. Malawi national tuberculosis control programme manual. 7th ed. Lilongwe (Malawi); Ministry of Health, Malawi; 2012.

Case 3

Presentation

A 44-year old patient was seen in the clinic with chest pain. He was referred to you for assessment of possible TB. He reported that a previous HIV test was negative, but he does not remember when that was done. He was asked to show his tongue.



Questions

- 1) What is shown?
- 2) What important questions should be asked to assess the extent of the infection?
- 3) What would you assume about the patient's HIV status?
- 4) How would you treat this condition?

Diagnosis

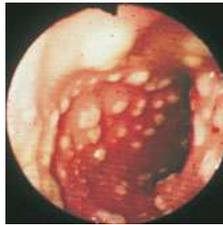
Oral candidiasis (thrush)

Answers

- 1) White cheesy exudate suggestive of mucosal candida infection. It is most commonly seen on the tongue and gingival mucosa, but the hard palate can also be affected.
- 2) It is important to ask whether the chest pain is associated with swallowing, or whether he has difficulties swallowing. Candida oesophagitis is a common cause of odynophagia, as well as dysphagia. In the presence of oral infection, painful swallowing practically makes the diagnosis of oesophagitis; upper GI endoscopy is rarely indicated.
- 3) Oral candidiasis generally occurs in patients with fairly advanced HIV infection, commonly with CD4 counts <300 cells/ μL . The HIV test should be repeated. If negative, other causes should be considered, such as diabetes mellitus.
- 4) Oral lesions only can be treated with nystatin solution 2.5 mL five times per day, or 0.5% Gentian violet aqueous solution painted in the mouth three times daily. If oesophagitis is probable (painful swallowing), fluconazole 200 mg od for 7 to 14 days is indicated.

Outcome and Follow-up

The patient went for another HIV test; this one was positive. He reported painful swallowing, so he was started on fluconazole 200 mg to treat candida oesophagitis. His CXR was normal, so no TB treatment was started. ART and, additionally, CPT were given. His CD4 count was 88 cells/ μL .



Candida oesophagitis (in a different patient).
Upper GI endoscopy is rarely indicated.

Comments

The disease usually responds well to anti-fungal therapy. Relapses do occur and fluconazole resistance can be seen, especially in patients receiving fluconazole for long periods of time (e.g., patients with cryptococcal meningitis on prophylactic therapy). Amphotericin B might be an option in these cases, but it is rarely required.

Rhomboid median glossitis (red smooth area on the middle of the tongue anterior to circumvallate papillae) and a geographic tongue (red smooth depapillated patches of the tongue that change locations on the tongue periodically) should not be confused with oral candidiasis.

Key Learning Point

In the presence of oral candidiasis, always ask the patient about dysphagia and odynophagia to investigate for candidal oesophagitis.

Suggested Reading

Fichtenbaum CJ, Aberg JA. Candidiasis and HIV. San Francisco (CA): University of California, San Francisco HIV InSite Knowledge Base. 2006 Feb. Available from: <http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-02-03>.

Case 4

Presentation

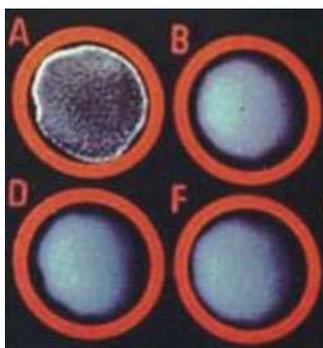
An 18-year old female patient was admitted to the ward with headache and vomiting. Her sister reported that she was becoming increasingly somnolent, and had displayed altered behaviour.

A clinical examination revealed cachexia and marked neck stiffness; there was also evidence of oral candidiasis. The guardian did not know her HIV status, and the HIV counsellor refused to administer the test, as the patient was too confused to consent.

A lumbar puncture was done; it showed the following:

CSF-polymorphs	0 cells/mL	(normal <5)
CSF-lymphocytes	24 cells/mL	(normal <5)
CSF-protein	0.63 g/L	(normal 0.15–0.4)
CSF-glucose	3.1 mmol/L	(normal 2.7–4.1)

A test for cryptococcal antigen, which was done in the lab, is shown in panel A.



Questions

- 1) What types of tests are used to diagnose cryptococcal meningitis? What does the result in panel A show?
- 2) How should this patient be treated?
- 3) Comment on the counsellor refusing to test for HIV. What would you do?

Diagnosis

Cryptococcal meningitis

Answers

1) Cryptococcal meningitis is extremely common (it is now the most common cause of meningitis in adults in parts of Southern Africa), and should be considered in all patients with headache, unexplained fever, nausea, vomiting, neck stiffness, abnormal behaviour, and/or other CNS or psychiatric symptoms. Lumbar puncture is the test of choice. CSF analysis results indicate pleocytosis in 70% of cases (often mild with lymphocytic predominance), elevated protein levels in more than 90% of cases, and decreased glucose in 60% of cases. CSF should be analysed by India ink stain (to find the cryptococcal yeast cells, positive only if a large number of cells are present), and a rapid cryptococcal antigen test.

The picture shows a latex agglutination test. In panel A the flocculated material proves the presence of cryptococcal antigen; the other panels show no agglutination. The test is very sensitive—but, as it detects antigen, it stays positive even long after appropriate treatment has been initiated.

2) Cryptococcal meningitis should be treated with amphotericin B 1 mg/kg/dose IV for two weeks (minimum one week). The main limitation of amphotericin B is nephrotoxicity; additionally, many patients react with fever, rigor, and headache. To minimise the side effects, the following should be prescribed:

- Give potassium chloride 20 mmol in 1 L normal saline IV for two hours
- Panadol 500 mg po before Ampho infusion
- Ampho xx (=body weight) mg in 1 L dextrose 5% IV over five hours, continue for seven days
- If rigor develops, give one vial of hydrocortisone 100 mg stat
- SlowK tablets od or bd if available

Renal function should be monitored. International guidelines recommend combining amphotericin with flucytosine, but this is rarely available. Fluconazole 1 200 mg po od for 14 d can also be used as an alternative to amphotericin B. This intensive initial phase is followed by a consolidation phase with fluconazole 400 mg po od for eight weeks. After this, secondary prophylaxis is given (fluconazole 200 mg po od) for life, or until CD4 >200 cells/μL.

3) The counsellor can perform HIV tests after obtaining consent from the patient (or a parent, if the patient is a minor). In comatose or confused patients, the clinician can order a HIV test for 'medical indication' without consent, if necessary for diagnosis or treatment of life-threatening disease. The order should be documented in writing in the file.

Outcome and Follow-up

The patient was treated for cryptococcal meningitis, as detailed above. The HIV test was positive. The patient deteriorated despite therapy; two more LPs were done to relieve CSF pressure; she finally became comatose, and died on the sixth day in hospital.

Comments

Amphotericin B is the drug of choice; it should be used whenever possible as initial treatment. If this is not available, another (suboptimal) option is to substitute amphotericin B induction phase with fluconazole 1200 mg po od for two weeks, followed by fluconazole 400 mg daily for eight weeks. As drug shortages frequently occur, we currently treat with amphotericin B for one week.

It has been shown that CSF pressure management is a very important aspect of treatment, but there are practical difficulties in our setting. CSF opening pressure should be measured, as patients with raised intracranial pressure (>20 cm CSF) experience considerable relief if pressure is released by draining up to 20 mL of CSF. Ideally, measurement is done with a plastic manometer (a tube with cm markings to show the height of the CSF column); alternatively, it can be done by connecting a giving set to the spinal needle and measuring the column of CSF with a ruler (note: the patient must lie on his side!). The need for pressure relief is guided by the recurrence of symptoms. Patients may require daily LPs.

Key Learning Points

- Cryptococcal meningitis is now the most common cause of adult meningitis in many parts of Africa.
- CSF pressure management can reduce morbidity and mortality.

Suggested Reading

Loyse A, Wilson D, Meintjes G, Jarvis JN, Bicanic T, Bishop L, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis.* 2012 Jan 1;54(1):121–8.

World Health Organization. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents, and children. Geneva (Switzerland); World Health Organization; 2011.

Notes

Case 5

Presentation

A 56-year-old woman attended clinic with complaints of fatigue, frequent urination, and constant thirst. When asked, she reported intermittent blurred vision. Initially she had been taking d4T/3TC/EFV for more than two years, and then was switched to TDF/3TC/EFV. Her last documented CD4 count was 320 cells/ μ L, her last VL (about eight months ago) was suppressed. Her blood sugar was measured by the nurse as 390 mg/dL. Other than obesity, her examination was unremarkable. Type II diabetes mellitus was diagnosed.

Questions

- 1) What would you recommend as treatment for diabetes mellitus?
- 2) How would you monitor the patient's diabetes in our setting?
- 3) What other risk factors would you like to exclude?

Diagnosis

Type II diabetes mellitus in an HIV patient on ART

Answers

- 1) The first step in management of diabetes is appropriate lifestyle change, such as increased exercise. It is important to explain what is meant by 'exercise'. Brisk walking for 45 min three times per week is adequate. Additionally, it is important to explain dietary modifications (e.g., reduce sugar and starches, increase fresh vegetables and fruits), which might be difficult for patients with limited financial resources to implement. More often than not, drugs will be needed to control the diabetes, particularly with blood sugar of >300 mg/dL.
Metformin (start 500 mg od or bd, max. dose 850 mg tds) is a treatment option and reduces weight. When provided in combination with ART, remember that metformin increases the risk of lactic acidosis, particularly in people taking d4T, ddI, and AZT. If metformin is not enough to control hyperglycaemia, treatment with a sulphonylurea (e.g., glibenclamide) can be added. Start with 2.5 to 5 mg/day, max dose 10 to 15 mg/day; give two-thirds of the dose in the morning, and one-third in the evening. The drawback of this class of drugs is that they can cause weight gain. Insulin may be required for refractory cases, but it poses logistical problems (cool storage, blood sugar measurement) → check with diabetes clinic.
- 2) Often patients present with random sugar levels, which are of little to no help in guiding treatment, as their relation to the last meal is unknown. The best way to monitor blood sugar in our experience is the fasting blood sugar level. Patients need to understand the procedure! After the drugs are prescribed, the patient is asked to come back after one week to measure his sugar before breakfast. A fasting sugar level between 110 to 150 mg/dL is considered acceptable. Above 150 mg/dL, the drug dose should be increased. Unfortunately, 'ideal' blood sugar targets are very difficult to reach in our environment. (HbA1c would be an option for monitoring long-term average blood sugar levels—however, HbA1c is available only in the private sector.)
- 3) The other most important treatable risk factor is hypertension, which should be controlled (ACE inhibitors would be the optimal first-line treatment). Serum cholesterol could be measured, if drugs are available to treat hypercholesterolemia. Otherwise, it might be easier to recommend lifestyle modification without measuring the actual level.

Outcome and Follow-up

The patient was informed about lifestyle modifications, and started on metformin 500 mg bd. The following week, she had a fasting blood sugar of 190 mmol/L, so the dose was increased. A reasonable value of 150 mmol/L was achieved with metformin 500 mg tds per day.

Comments

The development of type II diabetes has been reported in 2% to 10% of HIV-infected individuals on ART. ART (particularly PIs and EFV) significantly increases risk of hyperglycaemia, but other factors, including HIV disease severity and CD4 cell count, also seem to play an important role. A few cases of type II diabetes in African men with advanced HIV infection have also been reported, which resolved with antiretroviral therapy linking HIV itself to diabetes. Liver injury caused by concomitant chronic hepatitis infection and ART-related hepatic steatosis might add further risk to the patient.

Key Learning Point

Use of metformin together with AZT, ddI, and d4T significantly increases the risk of lactic acidosis (and should therefore be used with caution).

Suggested Reading

Ministry of Health, Malawi. Malawi standard treatment guidelines (MSTG). 5th ed. Lilongwe (Malawi); Ministry of Health, Malawi; 2015.

Case 6

Presentation

A 43-year-old patient was seen because he did not feel well, felt like he had to pass more urine, and had vague abdominal symptoms with nausea. He was HIV positive, and had started TDF/3TC/EFV and CPT two months ago. A MRDT test was negative; a urine dipstick was positive for protein and glucose. The patient was not known to be diabetic; a random blood sugar showed 86 mg/dL. His weight was 73 kg, his height 1.74 m.

The following lab values were obtained:

Crea	1.8 mg/dL	(normal <1.2 mg/dL)
Urea	32 mg/dL	(normal 20–40 mg/dL)
ALT	37 U/L	(normal <60 U/L)
Bili tot	0.7 mg/dL	(normal <1.1 mg/dL)

Questions

- 1) How is the creatinine clearance (CrCl) calculated?
- 2) The side effects of which drug could explain the renal impairment in this patient? Should it be stopped?
- 3) Which other nephrotoxic drugs are frequently co-administered to HIV patients?
- 4) How can the sugar in the urine be explained?

Diagnosis

TDF-induced nephrotoxicity, Fanconi syndrome

Answers

1) The easiest formula to use with a normal calculator is the Cockcroft-Gault formula:

$$\text{CrCl} = ((140 - \text{age (yrs)}) \times \text{body weight (kg)}) \div (72 \times \text{Crea (mg/dL)})$$

(for female patients, multiply result by 0.85).

So, calculate: $[(140 - \text{age}) \times \text{body weight}] \div (72 \times \text{crea})$.

For this patient, that gives us: $[(140 - 43) \times 73] \div (72 \times 1.8) = 54.6 \text{ mL/min}$.

- 2) Tenofovir is an ART drug with known nephrotoxicity. Additionally, CPT is known to cause acute kidney injury (AKI), but that is far less probable. Tenofovir is not recommended in patients with CrCl <50 mL/min. Although the CrCl is still 54, given that the patient shows symptoms, and there are no other explanatory causes for renal impairment, it would be prudent to stop TDF and switch to another drug (probably AZT or ABC).
- 3) Streptomycin (retreatment TB) and other aminoglycosides used in MDR-TB treatment, amphotericin (cryptococcal meningitis). Rarer causes: CPT, RIF
- 4) Fanconi syndrome is a form of tubular kidney damage as a consequence of tenofovir therapy. In these cases, the tubular function to reabsorb molecules is impaired, leading to loss of water (dehydration), sugar (normoglycemic glucosuria, explaining the finding in this patient), HCO₃⁻ (metabolic acidosis), phosphate (low blood phosphate, osteoporosis), and potassium (hypokalaemia).

Outcome and Follow-up

The patient was switched to AZT/3TC/EFV; rehydration was recommended. His renal function was found to be normal after two months.

Comments

A possible algorithm to think about renal disease in our patient population is given in the following set of questions:

1. Does it look like chronic kidney disease (CKD)?

Commonly, poorly controlled diabetes and/or hypertension. Tx: improve management of the chronic condition, stop smoking, avoid NSAIDs, and adjust drug doses as needed.

2. Could this be HIVAN?

Proteinuria ≥ 2+ on dipstick, with no haematuria, normal bp, no oedema, and no rash; definitive diagnosis by biopsy, but diagnosis suggestive if other conditions are excluded (below) and echogenic kidneys on ultrasound. Tx: continue ARVs, consider TDF sparing regimen, and start enalapril.

3. Could this be an acute kidney injury (AKI)?

A. Could this be pre-renal?

Dehydration usually associated with hypovolaemia and low bp; if ultrasound available: IVC and hepatic veins small. Tx: give fluid and re-check.

B. Could this be an obstructive nephropathy (post-renal)?

Possibly due to large lymph nodes (TB, malignancy) or schistosomiasis; ultrasound to confirm diagnosis. Tx: according to cause

C. Could this be an intrinsic nephropathy (intra-renal)?

1. Tubular necrosis (85%) usually follows an episode of severe dehydration or sepsis (pre-renal), or due to toxics; TDF and other toxicity belong here. Tx: IV fluids and monitoring.
2. Acute interstitial nephritis (10%) may occur with extra-renal manifestations of hypersensitivity (rash, fever, joint pain, eosinophilia), and can look like pyelonephritis with fever and flank pain; recurs with re-exposure. Possible causes in TB/HIV setting: cotrimoxazole, rifampicin. Tx: stop offending drug; sometimes give steroids.
3. Acute glomerulonephritis (5%) usually presents with haematuria, proteinuria, hypertension, oedema. Tx: steroid, enalapril.

Suggested Reading

Medicins Sans Frontieres. Renal disease in HIV: A practical manual for primary care physicians. Geneva (Switzerland): Medicins Sans Frontieres; 2012. Available from: <http://samumsf.org/documents/2015/12/renal-disease-in-hiv.pdf>.

Case 7

Presentation

A 27-year-old woman presented to the clinic with generalised, pigmented lesions, some of which were macular, and some of which were nodular. Her primary complaint was pain and difficulty swallowing. She was HIV positive, and had a CD4 count of 17 cells/mL.

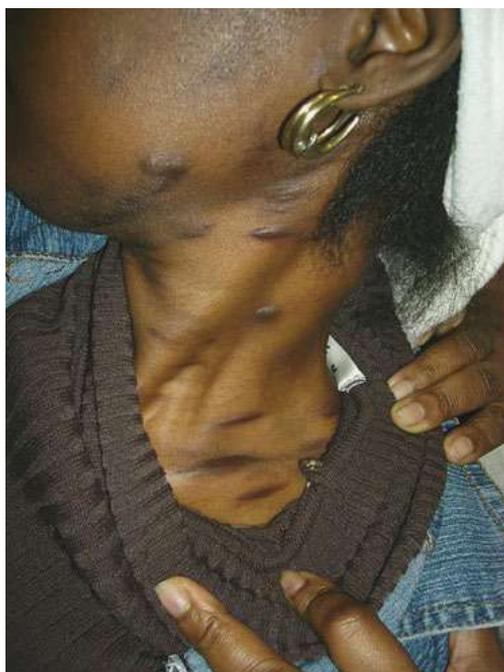
Blood tests:

FBC

Hb	6.4 g/dL	(normal 11.5–16.5)
WBC	5.4 $10^9/\text{mm}^3$	(normal 4.0–11.0)
Plt	35 $10^9/\text{mm}^3$	(normal 150–500)

U&E and LFT

Crea	2.3 mg/dL	(normal <1.1)
BUN	110 mg/dL	(normal 12–50)
TBIL	3.1 mg/dL	(normal <1.1)
GGT	125 U/L	(normal 7–62)
ALP	37 U/L	(normal 42–121)



Questions

- 1) What is the diagnosis?
- 2) How is the diagnosis confirmed?
- 3) How is it staged? Which treatment is available?

Diagnosis

Kaposi sarcoma

Answers

- 1) Kaposi sarcoma
- 2) Diagnosis should be confirmed by a skin biopsy using a puncher with a circular blade (i). This is done as follows:
 - a) Find a slightly raised lesion.
 - b) Choose an area where pressure can be applied easily, as the lesion may bleed.
 - c) Choose an area at the margin of the lesion.
 - d) Disinfect the area thoroughly.
 - e) Infiltrate with Lignocaine 2%.
 - f) Punch out the sample by applying gentle pressure on the puncher and rotate it to and fro between your fingers (ii).
 - g) Cut the cylinder with a blade and put it into formalin (iii).
 - h) Apply pressure and dressing.
- 3) The extent of disease is graded according to the AIDS Clinical Trial Group (ATCG) classification, based on tumour size (T0/T1), and whether systemic involvement is present (S1) or not (S0):



T0	Kaposi sarcoma is confined to skin and/or lymph nodes, and/or demonstrates minimal oral disease (roof of mouth). The Kaposi sarcoma lesions in the mouth are flat rather than raised.
T1	Kaposi sarcoma lesions are widespread. One or more of the following is present: <ul style="list-style-type: none"> • Oedema (swelling) due to the tumour. • Extensive oral Kaposi sarcoma: nodular lesions (raised) and/or lesions in areas of the mouth besides the palate.
S0	No systemic illness present; all of the following are true: <ul style="list-style-type: none"> • None of the following B symptoms is present: unexplained fever, night sweats, >10% involuntary weight loss, diarrhoea persisting for >2 wks. • Karnofsky performance status score is ≥ 70 (i.e., patient is up and about most of the time, and able to take care of him- or herself).
S1	Systemic illness present; one or more of the following is true: <ul style="list-style-type: none"> • One or more B symptoms is (are) present. • Karnofsky performance status score <70.

All patients with KS must receive antiretroviral therapy. ART can lead to regression in the size of existing KS lesions, and in itself improves chances of survival in patients with or without chemotherapy. If a patient is not yet on ART, start ART as soon as possible. If the patient is on ART and develops new KS, check VL (and CD4) to see if he or she is failing antiretroviral therapy. Except for very few patients with T0/S0 with minimal disease (few lesions, patient asymptomatic, non-raised lesions only on the skin), all patients should receive low-intensity chemotherapy. Patients with minimal T0/S0 may receive only ART; nevertheless, the KS has to be well documented at

baseline to assess disease's progression. For ALL others we use vincristine 2 mg iv every two weeks + bleomycin 0.1 units/BSA IV every two weeks. Usually, six cycles are given, and then the response is assessed. The total dose of bleomycin should not surpass 300 to 350 mg, as lung toxicity is a problem. Local treatment options include radiotherapy for obstructing or localised lesions, especially those affecting the eyelid or tongue—but these are not available in Malawi.



Kaposi sarcoma of the eyelid.

Outcome and Follow-up

The severity of her skin lesions and blood parameters suggested that this woman had extensive KS with disseminated skin, and possible gastrointestinal, liver, and bone marrow involvement. She had an abdominal ultrasound, which showed liver involvement. She was started on ART, followed by chemotherapy with vincristine and bleomycin.



Infiltrating disease of the lower limb with accompanying lymphoedema is frequently seen. In this male patient the disease, involved the genitalia.

Suggested Reading

Mwafongo AA, Rosenberg NE, Ng'ambi W, Werner AB, Garneau WM, Gumulira J, et al. Treatment outcomes of AIDS-associated Kaposi's sarcoma under a routine antiretroviral therapy program in Lilongwe, Malawi: bleomycin/vincristine compared to vincristine monotherapy. *PLoS One*. 2014;9(3):e91020.

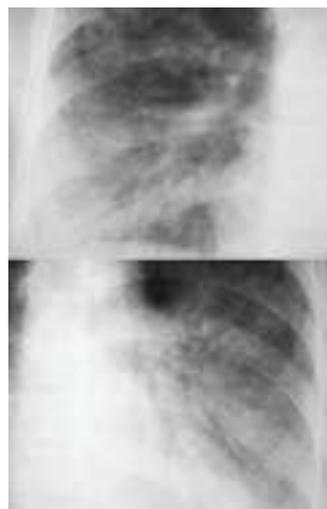
Notes

Case 8

Presentation

A 35-year-old woman presented with severe dyspnoea of two weeks' duration and a dry cough. She was unable to walk without developing profound respiratory distress. She was HIV positive, with a CD4 count of 10 cells/mL.

At rest, the patient looked surprisingly well, and initially did not appear distressed. However, her respiratory rate with minimal exercise (walking to the toilet) was 70/min. She was febrile (38.8° C) and tachycardic (120/min). Her chest was clear to auscultation with normal breath sounds throughout. Her CXR is below; the small images show details.



Questions:

- 1) What do the x-rays show?
- 2) What is the most likely diagnosis?
- 3) What is the appropriate treatment?

Diagnosis

Pneumocystis jiroveci pneumonia (PCP)

Answers

- 1) The images display bilateral, diffuse, symmetrical, ground-glass infiltration that is more pronounced in the central regions of the lung than in the periphery.
- 2) The most likely diagnosis is PCP. Progressive exertional dyspnoea is the hallmark of PCP, and may be associated with cough (usually non-productive) and fever (usually mild). Chest examination may be normal, or have crackles. Radiographic abnormalities are diffuse bilateral interstitial or alveolar infiltrates, often described as ground-glass infiltrates. However, CXRs may show other abnormalities or be normal (in 5–10% of cases), especially with lower CD4 counts. Induced sputum or bronchoalveolar lavage (BAL) can be performed to get specimens for microscopic examination. In our setting, this is rarely done. Of high diagnostic value is clinical assessment of oxygenation, both at rest and with exercise.
- 3) PCP is treated with high-dose CTX according to weight (< 60kg 3 tabs tds, >60 kg 4 tabs tds) for 21 days. Patients with PCP usually become worse after two to three days of therapy, presumably due to increased inflammation in response to dying organisms. Corticosteroids as adjunctive therapy decrease mortality and respiratory failure. Steroids are indicated in patients who are hypoxic. In the absence of blood gas analysis, clinical judgment and oxygen saturation measurement is used. Recommend doses are 80 mg prednisone daily for five days, followed by 40 mg daily for five days, followed by 20 mg daily for 10 days. In general, with effective treatment, a response is expected in 7 to 10 days.

Outcome and Follow-up

The diagnosis of PCP was made, and the patient was commenced on the above-mentioned treatment, including steroids. She made a good recovery over the next few weeks, and was able to get up and walk around after two weeks. She started ART in the ward, and was then discharged for further treatment in the clinic.

Comments

Pneumocystis jiroveci pneumonia (PCP, previously named *Pneumocystis carinii* pneumonia) was the archetypal AIDS-defining illness in the early 1980s. It was initially reported to be less common in Africa, but recent reports describe an increase in cases.

It is noteworthy that patients who show severe drug reactions to CTX can be treated with clindamycin (600 mg tds po) plus primaquine (15 mg od po) for 21 days.

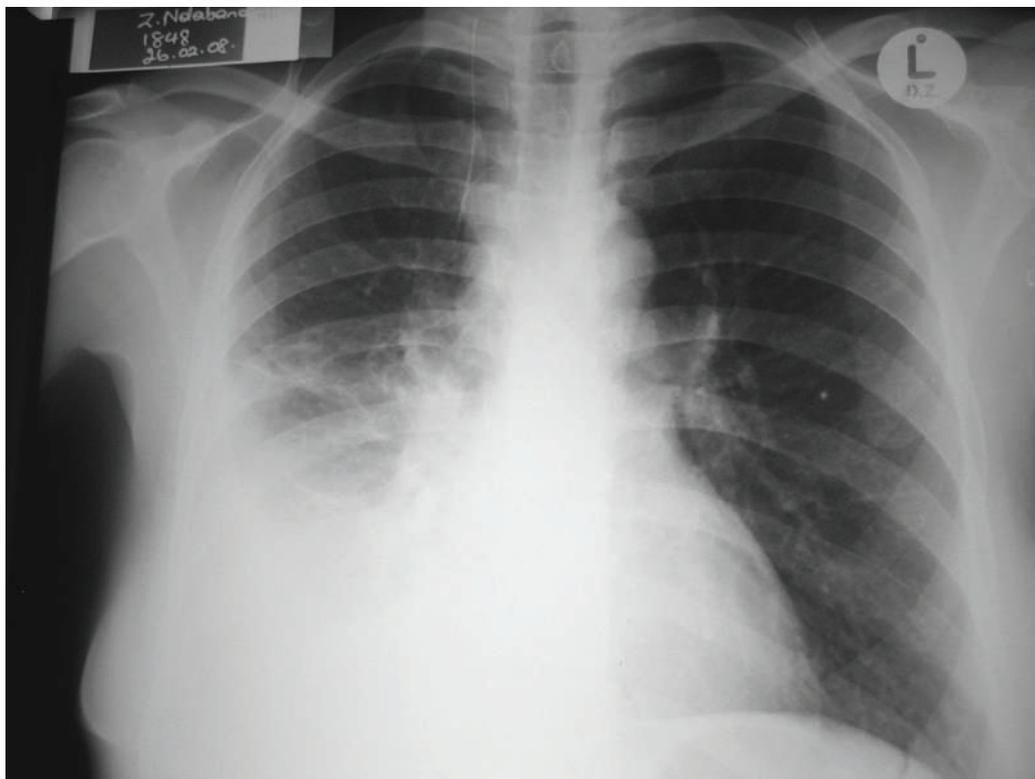
Key Learning Point

Severe dyspnoea is a hallmark of PCP, and can be useful to distinguish PCP from TB. Steroids are indicated in severe cases.

Case 9

Presentation

A 33-year-old man was seen with symptoms of chronic cough of two months' duration and chest pain. He reported night sweats and weight loss, but did not look extremely unwell. Sputum AFB samples were negative at his PHC clinic; antibiotics (amoxicillin + erythromycin) given by the clinic for one week were not effective. He was referred for a CXR, which showed a right pleural effusion, and a lower lobe infiltrate. TB was diagnosed on clinical grounds, and treatment started.



Questions

- 1) What types of pleural involvement are seen in tuberculosis?
- 2) How would you investigate the patient?
- 3) How would you manage the effusion?

Diagnosis

TB with pleural effusion

Answers

- 1) The pleura as part of the respiratory system might be affected in four different ways:
 - a) Effusion, which develops usually a few months after the primary infection, usually in young adults or children when there is rupture of a sub-pleural component of the primary infection. Pathophysiologically, this is often a hypersensitivity reaction of the pleural serosa to a small number of bacilli. AFB from the pleural effusion will invariably be negative, and a culture might grow mycobacteria. This may resolve without treatment, but will often relapse.
 - b) Effusion developing as a result of lung disease in older adults, which might develop into purulent effusion (empyema).
 - c) Rupture of a cavity, and escape of bacteria and air into the pleural space. Empyema will result, and, due to the escaping air, pyo-pneumothorax could also result.
 - d) Complicating miliary TB, which involves polyserositis.
- 2) Remove a small amount of fluid, and send it to the lab. Protein and cells should be assessed, and AFB and material sent for GeneXpert.

Often, the fluid is clear and straw-coloured, the protein is high ($> 1.5\times$ serum protein \rightarrow exudate), and the cells are predominantly lymphocytic. If total WBC count is higher than 500 cells and protein > 2.5 g/dL, an empyema can be diagnosed. It can be differentiated between thin empyema (possible to mobilise through cannula) and thick empyema (which needs a transthoracic drain to be mobilized).

A pleural biopsy (using an Abraham's needle) can be attempted if the effusion is large enough, and the necessary equipment and training are available. We do not usually use this.
- 3) Treatment is standard chemotherapy with RHZE; the end result is usually satisfactory. Therapeutic drainage is only indicated in patients with respiratory distress, and can usually be done by inserting a large IV cannula into the pleural space. In some cases, thoracic drains might be necessary. Unfortunately, in these cases, which often have thick empyema, even this drainage might be insufficient, and an operation (rib resection) might be necessary.

Outcome and Follow-up

No further diagnostic tests were performed for this patient, as his respiratory system was not compromised. He had an HIV test, which was positive. This makes TB an even more likely diagnosis. His CD4 count was 154 cells/mL. TB treatment was started, followed two weeks later by ART.

Comments

Puncture of pleural space with a small cannula to drain fluid is often possible; this is far less invasive than a formal intercostal drain. Most often, the main effective treatment (also for empyema) is drug treatment. Thus, the indication to place a drain (with all the possible complications like bleeding, infection, and chronic fistulas) needs to be considered carefully.

Key Learning Point

All (unilateral) pleural effusions with a consistent clinical history can be considered TB in our setting, if there is no alternative explanation.

Case 10

Presentation

A 22-year-old woman was seen at the clinic for initiation of ART. She had received *Pneumocystis jiroveci* pneumonia treatment two weeks prior, and explained that her shortness of breath and cough had improved. She otherwise only admitted to weight loss of <10%. The patient had a two-year-old child, but had never taken NVP in the PMTCT programme. She reported that she would like more children. Her CD4 count was 158 cells/mL. She was classified as Stage 4 because of the PCP, and was started on TDF/3TC/NVP.

Questions

1) How should these antiretrovirals be taken initially (dose, timing)? What follow up should she have?

At two- and four-week follow-up visits, the patient reported no problems. No blood tests were taken. She attended the clinic two months after initiation of treatment, complaining of a rash that had been gradually worsening over seven days. She had fatigue, occasional fevers, and severe nausea, but no vomiting. She explained that even that morning she had managed to take her tablets.

On examination, the patient had a desquamating rash. She was deeply jaundiced, but showed no signs of encephalopathy. Her temperature was 37.3° C, BP 90/60 mm Hg, HR 95/min. Otherwise, examination was normal.

- 2) What is the differential diagnosis?
- 3) What are the risk factors for this condition?
- 4) What is the management indicated for this patient?

Diagnosis

NVP-related hepatotoxicity

Answers

- 1) Initially, NVP is taken at 200 mg once per day for 14 days; then, if there are no signs of toxicity, the dose is increased to 200 mg twice per day. The patient should be assessed during these visits, and, ideally, LFTs are collected. If there are any signs of toxicity (jaundice or rash), the doctor should be alerted before increasing the dose. In South Africa, monitoring involves routinely checking ALT.
- 2) Nevirapine-associated acute hepatitis is the most likely diagnosis. Acute hepatitis could also be caused by other drugs—e.g., anti-TB drugs, cotrimoxazole, and traditional medicines. Viral causes include hepatitis B (especially an immune reconstitution to HBV after initiation of ART or flares after stopping TDF or 3TC), hepatitis A, CMV, or EBV. Bacterial causes are hepatic TB (again, can present as IRIS), and, less commonly, leptospirosis.
- 3) One in 20 people will have some degree of reaction to NVP (rash and/or hepatitis), usually within the first four months. Risk factors for hepatitis include: female sex, HBsAg positivity, HCV infection, alcohol excess, concomitant hepatotoxic medications (such as anti-TB drugs), and CD4 >250 in women, >400 in men.
- 4) Management is to stop the offending drug—i.e., NVP. Otherwise, management is purely supportive. No additional treatments have shown to improve mortality outcomes.

Outcome and Follow-up

The patient's LFT showed the following results:

Bili tot	10.6 mg/dL	(normal <1.1)
ALP	198 U/L	(normal 42–121)
ALT	1 030 U/L	(normal 10–60)

The patient was admitted to the ward. All of her medications were stopped, and she was started on IV fluids.

Comments

Hepatotoxicity is a common problem with ARVs, as well as with anti-TB drugs. Local protocols recommend the following action in reaction to abnormal ALT values on treatment:

- **If ALT = 2–5x upper normal limit**
 - Reassure patient
 - Repeat test at suitable interval (two weeks)
 - Check HBsAg if not done already
- **If ALT = 5–10x upper normal limit**
 - Inform doctor
 - Check HBsAg if not done already
 - If systemic symptoms occur, then stop ART
- **If ALT > 10x upper normal limit**
 - Stop ART (and other drugs)
 - Admit to hospital

Key Learning Point

Monitoring of ALT is indicated for patients started on NVP.

Case 11

Presentation

A 28-year-old female patient who has been on ART for eight months was seen with a one-week history of cough and shortness of breath. Her last CD4 count was 354 cells/ml. She was febrile (38.9° C), and looked distressed. An antibiotic (amoxicillin/clavulanic acid) was prescribed. Two days later, she was seen again at the clinic, complaining about worsening symptoms, plus nausea and vomiting. A CXR was done, and the patient admitted.

Her FBC showed an Hb of 8.3 g/dL and WBC of $12.0 \times 10^3/\text{mm}^3$.

U&E

Creat

5.2 mg/dL

(normal <1.2)



Questions

- 1) What is the most likely diagnosis?
- 2) What organism(s) could cause this picture? How should it (they) be treated?
- 3) What might have caused the patient's renal failure?

Diagnosis

Pneumonia with acute renal failure

Answers

- 1) Community-acquired pneumonia (CAP) is the most likely diagnosis, but atypical presentation of TB or PCP should always be considered. The patient's relatively short history and relatively high CD4 count point more towards CAP.
- 2) *S. pneumoniae* and *H. influenzae* are the most common pathogens encountered in our setting. The clinical presentation is similar to that of HIV-negative patients, but complications are more frequent in the immunocompromised patient.
For outpatient treatment, oral amoxicillin plus erythromycin can be used. In more severe cases, oral amoxicillin/clavulanic acid can be considered. If the patient needs hospital admission, IV ceftriaxone is the agent of choice. Combination with a macrolide or a quinolone is possible to cover for atypical causes of pneumonia. (Caution: quinolones are active against TB, and may thereby induce resistance if given as monotherapy.)
- 3) The patient was possibly suffering from mild HIV-associated nephropathy. As consequence of the acute severe infection, organ failure (acute or chronic renal failure) is not uncommon, and should be treated with careful fluid management. Often, renal replacement therapy can be avoided (this is difficult to obtain in a resource-limited hospital).

Outcome and Follow-up

The patient was admitted to the ward, where her antibiotics were changed to ceftriaxone 2 g od IV and erythromycin 500 mg tds po. Metoclopramide was given for the nausea. Additionally, IV fluids (2 000 ml Ringer's lactate) were ordered, but it was unclear how much of this she received. The following day, the patient deteriorated clinically, became more distressed and confused, and was transferred to our high-care unit (although the high-care unit does not have the equipment for mechanical ventilation or renal replacement therapy). Five litres of normal saline solution were ordered and given over the next 24h. The antibiotic therapy was continued. Clinically, the patient improved slowly over the next few days, and she was ultimately discharged in her normal state. By this time, her creatinine had fallen to 1.3 mg/dL; three weeks later, it had returned to normal.

Comments

The rate of CAP is approximately two to three times higher in HIV-infected individuals than in the general population. Patients seem particularly prone to infections with encapsulated pathogens; this might be due to altered B-cell or neutrophil function secondary to the HIV infection. The incidence of pneumococcal pneumonia is six times greater in HIV patients, and pneumococcal bacteraemia 100 times more frequent. This might cause septic complications, such as organ failure.

Key Learning Point

Hospital treatment is often required for pneumonia, especially in severe or complicated cases where impairment of other organs is involved.

Case 12

Presentation

A 32-year-old woman who recently tested HIV positive was seen at the clinic. Her CD4 count was 23 cells/mL; baseline LFT, U&E, and FBC were normal; and sputum was negative for AFB. She was fast-tracked for initiation, and started on ART (TDF/3TC/EFV) and CPT.

Two weeks later, the patient presented with a rash on her face and upper body. CTX was identified as the most probable cause, and was stopped. A steroid cream and chlorpheniramine 4 mg nocte were prescribed. The rash subsided within a week. CTX was reinitiated at a very low dose, and slowly increased over the following days, according to WHO guidelines. She was seen after two weeks, and did not develop the rash again. Desensitisation was considered successful. Another three weeks later, the rash reappeared; CTX was stopped, and dapsone 100 mg started.

Another month later (now a total of 2½ months after starting ART), the patient complained of new chest pain, cough, and haemoptysis. A CXR was performed.



Questions

- 1) What do the findings suggest? How would you treat the patient?
- 2) How would you comment on the fact that screening AFB was negative?
- 3) Would you agree with the attempt to use CPT in a patient with known reaction to the drug?

Diagnosis

CTX hypersensitivity, TB-IRIS after starting ART

Answers

- 1) The patient began to show TB symptoms after 10 weeks of ART. This is suggestive of an immune reconstitution inflammatory syndrome (IRIS) response to TB. As immune function slowly improves, the body starts to actively fight the TB infection (which was obviously there at the time of HIV diagnosis, but masked due to the low immunity). The patient should be started on RHZE.
- 2) Screening for TB in HIV-infected individuals is performed using AFB smear and GeneXpert. It is well known that TB in HIV patients is often smear-negative, so a negative smear cannot rule out tuberculosis. Additionally, screening is often not done, and patients may even be missed because screening questions (e.g., *Fever >2 weeks?*, *Cough >2 weeks?*, *Loss of weight?*) are not asked. It is therefore not uncommon to see a subsequent 'unmasking' of undiagnosed TB; a significant number of patients are admitted to hospital after six to eight weeks of ART.
- 3) CTX is a very effective prophylactic drug; it reduces the rate of not only pneumocystis pneumonia, but also bacterial infections, especially with enteric bacteria and malaria. It is therefore preferable to other drugs (e.g., dapsone 100 mg, which can be used as a second-line prophylaxis for PCP). According to WHO guidelines, desensitisation can be attempted two (2) weeks after a non-severe reaction to CTX. Usually, an antihistamine is started, then CTX is given in increasing doses (*day 1*: 2 ml CTX susp (80/16 mg); *day 2*: 4 ml susp (160/32 mg); *day 3*: 6 ml susp (240/48 mg); *day 4*: 8 ml susp (320/64 mg); *day 5*: one (1) single-strength tablet (400/80 mg); *day 6 onwards*, two (2) single-strength tablets (800/160 mg). Desensitisation should never be attempted in patients with severe reaction to the drug.

Outcome and Follow-up

After four weeks of TB treatment, the patient improved; her cough and chest pain stopped, and she continued therapy uneventfully.

Comments

When clinical deterioration occurs during immune recovery, and it is associated with the host inflammatory response to opportunistic pathogens, this reaction is called IRIS. Tuberculosis is the most frequent presentation of IRIS, but cryptococcal meningitis, Kaposi sarcoma, and many other infections are described in this context. Low CD4 counts at initiation are a risk factor for the development of IRIS. Most cases are mild; only rarely steroids have to be administered (in 9% of patients, according to a study from Cape Town). Death is rare; it is most commonly due to intracerebral IRIS. The fear of IRIS should not prevent patients from being started on ART!

We suggest patients taking TB treatment should start ART at least within the next two weeks. Sometimes it is helpful to space things out a few days, to make sure that patients tolerate TB treatment before starting ART. In particular, patients with a CD4 count below 100 cells/mL should start ART within two weeks, as the risk of severe immunosuppression outweighs the risk of IRIS. As mentioned above, in case of opportunistic intracerebral infections (TB meningitis, cryptococcal meningitis, toxoplasmosis), it is advisable to exercise prudence (e.g., starting ART only after 4–6 weeks of effective OI treatment).

Key Learning Point

Desensitisation is difficult to perform in this setting; it should be performed only if CTX is the only treatment option.

Suggested Reading

Murdoch DM. Incidence and risk factors for IRIS in HIV patients in South Africa: a prospective study. *AIDS*. 2008;22:601.

World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Geneva (Switzerland); World Health Organization; 2006.

Case 13

Presentation

A 26-year-old male patient presented at the clinic, reporting new onset of epileptic fits. He reported three convulsions in the preceding week during which he had lost consciousness and bit his tongue. He could not provide a detailed description of the convulsions as he 'lost his mind' during the episode, and there was no reliable eyewitness account. Additionally, he complained of headache for the past few weeks. There was no meningism, and no focal neurology on examination.

The patient otherwise looked healthy; he was sent for VCT, and tested HIV positive.

Questions

- 1) What causes of epilepsy would you consider in this HIV-positive patient?
- 2) Which diagnostic steps would take to assess the patient?
- 3) Which anticonvulsants can be used in this setting?

Diagnosis

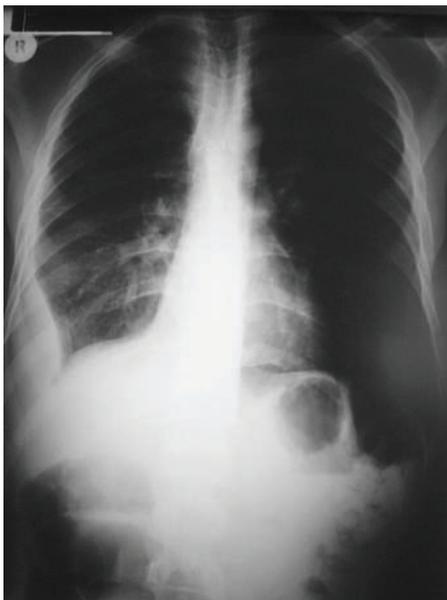
Cerebral toxoplasmosis with new onset seizures

Answers

- 1) The most common causes of new onset seizures in HIV patients are space-occupying lesions (toxoplasmosis, pyogenic abscess, tuberculoma, lymphoma), and meningitis (mostly cryptococcal). Other causes related to HIV are PML (progressive multifocal leukoencephalopathy) and HIV encephalopathy—but these are rarely diagnosed in our setting. Electrolyte imbalances (hyponatraemia, hypomagnesaemia, hypocalcaemia, renal failure) are less common reversible causes.
- 2) CT scan, lumbar puncture, and electrolytes in serum need to be considered. As toxoplasmosis is the most common cause of intracranial masses in our setting, and generally responds promptly to therapy, a treatment trial with CTX before a CT scan is warranted. If there is no improvement after one (1) week, the patient can be sent for a CT brain scan. If clinical signs point towards meningitis, the threshold for lumbar puncture should be low.
- 3) Carbamazepine (200 mg bd up to 600 mg bd) and phenytoin (4–5 mg/kg od) are the drugs commonly available to control seizures. They are started at low dose and titrated up in two-week intervals to reach effective levels. In patients receiving ART, it must be considered that both drugs are strong liver enzyme inducers, and may thus reduce levels of antiretrovirals (and NNRTIs will affect levels of the anticonvulsants). The drug of choice in this case is sodium valproate 200 mg bd, which can be increased to max. 1 200 mg bd.

Outcome and Follow-up

Cerebral toxoplasmosis was considered as the most probable diagnosis; the patient was treated with CTX 4 tbl bd. When seen two weeks later, he reported having had no more fits, and his headache had disappeared. His CD4 count was 139 cells/mL. Treatment was continued, and re-



duced to 2 tabs bd after four weeks. The patient was prepared for ART. Two weeks later he was seen again, now complaining about chest pain and cough. A CXR was done, which showed a pleural effusion and an infiltrate on the right side. A diagnostic pleural aspirate was performed, producing turbid exudate, which was sent for TB culture. The patient was started on RHZE; ART was delayed for another four weeks.

Comments

This case illustrates the fact that our immunocompromised patients frequently present with more than one pathological condition. It is often necessary to treat one condition after another; due to the risk of IRIS, initiation of ART might be delayed.

The relatively high CD4 count would normally lower the clinical suspicion of toxoplasmosis, but, in this case, there was a marked improvement in symptoms with the administration of CTX, so it was felt that further tests were not warranted.

CTX 4 tabs bd for one month, followed by 2 tabs bd for three months, is the treatment of choice for cerebral toxoplasmosis. In patients not tolerating CTX, clindamycin 600 mg tds and pyrimethamine 100 mg bd should be given for one day, followed by 50 mg od for three to six weeks (with 15 mg of folinic acid added initially to counteract the marrow toxicity of pyrimethamine).

Case 14

Presentation

A 52-year-old woman was recently diagnosed with HIV. She was overweight (weight 94 kg, height 161 cm, BMI 36 kg/m²), and her blood pressure was measured at the clinic as 210/114 mm Hg. Looking at her former blood pressure values, she repeatedly had systolic values higher than 200 mm Hg, and diastolic values of up to 135 mm Hg. She was currently taking hydrochlorothiazide 12.5 mg and enalapril 5 mg od.

Questions

- 1) Which anti-hypertensive drugs on the essential drug list (EDL) are available? How would you escalate her hypertension treatment?
- 2) Which laboratory investigations are indicated (and feasible) in the clinic setting? How would you monitor her blood pressure?

Diagnosis

Severe hypertension, obesity Grade III

Answers

- 1) Drugs and stepwise anti-hypertensive therapy.
 1. Determine grade of hypertension:
 - Grade 1: Systolic 140–159 or Diastolic 90–99 → go to **Step A**
 - Grade 2: Systolic 160–179 or Diastolic 100–109 → go to **Step A**
or if patient readily consents to treatment, go to **Step B**
 - Grade 3: Systolic >180 or Diastolic >110 → go to **Step B**
 2. **Step A:** Lifestyle changes
 - a) reduce weight (BMI <25)
 - b) restrict salt (remove from table, reduce in food)
 - c) increase fresh fruits and vegetables
 - d) moderate exercise (brisk walking) for 30 min three times a week
 3. If BP is still high at next visit → **Step B:** reinforce lifestyle changes + **Hydrochlorothiazide (HCT) 25 mg**
—reinforce adherence and re-check after one month.
 4. If BP is still high at next visit → **Step C:** reinforce lifestyle changes + **Hydrochlorothiazide (HCT) 25 mg q24h + Enalapril (ACE inhibitor) 5 mg q12h**
If tolerated well, increase **Enalapril to 10 mg q12h**
(Side effects of ACE inhibitors: dry cough, angioedema!)
—reinforce adherence and re-check after one month.
 5. If BP is still high at next visit → **Step D:** reinforce lifestyle changes
Hydrochlorothiazide (HCT) 25 mg q24h + ACE inhibitor Enalapril 10 mg q12h + Amlodipine 5-10 mg q24h
or if patient has known coronary heart disease, myocardial infarction:
+ Atenolol 50-100 mg q24h as alternative (Avoid with asthma!)
 6. If BP is still high at next visit → **Step E: Refer to Kamuzu Central Hospital** for further investigation, or add other drugs (e.g., spironolactone, furosemide, hydralazine, prazosine).
- 2) Laboratory investigations are often difficult to do in our clinic settings, as samples, results, and patients have a tendency to get lost. Feasible on-spot diagnostic tests available to us are:
 - Urine dipstick**
 - Protein*—to assess kidney damage
 - Blood*—to search for reason for hypertension (glomerulonephritis)
 - Glucose*—to search for other vascular risk factors (diabetes)
 - Blood glucose (random)**
 - If <7 mmol/l = no diabetes
 - 7–11 mmol = suspect diabetes → do fasting HGT
 - If >11 mmol/l = diabetes
 - Creatinine** and **cholesterol/triglyceride** tests are desirable, but require venous blood samples, logistics, and functioning lab services.

Comments

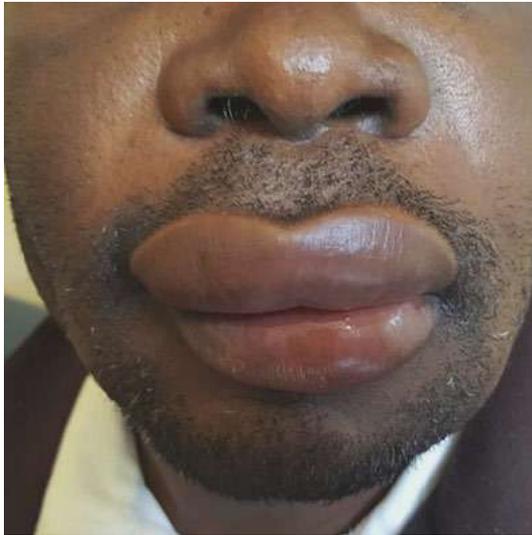
In a population with high HIV prevalence, especially among elderly patients, the infection is often combined with other comorbidities, such as hypertension and diabetes. It is important to be aware of these, and to treat concomitant chronic diseases. The difficulties in our setting (laboratory and drug shortages) make it advisable to use standardised regimens. In resistant cases of HTN, it may be useful to add spironolactone 25 mg od to achieve better BP control.

Key Learning Point

Most hypertensive patients require more than one drug to control hypertension.

Suggested Reading

Ministry of Health, Malawi. Malawi standard treatment guidelines (MSTG). 5th ed. Lilongwe (Malawi); Ministry of Health, Malawi; 2015.



Angioedema of the lips as side effect of ACE inhibitors.

Notes

Case 15

Presentation

A 34-year-old man was seen in the outpatient department with painful blisters in the area of the ophthalmic nerve. Zoster ophthalmicus was diagnosed; the patient was sent for HIV testing, which was positive. He also complained of severe headache and photophobia. On examination, the conjunctiva of the right eye was red and inflamed.



Questions

- 1) How would you treat the patient?
- 2) Which area(s) of the body is (are) most commonly affected by herpes zoster?
- 3) Name three complications.

Diagnosis

Herpes zoster

Answers

- 1) Acyclovir 800 mg five times per day po is the drug of choice, and should be started as soon as possible. Ideally, the drug should be available at the clinic, in order to prevent delay in treatment. Alternatively, valacyclovir 1 g tds can be given, if available, with a lower pill burden and better pharmacokinetics.
- 2) Thoracic (>50%), trigeminal (10–20%), lumbosacral (see picture below) and cervical (10%).
- 3) Complications that may be encountered:
 - a) **Bacterial superinfection.** Local antiseptic solutions might prevent this complication. However, if indicated, systemic antibiotics must be given.
 - b) **Scarring.** Herpes zoster scars are a disfiguring complication (and, because of their association with HIV, often stigmatising). Early acyclovir treatment seems to be the only possible preventive strategy.
 - c) **Ophthalmic complications.** If the ophthalmic nerve is affected, then the eye might be involved, and sight at risk. Keratitis, iridocyclitis, and secondary glaucoma, as well as ophthalmic nerve paralysis, are seen. Involvement of the nasociliary nerve, with vesicles on the side and the tip of the nose (!), indicates corneal involvement, although absence of these does not guarantee corneal sparing. Refer to an ophthalmologist, if possible.
 - d) **Post-herpetic neuralgia.** This complication is seen in more than half of patients for one month, but even after six months, approximately 10% complain of pain. Treatment options include carbamazepine and sodium valproate (preferable in patients receiving ART), as well as tricyclic antidepressants (e.g., amitriptyline 25–75 mg nocte)
 - e) **Dissemination.** Cutaneous dissemination—as well as involvement of organs, such as the lung, liver and pancreas—is often seen, especially in immunocompromised patients.
 - f) **Neurological disease.** Meningitis, encephalitis, myelopathy, and radiculitis have been reported; these are not necessarily associated temporally with the cutaneous disease.



Outcome and Follow-up

The patient was admitted, and acyclovir given. After two days, no improvement was seen, so the drug was changed to acyclovir 10 mg/kg IV. Additionally, an antibiotic (amoxicillin) and antibiotic eye drops were added to treat secondary bacterial superinfection in the eye. The patient complained about severe sharp pain, so diclofenac and amitriptyline were initiated. The skin lesions healed with substantial scarring, but the patient's vision remained completely normal.

Comments

Herpes zoster has been recognised as a frequent infection in patients with HIV infection, occurring in approximately 10% of patients. An HIV test should always be recommended. The complications of cutaneous dissemination are infrequent, but can present as recurrent disease, CNS involvement, and visceral involvement (pneumonitis, pancreatitis).



Key Learning Point

Intravenous acyclovir is often indicated for herpes zoster in HIV infection, particularly if there is ophthalmic involvement or other organ disease.

Case 16

Presentation

A 28-year-old woman was seen in the clinic. She was HIV positive, and had been treated with ART (TDF/3TC/EFV) for three years. ART was well tolerated, and her last VL was suppressed. The patient was sent for VIA screening, where the lesion below (from 3 o'clock to 6 o'clock) was seen; as the nurse was not sure what to do, she requested the clinician's opinion.



Questions

- 1) What causes the lesion shown?
- 2) What is VIA? How is it done? How often should it be repeated?
- 3) What would you recommend for the woman with the above lesion?

Diagnosis

Cervical dysplasia (probably due to HPV infection)

Answers

- 1) Cervical dysplasia is caused by the human papilloma virus (HPV). While young healthy women will often clear HPV infection, immunosuppressed women with HIV will not clear it as easily. In addition, cervical lesions can take years to develop into cancer. Therefore, screening for cervical cancer in this population is especially important.
- 2) Visual inspection with acetic acid (VIA) is performed by applying acetic acid to the cervix and observing for acetowhite changes. If any suspicious lesions are revealed, cryotherapy or excision should be performed. If the lesion is suspicious for cancer in situ, the patient should be referred to a gynaecologist for evaluation. VIA should be done yearly for women with HIV.
- 3) This lesion looked suspicious; therefore, cryotherapy was considered appropriate in this situation, and the procedure was performed.

Outcome and Follow-up

The patient was treated with cryotherapy; this was followed up with another VIA after 6 months, which showed a normal cervix.

Comments

Human papillomavirus (HPV) infects the epithelia of the body, causes tumours that can either be benign (e.g., warts) or malignant (e.g., uterine cervical adenocarcinoma). HPV types 16 and 18 cause the great majority of cancers, and are defined as high-risk oncogenic. For the screening of cervical cancer, VIA and cytology (pap smear) comprise the primary diagnostic approach; supplementary HPV DNA screening can also be used. Therapeutic modalities for the treatment of HPV-induced lesions include cryotherapy and excision. Two highly effective vaccines are available: one is quadrivalent, and protects against HPV-6, HPV-11, HPV-16, and HPV-18; the other is bivalent, and only covers HPV-16 and HPV-18. The vaccines are given intramuscularly in three doses, especially to young girls before sexual debut.

Key Learning Point

There is a low threshold for treatment of cervical dysplasia in HIV positive women, due to their increased risk for cervical dysplasia becoming cancer.

Suggested Reading

Digital Learning Series. Lyon: World Health Organization IARC Screening Group (France); (no date). Available from: <http://screening.iarc.fr/digitallearningserie.php?lang=1>.

IARC Screening Group. Digital learning series—A training course in VIA: VIA technique and outcome [audiovisual slideshow]. Lyon (France): World Health Organization IARC Screening Group; 2005. Available from: <http://screening.iarc.fr/digital/cdVIAen/cdVIAen.html>.

Case 17

Presentation

A 26-year-old woman was seen at the clinic; the patient complained about haemoptysis, fevers, and night sweats for the past three months. She was losing weight, which was clearly documented in her file. Six weeks prior, she was started on TB treatment. She was found to be HIV positive (CD4 count was 272), and also started on ART.

Her skin showed multiple typical KS lesions; her palate is shown in the picture below.



Questions

- 1) What is the aetiology of KS?
- 2) Does the CD4 count matter to the diagnosis?
- 3) Why is it important to inspect the mouth carefully (palate, gingiva, tongue, and buccal mucosa)?
- 4) How should the extent of KS be documented to assess disease? How does it influence treatment decisions?

Diagnosis

Kaposi sarcoma

Answers

- 1) Kaposi sarcoma is associated with human herpes virus 8 (HHV-8). In South African adults, seroprevalence approaches 40%; in Europe, it is significantly lower, at 5%. Modes of transmission have yet to be fully elucidated. The incidence of clinical disease has increased dramatically in the face of the HIV epidemic; KS is now the most common cancer among men in Africa.
- 2) CD4 does not matter in the diagnosis, as KS is seen with both higher and lower CD4 counts.
- 3) Oral lesions are indicators, suggesting organ involvement of KS (lung, intestinal, serosal KS).
- 4) The extent of disease needs to be carefully documented to allow for assessment of progress:
 - a) Choose three to five marker lesions; draw and mark them on the body map. Measure the lesions (length x width in mm), and add together the surface area of all five lesions. Note these on the body map.
 - b) Count all the lesions on the body if there are fewer than 50. If there are more than 50, choose a target area only (e.g. left arm or right leg or any other), and count these lesions. Note the number on the body map.
 - c) Check if there is oedema (usually of the legs) present. If yes, measure to 10 cm below the lower edge of the patella → measure circumference on both legs and note on the body map.
 - d) Check carefully the palate, gingiva, tongue, and buccal mucosa for lesions; document them on the body map.

After six cycles of chemotherapy, the patient is reassessed by following these same steps. Their progress is then categorised:

- a) **Complete remission.** Absence of residual disease including tumour-associated oedema.
- b) **Partial remission** (any of the following AND iv.).
 - i. Number of lesions decreases >50% (either total number or number in the target area)
 OR
 - ii. Surface area of marker lesions decreases >50% OR
 - iii. Oral lesions decrease >50%
 - iv. AND no sign of disease progression (see c. above)
- c) **Progressive disease** (any of the following).
 - i. Number of lesions increases >25% (either total number or number in the target area—at least five new lesions)
 OR
 - ii. Surface area of marker lesions increases >25% OR
 - iii. Oral lesions increase >25%
- d) **Stable disease.** Any disease that qualifies neither for complete or partial response nor for progressive disease.

After six cycles, this may lead to one of the following decisions:

 - Complete remission, partial remission, or stable disease. Treatment may be stopped, but patient should be monitored for relapsing lesions (minimum of five new lesions).
 - Progressive disease. The same chemotherapy treatment is continued for up to another six cycles. Be aware that bleomycin has to be stopped once the maximum dose is achieved (300 mg). Lung fibrosis is a side effect, especially during the second six cycles. Refer early in case of shortness of breath.
 - Progressive disease after 12 cycles. Treatment needs to be escalated (doxorubicin, paclitaxel); for this, the patient must be referred to the KCH Oncology department.

Key Learning Point

Kaposi sarcoma can present at any CD4 count; it is a stage IV condition requiring ART as an integral part of management.

Case 18

Presentation

A 45-year-old HIV-positive man presented to clinic having been on ART (d4T/3TC/EFV then TDF/3TC/EFV) for two years. His baseline VL was 1 500 000 copies/mL, with a CD4 count of 33 cells/mL. The patient had made significant clinical improvement; his most recent viral load was <40 copies/mL. He presented to the clinic limping in pain.

For the past few months, the patient had been experiencing painful burning feet. They were worse at night, but he also had problems walking because of the pain. More recently, he complained of tingling in his fingertips.

On examination, glove-and-stocking distribution of sensory neuropathy was found. There was also reduced joint position sensation to the ankles. Otherwise, the neurological examination was normal.

Questions

- 1) What is the diagnosis?
- 2) What questions should you ask to establish the diagnosis?
- 3) What tests can be used to confirm the diagnosis?

Diagnosis

Sensory peripheral neuropathy.

Answers

- 1) Sensory peripheral neuropathy, most likely caused by stavudine.
- 2) In addition to what is given in the history, you should establish whether the symptoms started before or after initiation of ART to establish HIV-related polyneuropathy.

Use of other concurrent medications should be investigated.

Isoniazid-associated neuropathy is common for patients on TB treatment. It can be prevented by pyridoxine supplementation, which is usually given 25 mg od. If the patient develops symptoms of polyneuropathy, the dose can be increased to 100 mg or 150 mg od. Similarly, vincristine, used in the treatment of KS in our setting, can cause severe polyneuropathy. Dapsone can cause it, and is the alternative drug to cotrimoxazole, used in opportunistic infection prophylaxis. The composition of traditional medications is not known, but heavy-metal ingestion can cause neuropathy; the patient should be advised to stop these. Alcohol excess is another common problem, which can be associated with a dietary associated thiamine (vitamin B1) deficiency, which in turn can cause polyneuropathy.

Vitamin B12 deficiency is frequent; it can be associated with pernicious anaemia (auto-immune or secondary to stomach pathology—e.g., chronic gastritis), but can also be due to increased need for Vitamin B12 (high cell turnover). IM vitamin B12 injections are a treatment option. Finally, history of other concomitant illnesses—especially diabetes mellitus—should be sought.

- 3) A full blood count revealing a macrocytic anaemia can indicate vitamin B12 or folate deficiency, though it should be noted that antiretroviral therapy (mainly AZT, to a lesser extent d4T) could cause macrocytosis. Random or fasting glucose can be checked to screen for diabetes.

Comments

ART is well known to cause peripheral neuropathy. All patients showing symptoms should be started on vitamin B-complex tablets. Additionally, analgesics are prescribed using the analgesia ladder (paracetamol → NSAIDs (ibuprofen or diclofenac) → mild opiates (codeine) → strong opiates (morphine)). Amitriptyline should be added as a co-analgesic drug, starting at 25 mg at night; gradually increase up to 100 mg at night until symptom relief.

If symptoms cause grade 3 or 4 toxicity, and other potential causes of neuropathy have been excluded, alternative ART could be attempted. It is important to remember that there are only limited drug choices available in the public sector, so care has to be taken not to switch ART regimens unless necessary.

Key Learning Point

Peripheral neuropathy is extremely common, and is often multifactorial. Treatment essentially consists of addressing symptoms and switching ART regimens.

Case 19

Presentation

A 23-year-old HIV-positive male patient was admitted to the ward with progressive loss of weight, fatigue, and increasing shortness of breath.

His examination showed a thin, generally unwell looking man. Fine crackles were noted over both lungs; heart sounds were faint, but seemed normal.

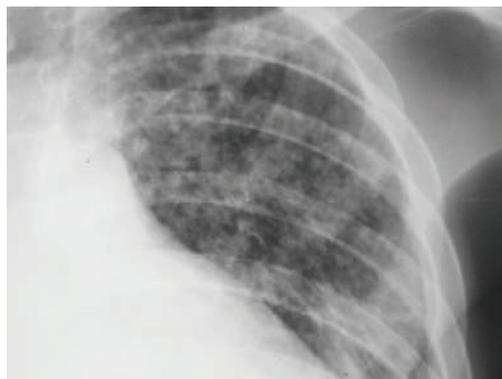
The blood results and his CXR are shown below.

FBC

Hb	10.8 g/dL	(normal 11.5–16.5)
WBC	5.6 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	220 $10^3/\text{mm}^3$	(normal 150–500)

U&E and LFT

Crea	0.7 mg/dL	(normal 0.7–1.3)
BUN	18 mg/dL	(normal 12–50)
TBIL	0.6 mg/dL	(normal 0.2–1.0)
GGT	84 U/L	(normal 7–62)
ALP	212 U/L	(normal 42–121)
ALT	31 U/L	(normal 10–60)



Questions

- 1) How would you describe the CXR?
- 2) What is your presumptive diagnosis? What diagnostic steps would you take?
- 3) What would you expect to find on an ultrasound scan?
- 4) How would you treat the patient?

Diagnosis

Miliary TB with pericardial effusion.

Answers

- 1) Enlarged heart shadow; multiple small nodules, widely distributed throughout both lung fields.
- 2) Miliary TB. The patient should give a sputum sample for AFB stain, GeneXpert, and, if possible, TB culture. The diagnostic yield of AFB is low in patients with miliary TB (around 25%), but culture is positive in a larger proportion (approximately two-thirds of patients). The differential diagnosis of a miliary pattern on CXR includes other infections and malignancies. Histoplasmosis, PCP, and haematogenous spread of metastasis (e.g., of the thyroid) need to be mentioned. In our setting, TB is by far the most probable cause.
- 3) Pericardial effusion. Often, patients with disseminated TB also show enlarged lymph nodes in the abdomen, as well as small focal lesions in the spleen.
- 4) Standard TB treatment is indicated for miliary TB; the TB pericarditis might benefit from concomitant steroid therapy (as it reduces the risk of constrictive pericarditis).

Outcome and Follow-up

The patient was started on TB treatment. After confirming a large pericardial effusion with ultrasound, steroids (prednisolone 60mg for one week, followed by 30 mg, 15 mg, and 5 mg for the following weeks) were added. The patient's clinical symptoms improved quickly. His CD4 count was found to be 122 cells/ml. He started ART after two weeks of TB treatment.

Comments

Classically, miliary nodules are approximately 1 to 2 mm in diameter, numerous, and diffusely distributed. This is more frequently seen in HIV-positive patients. It is often difficult to confirm the diagnosis through microbiological assessment; sputum cultures might be used instead. Bronchoscopy with lavage is an option—but is not frequently used in our setting. Blood cultures have a good yield in miliary TB (up to 60%), and therefore are a diagnostic option if mycobacterial blood culture bottles are available. Alternatively, blood samples can be submitted for GeneXpert, which may show positive results. If the patient has haematological changes (cytopenias), bone marrow aspiration and culture has a good diagnostic yield. Liver biopsy for culture is another option—but is invasive, and therefore not done regularly.

Most of these tests are time consuming, and therefore not helpful for management of acute symptoms, but could give useful confirmatory information.

Key Learning Point

Miliary TB involves haematological spread of mycobacteria, and is therefore a multi-system disease.

Suggested Reading

Feasey NA, Banada PP, Howson W, Sloan DJ, Mdolo A, Boehme C, et al. Evaluation of Xpert MTB/RIF for detection of tuberculosis from blood samples of HIV-infected adults confirms mycobacterium tuberculosis bacteremia as an indicator of poor prognosis. *J Clin Microbiol.* 2013;51:2311–2316.

Case 20

Presentation

A 21-year-old HIV-positive man on ART (TDF/3TC/EFV) was seen with fever, abdominal discomfort, and vomiting. A malaria rapid test was positive; the patient was started on artesunate IV, then switched to lumefantrine-artemisinin (LA). The next day, he started vomiting heavily again; it was felt that he was not absorbing the LA, and was therefore given additional artesunate. His U&E were taken; the creatinine was found to be 9.6 mg/dl, WBC was 7.800 cells/mm³, Hb 7.6 g/dL, and Plt 54.000/mm³. ART was stopped. The patient's urine output was unclear, so a Foley catheter was inserted.

The following day, the patient's fever had subsided, and his urine output was measured as 5.6 L/24h. He was transferred to the high-care unit.



Questions

- 1) What are the renal problems in this patient? What are the most important steps to take?
- 2) What is shown in the picture (of a different patient than described in the case)? What are the complications of severe malaria? How are they treated?
- 3) What is the recommended malaria treatment in our setting?
- 4) When would you restart ART? Which ART would you choose?

Diagnosis

Polyuric acute kidney injury (AKI) due to severe malaria

Answers

- 1) The patient is suffering from severe malaria, and secondary AKI. He is seen in the polyuric phase of the disease due to acute tubular injury. The most important measure to take is to replace the fluid loss (best with normal saline). Kidney replacement therapy is indicated (often only for the short term) if signs or symptoms of uraemia present.
- 2) One of the old names for malaria is 'black-water fever', due to hemolysis and hemoglobinuria, which is shown in the first picture.

Complications of severe malaria are:

Cerebral malaria (coma, convulsions, eye movement abnormalities, abnormal posture)	Treat early with artemisinin/lumefantrine; for convulsions, give phenytoin or diazepam. Also, nursing care.
Anemia	Treat with transfusion if Hb <7 g (provided screened compatible blood is available).
Hypoglycaemia (esp. if treated with quinine)	Treat with dextrose 10% IV.
Pulmonary oedema	Place patient in upright position; treat with oxygen and furosemide.
Metabolic acidosis	This is difficult to diagnose and treat in our setting.
Acute kidney injury	Treat as mentioned in answer 1) above.

- 3) For uncomplicated malaria, start lumefantrine-artemeter (LA 120 mg/20 mg) 4 tbl bd for three days. If vomiting occurs within 30 minutes, repeat dose. If malaria persists >72 hours (peripheral smear), give artesunate-amodiaquine (AA) 2 tbl od for three days. If the patient cannot swallow, consider parenteral artesunate or quinine.
- 4) The patient should restart ART as soon as he is stable, can swallow, and his renal situation has been stabilised. The choice of which ART regimen to continue depends on the amount of residual renal impairment.

Outcome and Follow-up

The patient received balanced iv fluid replacement therapy for three days. After that, he showed significant clinical improvement; his creatinine was now 1.8 mg/dL. As it was felt that the patient's kidneys were injured, TDF was omitted from the treatment regimen. As his Hb was low, AZT was avoided; he was started instead on ABC/3TC/EFV. The patient was discharged; his further course of treatment was uneventful.

Comment

In areas of stable malaria transmission, findings suggest that HIV infection not only may interfere with parasite control (higher parasite counts), but also—perhaps more importantly—may cause the loss of antitoxic immunity, which protects persons with parasitemia from clinical disease. In regions of unstable malaria, transmission is intermittent and pre-existing anti-malarial immunity is limited. The disease burden here is more similar. Also of concern are interactions between anti-malarials and ART:

	NRTI	NNRTI	PI
Lumefantrine	—	Lumefantrine level decreased	Lumefantrine level increased
Artemisins	—	Artemeter levels decreased	Increased artemisinin levels, but decreased active metabolite dihydroartemisinin
Amodiaquine	AZT (share bone marrow toxicity)	EFV increases amodiaquine levels (→ liver toxicity)	—
Quinine	—	Decreased quinine levels	Decreased quinine levels

For patients receiving nevirapine or efavirenz, drug interactions may reduce the concentrations of LA, thereby increasing the risk of treatment failure. LA should be used with caution with patients receiving ATV/r, because of excessive risk of toxicity (long-QT); for LPV/r, data suggests no dosage adjustments are required. Amodiaquine co-administration with EFV is the most problematic (clinical liver toxicity).

Key Learning Point

Drug interactions between ART and other drugs are of concern. Clinicians should be vigilant—but often do not have many alternatives.

Suggested Reading

HIV Drug Interaction Checker. Liverpool (UK): University of Liverpool; [no date]. <http://www.hiv-druginteractions.org/>

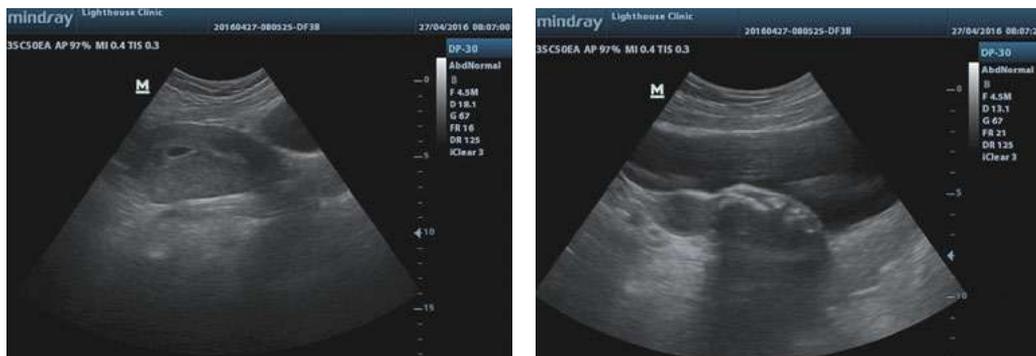
World Health Organization. Management of severe malaria: a practical handbook. 3rd ed. Geneva (Switzerland); World Health Organization; 2012.

Notes

Case 21

Presentation

An 18-year-old HIV-positive woman on ART for the last eight months was seen for abdominal pain and swelling. The pain was more marked in the lower abdomen. On careful questioning, she reported that she had twice received symptomatic STI treatment for PID (pelvic inflammatory disease), but this time the pain seemed different. It was considered to treat her again for PID, but something seemed 'not quite right' about her. As the clinician was recently trained in point-of-care limited ultrasound, he did an ultrasound of her abdomen.



Ultrasound of the lower abdomen: central longitudinal (L) and slightly left lateral transverse (R).

Questions

- 1) What is visible in the ultrasound images?
- 2) What is your differential diagnosis? What is the other most important test in a female patient with acute lower abdominal pain?

Diagnosis

Ruptured extra-uterine pregnancy

Answers

- 1) The ultrasound shows free fluid. Additionally, the first scan shows a small intrauterine fluid collection, but no intact intrauterine pregnancy. The second picture shows a visible mass next to the free fluid. The mass is heterogenous and contains echogenic areas, which throws a shadow suggesting calcified tissue.
- 2) Lower abdominal pain in a sexually active woman should always raise the suspicion of extra-uterine pregnancy. The most important test is a pregnancy test. By the time the pregnancy test becomes positive, an intrauterine pregnancy is almost always visible in a trans-abdominal ultrasound of the uterus. Therefore, the combination of a positive urine test without visible intra-uterine pregnancy is highly suggestive of an extra-uterine localisation.

Alternative diagnoses are infections (pelvic inflammatory disease and abscesses), endometriosis, ovarian cysts, fibroids, and other gynaecological diseases.

Outcome and Follow-up

A pregnancy test was ordered, and was positive. The patient was immediately referred to the gynaecology department for suspected ectopic pregnancy; she was operated on the same day, and the diagnosis confirmed. She recovered without complication.

Comments

PID and ectopic pregnancy are common gynaecological problems in HIV-infected women. PID symptoms may vary, from asymptomatic, to abnormal vaginal discharge, lower abdominal pain, cervical motion tenderness, and fulminant infection with fever and peritonitis. Pelvic inflammatory disease can be considered the most important risk factor for ectopic pregnancy.

Ectopic pregnancy is the leading cause of maternal death in the first trimester, with a very high case-fatality rate—especially due to late diagnosis. In female patients of childbearing age who present with pelvic pain and/or vaginal bleeding, ectopic pregnancy must therefore always be excluded. Urinary beta human chorionic gonadotropin (b-HCG) plus trans-abdominal US are simple, inexpensive diagnostic tests for ectopic pregnancy; therefore, they should be used in all women of childbearing age with lower abdominal pain. The diagnostic approach is to search for an intra-uterine pregnancy, as a positive urinary b-HCG without a visible intrauterine pregnancy is virtually diagnostic for ectopic pregnancy. Only after this should the clinician look for the ectopic pregnancy itself. Ninety-five percent of ectopic pregnancies develop in the Fallopian tubes. However, they also occur in the ovaries, cervix, and peritoneal cavity, and may often not be found. The clinician should look for free fluid, which can be present in both ruptured and non-ruptured ectopic pregnancies, with larger quantities usually seen after rupture.

Key Learning Point

In a young female patient of childbearing age who presents with pelvic pain, pregnancy tests and ultrasound exams are high-priority tests.

Case 22

Presentation

A 34-year-old HIV-positive male patient with a CD4 count of 144 cells/mL was seen at the clinic because of general malaise, weight loss, and swelling under his arms. The swelling was felt to be due to lymph node masses, larger in the right axilla than the left. They were punctured, and pus was aspirated.



Questions

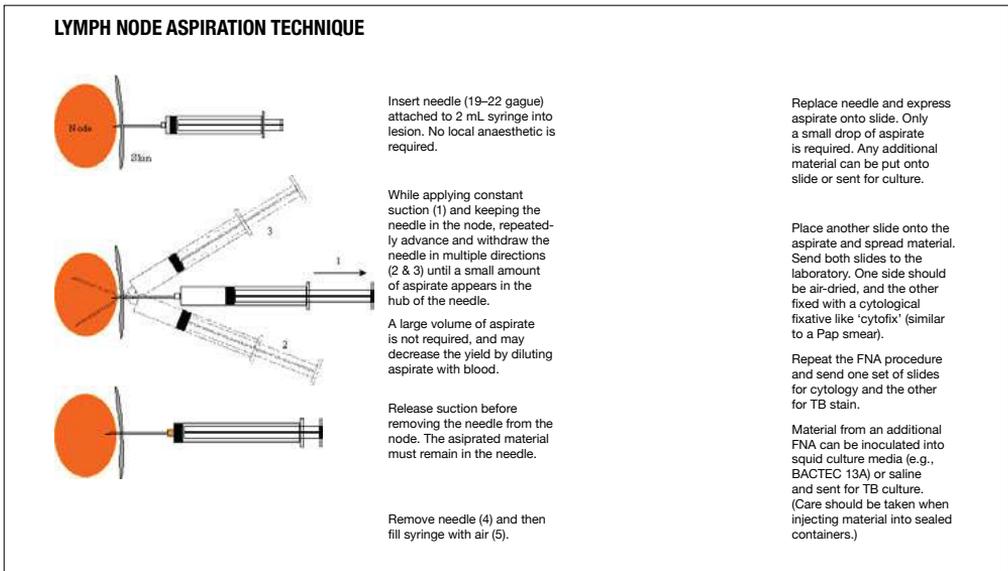
- 1) Describe the technique of diagnostic lymph node aspiration.
- 2) Which differential diagnoses might be considered in patients with lymphadenopathy?
- 3) How would you manage this patient?

Diagnosis

TB lymphadenitis

Answers

1)



Lymph Node Aspiration Technique chart (adapted from Safety in Mines Research Advisory Committee SIMRAC PROJECT SIM 02-08-02, Link 10).

2) The following clinical signs should be considered for the differentials:

- TB (loss of weight, night sweats, cough)
- Kaposi sarcoma (watch for lesions on the skin, or in the mouth)
- Lymphoma (symmetrical, often larger nodes)
- HIV lymphadenopathy (PGL) (symmetrical, generalised)
- Local bacterial and fungal infections (tender, inflamed, purulent LN, local infections visible); this contrasts with the cold abscesses associated with TB

3) TB lymphadenitis is treated with the same six-month regimen as other forms of TB. Longer (nine-month) treatment was recommended previously, but recent studies have shown this to be no more effective than the six-month course. WHO guidelines recommend six-month regimens for 'virtually all forms of EPTB'.

Outcome and Follow-up

The pus was sent to the lab; it came back positive for AFB and GeneXpert MTB/RIF. The patient's further course of treatment was uneventful; the swelling subsided with therapy, and he started ART two weeks later.

Comments

Fine-needle aspiration of lymph nodes is a safe first step in the diagnostic workup of lymphadenopathy, as it yields a diagnosis in the majority of patients. It has been said to cause sinus tract formation along the needle path, but recent experience in an era of active antibiotic therapy indicates that this is not (or is only very rarely) the case.

Suggested Reading

World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva (Switzerland): World Health Organization; 2007. (WHO/HTM/TB/2007.379; WHO/HIV/2007.1)

Key Learning Point

Aspiration of lymph nodes is an important diagnostic tool, especially to determine sensitivities in suspected MDR-TB cases.

Case 23

Presentation

A 34-year-old HIV-positive nurse was seen in the staff clinic; she complained about distressingly itchy lesions, especially on her arms, and, to a lesser extent, on her lower limbs. She had a CD4 count of 34 cells/ μ L, and was about to start on ART.



Questions

- 1) What is your differential diagnosis?
- 2) How would you treat the patient?
- 3) Would you delay ART?

Diagnosis

Papulopruritic eruption

Answers

- 1) Papular lesions with prurigo ('itchy bump disease'); excoriations that heal with post-inflammatory hyperpigmentation are often seen in HIV-infected black patients. The differential diagnosis includes:
 - a) **Papulopruritic eruption.** One of the most common skin manifestations. Severe itching, involving the limbs more than the trunk. Associated with low CD4 counts.
 - b) **Eosinophilic folliculitis.** Intensely itchy lesions with an urticarial aspect. Concentrated on the face, neck, upper trunk, and proximal parts of the upper limb. May also heal with hyperpigmentation.
 - c) **Papular urticaria.** Papulo-urticarial lesions, which are exaggerated reactions to insect bites, sometimes with formation of vesicles or bullae, mainly on exposed areas, like the hands, arms, and face. A linear distribution might be seen when caused by fleas or bedbugs
 - d) **Bacterial folliculitis/ecthyma.** Papules and pustules, which might become excoriated. Usually less itchy than the lesions mentioned above.
 - e) **Scabies.** Intensely pruritic papules, commonly found on interdigital spaces of hands and feet, as well as on ankles, elbows, axilla, and groin area. (Treatment: Topical benzyl benzoate 25%, to whole body below neck; leave for 24 hours. Consider Ivermectin 200 µg/kg single dose, in combination with topical drugs.)
 - f) **Secondary syphilis.** Can have many cutaneous manifestations; mildly itchy. Syphilis should always be considered! Any of these conditions may at times be confused with Kaposi sarcoma lesions.
- 2) Papulopruritic eruption might be difficult to distinguish from eosinophilic folliculitis and papular urticaria. However, therapy is the same; an exact diagnosis is often not needed. Oral antihistamines (e.g., chlorpheniramine 4 mg nocte) are used in combination with topical steroids (hydrocortisone cream for face, betamethasone valerate for the body).
- 3) No. Some skin disease may exacerbate or recur as the immune system is reconstituted with antiretroviral therapy, however this is no reason to delay treatment.

Outcome and Follow-up

The patient was treated with betamethasone valerate cream and chlorpheniramine 4 mg nocte; the itching improved. ART was started, and well tolerated.

Key Learning Point

Skin conditions are frequent. A specific diagnosis is often difficult, and not required.

Suggested Reading

Dlova CN, Mosam A. A clinical atlas of skin conditions in HIV/AIDS: an illustrated management guide for healthcare professionals. Pretoria: Health & Medical Publishing Group; 2005.

Case 24

Presentation

A 46-year-old female patient was seen in the staff clinic. She was diagnosed HIV positive in 2002, and started on DDI/D4T/EFV in 2003, with treatment at that time covered by private-sector medical insurance. Her CD4 count then was 180 cells/mL. The patient developed diabetes mellitus the following year; metformin 500 mg bd and glibenclamide 5 mg od were prescribed. In 2006, she entered the public ART programme. Her ART drugs were changed to AZT/3TC/EFV; later she was switched to TDF/3TC/EFV. She complained about the fact that she had not gained weight, and especially that her face 'was thin'. Her blood sugar was well controlled, her lactate was 2.6 mmol/L, and her body weight was stable, at around 70 kg. Her most recent CD4 count was 643 cells/mL; viral load was suppressed.



Questions

- 1) What is the most probable cause of the patient's complaints?
- 2) How would you treat the patient?
- 3) Which other side effects would you expect in the above-mentioned old drug combinations?

Diagnosis

Lipodystrophy, predominantly facial lipoatrophy

Answers

- 1) The most probable explanation for her problem is lipodystrophy as a side effect of ART treatment. It may present as lipohypertrophy (weight gain in the abdominal area, increased breast size), and/or as lipoatrophy (reduced size of buttocks, facial fat reduction).

The 'buffalo hump' (dorsocervical fat pad)—often caused by protease inhibitors, but also by other ART medications—is the best-known form of lipohypertrophy.

The metabolic complications occur with many antiretroviral drugs. Nucleoside reverse transcriptase inhibitors, especially the old d4T and ddI (but also, to a lesser extent, AZT), are known to interfere with mitochondrial metabolism, and to be toxic to the mitochondria of adipocytes. Risk factors for lipodystrophy are: longer duration of antiretroviral therapy, therapy with d4T/ddI > AZT > TDF/ABC/3TC, prior AIDS diagnosis, lower CD4 nadir, and older age. Metformin may have added to the fat reduction in this patient.

- 2) Given the availability of TDF, the decision to change her antiretrovirals was correct, especially as her HIV disease now seems well controlled. Even after changing the drugs, the fat changes are not necessarily reversible.

Metformin should be stopped, and alternative anti-diabetic agents given—even insulin, if needed. The patient needs to be counselled about the origin of the changes, and the limited possibilities of treatment options.

- 3) The initial combination of ddI, d4T, and metformin put the patient at a high risk of lactic acidosis.



Outcome and Follow-up

Metformin was reduced, and later stopped completely. The patient still had sufficient blood sugar control with glibenclamide 5mg daily alone.

The changes in body fat were explained to the patient, and her ART regimen left unchanged. She was seen after three months; her compliance was still good. However, her facial appearance had not changed.

Comments

Changing antiretrovirals because of side effects is desirable—but is sometimes difficult, given the limited drug choices available. The possibility of reduced or absent further future treatment options has to be balanced against the severity of side effects; the patient's opinion must be included when making the treatment decision, as side effects could impair adherence, and thus endanger treatment success. Abacavir and tenofovir are the agents least likely to cause lipodystrophy.

Suggested Reading

Behrens C. Metabolic complications of HIV infection and antiretroviral therapy [PowerPoint presentation]. Seattle: Mountain West AETC; 2006. Available from: https://aidsetc.org/sites/default/files/resources_files/nw_metabolic_comp.ppt.

Case 25

Presentation

An 18-year-old woman was admitted with severe diarrhoea and dehydration. She described the diarrhoea as watery, with a frequency of six to eight times per day. She could not say whether blood was present, since she used a latrine. On admission, the patient tested HIV positive.

On examination, the patient appeared cachectic ('unable to stand'), although her body weight was not measured. An IV line was inserted, and Ringer's lactate solution 3 L per day commenced.

The blood results were as follows:

U&Es

Creat	8.2 mg/dL	(0.5–1.3 mg/dL)
Urea	80 mg/dL	(normal 20–40 mg/dL)

During the next days, the patient had an abdominal ultrasound, which showed thickening of the bowel walls, often seen as a sign of colitis.

Ultrasound of bowel loops: longitudinal (L), transverse (R). Bowel with hypoechoic walls up to 8 mm thick (normal < 3mm). The bowel was visible down to the sigmoid.

Questions

- 1) What are the most common causes of diarrhoea in HIV patients? How would you diagnose and treat them?
- 2) What is 'slim disease'? How is it caused?

Diagnosis

Diarrhoea with colitis (unknown aetiology)

Answers

- 1) Bacteria, parasites, and viruses may cause diarrhoea in HIV-positive patients. Additionally, one has to consider drug side effects (particularly with protease inhibitors) and tumours (generalised Kaposi sarcoma and gut lymphoma). Often, the cause remains unknown, with ART and symptomatic treatment (loperamide) the only available options.

Organism	Frequency (in HIV + pat)	Diagnosis	Treatment
<i>Parasites</i>			
Cryptosporidium	13–20%	Stool microscopy (modified acid fast stain)	No specific tx
Cyclospora	?	Stool microscopy (modified AF stain)	CTX 4 tabs bd for 2–3 weeks
Isospora	14%	Stool microscopy (modified AF stain)	CTX 4 tabs bd for 2–3 weeks
Microsporidia	20%	Stool microscopy (Trichrome stain)	Albendazole 400 mg bd for 4 weeks
<i>Bacteria</i>			
Campylobacter	20%	Stool culture	Ciprofloxacin Erythromycin
Salmonella	10%	Stool culture	Ciprofloxacin
Shigella	2%	Stool culture	Ciprofloxacin
C. difficile	?	Toxin test in stool	Metronidazole
Tuberculosis	?	Biopsy	TB treatment
MAC	10%	Blood culture	Clarithromycin + Ethambutol
<i>Viruses</i>			
CMV	13–20%	Biopsy	Gancyclovir
HIV	?	Exclusion of others	ART

- 2) Weight loss and wasting in HIV patients. Possible causal factors include decreased energy intake (oesophageal disease, economic reasons), malabsorption (diarrhoea), and increased metabolic rate (HIV turnover, TB, MAC, malignancy)

Outcome and Follow-up

The patient's condition was stabilized with IV fluids; she was started on CTX 2 tbl bd and loperamide 4 mg tds.

Additionally, ART (TDF/3TC/EFV) was started. The diarrhoea did not improve after three days, so ciprofloxacin 400 mg bd was added. The frequency of stools decreased, but the diarrhoea did not subside completely. A follow-up ultrasound one week later showed the thickened bowel loops had disappeared, despite mild diarrhoea being still present.

Comments

About 40 to 90% of HIV-positive patients will develop diarrhoea. Diagnostic algorithms need to be balanced with treatment trials based on the laboratory facilities available. Initiation of ART is often an important component of treatment, regardless of the underlying cause.

Differentiation between large-bowel diarrhoea (blood, mucus, fever) and small-bowel diarrhoea (watery) can be difficult, as patients use latrines and do not inspect their stool. We use the following treatment steps:

1. Ciprofloxacin for three to five days + Metronidazole for 10 days.
2. If no improvement after five days, add high dose CTX 4 tbl bd for two weeks.
3. If still no improvement, then albendazole 400 mg bd for three weeks.

Key Learning Point

Diarrhoea is very common with advanced HIV disease; ART may be the only effective treatment.

Suggested Reading

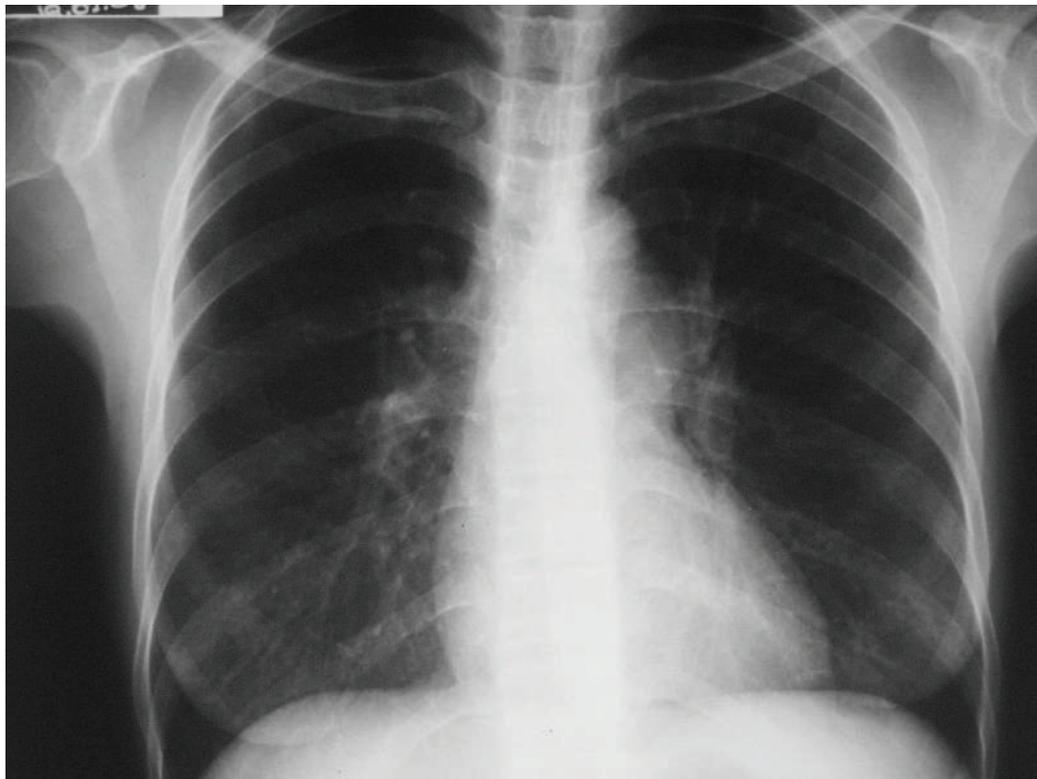
Saag MS, Chambers HF, Eliopoulos GM, Gilbert DN. Sanford guide to HIV/AIDS and viral hepatitis therapy. 22nd ed. Sperryville: Antimicrobial Therapy, Inc.; 2014. p. 108–109.

Notes

Case 26

Presentation

A 22-year-old woman complaining of cough was seen in the clinic. The patient reported a dry cough for the last three weeks, with no shortness of breath, no chest pain, and no night sweats. She had lost weight, although she did not know how much. Her HIV status was unknown. A chest x-ray was performed.



Questions

- 1) How would you interpret the CXR? What is your diagnosis?
- 2) Which additional tests would you request?

Diagnosis

Hilar TB lymphadenitis

Answers

- 1) The CXR shows no infiltrate and no effusion. The silhouette of the heart is normal in size. Increased size of the hila is noted on both sides, but more pronounced on the left, suggestive of lymphadenopathy. This is likely to be secondary to TB in a high-prevalence setting. Other differential diagnoses are lymphoma, carcinoma, other infections, and sarcoidosis.
- 2) The patient should be referred for an HIV test.

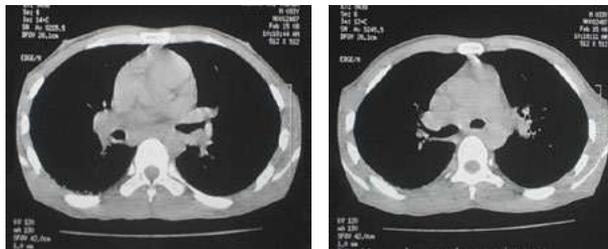
Outcome and Follow-up

Amoxicillin 500 mg tds plus erythromycin 500 mg tds were prescribed, and the patient asked to come back if no improvement was seen after two weeks. She did not return for follow-up.

The patient was seen again five months later, this time complaining of productive cough and weight loss. A severe right upper lobe infiltrate with cavities was seen on the CXR. She was started on RHZE. Additionally, she was found to be HIV positive. Her CD4 count was 178 cells/mL; ART was started after two weeks of TB treatment.



CXR five months later



Lymphadenopathy is also visible on CT scans of the chest. CT is rarely indicated in our setting, except in doubtful cases, or when lymphadenopathy is unresponsive to TB treatment.

Key Learning Point

In a patient with persistent non-productive cough and apparently normal CXR, look again at the hila/mediastinum for lymphadenopathy.

Case 27

Presentation

A 26-year-old woman was brought to the clinic by her home-based care nurse because of a painful tumour in the area of her vulva. The patient was unable to sit or walk properly. She was known to be HIV positive, and had started ART a few weeks earlier, with a baseline CD4 count of 38 cells/mL. On examination, a cauliflower-like growth in the genital area was observed.



Questions

- 1) What is the cause of the tumour?
- 2) How do you treat smaller lesions? How do lesions of this size need to be treated?
- 3) What other diseases are associated with this condition?

Diagnosis

Condylomata acuminata (giant genital warts)

Answers

- 1) Human papilloma virus (HPV) is the cause of genital warts. More than 20 types of HPV can infect the genital tract, with Types 6 and 11 occurring most commonly. Other types that infect the genital tract include Types 16, 18, 31, and 33.
- 2) Small warts: apply topical podophyllin 20% once or twice per week for four hours each. Solution is applied with a cotton swab, and afterwards washed off with water. Treatment can be repeated as necessary, up to 4 to 5 times. Normal skin should be protected by applying vaseline.

Large warts require surgical treatment. Excision and reconstructive surgery is the therapy of choice (especially if growth is rapid); patients should be referred to gynaecology or urology.

- 3) HPV Types 16, 18, 31, and 33 have oncogenic potential. They are a major aetiological factor for cervical dysplasia and squamous cell carcinoma (of both the vulva and the penis). As treatment of external warts does not influence the development of cervical cancer, regular VIA—and, if possible, pap smears—need to be stressed to women with genital warts.



Penile carcinoma

Outcome and Follow-up

The patient was referred to the gynaecology clinic, and the warts removed surgically. A pap smear was normal; the patient continued ART.



(Pictures courtesy of Dr Mayat, NPA Hospital, Ngwelezane)

Comments

HPV is highly infectious; most people who develop warts do so two to three months following infection. Spontaneous regression within three months occurs in 20 to 30% of patients, but this is associated with an appropriate cellular immune response. Immunosuppressed patients often present with severe disease, and do not respond well to treatment. Initiation of ARVs is important, and should not be delayed.

Key Learning Point

Large or rapidly growing genital warts require surgical excision, especially as they may have malignant potential.

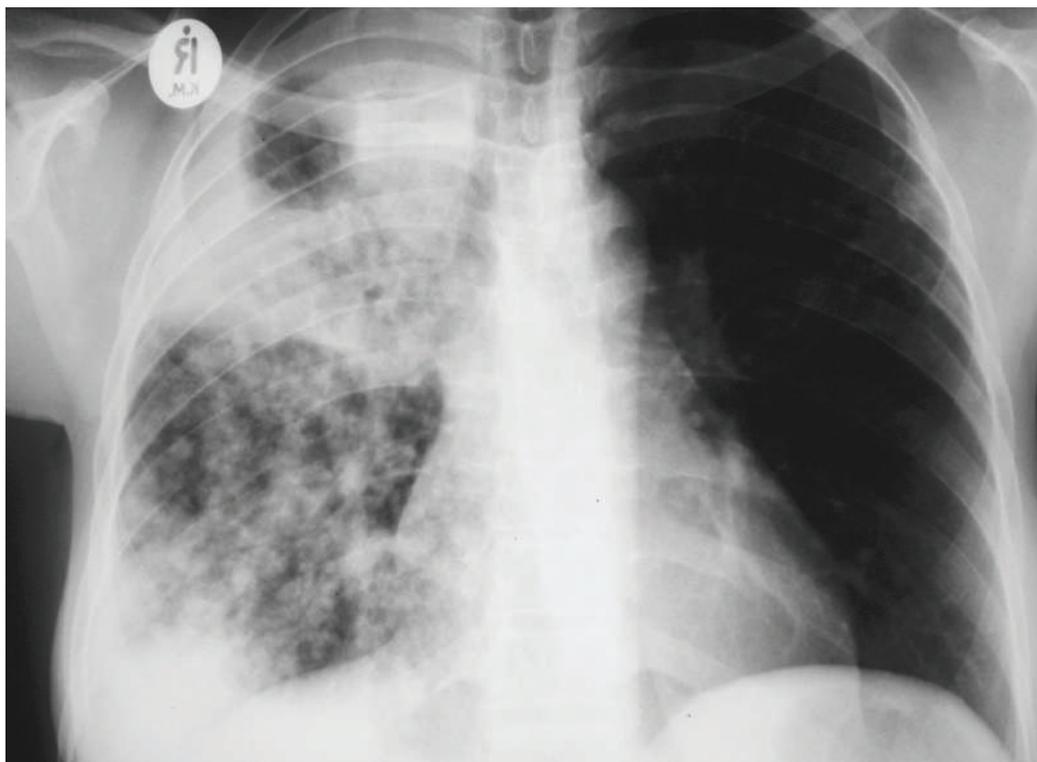
Case 28

Presentation

A 36-year-old HIV-positive male patient was seen in the TB ward, where he was admitted for streptomycin injections as part of his retreatment regimen. The patient first had TB six years previously, and was treated at that time—apparently successfully. Now, he was suffering again from cough, night sweats, and loss of weight. His CXR is shown.

His sputum was AFB negative. The sample sent for GeneXpert MTB/RIF showed MTB 'DETECTED' and RIF 'NOT DETECTED'. An MTB culture was positive; the drug-sensitivity test (DST) result, received from the central TB laboratory after seven weeks of treatment, showed resistance to RIF and INH.

As the patient was diagnosed with HIV about five years ago, and was on ART (TDF/3TC/EFV), he was asked about his VL; he reported that it was taken about four months ago at his ART clinic, but the result did not come back.



Questions

- 1) How would you interpret his CXR?
- 2) How can it be explained that the Xpert test showed no resistance, but the DST did? How should the patient be treated?
- 3) If patients are found to be AFB negative and Xpert positive, should the results be recorded as 'smear positive' or 'smear negative'? Should their treatment be monitored using Xpert after two and five months of treatment?
- 4) His HIV-VL results are not known; do you consider that important? What would you do?
- 5) Sputum can be submitted as a sample for Xpert testing; what other material(s) can be submitted?

Diagnosis

Pulmonary TB with MDR-TB

Answers

- 1) His CXR is compatible with extensive pulmonary TB disease, but it can only be fully interpreted by examining the CXR changes, which persisted after the last episode of TB. In light of the patient's clinical symptoms, the x-ray definitely needs to be re-interpreted.
- 2) The Xpert test can miss RIF resistance in individual cases (false negative), especially in regions with high prevalence of TB. Infections with more than one TB strain (mixed infections) can occur. In cases of a mixture of resistant and non-resistant strains, the DNA of the non-resistant strain is amplified—and therefore resistance is missed. The specificity of the Xpert test for RIF resistance in mixed-infections is far lower (possibly only 80%); Xpert probably detects resistance only when more than 90% of the bacteria are resistant.
- 3) The results should be recorded as smear negative. The WHO recommends that Xpert should be used only for diagnosis of TB, not for treatment or follow-up. Xpert is very sensitive; it can detect DNA of dead bacilli even in patients who have been successfully treated (false positive). How long the test can detect dead bacilli has not yet been fully studied, but as many as one in seven 'Xpert positive' cases in re-treatment patients may be false positives.
- 4) This is clearly a situation where potential ART failure must be considered (new opportunistic infection); in such cases, the VL result is important. A targeted VL should be repeated to assess the effectiveness of ART.
- 5) Initially, Xpert was tested and recommended for sputum, but TB-DNA can also be detected in other material (lymph node aspirate, pus, pericardial, pleura and peritoneal effusion and even CSF and blood). It must be remembered that sensitivity may be lower, especially when the bacterial burden in the sample is low. A positive result in these sterile fluids is of diagnostic value.

Outcome and Follow-up

This case illustrates the importance of TB cultures and DST. After receiving the culture results, the patient was switched to MDR-TB treatment according to national guidelines.

The VL was repeated; it showed a non-suppressed VL of 31.300 copies/mL. Considering his new TB diagnosis and the extent of the disease, the patient was felt to be also clinically failing, and his life in peril; he was therefore immediately switched to second-line ART using AZT/3TC and LPV/r in double dose. Later, after switching to the MDR-TB treatment, his ART regimen was adapted to ATV/r.

Key Learning Point

Xpert MTB/RIF results can return false positives and false negatives; therefore, they must be interpreted, like any other test, in light of the patient's clinical findings.

Suggested Reading

Theron G, Venter R, Calligaro G, Smith L, Limberis J, Meldau R, et al. Xpert MTB/RIF results in patients with previous tuberculosis: can we distinguish true from false positive results? *Clin Infect Dis*. 2016 Apr 15;62(8):995–1001.

Vadwai V, Boeheme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol*. 2011 Jul;49(7):2540–5.

Zetola NM, Sanghyuk SS, Tumedi KA, Moeti K, Ncube R, Nicol M, et al. Mixed mycobacterium tuberculosis complex infections and false-negative results for rifampin resistance by GeneXpert MTB/RIF are associated with poor clinical outcomes. *J Clin Microbiol*. 2014 Jul;52(7):2422–9.

Case 29

Presentation

A 24-year-old female patient was seen in the clinic because of the skin changes shown below; she had started ART four weeks prior. She reported no further complaints, except that she was 'ashamed of her body'.

The areas mainly affected were her legs, and the distal parts of her arms. Additionally, she had an abscess in her right axilla.



Questions

- 1) What are the skin changes shown here?
- 2) How would you treat the patient?

Diagnosis

Ecthymata and axillary abscess

Answers

- 1) Ecthymata are crusted ulcers often seen on the distal limbs; they are caused by bacterial infection of the dermis. The most common causes are *Staphylococcus aureus* and Group A Streptococcus. The axillary abscess is most likely also caused by one of these organisms.
- 2) For ecthymata, local cleaning and antibacterial cream (e.g., mupirocin) comprise the first approach to management. In severe cases, it may be worthwhile to attempt systemic antibiotic treatment. Antibiotics active against streptococci and staphylococci should be used (e.g., flucloxacillin, amoxicillin-clavulanic acid).

Outcome and Follow up

The axillary abscess was incised, and pus drained. Amoxicillin-clavulanic acid was prescribed for 10 days, and mupirocin cream given for the peripheral lesions. The lesions did heal, albeit with some scarring.

Comments

S. aureus is the most common cutaneous bacterial infection in people living with HIV/AIDS. High rates of staphylococcal carriage are reported in HIV patients, serving as a reservoir for soft tissue and skin infections. It often causes a superinfection on top of eczema or scabies. Other presentations commonly seen are folliculitis, furuncles, and bullous impetigo.

Key Learning Point

If there's pus about → LET IT OUT.

Suggested Reading

Dlova CN, Mosam A. A clinical atlas of skin conditions in HIV/AIDS: an illustrated management guide for healthcare professionals. Pretoria: Health & Medical Publishing Group; 2005.

Case 30

Presentation

A 22-year-old female patient was seen at the clinic to start ART. She complained about mild abdominal discomfort, hiccups, and intermittent diarrhoea. She has lost 'a lot of weight'; her BMI was 16.8 kg/mm².

On examination, her abdomen was tender without peritonitis. Her blood tests showed anaemia (Hb 7.1 g/dL), and a CD4 count of 23 cells/ml (Serum-CrAg: negative, Urine-LAM: negative). She was sent for FASH ultrasound; the following images were recorded:



From L to R: a) Subxyphoid scan of the heart. b) Epigastric scan. c) Left lateral scan of the spleen with linear probe.

Questions

- 1) What can be seen in the images? What is the most probable diagnosis? What are the differential diagnoses?
- 2) Which further diagnostic steps would you attempt?
- 3) How would you treat the patient?

Diagnosis

Abdominal/disseminated TB

Answers

- 1) The ultrasound images show:
 - a) Anechoic pericardial effusion
 - b) Hypoechoic epigastric nodules, representing enlarged lymph nodes
 - c) Hypoechoic small micro-abscesses in the spleen.

Mycobacterium tuberculosis infection is by far the most common cause of abdominal lymphadenopathy and spleen abscesses in HIV-infected patients in our setting. Alternative diagnoses include lymphoma, infections with mycobacteria other than tuberculosis (MOTT), and Kaposi sarcoma, but these usually do not show spleen abscesses.

- 2) In a high-prevalence setting, no further diagnostic steps need to be taken; patients can be treated for TB and followed clinically, including monitoring for weight gain. When in doubt, and if no clinical improvement is observed, ultrasound-guided biopsy of the nodes is an option. Fine-needle aspirate can be used for mycobacterial culture, also to rule out drug resistance; core biopsies can be used to investigate for lymphoma.
- 3) Abdominal TB should be treated like other forms of TB, with two months of four anti-tuberculosis drugs (RHZE), followed by four (months of two drugs (RH); additionally, pyridoxine should be given. In this case, it is important to start the patient on CTX prophylaxis and ART.

Outcome and Follow-up

The patient was started on RHZE and CTX prophylaxis, which she tolerated well. After one week, she started ART treatment. Her abdominal pain and tenderness had subsided; she still reported intermittent diarrhoea, which was treated symptomatically.

Comments

FASH ultrasound is the fastest and easiest way to diagnose abdominal lymphadenopathy. As most HIV patients, especially those with abdominal or disseminated TB, are slender, image quality is usually very good. The spleen might be mildly enlarged, and will often show hypoechoic lesions (2–10 mm in size) when scanned with a linear probe. Very large lymph nodes (>5 cm), as well as infiltrations into the liver, point more towards lymphoma, and should initially be biopsied.

Typically, a careful search will reveal small amounts of free abdominal fluid. The free fluid can be aspirated; it usually shows an exudate with lymphocytic predominance. AFB stain of the ascites is usually negative; it may be sent for GeneXpert MTB/RIF.

Key Learning Point

Significant weight loss (in the absence of pulmonary symptoms) should prompt abdominal ultrasound, as abdominal TB is frequently found in HIV patients.

Suggested Reading

Heller T, Wallrauch C, Goblirsch S, Brunetti E. Focused assessment with sonography for HIV-associated tuberculosis (FASH)—a short protocol and a pictorial review. *Crit Ultrasound J.* 2012;4:21. DOI: 10.1186/2036-7902-4-21

Case 31

Presentation

A 34-year-old male patient was seen to begin ART. The patient was severely malnourished, and reported having lost weight (height: 1.63 m, weight: 43 kg, BMI: 16.2 kg/m²). His CD4 count was 206 cells/mm³. ART and CPT were started. At the same time, he was referred to the therapeutic feeding unit to receive nourishment.

Questions

- 1) How is the BMI most easily calculated using a calculator? Which BMI bands should receive therapeutic feeding?
- 2) How many calories should be given and what types of 'feeding' exist?
- 3) What are common causes of malnutrition in our patient population?
- 4) What are micronutrients? Which of these should be substituted?

Diagnosis

Severe malnutrition in an TB/HIV co-infected patient

Answers

- 1) Calculate: $\text{weight in kg} \div (\text{height in m} \times \text{height in m}) \rightarrow 43 \div (1.63 \times 1.63) = 16.2 \text{ kg/m}^2$

Patients with a BMI $< 17 \text{ kg/m}^2$ should receive therapeutic feeding, which is provided to patients with moderate and severe malnutrition. Moderate malnutrition is defined by a BMI of 16 to 16.9 kg/m^2 ; severe malnutrition is defined by a BMI $< 16 \text{ kg/m}^2$ (especially in presence of oedema without other medical cause).

- 2) According to MoH recommendations, patients with moderate malnutrition should receive 1 500 kcal/day; patients with severe malnutrition should receive 3 000 kcal/day. Ready-to-Use Therapeutic Foods (RUTF, Plumpy'Nut®, and other peanut-based pastes) are individually packed, high-caloric foods, usually in the form of a peanut-based paste, with sugar, vegetable oil, and skimmed milk powder, and fortified with vitamins and minerals. One sachet contains 92 g (equal to 500 kcal). RUTF is not widely available for adult use.

An available alternative is Likuni Phala (fortified soya protein-enriched maize flour, 395 kcal/100 g). However, it is difficult to reach recommended calorie levels with Likuni Phala; therefore, vegetable oil (120 kcal/tbsp) is added. Although still short of the recommended energy intake, one possible recommendation is:

Moderate malnutrition: 3 tbsp Likuni Phala (100 g = 395 kcal) + 1 tbsp vegetable oil (15 g = 120 kcal) twice a day (= 1 030 kcal/day). Provide 6 kg of Likuni Phala + 1 L vegetable oil per month.

Severe malnutrition: 6 tbsp Likuni Phala (200 g = 790 kcal) + 2 tbsp vegetable oil (30 = 240 kcal) twice a day (= 2 060 kcal/day). Provide 6kg of Likuni Phala + 1 L vegetable oil per 14 days.

- 3) Patients with HIV experience weight loss for a variety of reasons; the negative prognostic impact of a low body weight has been known since the beginning of the epidemic (10% decrease in body weight with chronic diarrhoea or chronic weakness and fever is an AIDS-defining clinical condition, a/k/a 'slim disease'). A low BMI at the start of ART is an independent predictor of early mortality in several analyses from sub-Saharan Africa. Besides general food scarcity, oral and gastrointestinal infections, as well as constitutional manifestations of advanced HIV disease (fatigue, fever, dyspnea), contribute to disability and interfere with an individual's ability to obtain and ingest food. Infections caused by intestinal parasites and *Mycobacterium tuberculosis* ('consumption'), decreases small bowel transit time and carbohydrate absorption, and bowel-wall oedema can add to malabsorption. Another primary cause of weight loss in HIV-infected patients is thought to be anorexia caused by elevated cytokines (IL-1, IL-6, and TNF).
- 4) Micronutrients are vitamins (A, multiple B's, C, D, and E), as well as selenium and zinc. A review from 2010 indicated that micronutrient supplements conferred multiple clinical benefits to pregnant women and their offspring in a large Tanzanian trial. Supplementation in another Tanzanian trial reduced the recurrence of pulmonary TB and increased weight gain in co-infected patients. Zinc supplements reduced diarrhoeal morbidity in HIV-infected children. Additional research is needed to determine if these are generalizable findings, but no significant adverse effects were reported. These findings suggest that the threshold for prescribing multivitamins to individual patients should be low, but they are not part of the routine management of ART patients.

Outcome and Follow-up

As it was felt the patient could have underlying TB, a sputum sample was sent to the lab; it came back AFB positive. A FASH ultrasound showed enlarged lymph nodes, suggesting abdominal TB involvement. TB treatment was started. In addition, the patient received therapeutic feeding for four months, plus multivitamins.

Key Learning Point

Low BMI is an independent predictor of mortality in ART patients; although the benefits have not yet been proven in studies, we try to supplement calories as much as possible.

Suggested Reading

Irlam JH, Visser MM, Rollins NN, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database Syst Rev.* 2010 Dec 8;(12):CD003650.

Koethe JR, Chi BH, Megazzini KM, Heimburger DC, Stringer JSA. Macronutrient supplementation for malnourished HIV-infected adults: a review of the evidence in resource-adequate and resource-constrained settings. *Clin Infect Dis.* 2009 Sep 1;49(5):787–798.

Notes

Case 32

Presentation

A 44-year-old male patient was seen for swelling in the left supra-clavicular fossa; it looked like a cold abscess. Sonographically, an enlarged hypoechoic LN was observed. The patient was started on TB treatment (the diagnosis was later confirmed by biopsy). Additionally, he started ART for his HIV infection.

Six weeks later, the patient travelled to Uganda; during his stay there, the abscess looked increasingly 'hot' (i.e., red and warm—see the picture below left). Colleagues in Uganda incised the abscess, and drained pus. Afterwards, a skin defect ensued. He presented with this defect (below right).



Questions

- 1) What needs to be done?
- 2) Some people recommend against aspiration or incision of tuberculous LN and abscesses, 'as chronic fistulas could form'. What is your opinion?
- 3) What is IRIS?

Diagnosis

TB lymphadenitis with IRIS

Answers

- 1) Both the TB treatment and ART should be continued. In addition, local dressings should be applied to prevent secondary infection and facilitate healing.
- 2) This is certainly a frequently encountered opinion. In our experience, the fistulas and defects associated with TB heal quite well as long as active systemic TB treatment is given. The clinical experience of non-healing fistulas probably derives from the pre-antibiotic era, when treatment was highly frustrating (for both patient and physician).
- 3) Immune reconstitution inflammatory syndrome (IRIS) is an important early complication of ART. Immune recovery following ART initiation is associated with a pathological inflammatory response, usually directed toward microbial antigens. Although there is considerable clinical heterogeneity, key features of IRIS are clinical deterioration in the first weeks to months of ART, with evidence of inflammation, with or without a systemic inflammatory response. The most important forms are TB-associated IRIS (TB-IRIS), cryptococcal IRIS, and Kaposi sarcoma (KS-) IRIS.

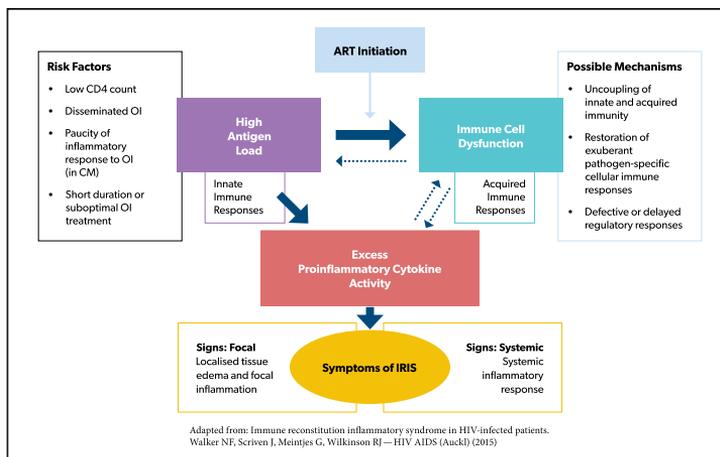
Outcome and Follow-up

Both TB treatment and ART were continued. The wound was dressed with non-sticky dressing; over the following weeks, it healed without complication, forming a small scar.



Comments

Two distinct time patterns of IRIS are commonly described: paradoxical IRIS and unmasking IRIS. With paradoxical IRIS, symptoms and signs associated with a known opportunistic infection (OI) that has already been treated recur or become acutely worse after initiating ART. With unmasking IRIS, a previously unknown OI presents following ART initiation. Risk factors and pathophysiology are summarised in the diagram below.



Open access via https://openi.nlm.nih.gov/detailedresult.php?img=PMC4334287_hiv-7-049Fig2&req=4

Key Learning Point

IRIS-associated morbidity may be considerable, but ART is still the key to surviving HIV. It is rarely necessary to interrupt or discontinue ART because of IRIS!

Suggested Reading

Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS (Auckl). 2015;7:49–64.

Case 33

Presentation

A 21-year-old student was seen because his previous routine VL showed 10 400 copies/mL. He was otherwise well, and had no complaints. He received counselling; upon careful questioning, he stated that he was taking his ART medication (TDF/3TC/EFV) every day, and never missed any doses. However, he did admit that, about two to three years ago, he was less exact, often missing doses because he was 'hanging out with friends', and because of 'issues with [his] girlfriend' at that time. He was instructed to take his ART with utmost care; two months later, a Point-of-Care (POC-) VL was ordered (on the 'GeneXpert HIV quant'). The patient was asked to wait for the result; two hours later, he was seen again, with the result shown below.

Test Report

Patient ID*: P170100100582
Sample ID*: 222100
Test Type: Specimen
Sample Type: plasma

Assay Information

Assay	Assay Version	Assay Type
Xpert HIV-1 Viral Load	1	In Vitro Diagnostic

Test Result: HIV-1 DETECTED 6.02E03 copies/mL (log 3.78)

Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
HIV-1	31.4	335	POS	PASS
IQS-H	24.1	284	PASS	PASS
IQS-L	34.3	698	PASS	PASS

Questions

- 1) The GeneXpert result displayed 6.02E03 copies/mL (log 3.78). What does this mean?
- 2) The VL appears to be falling. Is this due to better adherence? Should the patient continue on the same regimen to see his progression? How would you interpret the result?
- 3) For which patients would you like to consider for POC-VL testing? For which patients would you send samples to the laboratory? How do you decide?

Diagnosis

Virological failure on first-line ART

Answers

- 1) Because of the wide range (from ten to millions of viral copies per mL of blood), VL results are often reported in logarithmic terms. In the expression *6.02E03 copies/mL*, E03 means that decimal point needs to be shifted three places to the right. This gives 6 020 copies/mL. *log 3.78* means the logarithm (base-10) of the result; the result is therefore $10_{3.78}$, which is again 6 025 copies/mL.
- 2) Viral load measurements are not very exact, especially when different technologies (in this case lab-based-VL vs. POC-VL) are used. As a general rule, assay precision allows us to discern only changes in viral load that are three-fold or greater ($0.5 \log_{10}$ copies/mL) as biologically significant. The difference for this patient (10 400 vs. 6 020) is not even two-fold (i.e., not even half) (In logarithmic terms: $10\ 400 = \log 4.02$ vs. $6\ 020 = \log 3.78$, a difference of $0.24 \log_{10}$). The ability to detect $0.5 \log_{10}$ may even decline at the lower end of the range for some assays, which means that the comparison of low VL results requires even greater caution. Effective therapy should result in at least a 10-fold ($1.0 \log_{10}$) decrease in HIV-1 RNA copies/mL in the first month, with suppression to less than 50 copies/mL by 24 weeks.
- 3) Routine VL monitoring samples should be sent to the laboratory. Usually, laboratory-based tests are cheaper, and a greater number of tests can be performed each time (higher throughput). Because of the time it takes to transport samples from the clinic to the lab, to transport results back to the clinic, and to delays within the lab itself, the results will not be very timely (usually taking weeks or months to come back). For a targeted VL, it is desirable to have results quickly, in order to decide on changes required to treatment of the patient. In this case, the POC-VL is preferable, if available. The higher costs are less important, as the number is much smaller (\rightarrow the throughput does not need to be high). We would consider the following samples as 'targeted':
 - a) suspicion of clinical (or immunological) treatment failure
 - b) follow-up VL after a previously high VL (e.g., after adherence step-up)
 - c) follow-up at six months after changing to second-line treatment.

Outcome and Follow-up

The VL test result was still high, so the patient was switched to a second-line treatment of AZT/3TC/ATV/r. He was well adherent to this regimen; three months later, a follow-up VL test was done on the GeneXpert, with a result of <40 copies/mL.

Comments

The 'GeneXpert HIV quant' amplifies RNA from the 3'-end of 5' LTR of the HIV genome. It can detect Group M Subtypes A-H, AB, AE, AG J, and K; Group N and Group O virus RNA; and has a linear range of $40\text{--}10^7$ HIV-1 copies/mL. A real-time RT-polymerase chain reaction is a technique of molecular biology, based on the polymerase chain reaction (PCR). It monitors the amplification of a targeted RNA molecule during the PCR (i.e., in real time), using fluorescence. It can be used quantitatively by comparing the speed of the amplification to that of internal quantitation standards—an IQS High (10^6 copies) and an IQS Low (10^3 copies). The number of PCR cycles ('C') is counted until a threshold of fluorescence is reached ('Ct'), and then it is compared to the number of Ct of the IQS.

Key Learning Point

Viral load measurements are not very exact; with effective therapy, you would expect at least a 10-fold decrease in VL in the first month.

Suggested Reading

Liegler TJ, Grant RM. Nucleic acid-based HIV-1 viral load assays. San Francisco (CA): University of California, San Francisco HIV InSite Knowledge Base. 2006 May. Available from: <http://hivinsite.ucsf.edu/InSite?page=kb-02-02-02-01>.

Case 34

Presentation

A 54-year old man complaining of prolonged cough, night sweats, and weight loss was seen in the clinic. The patient had TB more than 15 years ago; based on his clinical symptoms, he was started on RHZE. A week later, he was seen again—now complaining about coughing up blood-stained sputum, reporting that it was not ‘pure blood’. FBC was taken and showed:

Hb	13.6 g/dL	(normal 11.5–16.5)
WBC	3.5 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	71 $10^3/\text{mm}^3$	(normal 150–500)

A CXR was taken.



Questions

- 1) What are the most common causes of haemoptysis?
- 2) What is considered ‘massive haemoptysis’? How would it be treated?
- 3) How would you treat this patient?

Diagnosis

Persistent haemoptysis in PTB.

Answers

- 1) Common causes of significant pulmonary bleeding are tuberculosis, bronchiectasis, mycetoma, and carcinoma. Smaller amounts of blood are seen in pulmonary embolism, bronchitis, pneumonia, and pulmonary hypertension (e.g., secondary to mitral valve stenosis). Autoimmune (Wegener's granulomatosis, Goodpasture syndrome) and haematological disorders (leukaemia, ITP) might be considered as rarer causes.
- 2) Massive haemoptysis is extremely anxiety-provoking for patients (and doctors!). It is broadly defined as 100 to 600 mL blood loss within 12 to 24 hours. The priority is to localise the bleeding. CT may help, although ultimately the patient should undergo bronchoscopy. In cases of massive bleeding, rigid instruments are preferred. In cases of chronic bleeding, localisation of the bleeding vessel by angiography and coiling (occlusion of the vessel) is a feasible option. For these interventions, the patient needs to be transferred to a tertiary hospital.
- 3) This patient suffers from mild haemoptysis, which is likely due to TB. On the CXR for this patient, it can be seen that he has left upper lobe bullae and cavities; bronchiectasis due to the infection, and to scars (from his previous TB), can be assumed. The mild thrombocytopenia may have added to the bleeding. TB treatment should be continued; it may be useful to add a cough suppressant to reduce the severity of cough, and thus increase the chance of healing. Additional antibiotics can be used to cover superimposed bronchial and pulmonic infections. Tranexamic acid may also help reduce bleeding. Platelets should be checked in the interval.

Outcome and Follow-up

The patient was informed about his low platelet count, and his TB treatment continued. He was advised to return in one week to repeat an FBC. After five-and-a-half months of treatment, he again complained about 'coughing up blood-stained sputum'. FBC and CXR were repeated. The CXR showed no change.

FBC

Hb	13.6 g/dL	(normal 11.5–16.5)
WBC	5.8 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	612 $10^3/\text{mm}^3$	(normal 150–500)

Upon questioning, the patient reported that his constitutional symptoms had improved with therapy, he had regained some weight, and the cough was significantly less. A sputum TB culture was sent to the lab, and the patient prescribed vitamin B complex. Final mycobacterial cultures were sterile.

Comments

In South Africa, 85% of 120 consecutive cases of significant haemoptysis (>200 ml) were found to be due to TB. In countries with lower TB prevalence, this rate will be lower—but we can extrapolate the data to other Southern African countries, indicating that TB is the main cause.

Other aetiologies of pulmonary bleeding in TB patients may include ectatic blood vessels traversing a cavity (Rasmussen's aneurysm), calcified lymph nodes eroding the wall of the airway (broncholith), and aspergillomas. Another reason is simple bronchiectasis, in which vessels are vulnerable to erosion by the chronic inflammation that is typical of this disorder.

Key Learning Point

If the patient has had prior TB, haemoptysis could be caused as a consequence of the previous occurrence of the disease.

Suggested Reading

Knott-Craig CJ, Oosthuizen JG, Rossouw G, Joubert JR, Barnard PM. Management and prognosis of massive hemoptysis. Recent experience with 120 patients. *J Thorac Cardiovasc Surg.* 1993 Mar;105(3):394-7.

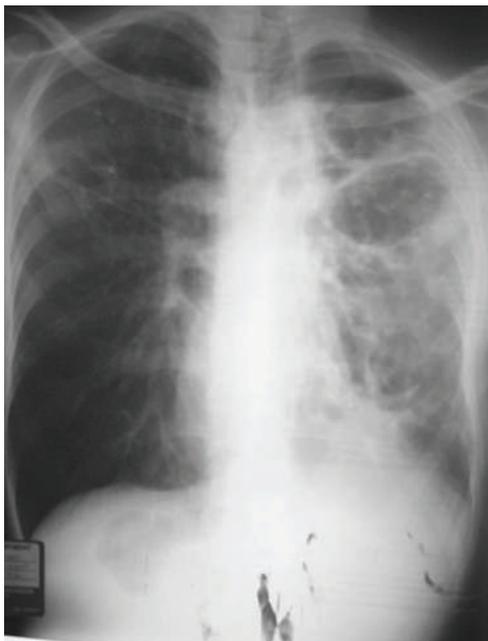
Case 35

Presentation

A 33-year-old man is sent to you because of adherence issues with his TB treatment.

The patient had been tested for TB because of chronic cough and weight loss; his sputum smear was positive for AFB. He was then started on standard TB treatment, but refused HIV testing. After the first six weeks of treatment, he was feeling better; he defaulted from the clinic, and 'left the area to work'. Two months later, his symptoms having returned, the patient came back to the clinic. The TB nurse was undecided what to recommend and referred him to you.

A CXR was taken.



Questions

- 1) What does the CXR show?
- 2) What other tests would you suggest?
- 3) What would you recommend to the patient?

Diagnosis

Extensive TB of the left lung; treatment defaulter

Answers

- 1) The CXR shows extensive disease of the left lung, with infiltrates and multiple large cavities.
- 2) Sputum should be sent for AFB testing to assess whether the patient is smear positive again, and for GeneXpert testing to check for potential RIF resistance. Additionally, TB culture and resistance testing could be requested. This should ideally be done in all cases of defaulting patients, re-treatment cases, and cases that fail to improve with treatment. (In the strictest sense, treatment failure is defined as being smear-positive after five months or more of treatment. This definition is difficult in a setting with many smear-negative TB cases). Have a low threshold to send for culture when clinical findings suggest.
- 3) The decision for retreatment in patients who have defaulted depends on a variety of factors, which necessitate further caution, and probably intensification of treatment:
 - The patient is found to be smear- or culture-positive upon returning from defaulting.
 - Interruption occurs in the intensive phase, rather than the continuation phase.
 - Interruption occurs early (rather than later) in the continuation phase.
 - The interruption is of long duration (>2 months).
 - The patient is immunocompromised (living with HIV or another condition).
 - The patient had poor response to treatment before the interruption.
 - GenXpert detects RIF resistance.

One possible algorithm could be:

Interruption less than 1 month			
Solve the cause of interruption Continue treatment and extend by the number of missed doses			
Interruption for 1-2 months			
Solve the cause of interruption Do AFB and GeneXpert tests	If tests negative or EPTB	Continue treatment and extend by the number of missed doses	
	If smear or Xpert positive	<5 months	Continue treatment and extend by the number of missed doses
		>5 months	If Category 1: Start Category 2 If Category 2: Culture! Consider MDR
Interruption for more than 2 months			
Solve the cause of interruption Do AFB and GeneXpert	If tests negative or EPTB	Individual decision whether to restart or continue treatment, or to give no further treatment	
	If smear or Xpert positive	Category 1	Start category 2
		Category 2	Culture! Consider MDR

(Based on Treatment of tuberculosis guidelines for national programmes, WHO, 2003, p. 52)

Outcome and Follow-up

The patient had extensive disease, with treatment interrupted for more than two months. He was found to be smear-positive again, and was started on RHZES, followed by one month on RHZE, then five months on RH. His TB culture was subsequently positive, showing a fully sensitive strain.

Comments

TB patients defaulting from treatment because of its long duration is a frequent problem. It is important to stress to patients the importance of continuing treatment even after symptoms have improved. If possible, DOTS (directly observed treatment with support) should be implemented, especially with patients who have previously defaulted.

Key Learning Point

A sputum culture should be sent for every patient who has previously defaulted from treatment.

Suggested Reading

World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. Geneva (Switzerland); World Health Organization; 2010.

Case 36

Presentation

A 31-year-old female patient was admitted because of general weakness, significant weight loss, and abdominal pain. Clinically, she had features of advanced HIV, and was confirmed to be HIV positive. Her CD4 count was 23 cells/mL. An abdominal ultrasound revealed enlarged abdominal lymph nodes, and a small amount of ascites, as well as mild splenomegaly. Abdominal TB was the most likely diagnosis; she was started on standard TB treatment. The patient reported vaginal discharge; the nurses observed genital ulcers. On examination, large painful ulcers were present, and the patient's inguinal lymph nodes were minimally swollen.



Questions

- 1) What are the most common causes of ulcerative sexually transmitted infections (STIs)?
- 2) How would you treat this patient?
- 3) STIs are commonly grouped as syndromes for the purpose of treatment guidelines. Which syndromes do you know? How are they treated?

Diagnosis

Extensive herpes genitalis

Answers

- 1) *Herpes simplex virus* (HSV) Type 2 (but also Type 1) (painful ulcer), *Treponema pallidum* (syphilis, painless ulcer), and *Hemophilus ducreyi* (chancroid, painful ulcer) are the most common causes of genital ulcers in the area. Granuloma inguinale (donovanosis) is unusual in sub-Saharan Africa. Lymphogranuloma venereum (LGV) presents initially with a small painless ulcer that often heals unnoticed, and then develops inguinal lymph node swelling.
- 2) Acyclovir 400 mg tds for three to seven days + benzathine penicillin 2.4 MU IM stat + ciprofloxacin 500 mg bd for three days can be used against chancroid. Doxycycline (100 mg bd for 5 days) could be added if LGV is suspected.
- 3) STI syndromes for the purpose of treatment guidelines:
 - **Genital ulcer.** See above for cause and treatment.
 - **Inguinal bubo.** *Cause:* lymphogranuloma venereum (LGV) and chancroid; consider systemic (e.g., TB or KS) and lower leg infection. *Treatment:* doxycycline 100 mg bd for 10–14 d + ciprofloxacin 500 mg bd for three days
 - **Urethral or vaginal discharge.** *Cause:* *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most common causes of male and female genital discharge. In cases of vaginal discharge, *Trichomonas vaginalis* should also be considered. *Treatment:* Gentamycin 240 mg IM (gonorrhoea) + doxycycline 100 mg bd for seven days (chlamydia); for women, you can add metronidazole 2 g stat (trichomoniasis).
 - **Scrotal swelling.** *Cause:* In men younger than 35 years of age, STIs are the most common cause. Gonorrhoea and chlamydia must be treated (gentamycin + doxycycline). In older men, and in cases that persistent after treatment, other causes (*E. coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, TB orchitis) need to be considered. It is also important to consider non-infective causes, such as testicular torsion, tumour, hydrocele, and trauma.
 - **Pelvic inflammatory disease (PID)/lower abdominal pain.** Salpingitis/endometritis is a common cause of lower abdominal pain in women, and may be caused by *N. gonorrhoeae*, *C. trachomatis*, anaerobic bacteria, or gram-negative rods. Treatment must be effective against a broad range of pathogens; ceftriaxone or gentamycin (240 mg im stat) + doxycycline (100 mg bd for 14 days) + metronidazole (400 mg bd for 10–14 days) is a recommended combination. It is important to consider ectopic pregnancy; any patient with a positive pregnancy test should be referred for proper diagnosis (ultrasound).

Outcome and Follow-up

The patient was treated with acyclovir 400 mg tds; additionally, depot penicillin (2.4 MU) stat was given IM. The ulcers were also treated, with topical antiseptic dressing. They started to improve, and had become significantly smaller by the time the patient was discharged. The patient started on ART two weeks after starting TB treatment.

Comments

HSV-2 infections are frequent; antibodies were found in up to 67% of women in South Africa. HSV-2 infection is associated with a 3x to 5x increased risk of HIV transmission. The disease is more severe; lesions are larger and recur more frequently in HIV/HSV co-infected individuals.

Key Learning Point

In HIV/HSV co-infection, ulcers become less frequent and are less severe following initiation of ART.

Suggested Reading

Ministry of Health, Malawi. Management of sexually transmitted infections using syndromic management approach. Lilongwe (Malawi); Ministry of Health, Malawi; 2008.

Case 37

Presentation

A 20 year-old-male patient was referred to the TB clinic with a cough and increasing shortness of breath for two months. Chest sounds were clear, cardiac sounds were normal, and there was no oedema—but the patient was in obvious respiratory distress, with a respiratory rate of 20 breaths per minute.

The patient did not report constitutional symptoms, and his HIV test was negative, as were his sputum smear and sputum GeneXpert MTB/RIF. A CXR was done.



Questions

- 1) How would you describe the lesions in the CXR? Are they typical for TB?
- 2) Does the history support TB as a diagnosis? Which further tests would you suggest?

Diagnosis

Cannonball lesions in the lung, metastatic sarcoma

Answers

- 1) On the CXR, numerous round opacities are visible in both lungs. The lesions are variable in size, and well defined. They are predominantly in the lower lobes; there is no pleural effusion. We cannot speak to hilar lymphadenopathy, as the lesions overlap this area, but it is certainly possible. The lesions are not typical for TB.
- 2) The history is not typical for TB. The respiratory symptoms are present, and sufficient to prompt a referral to the TB clinic, but constitutional symptoms are missing, and there was no AFB found in sputum or GeneXpert. In HIV-negative patients one would expect these tests to be positive (although they do not have to be).

Outcome and Follow-up

It was felt that this case was not typical for TB, and needed further diagnostic work up. As the lesions in the right lower lobe seemed to have contact, an ultrasound of the chest was done. The lesions were visible close to the thoracic wall. An ultrasound-guided core biopsy was performed, yielding the sarcoma diagnosis; the patient was referred to oncology for chemotherapy.

Comments

It is important to remember the different presentations of TB on the CXR to differentiate it from other diseases.

The 'typical' (post-primary) TB CXR is characterised by infiltrates, which are located in the upper lobes 85% of the time. Cavitation is common; an effusion may or may not be present. Hilar adenopathy is uncommon. In 'atypical' (primary) TB, the infiltrates are also frequently seen in the lower lobes (upper-lower ratio of 60:40), cavitation is uncommon, and lymphadenopathy is seen in about 30% of adult cases (more frequently in children). Again, a pleural effusion may be present. HIV patients can present with both patterns of findings; low CD4 counts (<200) correlate more with the 'atypical' features, whereas the 'typical' pattern is more often observed in less immunosuppressed patients.



Typical TB pattern



Atypical TB pattern

Key Learning Point

Not every cough is TB—use the diagnostic means available to determine the probability.

Suggested Reading

Daley CL, Gotway MB, Jasmer RM. Radiographic manifestations of tuberculosis: a primer for clinicians. 2nd ed. San Francisco: Francis J. Curry National Tuberculosis Center; 2006. Available from: <http://www.currytbcenter.ucsf.edu/products/view/radiographic-manifestations-tuberculosis-primer-clinicians-second-edition-printed-book>.

Case 38

Presentation

A 29-year-old HIV-positive man not yet on ART was admitted because he had been coughing for two months and becoming increasingly short of breath. The patient was dehydrated, but afebrile. His general status was weak, and he was severely underweight. The following day, the clinician noticed confusion and irritability. A lumbar puncture was performed, and empirical meningitis treatment initiated. Blood sugar was 96 mg/dL. In the afternoon, the patient was assessed again; he was reacting with groans and not talking. The following results were received at the end of that day:

FBC

Hb	7.8 g/dL	(normal 11.5–16.5)
WBC	2.8 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	29 $10^3/\text{mm}^3$	(normal 150–500)

CSF

CSF-polymorphs	30 cells/mL	(normal <5)
CSF-lymphocytes	88 cells/mL	(normal <5)
CSF-protein	1.79 g/L	(normal 0.15–0.4)
CSF-glucose	0.7 mmol/L	(normal 2.7–4.1)
Crypto Ag and India ink	negative	(normal negative)

Questions

- 1) What would be your empirical treatment for meningitis?
- 2) Which CSF findings are commonly seen in meningitis caused by bacteria, TB, and cryptococcus?
- 3) How would you change your management of this case after receiving the lab results?

Diagnosis

TB meningitis

Answers

- Empirical treatment should cover the bacterial pathogens, as well as cryptococcal infection, which is very common in African HIV patients with (assumed) low CD4 count. Ceftriaxone 2 g IV bd and fluconazole 800 mg po od would be a possible empirical regimen.
- The following table summarizes the changes of CSF in different diseases:

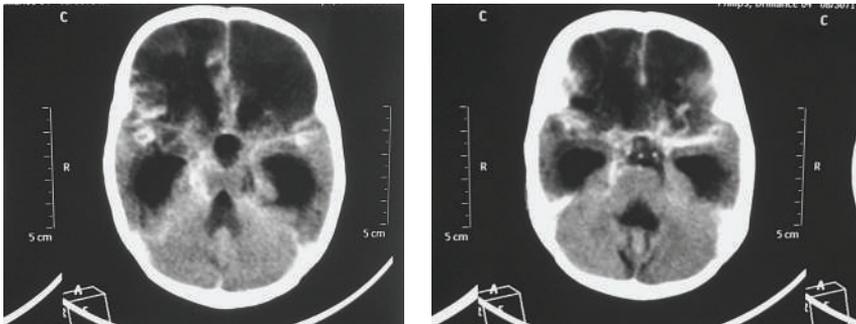
	Polymorphs	Lymphocytes	Protein	Glucose	CryptoAg
Bacterial	↑↑	mildly ↑	↑↑	↓↓	neg
Mycobacterial	mildly ↑	↑	↑↑	↓↓	neg
Viral	↔	mildly ↑	↑	↔	neg
Fungal	mildly ↑	↑	↑↑	↓	pos

- The lab results do not suggest cryptococcus or bacteria as the cause of the patient's meningitis. The most likely diagnosis, especially given his respiratory symptoms, is TB meningitis. Fluconazole and ceftriaxone can be stopped; TB treatment should be started. In addition, a steroid (e.g., prednisolone 60 mg od tapered over a one- to two-month period) should be added.

Outcome and Follow-up

Therapy was adjusted as explained above. The patient was referred for HIV testing; the result was positive, and he was categorised as HIV stage 4 (because of extrapulmonary TB). He spent almost six weeks in the TB ward, and improved slowly. Physiotherapy was prescribed. However, during his stay, the patient developed bedsores; they improved, but were still present at the time of discharge.

The patient's CD4 count was 33 cells/mL. Nevertheless, ART was started only after six weeks of effective TB treatment, as the risk of IRIS in partially treated cases of meningitis is high.



Meningeal enhancement seen in the CT scans of a different TB meningitis patient (hydrocephalus is also visible).

Comments

About 30% of patients with tuberculosis meningitis die despite receiving anti-tuberculosis chemotherapy. Delays in diagnosis and treatment are regarded as major contributing factors to the high mortality. The diagnosis relies on isolation of *M. tuberculosis* from the CSF, but culture tests are slow, and AFB staining often too insensitive, to aid clinical decision-making. Consequently, the decision to treat a patient for TB meningitis is frequently empirical.

TB meningitis is the sole form of adult EPTB that is treated with a different regimen; streptomycin is added to the intensive phase, and the treatment is longer: 2SRHZE/7RH. If streptomycin is not available, start treatment with RHZE immediately, and transfer the patient.

Suggested Reading

Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. *Lancet*. 2002 Oct 26;360(9342):1287–92.

Key Learning Point

The use of steroids in TB meningitis has been shown to improve neurological outcomes, and is therefore part of the treatment protocol.

Case 39

Presentation

A 20-old-male patient was seen due to yellowing of his eyes. In addition, he presents with fever and abdominal discomfort. He reports that his urine appears dark, and his stools pale. On examination, the patient had marked scleral icterus, and mild RUQ tenderness with hepatomegaly. His lab values showed:

<i>FBC</i>		
Hb	13.1 g/dL	(normal 11.5–16.5)
WBC	12.2 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	308 $10^3/\text{mm}^3$	(normal 150–500)
<i>LFT</i>		
TBIL	17.2 mg/dL	(normal <1.1)
DBIL	8.0 mg/dL	(normal <0.3)
GGT	105 U/L	(normal 7–62)
ALT	230 U/L	(normal 10–60)



Questions

- 1) What questions would you like to ask? Which tests would you order?
- 2) What is the most likely diagnosis?

Diagnosis

Acute viral hepatitis

Answers

- 1) The patient needs to be asked whether he takes any drugs—in particular, TB medication (like isoniazid, pyrazinamide, or rifampicin) or ARVs (NVP)—that cause hepatitis or liver injury. Hepatitis A and B serology might be ordered. Ultrasound of the abdomen is useful to rule out obstructive biliary disease—as, for example, in portal lymphadenopathy in abdominal TB.
- 2) The patient did not report taking medication for HIV or TB. He has not received any blood transfusions. The first, most probable, diagnosis is acute hepatitis A. The relatively high bilirubin compared to the ALT suggests a late stage of the disease.

Outcome and Follow-up

The patient was sent for an abdominal ultrasound, which was normal, except for one small (8 mm) lymph node next to the portal vein.

His serology revealed acute hepatitis A infection.

By the time the serological results were received, the patient reported he already felt better without specific therapy. He was tested for HIV, and found to be HIV positive; ART was initiated.

Comments

It is important to remember that, in a high HIV-prevalence area, even patients presenting to the health system with non-HIV related disease should be encouraged to test for HIV. The WHO recommends this provider-initiated testing and counselling (PITC) approach in all settings where HIV prevalence is high.

In contrast, under the voluntary counselling and testing (VCT) approach, the initiative to seek an HIV test comes from the individual patient, instead of from the health care provider.

Key Learning Point

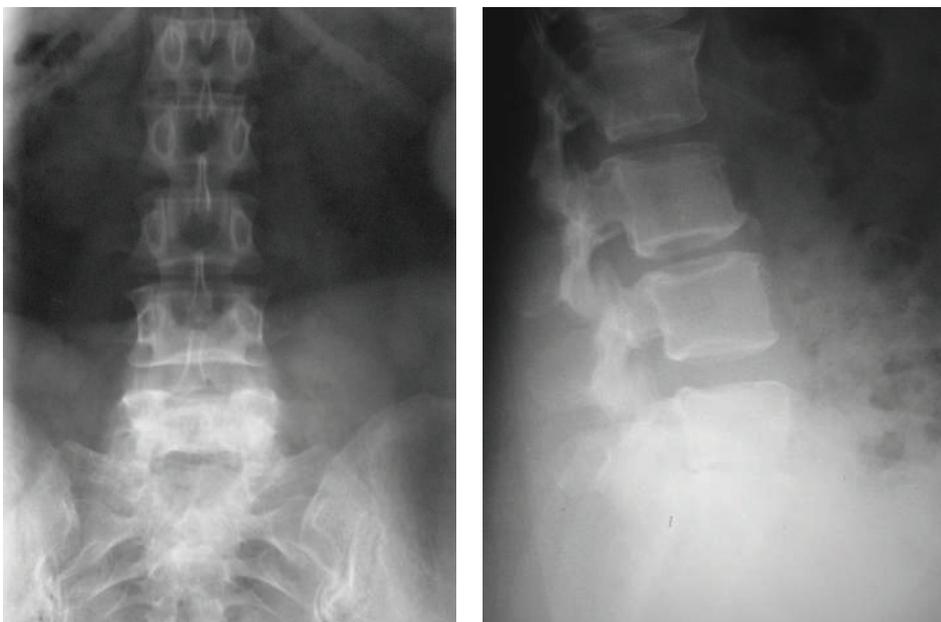
A thorough drug history is essential for anyone presenting with jaundice (including traditional and non-prescribed medications).

Case 40

Presentation

A 34-year-old woman was seen at the clinic because she was diagnosed HIV positive; her CD4 count was 146 cells/mL. During her first visit, the patient complained about lower back pain and was given NSAIDs. When she was seen again a month later, she again complained about back pain, as well as new hip pain. ART was continued, and more NSAIDs were prescribed.

A month later, the patient was still complaining about pain; the physician sent her to the hospital for lumbar x-ray. This was done in the outpatient department; she returned to the clinic with the report that no abnormality was detected. Treatment was continued with diclofenac and amitriptyline. She was seen again two months after that; now in more severe pain, she was hardly able to walk, and unable to stand on her toes. No sensory deficit was found. She was referred back to the hospital, where new x-rays of her spine and pelvis were ordered.



Questions

- 1) What do you see on the x-rays? What is the differential diagnosis?
- 2) Which additional diagnostic steps might be taken?
- 3) Should the patient be treated surgically?

Diagnosis

Spinal TB

Answers

- 1) L5 seems to be much more dense than the other vertebrae; additionally, the 'eyes of the vertebrae' (roots of the vertebral arc) cannot be delineated, suggesting a destructive process. Differential diagnosis will include TB (the most likely cause in our setting), bacterial osteomyelitis (*S. aureus*), and tumour destruction/infiltration (e.g., plasmocytoma, mammary carcinoma).
- 2) Clinical presentation and radiological imaging can be highly suggestive of spinal TB. Definite diagnosis can only be obtained by percutaneous (e.g., CT-guided) or open surgical biopsy, this is often not indicated in the high-prevalence setting; a treatment trial might well be warranted.
- 3) The following circumstances are generally considered as indications for surgical intervention (in tertiary hospitals):
 - a) Neurological deficits (with acute or non-acute onset) caused by compression of the spinal cord
 - b) Spinal instability caused by collapse or destruction of vertebrae, or kyphosis of more than 30°
 - c) No response to medical treatment
 - d) Large paraspinal abscesses
 - e) Diagnostic intervention (in case of doubt about the diagnosis)

Outcome and Follow-up

The patient was found to have a destructive lesion in L5. The previous x-rays were assessed again; in retrospect, lesions were found on these as well, but unfortunately went unnoticed at the time. The height of the vertebrae is not massively reduced, which is probably the reason why it was initially overlooked. The patient was referred for an MRI of the spine for the following week; TB treatment was started in the meantime. The MRI confirmed the diagnosis. Neurosurgeons were consulted, but it was agreed to continue TB treatment to assess the clinical course. The patient was seen again after two months of TB treatment; her condition had substantially improved. She still reported mild pain in the morning, but no longer required analgesics. TB treatment was continued for a total period of six months.



Comments

Weight-bearing bones are most commonly involved in TB infections, possibly due to the increased blood supply in these areas. Pott's disease was originally described in the thoracic spine, but the lumbar spine is also commonly affected.

Until recently, longer regimens (9–12 months) were recommended for spinal TB. However, there is minimal evidence in the modern literature to support this; a six-month regimen has been found to be equally effective.

Key Learning Point

The case illustrates that one should doubt findings and reports if they are not compatible with the clinical picture.

Suggested Reading

Loenhout-Rooyackers JH, Verbeek ALM, Jutte PC. Chemotherapeutic treatment for spinal tuberculosis. *Int J Tuberc Lung Dis*. 2002 Mar;6(3):259–265.

Case 41

Presentation

A 32-year-old male patient is seen in the TB clinic because of swelling of his cervical lymph nodes. He reports that he has had the swelling for six months; recently it has become difficult to open his mouth, and now he can only tolerate fluids PO.

On examination, a large lymph node mass, which was firm and immobile, was observed on the left side of his neck. In his mouth, multiple elevated ulcers were visible, which were suggestive of infiltration.

<i>FBC</i>		
Hb	11.7 g/dL	(normal 11.5–16.5)
WBC	5.3 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	551 $10^3/\text{mm}^3$	(normal 150–500)



Questions

- 1) What is the most likely diagnosis?
- 2) What tests are useful to assess the extent of the disease?
- 3) Which prognostic factors determine survival?
- 4) Which pathogens are involved in this disease?

Diagnosis

Lymphoma

Answers

- 1) HIV-associated lymphoma is the most probable diagnosis, as the mass is described as firm and immobile, and there is suspicion of infiltration in the mouth. TB is a possible differential diagnosis. Fine needle aspiration could be done easily—but, if lymphoma is suspected, it is preferable to obtain a core biopsy, or even a surgical lymph node biopsy, for histology and immunohistochemical staining (IHC).
- 2) CXR and ultrasound of the abdomen might be used as staging tests that are readily available. Bone marrow examination and CSF cytology can be done at the oncology treatment centre.
- 3) The Ann Arbor classification is commonly used for staging:
 - I. One lymph node region
 - II. Two or more lymph node regions on one side of the diaphragm
 - III. Two or more lymph node regions on both sides of the diaphragm
 - IV. Disseminated involvement of extralymphatic organs

However, the correlation of stage and prognosis is weaker than in normal non-Hodgkin lymphoma (NHL). Prognosis is also related to immune function. Studies show that adverse prognostic factors were: CD4 counts less than 100 cells/mL, age older than 35 years, Ann Arbor stage III or IV, IV drug use, and raised LDH.

- 4) Systemic NHL is not associated with a specific pathogen; CNS lymphomas are associated with Epstein-Barr virus, and body cavity lymphomas with human herpes virus 8 infection.

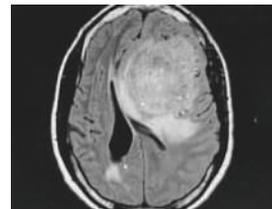
Outcome and Follow-up

The patient was admitted for biopsy. An ultrasound of the abdomen revealed no further lymph nodes; liver and spleen were normal. The CXR was also unremarkable; no further lymphadenopathy was detected there. The patient was found to be HIV positive; his CD4 count was 146 cells/mL. The lymph node biopsy showed a high-grade non-Hodgkin lymphoma. The patient was referred to the oncology department, where he received further treatment.

Comments

HIV-positive patients have a high incidence of lymphoma, especially high-grade NHL. When the lymphomas involve the CNS, they have a particularly poor prognosis. CNS lymphomas are associated with Epstein-Barr virus infection; if lumbar puncture is performed, EBV-PCR is a sensitive and specific test. Malignant cells are found in about a quarter of the CSF samples.

Treatment is a combination of ART and systemic chemotherapy. In Malawi, CHOP is administered every 21 days with cyclophosphamide, doxorubicin, vincristine on day 1, and prednisone on days 1–5. Intrathecal methotrexate 12.5 mg and hydrocortisone 50 mg may be recommended for patients at high risk of leptomeningeal involvement. Usually six cycles are administered. Patients who achieve partial response and tolerate treatment without severe adverse events could receive up to eight cycles.



MRI of a primary CNS lymphoma in a different patient

Key Learning Points

- Not all lymph node swellings are TB.
- Nodes that are firm, large, or unresponsive to treatment require biopsy.

Suggested Reading

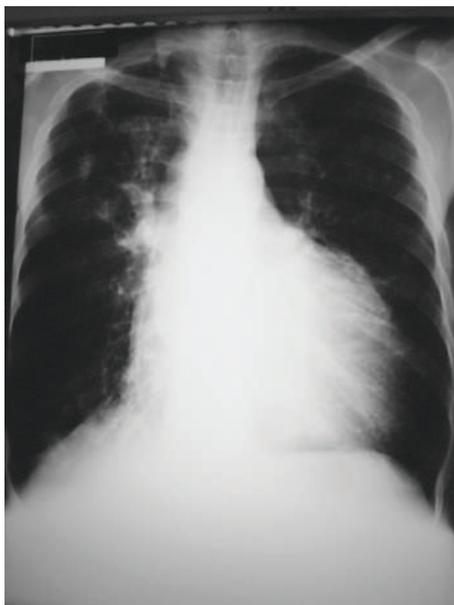
Gopal S, Fedoriw Y, Kaimila B, Montgomery ND, Kasonkanji E, Moses A, et al. CHOP chemotherapy for aggressive non-Hodgkin lymphoma with and without HIV in the antiretroviral therapy era in Malawi. *PloS One*. 2016;11(3):e0150445.

Case 42

Presentation

A 33-year-old male patient came to the clinic because of increasing shortness of breath. He had been on ART for two years. His CD4 count had increased, from 88 cells/ μL at baseline to 296 cells/ μL . In the notes in his patient file, there was repeated mention of cough during his time on ART.

The patient looked unwell, sweaty, and was severely tachypnoeic (respiratory rate 40/min, blood pressure 100/60 mm Hg, heart rate 128/min). Jugular venous pressure was raised. His fingers showed the changes pictured below. A CXR was done.



Questions

- 1) What changes are shown in the patient's hands? What is the differential diagnosis?
- 2) Describe the changes shown in the x-ray.
- 3) What are the next steps in investigation and management?

Diagnosis

Pulmonary and pericardial TB

Answers

- 1) Finger clubbing is mainly due to pulmonary causes (TB, emphysema, bronchial carcinoma, among others), but can also be found with cardiac diseases (e.g., congenital cyanotic malformations), liver cirrhosis, and other diseases (thyroid disease, malignancy).
- 2) Hyperinflated lungs with little visible lung structure (suggestive of COPD, also consider overexposure due to poor technique) and fibrotic/infiltrative changes in the right upper lobe (suggestive of TB), massively enlarged heart (possible effusion).
- 3) Given the clinical picture of a very distressed patient, he should be transferred to the hospital for admission. Cardiac ultrasound can be used to confirm the pericardial effusion, and to guide pericardiocentesis in case of confirmed tamponade. TB treatment and adjunctive steroids should be started to reduce the size of the pericardial effusion. Adjunctive steroids may reduce the rate of re-accumulation and the incidence of constrictive pericarditis. (Suggested dose: Prednisone 60 mg daily, tapered over 6–12 weeks.)



Ultrasound showing large pericardial effusion with fibrinous material

Outcome and Follow-up

The patient was transferred to the hospital for further assessment and treatment. In addition to his ART, TB treatment and 60 mg of prednisolone od were given. He was seen in the ward the following day, was taken for an ECHO. A large pericardial effusion was noted; the filling of the right atrium and ventricle seemed impaired. In combination with his vital signs, it was concluded the he had cardiac tamponade; pericardiocentesis was performed using a grey IV cannula. 90 mL of a bloody effusion were aspirated, and sent for TB culture and cytology. The patient felt substantial improvement after the procedure, and was discharged a few days later on RHZE, prednisolone, and ARVs.

Comments

Tuberculosis is the cause of about 90% of HIV-related pericardial effusion, but a lower percentage (50% to 70%) of pericardial effusions in HIV-negative individuals. Adjunctive steroids should be given to patients with tuberculosis pericarditis. Remember when choosing the dose that steroid metabolism is increased when rifampicin is co-administered.

Key Learning Point

Chronic cough should never be overlooked in HIV patients. Even if AFB is negative, further diagnostic steps (CXR) are essential.

Suggested Readings

Heller T, Lessells RJ, Wallrauch C, Brunetti E. TB pericarditis with cardiac tamponade: management in the resource-limited setting. *Am J Trop Med Hyg.* 2010 Dec 6; 83(6):1311–1314.

World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: recommendations for HIV-prevalent and resource-constrained settings. Geneva (Switzerland); World Health Organization; 2007. Available from: http://apps.who.int/iris/bitstream/10665/69463/1/WHO_HTM_TB_2007.379_eng.pdf.

Case 43

Presentation

A 27-year-old woman with a CD4 count of 71 cells/mL presented to the clinic for initiation of ART. She had been on TB treatment for two months. She was unwell, and described three weeks of shortness of breath, chest pain, dry cough, and peripheral edema. She was afebrile; BP was 98/60.

Examination revealed mild peripheral oedema, a galloping heart rhythm, and reduced breath sounds throughout the chest. Her blood results were:

Hb	9.9 g/dL	(normal 11.5–16.5)
WBC	12.2 $10^9/\text{mm}^3$	(normal 4.0–11.0)
Plt	390 $10^9/\text{mm}^3$	(normal 150–500)
Creat	3.2 mg/L	(normal <1.2)
LFTs	normal	



Questions

- 1) What does the CXR show? What other tests would you suggest?
- 2) What are the possible diagnoses? How should this patient be managed?

Diagnosis

HIV-associated cardiomyopathy
Possible HIV-associated nephropathy (HIVAN)

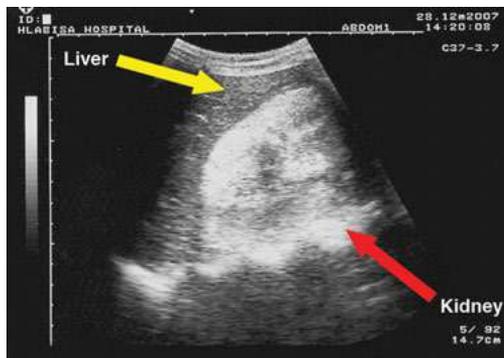
Answers

- 1) Increased cardio-thoracic ratio. Suggest cardiac and renal US, urine dip for protein, BP testing and random blood glucose test.
- 2) Possible diagnoses:
 - a) In adults, cardiomyopathy can be caused by ischaemia, untreated hyperthyroidism, chronic alcohol excess, post-partum CMP, vitamin deficiencies, haemochromatosis, or cardiotoxic drugs; it can also be a consequence of viral myocarditis. With HIV infection, myocarditis can be caused by a number of opportunistic infections, including *Toxoplasma gondii* (although cerebral infection is seen more frequently), or occur in association with other viruses (i.e., Coxsackie, EBV and CMV). In patients with HIV infection, 8% to 12% have some evidence of left ventricular dysfunction; it has been suggested that this is caused by the HIV infection itself. Doxorubicin, used in the treatment of Kaposi's sarcoma, is myotoxic, and can also cause cardiomyopathy.
 - b) This patient could have had renal impairment from hypoperfusion, due either to the reduced left ventricular output, or simply to her advanced HIV. Proteinuria and echogenic kidneys on USS suggest the possibility of HIV-associated nephropathy (HIVAN). A biopsy is required to confirm the diagnosis, but is rarely performed in our setting. HIVAN is a focal segmental glomerulosclerosis. In studies from the USA, it is more common in African-Americans, but there is still limited data regarding its prevalence in Africa. HIVAN includes renal impairment with nephrotic range proteinuria. Usually the serum albumin is reduced; occasionally there is hypertension. It is associated with a CD4 of less than 200 cells/mL. The impact on survival is difficult to assess. Treatment is with ART and ACE-inhibitors.

Outcome and Follow-up

The patient was referred for an ultrasound, which showed left ventricular dilatation with reduced LV function, no pericardial effusion, a normal liver, and echogenic kidneys.

Urine dip displayed protein +++ and no other abnormalities. Blood sugar was 102 mg/dL. Due to the reduced renal function, she was started on AZT/3TC/EFV, avoiding TDF. Additionally, enalapril 10mg bd and furosemide 20mg od were initiated. After one week, her urea and creatinine were unchanged. After four weeks, her creatinine had fallen to 1.5 mg/dL; by two months, it had normalized. A CXR taken after two months was similar, but the patient was symptomatically better, even after reducing the diuretic.



Echogenic kidneys are frequently seen in HIV-positive patients. The significance of this is unclear; in these patients, urea and creatinine are often within normal limits (although we do not routinely measure creatinine clearance or proteinuria).

Key Learning Point

In HIV-related cardiomyopathy and nephropathy, ACE inhibitors, together with ART, are the cornerstone of treatment.

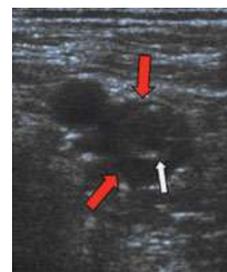
Case 44

Presentation

A 19-year-old female patient was seen in the TB ward (where receiving re-treatment TB therapy) because of swelling in her left leg. She did not complain of either shortness of breath or chest pain. She was HIV-positive; her CD4 count eight months earlier was 120 cells/mL. The patient had not started ART, due to 'problems with her husband and the family'.

On examination, her left leg was swollen to double the size of the right leg, and she was cachectic.

Ultrasound (at right) shows echogenic material in the common femoral vein. On compression ultrasound, the vein is not compressible.



Questions

- 1) What is the most likely diagnosis? What is the differential diagnosis?
- 2) How would you treat the patient? What problems do you expect to encounter?
- 3) As she requires both antiretroviral and anti-tuberculosis treatment, what do you have to consider?

Diagnosis

Deep vein thrombosis of left leg

Answers

1) Venous thrombosis is the most likely diagnosis.

Differential diagnosis:

- Lymphoedema—e.g., due to infiltrating malignancy, like Kaposi sarcoma.
- Elephantiasis due to filarial disease (rare in our area, more common towards Mozambique).

2) Patients with venous thrombosis often need to be admitted to the hospital, as outpatient anticoagulation at the clinic level can be virtually impossible. Weight-adapted low-molecular weight heparin would be the most preferred initial treatment option, as it does not require monitoring of the APTT. Unfortunately, this option is often not available; as an alternative, 10 000 units normal heparin tds s.c. can be used. Sequentially, anticoagulation with warfarin should be started, but further monitoring of INR may be difficult or impossible (see below).

3) Drug interactions need to be considered when treating patients for concomitant TB or HIV. Rifampicin is an inducer of hepatic enzymes, and may lead to suboptimal levels of anticoagulation. NVP and EFV have unpredictable effects; both have been reported to decrease warfarin levels—but have also been known to increase levels, thus risking haemorrhage. The amount of warfarin needed for the individual patient needs to be determined by INR monitoring. INR monitoring using a point-of-care Coagulocheck is possible at Lighthouse for these patients (exceptions).

Outcome and Follow-up

The patient was started on anticoagulant therapy, i.e. heparin tds. Abdominal ultrasound showed enlarged abdominal lymph nodes and free fluid, making the diagnosis of abdominal TB highly likely. The patient continued SRHZE. After finishing the intensive phase of her TB treatment (two months), her leg looked completely normal; considering the difficulties of INR monitoring and the associated risks, anticoagulation was terminated.

Comments

The incidence of venous thrombosis is increased two- to ten-fold in HIV patients, compared to HIV-negative individuals of the same age. Advanced disease is associated with a further increase in the incidence of thrombotic events.

The higher risk could be explained by the presence of a hypercoagulable state, characterised by an increase in pro-coagulant factors, endothelial tissue factor expression, and thrombogenic properties of microparticles. In HIV patients, microparticles originate from CD4+ lymphocytes, as a direct consequence of HIV infection, and possibly as a reflection of CD4+ lymphocyte apoptosis. A decrease in anticoagulant factors, including antithrombin III and the protein C pathway, might add to the pathophysiology.

Key Learning Point

Caution is advised when administering anticoagulant therapy, as there are many drug interactions, and INR monitoring is difficult in this setting.

Suggested Reading

Klein SK, Slim EJ, de Kruijff MD, Keller TT, ten Cate H, van Gorp EC, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. *Neth J Med.* 2005 Apr;63(4):129–136.

Case 45

Presentation

A 32-year-old HIV-positive female patient was admitted because of progressive weakness, loss of weight and loss of appetite. Her CD4 count was 46 cells/mL. It was noted that she was constantly spitting saliva into a tissue, and that she was drooling. The patient reported a painful ulcer of the lip, and another one on the back of her tongue. She also reported severe chest pain whilst swallowing; this was why she let the saliva drop from her mouth.



(Courtesy of Dr Dediccoat, Ngwelezane Hospital)

Questions

- 1) What are the most common causes of mouth ulcers in HIV patients?
- 2) How would you explain the patient's pain while swallowing?
- 3) How would you treat this patient?

Diagnosis

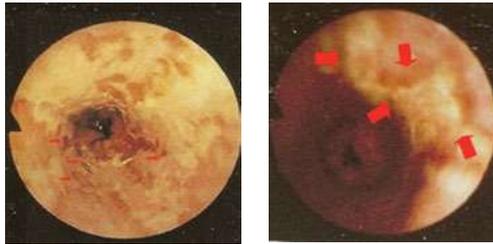
Herpes simplex mouth ulcer and oesophagitis

Answers

- 1) Herpes simplex virus causes ulcers in the mouths of HIV patients; they are more severe and recur more frequently than in non-HIV patients. Differential diagnoses are recurrent aphthous ulcers, which can be single or multiple, small or large, and are usually deeper and better defined than the herpetic lesions. Both are associated with pain. Diagnosis can be attempted by biopsy.
- 2) Oesophagitis can occur frequently in HIV patients. When associated with ulcerations, (if an oesophagoscopy is performed, rarely indicated in our setting) HSV and CMV infections are the most commonly observed causes. Aphthous ulceration can also affect the oesophagus.
- 3) Acyclovir is the treatment of choice for ulcers associated with HSV. Recurrent aphthous ulcers are more difficult to treat. Antiseptic mouthwash (chlorhexidine 0.2% or polyvidone-iodine 1%) might be helpful. Local steroids (in form of a cream, or as puffs from an inhaler) can be used. It is recommended to treat first with acyclovir to rule out HSV infection, as this can be exacerbated by steroid use.

Outcome and Follow-up

The patient received acyclovir 400 mg tds po. Her chest pain quickly improved; over the course of two weeks, the ulcerations on her tongue and lip improved as well. The patient was discharged to the clinic, and ART initiated.



Herpes oesophagitis usually presents with multiple smaller ulcers, whereas CMV causes larger, and even circumferential, ulcers. Differential diagnosis is difficult, but can be made through biopsy.

Key Learning Point

Acyclovir is indicated if there are severe mucosal ulcers, particularly if there are symptoms of more extensive GI tract involvement.

Case 46

Presentation

A 42-year-old man was brought to the OPD by his relatives late in the afternoon. They reported that he had been acting strangely all day, staring into space and not talking since morning. In addition, they had observed intermittent episodes of left hand rhythmic movements and facial twitching; these had increased in both frequency and duration during the course of the day. His HIV status was unknown.

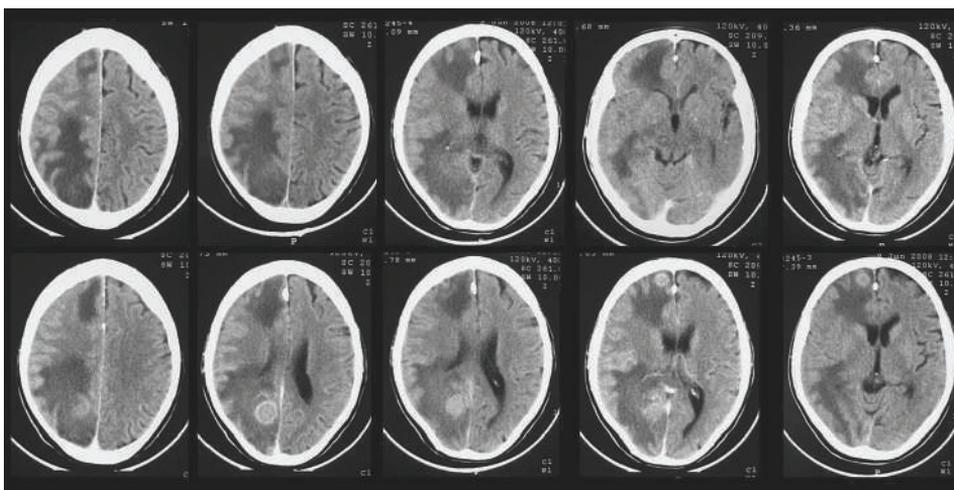
On examination, he had persistent left upper limb and facial seizure activity, and did not appear to be aware of his surroundings. He had nuchal rigidity, but was afebrile and haemodynamically stable. The remainder of his physical examination was unremarkable. His blood sugar was normal.

A diagnosis of focal status epilepticus was made; three separate doses of 10 mg diazepam were administered without resolution of his seizure activity. A loading dose of phenytoin was given, and regular doses prescribed.

Additionally, he was commenced on ceftriaxone, high-dose cotrimoxazole, and fluconazole. A lumbar puncture was performed.

CSF-polymorphs	0 cells/mL	(normal <5)
CSF-lymphocytes	8 cells/mL	(normal <5)
CSF-protein	1.13 g/L	(normal 0.15–0.4)
CSF-glucose	46.5 mg/dL	(normal 50–75)
Crypto Ag and India ink	negative	(normal negative)

An HIV test was positive; a CT scan was done a few days later.



CT: First row—without contrast; second row—corresponding images with contrast

Questions

- 1) What are the most likely diagnoses to be considered for altered mental status or neurological abnormalities in an HIV-infected individual?
- 2) What tests facilitate more specific diagnosis?
- 3) What is the treatment?

Diagnosis

Cerebral toxoplasmosis

Answers

1) The differential diagnoses for altered mental status or neurological abnormalities in an HIV-infected patient are determined by the degree of immunosuppression.

In cases of more advanced disease, opportunistic infections (cryptococcal, TB, and toxoplasmosis), primary CNS lymphomas, progressive multifocal leukoencephalopathy, HIV-related encephalitis, and other viral encephalitides (HSV, VZV, CMV) are the most likely diagnoses.

At higher CD4 counts, the differential is the same as for immunocompetent people, and includes bacterial meningitis and tumours. Bacterial meningitis seems to be exceedingly rare in our area, but empiric treatment is considered good practice. Neurocysticercosis is also a possibility in our population, but it is not necessarily associated with HIV infection.

2) CSF findings in cerebral toxoplasmosis are non-specific, and may include a mild mononuclear pleocytosis and elevated protein. Radiographic assessment is essential. Toxoplasmosis lesions are generally multiple, and tend to develop in the parietal or frontal lobes, in the thalamus or basal ganglia, or at the cortico-medullary junction. Most lesions (90%) enhance with contrast; surrounding oedema with mass effect is often seen, and can result in tonsillar herniation. Serum IgG antibodies are usually positive, but testing is not available in our setting.

3) High-dose CTX (4 tabs bd) for 28 days, followed by three months of 2 tabs bd. Patients usually respond to treatment within 10 days; empirical treatment can be attempted, and CT exams reserved for patients not responding. If CTX is not tolerated, pyrimethamine (200 mg loading dose po followed by 75 mg/day) plus clindamycin (600 to 1200 mg iv or 450 mg po four times a day) may be given, if available.

Outcome and Follow-up

The patient was transferred to the high-care unit. The following day, he was alert, with a GCS of 15; he requested discharge, but he was kept in the ward. He remained stable, and subsequently had a CT scan. The scan showed two round ring-enhancing lesions in the right parietal and frontal lobes, with marked associated oedema. The presumed diagnosis was toxoplasmosis, although tuberculomas remain a possibility. Other possible causes are pyogenic abscesses (e.g., staphylococci, streptococci, nocardia).

Key Learning Point

In a resource-limited setting, a trial of treatment prior to imaging is acceptable in cases of suspected toxoplasmosis.

Case 47

Presentation

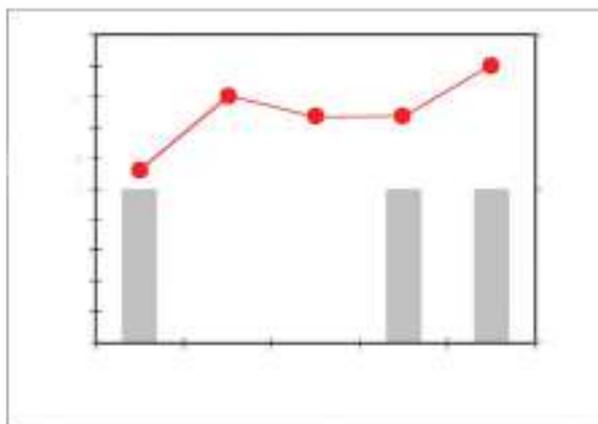
A 36-year-old woman was referred with profound anaemia. She was HIV positive, and had commenced ART three months previously. She was taking TDF/3TC/EFV and CTX. The patient complained of a severe frontal and occipital headache, which had commenced two weeks prior to admission. She was comfortable at rest, but became profoundly short of breath on exertion. In addition, she described visual field disturbances on exertion, including wavy lines and scotomata.

On examination she was tachycardic, HR 110/min. She had marked pallor. Physical examination was otherwise normal.

The following values were found in her FBC:

Hb	2.8 g/dL	(normal 11.5–16.5)
MCV	96 fL	(normal 76–96)
MCH	31 pg	(normal 27–32)
WBC	12.2 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	308 $10^3/\text{mm}^3$	(normal 150–500)

The course of her Hb over the next two weeks with transfusions is shown in the graph below.



Questions

- 1) What is the aetiology of anaemia in HIV patients in our area?
- 2) Which investigations/tests could be done?
- 3) How is parvovirus B19 infection diagnosed and treated?

Diagnosis

Severe anaemia of chronic disease, possibly aggravated by myelotoxicity.

Answers

1) Microcytic, hypochromic anaemia

- Iron deficiency (e.g., due to chronic blood loss, nutritional, parasites)
- Anaemia of chronic disease (see below; in these cases, continuous iron supplementation is useless, and may even have negative effects!)
- Sideroblastic anaemia (mainly caused by INH in the absence of Vitamin B6)

Normocytic, normochromic anaemia

- Anaemia of chronic disease
 - Secondary to disseminated infections (TB, MAC, PCP, CMV, EBV, schistosomiasis)
 - Secondary to malignancies (lymphoma, KS)
 - Secondary to HIV infection itself
- Haemolytic anaemia (malaria, autoimmune haemolytic anemia due to drugs or infection)
- Microangiopathic anaemia (thrombotic thrombocytopenia purpura-TTP and haemolytic uremic syndrome-HUS). (Inherited haemolytic anaemias, such as sickle-cell anaemia and thalassaemia, are not prevalent in our area. Glucose-6-phosphate deficiency is also not common.)
- Marrow toxicities (e.g., CTX, beta-lactams)
- Aplastic anaemia (e.g., due to parvovirus B19 infection)
- Pure red cell aplasia (rare, but reported with 3TC use)

Macrocytic, hyperchromic anaemia

- Vitamin B12 and folate deficiency—due to parasitic infections with *G. lamblia*, strongyloides, but also due to increased cell turnover (e.g., HIV-induced T-cell destruction) or resorption disturbances (e.g., ileocaecal TB)
- Marrow toxicities (e.g., alcohol, AZT)

2) These investigations/tests could be done:

- Drug history.
- Lab tests, including where appropriate: Malaria rapid diagnostic test (MRDT), FBC, and peripheral blood film. Vitamin B12, folate, iron, ferritin would be desirable, but are often not available.
- Faecal occult blood test, parvovirus B19 serology would be further tests needed.

If all these investigations provide no explanation, it is advisable to contact the haematology department to do a bone marrow aspiration. If a bone marrow aspiration is done, additional material for parvovirus B19 PCR and mycobacterial culture could be considered.

Available imaging studies will include a CXR and ultrasound.

3) Diagnosis of parvovirus infection in HIV infection is likely to be missed if only serology is relied upon. Diagnosis depends on detection of viral DNA by PCR in the serum or bone marrow. Treatment: stat dose of IV immunoglobulin 1 g/kg, to which improvement is seen promptly (within days).

Outcome and Follow-up

The CTX was ceased. Serum was sent for parvovirus B19 serology, which was negative. Iron studies showed elevated ferritin and reduced iron, so iron supplements were discontinued. Vitamin B12 and folate levels were normal. The patient received transfusions over the following two weeks, and her ART was continued. She left the hospital before a bone-marrow examination could be done, and was subsequently lost to follow-up.

Key Learning Point

Anaemia of chronic disease is characterized by low iron and raised ferritin, and is unresponsive to iron supplementation.

Case 48

Presentation

A 35-year-old female patient was seen at the clinic, where she reported that she was feeling weak and tired, and that this was associated with nausea and vomiting for the past four weeks. She also endorsed painful swallowing. On examination, the patient had severe oral candidiasis. On reviewing her file, it was found that she started ART four years ago, and was undergoing TB treatment at the time of ART initiation.

Her file contained many CD4 count and viral load results collected during her treatment (some as part of studies, not conducted at national guideline milestones).

The results over time were:

Months on ART	0	9	15	24	38 (2 months ago)
CD4	98	159	161	18	66
VL	530 000	950	No result	8 000	50 000

Questions

- 1) What do these results and the patient's clinical history indicate?
- 2) What should be done for this patient?

Diagnosis

Clinical, immunological, and virological treatment failure, with probable resistant virus.

Answers

1+2) The course of the results suggests the above-mentioned diagnosis. Current opportunistic infections should be treated (she likely has oesophageal candidiasis, treated with two weeks of oral fluconazole 200 mg). Step-up adherence counselling should be initiated, and second-line ART (AZT/3TC/ATV/r) given.

Outcome and Follow-up

This patient was treated for oesophageal candidiasis, which also reduced the vomiting. She started second-line treatment; after three months, she had a suppressed viral load (<40 copies/mL).

Comments

Treatment failure is defined as failure to suppress viral load to undetectable levels despite adequate levels of antiretroviral drugs in the blood. This must be carefully differentiated from poor compliance, in which there is a detectable viral load because the patient takes the treatment either intermittently or not at all. Other explanations can include vomiting of the drugs, poor absorption because of diarrhoea or other gut pathology, or interference with metabolism due to other concurrent medication.

Treatment failure can be identified in one of three ways (although not all of these are definite indicators of failure):

- **Virological:** Detectable viral load on ART (with adequate adherence)
- **Immunological:** CD4 drops to pre-ART level or lower (drop of 30% or more)
- **Clinical:** Progression of disease, with development of OI or malignancy occurring three or more months after initiation of ART

The national ART guidelines on testing of viral loads, and identification of those who should be switched to second-line therapy are as follows:

- **VL result (any) = 0–999:** Successful ART; continue first-line ART.
- **VL result (routine) = 1 000+:** potential failure. Intensive adherence counselling and support; repeat VL when good adherence (in 1–3 months).
- **VL result (repeat or targeted) = 1000+:** Confirmed failure; start second-line ART.

The milestones at which VL should be taken are six months, 24 months, and then every 24 months thereafter, following initiation of ART. Many patients are seen between milestones, and often do not have any VL result recorded. In these cases, use clinical judgement and discretion; take a VL even if between milestones. If any suppressed result is recorded in the file, the patient feels well, and there is less of an urge to ‘catch up’, then waiting may be indicated. If the patient reports feeling ‘not well’, the threshold for a targeted VL should be low.

HIV produces 10 billion copies of itself per day in untreated individuals. The replication process is prone to errors; mutated virions are produced continually. If viral replication is allowed to continue in the presence of fluctuating drug levels, or levels not high enough to suppress active replication, resistance will be selected. Development of resistance to some drugs is relatively quick—for example, resistance to NNRTIs requires only one mutation. Adherence to lifelong antiretrovirals is difficult; poor adherence is often not recognised or acted upon. Support and information for patients, their relatives, and the staff looking after them is an essential part of improving adherence and preventing the development of drug resistance.

Key Learning Point

Laboratory monitoring is important: detectable viral load in a patient on ART needs to be acted upon.

Case 49

Presentation

A 43-year-old man presented to the hospital with a few days of blistering rash, which began on his face, then spread to his torso, arms, and legs. The rash was neither painful nor pruritic. However, he did report painful eyes with discharge. The patient was HIV positive, and on ART and CPT. Four months prior to presentation, he had been diagnosed with TB on clinical grounds, and was started on RHZE. The patient was on no other medications, and denied taking any traditional remedies/medicines.



Questions

- 1) What are the possible diagnoses?
- 2) What are the common causes of this condition?
- 3) How should this patient be managed?
- 4) What are the likely complications of this condition?

Diagnosis

Stevens-Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN)

Answers

- 1) This is most probably a skin reaction to the drugs, where apoptosis of keratinocytes results in exfoliation of the skin. SJS and TEN are characterized and categorized as follows:

	SJS	SJS/TEN	TEN
Primary lesions	Purple-red lesions Flat/mildly papular Atypical target lesions	Purple-red lesions Flat/mildly papular Atypical target lesions	Widespread erythema, and exfoliation of the skin
Distribution	Isolated lesions Confluating (+) Face and chest	Isolated lesions Confluating (++) Face and chest	Isolated lesions Confluating (+++) Generalized
Mucous membranes	Involved	Involved	Involved
Systemic symptoms	Often	Always	Always
Affected body surface area	<10%	10–30%	>30%

- 2) The most common causes of drug rashes are CTX, penicillin, anti-TB drugs, and ART (especially NNRTIs [NVP, EFV], but also ABC). Non-steroidal analgesics and antiepileptic drugs should also be considered as possible causes. Most cases occur within the first two months of therapy.
- 3) Stop all medications!! Manage fluids carefully: Oral fluid replacement is preferable, if possible, as it prevents adhesions in the oropharynx. Consider eye care with ointments and saline eye-washes. Analgesia should be provided before daily bathing and dressing changes (non-stick dressings, or dressing towels and soft barrier cream, soaking off in a bath). Antibiotics are not used prophylactically, but when signs of infection appear. Mucous membrane involvement can result in gastrointestinal haemorrhage, respiratory failure, ocular abnormalities and blindness, and genitourinary complications. Routine steroid use is not recommended, but is often tried empirically.
- 4) The most serious complication is sepsis—facilitated by the loss of the skin's protective barrier function. Involvement of the digestive tract, including oropharyngeal and oesophageal sloughing, as well as ocular complications, does occur. Mortality of SJS/TEN is high (25–35%).



Oral mucosal involvement in SJS due to anti-TB drugs (different patient)

Outcome and Follow-up

The patient was managed in the ward, and recovered slowly. He later continued ART (TDF/3TC/EFV), but prophylactic CPT was not given, as it was the most likely cause of his skin condition. A decision was made also not to restart the TB therapy, as it was felt that the risks of a possible repeated reaction out-weighed the benefits of treating a TB infection, which was diagnosed on soft clinical indicators.

The patient was discharged three weeks later, with follow-up to take place in the clinic. He did not develop further skin changes or TB symptoms.

Comments

Drug reactions—particularly to TB drugs—are far more common in HIV-infected patients than in the general population. In some cases (esp. with NVP), hepatic involvement with deranged LFTs is seen. In non-severe cases, the offending drug can sometimes be maintained (not in TEN and SJS!!). The underlying immune mechanisms of the allergic-type reaction are unknown. HIV-infected patients have been noted to have elevated IgE levels, which increase as CD4 counts decrease. Anaphylactic reactions are rare.

Key Learning Point

Cutaneous drug reactions are very common. In this setting, CTX is the most common cause, followed by TB drugs, and ART.

Case 50

Presentation

A 36-year-old man presented to the clinic, unable to walk. He had started ART recently, and generally tolerated the drugs well. His guardians reported that he was intermittently confused, and increasingly forgetful. A lumbar puncture was performed to rule out meningitis; this showed no abnormality. Given the possibility that toxoplasmosis might be the cause for the neurological changes, a CT brain scan was requested, but the CT images showed no focal abnormalities. The patient was nevertheless started on high dose CTX, with a few days of steroids added (under the assumption of a vasculitis). Initially, the patient improved, and was able to walk again, but his memory disturbances increased. Additionally, psychomotor slowing (impairment) and mild apathy were noted during subsequent visits.

Questions

- 1) What could be the diagnosis of neuropsychiatric changes in an HIV patient?
- 2) How do you screen or test for psychomotor slowing and other abnormalities?

Diagnosis

HIV-associated neurocognitive disorder (HAND)

Answers

- 1) This patient most likely suffers from HAND. HAND presents with a relatively characteristic sub-cortical deficit pattern, including psychomotor slowing; impaired memory, attention, and language; and behavioural apathy. Based on the extent of the neurological and functional impairments, HAND can be categorised into nd HIV-dementia (HIV-D).
- 2) There is no globally accepted screening policy or practice for HAND-associated disorders. A widely used and validated (in South Africa) tool is the International HIV Dementia Scale (IHDS):

International HIV Dementia Scale	
Memory-Registration—Give four words to recall (dog, hat, bean, red)—1 second to say each. Then ask the patient all four words after you have said them. Repeat the words if the patient does not recall them all immediately. Tell the patient that you will ask him later for the words.	
1. Motor Speed: Have the patient tap the first 2 fingers of the non-dominant hand as widely and as quickly as possible.	
≥15x in 5 seconds	4 points
11–14x in 5 seconds	3 points
7–10x in 5 seconds	2 points
3–6x in 5 seconds	1 point
0–2x in 5 seconds	0 points
2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible:	
1) Clench the hand in fist on table	
2) Put hand flat on the table with palm down	
3) Put hand perpendicular to flat surface on the side of the 5th digit.	
Demonstrate and have the patient perform twice for practice.	
4 sequences in 10 seconds	4 points
3 sequences in 10 seconds	3 points
2 sequences in 10 seconds	2 points
1 sequence in 10 seconds	1 point
Unable to perform	0 points
3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a clue, as follows: animal (dog), piece of clothing (hat), vegetable (bean), colour (red):	
1 point for each word recalled	
0.5 points for each word recalled after prompting	
Total Score: _____	
If the total score is ≤10, consider HIV dementia; repeat the test after the patient has received six months of therapy.	

Outcome and Follow-up

The patient stabilised, and was seen regularly afterwards. According to his wife, he was able to drive a car (as he has been a driver all his life), but had difficulties adjusting to new situations and remembering new things. As a result, he was heavily dependent on his wife.

Comments

The incidence of HIV-D in untreated HIV patients is 35/1 000 person years; in patients receiving ART, it falls to 3/1 000 person years. The key to treatment is the initiation of ART. Adjusting the ARV regimen to enhance CNS penetration is not recommended, as the evidence in this regard is conflicting. Therefore, standard regimens are used. It is important to engage the family/partner for treatment support, and to diagnose and treat confounding conditions (depression, alcohol abuse, head injury, epilepsy, nutritional deficiency, CNS OI, and neurosyphilis). Receiving ART usually mitigates the course of disease. Mild forms often persist during ART; these can have significant effects on functional outcomes—e.g., poor adherence, unemployment.

One differential diagnosis is progressive multifocal leukoencephalopathy (PML), a central nervous system infection with the papova (JC) virus, which causes demyelination of the white matter

of the brain. PML presents with rapid evolution over weeks or months, with altered mental state, visual defects, motor weakness, speech dysfunction, sensory deficits, and cerebellar disorders. Because there is no mass effect in the brain, symptoms of headache, vomiting, and impaired consciousness are rare. Prognosis is also very poor, although there may be some temporary relief with antiretroviral therapy. Diagnosis is supported by CT revealing asymmetric focal zones of low attenuation that involve the periventricular and subcortical white matter. This appearance is a differential diagnostic feature, compared with the typically more symmetric areas of low attenuation seen in patients with HIV encephalopathy.

Key Learning Point

Without screening, many patients with gradual neurodegenerative changes go undiagnosed, due to infrequent self-reporting.

Suggested Reading

Jonsson G, Davies N, Freeman C, Joska J, Pahad S, Thom R, et al. Management of mental health disorders in HIV-positive patients by the Southern African HIV Clinicians Society. *S Afr J HIV Med.* 2013;14(4):155–165.

Notes

Case 51

Presentation

A 28-year-old female patient was seen to initiate ART. She looked slightly malnourished (BMI 19.1), but was otherwise fine, and reported no TB symptoms. A CD4 count was done, and found to be very low (8 cells/mm³). A serum CrAg test came back positive; a urine-LAM test was negative. Upon questioning, she reported no headache or other neurological symptoms. A lumbar puncture showed normal cells and protein; the CSF-CrAg and India ink tests were both negative.



Questions

- 1) What type of CrAg test is shown? What is the result?
- 2) With a positive CrAg in Serum, but not in the CS, how should this patient be treated?
- 3) Below what level of CD4 count are patients at higher risk? How does this affect your diagnostic strategy?
- 4) Which prophylaxis could be given to this patient population?
- 5) Which other disease do you want to consider in patients with very low CD4 counts?

Diagnosis

Cryptococemia without meningitis

Answers

- 1) A lateral flow assay (strip test) for cryptococcal antigen, which can be used with both serum and CSF. The result is positive, as two lines are visible.
- 2) Fluconazole 800 mg od for two weeks, then 400 mg od for eight weeks. After that, secondary prophylaxis of 200 mg od should be given. Discontinuation of anti-fungal prophylaxis is recommended when the patient is stable and adherent to ART and anti-fungal maintenance treatment for at least one year, has a CD4 cell count of ≥ 100 cells/mm³, and shows a suppressed viral load.
- 3) Patients with CD4 below 200 cells/mm³ (and esp. below 100 cells/mm³) are at higher risk of opportunistic infections (e.g., PCP, cryptococcosis, disseminated TB, Mycobacteria other than TB (MOTT), toxoplasmosis, and CMV infections). In this patient group (<100 cells/mm³), routine serum or plasma CrAg screening, followed by pre-emptive anti-fungal therapy if CrAg-positive, may be considered prior to ART initiation in areas where the population also has a high prevalence of cryptococcal disease (like Malawi). Also, screening for disseminated TB using urine-LAM is both feasible and more effective in these patients.
- 4) Other possible prophylaxis, in addition to CPT, could include albendazole, azithromycin, fluconazole, and INH (see comment).
- 5) CMV retinitis should be considered, especially if a clinician experienced in fundoscopy (through dilated pupil) is available, and treatment (e.g., gancyclovir i.o.) can be provided.

Outcome and Follow-up

The patient was treated with fluconazole 800 mg od for two weeks, followed by fluconazole 400 mg od for eight weeks. After that, prophylaxis of 200 mg od was given. Once cryptococcal meningitis was ruled out, ART was started immediately.

A FASH ultrasound was done; it showed no sign of EPTB. Because the patient was not coughing, a CXR was not done. It was felt that TB could be ruled out clinically (as much as possible); she was started on INH 300/Vit B6 25 mg for three months.

In addition, the patient was given a single dose of albendazole 400 mg, azithromycin 500 mg for three days, and CPT. She did not qualify for therapeutic feeding, and did not show lesions suggestive of KS; nor did she report vision problems (e.g., visual field defect, flashes, floaters, blurred vision, eye pain or redness, or photophobia), which could have suggested CMV retinitis.

Comments

The REALITY trial conducted in Malawi, Zimbabwe, Uganda, and Kenya showed that giving people with a CD4 count of <100 an enhanced prophylaxis package for the first 12 weeks of ART reduces mortality at 24 weeks by 3.3% (absolute difference)—representing a 27% relative reduction in mortality compared to ART with standard cotrimoxazole prophylaxis. The enhanced package consisted of (at least) 12 weeks of isoniazid/pyridoxine, 12 weeks of fluconazole, five days of azithromycin, and a single dose of albendazole.

Key Learning Point

Mortality is high among patients with low CD4 counts, as they are prone to many opportunistic infections. They need extra attention and vigilance!

Suggested Reading

REALITY trial finds way to reduce deaths among people starting HIV treatment late. MRC Clinical Trials Unit at University College London. 2016 Jul 22. Available from: http://www.ctu.mrc.ac.uk/news/2016/realty_trial_results.

Case 52

Presentation

A 48-year-old male patient was seen in the clinic, complaining of dizziness. He had been taking ART for about nine months. The patient initially started with TDF/3TC/EFV; although he did not report other findings typical of EFV toxicity, the EFV was changed to NEV after three months because of the dizziness. The switch did not improve the symptoms. As it was felt that there could be a cerebellar problem, a CT of the brain was done a month ago, and was reported normal.

Upon neurological examination, the patient's strength and sensation were normal, but his gait was slow, broad-based, and slightly uncoordinated. The finger-nose test was normal; dysdiadochokinesis was not observed. Cranial nerves were normal. Lower limb reflexes were reduced, and heel-shin coordination disturbed.

A VDRL in serum was ordered; it was found to be reactive.

Questions

- 1) What causes syphilis? What are the clinical stages of the disease?
- 2) How do you diagnose neurosyphilis in the laboratory? How do you balance diagnostic and therapeutic measures in a resource-limited setting?

Diagnosis

Neurosyphilis with dizziness and gait abnormality

Answers

1) Syphilis is caused by the gram-negative spirochetes *Treponema pallidum*. The disease is characterized by different stages:

Primary syphilis: Painless ulcer on the genitals (rarely on the mouth, hands, or anus)

Secondary syphilis: One to six months later, a slightly itchy maculopapular rash develops on the trunk and limbs, particularly the palms and soles. Other constitutional symptoms, aseptic meningitis, lymphadenopathy, arthritis, and a wide range of unspecific symptoms may also be seen.



Latent stage: Spontaneous resolution of the symptoms occurs, but many patients experience intermittent recrudescence of the disease.

Tertiary syphilis:

- Cardiovascular syphilis is characterized by arteritis with aortic dilatation, aneurysm, and aortic valve regurgitation.
 - Typical neurosyphilis has two forms: a) general paresis of the insane with confusion, hallucinations, and cognitive decline; and b) tabes dorsalis, presenting with ataxia, sensory loss, and shooting pains.
- 2) The proper diagnosis of neurosyphilis is made through CSF analysis, which would show mild mononuclear pleocytosis and elevated protein. A positive VDRL in CSF is specific, but not sensitive; the CSF FTA-ABS is sensitive, but not specific. Ideally, local antibody production is shown through a serological comparison of titers in serum and CSF.

In our setting, only the VDRL in serum is available. A suggestive clinical picture with a positive VDRL in serum merits treatment. Neurosyphilis is best treated with procain penicillin 2.4 MU od im plus probencid 500 mg od po for 10–14 days. Alternatively, ceftriaxone 2 g im for 10–14 days can be given. Other forms of syphilis are treated with benzathine penicillin 2.4 MU od im stat.

Outcome and Follow-up

The patient was treated with ceftriaxone 2 g im for 10 days. His dizziness improved slightly, but the rest of his symptoms persisted.

Comments

Both HIV and syphilis are sexually transmitted; co-infection is common. HIV co-infected syphilis patients more frequently have features of secondary syphilis, such as rash, fever, adenopathy, headache, or meningismus. In CSF, higher mean white blood cell counts, higher mean protein levels, and lower mean glucose levels are often seen. Syphilitic meningitis seems more common in HIV-seropositive patients. Immune reconstitution syndrome has rarely been reported in the context of syphilis infection, but exists.

Suggested Reading

Katz DA, Berger JR, Duncan RC. Neurosyphilis: a comparative study of the effects of infection with human immunodeficiency virus. *Arch Neurol.* 1993;50(3):243–249.

Key Learning Point

In case of unclear neurological or dermatological presentations, always ask yourself: *Could this be syphilis? Should I do a VDRL?* Syphilis is also known as the ‘great pretender’, as it has a plethora of symptoms, and thus is frequently missed.

Case 53

Presentation

A 21-year-old HIV-positive female patient came to the clinic to start ART (CD4 count 112 cells/mm³). She complained about a disfiguring, non-itching rash, mainly affecting her face; otherwise, the patient had no complaints.



Questions

- 1) What is the diagnosis? What is the cause? How can it be treated?
- 2) Should ART be started?

Diagnosis

Extensive molluscum contagiosum

Answers

- 1) Molluscum contagiosum is caused by a relatively harmless poxvirus (molluscum contagiosum virus, or MCV). It is commonly found with low CD4 cell counts (<200 cells/mm³). Infection is benign, and recovery usually spontaneous. Treatment may be sought for cosmetic reasons, particularly for multiple facial lesions. Various treatments have been tried. Local curettage is possible if a limited number of lesions are present. Chemical treatments include podophyllin, but irritation is a common adverse effect of this method. Topical application of an antiviral medication, such as 3% cidofovir cream or suspension, has been reported to be beneficial, but is not available in our setting. For HIV patients with molluscum, the use of ART, with consequently improved CD4 cell counts, was found to be effective.
- 2) ART should definitely be started.

Outcome and Follow-up

The patient started ART; because of the number of lesions, no local treatment was attempted. She improved spontaneously; when seen six months later, the lesions had disappeared.

Comments

Molluscum contagiosum is a disease that causes a benign, self-limited skin ‘tumour’ or papular lesions. It occurs worldwide, and is most often seen in children. The clinical appearance of the indented lesions is generally sufficiently characteristic to permit clinical diagnosis. In HIV-positive patients with disseminated cryptococcosis, similar umbilicated lesions are seen, and should lead to active treatment. When in doubt, a serum-CrAg test can help with this differential diagnosis.

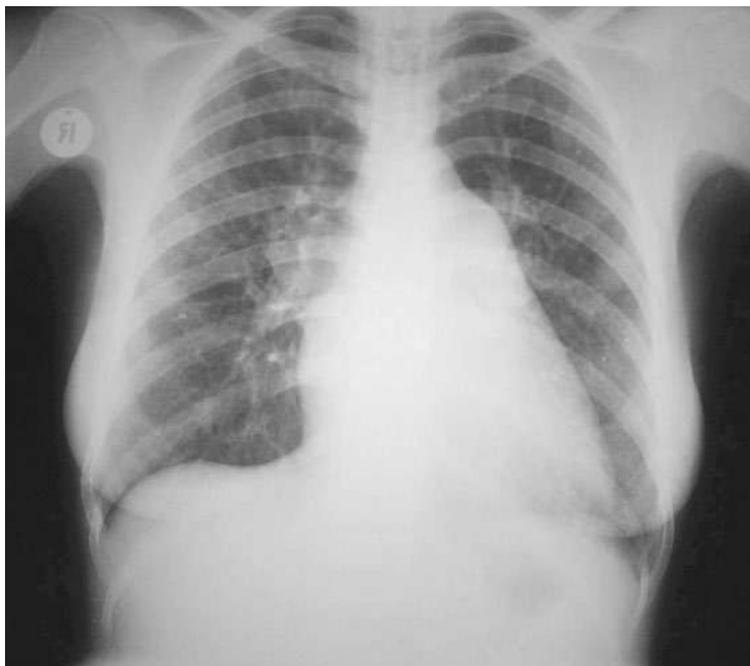
Key Learning Point

Molluscum contagiosum—like many HIV-related conditions—is best treated by restoring the patient’s immune system.

Case 54

Presentation

A 28-year-old HIV-positive female patient was seen at the clinic for ART initiation (her CD4 was 132 cells/mm³). She complained about mild dyspnea and intermittent cough, but no weight loss or night sweats. Clinically, she had no other symptoms suggesting any opportunistic infections, but she had a faint diastolic murmur, her blood pressure was 120/74 mm Hg, pulse 96/min, and she was arrhythmic. No peripheral cyanosis was visible. A CXR was ordered. As the heart shadow was found to be abnormal, the patient was referred for further tests.



Questions

- 1) What can be seen on the CXR?
- 2) What is the underlying condition? What is the most likely cause?
- 3) How should she be examined and treated?

Diagnosis

Post-rheumatic mitral valve stenosis/regurgitation

Answers

- 1) Enlarged cardiac shadow; abnormal silhouette, suggesting enlargement of the left atrium, and possibly the pulmonalis segment; congested vasculature in the lung (see the upper fields).
- 2) Rheumatic changes of the mitral valve are by far the most likely cause. The underlying pathology is that, after a throat infection with *Streptococcus pyogenes*, an immune reaction develops that attacks endo-, myo- and pericardial structures and joints in addition to the bacteria itself. Due to the (chronic) inflammation of the valves, especially at the line of closure, these become fibrosed and tethered. Consequently, the valves become rigid (incompetent) and stenotic.
- 3) The patient should be referred for echocardiography or ultrasound of the heart. In mitral stenosis, the left atrium is often grossly dilated; the left ventricle is small, with normal contractility. The valve can also appear to be 'doming'. Due to the congestion in the lung, the right side of the heart (ventricle and atrium) enlarges. Sometimes left atrial thrombi can be seen. Medical treatment is the secondary prevention of recurrent *S. pyogenes* infection with penicillin 1.2 MU i.m. monthly for 10 years, or up to age 40. Symptoms of cardiac failure can be treated with diuretics. The heart rate should be controlled (up to digoxin 0.25 mg/day), especially once tachycardic ventricular fibrillation is present.



Black and white ultrasound of the heart showing an enlarged left atrium and a 'dome-like' appearance of the mitral valve leaflets

Outcome and Follow-up

The patient was started on ART. Additionally, she received furosemide 40 mg od and spironolactone 25 mg od, which improved both her postural coughing and the dyspnea. Because of her arrhythmia, which was tachycardic, she also received digoxin 0.25 mg od to control the heart rate. The patient tolerated the medication well, and reported feeling better.

Comments

Patients with mitral stenosis are at risk for formation of intra-atrial thrombi when atrial fibrillation ensues, and then of a peripheral embolism, with the most devastating consequence being a stroke. Anticoagulation could be considered, but, in practical terms, is often difficult to manage. The definitive therapeutic approach is surgical correction of the underlying anatomical changes, either by valve replacement, or by valvuloplasty (both not widely available in our setting, and therefore very rarely done in our patients).

The cardiac disease does not influence ART, which should be started as with any other patient. The treatment (e.g., im penicillin) can be incorporated into the patient's ART clinic visits.

Key Learning Point

Not every chronic cough is TB—cardiac causes need to be considered, especially when the cough presents after lying down.

Case 55

Presentation

A 36-year-old woman was seen at the clinic. The patient had been on ART for four years (d4T/3TC/EFV at first, then TDF/3TC/EFV), initially with very good success. However, during the last year, she was deteriorating clinically: She was found to have chronic anemia (Hb \leq 7.0 g/dL), and initially received iron. She was admitted to hospital twice during the last three months for severe anemia; the first time, she received one unit of blood, Fe, and ampicillin. On the second admission, four units were transfused. On this visit, her CD4 count was 17 cells/mm³; a VL sample was taken and sent to the lab.

In addition, the patient complained of significant weight loss (>8 kg); her weight at this visit was 42 kg. Her CXR did not show anything remarkable; her sputum GeneXpert MTB and AFB were both negative. To assess her for malignancy, a VIA was done, and found to be normal; an ultrasound of the abdomen showed a gallstone, but no signs of EPTB or malignancy.

Her hands and feet showed the following:



Questions

- 1) What are the lesions on the patient's hands and feet? What causes them?
- 2) Looking at the patient's overall case, what would your proposed treatment be, especially given that the VL results will take 6 to 12 weeks to come back from the lab?
- 3) What is the Koebner phenomenon? Which dermatological diseases show it?

Diagnosis

Cutaneous warts, deterioration due to clinical ART failure

Answers

- 1) Common warts are caused by the human papilloma virus (HPV).
- 2) Local treatment of the cutaneous warts could be salicylic acid ointment (20%). Cryotherapy and liquid nitrogen are alternatives, but not readily available in this setting.
More important is the patient's general deterioration, with weight loss, recurrent anaemia, and recurrent hospital admissions. Together with new opportunistic infections (extensive warts), this may suggest ART failure. In light of a very long turnaround time for VL results, and the risk of loss to follow-up, a switch of ART on clinical grounds can be considered.
- 3) *Koebner phenomenon* refers to skin lesions appearing on lines of minor trauma caused by self-scratching/auto-inoculation. Other conditions that show this pattern are molluscum contagiosum, and such non-infective conditions as psoriasis and lichen planus.

Outcome and Follow-up

It was determined that the patient was clinically and immunologically failing. She adamantly insisted that she was adherent to her ART, especially as she remembered how well it helped her in the beginning. The decision was taken to switch her to second-line treatment, even in the absence of proof of a high VL, as it was felt that she was clinically too fragile to sustain a longer wait on a failing ART regimen. As she was still anaemic, she was switched to ABC/3TC/AZT/r. When seen at the clinic a few months later, her warts were almost gone, she was gaining weight, and reported feeling well. Clinically, anaemia was no longer apparent.

Comment

HPV are small, non-enveloped DNA viruses. At least 184 types have been identified, but only a small number of types are frequently isolated in disease. HPV types 1, 2, and 4 are the most common types found in cutaneous warts. HPV types 6 and 11 account for most genital warts. HPV types 16 and 18 cause the great majority of cancers of the cervix, anogenital tract, and oropharynx, and are thus defined as high-oncogenic risk.

Key Learning Point

Even in the absence of virological proof of a high VL, some patients may require switching to second-line treatment, because waiting for the lab results may put them in peril in the meantime.

Suggested Reading

Department of HIV and AIDS; Ministry of Health, Malawi. Clinical management of HIV in children and adults: Malawi integrated guidelines and standard operating procedures for providing HIV services. 3rd ed. Lilongwe (Malawi): Ministry of Health, Malawi; 2016.

Case 56

Presentation

A 53-year-old patient came to the clinic with swelling of the neck. He had twice been treated for tuberculosis, 16 and six years prior to this admission, both times with success (according to the patient). The patient was initiated on ART about one year ago. The swelling started about six months ago, but he did not report night sweats, weight loss, or cough. On this occasion, he had been referred for a lymph node biopsy for his swollen neck nodes.



Questions

- 1) Do you think lymph node biopsy is the appropriate diagnostic procedure?
- 2) What is your diagnosis?

Diagnosis

Parotid swelling due to diffuse infiltrative lymphocytosis syndrome (DILS)

Answers

- 1) The localisation and symmetry of the swelling make a lymph node aetiology unlikely; the swelling is more likely to be due to parotid enlargement. A biopsy is therefore not the procedure of choice.
- 2) Diffuse infiltrative lymphocytosis syndrome (DILS) is a Sjögren's-like syndrome, with painless salivary gland swelling, peripheral CD8 lymphocytosis, and sicca-like symptoms of dry mouth and insufficient saliva production. Benign lympho-epithelial cysts of the salivary gland can be seen with ultrasound. Treatment modalities are simple aspiration and surgical resection; radiotherapy might be an option, where available. Regression of the swelling has been demonstrated in patients who continue treatment with ART.

Outcome and Follow-up

An ultrasound of the patient's neck was done, confirming the salivary glands as the source of the swelling, and showing typical hypoechoic and cystic lesions in the gland. Because the patient was concerned, a core biopsy for histology was taken; this confirmed both the diffuse lymphocytic infiltration and the DILS diagnosis. ART was continued, and prednisolone 20 mg od was ordered and tapered over four weeks with good results. Additionally, chewing gum was recommended to help stimulate saliva production.



Comments

Parotid swelling occurs in 5% to 10% of patients with HIV-1 infection (it is more common with advanced disease). DILS is more common in patients of African descent than in Caucasians. In some cases, extra-glandular involvement is found. The most common extra-glandular sites of disease are the lung (lymphocytic interstitial pneumonitis, 31%), muscle (polymyositis, 26%), and liver (lymphocytic hepatitis, 23%). Neurological complications, such as mononeuritis (e.g., VII nerve palsy) and aseptic lymphocytic meningitis, are also seen. Low-dose steroids are effective in the treatment of the glandular swelling and its symptoms.

Key Learning Point

Not all neck swellings are lymph nodes—consider other causes (e.g., thyroid, parotid).

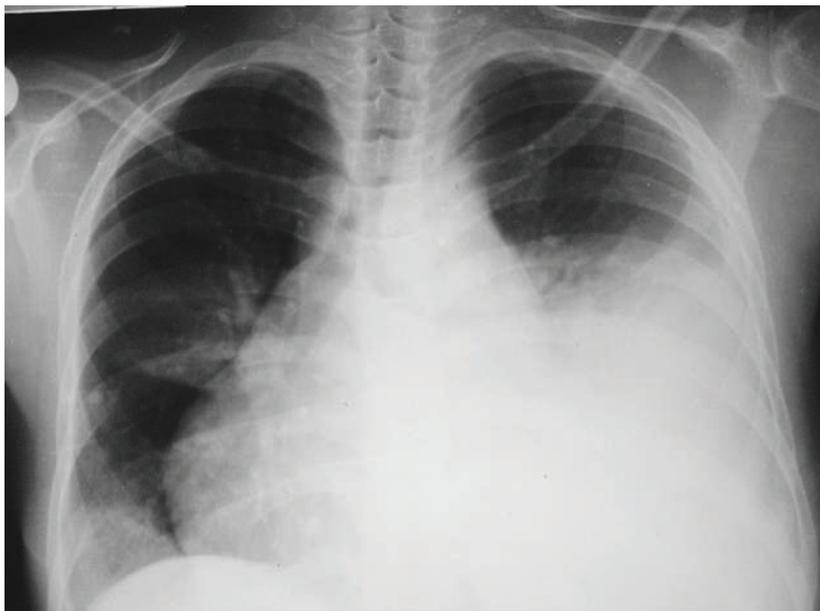
Suggested Reading

Levay PF, Botes ME. Diffuse infiltrative lymphocytosis syndrome (DILS). SA Fam Pract. 2008;50(2):42–44.

Case 57

Presentation

A 26-year-old woman presented to the outpatient department with a three-week history of progressive dyspnoea on exertion and lower limb oedema. She reported no cough, fever, night sweats, or loss of appetite. The patient had no previous history of TB, or of TB contact at home. She had tested HIV positive during her recent pregnancy, with a CD4 count of 356 cells/ μ L. At the time of this visit, she was four weeks post-partum. On examination, the patient did not look unwell, and was not in any respiratory distress. She had a left-sided pleural effusion, as well as bilateral pitting oedema of the lower limbs.



Questions

- 1) What is the most likely diagnosis?
- 2) What other readily available procedures would be useful in this setting?
- 3) How should this patient be managed?
- 4) What is the prognosis of this condition?

Diagnosis

Post-partum cardiomyopathy (PPCM)

Answers

- 1) Post-partum cardiomyopathy is the most likely diagnosis, since the patient is four weeks post-partum. Other possibilities: HIV cardiomyopathy, autoimmune disease, alcohol, and other infections.
- 2) A cardiac ultrasound is the most important procedure to rule out pericardial effusion as a cause of cardiomegaly and increasing cardiac failure. The ultrasound in her case showed a grossly dilated heart, with extremely reduced left ventricular function.
- 3) Medical management of patients with PPCM is similar to that for other forms of heart failure. ACE inhibitors are usually used to reduce afterload by vasodilation, whereas during pregnancy, hydralazine is used instead. β -blockers are used to prevent arrhythmia and sudden death. Digoxin is safe during pregnancy, and may help to maximize contractility. Diuretics are used to reduce the preload as needed. Because of the high risk of thromboembolism, the use of heparin is indicated.
- 4) In a single centre prospective study of 100 South African patients with the condition, 15% died; only 23% recovered normal left ventricular function after six months of treatment. Subsequent pregnancy after a diagnosis of PPCM carries a high risk of relapse.

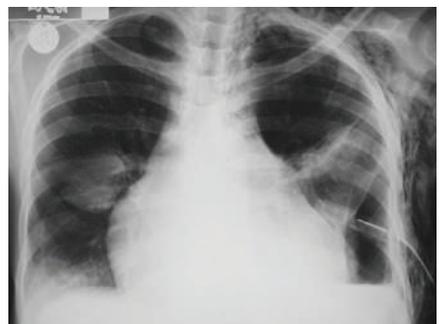
Outcome and Follow-up

The pleural effusion was tapped and sent for routine biochemistry, which showed a transudate. The patient was then sent home with furosemide 20 mg od; in retrospect, this was a low dose.

One month later, the patient presented with worsening shortness of breath. A new CXR showed a large pneumothorax, most likely secondary to the pleural tap; a chest drain was inserted. The pneumothorax resolved, but the patient developed significant subcutaneous emphysema, which caused her considerable pain. She was started on enalapril and increasing doses of furosemide. Subsequently, despite increasing the furosemide, and adding spironolactone, the patient suffered from increasing peripheral oedema and shortness of breath. She became progressively hypotensive until she died three weeks after admission.



Ultrasound of the heart: all four chambers massively dilated



Comment

Risk factors associated with post-partum cardiomyopathy include extremes of age, high parity, African origin, and twin pregnancy. The causes and pathogenesis are poorly understood. Molecular markers of an inflammatory process are found in many patients. An association with HIV infection has not been investigated.

Key Learning Point

Post-partum cardiomyopathy should be considered (and managed aggressively) if there are features of heart failure towards the end of pregnancy, or in the post-partum period.

Suggested Readings

McNamara D. Treatment of peripartum cardiomyopathy. Buenos Aires: Federación Argentina de Cardiología 2nd Virtual Congress of Cardiology. c2001. Available from: <http://www.fac.org.ar/scvc/llave/cardio-llnamara/namarai.htm>.

Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. *Lancet*. 2006 Aug 19;368(9536):687–93.

Case 58

Presentation

A 40-year-old female nurse working on the TB ward presented to the staff clinic with cough, fever, night sweats, and weight loss. Her HIV status was unknown, but she had been treated for TB two years ago. A CXR showed bilateral patchy changes consistent with active TB; she was started on RHZES. An HIV test came back positive.

Two weeks later, she returned to the staff clinic, complaining of increasing fatigue, lethargy, on-going fever, and a tremor. She reported no headaches at this stage. Her CXR was unchanged; it was felt she may have had a superimposed pneumonia. She was admitted to the TB ward. Her CD4 count result was 42 cells/mL.

Whilst on the ward, she complained of dizziness and hearing loss; this was presumed to be a side effect of streptomycin, so the dose was reduced. As she continued to have spiking temperatures, a lumbar puncture was performed as part of a general septic screen. At this point, she still reported no headache.

Her CSF revealed:

CSF-lymphocytes	88 cells/ μ L
CSF-protein	2.16 g/L
CSF-glucose	36 mg/dL
Crypto Ag and India ink	negative

The patient was prescribed steroids in addition to TB treatment. Unfortunately, she was unable to get them, as all forms of steroid were out of stock. Two days later, she began having seizures; the doctor was called to the ward. The patient was given diazepam, and transferred to the high-care unit, where a loading dose of phenytoin was given. She continued to have seizures, and never regained consciousness. She died early the following morning. One month later, her sputum culture and sensitivity results came back from the lab. They showed growth of *M. tuberculosis* resistant to isoniazid and rifampicin (MDR-TB). Her CSF culture was also positive for *M. tuberculosis*.

Questions

- 1) What factors contributed to her death?
- 2) What can be done to prevent nosocomial infections of health care workers in a resource-limited setting?
- 3) What can be done to improve timely diagnosis of MDR-TB?

Diagnosis

MDR-TB meningitis in an HIV-positive health care worker.

Answers

1) There are several factors that may have contributed. First, the patient lived and worked in a high-risk environment, in an area with extremely high TB and HIV prevalence. She did not know her HIV status prior to becoming ill; even then, she was extremely reluctant to get tested. By the time she was diagnosed HIV positive, she had advanced immunosuppression. Although measures are taken in the ward to reduce risk, a person with immunosuppression should not work in this section. The diagnosis of MDR-TB was not made at the outset, as the diagnostic process is very slow; consequently, the results were received only after she had died. Steroids are an integral part of management of TB meningitis, but the lack of essential medications is a frequent issue in resource-poor settings.

When the seizures started, there was a long delay in the administration of diazepam, as many wards neither equipped nor trained to respond quickly to emergencies. The recommended management for status epilepticus is to anaesthetise and ventilate the patient, a procedure that is not possible in our setting.

- 2) Health care workers must be encouraged to learn their HIV status, and to seek prompt medical care. This will remain a challenge as long as the fear and stigma associated with HIV persist. Strategies to reduce occupational exposure to TB must be employed. These include prompt identification and effective treatment of TB cases, maintaining good ventilation on wards, and personal protective equipment for staff.
- 3) All TB retreatment cases and poor responders to first treatment should have sputum sent for TB culture and sensitivity. Current laboratory techniques mean that takes approximately six weeks to receive sensitivity results. The GeneXpert MTB/RIF test could have provided a faster result, providing at least the information about RIF resistance, which could then have been used as a proxy for multi-drug resistance (MDR)—but this test was not widely available at the time (2008).

Comments

TB is probably the most common acquired occupational illness amongst health care professionals. Nursing students have an extremely high tuberculin skin test conversion rate (12.5 conversions per 100 person years, according to a study from Zimbabwe). This underlines the importance of having a practical infection-control plan implemented in every health care facility. WHO guidelines for the prevention of nosocomial TB in health care facilities in resource-limited settings address specific issues of infection control with regard to HIV care and treatment in a very practical way, without the need for sophisticated equipment, including administrative, environmental and personal protection measures.

It is important to stress to all health care workers that they need to know their HIV status, in order to protect themselves as much as possible from nosocomial TB.

Key Learning Point

Health care workers should be encouraged to know and regularly check their HIV status.

Suggested Reading

World Health Organization. Tuberculosis infection-control in the era of expanding HIV care and treatment: addendum to WHO guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva (Switzerland): World Health Organization; 2006. Available from: http://whqlibdoc.who.int/hq/1999/WHO_TB_99.269_ADD_eng.pdf

Case 59

Presentation

A 16-year-old girl recently diagnosed HIV positive was seen in the clinic, complaining of painful joints. Her CD4 count was 120 cells/mL, and she was about to start ART. She reported pain and swelling in her right ankle, as well as in the middle finger of her left hand.

On examination, the two joints were swollen, warmer than other joints, and painful with movement.



Questions

- 1) What are the most common causes for joint pain in HIV patients?
- 2) What is shown in the picture?
- 3) What other symptoms would you look for?
- 4) How should this patient be treated?

Diagnosis

HIV-associated arthritis

Answers

1) Joint pain with signs of inflammation (swollen, warm joints) can be due to infectious or inflammatory causes. Mono-articular involvement points more towards infectious aetiologies, while oligo- and polyarticular disease tends to be more often associated with inflammatory diseases.

The main causes of oligo/polyarthritis are:

- Reiter's syndrome
- Psoriatic arthritis
- HIV-associated arthritis
- Rheumatoid arthritis
- Gout (can be secondary to pyrazinamide)

2) Dactylitis, a/k/a 'sausage fingers', is frequently seen with reactive forms of arthritis.

3) Other symptoms to look for:

- Psoriatic arthritis: change of skin and nails
- Reiter's syndrome: urethritis and conjunctivitis

4) Symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) is the approach of choice for this patient. Disease-modifying drugs (e.g. methotrexate) are rarely indicated, and are difficult to provide in our setting. In severe cases, temporary treatment with steroids might be indicated, after carefully balancing the immuno-compromising effect of the drug in patients who are already immunosuppressed with the treatment benefits.

Outcome and Follow-up

Diclofenac 25 mg bd and paracetamol 1 g qds were prescribed for the patient. After one week, the arthritis had not improved, and the patient became unable to walk due to the pain; the diclofenac dose was increased to 25 mg tds. A week later, the patient was using a wheelchair, due to the pain in the ankle. A course of prednisolone (40 mg od for one week, then tapered to 10 mg over the next two weeks) was administered. She significantly improved with this treatment, so she was kept on prednisolone 10 mg od plus diclofenac 25 mg bd for an additional four weeks. She began ART and collected her ART medications in the following months, but did not seek further arthritis treatment.

Comments

A seronegative arthritis distinct from the spondyloarthropathy or rheumatoid arthritis that occurs in HIV-positive individuals was first described in 1988. Studies from rheumatology clinics in Africa (Congo, Zimbabwe, Rwanda) have shown that HIV-associated arthritis and Reiter's syndrome are frequent in untreated African patients with HIV infection. Patients present with asymmetric oligoarthritis, predominantly in the lower extremities. Dactylitis is often apparent. Classical Reiter's syndrome includes symptoms of conjunctivitis and urethritis, and is frequently triggered by chlamydia infection. In a high proportion of patients, the disease is self-limited. Doxycycline is often given for two weeks for Reiter's syndrome. In severe cases of arthritis, sulfasalazine and methotrexate might be indicated.

Key Learning Point

Corticosteroids are often indicated in severe inflammatory conditions; they should not be withheld, even in HIV patients with low CD4 counts.

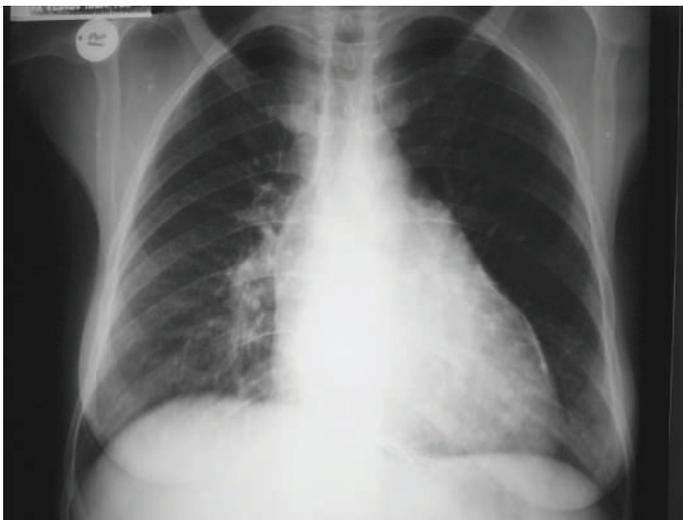
Suggested Reading

Reveille JD. The changing spectrum of rheumatic disease in human immunodeficiency virus infection. *Semin Arthritis Rheum.* 2000 Dec;30(3):147–66.

Case 60

Presentation

A 46-year-old HIV-positive woman complained of a mild cough without major weight loss, fever, or shortness of breath. She had started to take ART about a year ago, and her CD4 counts had risen from 153 cells/mm³ to 368 cells/mm³. As she had pulmonary TB about eight years ago, she was worried she might have tuberculosis again. A CXR was taken.



Questions

- 1) What is the pathological finding? What signs and symptoms should be asked about and looked for?
- 2) Are further technical procedures necessary?
- 3) Given that the patient's CD4 count is rising, is she still at increased risk of developing TB?

Diagnosis

Post-tuberculous calcification of the pericardia (no constrictive pericarditis)

Answers

- 1) A calcification is seen at the left border of the heart. It is important to assess the patient for signs and symptoms of constrictive pericarditis—mainly, swelling of the abdomen due to ascites and enlarged liver. Pulmonary oedema is seen only when the constriction is observed predominantly around the left side of the heart; signs include pulsus paradoxus (pulse amplitude smaller during inspiration) and high jugular venous pressure.
- 2) As the patient does not show clinical signs of constrictive pericarditis, no further diagnostics are required. However, a cardiac ultrasound can be done.



A cardiac ultrasound showing organized pericardial thickening due to a previous TB pericarditis in a different patient. The liver veins need to be assessed for congestion.

- 3) The risk of TB is still present, as TB can also occur even when the CD4 count is normal. The risk of extrapulmonary and disseminated TB correlates more with the CD4 count.

Outcome and Follow-up

The patient showed no clinical signs of constrictive pericarditis. Although clinically not really necessary, an ultrasound of the heart was performed, which showed normal cardiac function; calcification was visible in the area of the left ventricle and left atrium. Mildly dilated hepatic veins and mildly enlarged atria were also seen. The patient was started on 12.5 mg hydrochlorothiazide, and prescribed a short course of amoxyl for a respiratory infection. A sputum sample was negative for MTB in both AFB smear and GeneXpert.

Comments

Pericardectomy is the surgical treatment of choice for clinically severe disease, as it can restore the cardiac function. Some signs of constriction may persist, due to subjacent myocardial fibrosis.

Key Learning Point

Nearly all cases of constrictive pericarditis are due to previous TB pericarditis—adjunct steroid therapy reduces the risk.

Suggested Reading

Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. *Circulation*. 2005 Dec 6;112(23):3608-16.

Case 61

Presentation

A 33-year-old man was seen in the clinic complaining about the fact that he had developed 'a woman's breast' during the last two months. He reported the swelling to be painful, and was concerned about the cosmetic appearance. He had been taking TDF/3TC/EFV for seven months, along with CPT and multivitamins. He reported taking no other medications, including traditional medicines. On examination, he had unilateral gynaecomastia (Tanner stage III to IV) on the left side.



Questions

- 1) What might cause the gynaecomastia, especially if we consider drug side effects?
- 2) Which lab tests might be ordered?
- 3) How should the patient be treated?

Diagnosis

Gynaecomastia, most probably due to ART

Answers

- 1) EFV and some of the NRTIs (D4T, DDI) have been reported to be associated with gynaecomastia in HIV patients on ART. Other known causative drugs include spironolactone, H1-antagonists, omeprazole, ketoconazole, metronidazole, isoniazid, digoxin, and phenytoin. Chronic liver disease should also be considered.
- 2) In an adult presenting with unilateral or bilateral gynaecomastia, and where the patient's history and physical examination do not reveal a cause, luteinising hormone (LH), testosterone, oestradiol, and prolactin could be measured; however, these are often found to be of normal levels, and are rarely available in our setting. Hepatitis B surface antigen, LFTs, and an ultrasound of the liver should be checked, as gynaecomastia can be a consequence of liver disease (cirrhosis).
- 3) The patient should be carefully counselled regarding this condition making sure he understands it is benign in nature. It is also important to determine whether it will interfere with his adherence to ART. If this cannot be ensured, changing his treatment regimen should be considered. The most likely causative agent amongst his current medications would be EFV.

Outcome and Follow-up

The patient was counselled about the side effects of ART, and the origin of his breast development. He opted for switching to NVP. NVP was started in the normal dose of 200 mg. (The 'starter pack', with double-dose NVP, was not given.) He was also prescribed ibuprofen to ameliorate the pain.

Comments

Gynaecomastia is a well-described side effect of ART. In our patient population, we have found approximately 14% of male patients to be affected, with about two-thirds having unilateral gynaecomastia, and about one-third bilateral gynaecomastia. It usually resolves in a number of cases if ART is continued. Other South African centres have reported similar rates, which seem to be higher than those reported from European cohorts (3%). Other medications need to be considered as possible causes. Drug abuse (e.g., alcohol, marijuana, opioids, or anabolic steroids) should be considered.

It must be remembered that female patients, especially young girls, also suffer from EFV-induced growth of the breasts; this can lead to gigantomastia, with effects such as back pain, and become even worse with severe psychological problems. In some cases, the condition may require breast reduction surgery.



A 16-year old girl who experienced severe pressure at school from peers ridiculing her for the disproportionate breast growth caused by EFV

Key Learning Point

Gynaecomastia is frequently observed; a change in treatment may be indicated. Good counselling is essential to ensure continued adherence to ART.

Suggested Reading

Mira JA, Lozano F, Santos J, Ramayo E, Terrón A, Palacios R, et al. Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment. *Antivir Ther.* 2004 Aug;9(4):511-7.

Case 62

Presentation

A 4-year-old boy was seen at the clinic with his parents. The parents reported longstanding (weeks to a month) skin changes on his extremities, especially on the hands and feet. The lesions were neither painful nor itchy. The child was admitted for examination; he tested HIV negative. Swabs from the skin lesions were sent for bacteriology, which grew *S.aureus*, as well as two (probably contaminating) gram-negative rods.

As he did not improve on antibiotic treatment, a skin biopsy was performed. This showed histological features of skin tuberculosis. Standard anti-TB treatment was initiated.



Questions

- 1) Which forms of skin tuberculosis do you know about? What would be the result of the skin test?
- 2) How would it be treated?
- 3) BCG vaccination is not without risk in immune-compromised children. What are the complications? How are these treated?

Diagnosis

Tuberculosis verrucosa cutis

Answers

- 1) Cutaneous TB is not very common—but it is often missed, as it is not well known. The different forms can be grouped by the routes via which the mycobacteria reach the skin.

Exogen

- a) Primary inoculation (TB chancre) develops at the site of small trauma, and TB inoculation usually in the face or limbs. A small nodule forms, and becomes an ulcer. Lesions are usually single. Skin tests change from initially neg→pos.
- b) Tuberculosis verrucosa cutis (warty TB) is seen on the hands and feet (especially in children, but also in physicians, butchers, and others who have been exposed). There may be a single or multiple lesions; the skin test is usually positive (good immune response).

Endogen

- c) Lupus vulgaris occurs on the face in 80% of cases. It is a reddish-brown, soft gelatinous plaque, which grows leaving a scar in the centre. Usually, single lesions are seen; the skin test is commonly positive.
 - d) Scrofuloderma results from contiguous spread—mostly from neck LNs, which break through the skin, and form nodules that break into ulcers. Depending on the patient's immunity, the skin test may be either positive or negative.
 - e) Metastatic TB abscess may form after haematogenous spread at any site (limbs or trunk), and present as cold abscess (TB gumma) resembling scrofuloderma (without the lymph node TB). Again, the skin test may be either positive or negative.
 - f) Miliary TB of the skin presents as minute maculopapular lesions, pinhead-sized papules, possibly with vesicles in the centre. The skin test is usually negative.
 - g) Orificial TB are ulcers around the mouth and nose in patients with advanced pulmonary TB, who auto-infect the mucocutaneous border with MTB. Skin tests can be either positive or negative.
- 2) Skin TB is treated like all other forms of TB, with 2RHZE/4RH.
- 3) As a complication of the intradermal injection of BCG (an attenuated live strain of *Mycobacteria bovis*), local abscesses and lymphadenitis can occur. The recommended therapy is drainage, and direct instillation of an anti-TB drug. Systemic treatment has little effect. In immunosuppressed children, the infection can disseminate; then it is often fatal. This is treated similarly to active TB; only PZA is not active, as BCG strains are always resistant.



Outcome and Follow-up

Regular TB treatment was initiated, which the small patient tolerated well. The lesion disappeared after a few weeks of TB treatment.

Key Learning Point

Remember the possibility of skin TB whenever you see a chronic painless skin condition. Always look for TB elsewhere.

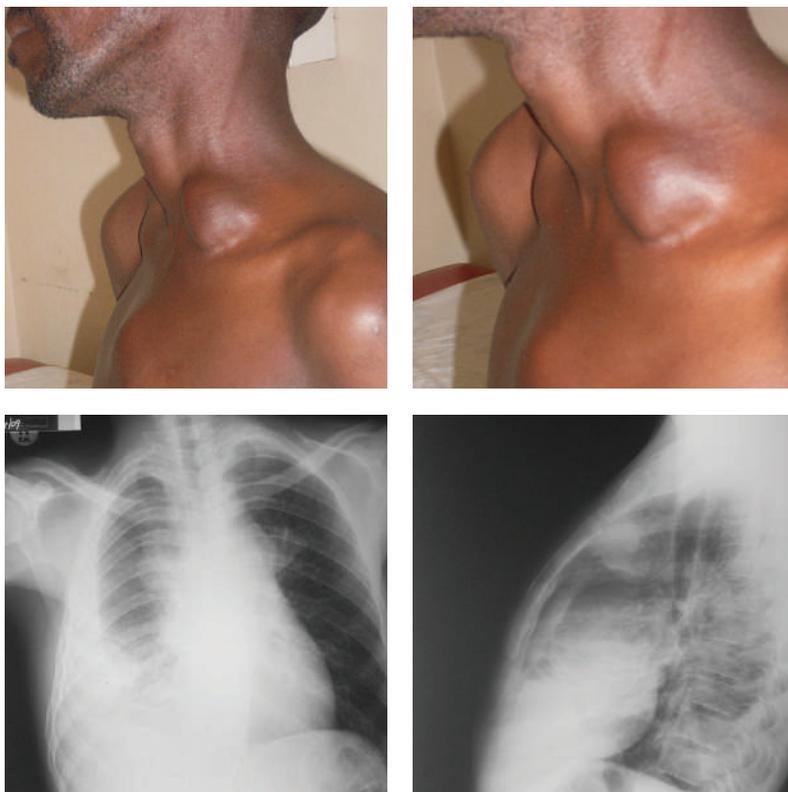
Suggested Reading

Rieder HL, Chen-Yuan C, Gie RP, Enarson RA. Crofton's clinical tuberculosis. 3rd ed. Oxford: Macmillan; 2009.

Case 63

Presentation

A 34-year-old male patient reported weight loss, weakness, and cough at his clinic; accordingly, he was sent to the TB nurse. He tested HIV positive; the nurse found the swellings shown, and sent the patient to the hospital with suspicion of lymph node TB. On examination, the very fluctuant lesions below were seen. A CXR in two planes was ordered.



Questions

- 1) Do you think this is LN TB?
- 2) What does the CXR show?
- 3) What exam would you do next? How would you diagnose the patient?

Diagnosis

Empyema necessitans due to TB

Answers

- 1) The location of the swellings is not typical. In particular, the parasternal swelling does not correlate with any anatomical LN station. Lymph node TB is therefore less likely. Given the clinical history of an HIV-positive patient with weight loss and cough, TB is nevertheless probable as an underlying disease.
- 2) The CXR shows large pleural effusion on the right side. Additionally, on the p.a. x-ray, a structure is visible that suggests an enlarged right hilum. Correlating with the lateral view, this structure projects directly retrosternally, and correlates well with the location of the externally visible swelling next to the sternum.
- 3) A possible next exam would be sputum for AFB, as well as for GeneXpert MTB/RIF. This could prove TB as an underlying cause. An ultrasound can help to better characterize the visible subcutaneous structures.

Outcome and Follow-up

An ultrasound of the lesions was done, showing a large pleural effusion and anechoic fluid collections under the skin (left). The parasternal lesion showed that the fluid had communication with the intra-thoracic space (right). The fluid was aspirated, and found to be pus. It was sent for GeneXpert MTB, which came positive—confirming the diagnosis of TB. The communicating intra-thoracic/extra-thoracic pus make the diagnosis of an empyema necessitans. TB treatment was started, and the patient referred for surgical drainage of the pleural effusion.



Comments

Empyema necessitans (sometimes spelt as empyema necessitatis) refers to a pleural infection that extends out of the thorax, and into the neighbouring chest wall and surrounding soft tissues. It occurs commonly in subcutaneous tissues of the chest wall, but can also spread to involve other sites, such as the retroperitoneal regions (wandering abscess towards the renal/psoas area). If the abscess reaches the skin, it may eventually rupture through the skin. *M. tuberculosis* is the most common cause; other causative agents observed are *Actinomyces*, *Blastomyces*, *Mucormycosis*, and *Fusobacterium*. In our setting, these are not relevant.

Appropriate antibiotic therapy is the mainstay of treatment. Additional management options include drainage of the pleural space to reduce the risk of fibrosis and facilitate expansion of the lung.

Key Learning Point

Not all swellings are lymph nodes—remember your anatomy.

Case 64

Presentation

A 27-year-old woman was referred from a district facility with a new hemiparesis, epileptic seizures, and minimal fever. The patient was HIV positive, and had started ART two months prior. She was started on ceftriaxone on admission, and a CT scan was ordered. The CT revealed a ring-enhancing lesion.

By the time the CT was received, the patient had improved clinically on the antibiotic treatment. A bacterial brain abscess was assumed, and metronidazole added to the treatment. An echocardiography was performed to identify endocarditis as a potential source of embolic infection, but was normal.

The patient was kept hospitalised on this dual antibiotic treatment for six weeks, as she came from a district far away. She was able to move normally after this period, and had no further seizures. Before the patient was discharged, another CT was requested. It showed substantial reduction in size of the lesion; additionally the surrounding dark oedema had decreased. She was discharged.



CT scans of the brain; with contrast at admission (L), and after six weeks of treatment with ceftriaxone and metronidazole (R).

Questions

- 1) What would have been your recommendation for initial antibiotic treatment for this patient?
- 2) Which treatment should be given after discharge? Would you change the patient's ART?
- 3) Should steroids have been given at some stage?
- 4) What information points against toxoplasmosis as a cause?

Diagnosis

Bacterial brain abscess

Answers

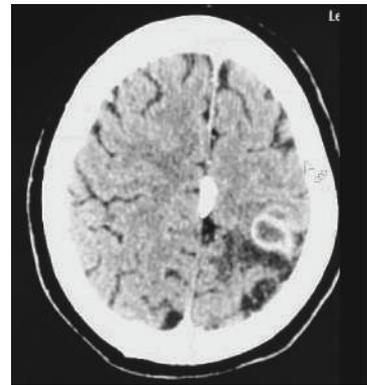
- 1) In an HIV-infected patient with new epilepsy, toxoplasmosis is one of the differential diagnoses; therefore, cotrimoxazole 3 tbl tds could be added to the initial regimen.
- 2) Antimicrobial therapy with high-dose intravenous agents is traditionally given for six to eight weeks. This could be followed by a longer course of oral antibiotics, especially with larger abscesses. The timing of the symptoms suggests that her ART is working well; the deteriorating symptoms are due to her improving immune function causing IRIS.
- 3) Steroids could have helped to reduce the inflammatory perifocal edema, and should have been given if the patient deteriorated. Generally, one should try to avoid the use of steroids because the only 'diagnostic' test we have is response to therapy. Steroids non-specifically ameliorate symptoms in all underlying conditions. If there is significant neurological deficit, and/or concerns about herniation, then you have no choice but to use steroids.
- 4) The initial improvement on ceftriaxone points against toxoplasmosis, as does the slow resolution of the radiological findings, which are atypical for this disease.

Outcome and Follow-up

The patient took cotrimoxazole in high dose (as it also has good antibacterial effect) and metronidazole (to cover anaerobic bacteria) for another six weeks. She came back for another CT scan, which showed a small residual abscess. It was recommended that she should continue the oral antibiotic for another month. In follow-up, she reported by telephone that she had improved further, and stopped treatment thereafter.

Comments

A brain abscess is a focal, intra-cerebral infection that begins as a localised area of cerebritis, and develops into a collection of pus surrounded by a well-vascularised capsule. It presents more like a mass than an infection, and may not be accompanied by fever. Microbiology depends upon the underlying causes: sinusitis, otitis, mastoiditis, or dental origin suggest mixed organisms, as do underlying bronchiectasis, lung abscess, or empyema. In endocarditis, often a single organism (usually *Staphylococcus aureus*) is found. About 30% do not have an underlying cause. These tend to have multiple organisms, so are presumed to come from sub-clinical sinus, ear, or pulmonary sources.



CT scan with contrast, after total of 12 weeks of antibiotic treatment.

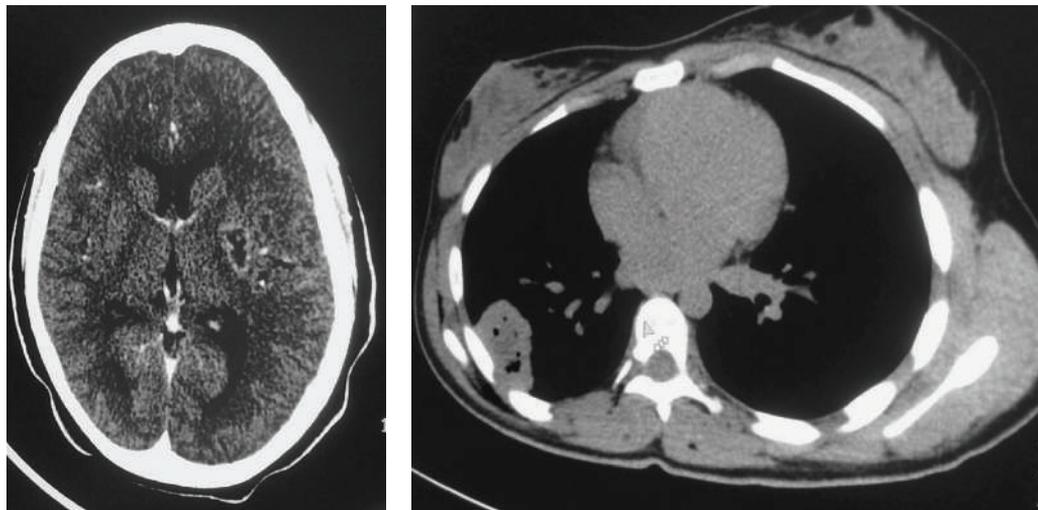
Key Learning Point

Brain abscess is often managed empirically—in most parts of the world—as a brain biopsy is often not obtainable.

Case 65

Presentation

A 17-year-old HIV-positive girl on ART for many years was seen at the clinic, complaining of headaches, which had been troubling her for a while, and a new right-sided hemiparesis. An LP displayed normal results, and a negative CrAg. A CT with contrast showed a ring-enhancing lesion. On careful questioning, she reported that she had stopped treatment, without telling anybody, five months ago when she went to school, because she was afraid her fellow students would see her tablets. Her CXR clearly showed an additional right-sided pleural-based mass.



Questions

- 1) What is the differential diagnosis of the ring-enhancing lesion and the chest process?
- 2) What should be the next steps?

Diagnosis

Cryptococcoma of the brain and lung

Answers

1) Differential diagnosis:

Ring-enhancing lesion in the brain: mainly toxoplasmosis, cerebral abscess (bacterial or fungal), tuberculoma; less probable: lymphoma, neurocysticercosis, metastasis, glioblastoma.

Pleural-based mass: localized pleural effusion, bacterial or fungal infection including tuberculosis, empyema, pleural tumours (e.g., lymphoma, mesothelioma, metastasis), and chest wall tumours (e.g., Ewing sarcoma)

In this immunosuppressed patient, tuberculosis, bacterial or fungal infections, or lymphoma should be considered to explain both lesions.

2) One option would be empiric treatment, most likely for tuberculosis. Alternatively, a biopsy of the thoracic lesion can be attempted, as this is easily accessible by ultrasound- (or CT-) guided biopsy. In any case, it is important to re-start the ART and ensure adherence.

Outcome and Follow-up

A biopsy of the chest mass was taken, and sent for histology and culture. The cultures were positive after a few days, and grew *Cryptococcus neoformans*. The patient was started on amphotericin and fluconazole, as well as physiotherapy. She improved greatly; her brain lesion was hardly visible after two weeks, and she regained the ability to walk. She was restarted on ART, and was adherent over the following months.

Comments

Meningitis is by far the most common cryptococcal infection seen in HIV patients. Beside this, cryptococcomas of the brain do occur. Infections of the lung are another common site of infection, as it is the portal of entry for this yeast, and can manifest as pneumonia or cryptococcoma. Skin lesions are well described. In the eye *Cryptococcus* can cause endophthalmitis. Bone lesions are typically one or more well-circumscribed osteolytic lesions in almost any bone. Other body sites are only rarely described, but cryptococcosis can manifest basically anywhere.

It is important to remember the possibility of biopsy for histology, especially when treatment for common conditions is not successful (and lab facilities are available). Surprising diagnoses may be found, as this case—and the case below—illustrate.

Cryptococcoma of the bone (tibia, histologically confirmed).

Echinococcal cyst with super-infecting aspergilloma (L). An old, partly calcified echinococcal cyst paravertebral (R) found in a patient with chronic productive cough, but without B-symptoms. He received TB treatment three times before the histological diagnosis was made.

Case 66

Presentation

A 16-year-old female student was brought to the clinic by her mother, complaining of pain in both of her shins. She reported having a previous negative HIV test, and was confirmed negative.

The examination showed livid, bruise-like nodules on her lower limbs, which were painful to the touch.



Questions

- 1) What is the diagnosis?
- 2) What are the most common causes?

Diagnosis

Erythema nodosum

Answers

1+2) Erythema nodosum can be caused by tuberculosis (usually as a manifestation of primary infection), streptococcal infections, sarcoidosis, and drug reaction (e.g., sulphonamides, oral contraceptive pill).

Outcome and Follow-up

Upon further questioning, the patient reported that she had recently had a pharyngeal infection. Accordingly, she was treated with amoxicillin and ibuprofen. A CXR to assess for TB was performed, which was normal. A tuberculin skin test was ordered; the test came back strongly positive. The patient was started on standard TB treatment, and the lesions improved very rapidly.



Comments

Erythema nodosum is rare in young children, but more common in females at all ages. The lesions are often associated with a fever; sometimes pain in the larger joints is reported. The most obvious finding is of tender blue-red nodular lesions on the front of the leg. They are generally 1 to 4 cm in diameter with ill-defined margins, and can be felt deep under the skin. If caused by TB, the tuberculin skin test is usually strongly positive.

Key Learning Point

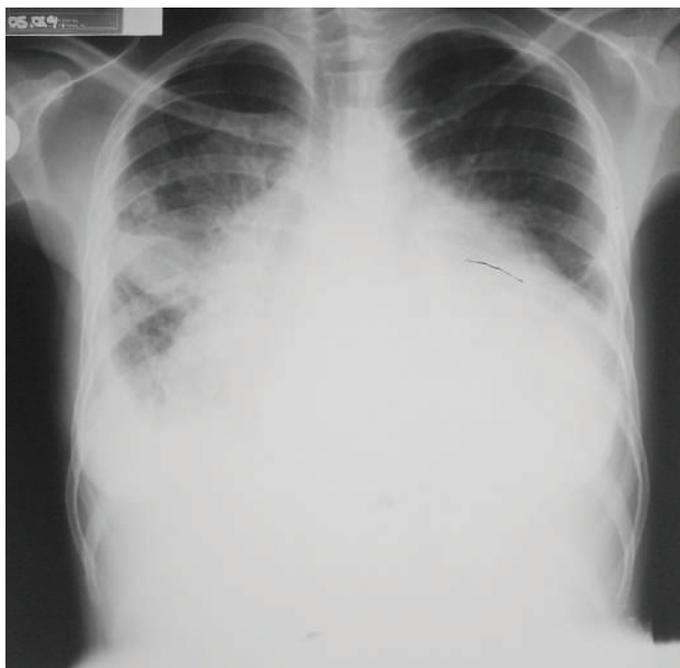
A tuberculin skin test is indicated for any case of erythema nodosum.

Case 67

Presentation

A 23-year-old HIV-positive woman was seen in the hospital, complaining of weight loss, fever, and increasing shortness of breath. Her CD4 count was 240 cells/mm³. Because of the shortness of breath, she was admitted. A CXR was performed, which showed an extremely large heart shadow. An ultrasound confirmed a pericardial effusion, and the patient was started on anti-TB treatment (RHZE) and prednisolone (80 mg/day for one week, then 40 mg/day, 20 mg/day, and 10 mg/day, each for one) for suspected TB pericarditis.

After a few days, the patient's status improved, and she was discharged. Six weeks later, she was admitted again, this time with extreme shortness of breath and low blood pressure. A CXR was done (see picture below left). As the patient showed signs of cardiac tamponade, an US-guided pericardiocentesis was performed, by inserting a grey cannula in the ventral section of an intercostal space. After 500 ml of a blood-stained fluid (see picture) was drained, the plastic cannula was withdrawn. The patient clinically stabilized quickly during the procedure.



Questions

- 1) Suggest possible explanations for the deterioration of the patient's condition despite initial improvement on treatment.
- 2) What is your differential diagnosis, especially after the pericardiocentesis? For which tests would you send the sample?
- 3) What is the procedure for pericardiocentesis? How much fluid needs to be drained?

Diagnosis

Pericardial involvement in generalized KS

Answers

1) In patients failing on TB treatment, four explanations should usually be considered:

- | | |
|-----------------------------------|--|
| a) Non-adherence to medication | c) TB-IRIS |
| b) Multi-drug-resistant (MDR-) TB | d) Alternative (or additional) diagnosis |

With this patient, it has to be noted that she not only started TB treatment and improved, but started TB treatment AND prednisolone and improved. Steroids improve inflammatory effusions (as well as other inflammatory caused symptoms) irrespective of the cause. The use of steroids therefore precludes use of the information of a 'diagnostic treatment trial'. The timing of the relapse after tapering the steroids supports this hypothesis.

- 2) Effusions caused by TB can be blood-stained. Nevertheless, the most important cause of blood-stained effusions in HIV-positive patients is serosa involvement in Kaposi's sarcoma (and, less likely, other malignancy).
- 3) According to standard protocols, a dedicated needle attached to an ECG lead is inserted into the pericardial space, commonly from a sub-xiphoid approach. Echocardiographic control is recommended, but such expertise is often not available. In settings where dedicated pericardiocentesis equipment is lacking, the use of alternative approaches, such as an intercostal approach with a simple cannula (as described in this case) may be used, but should also be guided by ultrasound. It is necessary to drain enough fluid to relieve the signs of haemodynamic instability. Many patients experience rapid clinical improvement, despite the continuing presence of pericardial effusion. It is worth remembering that the aim to reduce pressure in the pericardial space rather than volume; therefore, the drainage of 50–100 mL of fluid might be sufficient for resolution of tamponade.

Outcome and Follow-up

After the patient was stabilised, a careful examination of the skin was performed. Skin lesions suggesting Kaposi sarcoma were found in the left groin area. The patient reported having had these for a long time, but she had not mentioned them during the first admission, so a complete skin examination was not done at that time. A skin biopsy was performed, which confirmed the diagnosis; the patient was transferred for chemotherapy.



Comments

In countries with a high prevalence of TB, this disease has been reported as the cause of more than 90% of large pericardial effusions in HIV-infected persons. Nevertheless, other potential causes—such as bacterial pericarditis (e.g., non-typhoidal *Salmonella*), human-herpes-virus-8-related disease, and lymphoma—should be kept in mind.

Key Learning Point

Steroids non-selectively suppress inflammatory symptoms regardless of the cause.

Case 68

Presentation

A 33-year-old man came to the centre for advice. He tested HIV positive five years ago; at that time, his CD4 count was 227 cells/mm³. He started ART and his CD4 count rose to 806 cells/mm³ over the following year. He never felt ill, and his wife repeatedly tested HIV negative.

Last year, he tested for HIV again, at home, for a study; the result came back negative. He was therefore referred to a testing centre, where his tests showed discordant results (one test positive, one negative). In total, he was tested four times; each time, the results were discordant. Two consecutive blood samples were sent for DNA PCR, which were both negative (on ART).

The patient wonders what to do, and what to believe.

Questions

- 1) What is the recommended strategy for discordant HIV test results?
- 2) What would you recommend to the patient?

Diagnosis

Discordant HIV rapid test results in an HIV-infected patient

Answers

- 1) The guidelines for confirmatory HIV testing recommend attaching an experienced dedicated HIV testing provider to do confirmatory testing. All quality assurance protocols for HIV testing (proficiency testing, quality control) have to be followed. The first and second rapid tests are used in parallel for confirmatory HIV testing. If the tests are repeatedly discordant, *Confirmatory test Inconclusive* is noted in the HIV testing register. Then, a blood sample is sent to the reference lab to repeat regular and molecular HIV testing.
- 2) This patient was asking himself whether he is on ART with no good reason; these doubts may jeopardise his long-term adherence (although he was very adherent, and well informed about treatment). Every attempt should be made to reach a conclusive diagnosis. ART could be stopped, as it renders the VL undetectable. The molecular diagnosis (as well as the antibody tests) should be repeated after a short interval (1–2 months) to avoid inadvertent immunosuppression.

Outcome and Follow-up

It was decided to stop ART under close supervision (continuing to have protective sex). Three months later, all tests were repeated; both HIV tests (Unigold® and Determine®) were positive, and his VL was 37.000 copies/mL. ART was reinitiated (TDF/3TC/EFV); after three months of treatment, his VL was again non-detectable. The patient had no further problems in the course of the treatment.

Comments

In resource-limited settings, WHO recommends using two HIV rapid point-of-care tests for diagnosis. The frequency of discordant (one reactive, one non-reactive) rapid test results ranges from 0.7% to 2.3% in various studies. If the results of two tests are discordant, a tiebreaker test is usually recommended—a third rapid test, an enzyme immunoassay, or an RNA test.

A variety of reasons can lead to discordant, and thus inconclusive, testing results. In many patients, it is due to acute HIV infection in which antibody production is not yet sufficient (window period).

Another factor that may potentially impact the performance of different HIV testing algorithms is the HIV-1 subtype. Subtype D HIV infection is associated with lower levels of anti-HIV antibodies, and lower avidity of anti-HIV antibodies for target antigens. In comparison to South Africa, where subtype C is predominantly found, other African countries reveal a mixture of HIV subtypes (e.g., Tanzania: 44% subtype A, 22% subtype C, 10% subtype D).

HIV-infected individuals with natural or ARV-induced viral suppression have low levels of circulating virus antigen; their antibody levels may also be low. HIV infection may therefore be missed, even when multiple HIV screening tests are used. In the absence of ART, they are likely to be elite controllers. Criteria used to identify elite controllers usually include documentation of viremic control for at least one year. Some reports suggest that elite controllers represent <1% of HIV-infected individuals; however, other studies have found higher prevalence of elite controllers.

Key Learning Point

In patients with discordant tests, all attempts to reach a conclusive result should be undertaken to properly inform the patient.

Suggested Reading

Fogel JM, Piwowar-Manning E, Donohue K, Cummings V, Marzinke MA, Clarke W, et al. Determination of HIV status in African adults with discordant HIV rapid tests. *J Acquir Immune Defic Syndr*. 2015 Aug 1;69(4):430–438.

Case 69

Presentation

A generally asymptomatic 44-year-old man was seen at the clinic to start ART. His CD4 count was found to be 68 cells/mm³. He was therefore screened with the cryptococcal antigen (CrAg) test, which was positive, and a urine-LAM, which was negative. He reported that he was treated for cryptococcal meningitis two months earlier, when he first tested HIV positive (one week of amphotericin IV and fluconazole po). The clinicians treating him at that time told him to wait until now to initiate ART. An LP was done; the CrAg test in the CSF was also positive. Admitting the patient for cryptococcal treatment was considered; but, because of the absence of complaints, this was debated.

Questions

- 1) Would you recommend admitting the patient and treating him with amphotericin B?
- 2) What other tests could help you determine further treatment?
- 3) Was it correct to delay ART initiation for the patient, especially in this era of 'test-and-treat'?

Diagnosis

Residual positive CrAg test in a patient after CM treatment

Answers

- 1) No, in the absence of clinical signs—and especially with previous treatment of cryptococcal meningitis—this could well be a false positive. Amphotericin B is a relatively toxic drug (nephrotoxicity, allergic reactions); therefore, the benefit to the patient must be carefully weighed.
- 2) India ink, and especially fungal culture to determine the presence of viable cryptococcal yeast cells, could be performed next.
- 3) It was prudent and wise to delay initiation of ART, especially in a resource-limited setting where antifungal treatment for CM is often suboptimal. CM-IRIS is a well-documented problem. Unlike TB-IRIS, which often leads to increase of symptoms (increased morbidity), but not to the death of the patient (mortality), CM-IRIS can lead to increased intracranial pressure—and, thereby, death (as is also true for TB meningitis-IRIS). A Zimbabwean study also showed that in resource-limited settings where CM management may be suboptimal, early initiation of ART results in increased mortality, when compared with a delay of 10 weeks after a CM diagnosis.

Outcome and Follow-up

Because the patient was asymptomatic, plus the protein and cells in the CSF were not very high, the patient was not admitted, and only continued to receive fluconazole (which he was already taking in a dose of 200 mg/day). CSF was sent for fungal culture, which showed no growth of *Cryptococcus*. He was started on ART (TDF/3TC/EFV) that day, and had no further complaints during follow-up.

Comments

CM can relapse; this is distinct from a persistent infection (i.e., primary treatment failure), in which case sterility of CSF has never been achieved. This is obviously difficult to distinguish without a serial CSF culture. A positive CSF culture for *C. neoformans* is diagnostic for either microbiologic relapse or treatment failure. A positive CSF India ink by itself is not sufficient, as the presence of non-viable yeast in CSF is common, and can be observed to up to a year after diagnosis. Changing cryptococcal antigen (CrAg) titers and abnormal cell counts or chemistries are also insufficient to diagnose microbiological relapse. Culture is essential; quantitative cultures are even more informative. Most cases of relapse are due to inadequate primary therapy (dose and/or duration), and especially to non-compliance with consolidation or maintenance of fluconazole treatment. Persistent infection can suggest fluconazole resistance; susceptibility testing is advisable. Clinically, it is also impossible to distinguish between CM-IRIS and relapse. Again, the critical distinguishing finding here is a sterile CSF fungal culture with increasing neurological symptoms on ART.

Key Learning Points

- CM-IRIS is a potentially deadly condition, so ART should be delayed for 8–10 weeks.
- POC tests, like all tests, need to be interpreted in light of the history and symptoms of the patient.

Suggested Reading

Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis*. 2010 Jun 1;50(11):1532–8.

Musubire AK, Boulware DR, Meya DB, Rhein J. Diagnosis and Management of Cryptococcal Relapse. *J AIDS Clin Res*. 2013 Apr 29; Suppl 3(3): S3-003. doi:10.4172/2155-6113.S3-003.

Case 70

Presentation

A 34-year-old woman was admitted for new-onset blistering skin lesions. She was known HIV positive, and had been on ART for five years. (The HIV was discovered because her husband had been infected.) For reasons that are unclear, the patient was initially started on TDF/3TC/LPV/r, and then switched to TDF/3TC/ATV/r two years later. She had always tolerated the drugs well, and was well adherent. For two weeks now, she had been developing skin lesions, which were increasingly severe and blistering. Her medical passport did not reveal a change in drug regimen, but a check of her drugs showed that she was given NVP at her last visit, instead of ATV/r.



Questions

- 1) What is the cause of the patient's problem? How should it be treated?
- 2) How should NEV be started? How should it be started when used as a 'switch' drug?
- 3) What is the 'tail end' of ART?
- 4) What do you need to consider when changing a single drug in an ART regimen?

Diagnosis

NVP skin toxicity, TEN/SJS

Answers

- 1) Severe NVP skin toxicity, as in this case, should be treated with immediate cessation of the drug (and all other potential causative drugs, especially CPT). The patient may need to be admitted, and given fluid replacement, hygienic dressings, and analgesic treatment. As soon as signs of infection develop, antibiotic coverage is recommended. The use of steroid is controversial, because it can increase the risk of infection, but may be considered.
- 2) NVP should be started with a half dose (200 mg od) starter pack; only after two weeks should the full dose be given. This is necessary at new ART initiation, and after an interruption in ART of more than two weeks. If a patient is switched directly from EFV to NVP, this is not needed.
- 3) NVP and EFV remain in the body much longer than the other ARVs. Stopping any first-line regimen due to side effects (or to the patient's decision) therefore requires giving a 7-day 'tail' of the other two ARVs in the regimen to avoid exposing the virus to only NVP or EFV, as that would risk development of NVP- and EFV-resistant HIV, and spoil future treatment options. However, in the case of severe potentially life-threatening side effects (lactic acidosis, SJS), all ARVs are stopped immediately.
- 4) To change a single drug in a regimen is always tricky, as the patient may be failing on this regimen (without patient or clinician knowing). In this case, a single drug would be added to a failing regimen—which would be the equivalent of monotherapy, and could quickly lead to development of resistance to that drug as well. Whenever possible, VL should be determined; if suppressed, a switch of just the one drug can be made.

Outcome and Follow-up

All drugs were stopped. The patient was given IV fluid and pain medication; at one point, even morphine became necessary. For her severe conjunctivitis, tetracycline eye drops were given. After an initial deterioration, it was decided to add prednisolone (although not clearly recommended



Day 7

Day 11

in TEN/SJS) on day 5 of her stay. The patient's skin gradually improved over the following days; her hand and soles developed severe scaling. Upon discharge from hospital, she resumed her previous ART with TDF/3TC/ATV/r.

Comments

Drug mistakes happen on both sides—patients and health care providers. It is therefore prudent, when the situation is unclear, to

ask the patient to bring in and show ALL their medications to ensure that they did not accidentally take the wrong drug(s). The wrong medications are taken surprisingly often; usually, there is a difference between what has been prescribed and what is actually taken.

Key Learning Point

When in doubt—physically look at all the drugs the patient is taking.

Case 71

Presentation

A 46-year-old HIV positive man on ART (d4T/3TC/NVP for nine years, then TDF/3TC/ATV/r for two years, current VL suppressed) was referred with a history of productive cough and weight loss of 11 kg over six months. He had no previous history of TB, but eight years ago he was living with someone suffering from TB. Inspection and palpation of the abdomen indicated the liver was enlarged. His sputum AFB and GeneXpert MTB/RIF were both negative, and a CXR unremarkable. On ultrasound, a minimal pericardial effusion was seen, with no pleural effusion. His liver was enlarged, had a coarse texture (with a large, slightly echogenic, ill-defined focal lesion), and a nodular surface; the spleen was enlarged, no ascites.

His lab work showed the following:

HBsAg	positive	
Hep C quick	reactive	
INR	1.8	(normal <1.2)
Albumin	2.8 g/dL	(normal 3.5–5.2)
TBIL	2.6 mg/dL	(normal <1.1)
AST	45 U/L	(normal <40)
ALT	78 U/L	(normal <40)
GGT	157 U/L	(normal <60)



Questions

- 1) What is the probable diagnosis?
- 2) What epidemiological roles do Hep B and Hep C play in our patient population?
- 3) What are complications of Hepatitis B? What treatment considerations are relevant in Hep B/HIV co-infected patients?
- 4) What is HCC? What are its differential diagnoses? How is it treated in our setting?

Diagnosis

Hep B-induced liver cirrhosis, with probable hepatocellular carcinoma (HCC)

Answers

- 1) (See above.)
- 2) Hepatitis B virus (HBV) infection is common in our setting; in our patient population, a seropositivity rate of approximately 8% to 10% can be assumed. It is thus an important cause of liver injury leading to cirrhosis, and an important risk factor for hepatocellular carcinoma. Hepatitis C is less common; it plays a bigger role in ART cohorts where more IV drug users are treated.
- 3) HBV infection can present as an acute hepatitis (in about one-third of cases), but often can have an asymptomatic course (two-thirds). In a small proportion (5%–10%) of patients, the virus persists (chronic HBsAg+), and can lead to chronic hepatitis (HBsAg+ and elevated LFTs). In these cases, the chances of developing cirrhosis are high (approx. 20% within 10 years). Because HBV is an oncogenic virus, patients with cirrhosis are at high risk of developing HCC (also rarely seen in chronic HBV infection without cirrhosis). It is important to remember that two commonly used ARTs (TDF and 3TC) have an antiviral activity against HBV. They are therefore recommended therapy in cases with dual infection.
- 4) HCC is the most common primary liver tumour (mainly due to HBV). Another tumour seen relatively frequently is cholangiocarcinoma (CCC), often central in the liver, and more frequent in non-cirrhotic livers, causing early and sonographically visible biliary obstruction (associated with chronic liver fluke infection in Asia, this is not described in our setting). Other differentials are liver metastasis, and hepatic involvement in lymphoma (both less associated with cirrhosis). Treatment of HCC is possible with direct US-guided alcohol injections (in very limited disease), and with doxorubicin-based systemic chemotherapy. Unfortunately, conventional chemotherapy is of limited or no benefit; therefore, palliative treatment is often the only option. ART (TDF/3TC) should be continued to reduce HBV activity.

Outcome and Follow-up

The patient was counselled, and linked to the palliative-care team. ART was continued.

Comments

HBV can be treated with TDF and 3TC; these are the WHO-recommended drugs for ART in HBV/HIV co-infected patients. In patients infected only with chronic HBV, as a priority, all adults, adolescents, and children with clinical evidence of compensated or decompensated cirrhosis should be treated for life. Treatment is also recommended for adults with chronic HBV who do not have clinical evidence of cirrhosis, but are aged more than 30 years and have persistently abnormal ALT levels and evidence of high-level HBV replication (HBV DNA >20 000 IU/mL, HBV viral load mainly available in South Africa).

Discontinuation of TDF/3TC therapy may be considered (exceptionally) in persons without clinical evidence of cirrhosis, and with repeated normal ALT levels, who can be followed closely over the long term for reactivation; and if there is evidence of HBeAg loss and seroconversion to anti-HBe, plus completion of at least one additional year of treatment. Ideally, there are persistently undetectable HBV DNA levels (where HBV DNA testing is available).

Key Learning Point

TDF and 3TC are drugs for ART in HBV/HIV co-infected patients; these should especially be maintained in patients with HBV complications (cirrhosis, HCC).

Suggested Reading

World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva (Switzerland): World Health Organization; 2015.

Case 72

Presentation

A 24-year-old female patient from a remote district was referred for assessment of jaundice. She was a known HIV-positive patient; she had started ART four months ago (TDF/3TC/EFV), but it was stopped after three weeks because she developed jaundice. LFTs were performed. However, the jaundice never improved, and actually increased (clinically) over time. The patient complained about right upper quadrant pain and intermittent nausea. Additionally, she had a typical T1 Kaposi sarcoma on both legs with moderate oedema, which had not been treated.

An abdominal ultrasound was done; it showed significant biliary dilatation of the intrahepatic bile ducts, and large abdominal lymph nodes in both the epigastrium and the periportal area.



Questions

- 1) Why was ART stopped? What do you think about this decision? What should have been done?
- 2) What are the most common reasons for elevated LFT and elevated bilirubin in patients starting ART?
- 3) ATV/r can cause jaundice. How should that be interpreted?
- 4) What is HIV-associated cholangitis? What causes it? How can it be treated?

Diagnosis

Obstructive jaundice probably due to LN enlargement

Answers

- 1) ART was stopped because the clinician felt that ART-induced liver injury was present. The patient was then neither followed nor referred while the jaundice persisted. The most important examination in a jaundiced patient is an ultrasound of the liver to further diagnose the underlying condition.
- 2) ART-DILI, TB-DILI, herbal drug toxicity, and Hepatitis B (especially IRIS), but also other flares, TB-liver-IRIS, liver cirrhosis (HBV or alcohol), biliary obstruction due to tumours, lymphoma or lymph nodes, HIV-associated cholangitis, hepatitis (A,B,C other viruses), haemolysis (due to malaria or other), focal liver infections (amoebic or bacterial abscess), and fatty liver (due to NRTI) are amongst the reasons that need to be considered in a jaundiced patient.
- 3) Atazanavir may cause unconjugated hyperbilirubinaemia (similar to Gilbert's syndrome), which is not accompanied by liver injury. The drug should only be substituted if jaundice is marked or not tolerated by the patient.
- 4) HIV-associated cholangiopathy has been well described as an inflammatory disease of the bile ducts associated with severe immunosuppression (CD4 <200). Several agents have been implicated, including CMV, cryptosporidium, and microsporidium. Abdominal pain is the most common symptom, but many patients are asymptomatic. Post-hepatic jaundice is seen with biliary obstruction. Often papillary stenosis is the cholangiographic finding; others develop sclerosing cholangitis. Both are difficult to see on ultrasound; most often, biliary dilatation without visible cause (tumour) is the finding that suggests the disease. Treatment is ART (and, potentially, antibiotics, in cases of bacterial superinfection), as ERCP is commonly not available.

Outcome and Follow-up

It was felt that the jaundice was not an ART-DILI. The cause seemed to be an obstructive jaundice, most probably due to the many enlarged lymph nodes in the portal region. The nodes are most likely due to disseminated KS, although other causes (TB, lymphoma) could not be fully ruled out. The correlation of the jaundice with ART initiations (starting after three weeks) may suggest an element of IRIS, with increased swelling of the nodes—although the sustained obstruction long after stopping the ART is more difficult to explain.

ART was re-initiated (TDF/3TC/EFV), and the patient started on vincristine/bleomycine for disseminated KS. She improved gradually, although the dilated bile ducts were still visible after one month of treatment. She eventually returned to her village, and was subsequently lost to follow-up.

Comments

Ultrasound is the most important first exam to narrow the wide differential diagnosis in jaundice in HIV/TB patients. Further diagnostic work-up needs to be balanced with treatment trials, and the stopping and starting of drugs under careful and frequent monitoring of LFTs to find suitable options for the patient. This can be one of the most complex tasks in ART treatment.

Key Learning Point

Jaundice in HIV/ART patients is complex; therefore, patients need a careful diagnostic work-up. If that cannot be done locally, the patient should be referred! Stopping all treatment is definitely not a good long-term option.

Case 73

Presentation

A 24-year-old HIV-negative man was seen in the clinic. He had started TB treatment a month ago for pulmonary TB. He recently started vomiting; and his family realized that he had developed increasingly yellow eyes. This was confirmed by physical examination. In addition, his liver was slightly enlarged; his spleen was also palpably enlarged. The patient admitted to drinking about 5 to 6 beers per day. His HIV test was negative; he was found to be Hep B positive.

His labs showed:

AST	207 U/L	(normal <40)
ALT	119 U/L	(normal <40)
Bilirubin tot	2.9 mg/dL	(normal <1.1)
Albumin	24 g/L	(normal 35–52)

An ultrasound was done. It showed an enlarged liver and spleen, with no biliary dilatation; the liver parenchyma was coarse, the surface nodular, and the vascular structures massively reduced. Minimal ascites was seen next to the liver.



Questions

- 1) What is the underlying pathology? How could this patient be treated?
- 2) In cases of drug-induced liver injury (DILI) on TB treatment, what are some possible strategies?
- 3) Which ART can also cause ART-DILI?

Diagnosis

Jaundice due to liver cirrhosis (HBV, alcohol), and possible DILI

Answers

- 1) The patient has a pre-existing liver disease, which was aggravated by drug-induced liver injury (DILI), as TB drugs were started.
- 2) Incidence of DILI caused by TB drugs is highest with PZA, followed by INH and RIF. EMB carries little risk of DILI. If DILI develops, all potential hepatotoxic TB drugs (PZA, INH, RIF) should be stopped.

At this stage, it is important to review the diagnosis of TB. If the diagnosis is solid, three different TB drugs (streptomycin, moxifloxacin, and EMB) should be given ('liver-sparing TB Tx'), and continued throughout rechallenge. Once the ALT has fallen to <100, a rechallenge with TB drugs may be considered, while carefully monitoring ALT. TB drug rechallenge has been found to be successful without recurrence in 60% to 90% of patients.

One possible regimen is to start RIF (normal dose) on day 1, then add INH (normal dose) on day 8 (and possibly pyrazinamide on day 15—but often PZA is omitted, and streptomycin continued). Alternatively, all (RIF, INH, PZA) drugs are re-introduced from day 1; often, no new DILI ensues.

Sequential re-introduction may be difficult, as drugs are often not readily available individually (only in fixed drug combinations), and non-standard treatments may be difficult to explain to staff and patients. Luckily, the same drug combination is often tolerated on re-introduction; we suspect that many of the cases actually represent adaptation rather than true hepatocellular injury.

- 3) All currently available antiretrovirals can cause hepatotoxicity. NVP is most often associated with hepatotoxicity (sub-clinical significant increase in liver enzymes 5 to 15%, clinical hepatitis in 2%). Other NNRTIs, all PIs, and raltegravir can also cause DILI. Remember also that CPT can cause liver injury; it should be stopped, unless there are compelling reasons (e.g., CD4 count <200) to keep it.

Outcome and Follow-up

All TB drugs were stopped initially. The patient's jaundice subsided over the next two weeks, and a liver-sparing regimen was initiated. He received a combination treatment of RIF/INH/EMB with moxifloxacin during the initial phase, after which RIF/INH was continued, which he tolerated well.

The patient was advised to reduce his alcohol consumption, which he did. After his TB treatment was finished, TDF/3TC was prescribed as treatment for the hepatitis B infection.

Comments

As a confusing differential diagnosis to DILI, hepatitis flares can be seen when starting ART because of an increase in HBV-specific T-cell responses (HBV IRIS, role of steroids controversial). Risk factors are high baseline ALT, and high HBV DNA. Ideally, this is accompanied by reduced HBV viremia, and seroconversion from HBeAg+ to HBsAb+. On the other side, discontinuation of HBV-active drugs (3TC, TDF) may also lead to HBV flares. Alternatively, other hepatitic superinfections (hep A, hep C, herpes) and breakthrough of drug-resistant HBV may be considered.

Liver TB-IRIS is also well documented as a cause of elevated LFTs. Patients usually show hepatomegaly and mainly elevated AP without evidence of biliary obstruction on US (an enlarged, echogenic liver may be seen). In most cases, there is evidence of TB-IRIS at another anatomic site (e.g., intra-abdominal LN).

Key Learning Point

Many patients with TB-DILI tolerate TB drugs when re-introduced under careful monitoring.

Suggested Reading

Heller T, Wallrauch C, Lessells RJ. Reply to Sharma et al and Saukkonen et al. *Clin Inf Dis*. 2010; 51(2):255.

Jong E, Conradie F, Berhanu R, Black A, John M-A, Meintjes G, et al. Consensus statement: management of drug-induced liver injury in HIV-positive patients treated for TB. *S Afr J HIV Med*. 2013;14(3):113–119.

Case 74

Presentation

An 18-year-old female patient was admitted for epistaxis. She recently tested HIV positive, but did not complain of weight loss, or of any other symptoms suggesting an opportunistic infection. Her CD4 count was found to be 643 cells/mm³. Upon careful questioning, she reported having regular but strong menstrual bleeding for a long time, as well as previous episodes of nosebleeds.

Her full blood count reveals:

WBC	5 800 cells/mm ³
Hb	8.6 g/dL
MCV	70 fL
MCH	31 pg
Plt	32 000/mm ³

Questions

- 1) What are common causes for cytopaenia—and especially thrombocytopaenia—in HIV patients?
- 2) How should this case be treated?

Diagnosis

HIV-associated ITP

Answers

1) Cytopenias, including thrombocytopaenia, are common complications of HIV. They are broadly classified as being caused either by a bone marrow production defect, or by increased peripheral loss and destruction of blood cells. Production may be disturbed by opportunistic infections infiltrating the bone marrow (*M. tuberculosis*, MAC, *Cryptococcus*), although patients in this group generally have advanced HIV disease. Malignant marrow infiltration (lymphoma) may be another cause for reduced production. HIV dysplasia is a non-clonal disease that is morphologically often indistinguishable from myelodysplastic syndrome, and is also more marked as the HIV disease progresses. A variety of drugs used in HIV patients can cause thrombocytopaenia, including CTX, RIF, fluconazole, and amphotericin.

Increased peripheral loss occurs in immunologically mediated cell destruction. Immune thrombocytopenic purpura (ITP) occurs in up to 30% of HIV patients, and is the most common cause of thrombocytopaenia in HIV. Thrombotic thrombocytopenic purpura (TTP) is characterized by thrombocytopaenia, haemolytic anaemia, neurological signs, fever, and renal impairment. The red blood cells are mechanically destroyed; these are seen as characteristic red-cell fragments, or schistocytes, on the peripheral blood smear.

2) Given the patient's history, and the absence of other symptoms, the most likely diagnosis is ITP. A microcytic anemia is also present, probably due to iron deficiency caused by bleeding. Management of ITP includes ART and prednisone (1 mg/kg/day if the platelet count is $<30 \times 10^9/L$). If the platelet count does not improve after two weeks, the dose is doubled; in refractory cases, splenectomy may be necessary. For the anaemia, iron and multivitamins can be substituted.

Outcome and Follow-up

The patient was started on ART, and prednisolone (60 mg) was given for one week. After one month, she reported reduced bleeding, and her platelets had increased to $54\,000/mm^3$. She continued ART uneventfully.

Comments

HIV-associated ITP is similar in clinical presentation to the non-HIV-associated disease. In HIV, the mechanism is thought to be due to an HIV-induced auto-antibody against the platelet surface glycoprotein IIIa. Many patients present with ITP as the first manifestation of HIV, although it can occur in both early and advanced disease. Where history, clinical examination, and laboratory findings are compatible with the diagnosis of ITP, the diagnosis can be made, and a bone marrow biopsy becomes unnecessary.

TTP is a far more dangerous and potentially lethal condition. Platelet microthrombi form in the capillaries, leading to intravascular haemolysis and organ ischaemia. HIV is the most common virus precipitating TTP. Severe thrombocytopaenia plus significant red-cell fragmentation on the blood smear are suggestive of TTP. Renal function is often impaired. However, in acute severe renal impairment, haemolytic uraemic syndrome (HUS) should also be considered. HIV-associated TTP typically occurs in young African females with high viral loads, and before ART. HIV-associated TTP can be treated with plasma infusion therapy (fresh-frozen plasma (FFP) infusions at 30 ml/kg/day + prednisone 1 mg/kg/day). ART should be initiated simultaneously.

Key Learning Point

ITP is the most common cause of thrombocytopaenia in HIV patients.

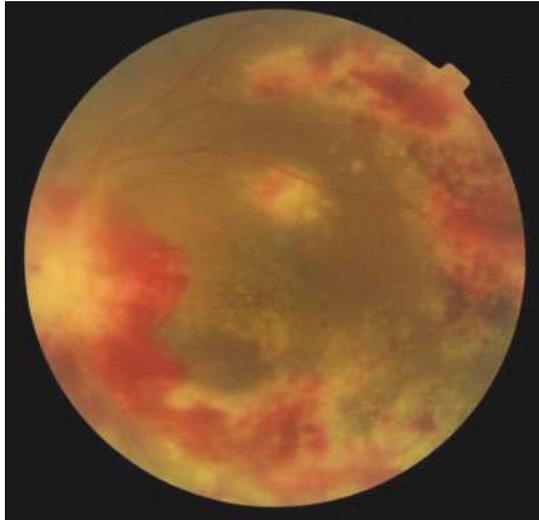
Suggested reading

Opie J. Haematological complications of HIV infection. *S Afr Med J.* 2012;102(6):465–468.

Case 75

Presentation

A 19-year-old woman was seen at the TB ward, where she was admitted for streptomycin injections for re-treatment of pulmonary smear-positive TB (SRHZE). The patient was HIV positive, and had started ART a few days prior to being admitted. She looked generally very unwell, was malnourished, and had oral candidiasis. Additionally, she reported that she could not see well with her left eye (she was unable to count fingers, but could see shadows); her vision on the right side was intact. She was referred to the ophthalmology clinician for fundoscopy.



Questions

- 1) What is the most likely diagnosis?
- 2) What is seen in the fundoscopy image?
- 3) How can it be treated in our setting?
- 4) A CD4 count was done. What result do you expect?

Diagnosis

CMV retinitis

Answers

- 1) CMV retinitis is the most likely diagnosis.
- 2) On the fundoscopic image, retinal infiltrates are seen, with areas of haemorrhage. These seem to follow the vessels, and are more pronounced in the periphery. Additionally, smaller central infiltrates are seen, with involvement (blurring) of the papilla (the whitish structure on the left side).
- 3) Ideally, the treatment of CMV retinitis is ganciclovir 5 mg/kg bd IV for 14 days (this is expensive, often not available, and requires the patient to be admitted to the hospital). Antiviral treatment prevents CMV retinitis progression, but does not reverse visual loss. Alternatively, the patient can be injected intravitreally with ganciclovir 2 mg in 0.08 mL once a week. The treatment can be discontinued once the CD4 count is > 100 cells/mm³ on ART.
- 4) CMV retinitis usually occurs when the CD4 cell count falls below 50 cells/mm³.

Outcome and Follow-up

CMV retinitis was diagnosed in both eyes. As only a very small quantity of ganciclovir was available (from a donation), the patient was transferred to the eye clinic at the central hospital. The ophthalmologist injected the patient on a weekly basis with intra-ocular ganciclovir. This treatment was continued until her stay in the TB ward was finished; her sight did not improve, but neither did it deteriorate. She continued her ART, but was subsequently lost to follow-up at our clinic.

Comments

Cytomegalovirus (CMV) retinitis is an opportunistic infection of all retinal layers; it results in progressive retinal destruction, leading to blindness within days. In the pre-ART era, CMV used to be a leading cause of blindness in developing countries with a high burden of HIV. CMV retinitis has the potential to involve and rapidly damage the macula and optic disc, which would ultimately lead to retinal detachments. The disease is usually recognized unilaterally at first, but may also present bilaterally. Disease progression often starts in the periphery of the retina; therefore, patients may not experience symptoms at first. Typical symptoms include reduced visual acuity (often worse when counting fingers), visual field defects, itchy or watery eyes, and flashes.

Cytomegalovirus retinitis is diagnosed based on the clinical appearance of the retina: characteristically fluffy retinal infiltrates occur, with areas of haemorrhage. Retinal involvement is often seen along blood vessels. In its most severe form, retinitis can include the optic disc (papillitis). CMV retinitis can also appear as granular white areas without haemorrhage, in which case it must be distinguished from cotton-wool spots that can be seen on the retina of AIDS patients unrelated to CMV. With ART being able to suppress HIV, the incidence of CMV retinitis has decreased substantially. ART must be started immediately, even if treatment for CMV is not available.

Key Learning Point

If possible, patients with low CD4 counts should be screened for CMV retinitis by fundoscopy.

Suggested Reading

Visser L. Managing CMV retinitis in the developing world. In: McGavin M, editor. A global review and practical manual for the prevention of world blindness: selected and updated articles from the Journal of Community Eye Health 1988–2003. London: International Centre for Eye Health; 2003, p.139–142.

Case 76

Presentation

A 35-year-old woman presented with severe headache and neck stiffness. The LP revealed only a slightly elevated protein of 0.65 g/L (normal 0.15–0.4). An HIV test was negative.

The severity of the headache warranted a CT of the brain, which showed meningeal enhancement consistent with meningitis. TB treatment for presumed TB meningitis was commenced, and the patient was discharged home.

She presented again to the OPD a month later, still complaining of headache. The LP was repeated, and again showed only a slightly elevated protein. It was felt that her headache and neck stiffness may have been secondary to cervical spine pathology, but an MRI of the cervical spine detected no abnormality; the patient was discharged on analgesics.

When she was seen again a few weeks later, she was still complaining about the same symptoms, except that she now had tenderness on the right side of her neck, with a firm lymph node, plus hypoglossal nerve palsy and weakness in her right arm. Clinically, she was cachectic; there was still concern that she might be HIV positive. Although her HIV test was again negative, a CD4 count was ordered; it came back at 290 cells/mL. This was taken to be suggestive of HIV; a viral load was ordered to confirm the presence of viral HIV RNA.

Questions

- 1) What would your next diagnostic step be?
- 2) How do you feel about the assumption that her low CD4 count indicated HIV infection? What other diseases can show reduced CD4 counts?
- 3) What clues are there that the patient may not be suffering from TB meningitis?

Diagnosis

Nasopharyngeal carcinoma

Answers

- 1) The lymph node should be excised for histological examination.
- 2) HIV is the most common cause of low CD4 counts, but there are many other diseases that cause reduced values; these need to be considered before assuming an HIV test to be a false negative:

Infections—*Mycobacterium tuberculosis*, atypical mycobacteria, CMV, EBV, Hepatitis B virus, Human T cell lymphotropic virus 1 and 2, influenza

Malignancy—Non-Hodgkin's lymphoma, Mycosis fungoides, myelodysplastic syndrome, other malignancies

Autoimmune diseases—Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis

Drugs—Corticosteroids, chemotherapy, cytotoxic immunosuppressants, and others (cephalosporin, IFN-a)

Primary immunodeficiency syndromes with possible adult onset

Idiopathic CD4 lymphocytopenia (ICL)

Aplastic anemia

Malnutrition

- 3) The results of her CSF studies are not highly suggestive of TB meningitis. Especially in an HIV-negative patient with no other known causes for immunosuppression, acellular CSF would be extremely unusual. The classical findings of TB meningitis usually display CSF with a lymphocytic predominance, with raised protein and low glucose. However, TBM can present with only one of these findings, so it can be difficult to diagnose definitively. Therefore, in our environment, it is common practice to start a patient on empiric treatment for presumed TB meningitis if the CSF is suggestive. Additionally, the initial CT displayed meningeal enhancement, which supported the diagnosis. It should be noted, however, that meningeal enhancement seen on CT could be a consequence of a lumbar puncture as well.

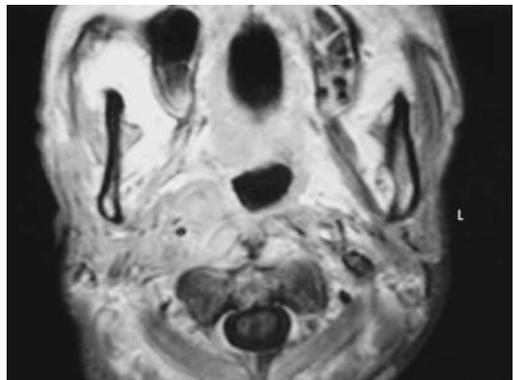
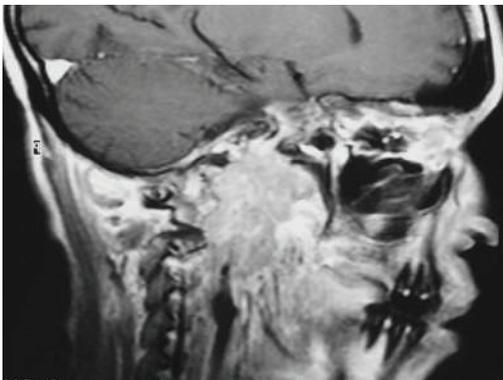
A mildly increased protein is very non-specific; it can occur in both infectious and non-infectious conditions, including conditions associated with CSF flow obstruction. Such conditions include TB; fungal, viral, or bacterial meningitis; leptomeningeal metastases; and inflammatory conditions, such as Guillain-Barre Syndrome.

The fact that the patient failed to improve on TB treatment suggested that she either did not have TB meningitis, or had a resistant strain of TB.

In addition, the severe tenderness of her neck pointed away from TBM.

Outcome and Follow-up

The nodule in her right neck was excised and sent for histopathology; it was shown to be a metastasis of a squamous cell carcinoma. Another MRI was ordered of her head and spine; this revealed a nasopharyngeal carcinoma. Her HIV1 PCR was negative. An appointment was made with oncology, but the patient was lost to follow-up.



Comments

Nasopharyngeal carcinoma is frequently associated with EBV infection. Expression of viral oncogenes (LMP1) in latently infected epithelial cells seems to be a critical early step in carcinogenesis. Additionally, there is recent evidence that HPV may be implicated in head and neck cancers, particularly in HIV patients. Cancer of the nasopharynx typically does not cause early symptoms, but local obstruction may lead to chronic sinusitis or otitis media. Advanced disease can cause neuropathies with pain of the cranial nerves.

Key Learning Points

- Rapid HIV antibody tests are very sensitive, and specific for HIV-1 infection.
- Low CD4 counts are not a proxy for HIV infection.

Notes

Case 77

Presentation

A 17-year-old female patient was brought to the clinic because of her generally poor health. She complained of longstanding diarrhoea and weight loss, in addition to headache and dizziness. The patient appeared to have advanced immunodeficiency; the diagnosis of HIV was confirmed by a rapid antibody test. On the skin there were multiple small ulcerations, and papules with central umbilication.



(Pictures courtesy of Dr. M. Johansson)

Questions

- 1) What is your differential diagnosis for the skin lesions?
- 2) What would be your next diagnostic and therapeutic steps?

Diagnosis

Cryptococcomata of the skin in disseminated cryptococcosis

Answers

1) Cryptococcosis is the most likely diagnosis.

The umbilicated lesions could make one suspect molluscum contagiosum. These are also frequently seen in children, but tend to evolve slower, and do not ulcerate.

Histoplasmosis of the skin is another possibility, although rare in our area (and rarely diagnosed).

2) Cryptococcal antigen (CrAg) testing in the serum would be the most appropriate test, when available. If positive, a lumbar puncture is urgently needed to assess for CNS involvement. A CXR should be done to check for pulmonary involvement (which is a bad prognostic sign). Systemic antifungal treatment should be started, as for cryptococcal meningitis.

Outcome and Follow-up

In the CSF, CrAg was found to be highly positive (+++). The patient was started on amphotericin B; a skin biopsy and CD4 count were scheduled for the following day. Despite the initiation of antifungal therapy, the patient died the same night.



Other examples of Cryptococcomata (different patients).

A patient with Molluscum contagiosum lesions (shown for comparison purposes).

Key Learning Point

If you have a clinical suspicion of cutaneous cryptococcosis, start empirical antifungal therapy.

Suggested Reading

Aberg JA, Powderly WG. Cryptococcosis and HIV. San Francisco (CA): University of California, San Francisco HIV InSite Knowledge Base. 2006 May. Available from <http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-02-05>.

Case 78

Presentation

A 33-year-old HIV-positive woman has been on d4T/3TC/NVP for eight months. The patient has had TB twice before (she completed the last course of treatment at the time of ART initiation). She is sitting in your consulting room in clinic, unable to give a history because of breathlessness, but shakes her head when asked about cough and diarrhoea. She is holding her abdomen; she is pale but not wasted. Her chest is clear on examination, and the abdomen soft but tender. Bowel sounds are present. There is no DVT clinically, and the patient appears adequately hydrated. Her pulse is 110/min, and her blood pressure 96/45 mm Hg. A lactometer reading shows 9.5 mmol/L.

Questions

- 1) What should you do right away?
- 2) What are the possible diagnoses?
- 3) How should the patient be managed in the hospital?
- 4) What should happen in the longer term?

Diagnosis

Lactic acidosis due to NRTI treatment

Answers

- 1) Oxygen and IV fluids should be initiated, if available. More history and information should be gathered from relatives (it is unlikely that she arrived on her own). Blood glucose should be checked, and hospital admission organised.
- 2) The patient has been on ART for a relatively short time, so she should still be considered immunocompromised. She could also be suffering from a complication of ART, or from a non-infectious, non-ART related condition, such as:
 - a) **Sepsis** from any source.
 - b) **Respiratory**—community-acquired pneumonia, PCP, TB, cryptococcosis or other fungal lung infection, CMV, or the occlusion of a bronchus by lymph nodes in lymphoma/KS/TB. Pulmonary embolism and pneumothorax should also be considered.
 - c) **Abdominal**—gastroenteritis, colitis, pancreatitis (ddl/d4T/traditional medicine/snake bites), embolic disease, abdominal TB.
 - d) **Cardiac**—effusion causing tamponade, cardiomyopathy.
 - e) **Acidosis**—renal failure, lactic acidosis, diabetic ketoacidosis.
- 3) Admission to the hospital for laboratory investigations and CXR. If the above causes have been excluded, lactic acidosis as a consequence of NRTI therapy can be diagnosed. Typical symptoms of lactic acidosis are nausea, vomiting, abdominal pain, weight loss, fatigue, myalgia, abdominal distension, abdominal pain, dyspnoea, and cardiac dysrhythmias. Blood results include an elevated anion gap, metabolic acidosis (low CO₂), and, occasionally, elevated ALT, LDH, and CK. Management is supportive, with the cessation of ARVs.
- 4) Practically all NRTIs can cause lactic acidosis. We would currently use TDF to replace d4T. ART should be restarted after the blood lactate has returned to normal (usually within 2–3 months), but lactate should continue to be monitored (e.g., monthly for 6–12 months), as lactic acidosis may recur. An alternative ART regimen that avoids the NRTIs most commonly associated with lactic acidosis (d4T/ddl) should be used. The risk is lower with AZT, and lowest with 3TC, TDF, and ABC. In very severe cases, a regimen omitting all NRTIs (e.g., only LPV/r/EFV) might be considered—but this needs to be discussed with an expert.

Outcome and Follow-up

The patient was treated for lactic acidosis as described above. After 10 weeks, her lactate was less than 3 mmol/L, and ART (TDF/3TC/EFV) was restarted.

Comments

This presentation has become increasingly rare in recent times, as neither d4T nor ddl are part of standard regimens anymore. All patients should be switched to newer regimens, even when they are asymptomatic. This does not mean that lactic acidosis should not be considered anymore, as all NRTIs can cause mitochondrial disturbances, and thereby lactic acidosis. Even with TDF, fatal lactic acidosis has been reported. Identifiable risk factors for the development of lactic acidosis in NRTI-treated HIV patients are pregnancy, female gender, obesity, low CD4 count, and poor liver function.

NRTI-associated lactic acidosis is thought to be due to mitochondrial toxicity by inhibition of mitochondrial polymerase- γ . Inhibition of mitochondrial DNA replication leads to impairment of the mitochondrial aerobic metabolism, resulting in accumulation of lactic acid. It is estimated that 5% to 20% of patients treated with NRTI have hyperlactataemia; luckily only 1% develop severe lactic acidosis. The reason why only a small number of patients who receive NRTIs develop mitochondrial toxicity is still unknown. TDF, 3TC, and ABC have a lower affinity for the enzyme, and are therefore less prone to cause lactic acidosis.

In case of acidosis, the following algorithm might be used to guide treatment of lactic acidosis/symptomatic hyperlactataemia.

Level	Lactate	HCO ₃	Action
Normal	<2.5	>20	None; look for other causes of symptoms
Mild	2.5–5	>20	Consider outpatient switch of ART regimen
Moderate	5–10	15–20	Stop ART, treat as inpatient, rehydrate, give Thiamine + Vit B If well, switch ART Otherwise, treat as severe
Severe	>10	<15	Stop ART, treat in high-care unit, balance fluids, give IV Thiamine + vitamin B, broad-spectrum antibiotic (ceftriaxone)

It is important to notice that lactate does not decline quickly after cessation of ART. If a decline is observed after a few days, it is almost always the case that something else (e.g., dehydration that was replaced, infection that was treated) was responsible for the elevated lactate.

If the patient's condition is stable enough, and the patient is receiving an NNRTI, the NNRTI should be stopped first, and the NRTIs should be continued for approximately one week to prevent ineffective monotherapy and resistance development. (The half-life of an NNRTI is far longer than that of NRTI.)

Key Learning Point

Rapid resolution of acidosis and normalisation of venous lactate level would suggest a cause other than ART-related lactic acidosis.

Suggested Reading

Editorial Office. Guidelines for the prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis. S Afr J HIV Med. 2006 Mar;6(1):8–14. Accessed from: <http://www.sahivsoc.org/index.php/guideline/index/5/37>.

Notes

Case 79

Presentation

A 57-year-old man presented critically ill with a two-week history of a swollen and painful left testicle, progressive scrotal swelling, and involvement of the left thigh. His HIV status was unknown.

On examination, he was hypotensive, febrile (39° C), tachycardic, and showed mild confusion. His scrotum was grossly swollen (diameter 15 cm), exquisitely tender, red and warm, with no surface lesions evident. PR examination demonstrated a firm, very tender prostate.

Blood investigations revealed renal failure and mild anaemia. He was oliguric, and the urine dipstick was positive for blood and protein.

The diagnosis of sepsis secondary to urogenital infection was made, and the patient admitted to the high-care unit, where his vital signs were monitored. Gram-negative sepsis was assumed to be the most likely cause; broad-spectrum IV antibiotics (ceftriaxone and ciprofloxacin) were given. In addition, large amounts of IV fluid were administered, and prophylactic heparin and omeprazole were prescribed.

An ultrasound of the scrotum is shown below.



Questions

- 1) What is evident on the ultrasound? What should be your next procedure?
- 2) When treating severe sepsis and septic shock, what are the most important steps that can be done with limited intensive-care resources?

Diagnosis

Gram-negative sepsis with multi-organ failure secondary to urogenital TB

Answers

- 1) The ultrasound shows fluid collection, with fibrin streaks surrounding the normal testicle. Considering the clinical picture, pyocoele is the most likely diagnosis; the fluid should be aspirated.
- 2) Severe sepsis/septic shock is difficult to manage in our setting, due to the limited availability of ICU resources, especially mechanical ventilation. Nevertheless, many of the recommended guidelines, especially those regarding initial fluid administration can be followed:
 - Begin fluid resuscitation immediately in patients with hypotension, using crystalloids or colloids; do not delay pending ICU admission. Resuscitation goals: CVP 8–12 mm Hg, mean arterial pressure > 65 mm Hg, urine output >0.5 mL/kg/hr.
 - Give fluid challenges of 1 000 mL of crystalloids, or 300–500 mL of colloids, over 30 mins. More rapid and larger volumes may be required.
 - Begin intravenous antibiotics as early as possible—and always within the first hour of recognising severe sepsis and septic shock.
 - Formally evaluate the patient for a focus of infection amenable to source control measures (e.g., abscess drainage, tissue debridement).
 - Norepinephrine centrally administered is the initial vasopressor of choice. Do not use low-dose dopamine for renal protection. It may rarely be available.
 - Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors. The hydrocortisone dose should be 200 mg/day. Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine history warrants it.
 - Do not use fresh-frozen plasma to correct laboratory clotting abnormalities unless there is bleeding, or invasive procedures are planned.
 - Use intravenous insulin to control hyperglycaemia. Aim: blood glucose <180 mg/dL.
 - Do not use bicarbonate.
 - Use either low-dose unfractionated heparin or low-molecular weight heparin (unless contraindicated) for DVT prophylaxis.
 - Provide stress ulcer prophylaxis using cimetidine or omeprazole.

Outcome and Follow-up

US showed a pyocoele; fine-needle aspiration was done. The aspirate was sent for microscopy and AFB stain, as well as bacterial and mycobacterial culture. The gram stain came back showing gram-negative bacilli and AFB. RHZE was commenced.

The following day, the pyocoele was incised and drained. The patient's renal function deteriorated; he became anuric and uraemic, requiring sedation when he attempted to remove the lines. Creatinine peaked on day 6, with subsequent improvement in renal function resulting in polyuria. Baseline maintenance fluids were ordered to compensate for insensible losses; in addition, replacement fluids were given by the nursing staff, guided by hourly measurement of urinary losses.

The patient showed some improvement; by day 7, he was able to hold a conversation. The patient tested positive for HIV. Unfortunately, on day 8, he developed GI bleeding and probable disseminated intravascular coagulation (DIC); his Hb and platelets dropped, and his INR rose. He was transfused one unit of packed cells; however, it is often difficult to get blood products in our setting. Further debridement was considered, but the patient's general condition deteriorated, and he died a week later.

TB culture results received two months later confirmed *Mycobacterium tuberculosis*, resistant to rifampicin, isoniazid, and streptomycin, but sensitive to ethambutol, kanamycin, and ciprofloxacin.

Key Learning Point

Urogenital TB is probably under-recognised; superimposed bacterial infections are common.

Suggested Reading

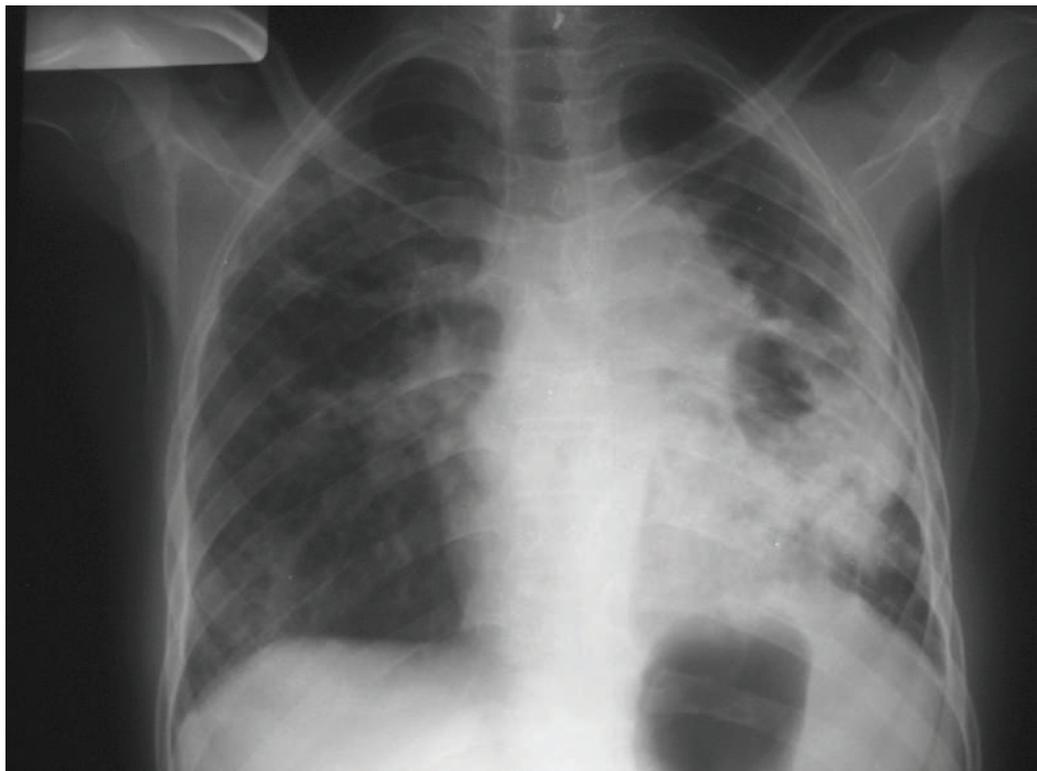
Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al: Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med.* 2017 Mar;43(3):304-377. Accessed from: http://journals.lww.com/ccmjjournal/Fulltext/2017/03000/Surviving_Sepsis_Campaign__International.15.aspx.

Case 80

Presentation

A 23-year-old female patient was admitted, suffering from typical TB symptoms, with chronic productive cough and loss of weight. She was treated for TB seven, three, and two years ago; on this occasion, she complained about recurrence of symptoms. A sputum GeneXpert was sent. It showed RIF resistance; the following culture grew *M. tuberculosis* resistant to isoniazid, rifampicin, and streptomycin; and sensitive to ethambutol, ciprofloxacin, and kanamycin.

On admission, the patient looked unwell, but did not show signs of respiratory compromise. She was counselled and tested for HIV; the test result was positive. A CXR was taken.



Questions

- 1) What is MDR-TB? What is XDR-TB?
- 2) How should this patient be treated after the Xpert result has been obtained?
- 3) What are the most common side effects of MDR-TB treatment?

Diagnosis

MDR-TB/HIV co-infected patient

Answers

1) Multi-drug-resistant TB (MDR-TB) strains are resistant to at least isoniazid and rifampicin. Strains resistant to only a single drug, or to other antibiotic combinations (e.g., isoniazid and streptomycin) are, by definition, not referred to as MDR strains. Worldwide, approximately 4% to 5% of all TB strains are resistant to multiple drugs.

Extensively drug-resistant TB (XDR-TB) strains also show resistance against the class of quinolones (ofloxacin and ciprofloxacin), and at least one of the injectable second-line drugs (kanamycin, amikacin, and capreomycin). XDR-TB is still more rare, although local outbreaks with extreme high mortality have been reported (e.g., in Tugela Ferry, KwaZulu-Natal).

2) The patient should be treated as soon as possible with an adequate combination of second-line TB drugs. The detection of RIF resistance in the Xpert can be taken as proxy for MDR-TB. The principle that a patient should be treated with a combination of at least three effective drugs still applies. Second-line drugs are less effective, and far more toxic than first-line drugs. A commonly used regimen is a combination of kanamycin (IM for six months), levofloxacin, ethionamide, cycloserine, ethambutol, and pyrazinamide (orally for 18–24 months).

3) The most common side effects of MDR-TB treatment vary according to medication:

- **Kanamycin**—nephrotoxicity (check creatinine) and ototoxicity (audiogram, ask for new tinnitus, loss of hearing or vertigo).
- **Levofloxacin**—musculoskeletal problems, tendon rupture; it is generally well tolerated, but NSAIDs might be indicated.
- **Ethionamide**—severe nausea and gastrointestinal side effects; try to treat with metoclopramide. This drug is often responsible for MDR patients not gaining weight despite successful treatment.
- **Cycloserine**—peripheral neuropathy and CNS disturbance. Pyridoxine (100–150 mg od) is given to ameliorate the side effects, but psychosis and depression (including suicides) are seen. Antipsychotic treatment should be initiated if necessary.
- **Ethambutol**—ocular neuritis, especially after longer treatment; look out for red-green deficiency.
- **Pyrazinamide**—hepatotoxicity and gout; this is usually one of the better-tolerated drugs.

Outcome and Follow-up

The patient's CXR showed extensive disease; the patient was started on MDR treatment. After three weeks, she developed symptoms of psychosis, and threatened to attack family and staff. Cycloserine was stopped, and haloperidol given. The patient's mental status improved; eventually, the patient was able to leave the hospital, and was treated at home (cycloserine was not restarted!).

Comments

One of the biggest problems associated with MDR-TB is the delay in diagnosis and initiation of treatment. Nucleic-acid-based tests (e.g., MDRTB plus line assay) shorten the time to diagnosis; field trials in South Africa have shown them to be both effective and feasible. To err on the safe side, we would treat a patient with RIF resistance detected by the GeneXpert test as MDR-TB until the culture results confirm otherwise.

Key Learning Point

GeneXpert MTB/RIF and sputum culture should be sent for any patient with TB symptoms who has had previous disease.

Suggested Readings

World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva (Switzerland); World Health Organization; 2014. Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf?ua=1.

Case 81

Presentation

A 34-year-old male patient was admitted to the ward due to painful feet for a few weeks. All the toes on his right foot, as well as the big toe of his left foot, had turned black.

The patient was HIV positive; his last CD4 count was 231 cells/mL. He was a non-smoker, and had no history of diabetes, hypertension, or other cardio-vascular disorders.



Questions

- 1) What is shown in the picture? How would you treat the patient?
- 2) Vasculitis is associated with different types of infections. Name three pathogens.

Diagnosis

Digital necrosis, HIV-associated vasculitis/vasculopathy

Answers

- 1) Digital ischemic gangrene of the hands and feet is a generally uncommon, but well-documented, dramatic presentation in patients with HIV infection. In our region, it is felt to be seen relatively more frequently. It is often widespread, and may involve multiple toes and fingers. The pathogenesis is unclear, but treatable conditions (e.g., cardiac emboli from endocarditis) should be ruled out. The optimal therapy is also unknown. Aspirin and heparin might be given, and steroids are an option, but frequently the patient requires amputation.
- 2) Three pathogens:
 - *Hepatitis B virus* (HBV)—associated with polyarteritis nodosa (PAN) of medium-size vessels.
 - *Hepatitis C virus* (HCV)—associated with cryoglobulinaemia; involves vessels of any size, but predilection for small vessels.
 - *Rickettsia* (e.g., African spotted fever (*R. africae*))—Ticks in sub-Saharan Africa transmit *rickettsiae*, which infect endothelial cells. They cause fever, headache, myalgia, and a spotted rash. Often an eschar (small ulcer) at the site of the tick bite is found, as well as regional lymphadenitis.

Outcome and Follow-up

Low-dose heparin and aspirin were prescribed. In addition, the patient needed opiate analgesia. A transthoracic echocardiogram showed a normal heart function, and normal cardiac valves. After a few days in hospital, his feet developed an offensive odour. A fever was recorded, and antibiotic therapy started. Eventually, he required an amputation.

Comments

Almost every pattern and type of vasculitis of small, medium, and large vessels has been encountered in the HIV setting. It is not fully clear whether HIV and vasculitis are causally or coincidentally related.

A polyarteritis nodosa (PAN)-like necrotising vasculitis is documented as involving muscles and nerves, as well as skin and the gastrointestinal tract. Peripheral neuropathy or digital ischaemia are also modes of presentation.

Infectious agents of all types and classes can cause vasculitis in immunocompromised patients. CMV, VZV, toxoplasmosis, pneumocystis, *Salmonella*, and *Mycobacterium tuberculosis* have all been associated with vasculitis in patients with HIV infection.

Key Learning Point

Secondary infection and bacteraemia are of concern with digital gangrene, especially in the immunocompromised; in the absence of specific therapy, amputation might be required.

Suggested Readings

Chetty R. Vasculitides associated with HIV infection. *J Clin Pathol.* 2001 Apr;54(4):275–278.

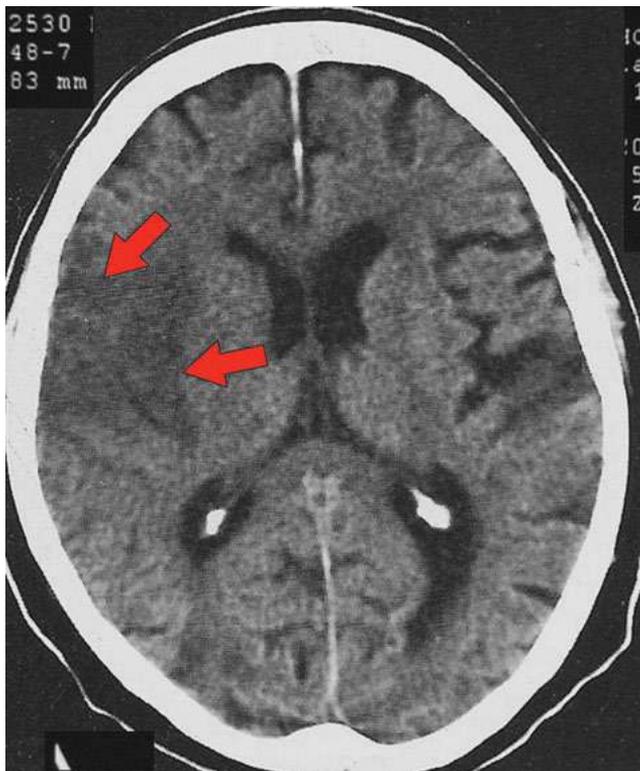
Dubé MP, Lipshultz SE, Fichtenbaum CJ, Greenberg R, Schecter AD, Fisher SD; Working Group 3. Effects of HIV and antiretroviral therapy on the heart and vasculature. *Circulation.* 2008 Jul 8;118(2):e36–40.

Case 82

Presentation

A 23-year-old HIV-positive woman was seen in the clinic with a left hemiparesis affecting mainly her face and arm. The patient had normal blood pressure, normal blood sugar, and was overweight. Her CD4 count was 59 cells/ μL , and she was ART naïve. She was transferred to the hospital for admission. A lumbar puncture revealed a minimally elevated protein, but was otherwise unremarkable.

The patient was started on CTX 4 tabs bd. After one week of treatment, she showed no improvement, and was sent for a CT scan of the brain.



Questions

- 1) What is shown on the CT?
- 2) What are the most common causes of stroke in HIV patients?
- 3) How should the patient be treated?

Diagnosis

Stroke in HIV patient, presumably HIV vasculopathy

Answers

1) A hypodense region in the right parietal area, most compatible with ischemic stroke in the area of the middle cerebral artery. No mass lesion was seen.

2) The following list summarises the causes of ischemic strokes in HIV patients in South Africa:

Opportunistic infections	28%
<i>Tuberculous meningitis</i>	15%
<i>Meningovascular syphilis</i>	5%
<i>Varicella zoster vasculitis</i>	5%
<i>Cryptococcal meningitis</i>	3%
HIV-associated vasculopathy	20%
Anti-cardiolipin antibody coagulopathy	19%
Cardioembolism	14%
Unknown cause	19%

Classical risk factors for ischemic stroke (hypertension, diabetes, hyperlipidaemia, and smoking) play a lesser role than in HIV-negative stroke patients. Intra-cerebral haemorrhages are rare, and are mainly due to hypertension.

2) Antiplatelet therapy (aspirin 150 mg od) is indicated, as in other cases of ischemic stroke. Additionally, the patient needs to be started on ART, especially as the CD4 count is low. ART might reduce the extent of the vasculopathy.

Outcome and Follow-up

There was no sign of toxoplasma infection, and syphilis serology was negative; the condition was diagnosed as a case of ischemic stroke due to presumed HIV vasculopathy. Aspirin 150 mg od was prescribed, and ART was started. The neurological deficit improved, but facial paralysis remained visible even after a few months.

Comments

HIV-associated cerebral vasculopathy has been reported as the aetiology of stroke in up to 20% of young (<46 yrs) HIV-positive stroke patients in a large South African series. The poorly defined vasculopathy often involves large or medium extracranial arteries (11%). It may manifest as aneurysmal and non-aneurysmal disease.

In addition, an intracranial small vessel vasculopathy has been described (9%). Often asymptomatic, it is characterised by hyaline small vessel wall thickening, and is associated with microinfarcts. This latter vasculopathy is difficult to define clinically. The cause and mechanism of the various HIV-associated vasculopathies is poorly understood.

Key Learning Point

Aspirin is indicated in any vascular complication of HIV, as it is for non-HIV infected patients.

Suggested Reading

Tipping B, de Villiers L, Wainright H, Candy S, Bryer A. Stroke in patients with human immunodeficiency virus infection. *J Neurol Neurosurg Psychiatry*. 2007 Dec;78(12):1320–1324.

Case 83

Presentation

A 36-year-old patient presented in the clinic with longstanding pain in the left ankle, which prevented her from walking normally.

The ankle was slightly warmer than the contralateral joint, and swollen without overlying erythema. The skin showed signs of a previous fistula; the patient reported that a pus-like discharge had come out a few months previously. She was HIV positive; her last CD4 count was 787 cell/ml. She was sent to the hospital for an x-ray of the ankle.



Questions

- 1) What does the x-ray show? What is the differential diagnosis?
- 2) What would be your next diagnostic steps?

Diagnosis

Osteomyelitis, most likely caused by TB

Answers

- 1) The ankle x-rays show demineralisation in the distal area of the tibia, as well as the fibula. This suggests a chronic pathological process, most likely infectious osteomyelitis. Neoplastic growth could be an alternative explanation, but the distribution in two bones makes that improbable.
- 2) A diagnostic biopsy (bone biopsy) should be performed, and sent for histology, as well as for bacterial and mycobacterial cultures.

Outcome and Follow-up

The patient had a bone biopsy. The sample was sent for histology, but the microbiology sample was lost during transport. Histology showed necrotising granulomatous inflammation. Although acid-fast bacilli were not identified, tuberculosis remained the favoured diagnosis. RHZE was started. Additionally, bacterial osteomyelitis was treated with clindamycin 600 mg tds for six weeks. The patient improved substantially after two months, and continued TB treatment uneventfully.

Comments

Bone and joint involvement in TB is quite common. Osteomyelitis is seen most commonly in the spine, although it can involve any bone. Tuberculous arthritis occurs mainly in the weight-bearing joints, most commonly the hips, knees, and ankles (in descending order). The period from onset of initial symptoms up until diagnosis is long, ranging from 12 to 36 months. Limitation of movement and joint swelling are commonly seen. Chronic sinus formation is reported in 25 to 50% of patients. Constitutional symptoms are absent in more than half of patients. The standard treatment is RHZE for two months, followed by RH for four months.

In this case, the patient was not started on ART, despite having a stage 4 disease (extrapulmonary TB). It was felt that, given her high CD4 count, she could be safely monitored with repeat CD4 counts.

Key Learning Point

In this setting, extrapulmonary TB is common; it can be seen in patients with relatively well-preserved CD4 counts, as well as in HIV-negative patients.

Case 84

Presentation

A 40-year-old HIV-negative man was seen in the hospital with right upper quadrant pain. He had no fever, diarrhoea, or any other complaints.

On examination, the patient looked generally unwell; he had diffuse abdominal tenderness without peritonism. The liver seemed enlarged on palpation.

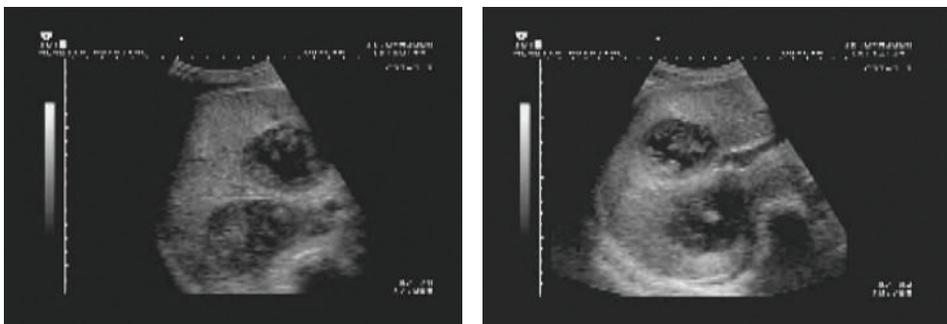
FBC

Hb	13.1 g/dL	(normal 11.5–16.5)
WBC	12.2 $10^3/\text{mm}^3$	(normal 4.0–11.0)
Plt	308 $10^3/\text{mm}^3$	(normal 150–500)

U&E and LFT

Creat	0.8 mg/dL	(normal <1.1)
Urea	35 mg/dL	(normal 12–50)
TBIL	0.7 mg/dL	(normal <1.1)
DBIL	0.1 mg/dL	(normal <0.3)
GGT	112 U/L	(normal 7–62)
ALP	231 U/L	(normal 42–121)
ALT	58 U/L	(normal 10–60)

An abdominal ultrasound was performed:



Questions

- 1) What do you see in the ultrasound images? What is the differential diagnosis?
- 2) What would you expect to find in the CXR?
- 3) Which tests would you order? How would you treat the patient?
- 4) Would stool examinations be helpful?

Diagnosis

Amoebic liver abscess

Answers

- 1) Two hypoechoic, partly anechoic lesions without a proper wall are found in the right lobe of the liver. The most likely diagnoses are amoebic and pyogenic liver abscess. Echinococcal cysts and necrotic liver tumours (necrotic metastases) are far less likely differential diagnoses.
- 2) An elevated right hemi-diaphragm, possibly with a small (sympathetic) pleural effusion, is compatible with a liver abscess.
- 3) One option is to aspirate the content of the cystic lesions. Pyogenic abscesses produce pus, which might grow organisms on culture. Amoebic abscesses produce a semi-liquid 'anchovy sauce' coloured material. Amoebae might be found in the material; although often only a time-consuming, enthusiastic search might produce a result, this is rarely indicated. Antibodies against amoebae are found in 95% of the sera of patients with amoebic liver abscess. A different approach is to treat with metronidazole, and follow the patient clinically.
- 4) Fewer than half of the patients with liver amoebiasis have amoebic cysts in the stool. On the other hand, in the tropics, where amoebiasis is endemic, many people excrete cysts so finding cysts in a patient with suspected amoebic liver abscess is of little significance.

Outcome and Follow-up

The patient was treated with metronidazole 400 mg tds for 14 days. He then came back to hospital; he reported feeling better, but still had mild pain. In the follow-up ultrasound, the abscesses appeared similar in size; their content was found to be less echogenic. To rule out other diseases, one of the collections was punctured and aspirated; 'anchovy sauce' coloured material was seen, which was found sterile on bacterial culture. The metronidazole treatment was continued for two more weeks. Neither diloxanide furoate nor paromomycin were available at this time, so bowel eradication treatment was not given.



Comments

In the differential diagnosis, it is important to consider that patients at risk for bacterial abscess are commonly older, have other infections (biliary tree, diverticulitis), or have had abdominal trauma, surgery, or intervention of the biliary system. The ultrasound appearance might often show multiple lesions; gas bubbles within the cavity confirm the bacterial origin.

Around 8% of patients with amoebiasis develop hepatic abscesses. It is more common in adults than in children, and more common in males than females. In animals, substantial necrosis is induced five to seven days after arrival of the amoeba in the liver, explaining the abrupt onset of pain in previously healthy individuals. The abscesses are usually round-shaped, and more commonly occur in the dorsal segments of the right lobe of the liver.

Key Learning Point

If an elevated right hemi-diaphragm or small right pleural effusion is found, an abdominal ultrasound should be performed to look for liver (or subphrenic) pathology.

Case 85

Presentation

A 12-year-old boy, recently diagnosed with HIV, was brought to the clinic by his grandmother, with pruritic skin lesions. The lesions were most pronounced on the patient's back and palms, but other areas were also affected. The scaly lesions were slightly elevated, and showed erythematous borders. He was otherwise healthy (his CD4 count was 138 cells/mL).



Questions

- 1) What is the diagnosis?
- 2) What is the differential diagnosis of scaly, itching skin lesions in an HIV-positive patient?
- 3) How can they be treated?

Diagnosis

De novo psoriasis in HIV infection

Answers

1) Psoriasis

2+3) The most frequently encountered pruritic, scaling skin diseases in HIV patients, and their treatments are:

- Tinea** (fungal infection): clotrimazole topical tid for two weeks (or nystatin or Whitfield's ointment, if available); if extensive, griseofulvin 0.5–1g od for three weeks can be given.
- Psoriasis**: 2% salicylic acid cream topical, possibly with coal tar. Alternatively, steroid creams may be used (e.g., hydrocortisone).
- Seborrhoeic dermatitis**: often no treatment indicated, if mild. In severe cases, use steroid cream (e.g., bethamethasone valproate)
- Scabies**: 25% benzyl benzoate lotion for 24 h; may be repeated after 72 h with washing of bed linens.
- Ichthyosis**: skin moisturizer or vaseline. If available, urea 5% preparations.



Seborrhoeic dermatitis is a differential diagnosis, the rash is here predominantly in the seborrhoeic areas of the body: scalp, face and intertriginous folds.

Outcome and Follow-up

The patient was initially treated with antifungal therapy. As the lesions were distributed over the whole integument, systemic therapy (griseofulvin) was given. After two weeks, he returned to the clinic, with the lesions unchanged; treatment for psoriasis with salicylic acid cream was initiated. The boy was seen a few weeks later (when he applied for a social grant); the lesions had improved substantially, and he did not complain about itchiness.



Pre-existing psoriasis can deteriorate in HIV infection, as seen in this different patient with severe generalized psoriasis.

Comments

The prevalence of psoriasis in HIV disease has been reported as approximately 1–3% of HIV-positive individuals. Associated arthritis seems to be more common; in general, the disease is more severe than in non-infected persons. Guttate psoriasis, in form of multiple raindrop lesions, as seen in this patient, is the most frequent form of psoriasis in HIV patients. Psoriasis of the palms and soles is also seen. Pre-existing psoriasis may undergo severe exacerbation with HIV disease; psoriasis is reported to become more severe with progression to AIDS. HIV-associated psoriasis has been found to respond to ART.

Key Learning Point

Fungal skin infections are by far the most common skin manifestation, and should be considered as the first, most likely diagnosis.

Suggested Reading

Mallon E, Bunker CB. HIV-associated psoriasis. *AIDS Patient Care STDS*. 2000 May;14(5):239-46.

Case 86

Presentation

A 34-year-old HIV-negative man presented with right hip pain, and increasing inability to walk. He had had hip pain for the past year, but it gradually became worse over the last two weeks. He had been diagnosed with spinal TB four years prior.

X-rays of his pelvis and his spine were done.



Questions

- 1) What do the x-rays show?
- 2) Which further tests would you order?
- 3) How would you treat the patient, especially with respect to his earlier episode of spinal TB?

Diagnosis

TB of the spine and right hip

Answers

- 1) Spine: destruction of L4/L5 vertebrae with osteolysis, and reactive osteosclerotic changes in the vertebrae
Pelvis: destructive arthropathy of the right hip joint with obliteration of the hip joint space, and associated severe osteopaenia of the femur.
- 2) As it is unclear to what extent the changes are a consequence of the previous TB infection or active disease (no previous x-rays available), an MRI may be helpful to differentiate. In case there is any doubt, it may be necessary to perform a biopsy.
- 3) The patient should be started on TB treatment, as he has clinical signs of progressing TB disease, compared to his relatively stable condition the last four years. As he was treated previously, he should receive TB regimen 2, which is RHZES for the first two months, RHZE for the third month, and then RH for the following five months.

Outcome and Follow-up

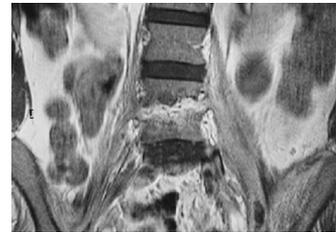
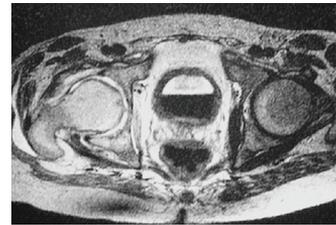
A diagnosis of TB of the spine and hip was made, and RHZES started. The patient responded quickly to TB treatment and simple analgesia (NSAIDs); within two weeks, he was walking with the aid of a walking stick. An MRI of his lumbar spine and left femur confirmed the active TB infection.

Comments

This case demonstrates the difficulty of assessing radiological changes when there is a history of previous TB. The same problem is encountered when chest X-rays are examined for TB in patients with previous pulmonary disease. If old images are available for comparison, the changes can be better interpreted; unfortunately, this is rarely the case.

The decision must be based on the clinical presentation.

In extrapulmonary TB, an additional problem lies in the difficulty in obtaining samples for microbiological investigation. Most cases have to be treated empirically, without mycobacterial culture, posing a difficult problem in the face of increasing MDR-TB rates.



Key Learning Point

Advanced imaging (CT, MRI) is often indicated for suspected extrapulmonary TB, especially in the setting of previous disease.

Case 87

Presentation

A 31-year-old male patient was brought to the clinic in a wheelbarrow by his relatives. He was cachectic, and unable to walk due to progressive weakness of his lower limbs. HIV infection was suspected.

On examination, the patient showed symmetrical flaccid paresis of his lower limbs; he was unable to stand, but could lift his legs against gravity. His patellar and achilles tendon reflexes were absent. He did not report sensory defects, but, on questioning, he mentioned burning sensation on the soles of his feet. No bladder or bowel dysfunction was reported.

He tested HIV positive, and was then transferred to the hospital ward for further examination and treatment.

Questions

- 1) What is the differential diagnosis of paresis of the legs, especially considering the patient's absent reflexes?
- 2) What tests should be done?

Diagnosis

Inflammatory demyelinating polyneuropathy

Answers

1) Differential diagnosis:

Tuberculosis of the spine is, in our experience, the most common cause of paresis of the legs in HIV patients. Due to pressure on the spinal cord, it frequently shows spastic features and increased reflexes.

Human T-cell lymphotropic virus 1 (HTLV -1), a retrovirus similar to HIV, causes a chronic spastic paraparesis. As the name suggests, this myelopathy is associated with increased tone and spasticity; additional signs are gait disturbances and back pain. Diagnosis can be made with serology.

CMV or VZV are other viruses that cause spinal syndromes/progressive polyradiculopathy. This causes a flaccid paraparesis, with only mild sensory losses, but is usually associated with back pain radiating in the cauda equina area. CSF shows elevated neutrophil polymorph cells.

Inflammatory demyelinating polyneuropathy (due to HIV) is a disease that causes few, if any, sensory symptoms, and flaccid muscle weakness. It often responds to steroid therapy.

Severe forms of distal symmetric polyneuropathy, as well as toxic neuropathy from ART, might lead to the inability to walk and paresis of the legs. These diseases show predominantly sensory symptoms; the burning pain and loss of sensations (temperature, touch) dominate the picture.

Other causes that should be considered are myelopathies due to malnutrition and vitamin deficiency, as well as syphilis.

2) Lumbar puncture with routine CSF tests, imaging (MRI) of the spine.

Outcome and Follow-up

The patient was admitted. A conventional x-ray of his lumbar spine showed no abnormality. His FBC displayed a mild normocytic anaemia; and his U&E and LFTs were normal. A lumbar puncture was done, which showed only a mildly elevated protein (CSF-protein 0.51 g/L, normal 0.15–0.4).

Empirical therapy with vitamin B complex and vitamin B1 was started. Additionally, the patient was started on prophylactic CTX (2 tabs od), as his CD4 count was found to be 37 cells/mL. An MRI of the spine showed signs of leptomeningeal enhancement characteristic of inflammatory demyelinating polyneuropathy. Steroids were prescribed (60 mg od for one week, then 40 mg od, 20 mg od, 10 mg od for the following weeks), and the patient discharged. By the time he was seen in the clinic two weeks later, he was able to walk with a stick, and reported general improvement. ART was initiated.



MRI showing leptomeningeal enhancement.

Key Learning Point

Absent lower limb reflexes make the diagnosis of spinal cord compression (e.g., due to TB or lymphoma) unlikely, although MRI may still be indicated to aid in diagnosis.

Suggested Reading

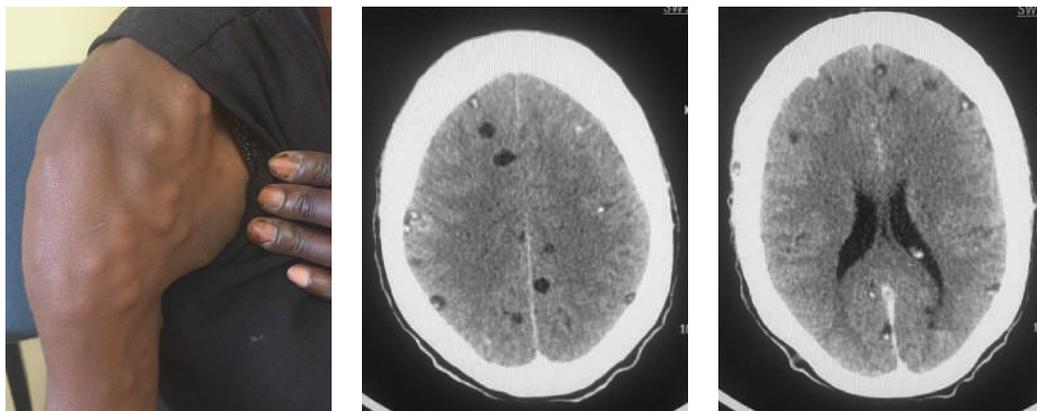
McGuire D. Neurologic manifestations of HIV. HIV San Francisco (CA): University of California, San Francisco HIV InSite Knowledge Base. 2003 Jun. Available from: <http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-04-01-02>.

Case 88

Presentation

A 41-year-old woman was seen in clinic. She was HIV positive, and had been on ART for six years. At the time of her clinic visit, she was taking TDF/3TC/EFV. She reported herself to be well adherent. Her last viral load was suppressed; a current CD4 count showed 471 cells/mm³.

Over a period of four years, she had developed multiple subcutaneous swellings (see image below), which made people look at her 'in a strange way'. The firm nodules were visible and palpable on all parts of the body. They were hard, and clearly located subcutaneously. She reported that she was told recently she 'is epileptic now'. In total, she had had four episodes of fits in the past year, but no antiepileptic drugs were prescribed. A CT scan was done.



Questions

- 1) What is the likely diagnosis? What is the pathophysiology?
- 2) How could you examine the skin nodules further?
- 3) How should this case be managed?

Diagnosis

Neurocysticercosis

Answers

1) Neurocysticercosis is caused by the larval stage of *Taenia solium*, the pork tapeworm. Cysticerci in the brain are initially viable, but do not cause much inflammation in surrounding tissues. This phase of infection is usually asymptomatic. The host develops a state of immune tolerance to the parasite; cysticerci can remain in this stage for many years. Clinical manifestations frequently develop when an inflammatory response develops around a degenerating cysticercus.

In the CT scan, viable cysts are seen as non-enhancing hypodense lesions. Degenerating cysts may enhance with contrast, and may have variable degrees of surrounding oedema and flare. Old cysts often appear as calcified lesions.

Ventricular cysts might block the passage of CSF, and then cause hydrocephalus with ventricular enlargement.

2) Ultrasound can be used to assess the nodules. Anechoic cysts with an echogenic scolex may be seen.

3) Cysticercosis can be treated with albendazole 15 mg/kg in two divided doses for 15 days, and/or praziquantel 50 to 75 mg/kg/day in three doses for 14 days. During treatment, and for a week or two after, the patient may experience increased headache due to the immune reaction around the dying cysts. Dexamethasone (0.1–0.2 mg/kg/day) is an adjunctive treatment to control the inflammatory reaction, and can be routinely given for two weeks. Anti-epileptic drugs should be continued for six months. Neurosurgical assistance should be sought for hydrocephalus. Single-dose niclosamide (1 g for children, 2 g for adults) can be given to family members (without epilepsy) to kill intra-intestinal cestodes.



Outcome and Follow-up

The patient was diagnosed with neurocysticercosis, and started on high-dose steroids (prednisolone 40 mg) and albendazole + praziquantel. She deteriorated on day 3, with severe vomiting and general body aches; the prednisolone dose was increased. By day 6, she was well, and the nodules were hardly visible anymore. She was discharged on day 7; treatment was followed up at the clinic without complication.

Comments

Humans can be the intermediate host of *Taenia solium*. Light peripheral infections cause few symptoms. The worm encysts in muscle and subcutaneous tissue. Small swellings (<1 cm) beneath the skin, and calcified nodules in the skeletal muscle (years later), can be often found.

Suggested Reading

Carpio A. Neurocysticercosis: an update. *Lancet Infect Dis.* 2002 Dec;2(12):751-62.



Key Learning Point

In an HIV-negative individual with focal neurological symptoms or signs, the threshold for brain imaging should be low.

Case 89

Presentation

A 42-year-old woman, who is HIV positive with a CD4 count of 201 cells/mL, presented with jaundice and anorexia not associated with abdominal pain or vomiting.

Three weeks prior she was diagnosed with pleural TB, and started on RHZE. She was also taking CTX, but no other medications.

Prior to commencement of the TB treatment her baseline creatinine was 0.71 mmol/L (normal <1.1); ALT was 16 U/L (normal 42–121).

On admission, investigations revealed acute renal failure, hyperbilirubinaemia, mild hepatic injury, and normal INR. Her haemoglobin was low, at 6.3 g/dL (normal 11.5–16.5). HBsAg was negative. The liver appeared normal on ultrasound.

Creat	2.4 mg/dL	(normal <1.1)
TBIL	17.2 mg/dL	(normal <1.1)
DBIL	10.6 mg/dL	(normal <0.3)
ALT	87 U/L	(normal 10–60)
ALP	104 U/L	(normal 42–121)
GGT	51 U/L	(normal 7–62)

Question

What could be a unifying cause for these abnormalities?

Diagnosis

Rifampicin-induced acute renal failure and haemolytic anaemia (with possible contribution of drug-related hyperbilirubinaemia)

Answer

Rifampicin can result in mildly raised serum bilirubin levels from the first day of treatment, but levels usually normalise within two weeks. Hepatitis due to rifampicin has also been well documented. Immune-mediated complications, including haemolytic anaemia, acute interstitial nephritis and glomerulonephritis with renal failure and respiratory failure (often together), have also been documented with rifampicin. Immune-mediated thrombocytopenia can also be seen with rifampicin.

Fortunately, these complications are rare, but mandate immediate discontinuation of the drug, and possibly treatment with steroids.

Outcome and Follow-up

A presumptive diagnosis of rifampicin-induced hyperbilirubinaemia was made. Additionally, acute renal failure with possible haemolysis (extremely high direct and indirect bilirubin, low haemoglobin) due to rifampicin was suspected. All medications were stopped, and IV fluids given. The hyperbilirubinaemia rapidly resolved, but renal function remained impaired until discharge. The patient was discharged, with plans to follow up in clinic, but the patient was subsequently lost to follow-up.

Summary Table of Investigations

Day	Creat	Urea	TBIL	DBIL	ALT
0	0.7	21			16
21	2.4	78	17.2	10.6	87
27	4.6	110	8.2	5.3	40
29	4.9	135	7.5	4.2	32
34	5.7	174	4.9	2.6	25
38	3.7	137	3.1	1.6	16

Comments

Renal toxicity of rifampicin has been reported sporadically. The deterioration in renal function typically appears acutely during the intensive phase of treatment. Histologically acute tubulointerstitial nephritis and/or acute tubular necrosis are seen; glomerular injury has also been documented. Full renal recovery is often seen, although cases accompanied by haemolysis seem to have a worse prognosis.

Key Learning Point

Jaundice does not always imply liver disease.

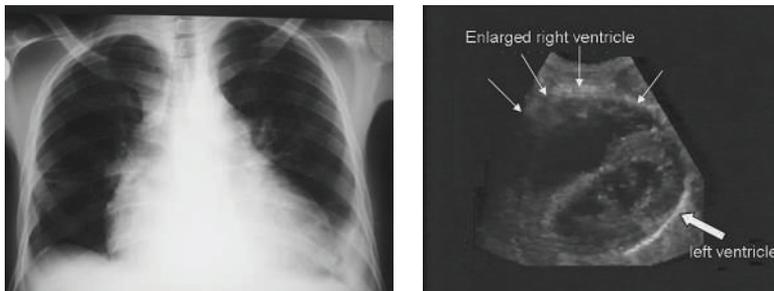
Suggested Reading

Covic A, Goldsmith DJ, Segall L, Stoicescu C, Lungu S, Volovat C, et al. Rifampicin-induced acute renal failure: a series of 60 patients. *Nephrol Dial Transplant*. 1998 Apr;13(4):924–9.

Case 90

Presentation

A 28-year-old man who recently tested positive for HIV, with a CD4 count of 149 cells/ μ L, presented with shortness of breath, abdominal distension, and swollen legs. On examination he was tachypnoeic, with distended jugular veins, a loud pan-systolic murmur heard loudest over the tricuspid valve, ascites, pulsatile hepatomegaly, and peripheral oedema. A CXR displayed an enlarged cardiac shadow, with no evidence of pulmonary oedema. Routine bloods were normal. US of the heart showed a massively dilated and hypertrophic right heart and a normal-looking left heart.



Questions

- 1) What disease processes could have led to this appearance?
- 2) How should this patient be examined and treated further?

Diagnosis

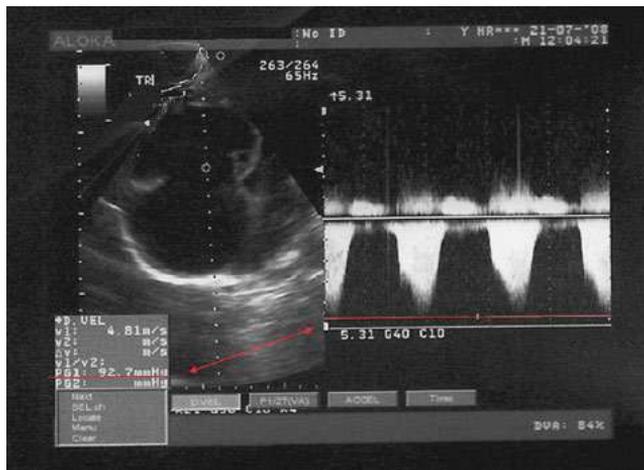
Right heart failure due to pulmonary hypertension, secondary to chronic thromboembolic disease

Answers

- 1) The causes of pulmonary hypertension and right-sided heart failure are many and varied, but can be grouped (not specific to HIV-positive patients) into:
 - a) **Group 1.** Pulmonary arterial hypertension (PAH)
Idiopathic pulmonary hypertension and diseases of the pulmonary muscular arterioles, including HIV.
 - b) **Group 2.** Pulmonary venous hypertension
PH due to left atrial, left ventricular, or left valvular heart disease.
 - c) **Group 3.** Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia (e.g., interstitial lung disease and chronic obstructive pulmonary disorder)
 - d) **Group 4.** Pulmonary hypertension caused by chronic thrombotic or embolic disease
 - e) **Group 5.** PH caused by inflammation, mechanical obstruction, or extrinsic compression of the pulmonary vasculature (e.g., sarcoidosis)
- 2) As mentioned above, HIV can be a cause of pulmonary hypertension, but it is important to exclude reversible causes.

Outcome and Follow-up

The patient was sent to our referral hospital for a formal echocardiogram, which confirmed the findings. His pulmonary pressure was measured at 102 mm Hg (!). He was then referred for a high-resolution chest CT scan. This revealed multiple small pulmonary emboli. He was started on warfarin and ART.



Comment

The incidence of thromboembolic disease is higher in HIV-infected individuals, particularly in more advanced stages of the disease.

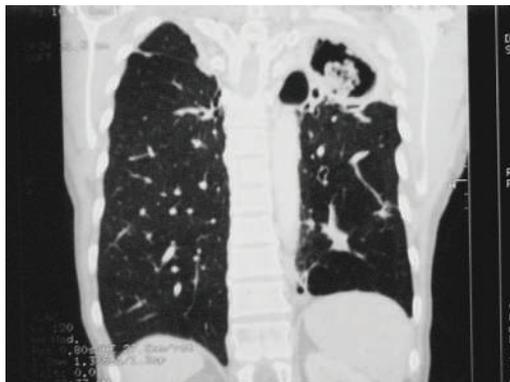
Suggested Reading

Barbarinia G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. *AIDS*. 2003 Apr; 17 Suppl 1:S46–50.

Case 91

Presentation

A 57-year-old woman presented with a six-week history of cough, haemoptysis, and chest pain. She had no significant weight loss or night sweats. She was diagnosed HIV positive three years ago, and started on ART. A recent CD4 count was 563 cells/ μ L. Relevant medical history included pulmonary tuberculosis treated eight years ago, and controlled hypertension. Sputum microscopy for AFB was negative; the patient had no improvement with a course of amoxicillin. A CXR was taken, and a CT thorax subsequently performed.



Questions

- 1) Describe the appearances of the CXR and CT thorax.
- 2) What are the possible causes for this appearance?
- 3) How could this condition be treated?

Diagnosis

Pulmonary mycetoma (aspergilloma)

Answers

- 1) The CXR shows volume loss in the left hemithorax, with a large cavity in the left upper lobe. The CT thorax confirms this cavity, and shows a solid mass within the cavity.
- 2) The appearances are characteristic of a pulmonary mycetoma, often known as pulmonary aspergilloma (*Aspergillus* species are the most common organisms found within the fungal mass).
- 3) The optimal treatment of pulmonary aspergilloma involves surgical resection of the affected lung. Medical therapy with antifungal agents has been shown to be largely ineffective in treating this condition.

Outcome and Follow-up

Sputum culture for TB was negative. However, having seen a private physician, the patient was commenced on RHZE to treat possible chronic pulmonary TB. Her family then requested a second opinion from another private physician; she subsequently had a left pneumonectomy performed.

Comments

This case illustrates the importance of lung imaging (CXR/CT) in the work-up of patients with chronic pulmonary symptoms, especially those with a history of pulmonary tuberculosis. Common sequelae of pulmonary TB include fibrosis, bronchiectasis, pleural thickening/calcification, and persistent cavitation. A mycetoma is formed when a mass of fungal hyphae (usually *Aspergillus* species), inflammatory cells, and cellular debris develops in a pre-existing cavity. From 25% to 50% of patients with pulmonary aspergilloma have a history of pulmonary tuberculosis. Often the mycetoma is asymptomatic, but chronic cough and haemoptysis can occur—and can be fatal. Most patients can be observed for progression of disease. Systemic antifungal agents are largely ineffective, due to lack of penetration into the cavity. Surgical resection is considered the treatment of choice for individuals with significant haemoptysis. Historically, surgical therapy has a high rate of morbidity and mortality, but recent results in specialist centres are more promising.

Key Learning Point

Oral antifungal therapy is ineffective in the treatment of pulmonary mycetoma.

Suggested Reading

Kim HY, Song KS, Goo JS, Lee JS, Lee KS, Kim TH. Thoracic sequelae and complications of tuberculosis. *Radiographics*. 2001 Jul–Aug;21(4):839–58; discussion 859–60.

Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest*. 2002;121:1988–99.

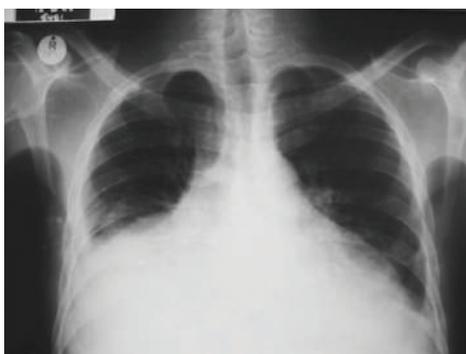
Case 92

Presentation

A 38-year-old male patient was referred from a peripheral clinic with a two-week history of being generally unwell, with cough, dyspnoea, chest pain, fever, and weight loss. He was newly diagnosed with HIV, and his CD4 count found to be 55 cells/mL. He had no history of TB, and no household contacts with TB. A course of amoxicillin had not alleviated his symptoms. On examination, he was distressed, with a respiratory rate of 36/min, BP of 109/75 mm Hg, heart rate of 109/min, and temperature of 37.4° C. Breath sounds were diminished at both lung bases, the right base was dull to percussion to the midzone, heart sounds were muffled, and the abdomen was soft and non-tender.

He had several raised, tender, violaceous plaques on his legs and trunk, and a purple plaque on his hard palate.

Presumptive diagnosis of disseminated Kaposi sarcoma had been made at the clinic, with a possible superimposed bacterial infection, and/or PCP. He had been started on ceftriaxone and high-dose CTX.



CXR showing cardiomegaly, large right pleural effusion, small left effusion, and bilateral nodular infiltrates.



Ultrasound image demonstrating massive pericardial effusion; the collapsing right ventricle during diastole (arrow) is a sign for disturbed filling, i.e., tamponade. Additionally, a right pleural effusion, a conglomerate of periportal lymph nodes in the abdomen, and free abdominal fluid were seen.

Questions

- 1) What is the differential diagnosis of pericardial effusion in an HIV-positive patient?
- 2) When is pericardiocentesis indicated?

Diagnosis

Pericardial effusion (due to TB or HHV-8) superinfected with *S. typhi*

Answers

- 1) Tuberculosis, HHV-8 disease, lymphoma, viral infection.
- 2) Pericardiocentesis is an invasive procedure; should be reserved for cases with large effusions (to make it safe) and haemodynamic impairment (to make it necessary). Clinical signs of tamponade (elevated jugular pressure, low BP, high pulse rate, and pulsus paradoxus), as well as sonographic signs (compromised right atrial and ventricular filling), can help the decision. We would recommend using ultrasound (if available) to guide the procedure.

It is important to note that even very large effusions may not cause tamponade if they develop slowly, and the pericardial fibres have time for dilatation. It is not the volume that causes the impaired filling, but the pressure!

Outcome and Follow up

The patient was transferred to the high-care unit, where an emergency pericardiocentesis was performed using a conventional central IV line. Approximately 1 200 ml of green-brown thick fluid with a sulphurous odour was aspirated and sent for cytology, microscopy, AFB stain, and TB and bacterial cultures. Post-procedure ultrasound demonstrated alleviation of the tamponade, but persistence of a mild effusion.

Given the appearance of the effusion, a diagnosis of pericarditis (TB? KS?) with superimposed bacterial infection was assumed. The patient was continued on high-dose ceftriaxone, and started on TB treatment and metronidazole to provide anaerobic cover. PCP treatment was stopped. The right pleural effusion was drained of 1.3 litres of blood-stained serous fluid.

The patient was transferred to the ward a week after admission. Although symptomatically better, and haemodynamically stable, he remained tachypnoeic and hypotensive. Ultrasound demonstrated persistent moderate effusion, but no signs of right atrial or ventricular collapse. Bacterial culture from the pericardial fluid grew *Salmonella typhi*; antibiotics were changed (after 14 days of ceftriaxone) to ciprofloxacin 750 mg twice daily. He remained on TB treatment. The patient requested discharge two weeks later; follow-up took place in clinic. Over the next few weeks, his general condition deteriorated; he was eventually lost to follow-up, and presumed dead.

(Footnote: Test results for the pericardial and pleural fluids eventually came back from the lab, but showed no evidence of malignancy. The pericardial fluid consisted of an acute inflammatory milieu. AFB stains and TB cultures were both negative. Skin biopsy from the leg showed Kaposi sarcoma.)



Aspirated pericardial effusion fluid.

Comments

The likelihood of this being a primary *Salmonella typhi* infection seems unlikely. It was possible that there was underlying TB or HHV-8 disease (primary effusion lymphoma). The diagnostic yield of fluid samples for both of these is low.

Key Learning Point

Bacterial superinfection of fluid infections is common; coverage with broad-spectrum antibiotics is indicated.

Case 93

Presentation

A 24-year-old woman with known KS was seen at the clinic. She had been on ART (TDF/3TC/EFV) for 12 months, and had received six cycles of vincristine chemotherapy. She was recently found to be pregnant (currently in her 26th week). She complained about increasing shortness of breath. She looked very wasted, sick, and breathless, and her oxygen saturation was found to be 84% (with oxygen).

The patient's VL was suppressed using the GeneXpert 'HIV quant assay' on the day of presentation. A CXR was performed; her leg is shown in the picture at right.



Questions

- 1) What is visible on the CXR? What would your diagnosis be?
- 2) What would be the best treatment? Why is this situation ethically difficult?

Diagnosis

Disseminated KS with beginning respiratory failure

Answers

- 1) Pulmonary infiltrates, most likely due to KS involvement and pleural effusion. The diagnosis is visceral KS.
- 2) The treatment would be to cover bacterial infection (antibiotic) while treating the KS with systemic chemotherapy at the same time. As with other malignancies occurring during pregnancy, KS comes with the ethical conflict between optimum management of the cancer and preservation of the pregnancy.

Outcome and Follow-up

The patient started bleomycin/vincristine combination chemotherapy, despite her pregnancy. After discussion with the oncology department, and amongst the ART clinicians, it was felt that the vital indication to protect the life of the mother outweighed the risk to the foetus, especially as it was already past the first trimester. She received two cycles of treatment, but continued to deteriorate, and died a few days after the second cycle.

Comments:

The incidence of pregnancy-associated malignancy ranges from 0.02% to 0.10%; the most common malignancies diagnosed during pregnancy are gynaecological, haematological, and skin cancers (malignant melanoma). For most of these cancers, as for Kaposi sarcoma, chemotherapy is necessary to achieve cure or efficient palliation of cancer-related symptoms. Few studies are available documenting in utero chemotherapy-exposed neonates. In one study, the mean gestational age at delivery was premature (35.8 weeks), the mean weight at birth was low at 2 647 g, and 4% of infants were born with congenital abnormalities. Risk of adverse effects from chemotherapy is highest during the first trimester (congenital malformation, and often spontaneous abortion). Termination of pregnancy or delay of chemotherapy treatment (if feasible) should be discussed with the patient. During the second and third trimesters, chemotherapy follows standard treatment guidelines, but delivery should be timed to a non-neutropenic period.

Key Learning Point

Malignancy during pregnancy poses an ethical problem; multiple teams (oncology, ART, obstetrics) may need to be involved to optimise treatment decisions.

Suggested Reading

Barnardt P. Managing AIDS-related Kaposi's sarcoma and pregnancy. *S Afr J HIV Med* 2013;14(2):87–88. DOI:10.7196/SAJHIVMED.851.

Case 94

Presentation

A 48-year-old HIV-positive male patient was seen in the clinic for shortness of breath. He started ART (TDF/3TC/EFV) five months ago; at the same time, he began chemotherapy (vincristine/bleomycine) for a Kaposi sarcoma on his left leg and palate (WHO Stage IV). The oedema on his leg subsided; the lesions on his palate disappeared. Two months ago, he started having SOB and chest pains with a dry cough, no fever, and normal BP and heart rate.

A FASH scan was done, revealing a minimal pericardial effusion, but a huge bilateral pleural effusion. A diagnostic and therapeutic tap was performed bilaterally over two consecutive days (2 000 ml were drained each side). The puncture yielded a whitish fluid with pus; empyema was suspected.



Questions

- 1) What can be seen in the ultrasound picture?
- 2) Look at the drained fluid. Do you think this is pus? What could be another explanation for the findings?



Diagnosis

Chylothorax due to thoracic KS

Answers

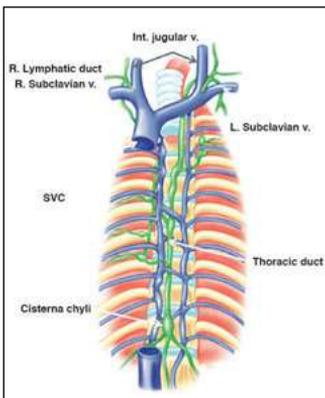
- 1) On the ultrasound, a large anechoic (black) pleural effusion can be seen. The echogenic line is the diaphragm; below this, the spleen can be seen.
- 2) From the look of it, pus is a first possibility. Nevertheless, bilateral empyema would be rare, plus you would expect the patient to show more systemic signs of infection. Another explanation is chyle, which also has a milky white appearance. The laboratory exam helped to differentiate the aetiology of the fluid; the fact that only a few leukocytes were seen points to something other than pus. A high amount of triglyceride would prove the diagnosis of chylothorax (but this exam is not widely available).

Outcome and Follow up

The fluid was sent to microbiology. No AFB was seen on wet film; GeneXpert MTB/RIF was also negative. No organisms were seen on the gram stain, and only a few cells. The patient acknowledged improvement with breathing after the tap. Chemotherapy was continued, as KS was assumed to be the cause of the chylothorax. The shortness of breath recurred a few weeks later, requiring further drainage. The procedure was repeated three times in total; after that, the patient improved, and did not request drainage again.

Comments

Chylothorax is a rare cause for unilateral or bilateral pleural effusion. Chyle consists of lymph of intestinal origin, which is a milky fluid rich in protein, triglycerides, and chylomicrons. It is conducted from intestinal lymphatics to the cisterna chyli, and eventually drains into the left subclavian vein via the thoracic duct. Obstruction of flow can result in mediastinal collection of chyle, which can leak into the pleural space, resulting in chylothorax. Typical symptoms are shortness of breath and chest discomfort due to compression of the lung. When drained, a milky white fluid is produced. KS is one of the most common causes of pleural effusion in patients with AIDS; the fluid is usually serosanguineous or haemorrhagic, but chylothorax is well documented. Lymphatic obstruction due to KS involvement is the assumed pathophysiology. Other causes in HIV patients include TB and lymphoma.



Key Learning Point

Pus is not the only whitish fluid drained from body cavities.

Suggested Reading

Verma K, Haverkamp M, Kayembe M, Musimar Z. Chylothorax associated with non-endemic Kaposi's sarcoma. *S Afr J HIV Med.* 2013;14(3):141–143.

Case 95

Presentation

A 41-year-old woman was admitted to the ward for anaemia. The patient was HIV positive, and successfully treated with ART for approximately 10 years (her current VL was suppressed). In recent months, she was diagnosed with anaemia, and had received a total of nine transfusions. On admission, her Hb was 4.9 g/dL; multiple enlarged hard lymph nodes were palpable, especially on the neck and supraclavicular fossa. She reported no night sweats or cough, but had lost weight (weight 59 kg, height 170 cm).

A lymph node core needle biopsy was performed and sent to pathology. It showed atretic follicles with vascularized germinal centres and interfollicular areas. Immunohistochemistry showed LANA-positive plasmablastic cells in the follicular area. The pathologist concluded it to be consistent with Multicentric Castleman disease (MCD).

Questions

- 1) What is Multicentric Castleman disease (MCD), and what causes it?
- 2) Which typical presentation should make you think about MCD?
- 3) How is MCD diagnosed and treated?

Diagnosis

Multicentric Castleman disease

Answers

- 1) MCD is a lymphoproliferative disease affecting plasma cells; it is associated with Kaposi sarcoma herpes virus (KSHV), which also causes KS, and has an aggressive clinical course, frequently resulting in death.
- 2) MCD is characterised by systemic inflammatory symptoms, lymphadenopathy, and hepatosplenomegaly. Because of the lymphadenopathy, patients have often been treated for EPTB. MCD patients commonly have low haemoglobin (the median for Malawian MCD patients 6.4 g/dL), and often receive multiple transfusions before the diagnosis is made. MCD patients are usually on ART at the time of diagnosis, often for a long time (among Malawian patients, the median is 56 months, the range 18–105), and with suppressed VL. The above-mentioned patient fits this clinical history very well.
- 3) MCD is diagnosed by lymph node biopsy. Especially in immunohistochemistry stains for the KSHV latency-associated nuclear antigen (LANA), a distinct pattern is seen that allows us to distinguish it from lymph node KS. MCD can be treated with chemotherapy, initially using etoposide (and prednisolone). If this treatment fails, cyclophosphamide, vincristine, and prednisone can be used as second-line treatment.

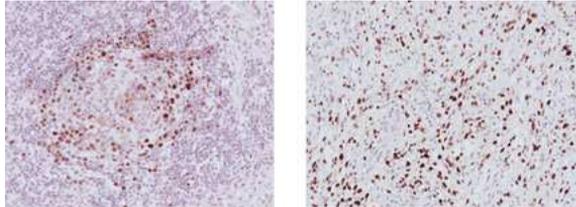
Outcome and Follow-up

The patient was referred to oncology for chemotherapy; initially, she received etoposide and prednisolone fortnightly. After two cycles, the steroid was stopped, and she was given etoposide only. Four months later, her weight had increased to 69 kg; and her Hb was 11 g/dL without further transfusions. No LNs were palpable.

Comments

Castleman disease is a rare lymphoproliferative disorder first described in 1956; it occurs in two forms, multicentric and localised. Localised Castleman disease is not associated with KSHV; it has an indolent clinical course.

Another rare lymphoma associated with KSHV in HIV-infected patients is primary effusion lymphoma (PEL), which occurs in the pleural, pericardial, and peritoneal cavities. PEL is of B-cell origin; the malignant cells are often co-infected with KSHV and Epstein-Barr virus (EBV).



Latency-associated nuclear antigen (LANA) immunohistochemical staining colours cells infected with HHV-8 brown. In MCD (left), numerous LANA-positive lymphoid cells localised to the perifollicular and mantle zones are typically seen. In nodes affected by Kaposi sarcoma (right), the KS effaces normal nodal architecture, and spindle-shaped LANA-positive malignant epithelial cells are seen diffusely. (Courtesy Dr Gopal)

Key Learning Point

Patients with severe anaemia and lymphadenopathy on long-term (successful) ART could suffer from Multicentric Castleman disease; biopsy should be considered.

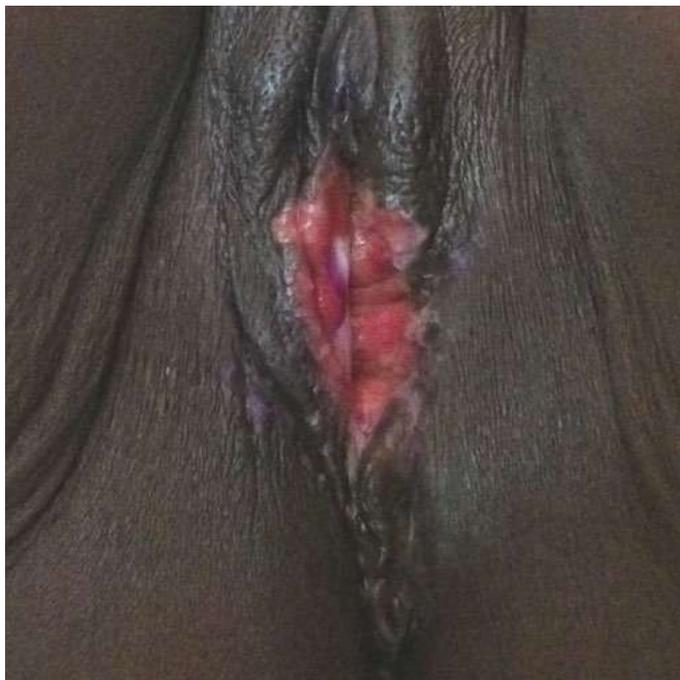
Suggested Reading

Gopal S, Liomba NG, Montgomery ND, Moses A, Kaimila B, Nyasosela R, et al. Characteristics and survival for HIV-associated multicentric Castleman disease in Malawi. *J Int AIDS Soc.* 2015;18(1):20122.

Case 96

Presentation

A 42-year-old female patient was seen for vulvar ulcers, which had been troubling her for years. She reported that she had been treated repeatedly with penicillin, ciprofloxacin, and doxycycline. In addition, she had had multiple courses of acyclovir for presumptive herpes virus, without success. The patient was seen in India, where a serology result was found negative for herpes simplex virus 1 and 2 antibodies. Parts of the ulcers were excised but the histology result was inconclusive, reporting only inflammatory changes. The ulcers were not very painful (only during urination), but were oozing. The patient was currently using gauze with an antifungal cream to control the skin from adhering to the gauze, as well as to control the oozing and bleeding.



Question

What other causes of ulcers can you think of that do not respond to anti-infective treatment?

Diagnosis

Behçet's disease

Answer

As the patient was treated multiple times for infective causes of ulcers, other causes have to be considered. Malignancy can cause ulceration, but usually it is accompanied by tissue growth and disease progression, neither of which was present in this patient. Lichen sclerosis or lichen planus can also cause vulvar skin changes, but should result on tissue histology. Therefore, other autoimmune inflammatory diseases of the skin need to be considered.

Outcome and Follow-up

Although Behçet's disease usually also affects the oral mucosa, it can also cause ulceration of genital mucosa alone. Therefore, Behçet's was assumed to be the underlying condition, and the patient was treated with prednisolone (initially 40 mg po). This led to a significant improvement of the patient's complaints, and the ulcers healed gradually. The steroid was tapered over the following weeks, and the patient was finally treated with topical steroid cream, but the ulcers flared again. Therefore, a small dose of steroid had to be maintained; zinc cream assisted with superficial skin healing.

Comments

Behçet's disease (BD) is an inflammatory systemic disorder of unknown aetiology. Clinical features include oral and genital ulcers, ocular inflammation, skin lesions (like erythema nodosum), as well as articular, vascular (thrombosis), neurological (brain stem symptoms, stroke), pulmonary, and gastrointestinal (resembling Crohn's disease) manifestations. The disease burden is highest in the early years (approximately 15 years) of its course; in many patients, the syndrome burns out later. The main goal of therapy in patients with BD is to induce and maintain remission, and improve the patients' quality of life. Steroids are a cornerstone of treatment for BD. It is important to not stop steroids abruptly, because relapses are very common after quick tapering of the steroid dose. A basal dose of 4–8 mg/day may be maintained for a long time. Adjunct immunomodulatory treatments available in our setting, and found to be effective in studies, are dapsone (100 mg od) and colchicine (0.5–2 mg od); these could be tried, particularly to reduce the need for steroids.

Key Learning Point

Although 'common is common', there are still times we should consider rarer conditions when patients do not respond to conventional treatment.

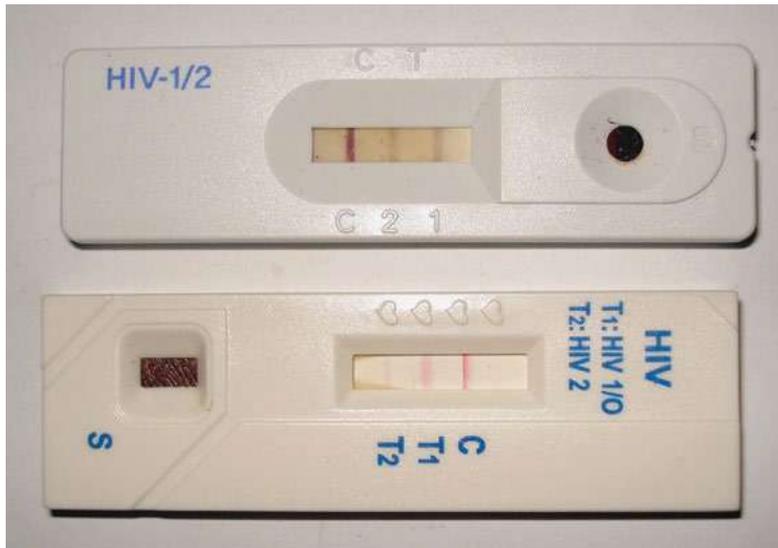
Suggested Reading

Saleh Z, Arayssi T. Update on the therapy of Behçet disease. *Ther Adv Chronic Dis.* 2014 May;5(3):112–134.

Case 97

Presentation

A 40-year-old woman was seen in the clinic, accompanied by the HIV counsellor. The counsellor was confused and upset by the VCT results, and presented the rapid tests for review.



Questions

- 1) What do these tests indicate?
- 2) Which confirmatory tests can be used in this setting?

Diagnosis

HIV-1 infection with probable serological cross-reactivity

Answers

- 1) Both tests confirm that the patient is HIV positive. C is the control band.
The first test appears to be positive for HIV-1 and HIV-2; the second test also shows a faint band in the HIV-2 position.
- 2) For indeterminate results, where the first test is positive, and the confirmatory (second rapid) test is negative, an ELISA can be sent in an EDTA tube. The ELISA uses antigens for both HIV-1 and HIV-2 (called a mixed ELISA), and therefore can determine seropositivity for antibodies to either HIV-1 or HIV-2. Western blot uses antigen for HIV-1 and HIV-2 separately; it can also be used to differentiate. HIV PCR is not available in the public sector, but would be the gold standard for differentiation and identification of viral subtypes.

Outcome and Follow up

This patient had a Western blot, which was positive for HIV-1, and negative for HIV-2.

Comments

The HIV-2 epidemic is centred in West Africa. Cases are rare in Southern Africa, where HIV-1 predominates. Countries with ties to West Africa, such as Mozambique, Angola, France, and Portugal, also have more cases of HIV-2.

HIV-2 is less pathogenic than HIV-1, allowing a longer time before AIDS-defining illness (some suggest 10–20 years). Dual infection has also been reported; these patients need to be treated for HIV-1 and 2. HIV-2 has a different structure to HIV-1 at the NNRTI binding site, making it inherently resistant to NNRTIs.

Key Learning Point

Rare diagnoses are rare. Even the presence of more stripes does not indicate a zebra!

Suggested Readings

Gilleece Y, Chadwick DR, Breuer J, et al. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. *HIV Med.* 2010;11(10):611-619. Available at http://www.bhiva.org/documents/Guidelines/HIV-2/hiv_889.pdf.

Case 98

A Malawian clinician travels to represent his clinic at the International AIDS Conference. During lunch with clinicians from different areas of the world, a few questions arise.

Questions

- 1) A clinician from Thailand suggests that umbilicated fungal lesions of the skin cannot only be caused by *Cryptococcus neoformans*; he shows images of his patient (CD4 28 cells/mm³, generalised skin lesions, fever, hepatosplenomegaly).



How do you respond?

- 2) After a German clinician learns that abacavir (ABC) is available in Malawi, he suggests that it should not be used without 'genetic testing'.
What is he referring to? What is your answer?
- 3) A colleague from Malawi shows a picture of one of his patients. She has discoloration of the tongue, but otherwise no problems. Which ART medicine is she probably on that is causing the discoloration?



Answers

1) Other fungal infections can cause umbilicated lesions of the skin.

Penicillium marneffei infections are commonly diagnosed only in Southeast Asia. In the mid-1990s, it was the third most common opportunistic infection seen in HIV-infected individuals in northern Thailand.

Histoplasma capsulatum may cause similar lesions. It is endemic in dry areas of North America, and causes pulmonary infections. Cases have been reported from many countries on the African continent, but the true burden of disease is unknown, as it is clearly under-diagnosed, due to the lack of available diagnostic assays. Generalised infections with fever, skin involvement, and osteolytic bone lesions are documented in African HIV patients.

2) The abacavir hypersensitivity reaction is a multi-organ process, manifested by at least two of the following:

- Fever
- Rash
- Gastrointestinal symptoms
- Constitutional symptoms
- Respiratory symptoms

Frequently, patients present in the first two to six weeks of ABC treatment with mild flu-like symptoms, fever, and a maculopapular rash (less marked than with CPT or NVP toxicity). In the following days, fever and malaise may increase, and nausea and vomiting or respiratory symptoms may ensue. The most important diagnostic clues are that symptoms are most prominent several hours after taking the medication in the morning, and that each day on ABC the symptoms seem to be getting progressively worse.

The incidence of abacavir hypersensitivity reported in clinical trials involving predominantly Caucasians is 6% to 8%. As genetic testing for HLA-B*5701 can predict the reaction, it is often common practice before starting ABC. The allele occurs at approximately 5% frequency in European populations, 1% in Asian populations, and less than 1% in African populations. Studies have confirmed the lower risk of abacavir hypersensitivity reactions in Africans. Additionally, the HLA-B*5701 seems here less predictive. It is therefore possible to start ABC in our patients without genetic testing, but clinicians must be vigilant for suggestive symptoms, and must ask for clues.

3) Many drugs are implicated in causing discoloration of tongue, nails, and skin. For example, diffuse hyperpigmentation on palms and soles may be present in patients taking cyclophosphamide or doxorubicin. Amongst ART drugs, AZT is known to cause an unusual grayish-blue discoloration of not only the tongue, but also the hands (see the picture at right, of another patient) and nails. Nail pigmentation with zidovudine occurs primarily in black patients. The mechanism responsible for the discolorations is unknown. It is important to be alert to these side effects, and to avoid unnecessary investigations.



Suggested Reading

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Singh SK, Rai T. A case of zidovudine induced pigmentation on palms and soles. *Indian Dermatol Online J.* 2014;5:98–9.

Case 99

Presentation

A 34-year-old man was seen for a high VL (144.000 copies/mL) after being on antiretroviral therapy for a long time. Initially, when he was diagnosed HIV positive, he briefly received d4T/3TC/EFV, but was then switched to AZT/3TC/EFV, as he had developed severe PNP. Five years ago, he was diagnosed with TB and falling CD4 counts (125 cells/mm³); second-line ART (TDF/3TC/LPV/r, later ATV/r) was started during his TB episode.

The patient had a high VL (237.000 copies/mL) during routine monitoring four months ago; after adherence counselling and another four months of TDF/3TC/LPV/r, it was now 144.000 copies/mL.

His serum sample was sent for genotype resistance testing, which showed the following mutation results (next page):

Drug Resistance Interpretation: PR

PI Major Resistance Mutations	I47A, I50L
PI Accessory Resistance Mutations	None
Other Mutations	M36L, L63P

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	Susceptible
lopinavir/r (LPV/r)	Intermediate Resistance

PR Comments

PI Major

- I47A is a non-polymorphic mutation selected by LPV. It usually occurs in combination with V32I and in this context it confers high-level resistance to LPV and FPV and low/intermediate-resistance to the remaining PIs except ATV and SQV.
- I50L is a non-polymorphic mutation selected by ATV. It causes high-level resistance to ATV and increases susceptibility to most of the remaining PIs.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations	M41L, M184V, T215Y
NNRTI Resistance Mutations	None
Other Mutations	None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Intermediate Resistance
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Low-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT Comments

NRTI

- M184V/I cause high-level in vitro resistance to 3TC and FTC and low-level resistance to ddI and ABC. However, M184V/I are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT, TDF and d4T and are associated with clinically significant reductions in HIV-1 replication.
- T215Y is a TAM that causes intermediate/high-level resistance to AZT and d4T, low-level resistance to ddI, and potentially low-level resistance to ABC and TDF.
- M41L is a TAM that usually occurs with T215Y. In combination, M41L plus T215Y confer intermediate/high-level resistance to AZT and d4T and contribute to reduced ddI, ABC and TDF susceptibility.

From the Stanford University HIV Drug Resistance Database (<https://hivdb.stanford.edu/hivdb/by-mutations/>)

It was recommended to start the patient on TDF/3TC/DRV.

Questions

- 1) Which drugs are available as third-line treatment under the Malawi national ART guidelines? What are their main side effects?
- 2) Why is 3TC continued, despite the fact that there is high-level resistance?
- 3) Why is it important to keep the patient on the failing regimen before doing the genotyping?
- 4) Why is the patient not restarted on EFV, which is reported as 'susceptible'?
- 5) How can the mutations best be interpreted? What algorithm can be used to guide third-line drug choice?
- 6) How long does it normally take to develop resistance to LPV/r or ATV/r? Are there any reasons why this patient might have developed resistance even sooner?

Diagnosis

Second-line ART failure

Answers

1) The following drugs are available for third-line treatment under national ART guidelines:

Darunavir boosted with ritonavir (DRV/r) = Protease inhibitor (PI)

Dose: Darunavir 600 mg (1 tablet) + Ritonavir 100 mg (1 tablet) bd p.o. with food

Most common side effects: headache, nausea, diarrhoea, amylase elevations, rash

Most significant side effects:

- Drug-induced hepatotoxicity in 0.5%
- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in 0.4%
- Hypersensitivity reactions = rash + constitutional findings (fever, general malaise, fatigue, muscle/joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia, angioedema).
- Like other protease inhibitors (LPV/r, ATV/r), it can cause metabolic changes, such as diabetes mellitus (new-onset DM and exacerbation of pre-existing DM), hyperglycaemia and fat redistribution (central obesity, buffalo hump, peripheral wasting, facial wasting, breast enlargement, and a 'Cushing appearance').

Raltegravir (RAL) = Integrase strand transfer inhibitor (INSTI)

Dose: 400 mg BD p.o. (1 film coated tablet) with or without food

If the patient is on rifampicin TB treatment, dose at 800 mg BD p.o. until 2 weeks after Rifampicin is stopped or completed

Most common side effects: insomnia, headache, dizziness, nausea, diarrhoea

Most significant side effects:

- Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN)
- Hypersensitivity reactions = rash + constitutional findings (see above)
- Hepatitis and hepatic failure (patients with Hepatitis B and/or C infection can be given RAL with monitoring of LFTs (if possible))
- Depression and suicidal ideation (in patients with pre-existing psychiatric illness)
- Rhabdomyolysis.

Etravirine (ETV) = Non-nucleoside reverse transcriptase inhibitor (NNRTI)

Dose: 200mg bd p.o. (2x100mg tablets) after food

Most common side effects:

- Rash common (9%) in first 2–4 weeks, usually mild, resolves within 1–2 weeks
- Nausea
- Diarrhoea
- Gynaecomastia.

Most significant side effects:

- Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)
- Hypersensitivity reactions = rash + constitutional findings (see above) possibly with hepatic failure
- Rhabdomyolysis.

2) M184V is a mutation that gives the virus resistance to 3TC. Nevertheless, 3TC 'cripples' the fitness of the virus, increasing its susceptibility to AZT and TDF. If 3TC is continued in the presence of the mutation, the VL level is approximately 0.5 log levels lower than if it is stopped. It is therefore usually kept in the regime, because it is well tolerated—and to make use of this 'crippling effect'.

3) The patient must be on the failing ART regimen when resistance testing is performed. When ART is stopped, many resistant mutations become overrun by wild-type HIV virus, and subsequently cannot be detected. They are present only in a small subset of viruses (= 'archived'), but the resistant strains immediately come back as soon as the same ART drugs are restarted. For this reason, we recommend that the patient must be fully adherent prior to resistance testing; we recommend one additional month of optimal adherence, before we proceed to send a sample.

- 4) For the same reason given in answer 3, test results may not detect mutations that developed during the failure of a previous regimen (they are also ‘archived’). Usually a patient fails a NNRTI-based first-line treatment and then starts on a PI-based second-line regimen. The test is only performed after second-line failure. The NNRTI resistance mutations may be archived, but it has to be assumed that they are present; therefore, EFV is not given. Generally, test results are better at indicating which drugs will NOT work, and less effective at showing which drugs will work.
- 5) There are many mutations found in HIV genes; it is difficult even for experts to remember all of them. A widely used analysis tool is the free Stanford University HIV Drug Resistance Database (see link on pg. 218). All mutations can be entered; the program determines the most likely degree of resistance, and gives information on the impact of the mutations. Once the resistance pattern is determined, a decision on a third-line treatment regime can be made using the following (possible) algorithm:
 - a) Low-level (or worse) resistance to either **LPV** or **ATV** → all patients get **DRV/r**
 - b) Keep all patients on **3TC** (or **FTC**), plus either **TDF** or **AZT** (whichever has the least resistance)
 - c) If there is intermediate (or worse) resistance to **TDF** and **AZT** OR low-level (or worse) resistance to **DRV** → add **RAL**
 - d) If there is intermediate (or worse) resistance to **TDF** or **AZT** AND low-level (or worse) resistance to **DRV** → add **ETR** (unless there is intermediate (or worse) resistance to **ETV**)
- 6) If PIs with ritonavir boosting are used, development of resistance to PIs takes longer, because of the high levels of PIs achieved through boosting. In addition, PI resistance needs multiple mutations to develop, which accumulate over a long time. Only patients failing PI regimens for long periods (1–2 years) develop PI resistance. The two exceptions that can lead to more rapid resistance development are when PIs are used in combination with RIF for TB treatment (as in this patient) without doubling of the LPV/r dose (thus leading to reduced PI concentration), or when the patient has ‘really, really poor adherence’ (that is, taking PI inconsistently, which leads to frequent, repeated, and prolonged sub-inhibitory PI concentrations in the serum).

Key Learning Point

When considering second-line failure, keep the patient on the failing regimen, ensure maximal adherence, and send a request to the third-line committee for genotyping. Decisions on third-line regimens have to be made in consideration of the full treatment history of a patient, which should be included when reporting to the committee.

Epilogue

(for the overwhelmed clinician)

To correct a natural indifference I was placed halfway between misery and the sun. Misery kept me from believing that all was well under the sun, and the sun taught me that history wasn't everything. —Albert Camus

You cannot create experience. You must undergo it. —Albert Camus

Why does Albert Camus, the French philosopher and writer, matter to us doctors working in rural Africa?

I think for various reasons. Camus, being born in Northern Africa, is inspired by the continent. He caught in many of his stories the flair and feeling of the region. His descriptions of the clarity and vastness of the sky, the beauty of land and seas, the richness of the spring flowers—but, at the same time, the cruelty of the climate, the staring sun, the harsh winds—give us a taste of the external conditions. Beautiful, but unforgiving.

Additionally, Camus was a person suffering from tuberculosis, the disease that concerns us a lot working in Southern Africa. For him, being a dedicated footballer in his youth, any aspirations in football disappeared at age 17, upon contracting the disease (incurable at this time), as he was bedridden for long periods. His plans, aspirations, and dreams were changed by a disease, which moved him to embrace theatre and literature (thank tuberculosis for that). It is this same need to constantly adapt life according to your diseases, and those of your family, that is exemplary for so many of our patients.

When working in the middle of a combined TB/HIV epidemic, definitely one of Camus' major works, *The Plague*, comes to mind. In this novel, he describes the Algerian city of Oran, befallen by an epidemic of plague. As the Wikipedia for Schools entry on Camus explains:

'The plague is a concrete and tangible facilitator of death. (...) As the epidemic "evolves" within the seasons, so do the citizens of Oran, who instead of willfully giving up to a disease they have no control over, decide to fight against their impending death, thus unwillingly creating optimism in the midst of hopelessness.'⁽¹⁾

It is in this spirit that we have to see our patients who struggle against the more 'chronic plague' of HIV and TB.

But, even more than on the victims of the epidemic, we need to focus on the protagonist, Dr Rieux, a medical practitioner. Throughout the course of the epidemic, he keeps working, keeps seeing his patients, keeps listening to their worries—and, despite the general hopelessness, he defends his sense of compassion and humanism. He understands that 'in the light of the bloody mathematics which unfortunately rule our destiny'.⁽²⁾ His efforts might seem ridiculous, but refuses 'to surrender to a destiny that kills innocent children'.⁽³⁾

The other book that needs mentioning is *The Myth of Sisyphus*, a short philosophical essay published in 1942. In this essay, Camus introduces his philosophy of the absurd, which is embodied in man's futile search for meaning, clarity, and unity in the face of an unintelligible world that gives no answers. The realisation of absurdity may lead to despair, but does it mean we need to surrender?

Camus answers no, it requires us to revolt.

In its final chapter, Camus compares the absurdity of our life with the situation of Sisyphus, from Greek mythology. 'The gods had condemned Sisyphus to ceaselessly rolling a rock to the top of a mountain, whence the stone would fall back of its own weight. They had thought with some reason that there is no more dreadful punishment than futile and hopeless labor.'⁽²⁾

But:

At the very end of his long effort measured by skyless space and time without depth, the purpose is achieved. Then Sisyphus watches the stone rush down in a few moments

toward the lower world whence he will have to push it up again toward the summit. He goes back down to the plain.

It is during that return, that pause, that Sisyphus interests me. A face that toils so close to stones is already stone itself! I see that man going back down with a heavy yet measured step toward the torment of which he will never know the end. That hour like a breathing-space which returns as surely as his suffering, that is the hour of consciousness. At each of those moments when he leaves the heights and gradually sinks toward the lairs of the gods, he is superior to his fate. He is stronger than his rock.⁽²⁾

Hopefully, we are superior to our fate. To see many sick patients every day, facing numerous handicaps—missing drugs, lacking equipment, and missing administrative support—repeating the same advice and warnings over and over again and still see them suffering and dying might be overwhelming. Nevertheless, we continue, though we may also seem like Sisyphus. But, as Camus concludes in his essay, “the struggle itself toward the heights is enough to fill a man’s heart. One must imagine Sisyphus happy.”¹⁽²⁾



«Il faut se imaginer le docteur comme heureux».

References

- 1) Wikipedia for Schools. Albert Camus. http://schools-wikipedia.org/wp/a/Albert_Camus.htm. Accessed 10/7/2008
- 2) Camus A. Le mythe de sisyphé [The myth of Sisyphus]. Paris: Gallimard; 1942.
- 3) Camus A. La peste [The plague]. Paris: Gallimard; 1947.

Lighthouse Drug Formulary

Drug	Route	Dose	Times Daily	Indications
Acyclovir	PO	400 mg 800 mg	3 5	Herpes simplex Herpes zoster
Albendazole	PO	400 mg 400 mg	1 2	Stat dose—treatment of worms Chronic diarrhoea
Amitriptyline	PO	25–150 mg nocte	1	For neuropathic pain or depression
Amlodipin	PO	10 mg	1	Hypertension
Amoxy/Clavulanic acid		375 mg	3	Infections (severe)
Amoxicillin	PO	250–500 mg	3	Bacterial infections
Amphotericin B	IV	1 mg/kg	1	Cryptococcal meningitis
Mupirocin Cream	Topical			
Antibiotic eye drops	Topical			Conjunctivitis
Artesunate/Amodiaquine (AA)	PO	2 tablets	1	Malaria
Aspirin	PO	150 mg 500 mg	1 up to 3	Stroke Pain management (level 1)
Atenolol	PO	50 mg	1	Hypertension, tachycardia
Azithromycin	PO	500 mg	1	STI, resp infect, ALUP
Beclomethasone inhaler	Inhaled	50–200 mcg	2	Breathlessness and airway obstruction Apthous ulcers
Benzathine Penicillin	IM	2.4 Mega Units	1	Genital ulcer disease
Benzyl Benzoate 25%	Topical		1	Scabies
Betamethasone cream	Topical			Inflammatory skin conditions
Bleomycin	IV	According to BSA		KS
Calamine lotion	Topical		1	Itching
Carbamazepine	PO	100–200 mg	2	For neuropathic pain
Ceftriaxone	IV or IM	2 g	1	For meningitis, for 7–10 days
Chloramphenicol	IV or PO	500 mg–1 g	4	Pneumonia, septicaemia and meningitis
Chlorhexidine 0.2%	PO		3	Periodontal disease
Chlorpromazine	PO/IM	25–200 mg	3	Psychotic disease; cough relief
Ciprofloxacin	PO	500–750 mg	2	Septicaemia
Clindamycin	PO	300 mg	3–4	Periodontal disease, alternative for PCP
Coal tar in salicylate ointment	Topical		2	Psoriasis

Drug	Route	Dose	Times Daily	Indications
Codeine phosphate	PO	15–30 mg	4	Cough, pain management (level 2) chronic diarrhoea
Cotrim syrup	PO			Desensibilisation
Cotrimazole 1%	Topical		2–3	Fungal infections
Cotrimoxazole (trimethoprim-sulphamethoxazole)	PO	< 50 Kg, 3 tablets	3	For PCP For Toxo
		50-80Kg, 4 tablets	3	
		> 80 Kg, 5 tablets	3	
		< 50 Kg, 3 tablets	2	
		50–80Kg, 4 tablets	2	
		> 80 Kg, 5 tablets	2	
Dapsone	PO	100 mg	1	Alternative prophylaxis
Diazepam	PO	5–10 mg	up to 3	Anxiety
Digoxin	PO	0.25 mg	1	Tachycardia, atrial fibrillation
Doxycycline	PO	100 mg	2	STI; pneumonia
Enalapril	PO	10mg	½–2	Hypertension, CHF
Erythromycin	PO	250–500 mg	3	Respiratory infections, STI; staphylococcal infections
Ferrous Sulphate	PO	200 mg	1–3	Iron deficiency anaemia
Flucloxacillin	PO	250–500 mg	4	Staphylococcal infections
Fluconazole	PO	200 mg	1	Oral/oesophageal candida Cryptococccemia/CM Secondary prophylaxis of cryptococcal meningitis
		800 mg then 400 mg	1	
		200 mg	1	
Folic Acid	PO	5mg	1	Folate deficient anaemia
Furosemid	PO	40 mg	1–10	CHF, cirrhosis, fluid overload
Ganciclovir	Intra ocular	2 mg in 0.08 mL	1	CMV retinitis, weekly for 3 month
Gentamicin	IV or IM	240 mg	1	STI; septicaemia; severe pneumonia
Gentian Violet	Topical		1	Fungal infections of mouth and skin
Glibenclamide	PO	40 mg	1–2	Diabetes
Haloperidol	PO	2.5–10 mg	3	Psychosis; agitation; confusion
HCT	PO	25 mg	1–2	Hypertension, CHF
Heparin	S.c.		2	DVT
Hydrocortisone cream	Topical			Inflammatory skin conditions
Ibuprofen	PO	200–400 mg	3	Pain management (level 1)
INH/VitB.6	PO	300 mg/25 mg	3	IPT
Likuni Phala	PO	100–200 g (+ vegetable oil)	2	Moderate and severe malnutrition
Loperamide	PO	2 mg	up to 5	Chronic diarrhoea
Lumefantrine/Arthemeter (LA)	PO	4 tablets	2	Malaria

Drug	Route	Dose	Times Daily	Indications
Metachlorpromide (MCP)	PO	10 mg	up to 3	Nausea; hiccoughs
Metformin	PO	850 mg	1–3	Diabetes
Metronidazole	PO	400 mg 800 mg 2 g	3 3 1	Chronic diarrhoea Amoebic dysentery Stat dose for STI
Morphine	PO	5–10 mg		Pain management (level 3) (dose needs to be adjusted)
Multivitamin tablets	PO	1 tablet	1	Micronutrient substitution
Normal Saline or Ringer's Lactate	IV	500 mL		Rehydration, AKI
Nystatin	PO Vaginal	100 000 units (= 1 mL) Pessaries	4 2	Oral candida STI management
Omeprazol	PO	40 mg	1-2	Gastric ulcer
Paracetamol	PO	500 mg– 1 g	4	Pain management (level 1), part of CM treatment
Podophyllin 20%	Topical		1	Genital warts, Mollusca
Praziquantel	PO	40 mg/kg	1	Schistosomiasis
Prednisolone	PO	Up to maximum 80 mg daily	1 or split in 2	For reducing inflammatory reaction (IRIS), DILS
Primaquine	PO	30 mg	1	Alternative regimen for PCP with clindamycin
Probenecid	PO	500 mg	4	for treatment of neurosyphilis— penicillin booster
Promethazine	PO	25 mg	3	Itching and skin rash, nausea
Propranolol	PO	20 mg	3	Anxiety
Salbutamol inhaler	Inhaled	200 mcg	up to 4	Asthma, airway obstruction
Salicylic acid ointment 20%	Topical		1	Cutaneous warts
Selsun shampoo (selenium sulphide)	Topical	2.5%	2x weekly	Seborrhoeic dermatitis
Slow K	PO			Cryptococcal TX with Ampho
Sodium Valproat	PO	200 mg	2–6	Epilepsy on ART
Spironolacton	PO	25 mg	1	CHF, hypertension
Steroid Eye Drops	Topical			Inflammatory eye condition
Sulfadoxine-pyrimethamine (SP)	PO	3 tablets 2 tablets	Stat dose 2	Malaria Cerebral toxoplasmosis (combined with clindamycin)
Valacyclovir	PO	1 g	3	Herpes simplex and zoster
Vincristine	IV	2 mg	1	Kaposi sarcoma
Vitamin B complex	PO	1–3 tablets	1	Polyneuropathy (adjunct)
Warfarin	PO	5 mg		DVT according to INR

Abbreviations and Acronyms

3TC	Lamivudine
ABC	Abacavir
ACE-I	Angiotensin Converting Enzyme Inhibitor
AFB	Acid-Fast Bacilli
Ag	Antigen
AKI	Acute Kidney Injury
ALP	Alkaline Phosphatase
ALT	Alanine Leucine Transferase
APTT	Activated Partial Thrombin Time
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
BCG	bacille Calmette-Guerin (vaccine)
Bd	Two Times Per Day
BMI	Body Mass Index
CHOP	Cyclophosphamide/Hyxdroxydanorubicin/Oncovin/Prednisone
CMP	Cardiomyopathy
CMV	Cytomegalovirus
CPT	Cotrimoxazole Preventive Therapy
CSF	Cerebrospinal Fluid
CTX	Cotrimoxazole
CXR	Chest X-Ray
D4T	Stavudine
DBIL	Direct Bilirubin
DDI	Didanosine
DILI	Drug-Induced Liver Injury
DST	Drug-Sensitivity Test
DVT	Deep Vein Thrombosis
EBV	Epstein-Barr Virus
EFV	Efavirenz
ELISA	Enzyme-Linked Immunosorbent Assay
EMB	Ethambutol
ERCP	Endoscopic Retrograde Colangiopancreatography
FASH	Focused Assessment with Sonography for HIV-Associated Tuberculosis
FBC	Full Blood Count
HAND	HIV-Associated Neurocognitive Disorder
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIVAN	HIV-Associated Nephropathy

HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
IHC	Immunohistochemical Staining
IM	Intramuscular
INR	International Normalised Ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
ITP	Idiopathic Thrombocytopenic Purpura
IV	Intravenous
KS	Kaposi Sarcoma
KSHV	Kaposi Sarcoma Herpes Virus
LFT	Liver Function Test
LP	Lumbar Puncture
LPV/R	Lopinavir/Ritonavir
MAC	Mycobacterium Avium Complex
MDR-TB	Multi-Drug-Resistant Tuberculosis
MTB	<i>Mycobacterium Tuberculosis</i>
NHL	Non-Hodgkin Lymphoma
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAID	Non-Steroidal Anti-Inflammatory Drug
NVP	Nevirapine
Od	Once per Day
OI	Opportunistic Infection
OPD	Outpatient Department
PCP	Pneumocystis Pneumonia
PH	Pulmonary Hypertension
PHC	Primary Health Care
PI	Protease Inhibitor
PITC	Provider-Initiated Testing and Counselling
PMTCT	Prevention of Mother-to-Child Transmission
P.O.	Per Os (by mouth)
PTB	Pulmonary TB
Qid	Four Times per Day
RH	Rifampicin/Isoniazid
RHZE	Rifampicin/Isoniazid/Pyrazinamid/Ethambutol
RHZES	Rifampicin/Isoniazid/Pyrazinamid/Ethambutol/Streptomycin
RIF	Rifampin
RUQ	Right Upper Quadrant
STI	Sexually Transmitted Infection
Tabs	Tablets
TB	Tuberculosis
TBIL	Total Bilirubin
TDF	Tenofovir
Tds	Three Times per Day

U&E	Urea and Electrolytes
US	Ultrasound
VCT	Voluntary Counselling and Testing
VDRL	Venereal Disease Research Laboratory (test)
VIA	Visual Inspection with Acetic Acid
VZV	<i>Varicella Zoster Virus</i>
XDR-TB	Extensively-Drug Resistant Tuberculosis

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Lighthouse Training Manual in HIV and TB Medicine

Tom Heller, MD

Specialist in Internal Medicine and Infectious Diseases (Germany)

Clinical Advisor

Lighthouse Clinic

Lilongwe, Malawi



The Lighthouse Training Manual in HIV and TB Medicine is written for the medical doctors, clinical officers, medical assistants, nurses, and midwives working at the Lighthouse and its supported sites. We hope it will serve health care workers as a valuable tool and knowledge resource.

— Prof. Sam Phiri, Executive Director, Lighthouse Clinic Trust



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