Hlabisa

Case Book in TB & HIV Medicine

Tom Heller MD (Ed.)

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

Dedication

To Claudia,

«no me quites tu risa»,

(T.H.)

and

to the people of Hlabisa subdistrict,

who continue laughing, despite all this.

(T.H., C.H., A.S., M.B., J.C., R.L.)

Table of content

Foreword

Due to a variety of reasons there is a chronic shortage of health care professionals in rural African hospitals. Despite South Africa being a relatively well resourced country in comparison to its neighbours it is not immune to this shortage. Often rural hospitals operate with less than 50% of the medical officers they are supposed to have.
Overseas trained doctors from more developed settings who act as a lifeline to rural hospitals often arrive with little or no preparation for the kind of cases they will meet, this is not the fault of the individual but often of the health system where due to shortage of personal it is not possible to fully induct a new doctor into their new environment.

I know from personal experience that arriving in a hospital such as Hlabisa from the UK despite having read numerous books and gone on tropical medicine courses I was really at sea for a few months.

The following series of cases prepared by doctors at Hlabisa hospital based on real patients that presented and were managed at Hlabisa using the resources available provide an invaluable educational tool. The cases include common and less usual presentations but probably all the conditions covered would be seen by a medical officer spending a year at Hlabisa.

The cases cover presentation, management outcome and give further reading. All are accompanied by useful images. Learning points are emphasized. These cases can be read as an educational series and then used as a resource.

The authors should be commended for compiling such a comprehensive and well researched set of presentations as well as managing to investigate and follow up their patients so well with the limited resources available.

Dr. Martin Dedicoat
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Acknowledgments

To come to a new place and deal with new conditions is always challenging for a doctor. The health system in Hlabisa subdistrict, as the health system in most rural parts of South Africa, rely heavily on physicians “who come new to the area”. Many hospitals are staffed with community service doctors, who are at an early stage in their clinical career, and by short-to-medium term physicians, who come from abroad. For many the exposure to the combined epidemic of TB and HIV is new and one can only be vaguely prepared for the number and the severity of the cases.

The idea to write a case collection was born out of our own experience of facing new conditions with different pathologies, but also with different diagnostic and therapeutic possibilities. These cases should give an idea which diseases can be expected but also which steps can be taken with the limited resources at our disposal.

Medical books are never written only by the authors and being in a district hospital we frequently liaise with other departments for advice and help. We would like to thank Dr. Martin Dedicoat, Infectious Diseases specialist in Ngwelazane Hospital for his frequent help and the possibility of “un-beurocratic” patient transfers, Dr. Swan, chief radiologist in Ngwelezane Hospital for the help and great support with CT and MRI studies. Dr. Ramjee and the MDR-TB team in King George V Hospital as well as the Cardiothoracic Surgery team at Inkosi Albert Luthuli hospital need to be thanked for the help with our TB problem cases.

We would like to thank Tracey Hudson from African Health Placements for helping our hospital and programme with recruitment and placement of physicians (if someone needs help to come to South Africa, contact her at TraceyH@ahp.org.za) as well as helping us to publish and print this book.

Additionally we would like to thank the colleagues we work with on a daily basis. L. Mhlongo, M. Ndlovu and the rest of the TB team helped to set up the chronic cough clinic, where many of the TB patients were seen. S. Hlabisa and the staff of the ART team in all our clinics are supporting us on a daily basis and I would like to thank the KwaMsane team in particular for finding patients, translating histories and asking permission to take the pictures.

Finally we want to thank the patients whose cases are shown in this book. They understood the need to train other doctors and health care workers.

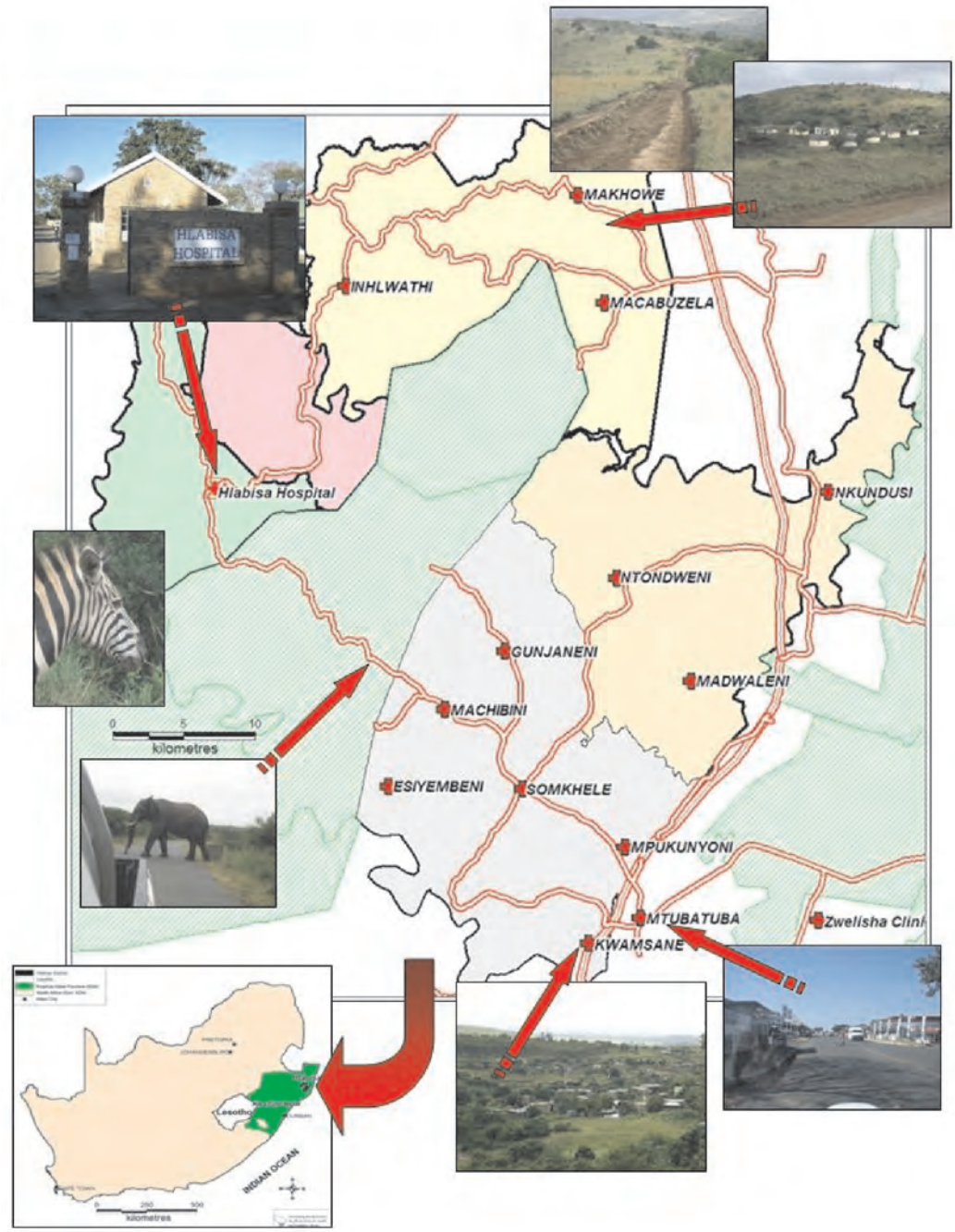
We hope that this book will be of help to all who come to rural Africa to practice medicine.

For the Hlabisa team

Tom Heller

Outline of health and disease and the health services in the Hlabisa Subdistrict of KwaZuluNatal, South Africa

Map of the clinics in Hlabisa area

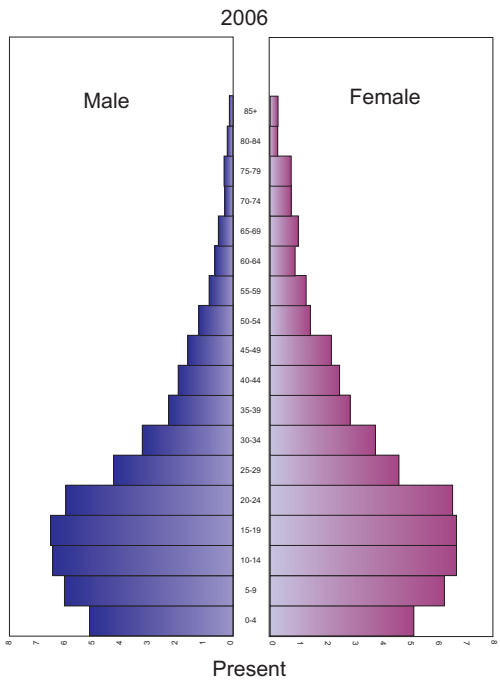


Every health care professional treating patients needs to be aware of the local epidemiology of diseases in the area. This does not necessarily mean to study bulletins on epidemiology and notifiable diseases (although these might be helpful sources of information) but can also mean to get “a feel” of what is common and what is not. We are all aware that "if you hear hoof beats, it's more likely to be a horse than a zebra" (House of God), but in a different geographical setting, especially in Africa, some “zebras” might be very common. In this chapter we describe the Hlabisa district where the cases reported in this book were seen to give a general idea on the underlying population as well as the medical services available to the patients.

Geography and Population

Hlabisa sub-district is located in northern KwaZulu-Natal, South Africa approx. 50 km from the coast of the Indian Ocean. It surrounds the northern part of the Hluhluwe-Umfolozi national park, the oldest and third largest of South Africa's “big-five” game reserves. In an area of approx. 1400 km^2 lives a mainly Zulu-speaking population of approx. 220,000. Large parts of the area are rural, also more urban areas exist in Mtubatuba and Kwamsane as well as around Hlabisa.

The demographic and economic profile of the region has been comprehensivly studied and the description is summarized here from the African Centre Mono-graph (1). The population pyramids exhibit the characteristics of a developing country, where there are large proportions of children under the age of 15 years. However, rather than a typical expansive pyramid the pattern shows some changes at the base due to declining fertility.



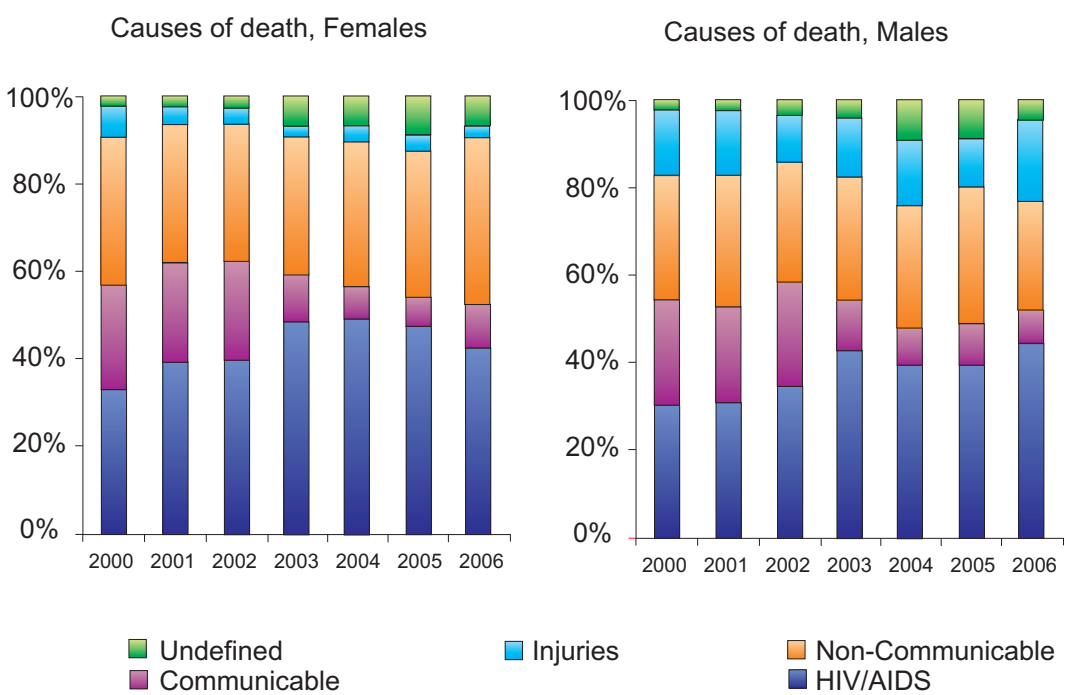
Age-distribution of the Hlabisa area population

On average a typical household in the area consists of about 7 people. A third of the households are female-headed and this proportion has been gradually increasing. Fortunately only about 1% of households are child-headed.

For many years, the area has experienced population losses due to people moving out of the area which offers very few employment opportunities. Out-migration of young adults from rural areas and small towns with limited job opportunities has been a persistent feature of South Africa.

The only industries in the area are forestry, sugar cane and pinapple cultivation, which do not provide sufficient employment opportunities. Unemployment is a serious problem with 48% of the urban and 74% of the rural population being unemployed. About 40% of all households report being poor or extremely poor in rural areas of our district. In 2005, about one in five households in both rural and urban areas reported that an adult had missed meals because there was not enough money for food. Government grants are an important source of income in the area. About a third of households have a resident who receives a pension. A second important grant widely available is the Child Support Grant which is received by 30-40% of households. Disability grants constitute an income for patients with disabling diseases (including HIV/AIDS and TB).

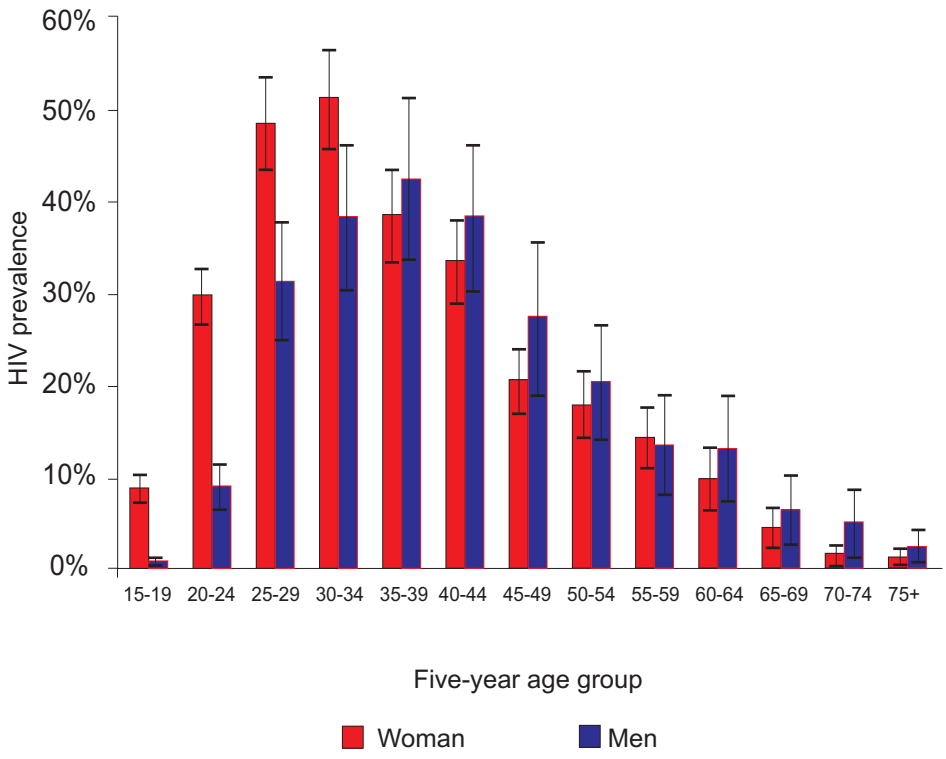
The average life expectancy in 2000 was about 49 years in females and 42 years in males. This declined and in 2005 life expectancy was 42 years and 38 years, respectively. The decline is largely attributable to the increased burden of HIV-related mortality. For both sexes HIV/AIDS is the most frequent cause of death. HIV/AIDS used to account for about 30% of deaths for females and males in 2000, this has subsequently increased substantially. The burden of HIV/AIDS is higher for females than males.



Changes in causes of death in the Hlabisa area 2000-2006

HIV

The prevalence of HIV is extremely high, with approx. 22% of adults infected with HIV. The prevalence peaks for women in 30-34 years old and every second woman in this age group is HIV positive. Younger women and girls are also affected in a significant proportion. Men are infected later and the peak is reached in the 35-39 year old group, when more than 40% are HIV positive (data from 2007 from (2)).



Age specific HIV prevalence 2007 in Hlabisa area

Due to repetitive annual HIV screening it is possible to calculate the new HIV infections per year. The incidence per 100 persons-years was 3.8 new cases for women and 2.3 new cases for men in 2007.

HIV is treated according to South African National guidelines. The first line regimen includes D4T, 3TC and EFV or NVP. In cases of treatment failure or serious side effects AZT, DDI and LPV/r are available as second line drugs, but need to be authorized by a central pharmacist. Before treatment is initiated every patients has three “treatment training sessions”, where patients are trained about important aspects of treatment including effects of treatment and importance of adherence. Baseline blood tests (ALT, Creat, TBIL, FBC, HBsAg) are taken and sputum is sent for AFB screening. After the training, each patient is seen with their results by a physician in the clinic and the ARVs are initiated.

Tuberculosis

The incidence of TB is very high, about 4000 new cases are reported each year. The incidence rate is thus around 2000 per 100,000 inhabitants per year. Many of the HIV/TB co-infected patients are found to be AFB smear negative and often need further investigations for diagnosis. Extra pulmonary TB (pericardial TB, pleural TB, abdominal TB and miliary TB) are frequently seen. Diagnosic decisions are commonly made on clinical ground, using e.g. the diagnostic criteria suggested by WHO guidelines.

TB is treated according to the National South African TB guidelines which are very similar to the WHO guidelines. MDR-TB is a serious problem in the area; XDR-TB is rarely seen. MDR-TB treatment is supplied by a central hospital in Durban on an outpatient basis, the patients are afterwards admitted in the MDR section of the TB ward in Hlabisa hospital for one month before they are discharged. Due to this strategy, the time between receiving the MDR result and initiation of treatment is short. Approx. 10 patients per month start MDR treatment.

Other medical problems

Malaria

Hlabisa lies at the border of the endemic malaria zone. Cases are seen particularly during the summer month (January to April). Plasmodium falciparum (causing Malaria tropica) is the main species, most patients come from the areas closer to sea-level next to St. Lucia and Hluhluwe. Chloroquine resistance is reported. The usual treatment is oral Coartem (combination of lumefantrine and arthemether); severe cases are treated with IV quinine.

Schistosomiasis

Schistosoma hematobium exists in the area and in schoolchildren aged 5-10 the prevalence is between 15 and 20%. A relatively high rate of bladder cancer has been reported in the area which might be partially attributable to the infection. Schistosoma mansonii is rarely seen.

Hepatitis

Rural South Africa is a high prevalence area for Hepatitis B and data from our area suggests that approximately 8-10% of the individuals starting ART have chronic hepatitis B. Hepatitis C is thought to be of lesser importance. Hepatitis A virus is a common cause of acute hepatitis in the area.

Rabies

Rabies is reported in the area. Especially in the rural areas towards the southern border of the game reserve a number of rabid dogs were captured. Dog bites are frequent and despite the availability of rabies vaccine and to a lesser extent immunoglobulin, fatalities are seen in Hlabisa hospital.

Sexual transmitted infections (STI)

The exact prevalence of STI in the population is not known. Preliminary findings from an ongoing study estimate the prevalence of gonorrhea in HIV negative women at approx. 8%, Chlamydia trachomatis 5%, Trichomonas infection 13%. Syphilis prevalence was 6 % (positive TPHA). Herpes Simplex Virus 2 antibodies were detected in 67% of tested women.

These figures probably underestimate the true prevalence as one would expect the risk to be higher in HIV positive patients.

Chronic diseases

Hypertension and diabetes mellitus are common chronic diseases. Although cardiac complications are not frequently diagnosed, secondary strokes are a frequent cause of hospital admission. As HIV prevalence is high in all age groups, frequently antiretroviral treatment needs to be given in combination with anti-hypertensive and anti-diabetic treatment. Drug interactions as well as metabolic side effects need to be considered.

The hospital and the clinics

The main medical facilities in the sub-district are Hlabisa hospital, a 350 bed district general hospital, as well as 15 primary health care clinics distributed in the area.
Medical service in Hlabisa was established as a clinic in 1932 by the Lutheran Mission Society, it became a hospital in 1948 and was later taken over by the KwaZulu government. It has medical staff of approx. 9-12 physicians which see approx. 30,000 outpatients per year. It has two surgical wards and one obstetric ward, approx. 3,500 babies are delivered per year. The pediatric ward has 30 beds and the nursery is equipped with 6 incubators.

Care for internal medicine patients is delivered in a male, a female and a TB ward, each with approx. 35 beds. The diagnostic services available are restricted. Plain X ray and ultrasound can be used as imaging modalities. In the hospital laboratory U&E, LFT and FBC are available, additionally microscopy of urine and CSF tests are done. CD4 counts are available in the hospital which makes results for patients in the clinics available within approx. 1 week (delay due to transport).

Patients who need further investigations (CT, MRI, Echo) need to be referred to the nearest provincial hospital (approx. 120 km distance) or to tertiary institutions in Durban (approx. 300 km).

Primary health care (PHC) is delivered in the peripheral clinics associated with the hospital. The biggest clinic is located in Kwamsane, next to the national N2 road. Nurses see up to 10.000 patients per month in this clinic and approx. 1000 to 3500 patients per month in the smaller clinics.

ART and TB program

The ART programme and the TB programme are decentralised and integrated in the PHC clinics. The TB programme treats more than 4000 patients per year at the local clinic level, supported by central TB coordinators and patient tracking teams for defaulting patients. Many patients, especially smear-negative patients are diagnosed in “chronic cough clinics” (localized on the hospital grounds and in Kwamsane clinic).

In the ART programme over 5600 patients have been treated (Oct. 2008) and are seen by more than 20 ART nurses and 60 counselors. Most clinics have an ART physician visiting once a week to initiate new patients and see problematic cases.

The integration of TB and ART services is a key priority. More than 85% of the patients diagnosed with tuberculosis consent to be HIV tested, four out of five test positive. They are consecutively transferred in the ART programme. Conversely, all patients started on ART are

screened for TB, in the near future this service will be expanded to patients whose CD4 counts are above the treatment threshold of 200 cells/ml.

The Africa Centre for Health and population studies

Established in 1997, the Africa Centre for Health and Population Studies is a joint project of the University of KwaZulu-Natal and the Medical Research Council of South Africa. The centre is situated near Somkhele and conducts research on population and health issues of importance to developing countries. The main focus is the longitudinal demographic survey as well as the population based HIV survey which are conducted every year in an area containing 11,000 households and approx. 80,000 people.

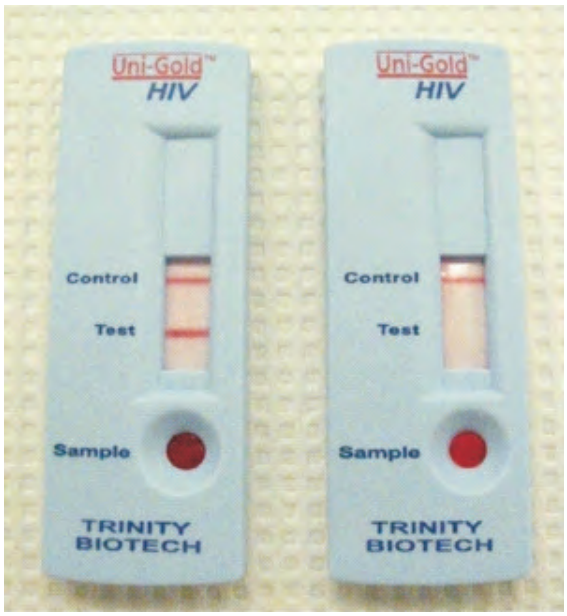
Since 2004 the centre has been actively involved in the roll-out of ART in the sub-district. Several physicians, nurses as well as other staff are employed through PEPFAR funding to support the Department of Health. The centre is now developing a clinical research agenda related to how best to deliver ART to rural populations through the primary health care system.

1) Muhwava W. and Nyirenda M (2007) Demographic and Socio-Economic Trends in the ACDIS,Monograph No 2. Africa Centre for Health and Population Studies, Mtubatuba, South Africa)
2) Baernighausen T et al. Measuring the force of the HIV epidemic in a rural area of South Africa: The Africa Centre, 15th CROI (2008), Abstract 127

Case 1

Case presentation

A 24-year old man tested HIV positive three weeks ago. He tested because an event of a local NGO made him wonder about his HIV status. He had no symptoms and felt well. His CD4 cell count was 188 cells/μl. Routine bloods were taken and he received ART training sessions by the HIV counsellors. He was referred for ART initiation.



Questions

1) What is shown in the picture and 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 and what are the main side effects?

Diagnosis: HIV-1 infection

Answers

1) A rapid HIV test is shown which uses spot capillary blood. In high prevalence settings (according to WHO areas with HIV prevalence >10%) a positive test result has to be confirmed with a second rapid test. Another rapid test from a different company is usually used. If this is positive, the patient is considered to be HIV positive.

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 for symptoms of peripheral polyneuropathy. You want to examine the patient physically for skin changes, mucosal changes, chest auscultation and abdominal palpation for organomegaly. Important lab values that should be checked and documented are CD4 count (for treatment indication < 200 cells/ml), ALT, bilirubin, creatinine, FBC and HBsAg. To know these baseline values will help you in case side effects develop at a later stage.

3) The patient should receive CTX 2 tabs od as prohylaxis for PCP and other infections (e.g. salmonella). Additionally multivitamins 1 tab od have been shown to delay disease progression and should be given as adjunctive treatment.
   First line ARV treatment in South Africa includes the following drugs:
   a) D4T 30 mg bd - Nucleoside reverse transcriptase inhibitor (NRTI)-Side effects: peripheral neuropathy, hepatic steatosis, lactic acidosis, lipodystrophy, gynecomastia.
   b) 3TC 150 mg bd - NRTI- Side effects: diarrhoea, pancreatitis; generally 3TC is a very well tolerated drug with rare side effects.
   C) EFV 600 mg nocte - Non-nucleoside reverse transcriptase inhibitor (NNRTI)- Side effects: CNS disturbances (dysphoria, vivid dreams, distractedness), skin rash, congenital anomalies (avoid in the first trimester of pregnancy). If the patient has taken EFV in early pregnancy and sees you at a later stage, it will probably not make much difference and many physicians continue EFV. (NB the neural tube is fully formed by 10 weeks).The drug is given in the evening to avoid the CNS symptoms from interfering with the daily life of the patient. Patients working night shifts might prefer to take the drug in the morning
   d) NVP 200 mg od for 14 days then 200 mg bd - Skin rash, nausea, vomiting, hepatitis (possibly fatal). As NVP induces P450 enzymes and shares the side effect of hepatitis it should ideally not be given with rifampicin. EFV is the preferred drug for these co-infected patients.

Outcome and follow up

The patient was started on D4T/3TC/EFV plus CTX and multivitamins. He was further treated and monitored by the ART nurse.

Comments

Rapid HIV tests have a high sensitivity (>99%) as well as a high specificity (99%). In a setting with a high prevalence confirmatory tests like ELISAs, western blots or PCR are only needed in ambiguous cases.

Key learning point

HIV is often asymptomatic and expansion of HIV Testing is important

Suggested reading

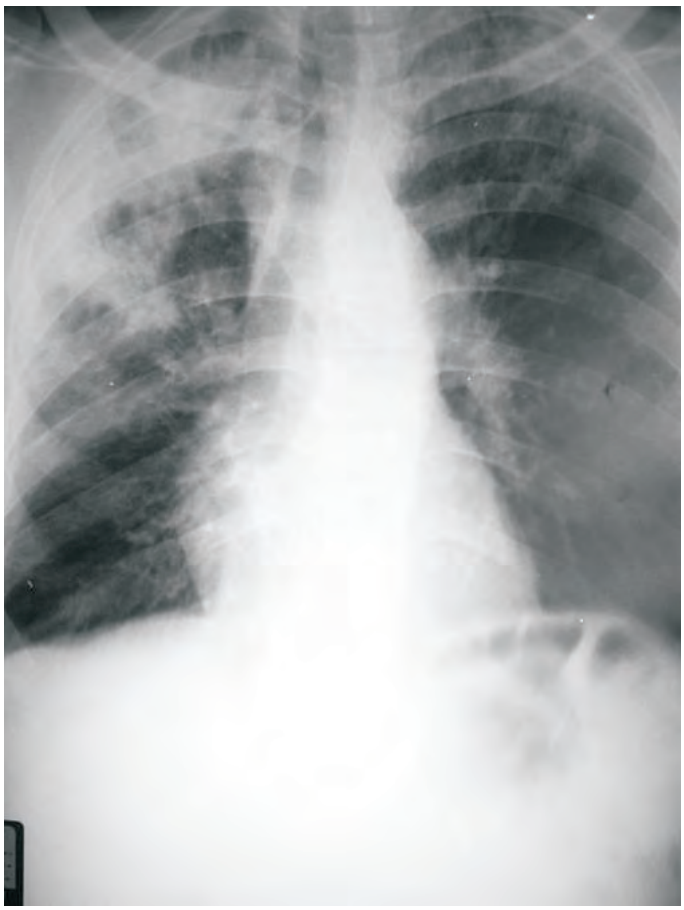
National Department of Health South Africa: National antiretroviral treatment guidelines 2004

Case 2

Case presentation

A 25-year old man was seen in the cough clinic at the hospital. He had been seen in his PHC clinic with three weeks of cough, weight loss, and drenching night sweats. He had never previously been treated for TB and he denied household TB contacts. Sputum had been sent for AFB, which was negative. In the PHC clinic, he had received amoxicillin 500 mg tds and erythromycin 500 mg tds for one week without improvement of his symptoms.

His HIV status was unknown, so the TB nurse referred him for VCT and he tested HIV positive. A CXR was taken.



Questions

1) Comment on the value of acid fast stain of sputum in diagnosing TB.
2) Are further diagnostic steps indicated?
3) Which treatment should be given?
4) Is it a useful step to send him for HIV testing and 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 the diagnosis of TB. In high prevalence setting, a positive stain can be considered diagnostic as Mycobacteria other than tuberculosis (MOTT) are comparatively rare. Unfortunately the number of AFBs in sputum needs to be high (5,000-10,000 organisms/ml). 35% of PTB cases are smear-negative under programme conditions. In HIV patients the rate of smear-positive cases is even lower. In KwaZulu-Natal only 34 % of the treated TB cases are smear positive, at least partly due to the high HIV prevalence.
   In summary, a positive AFB smear is very helpful to diagnose TB but conversely a negative smear can never rule it out.

2) Sputum TB culture is a possible next diagnostic step. Due to the long time the culture needs to become positive (3-6 weeks) and the administrative problems (transport to central lab, finding the patient once the result comes back, etc.) it is often no help in guiding the therapeutic decision. The clear advantage is the possibility to obtain a resistance profile of the TB strain, which is of particular importance in settings with high MDR rates. Invasive diagnostic steps like bronchoscopy are rarely possible and seldom indicated in our setting.

3) Standard TB treatment consists of 2 months of a 4 drug combination e.g. rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E), preferably in a fixed drug combination (intensive phase). This is followed by 4 months of RH (consolidation phase). Concomitant with the isoniazid, pyridoxine 25 mg (vitamin B6) should be given to prevent the hematological and neurological side effects of the drug.

4) TB and HIV infections are often found in the same patient. To screen TB patients for HIV is therefore an effective way to find HIV infected individuals. The radiological appearance of TB changes in HIV patients and it is helpful to know the patients immune status when interpreting the CXR. This patients x-ray shows a “classical” 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 CTX 2 tabs od were prescribed. He was registered by the TB assistant and the first month of therapy was supplied by the hospital pharmacy. He was than transferred back to his PHC clinic for further treatment.

His CD4 count was taken at the hospital's ART clinic and the result was sent his local ART clinic. The patient was not seen again in hospital and an uneventful course of TB treatment was assumed.

Comments

It has been shown that multivitamins slow the progression of HIV disease in the setting of a nutritional deficient population and should therefore be given to all HIV positive patients. CTX is indicated in all patients with advanced immunodeficiency and most guidelines recommend it in WHO Stage 3 and 4 disease and in patients with low CD4 counts (below 200 cells/ml according to South African guidelines, below 350 cells/ml according to WHO). All HIV positive patients with PTB should receive CTX prophylactic therapy.

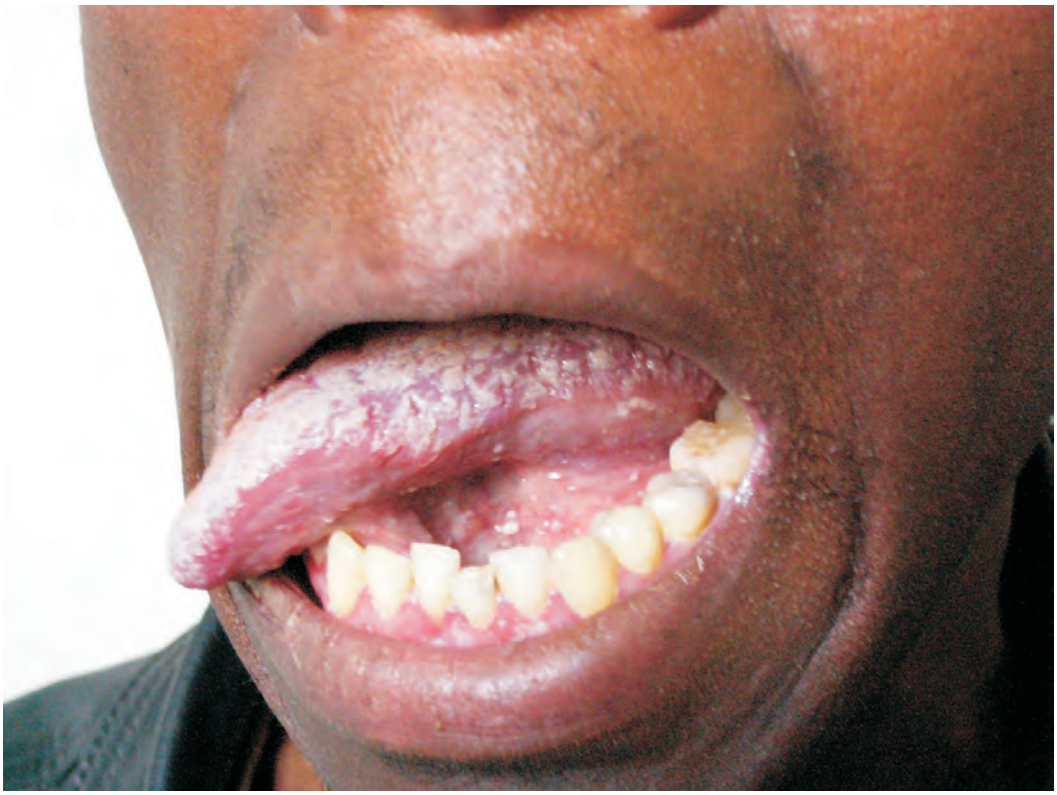
Key learning point

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

Case 3

Case presentation

A 44-year old patient was seen in the cough clinic with a painful chest. 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 his 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.

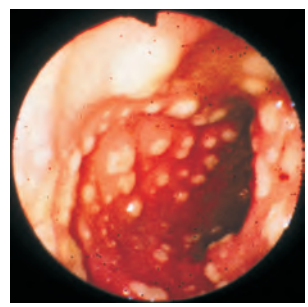
3) Oral candidiasis generally occurs in patients with fairly advanced HIV infection, commonly with CD4 counts <300 cells/îl. The HIV test should be repeated. If negative, other causes should be considered, such as diabetes mellitus.

4) Oral lesions only can be treated with nystatin solution 2.5 ml 5 times per day or topical amphotericin lozenges. If oesophagitis is a possibility fluconazole 200mg od for 14 days is indicated.

Outcome and follow up:

The patient went for HIV test again which was positive. He reported painful swallowing. He was started on fluconazole 200mg; additionally co-trimoxazole and multivitamins were given. His CXR was normal, so no TB treatment was started. His CD4 count was 88 cells/μl and he was referred to his nearest clinic for ART.

Further images



Candida oesophagitis (not this patient). Upper GI endoscopy is rarely indicated.

Comments

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

Key learning point

In the presence of oral candidiasis always ask the patient About dysphagia and odynophagia

Suggested reading

Fichtenbaum CJ, Aberg JA: Candidiasis and HIV, HIV Insite Knowledge Base Chapter, Feb. 2006, http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-02-03

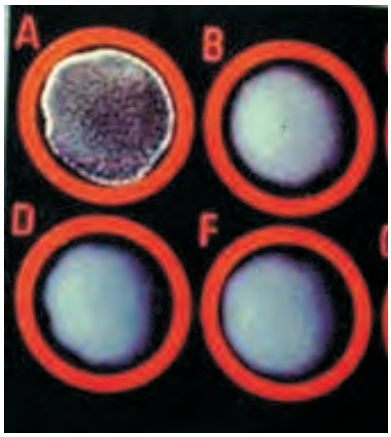
Case 4

Case presentation

A 23-year old male patient was admitted to the ward with headache and vomiting. His sister reported that he was increasingly somnolent and had displayed altered behaviour.
His clinical examination revealed cachexia and marked neck stiffness; there was also evidence of oral candidiasis. The sister did not know his HIV status and the HIV counsellor refused to test the patient as he was too confused to consent.
A lumbar puncture was done and showed the following:

CSF- polymorphs	0 cells/μl	(normal <5)
CSF-lymphocytes	24 cells/μl	(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 is shown in panel A.



Questions

1) What type 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 (now reported as 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 and vomiting, neck stiffness, abnormal behaviour or other CNS or psychiatric symptoms. Lumbar puncture is the test of choice, pleocytosis is seen in 70% of the cases (often mild with lymphocytic predominance), protein is raised in more than 90%, glucose reduced in 60% of cases. CSF should be analyzed 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 after appropriate treatment has been initiated.

2) Cryptococcal meningitis should be treated with amphotericin B 1 mg/kg/dose IV for 2 weeks (minimum 1week). The main limitation of amphotericin B is nephrotoxocity. It should be given slowly (over 4 hours) diluted in 1000 ml of 5% glucose. Giving 1000 ml of normal saline before and after the drug improves the hydration status; renal function should be monitored. The initial phase is followed by a consolidation phase with fluconazole 400 mg po od for 8 weeks. After this, secondary prophylaxis is given (fluconazole 200 mg po od) for life or until CD4 >200 cells/μl.

3) The lay counsellor can only perform HIV tests after obtaining consent from the patient (or a parent in case of minors). In comatose or confused patients the physician can order a HIV test for "medical indication" without consent, if this is necessary for diagnosis or treatment of life-threatening disease. The order must be documented in writing.

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; he finally became comatose and died on the sixth day of his hospital stay.

Comments

International guidelines recommend treatment with amphotericin B in combination with 5-flucytosine, but the latter drug is not available in South Africa. Amphotericin B is thus the drug of choice and should be used whenever possible as initial treatment. If this is not available a (suboptimal) option is to substitute amphotericin B induction phase with fluconazole 800 mg po od for 4 weeks followed by fluconazole 400 mg daily for 8 weeks. As drug shortages frequently occur in our area, we currently treat with amphotericin B for 1 week followed by fluconazole 800 mg for 3 weeks.

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. Measurement can be done by connecting a giving set to the spinal needle and measure the column of CSF with a ruler (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 point

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

Suggested reading

SA HIV Clinicians Society: Guidelines for the Prevention, Diagnosis and Management of Cryptococcal Meningitis and Disseminated Cryptococcosis in HIV-infected patients, Southern African Journal of HIV medicine, Spring 2007 http://www.sajhivmed.org.za/index.php/sajhivmed/article/viewFile/92/52

Case 5

Case presentation

A 56-year old woman attended clinic with complaints of fatigue, frequent urination and constant thirst. She had been taking D4T/3TC/EFV for more than a year. Additionally she complained about blurred vision. Her last CD4 count was 320 cells/μl. Her blood sugar was measured by the PHC nurse and was 22 mmol/l. Other than obesity her examination was unremarkable. Type II diabetes mellitus was diagnosed.

Questions

1) What would you recommend as treatment?
2) How would you monitor her in the PHC 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 is appropriate lifestyle change, such as increased exercise. It is important to explain what is understood by "exercise". Brisk walking for 45 min three times per week is adequate. Additionally it is important to explain diet changes (reduce sugar and starches, increase fresh vegetables and fruits) which might be difficult to implement for patients with limited financial resources.
   More often than not drugs will be needed to control the diabetes. The first line of treatment is a sulphonylurea e.g. glibenclamide (start with 2.5-5 mg /day, max dose 15 mg; give 2/3 of the dose in the morning and 1/3 in the evening). Gliclazide (start 40 mg od, max 160 mg bd) is an alternative in patients with renal impairment. The drawback of this class of drugs is that they can cause weight gain.
   Metformin (start 500 mg od, max. dose 850 mg tds) is a treatment option and reduces weight, it is less advisable in patients on ART as it increases the risk of lactic acidosis in people taking d4T, ddI and AZT. Insulin may be required for refractory cases but it poses logistical problems (cool storage, blood sugar measurement).

2) Often patients present with random sugar levels which are of little (to no) help in guiding treatment as the relation to the last meal is unknown. The best way to monitor blood sugar in the PHC setting in our experience is the fasting blood sugar. Patients (and clinic nurses) 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. If the fasting sugar is between 6-8 mmol/l it is considered acceptable, above 8 mmol/l the drug dose needs to be increased. Unfortunately "ideal" blood sugar target are very difficult to reach in our environment.
   HbA1c would be an option to judge the long-term average blood sugar. The drawing of venous blood, sending to central lab and receiving results back is often unreliable and to time consuming to help in the PHC setting.

3) The most important other 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 modification and was started on glibenclamide 5 mg. The following week she had a fasting blood sugar of 11 mmol/l. The dose was increased and finally a reasonable value of 8.2 mmol/l was achieved with 15 mg glibenclamide per day. She was then monitored by the PHC clinic nurse.

Comments:

The development of type II diabetes has been reported in 2 to 10% of HIV-infected inidividuals taking 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. 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 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 D4T significantly increases the risk of lactic acidosis (and should therefore be used with caution)

Suggested reading

The national department of health, South Africa: Standard treatment guidelines and essential drug list. 2006

Case 6

Case presentation

An 18-year old woman was admitted with severe diarrhoea and dehydration. She described the diarrhea as watery with a frequency of 6-8 times per day. She could not say whether blood was present as she used a latrine. In her local clinic, she tested HIV positive and her CD4 count result was pending.

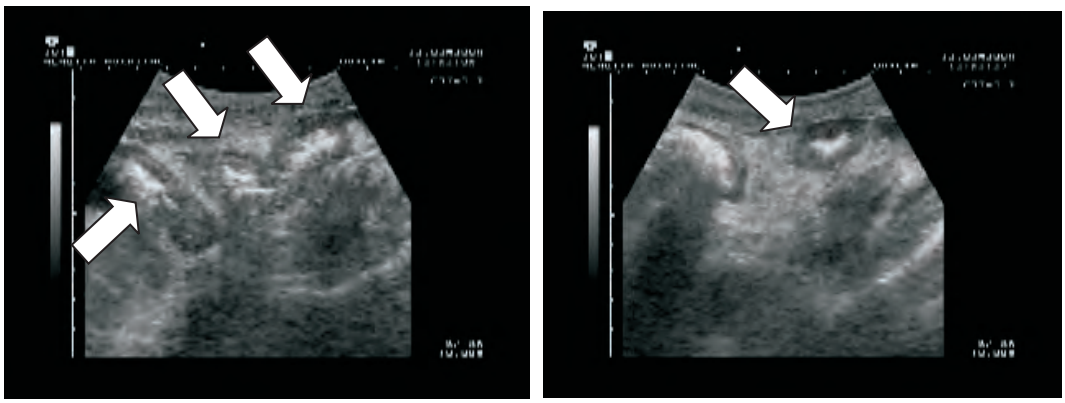
On examination, she appeared cachectic although her body weight was not measured ("unable to stand"). An IV line was inserted and Ringer's lactate solution 3 l per day was commenced.

Her blood results were as follows:

U&Es:

Na	148 mmol/L	(normal 133-153)
K	1.9 mmol/L	(normal 3.0-5.0)
CO2	20 mmol/L	(normal 22-33)
Creat	324 μmol/L	(normal 62-120)
Urea	16.2 mmol/L	(normal 3.5-6.5)

During the next days she had an abdominal ultrasound; signs of colitis were found.



Ultrasound of bowel loops a) longitudinal b) transverse
Bowel with hypoechoic wall 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 and how would you diagnose and treat them?
2) What is "slim disease" and how is it caused?

Diagnosis: Colitis (unclear aetiology)

Answers

1) Bacteria, parasites as well as viruses might cause diarrhea in HIV positive patients. Additionally one has to consider drug side effects and tumours (generalized Kaposi's sarcoma and gut lymphoma). Often the cause remains unknown and symptomatic treatment (loperamide) is the only available option.

Organism	Frequency	Diagnosis	Treatment
Parasites			
Cryptosporidium	13-20%	Stool microscopy (modified acid fast stain)	No specific tx
Cyclospora	?	Stool microscopy (modified AF stain)	CTX 4 tabs bd for 3 weeks
Isospora	14%	Stool microscopy (modified AF stain)	CTX 4 tabs bd for 3 weeks
Microsporidia	20%	Stool microscopy (Trichrome stain)	Albendazole 400 mg bd for 4 weeks
Bacteria			
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
Viruses			
CMV	13-20%	Biopsy	Gancyclovir
HIV	?	Exclusion of others	ART

2) Weight loss and wasting in HIV patients. Possible causing 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 stabilised by the IV fluid. CTX 2 tbl bd was given; additionally loperamide 4 mg tds was started. As the diarrhoea did not improve after 3 days, ciprofloxacin 400 mg bd was added. The frequency of stools decreased, but diarrhoea did not subside completely. On a follow up ultrasound one week later the thickened bowel loops had disappeared despite mild diarrhea being still present.
CD4 count was found to be 14 cells/μl. After further improvement the patient received counselling then started ART. She was discharged on D4T/3TC/ EFV, CTX, multivitamins, and loperamide.

Comments:

40-90% of HIV positive patient will develop diarrhoea. Diagnostic algorithms need to be balanced with treatment trials according to 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 diarrhea (watery) can be difficult as patients use latrines and do not inspect the stool. We use the following treatment steps: 1. Ciprofloxacin+Metronidazole 2. If no improvement after 3 days then high dose CTX 3. If no improvement then albendazole

Key learning point

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

Suggested reading

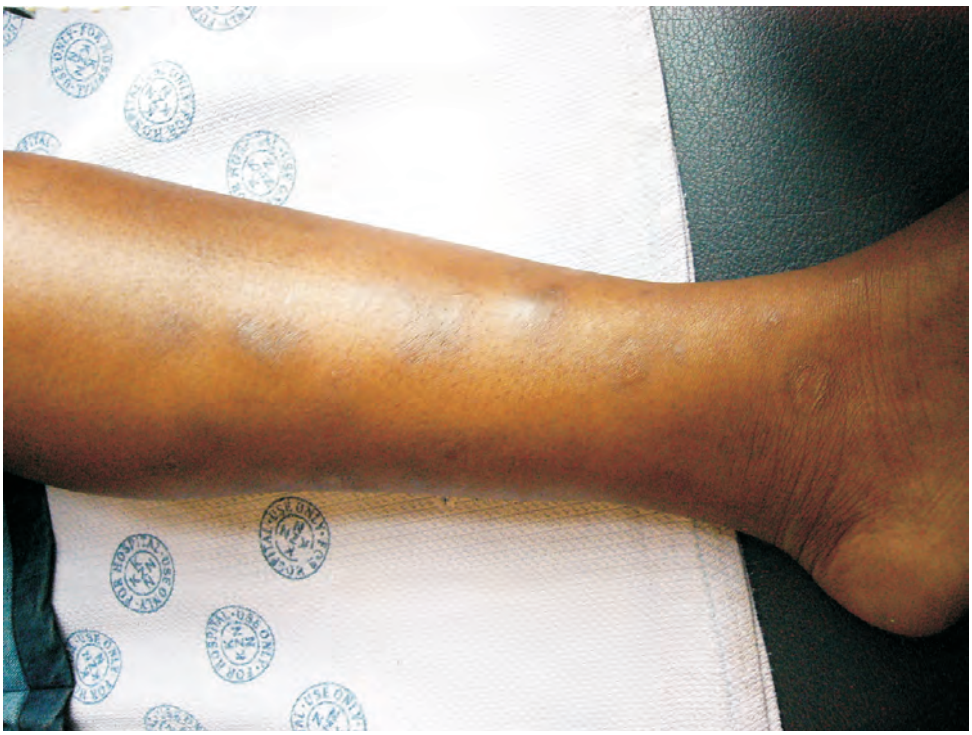
Sande MA et al: Sanford guide to HIV/AIDS therapy 2006-2007, 75-78

Case 7

Case presentation

A 16 year old female student was brought to the clinic by her mother complaining of painful shins. She reported a previous negative HIV test.

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



Questions

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

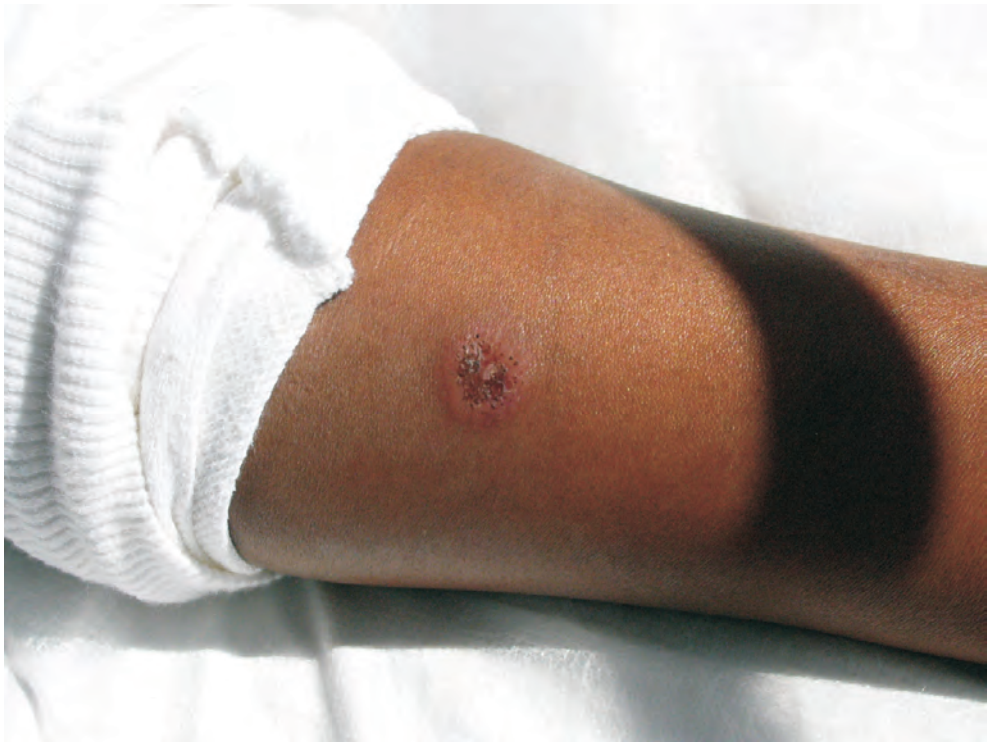
Diagnosis: Erythema nodosum

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 a pharyngeal infection recently. She is therefore treated with amoxicillin and ibuprofen. A CXR and a tuberculin skin test are ordered to assess for TB. After one week the symptoms had not improved, the CXR was normal, the skin test was strongly positive. The patient was started on standard TB treatment and the lesions improved very rapidly after this.



Comments:

Erythema nodosum is rare in young children and commoner in females at all ages. There is often a fever and 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 1-4 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.

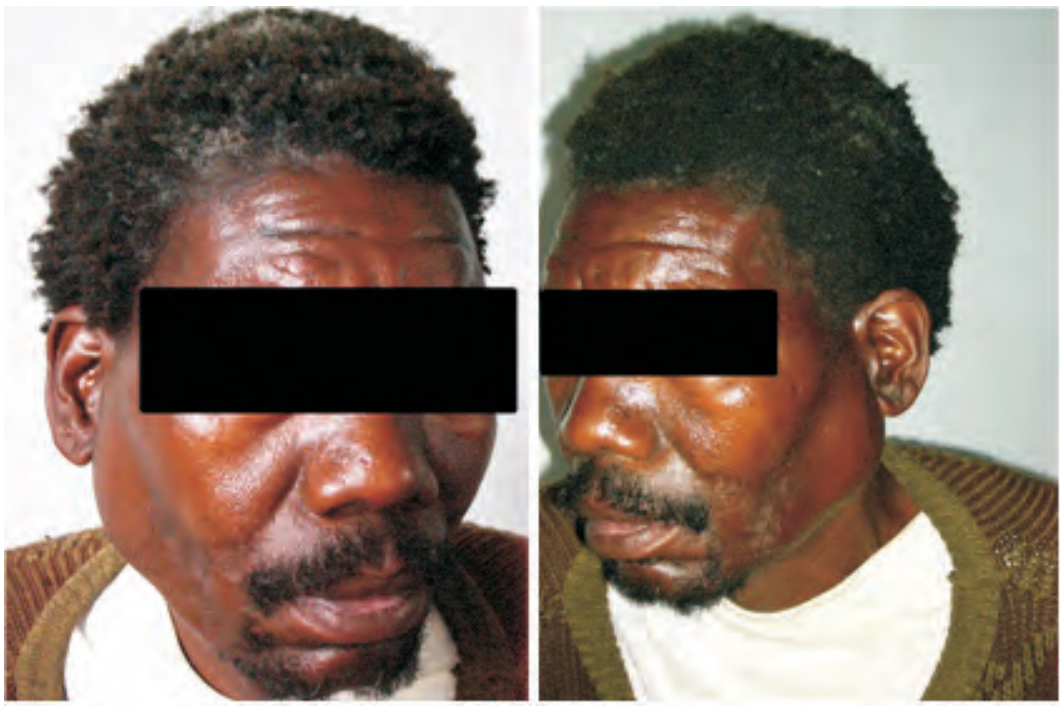
Key learning point

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

Case 8

Case presentation

A 53-year old patient attended hospital with symptoms of longstanding cough, weight loss, and night sweats. He was treated for tuberculosis 16 and 6 years prior to this admission, both times with success (according to the patient). He had now been referred for 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, probably diffuse infiltrative lymphocytosis syndrome (DILS)

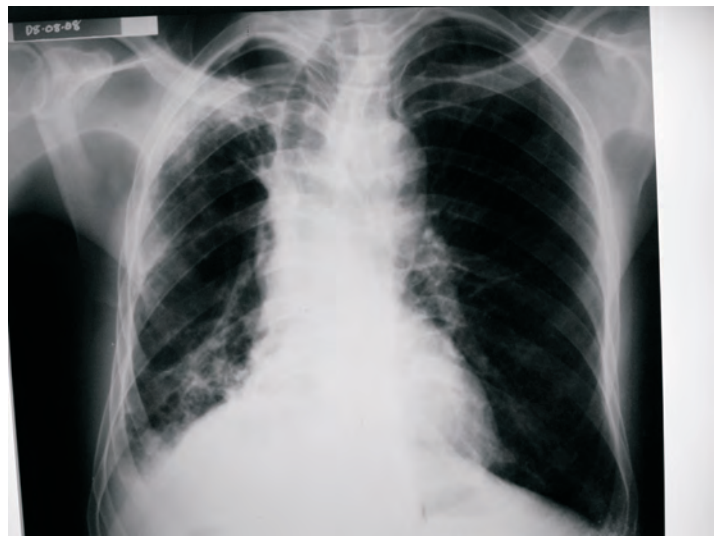
Answers

1) The localization and the symmetry of the swelling make lymph nodes as cause unlikely and it is more likely to be due to parotid enlargement. A biopsy is therefore not the investigation of choice. Given the reported cough a CXR should be done.

2) Diffuse infiltrative lymphocytosis syndrome (DILS) is a Sjoegrens like syndrome with painless salivary gland swelling, peripheral CD8 lymphocytosis and "sicca" symptoms of dry mouth and insufficient saliva production. Benign lympho-epithelial cysts of the salivary gland can be seen with ultrasound; diagnosis can be made through the use of fine needle aspiration. Treatment modalities are simple aspiration and surgical resection; radiotherapy might be an option where available. Regression of the swelling has been demonstrated in patients treated with ART.

Outcome and follow up:

The patient tested HIV positive. A CXR showed destruction and scarring in the right upper lobe with traction deviation of the trachea to the right. Because of his treatment history sputum TB culture was sent. TB treatment was started on the basis of the clinical symptoms. He was referred back to his clinic for CD4 count and further therapy. As he was only complaining of mild dry mouth no further treatment for the gland swelling was given.



Comments:

5-10% of patients with HIV-1 infection have parotid swelling (it is more common with advanced disease). DILS is more common in patients of African descent than in caucasians. In some cases extraglandular involvement is found. The most common extraglandular sites of disease are lung (lymphocytic interstitial pneumonitis, 31%), muscle (polymyositis, 26%), and liver (lymphocytic hepatitis, 23%). Neurological complications like mononeuritis (e.g. VII nerve palsy) and aseptic lymphocytic meningitis are also seen.

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: 42-44

Case 9

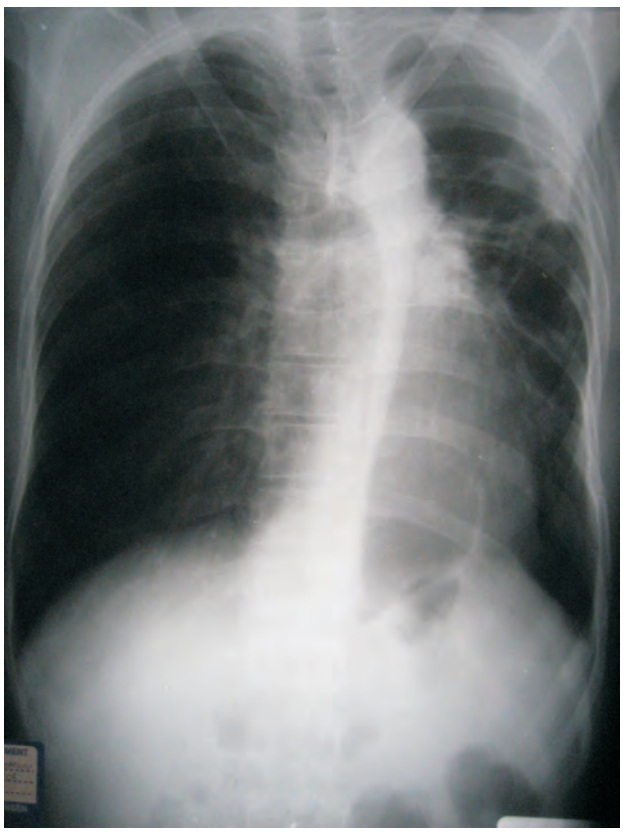
Case presentation

A 54-year old man was seen in the clinic complaining of prolonged cough, night sweats and weight loss. He had TB more than 15 years ago. He was started on RHZE on the basis of clinical symptoms. Additionally he had an HIV test; he tested positive and his CD4 count was 421 cells/μl.

A week later he was seen again complaining now about coughing up blood stained sputum. He reported 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/mm^3	(normal 4.0-11.0)
Plt	71 10^3/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" and 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. sec. to mitral valve stenosis). Autoimmune (Wegener's granulomatosis, Goodpasture's syndrome) and haematological disorders (leukemia, ITP) might be considered as rarer causes.

2) Massive haemoptysis is extremely anxiety provoking for patients (and doctors!). It is ill-defined as 100 to 600 ml blood within 12-24h. Priority is to localize the bleeding, CT might help although finally the patient should undergo bronchoscopy. In cases of massive bleeding rigid instruments are preferable. In cases of chronic bleeding localization 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. It is probably due to the TB. In his left upper lobe bullae and cavities are seen, so bronchiectasis due to the infection and to scars (old TB) can be assumed. The mild thrombocytopenia might have added to the bleeding. TB treatment should be continued, additionally it might be useful to add cough mixture to reduce the cough and thus increase the chance of healing. Tranexamic acid might reduce the bleeding, additional antibiotics can be used to cover superadded infection. The platelets should be checked in the interval.

Outcome and follow up:

The patient was informed about his low platelets, his TB treatment continued and it was recommended to return after one week to repeat the FBC. The patient did not come back for this.

After 5 ½ months of treatment he was seen again, complaining again about "coughing up blood stained sputum". FBC and CXR were repeated. The CXR showed no change.

Hb	13,3 g/dL	(normal 11.5-16.5)
WBC	5.8 10^3/mm^3	(normal 4.0-11.0)
Plt	612 10^3/mm^3	(normal 150-500)

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

Comments:

In a South African study 85% of 120 consecutive cases of significant haemoptysis (>200 ml) were found to be due to TB. In other countries with lower TB prevalence this is obviously lower.
Etiology of pulmonary bleeding in TB patients might be due to ectatic blood vessels traversing a cavity (Rasmussen's aneurysm), calcified lymph nodes that erode the wall of the airway (broncholith) and aspergillomas. Another reason is simple bronchiectasis, where vessels are vulnerable to be eroded by the chronic inflammation that is typical for this disorder.

Key learning point

If the patient has had prior TB, haemoptysis could be caused by a sequela of the previous disease

Suggested reading

Knott-Craig CJ et al: Management and prognosis of massive hemoptysis. Recent experience with 120 patients. JThorac Cardiovasc Surg 1993;105:394-397

Case 10

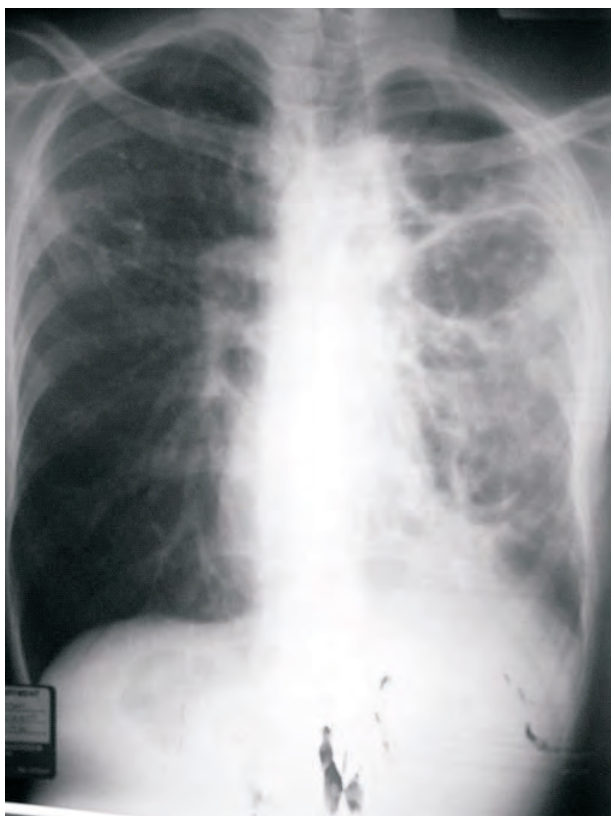
Case presentation

A 33-year old man was sent to the hospital because of adherence problems with TB treatment.

He had been tested for TB because of chronic cough and weight loss and his sputum smear was positive for AFB. He had then been started on standard TB treatment but refused HIV testing. After the first 6 weeks of treatment he had felt better and defaulted from the clinic and "left the area to work". Another 2 months later his symptoms had recurred and he returned to the clinic.

The TB nurse was undecided what to recommend and referred him to hospital.

A CXR was taken.



Questions

1) What does the CXR show?
2) What other investigations would you suggest?
3) What would you recommend to the TB nurse (and 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 to assess whether the patient is smear positive again. Additionally TB culture and resistance testing should be requested. This should be done in all cases of defaulting patients, retreatment cases and cases that fail to improve on treatment. ("Treatment failure" in the strict sense is defined as patients "who are smear positive at 5 month or later during treatment". This definition is difficult in a setting with many smear-negative TB cases and liberal use of culture based on clinical findings can be recommended).

3) The decision for re-treatment in patients who have defaulted depends on the severity of the disease, AFB status, duration of treatment before default and duration of interruption. The WHO recommendations in summary are as follows:

<table>
<tr><td colspan="4">Interruption for less than 1 month
• Trace patient
• Solve the cause of interruption
• Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td colspan="4">Interruption for 1–2 months</td></tr>
<tr><td>Action 1</td><td colspan="3">Action 2</td></tr>
<tr><td rowspan="3">• Trace patient
• Solve the cause of interruption
• Do 3 sputum smears. Continue treatment while waiting for results.</td><td>If smears negative or EPTB</td><td colspan="2">Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td rowspan="2">If one or more smears positive</td><td>Treatment received: ≤5 months</td><td>Continue treatment and prolong it to compensate for missed doses</td></tr>
<tr><td>>5 months</td><td>Category I: start Category II
Category II: refer (may evolve to chronic)</td></tr>
<tr><td colspan="4">Interruption for 2 months or more (defaulter)</td></tr>
<tr><td rowspan="3">• Do 3 sputum smears
• Solve the cause of interruption, if possible
• No treatment while waiting for results</td><td>Negative</td><td colspan="2">Clinical decision on individual basis whether to restart or continue treatment, or no further treatment</td></tr>
<tr><td rowspan="2">smears or EP
One or more smears positive</td><td>Category I</td><td>Start Category II</td></tr>
<tr><td>Category II</td><td>Refer (may evolve to chronic)</td></tr>
</table>

Outcome and follow up:

The described patient had extensive disease and interrupted for more than 2 month. He was found to be smear positive again and started RHZES, followed by 1 month RHZE, followed by 5 months RH. His TB culture was subsequently positive and showed a fully sensitive strain.

Comments:

TB patients defaulting treatment is a frequent problem due to the long treatment duration. It is important to stress to the patients the importance of prolonged treatment even after improvement of symptoms. If possible DOTS (directly observed treatment) should be implemented, especially for patients who defaulted previously.

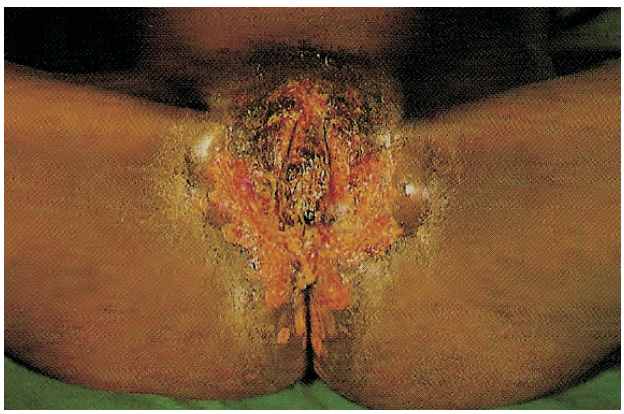
Key learning point

Sputum culture should be sent for every patient who has previously defaulted treatment

Case 11

Case 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 she tested positive. Her CD4 count was 23 cells/μl. An abdominal ultrasound revealed enlarged abdominal lymph nodes and a small amount of ascites as well as mild splenomegaly. Abdominal TB was the most probable diagnosis and she was started on standard TB treatment. The patient reported vaginal discharge and the nurses noticed genital ulcers. On examination large painful ulcers were present and 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 and 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 ulcer in our 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 presents inguinal lymph node swelling.

2) Acyclovir 400 mg tds plus benzathine penicillin 2.4 MU IM. Ciprofloxacin 500 mg bd for 3 days can be used against chancroid; doxycycline (100 mg bd for 5 days) should be added if LGV is suspected.

3) **Genital ulcer**- cause and treatment see above
Inguinal bubo- Cause: lymphogranuloma venereum (LGV) and chancroid, consider systemic (e.g.TB or KS) and lower leg infection
Treatment: Ciprofloxacin 500 mg bd for 5 days plus Doxycycline 100 mg bd for 10 d
Urethral discharge/Vaginal discharge- Cause: *Neisseria gonorrhoeae, Chlamydia trachomatis* are the most common cause of male and female genital discharge, in vaginal discharge also *Trichomonas vaginalis* should be considered
Treatment: Ceftriaxone 125 mg IM (gonorrhoea) plus doxycycline 100 mg bd for 7 days (Chlamydia), for women add metronidazole 2g stat (trichomoniasis)
Scrotal swelling- Cause: in man younger than 35 years STIs are the most common cause and gonorrhoea and Chlamydia need to be treated (see above). In older man and in cases persistent after treatment other causes (*E.coli, Klebsiella spp., Pseudomonas aeruginosa* as well as TB orchitis need to be considered). It is also important to consider non infective causes like testicular torsion, tumor, hydrocele and trauma.
Pelvic inflammatory disease (PID)-salpingitis/endometritis is a common cause of lower abdominal pain in women and might be caused by *N.gonorrhoeae*, *C.trachomatis*, anaerobic bacteria as well as gram negative rods. Treatment must be effective against a broad range of pathogens, Ceftriaxone, doxycycline and metronidazole is a recommended combination. It is important to consider ectopic pregnancy and 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 of discharge. The patient was referred to start ART in the clinic 2 weeks after discharge from hospital.

Comments:

HSV-2 infections are frequent, antibodies were found in 67% of the women in our area. HSV-2 infection is associated with a 3 to 5 times 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 coinfection, ulcers become less frequent and are less severe after the initiation of ART

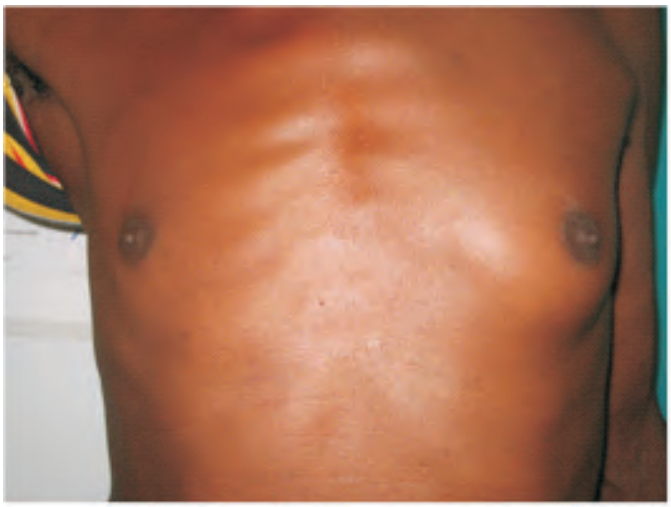
Suggested reading

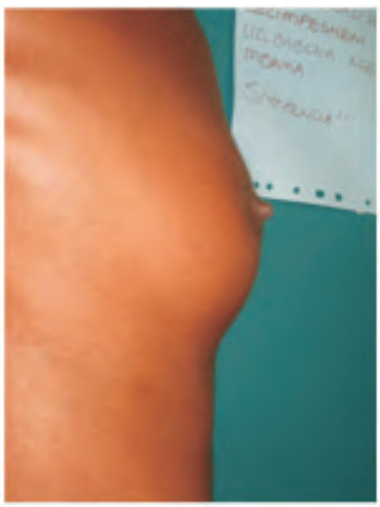
WHO: Guidelines for the management of sexually transmitted infections 2003, http://www.who.int/hiv/pub/sti/pub6/en/

Case 12

Case 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; additionally he complained about the cosmetic aspect. He had been taking D4T/3TC/EFV for seven months; additionally he was taking CTX and multivitamin tablets. He denied taking any other medication including traditional medicine. On examination left-sided unilateral gynaecomastia was found (Tanner stage III to IV)





Questions

1) What might cause the gynaecomastia, especially thinking of 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) D4T, DDI, and EFV have been reported to be associated with gynaecomastia in HIV patients on ART. Other known causative drugs are spironolactone, H1-antagonists, omeprazole, ketoconazole, metronidazole, isoniazid, digoxin, phenytoin, and others. Chronic liver disease needs also to 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, luteinizing hormone (LH), testosterone, oestradiol and prolactin could be measured, although they are frequently found to be normal. Hepatitis B surface antigen and LFTs should be checked if not already done.

3) The patient mainly needs to be carefully counselled. He needs to be informed about the benign nature of this condition and it is key to identify whether it will interfere with his adherence to ART. If this cannot be ensured then switch of treatment might be considered (although it may be unclear which is the causative agent). Also it has to be understood that this would reduce the options for future treatment changes in case he develops treatment failure.

Outcome and follow up:

To rule out endocrine causes of gynaecomastia LH, FSH, oestradiol, testosterone and prolactin levels were determined and found to be normal. The patient was counselled about the side effects of ART and the origin of his breast development. He was informed about the limited availability of alternative drug options in our setting and agreed to continue the same treatment regimen. Additionally he was prescribed ibuprofen to ameliorate the pain. He continued his ART.

Comments:

Gynaecomastia is a well described side effect of ART. In our patients we found approx. 14 % of male patients to be affected, about 2/3 having unilateral and 1/3 bilateral gynaecomastia. It resolves in a number of cases despite ART being continued. Other South African centres have reported similar rates which seem to be higher than 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.

Key learning point

Gynaecomastia is frequently seen but treatment switch is rarely indicated; good counselling is essential to ensure continued adherence to ART

Suggested reading

Mira JA et al. Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment. Antiviral Therapy 9 (2004): 501-517

Case 13

Case presentation

A 29-year old patient comes was admitted because he had been coughing for 2 months and was increasingly short of breath. He was dehydrated but apyrexial, his general status was weak and he was severely underweight. The following day, the doctor noticed confusion and irritability. A lumbar puncture was performed and empirical meningitis treatment initiated. Blood sugar was 4.6 mmol/L. In the afternoon the patient was assessed again and was reacting with groans but 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 $10^3/mm^3$	(normal 4.0-11.0)
Plt	29 $10^3/mm^3$	(normal 150-500)
U&E:		
Na	143 mmol/L	(normal 133-153)
K	5.4 mmol/L	(normal 3.0-5.0)
CO2	28 mmol/L	(normal 22-33)
Creat	131 μmol/L	(normal 62-120)
CSF:		
CSF- polymorphs	30 cells/μl	(normal <5)
CSF-lymphocytes	88 cells/μl	(normal <5)
CSF-chloride	112 mmol/L	(normal >120)
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)
CSF-TB culture sent		

Questions

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

Diagnosis: TB meningitis

Answers

1) 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 2g IV bd and fluconazole 400 mg po od would be a possible empirical regimen.

2) The following table summarizes the changes of CSF in different diseases:

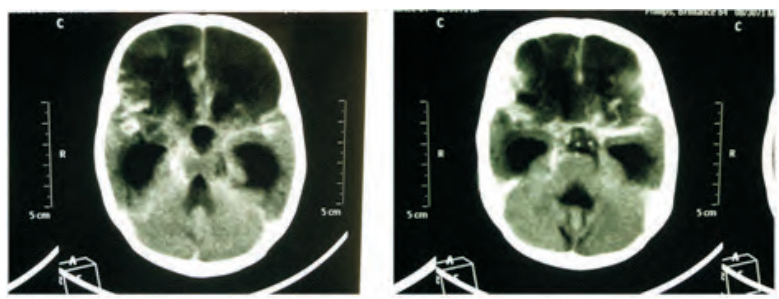
	polymorphs	lymphocytes	protein	glucose	CryptoAg
Bacterial	↑↑	mildly ↑	↑↑	↓↓	neg
Mycobacterial	mildly ↑	↑	↑↑	↓↓	neg
Viral	↔	mildly ↑	↑	↔	neg
Fungal	mildly ↑	↑	↑↑	↓	pos

3) The lab results do not suggest cryptoccocci or bacteria as cause of the meningitis. The most probable diagnosis, especially in combination with his respiratory symptoms, is TB meningitis. Fluconazole and ceftriaxone can be stopped, standard TB treatment should be added; additionally a steroid (e.g. prednisolone 60 mg od tapered over one to two month) should be added.

Outcome and follow up:

The above mentioned drug change was done. The patient was referred for HIV test which was positive and he was categorized as HIV stage 4 (because of extrapulmonary TB). He spent almost six weeks in the ward and improved only very slowly. Physiotherapy was prescribed. In the course of his stay, he developed bed sores which improved but were still present at the time of discharge. His CD4 count was 33 cells/μl, therefore ART was started before he was discharged from hospital. He was referred to the ART nurse of his clinic for further treatment and monitoring. His TB culture was later followed up but the sample had leaked during transport and therefore not processed.

Further images:



Meningeal enhancement seen in CT scan of a different TB meningitis patient (additionally hydrocephalus is visible)

Comments:

About 30% of patients with tuberculous meningitis die despite 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 cerebrospinal fluid, but culture is slow and AFB staining often too insensitive to aid clinical decision-making. Consequently, the decision to treat a patient for tuberculous meningitis is frequently empirical. The normal range of CSF chloride is 116 to 130 mmol/l, in HIV patients TB meningitis was associated with reduced CSF chloride (less than 110 mmol/l).These chloride changes are far less frequently seen in other pathogens. A CSF chloride of less than 100mmol/l is thought to be virtually diagnostic of TBM.

Key learning point

The use of steroids in TB meningitis has been shown to improve neurological outcome and is therefore part of our protocol

Suggested reading

G E Thwaite et al: Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features, Lancet 360 (2002): 1287

Stone J et al: CSF chloride - a useful marker for tuberculous meningitis in HIV infection? Int Conf AIDS. 1996: 327 (abstract no. Tu.B.2357).

Case 14

Case 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 brain which showed meningeal enhancement consistent with meningitis. TB treatment for presumed TB meningitis was commenced and she was discharged home.

She represented to OPD a month later still complaining of headache. The LP was repeated, and still showed only a raised 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 and she was discharged on analgesics.

When she was seen again a few weeks later she still complained about the same symptoms, except that she now had a tender right side of the neck with a firm lymph node. She now had a hypoglossal nerve palsy and weakness in her right arm. Clinically she was cachectic, and there was still concern that she might be HIV positive. Although her HIV test was negative again, a CD4 count was sent which was 290 cells/μl. This is taken to be suggestive of HIV, and a viral load is sent to confirm the presence of viral HIV RNA.

Questions

1) What would be your next diagnostic step?
2) How do you feel about the assumption that her low CD4 count indicated HIV infection and which other diseases show reduced CD4 counts?
3) What clues are there that she may not be suffering from TB meningitis?

Diagnosis: Nasopharyngeal carcinoma

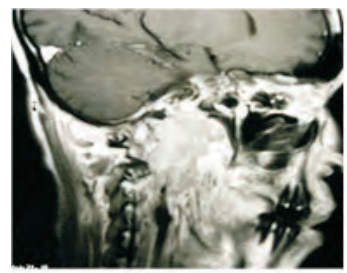
Answers

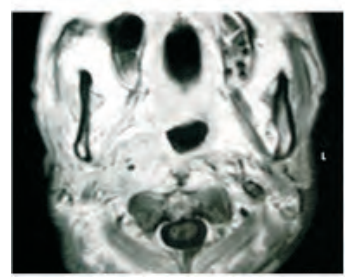
1) The lymph node should be excised for histological examination.

2) HIV is the most common cause of low CD4 counts but there are many other diseases that cause reduced values that need to be considered before assuming a HIV test to be false negative:
Infections: *Mycobaterium 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: Sjoegren's syndrome, Systemic lupus erythematosus, Rheumatoid arthritis
Drugs: Corticosteroids, Chemotherapy, cytotoxic immunosuppressants and others (cephalosporin, IFN-a)
Others: 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 immune suppression acellular CSF would be extremely unusual. The classical findings are a lymphocytic CSF with raised protein and low glucose. However, TBM can present with only one of these findings, and can than 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 showed meningeal enhancement which supported the diagnosis. It should be noted, however, that some meningeal enhancement on CT can be a consequence of lumbar puncture.

   A mildly increased protein is very non specific and can occur in both infectious and noninfectious 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 she failed to improve on TB treatment suggested either that she did not have TB meningitis, or that she had a resistant strain of TB.
   In addition, the exquisite 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 this time of head and spine ordered and revealed a nasopharygeal carcinoma. Her HIV1 PCR was negative. An appointment was made with an oncology department for further treatment.

Comments

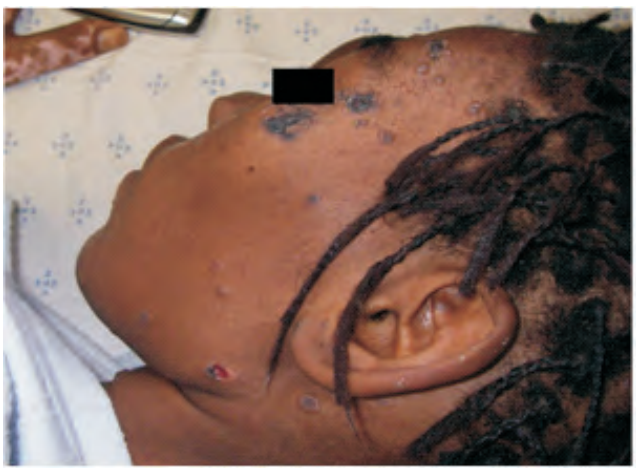
Nasopharynx carcinoma is frequently associated with EBV infection. Expression of viral oncogens (LMP1) in latently infected epithelial cells seems a critical early step in carcinogenesis. Additionally there is recent evidence that HPV may be implicated in head and neck cancers, particularly in HIV patients. Cancer of the nasopharynx typically does not cause early symptoms, local obstruction may lead to chronic sinusitis or otitis media. Advanced disease can cause neuropathies with pain of the cranial nerves.

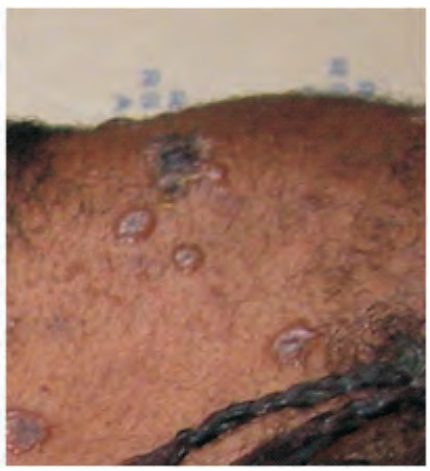
Key learning point
Rapid HIV antibody tests are very sensitive and specific for HIV-1 infection
Low CD4 counts are not a proxy for HIV infection

Case 15

Case presentation

A 17-year old female patient was brought to OPD because of her generally poor health. She complained of longstanding diarrhoea and weight loss, in addition to headache and dizziness. She appeared to have advanced immunodeficiency and the diagnosis of HIV was confirmed by a rapid antibody test. On the skin there were multiple small ulcerations and papules with central umbilication.





Questions

1) What is your differential diagnosis of the skin lesions?
2) What would be your next diagnostic and therapeutic steps?

Diagnosis: Cryptococcomata of the skin in disseminated cryptococcosis

Answers

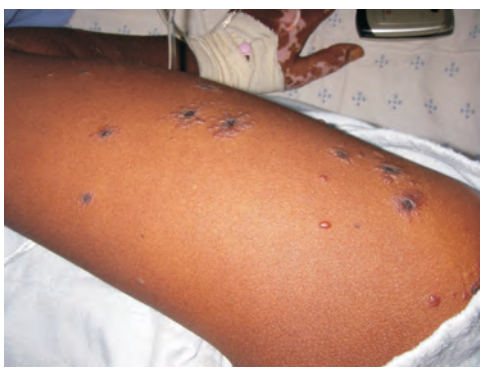
1) Cryptococcosis is the most probable diagnosis. The umbilicated lesions could make one suspect molluscum contagiosum. These are also frequently seen in children, tend to evolve slower and do not ulcerate.
   Histoplasmosis of the skin is another possibility, although rare in our area (and rarely diagnosed).

2) Lumbar puncture is urgently needed to assess for CNS involvement. Cryptococcal antigen testing of blood would be appropriate but is not currently available in our institution. A CXR should be done to check for pulmonary involvement (which is bad prognostic sign). Systemic antifungal treatment should be started as for cryptococcal meningitis.

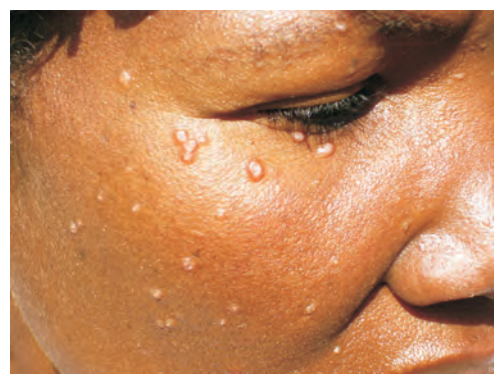
Outcome and follow up

A CSF sample was found highly positive (+++) for cryptocccal antigen. The patient was started on amphotericin B; skin biopsy and CD4 count were planned for the following day. Despite the initiation of antifungal therapy, the patient died the same night.

Further images



(Pictures courtesy of Dr. M. Johansson)
Cryptococcomata on the arm of the patient



For comparison a different patient with Molluscum contagiosum lesions is shown.

Key learning point

If you have a clinical suspicion of cutaneous cryptococcosis start empirical antifungal therapy

Suggested reading

Aberg JA, WG Powderly: Cryptococcosis and HIV, HIV Insite Knowledge Base Chapter, May 2006, http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-02-05

Case 16

Case presentation

A 56-year old woman was recently diagnosed with HIV; her CD4 count was 147 cells/μl. She was overweight (weight 94 kg, height 161 cm, BMI 36 kg/m^2) and her blood pressure was measured in the PHC clinic at 210/114 mmHg. Looking at her former blood pressure values, she repetitively had systolic values higher than 200 mmHg and diastolic values of up to 135 mmHg. She was currently taking hydrochlorothiazide 12.5 mg and enalapril 5 mg od.

Questions

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

Diagnosis: Severe hypertension, obesity Grade III

Answers

1) Antihypertensive therapy
   Step 1: lifestyle changes
      nutrition (reduce weight, restrict salt, increase fresh fruits and vegetables
      exercise (moderate exercise (brisk walking) for 30 min 3 times a week
      hydrochlorothiazide 12.5 mg
   Step 2: hydrochlorothiazide 25 mg
      enalapril 5 mg bd increase to 10 mg bd
   Step 3: hydrochlorothiazide 25 mg
      enalapril 10 mg bd
      amlodipine 5 to 10 mg bd or atenolol 25-50 mg bd
   Step 4: if no control with 3 drugs (especially with extremely high blood pressure values)
      hydralazine is very effective, initial dose 25 mg bd can be increased to 50 mg bd.

2) Laboratory investigations are often difficult to do in the primary health care clinic settings as samples, results and patients have a tendency to get lost. Feasible on-spot diagnostic investigations are:
   urine dipstick
   - protein to asses kidney organ damage
   - blood to search for reason of 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 electrolytes as well as **cholesterol/triglyceride** are desirable but involve venous blood sample and logistics.

Comments

In a population with high HIV prevalence, especially also in elderly patients, the infection is often combined with other frequent diseases like hypertension and diabetes. It is important to be aware of these and treat concomitant chronic diseases. The difficulties of rural clinic healthcare (laboratory as well as drug shortage) make it advisable to use standardized regimens (like in the EDL regimens which are available in the hospital pharmacy).

Key learning point
Most hypertensive patients require more than one drug to control hypertension

Suggested reading

National department of health, Republic of South Africa: Standard treatment guidelines and essential drug list, Hospital Level Adults, 2006

Case 17

Case presentation

A 33-year old HIV positive lady has been on D4T/3TC/NVP for 8 months. She has had TB twice before (and completed the last course at the time of ART initiation). She was sitting in your consulting room in clinic. She was unable to give a history because of breathlessness but shook her head when asked about cough and diarrhoea. She was holding her abdomen and was pale but not wasted. Her chest was clear on examination and abdomen soft but tender. Bowel sounds were present. There was no DVT clinically and she was adequately hydrated. Her pulse was 110 and blood pressure 96/45.
A lactometer shows 9.5 mmol/L.

Questions

1. What should you do instantly, what else should you ask for urgently?
2. What are the possible diagnoses?
3. How should she be managed in the hospital?
4. What should happen in the longer term?

Diagnosis: Lactic acidosis

Answers

1) A,B,C! The nurse should call an ambulance. Oxygen and IV fluids should be used if available. Venous lactate, blood sugar and temperature should be checked. Relatives should be asked for more history (it is unlikely that she arrived on her own)

2) She has been on ART for a relatively short time so should still be considered immunocompromised. She could also be suffering from a complication of ART or from a non-infectious, non ART related condition.
   a)Sepsis from any source
   b)Respiratory - community acquired pneumonia, PCP, TB, cryptococcosis / other fungal lung infection, CMV or the occlusion of a bronchus by lymph nodes in lymphoma / KS / TB. Pulmonary embolism and pneumothorax should be considered.
   c) Abdominal - gastroenteritis, colitis, pancreatitis (DDI / D4T / traditional medicine / snake bites), embolic disease, abdominal TB.
   d) Cardiac - effusion causing tamponade, cardiomyopathy.
   e) Acidosis - renal failure, lactic acidosis, diabetic keto-acidosis.

3) She should be admitted to hospital for laboratory investigation and CXR. If the above causes have been excluded as far as possible, lactic acidosis as a consequence of stavudine therapy can be diagnosed. Typical symptoms are nausea, vomiting, abdominal pain, weight loss, fatigue, myalgia, abdominal distention, abdominal pain, dyspnoea, and cardiac dysrhythmias.
   Blood results include a raised anion gap, metabolic acidosis (low CO_2), and occasionally raised ALT, LDH and CK. Management is supportive with the cessation of ARVs. There is limited (or no) evidence for IV bicarbonate and B vitamins (riboflavin).

4) She should be restarted on an alternative ART regimen avoiding the NRTIs which are most commonly associated with lactic acidosis (D4T/DDI). All NRTIs can cause lactic acidosis, but 3TC and AZT less commonly do so. We would currently use AZT to replace D4T but other institutions may have different policies (depending on availability of alternate drugs e.g. ABC or TDF). ART should be restarted after the blood lactate has returned to normal (usually this is 2-3 months) but lactate should to be monitored (e.g. monthly for 6-12 month) as lactic acidosis may recur. In rare severe cases a regimen sparing all NRTI (e.g. only LPV/r / EFV) might be considered but this needs to be discussed with pharmacy services.

Outcome and follow up:

She was treated for lactic acidosis as described above. After 10 weeks her lactate was less than 3 mmol/l and ART was restarted (AZT / 3TC / NVP).

Comments

The following algorithm might be used to guide treatment of lactic acidosis / symptomatic hyperlactaemia.

Level	Lactate	HCO3	Action
Normal	<2.5	>20	None, look for other causes of symptoms
Mild	2.5-5	>20	Consider Outpatient switch from D4T to AZT
Moderate	5-10	15-20	Stop ART, treat as inpatient, rehydrate, give Thiamine+Vit B If well, switch from D4T to AZT otherwise like severe
Severe	>10	<15	Stop ART, treat in high care unit, balanced fluids, give IV Thiamine + vitamin B, broad spectrum antibiotic (ceftriaxone) Consider NRTI sparing regimen (NNRTI + PI)

It is important to notice that lactate does <u>not</u> decline quickly after cessation of ART. If a decline is observed after a few days almost always a different diagnosis (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 is receiving NNRTI, the NNRTI should be stopped first and D4T and 3TC should be continued for approx. 1 week to prevent ineffective monotherapy and resistance development (The half-life of NNRTI is far longer 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

Prevention, diagnosis and management of NRTI-associated symptomatic hyperlactataemia and lactic acidosis. SA HIV clinicians society guidelines 2006,
http://www.sahivsoc.org/index.php/guideline/index/5/37

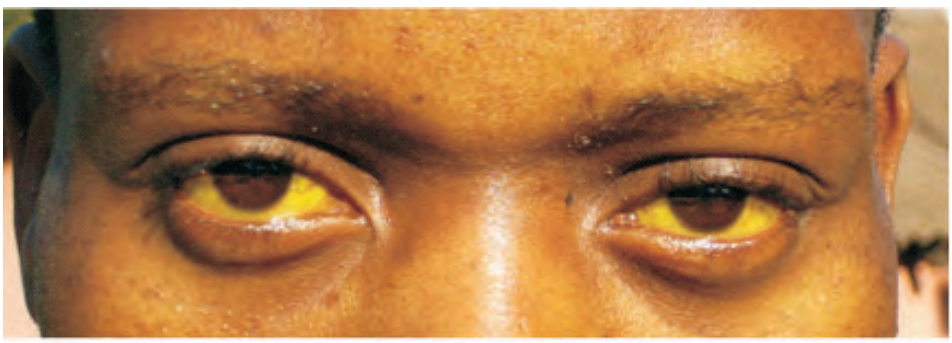
Notes

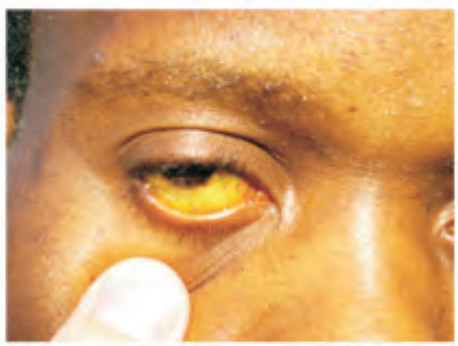
Case 18

Case presentation

A 20-old male patient was seen in OPD because his eyes turned yellow; additionally he complained of fever and abdominal discomfort.
His urine appeared dark, his stool pale.
On examination he had marked scleral icterus and mild RUQ tenderness with hepatomegaly.
He was admitted for investigation, his lab values showed:

FBC:		
Hb	13,1 g/dl	(normal 11.5-16.5)
WBC	12.2 $10^3/mm^3$	(normal 4.0-11.0)
Plt	308 $10^3/mm^3$	(normal 150-500)
LFT		
TBIL	454 µmol/L	(normal 3.0-17)
DBIL	227 µmol/L	(normal 0.0-3.0)
GGT	105 U/L	(normal 7-62)
ALT	230 U/L	(normal 10-60)
TP	66 g/L	(normal 60-80)
Alb	19 g/L	(normal 36-50)
LDH	846 U/L	(normal 140-280)





Questions

1) What questions would you like to ask and which investigations would you order?
2) What is the most probable 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, rifampicin) or ARV's (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 e.g. in portal lymphadenopathy in abdominal TB.

2) The patient did not report to take therapy for HIV or TB. He did not receive blood transfusions; the first most probable diagnosis is acute hepatitis A. The relatively high bilirubin compared to the ALT suggests late stage of the disease.

Outcome and follow up:

The patient was sent for abdominal ultrasound which was essentially 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 he already felt better without specific therapy and was discharged. He was tested for HIV and was HIV positive, he was referred to his local clinic and further treatment.

Comments:

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

In the contrasting "VCT" approach (voluntary counseling and testing) the initiative to seek an HIV test comes from the individual patient instead of the health care provider.

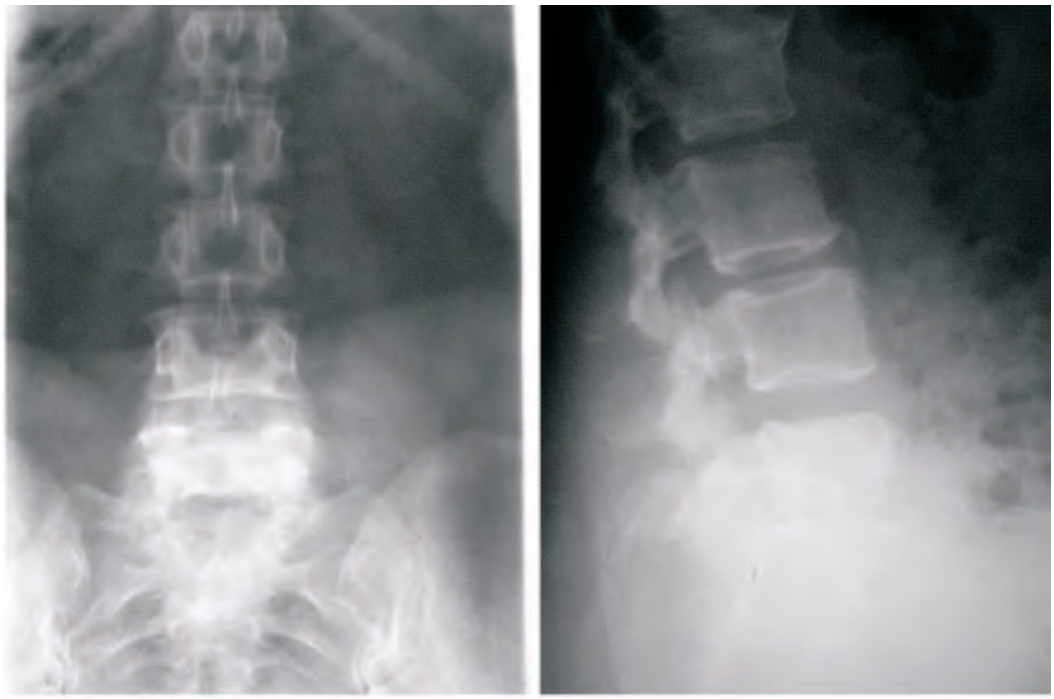
Key learning point
A thorough drug history is essential for anyone presenting with jaundice (including traditional and non prescribed medications)

Case 19

Case presentation

A 34-year old patient was seen in the clinic because she was diagnosed HIV positive and her CD4 count was 146 cells/μl. Already at the first visit to the nurse, she complained about lower back pain. She was given NSAIDs. A month later she was seen by the physician before starting ART and complained also about hip pain. D4T/3TC/EFV were started, further NSAIDs were prescribed, and physiotherapy was organised (every second week in the clinic).

A month later she was seen again by a physician still complaining about pain and was sent to the hospital for x-ray of lumbar spine. The x-ray was done in the outpatient department and she returned to the clinic with the report that no abnormality was detected. Treatment was continued with diclofenac and amytriptiline. Another two months later, she was seen again 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, and again 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?

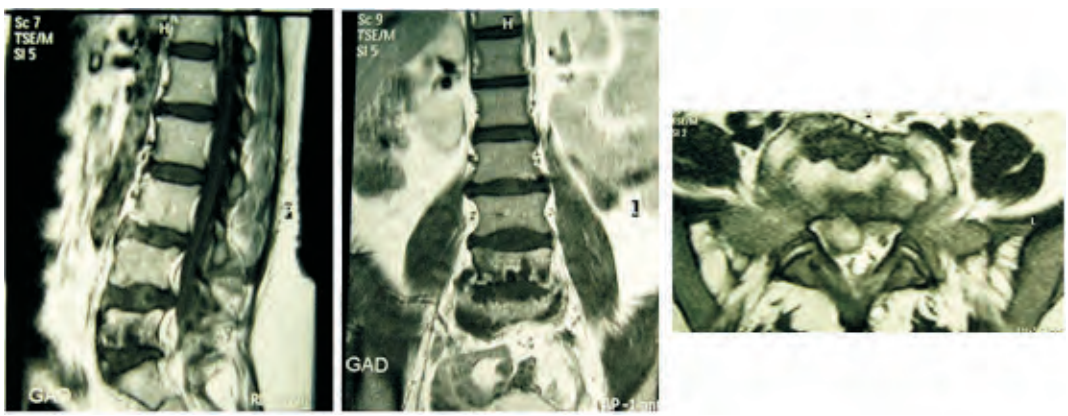
Diagnosis: TB spine

Answers

1) L5 seems to be much more dense than the other vertebrae; additionally the “eyes of the vertebrae” (roots of the vertebral arc) can not been delineated, suggesting a destructive process. Differential diagnosis will include TB (most likely cause in our setting), bacterial osteomyelitis, and tumor destruction/infiltration (e.g. Plasmocytoma)
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 and 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 over the diagnosis.

Outcome and follow up:

The patient was found to have a destructive lesion in L5. The previous x-rays were assessed again, and in retrospect, lesions were found on these as well, unfortunately unnoticed at that time. The height of the vertebrae is not massively reduced, which is probably the reason why it has been overlooked initially. The patient was referred for a MRI spine in the following week; in the meantime TB treatment was started. The MRI confirmed the diagnosis. The neurosurgeons were consulted but it was agreed to continue TB treatment to assess the clinical course. The patient was seen again after 2 months of TB treatment. She was substantially improved and although she still reported mild pain in the morning she no longer required analgesics. TB treatment was continued for a total period of 6 month.



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 month) were recommended for spinal TB. There is little in modern literature to support this and 6 month regimens have been found equally effective.

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

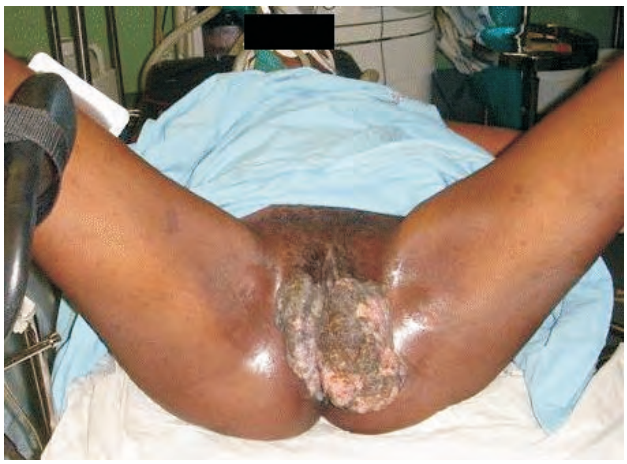
Suggested reading

Loenhout-Rooyackers JH, Verbeek ALM, Jutte PC: Chemotherapeutic treatment for spinal tuberculosis. Int J Tuberc Lung Dis 2002, 6: 259265

Case 20

Case presentation

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



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 can infect the genital tract, types 6 and 11 most commonly, also types 16, 18, 31, and 33.

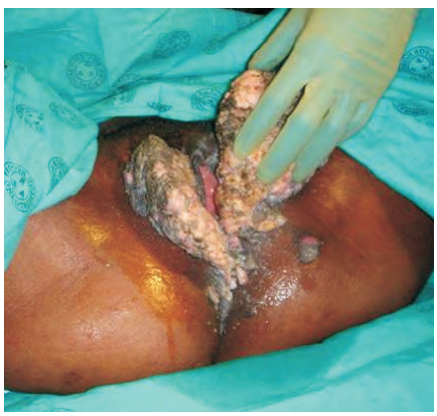
2) Small warts: apply topical podophyllin 20% once or twice per week for four hours. Solution is applied with a cotton swab, afterwards washed of with water. Treatment can be repeated as necessary for 4-5 times. Normal skin should be protected by applying vaseline.
Large warts require surgical treatment - excision and reconstructive surgery is the therapy of choice (especially if growth is rapid).

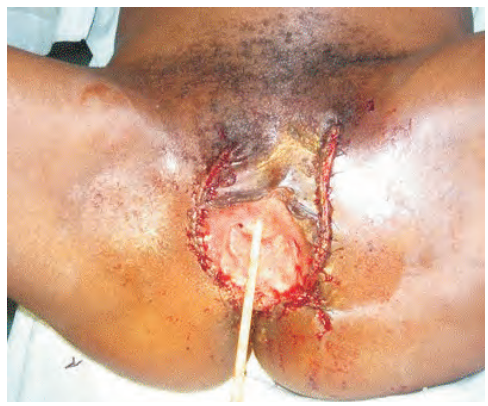
3) HPV types 16, 18, 31 and 33 have oncogenic potential. They are a major aetiological factor for cervical dysplasia and squamous cell carcinoma (of both the vulva and the penis). As treatment of the external warts does probably not influence the development of cervical cancer, annual Pap smears need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

Outcome and follow up:

The patient was referred to the gynaecology clinic and the warts were removed surgically. A Pap smear was normal, she continued ART.

Further images:





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

Comments:

HPV is highly infectious and most people who develop warts do so after 2 to 3 months. Spontaneous regression occurs in 20-30% of patients within 3 months, 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 21

Case presentation

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

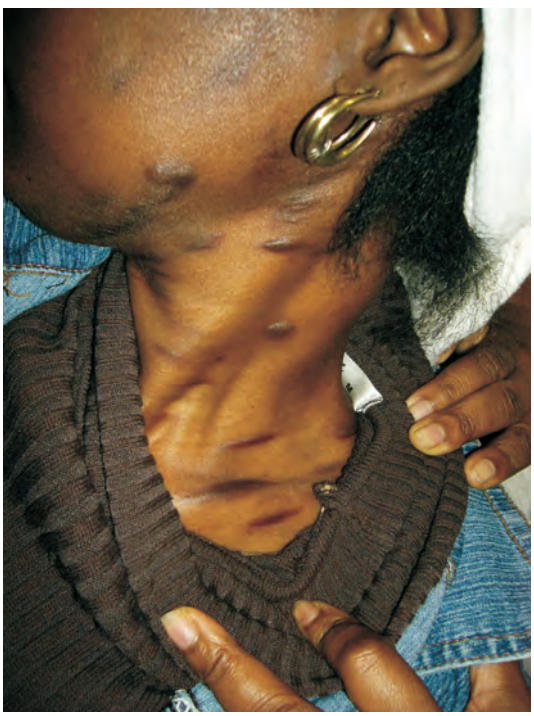
Blood tests:

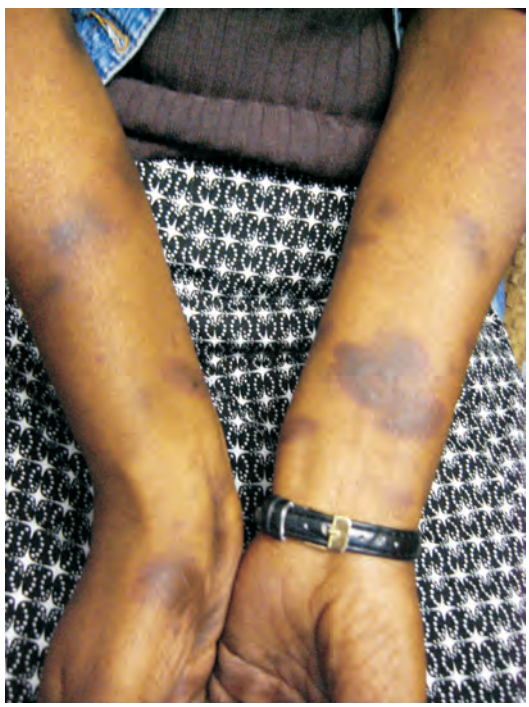
FBC:

Hb	6.4 g/dL	(normal 11.5-16.5)
WBC	5.4 $10^3/mm^3$	(normal 4.0-11.0)
Plt	35 $10^3/mm^3$	(normal 150-500)

U&E and LFT:

Crea	256 μmol/L	(normal 62-120)
BUN	19 mmol/L	(normal 3.5-6.5)
TBIL	32 μmol/L	(normal 3.0-17)
GGT	125 U/L	(normal 7-62)
ALP	300 U/L	(normal 42-121)





Questions

1. What is the diagnosis?
2. What treatment is available?
3. What are the prognostic factors determining outcome?

Diagnosis: Kaposi's sarcoma

Answers

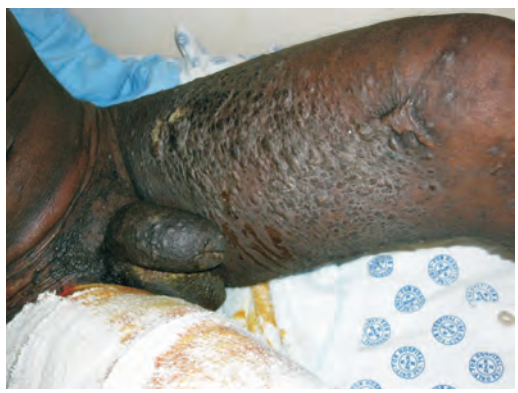
1. Kaposi's sarcoma

2. All patients with KS must receive antiretroviral therapy. HAART can lead to regression in the size of existing KS lesions, and possibly improve survival in patients with or without chemotherapy.
   Local treatment options include radiotherapy for obstructing or localised lesions, especially eyelid or tongue.
   Indications for systemic chemotherapy include widespread skin involvement, extensive cutaneous lesions not responsive to local therapy, extensive oedema and symptomatic visceral involvement. Etoposide is given for 3 weeks, followed by a one week break. About 6-8 cycles are usually given. In severe forms and if the patient is well enough to tolerate it, adriamycin, bleomycin and vincristine IV are given and repeated every 3 weeks for up to 6 cycles.
   Local protocols dictate that the patient's CD4 count must be higher than 180 cells/μl for the patient to be eligible for systemic chemotherapy. Local treatment can be given irrespective of the CD4 count.

3. Patients can be divided into good and poor risk categories on the basis of tumour extent (T), immune status (I), and severity of systemic illness (S). Respective median survivals for the good and poor risk categories were 27 and 15 months for T; 40 and 13 months for I; and 22 and 16 months for S.

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 commenced on ART, but continued to deteriorate and died prior to oncology referral.



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

Key learning point
Kaposi sarcoma can present at any CD4 count, and is a stage IV condition requiring ART as an integral part of management

Suggested reading

Pichardo DA, von Roenn JH: HIV-associated malignancies in Skeel RT: Handbook of Cancer Chemotherapy 2003, 546

Case 22

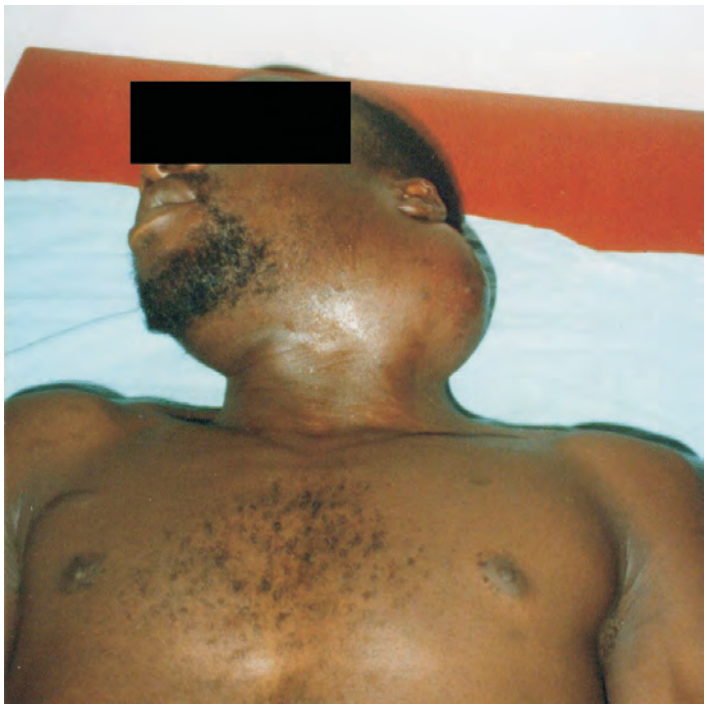
Case presentation

A 32-year old male patient was seen in the TB clinic because of swelling of his cervical lymph nodes. He reported that he had had the swelling for 6 months, recently it had become difficult to open his mouth and he was only able to take fluids.

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

FBC:		
Hb	11.7 g/dL	(normal 11.5-16.5)
WBC	5.3 $10^3/mm^3$	(normal 4.0-11.0)
Plt	551 $10^3/mm^3$	(normal 150-500)

Neutro	46%
Lympho	40%
Mono	7%
Eosino	5%



Questions

1) What is the most probable diagnosis?
2) What are useful investigations 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 surgical lymph node biopsy.

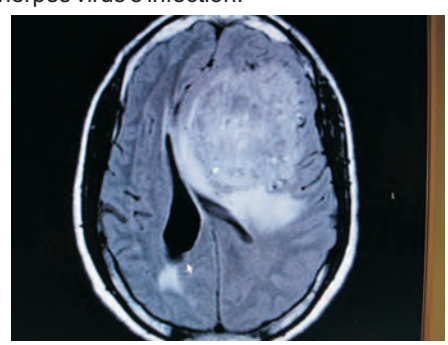
2) CXR and ultrasound might be used as staging investigations that are readily available. In the treating centre usually a "head to pelvis" CT will be done for staging.

3) The Ann Arbor classification is commonly used for staging
I) one lymph node region
II) 2 or more lymph node regions on one side of the diaphragm
III) 2 or more lymph node regions on both side 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 have shown that adverse prognostic factors were: CD4 counts less than 100 cells/μl, 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 lymphoma is associated with Epstein Barr virus, 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 and no further lympadenopathy was detected here. He was found to be HIV positive, his CD4 count was 146 cells/μl.
The lymph node biopsy showed a high-grade non-Hodgkin lymphoma. The patient was referred to the hematology department and lost to our follow up.



MRI of a primary CNS-lymphoma of a different patient

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 and 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. Chemotherapy is given in hematology departments in tertiary institutions. To refer the patient, it is important to have a histological diagnosis. Ideally the CD4 count would be higher than 200 and the patient on ART although these are not exclusion criteria. It might be helpful to send investigations like EBV, CMV, parvovirus B19, hepatitis B serology as well as vitamin B12, folic acid, iron and ferritin if the patient needs to wait for an appointment, as this might shorten the time needed before the start of treatment. Treatment is usually chemotherapy (CHOP) sometimes in combination with monoclonal antibodies (rituximab).

Key learning point

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

Suggested reading

Little et al. HIV associated Non Hodgkin Lymphoma: incidence, presentation and prognosis. JAMA 2001. 285;1880.

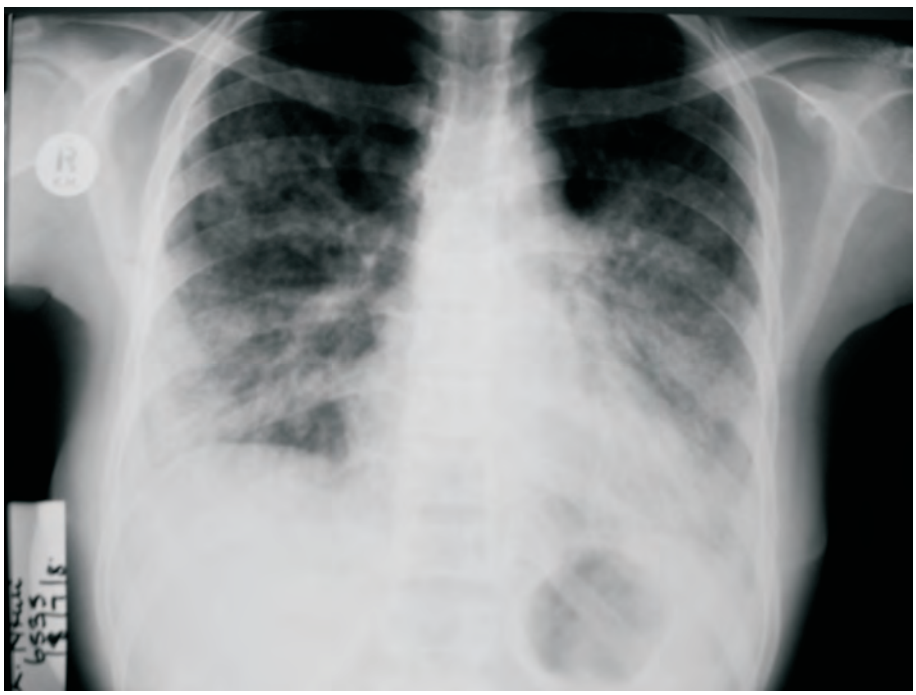
Case 23

Case 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/μl.

At rest she looked surprisingly well and did not initially 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 shown below



Questions

1) What do the Xrays show?
2) What is the most likely diagnosis?
3) What is the appropriate treatment?

Diagnosis: *Pneumocystis jiroveci* pneumonia (PCP)

Answers

1) The picture show bilateral, diffuse, symmetrical, ground-glass infiltration more pronounced in the central regions of the lung than in the periphery.

2) The most likely disgnosis 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 may be normal (in 5-10%) especially with lower CD4 counts. Induced sputum or brochoalveolar lavage (BAL) can be performed to get specimens for microscopical examination. In our setting this is rarely done. Of high value is clinical assessment of oxygenation at rest and with exercise.

3) PCP is treated with high-dose CTX according to weight (< 60kg 3 tabs tds, >60kg 4 tabs) 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 judgement and oxygen saturation measurement is used. Recommend doses are 80mg prednisone daily for 5 days, followed by 40mg daily for 5 days, followed by 20mg daily for 10 days. In general, with effective treatment a response is expected in 7-10 days.

Outcome and follow up:

The diagnosis of PCP was made and she was commenced on abovementioned treatment including steroids. She made a good recovery over the course of following weeks and was able to get up and walk around after two weeks. As her CD4 count was 10 cells/μl 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 1980's. 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 (600mg tds po) plus primaquine (15 mg od po) for 21 days, both drugs are available in the public sector.

Key learning point

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

Case 24

Case presentation

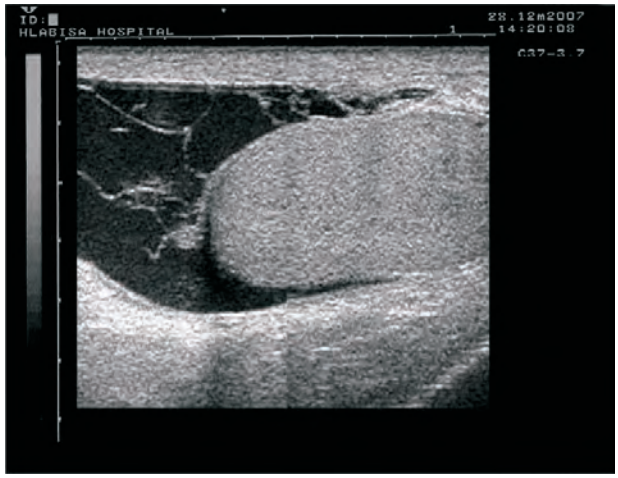
A 57-year old man presented critically ill with a 2-week history of a swollen and painful left testicle, with progressive scrotal swelling and involvement of the left thigh. His HIV status was unknown.

On examination he was hypotensive, febrile (39°C), tachycardic and showed mild confusion. His scrotum was grossly swollen (diameter 15cm), 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, urine dipstick was positive for blood and protein.

The diagnosis of sepsis secondary to uro-genital infection was made and he was admitted to the high care unit, where his vital signs were monitored and a central line was inserted. Gram-negative sepsis was assumed to be the most probable cause and 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.



Questions

1) What is evident on the ultrasound and what would be your next procedure?
2) Treating severe sepsis and septic shock, which are the most important steps that can be done with limited intensive care resources?

Diagnosis: Gram negative sepsis with multi-organ failure secondary to uro-genital TB

Answers

1) The ultrasound shows a 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 are difficult to manage in our setting as ICU resources and especially mechanical ventilation have limited availability. Nevertheless many of the recommended guidelines, especially 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 1000 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 patient for a focus of infection amenable to source control measures (e.g.abscess drainage, tissue debridement)
   - Norepinephrine and dopamine centrally administered are the initial vasopressors of choice. Do not use low-dose dopamine for renal protection.
   - Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors, Hydrocortisone dose should be <300 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 planned invasive procedures
   - Use intravenous insulin to control hyperglycemia. Aim: blood glucose <8.3 mmol/L
   - 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 demonstrated 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 showed gram negative bacilli and AFB were seen. RHZE was commenced. The following day, the pyocoele was incised and drained. His renal function deteriorated and he became anuric and uraemic, requiring sedation as 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, additionally replacement fluids were given by the nursing staff guided by hourly measurement of urinary losses. He showed some improvement by day 7 and was able to hold a conversation. He tested positive for HIV. Unfortunately, on day 8 he developed a 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. As it is difficult to get blood products in our setting he was transferred to the referral hospital on day 13 for further management. Further debridement was considered but his 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 and superimposed bacterial infection is common.

Suggested reading

Dellinger RP, Levy MM, Carlet JM, et. al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 Crit Care Med 2008; 36:296-327.
http://www.survivingsepsis.org/system/files/images/2008_Guidelines_Final_.pdf

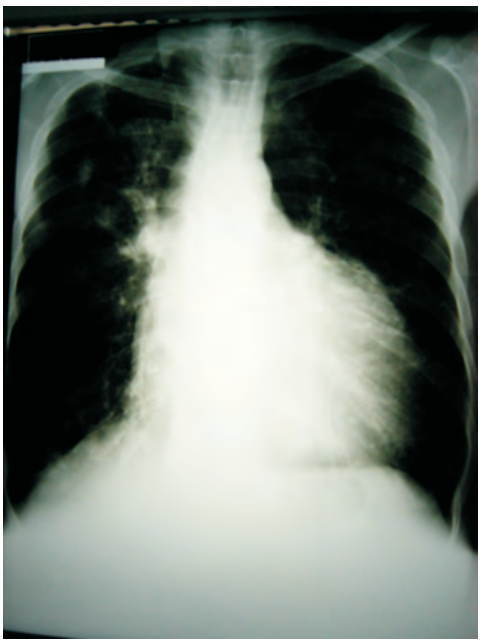
Case 25

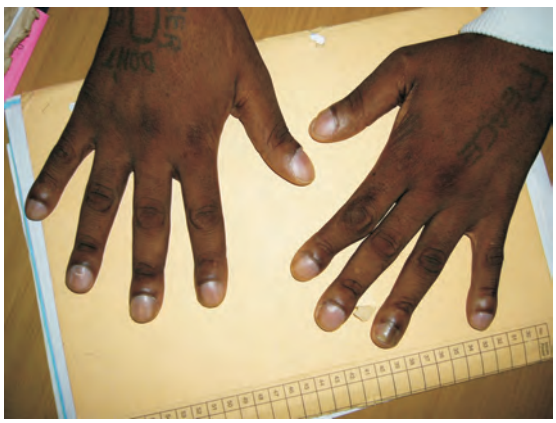
Case presentation

A 33-year old patient came to the clinic because of increasing shortness of breath. He had been on D4T/3TC/EFV for two years. His CD4 count had increased from 88 cells/μl at baseline to 296 cells/μl. In the notes there was repeated mention of cough during his time on ART.

He looked unwell, sweaty and was severely tachypnoeic (respiratory rate 40/min, blood pressure 100/60 mmHg, heart rate 128 /min). Jugular venous pressure was raised. His fingers showed the pictured changes.

To save time, he was immediately sent to a nearby private practitioner, who is compensated by a local NGO for CXR provided for ART patients and returned after 2 hours with the CXR.





Questions

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

Diagnosis: Pulmonary and pericardial TB

Answers

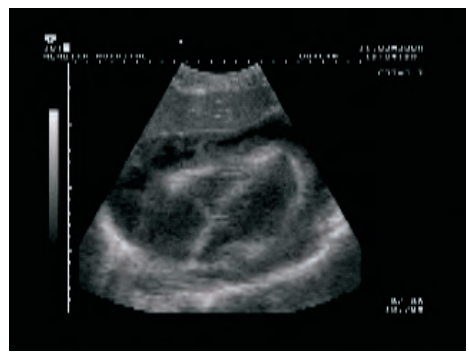
1) Finger clubbing is mainly due to pulmonary causes (TB, emphysema, bronchial carcinoma among others) but can also be found in cardiac diseases (e.g. congenital cyanotic malformations), liver cirrhosis and others (thyroid disease, malignancy).

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 hospital. Cardiac ultrasound can be used to confirm the pericardial effusion and to guide pericardiocentesis in case of tamponade. TB treatment should be started, adjunctive steroids reduce size of pericardial effusion, the rate of re-accumulation and might reduce the incidence of constrictive pericarditis. (Suggested dose: Prednisone 60 mg daily, tapered over 6 12 weeks)

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 on the following day and was taken for US. A large pericardial effusion was noted, the filling of the right atrium and ventricle seemed impaired. In combination with the vital parameters it was concluded the he had cardiac tamponade and pericardiocentesis was performed using a grey IV cannula. 90 mls of a bloody effusion were aspirated and send for TB culture and cytology. The patient felt substantial improvement after the procedure and was discharged the following day on RHZE, prednisolone and ARVs.



Ultrasound showing large pericardial effusion with fibrinous material

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 tuberculous 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, sputum culture) are essential.

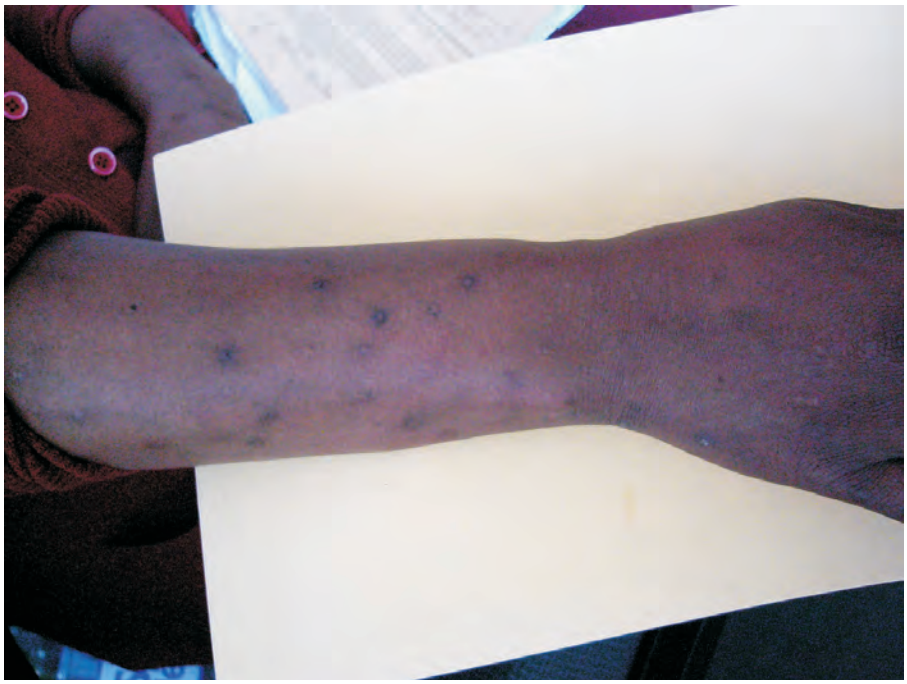
Suggested reading

Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary Tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings, WHO 2007, WHO /HTM /TB /2007.379

Case 26

Case presentation

A 34-year old HIV positive nurse was seen in the staff clinic as she complained about distressingly itchy lesions, especially on her arms and to a lesser extent on the lower limbs. Her CD4 count was 34 cells/*µ*l and she was about to initiate ART.



Questions

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

Diagnosis: TB meningitis

Answers

1) Papular lesions with prurigo; excoriations which heal with post-inflammatory hyperpigmention are often seen in HIV-infected black patients ("itchy bump disease"). 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 - intensively 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 hands, arms and face. A linear distribution might be seen when caused by fleas or bedbugs
   d) bacterial follicultis/ecthyma - papules and pustules which might become excoriated, usually are less itchy than above mentioned lesions
   e) scabies - intensely pruritic papules commonly on interdigital spaces of hands and feet as well as on ankles, elbows, axilla and groin area.
   f) Secondary syphilis - can have many cutaneous manifestations and should always be considered
   Any of these conditions may at times be confused with Kaposi's sarcoma lesions.

2) Papulopruritic eruption might be difficult to distinguish from eosinophilic folliculitis and papular urticaria. However, therapy is the same and an exact diagnosis often not needed. Oral antihistamines (e.g. chlorpheniramine 4 mg nocte) are used in combination with topical steroids (hydrocortisone cream for face, bethamethasone 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 bethamethasone valerate cream and chlorpheniramine 4 mg nocte and the itching improved. ART was started and well tolerated.

Key learning point

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

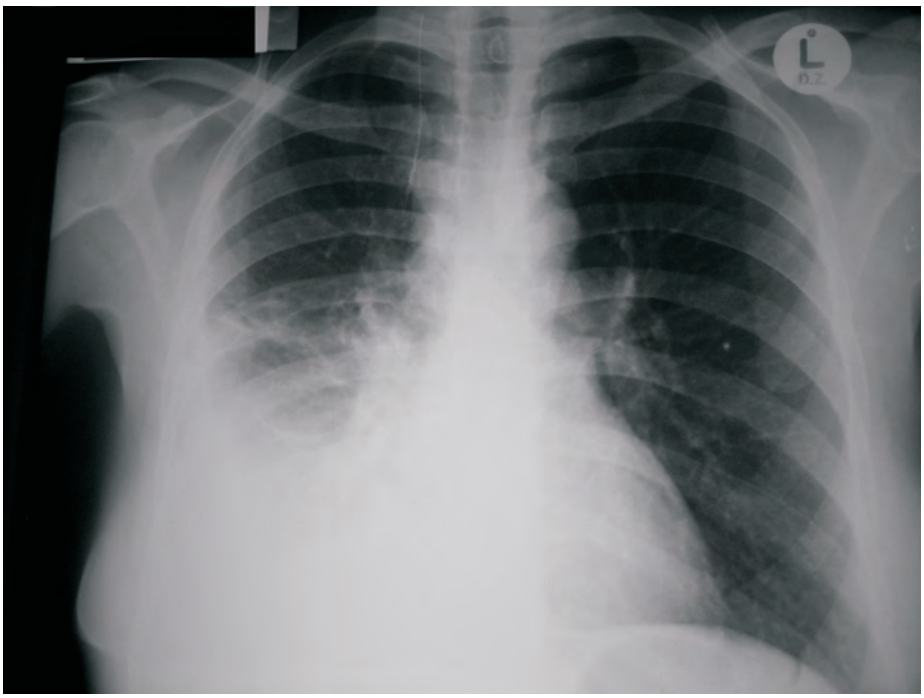
Suggested reading

Dlova, CN, Mosam A: A clinical atlas of skin conditions in HIV/AIDS: an illustrated management guide for health care professionals, The Health and Medical publishing group of the South African Medical Association, 2005 (e-mail: publishing@hmpg.co.za)

Case 27

Case presentation

A 33-year old man was seen with chronic cough of 2 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 and antibiotics given by the clinic (amoxicillin+erythromycin) for one week were not effective. He was referred for CXR, which showed right pleural effusion and 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 different ways:
   a) Effusion which develops usually few month after 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; 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 may 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 as well as AFB and material send for mycobacterial culture.
   Often the fluid is clear and straw colored, the protein is higher (>1.5x serum protein => exudate) and cells are predominantly lymphocytic. If total WBC count is higher than 500 cells and protein > 2.5g/dl an empyema can be diagnosed. It can be differentiated between “thin empyema” (possible to mobilize through cannula) and “thick empyema” (which needs a transthoracal 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 is available. We use it only in rare, exceptional cases.

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 done for this patient as he was not respiratory compromised. He had an HIV test which was positive. This makes TB an even more likely diagnosis. He was referred back to his clinic for TB treatment and assessment of CD4 count. As his CD4 count was 154 cells/μl, ART was started 2 month later.

Comments

Puncture of pleural space with a small cannula to drain fluid is often possible and 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 pleural effusions with a consistent clinical history can be considered TB in our setting if there is no alternative explanation

Case 28

Case presentation

A 22-year old lady was seen in the clinic for initiation of ART. She had received *Pneumocystis jiroveci* pneumonia treatment 2 weeks ago and explained that her shortness of breath and cough had improved. She otherwise only admitted to weight loss of <10%. She 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 was 158 cells/μl. Her baseline blood tests were normal, and her hepatitis B surface antigen was negative. She was classified as stage 4 because of the PCP.

She was started on D4T/3TC/NVP.

Question

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

At 2-week and 4-week follow-up visits she reported no problems. No blood tests were taken. She attended the clinic 2 months after initiation, complaining of a rash that had been gradually worsening over 7 days. She had fatigue, occasionally fevers, and severe nausea but no vomiting. She explained that even that morning she had managed to take her tablets.
On examination, she had a desquamating rash. She was deeply jaundiced but showed no signs of encephalopathy. Her temperature was 37.3°C, BP 90/60 mmHg, HR 95/min. Otherwise examination was normal.

Questions

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

Diagnosis: NVP-related hepatotoxicity

Answers

1) Initially NVP is taken at 200mg once per day for 14 days and then if there are no signs of toxicity, the dose is increased to 200mg twice per day. The patients are assessed by counsellor and nurse and LFTs taken. If there are any signs of toxicity (jaundice or rash) the doctor should be alerted before increasing the dose. Monitoring involves checking ALT at 2,4,8 weeks and 6 months.

2) Nevirapine associated acute hepatitis is the most likely diagnosis. Acute hepatitis could also be caused by other drugs e.g. anti-TB drugs, co-trimoxazole, and traditional medicines. Viral causes include hepatitis B (especially an immune reconstitution to HBV after initiation of ART), hepatitis A, CMV or EBV. Bacterial causes are hepatic TB (again, can present as IRIS), and less commonly leptospirosis.

3) 1 in 20 people will get some degree of reaction to NVP (either rash or hepatitis) usually within the first 4 months. Risk factors for hepatitis include; female sex, hepatitis B surface antigen 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 improved mortality outcomes.

Outcome and follow up

Her LFT showed the following results:

Bili tot	182.2 μmol/L	(normal 3.0-17)
ALP	198 U/l	(normal 42-121)
ALT	1030 U/L	(normal 10-60)

She was admitted to the ward. All of her medications were stopped and she was started on IV fluids. Unfortunately within 24 hours of admission she died.

Comments:

Hepatotoxicity is a common problem with ARVs as well as with anti TB drugs. Our local protocol recommends the following action in reaction to abnormal ALT values on treatment:

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

Key learning point

Monitoring of ALT is essential for all patients commenced on NVP

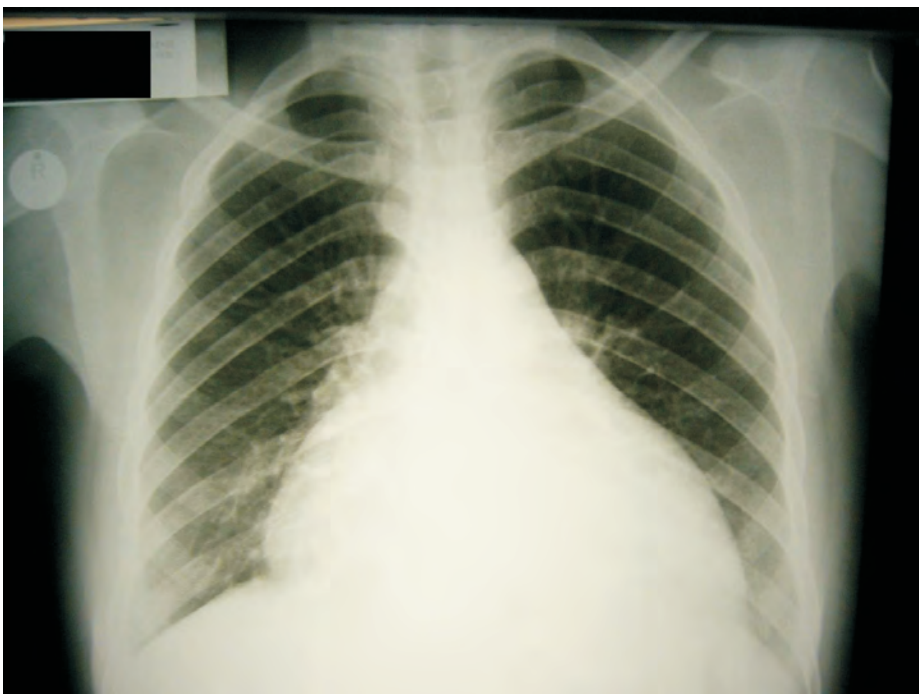
Case 29

Case presentation

A 27-year old lady with a CD4 count of 71 cells/μl presented to the clinic for initiation of ART. She had been on TB treatment for 2 months. She was unwell and described three weeks of shortness of breath, chest pain, dry cough and peripheral edema. She was afebrile and BP was 98/60.

Examination revealed mild peripheral oedema, gallop 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 $10^3/mm^3$	(normal 4.0-11.0)
Plt	390 $10^3/mm^3$	(normal 150-500)
Creat	360 μmol/L	(normal 62-120)
Urea	8.8 mmol/L	(normal 3.5-6.5)
LFTs	normal	



Questions

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

Diagnosis: HIV-associated cardiomyopathy
Probable HIV-associated nephropathy (HIVAN)

Answers

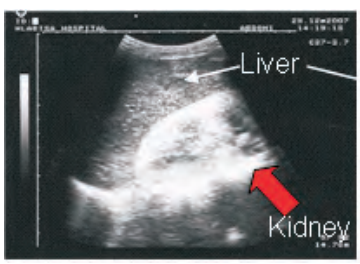
1) Increased cardio-thoracic ratio. Suggest cardiac and renal US, urine dip for protein, BP testing and HGT (random blood glucose test).

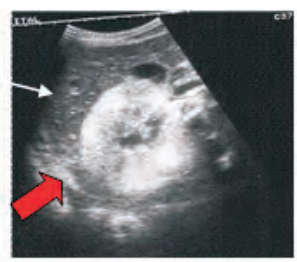
2) In adults, cardiomyopathy can be caused by ischaemia, untreated hyperthyroidism, chronic alcohol excess, post-partum, vitamin deficiencies, heamochromatosis, cardiotoxic drugs and as consequence of viral myocarditis. In HIV infection, myocarditis can be caused by a number of opportunistic infections including *Toxoplasma gondii* (although cerebral infection is seen more frequently) or in association with other viruses i.e Coxsackie, EBV and CMV. 8-12% of patients with HIV infection have some evidence of left ventricular dysfunction, and there is a suggestion that this can be caused by HIV infection itself. Doxorubicin, used in the treatment of Kaposi's sarcoma, is myotoxic and can cause cardiomyopathy.
This patient could have had renal impairment from hypoperfusion due to reduced left ventricular output or due simply to her advanced HIV disease. Proteinuria and echogenic kidneys on USS suggest the possibility of HIV associated nephropathy. Biopsy is required to prove the diagnosis but is rarely performed in this 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 the prevalence in Africa. HIVAN includes renal impairment with nephrotic range proteinuria. Usually the serum albumin is reduced and occasionally there is hypertension. It is associated with a CD4 of less than 200. The impact on survival is difficult to assess. Treatment is with ART and ACE-inhibitors.

Outcome and follow up

The patient was referred for ultrasound which showed left ventricular dilatation, no pericardial effusion, a normal liver and echogenic kidneys.
Urine dip showed protein +++, nil else, blood sugar was 5.5 mmol/l. She was started on ART (D4T/3TC/EFV). Additionally enalapril 10mg bd and furosemide 20mg od were given. After a week her urea and creatanine were unchanged. After 4 weeks her creatinine had lowered to 150 μmol/l and had normalized after 2 months. Her CXR after 2 months was similar but she was symptomatically better, even after stopping the diuretic.

Further images





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

Key learning point
In HIV-related cardiomyopathy and nephropathy, ACE-inhibitors in association with ART are the cornerstone of treatment

Suggested reading

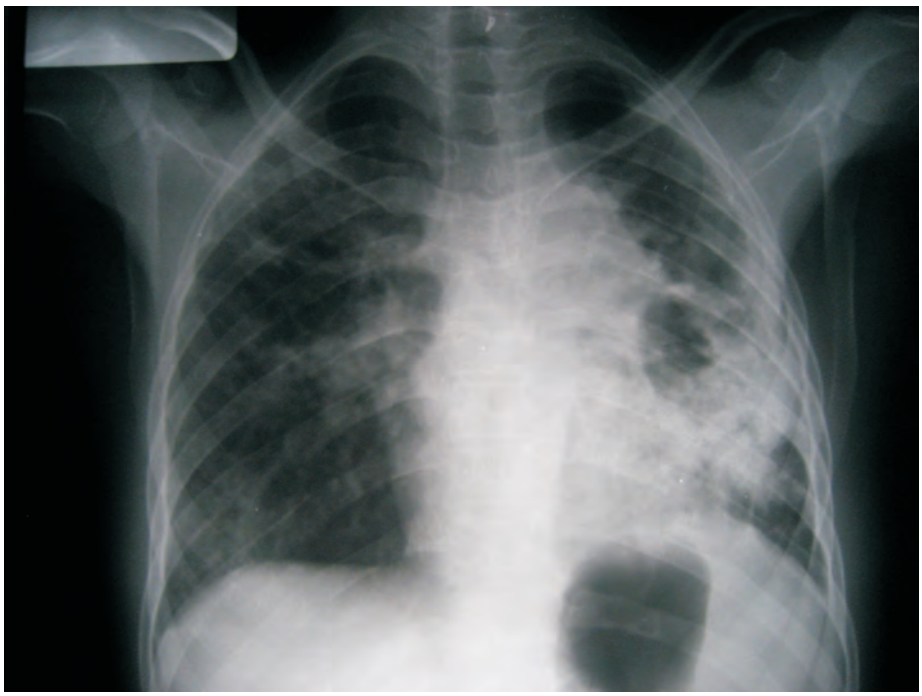
Restrepo et al. Cardiovascular complications of human immunodeficiency virus infection. Radiographics 2006; 26: 213

Case 30

Case presentation

A 23-year old female patient was admitted because she suffered from typical TB symptoms with chronic productive cough and loss of weight. She was treated for TB in 2002, 2006 and 2007 and now complained about recurrence of symptoms. A sputum culture was sent from her local clinic that grew *M. tuberculosis* resistant to isoniazid, rifampicin and streptomycin and sensitive to ethambutol, ciprofloxacin and kanamycin.

On admission she looked wasted but does not show signs of respiratory compromise. She was counselled and tested for HIV and the test was positive. A CXR was taken.



Questions

1) What is MDR-TB? What is XDR-TB?
2) How should this patient be treated?
3) What are the most common side effects of MDR-TB treatment?

Diagnosis: MDR-TB/HIV coinfected patient

Answers

1) Multidrug-resistant-TB (MDR-TB) strains are TB strains resistant to at least isoniazid and rifampicin. Strains resistant to a single drug or to other antibiotic combinations like e.g. isoniazid and streptomycin are (by definition) not called MDR strains. Worldwide approximately 4-5% of all TB strains have MDR.
   Extensively-drug resistant TB (XDR-TB) additionally shows 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 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 dugs. The principle that a patient should be treated with a combination of at least three effective drugs applies. Second line drugs are less effective and far more toxic than first line drugs. To determine a treatment regimen experts should be consulted and often treatment is initiated in a central MDR hospital (e.g. King George V Hospital, Durban). Unfortunately this often means long waiting periods before beds are available during which the patient remains untreated. New approaches like community based treatment need to be considered and evaluated in the future.
   A commonly used regimen is a combination of kanamycin (IM for 6 month), ofloxacin, ethionamide, cycloserine, ethambutol and pyrazinamide (orally for 18-24 month).

3) Kanamycin- nephrotoxicity (check creatinine) and ototoxicity (audiogram, ask for new tinnitus, loss of hearing or vertigo).
   Ofloxacin- musculo-skeletal problems, tendon rupture, generally well tolerated, NSAIDs might be indicated.
   Ethionamide- severe nausea and gastrointestinal side effects, try to treat with metoclopramide. Nausea 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, usually one of the better tolerated drugs.

Outcome and follow up:

The patient was sent to the MDR treatment centre and the abovementioned regimen was prescribed. After 3 weeks she developed symptoms of psychosis and threatened to attack other patients and staff. Cycloserine was stopped and haloperidol was given. The mental status improved and finally the patient was able to leave the hospital and was treated at home (cycloserine was not restarted!).

Comments

One of the biggest problems of MDR-TB is the delay in diagnosis and initiation of treatment. Nucleic-acid based tests (PCR) might shorten the time to diagnosis and have been shown in field trials in South Africa to be effective and feasible (MDRTBplus line assay). The delay between diagnosis and initiation of treatment needs to be addressed by increasing treatment capacity or changing policies (e.g. community based treatment).

Key learning point

Sputum culture should be sent in any patient with TB symptoms who has had previous disease

Suggested reading

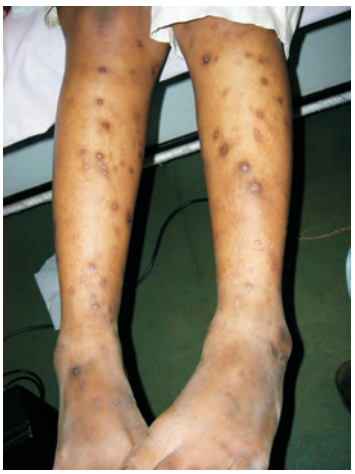
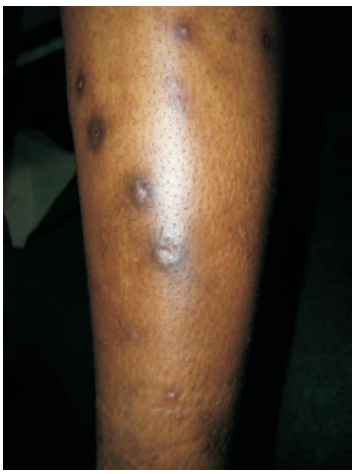
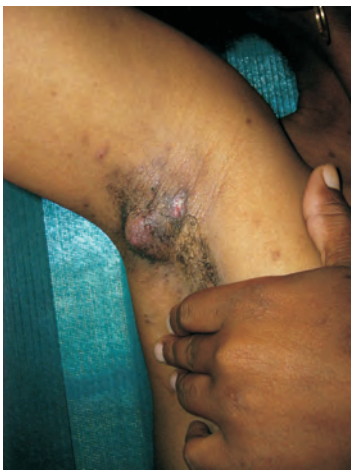
1) WHO Guidelines for the management of drug-resistant tuberculosis 1997, WHO/TB/96.210
2) Barnard M et al. Rapid molecular screening for multidrug-resistant tuberculosis in a high volume public health laboratory in South Africa, Am J Resp Crit Care Med 2008, 177: 787

Case 31

Case presentation

A 24-year old female patient was seen in the clinic because of the illustrated skin changes; she had started ART 4 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 illustrated skin changes?
2) How would you treat the patient?

Diagnosis: Ecthymata and axillary abscess

Answers

1) Ecthymata, which are crusted ulcers often on the distal limbs, are caused by bacterial infection of the dermis. The most common causes are *Staphylococcus aureus* and group A Streptococcus. The axillary abcess is most probably also caused by one of the above mentioned organisms.

2) For ecthyma, local cleaning and antibacterial cream (e.g mupirocin) are the first approach to management. It might be worthwhile to attempt systemic antibiotic treatment in severe cases. Antibiotics with activity against streptococci and staphylococci should be used (e.g. flucloxacillin, amoxicillin/clavulanic acid).

Outcome and follow up:

The axillary abscess was incised and drained pus. Amoxicillin/clavulanic acid was prescribed for 10 days, additionally mupirocin cream was given for the peripheral lesions. The lesions healed with 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 superinfection 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 health care professionals, The Health and Medical publishing group of the South African Medical Association, 2005 (e-mail: publishing@hmpg.co.za)

Case 32

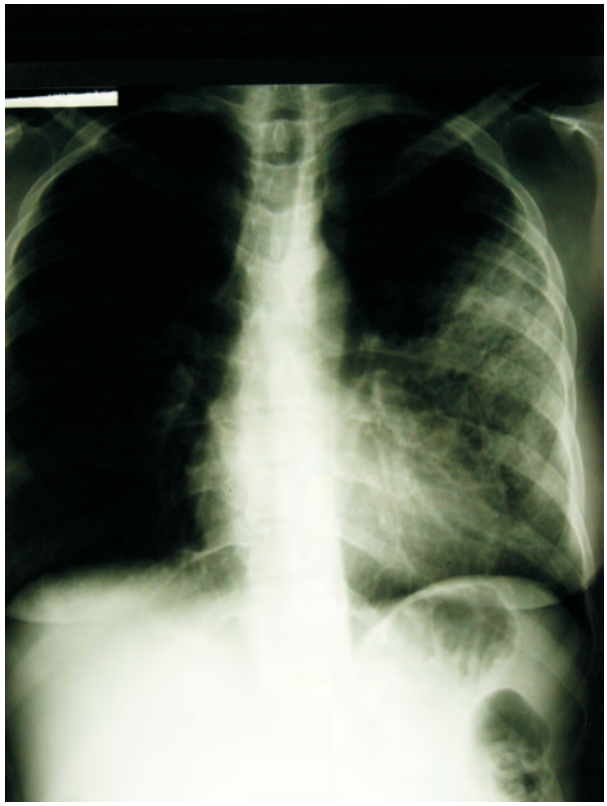
Case presentation

A 28-year old female patient who has been on ART for 8 months D4T/3TC/EFV was seen with a 1 week history of cough and shortness of breath. Her last CD4 count was 354 cells/μl. She was febrile (38.9°C) and looked distressed. An antibiotic (amoxicillin/clavulanic acid) was prescribed. After 2 days she was seen again in the clinic, then complaining about worsening symptoms and additional nausea and vomiting. A CXR was done and she was admitted.

Her FBC showed an Hb of 8.3 g/dl and WBC of 12.0 $10^3/mm^3$.

U&E:

Na	140 mmol/L	(normal 133-153)
K	4.8 mmol/L	(normal 3.0-5.0)
CO2	24 mmol/L	(normal 22-33)
Creat	521 μmol/L	(normal 62-120)
Urea	16 mmol/L	(normal 3.5-6.5)



Questions

1) What is the most likely diagnosis?
2) What organism could cause this picture and how should they be treated?
3) What might have caused her renal failure?

Diagnosis: Pneumonia with acute renal failure

Answers

1) Community acquired pneumonia (CAP), but atypical presentation of TB or PCP should always be considered. Her relatively short history and relatively high CD4 count point more towards CAP.

2) *S. pneumoniae* and *H. influenzae* are the most common pathogens in our setting. The clinical presentation is similar to that of HIV negative patients but complications are more frequent in the immunocompromised patients.
For outpatients 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 cefuroxime or IV amoxicillin/clavulanic acid are the agents of choice. Combination with a macrolide or a quinolone are possible to cover for atypical causes of pneumonia (caution that quinolones are active against TB).

3) The patient was possibly suffering from mild HIV associated nephropathy. As consequence of the acute severe infection, organ failure ("acute-on-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 the resource limited hospital)

Outcome and follow up:

The patient was admitted to the ward, the antibiotic was changed to cefuroxime 1.5 g tds IV. and erythromycin 500 mg tds po. Metoclopramide was given for the nausea. Additionally IV fluids (2000 ml Ringers lactate) were ordered but it was unclear how much of this she received. On the following day she 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). Her CO2 dropped to 12 mmol/l and her creatinine increased to 705 μmol/l. 5 l of normal saline solution were ordered and given over the next 24 h. Additionally she received Na bicarbonate 8.4% 100 ml IV prescribed by the physician on call to treat the acidosis.

The antibiotic therapy was continued. Clinically the patient improved slowly over the next few days and finally she was discharged in her normal state. At this time her creatinine had fallen to 132 μmol/l, 3 weeks later it was found in the normal range.

Comments:

The rate of CAP is higher in HIV infected individuals than in the general population (approx. two to three fold). 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 sixfold increased in HIV patients, pneumococcal bacteremia is 100 times more frequent. This might cause septic complications like organ failure.

Key learning point

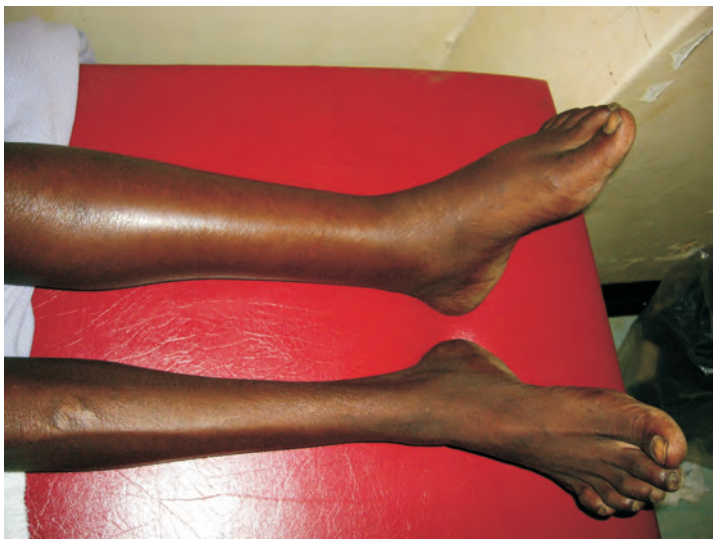
Hospital treatment is often required in pneumonia especially in severe or complicated cases where other organ impairment is involved.

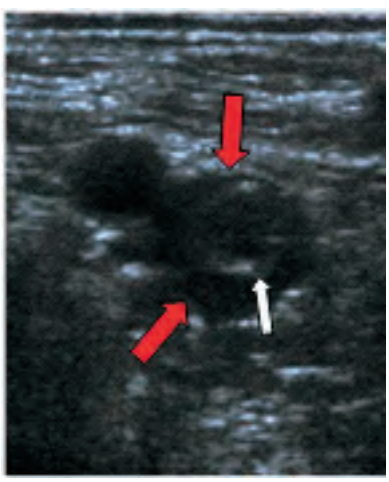
Case 33

Case presentation

A 19-year old female patient was seen in the peripheral clinic because of general fatigue, weight loss and swelling of her left leg. She did not complain of shortness of breath or chest pain. She was HIV positive and her CD4 count eight months previously was 120 cells/μl; she 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 shows echogenic material in the common femoral vein. On compression ultrasound the vein is not compressible.

Questions

1) What is the most probable diagnosis? What is the differential diagnosis?
2) How would you treat her and what problems do you expect?
3) If she requires 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 probable diagnosis.
   Lymphoedema e.g. due to infiltrating malignancy like Kaposi's sarcoma.
   Elephantiasis due to filarial disease (rare in our area, more common towards the border of Mozambique)

2) Patients with venous thrombosis often need to be admitted to hospital as the anticoagulation as outpatient on the clinic level can be virtually impossible. Weight adapted low-molecular weight heparin is the easiest initial option as it does not need monitoring of the APTT. Sequentially anticoagulation with warfarin should be started. A stable dosage needs to be achieved before discharge, as further monitoring of INR might be difficult (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 and have both been reported to decrease warfarin levels but also to increase levels thus risking haemorrhage. The amount of warfarin needed in the individual patient needs to be determined by INR monitoring.

Outcome and follow up:

The patient was admitted to hospital to confirm the diagnosis of thrombosis and to initiate anticoagulant therapy. Abdominal ultrasound showed enlarged abdominal lymph nodes and free fluid, making the diagnosis of abdominal TB highly likely. The patient commenced low-molecular weight heparin and warfarin, and additionally RHZE was started. After dose adjustment (approx. 2 week) the patient was discharged and sent to the clinic to see the physician after 1 week to check INR. The patient came only after 2 weeks, but at this point of time no citrate tubes were available at the clinic. A few days later the blood sample was taken by the nurse. When the physician saw the patient (with the INR result) for the next time the patient did not bring her tablets and the warfarin dose was unclear. The patient came again and now brought her tablets, which were almost finished (6 weeks supply). Her leg looked completely normal and, considering the difficulties of INR monitoring and the associated risks, anticoagulation was terminated.

Comments:

The incidence of venous thrombosis is increased by two- to tenfold 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 procoagulant 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 in this setting is difficult

Suggested reading

S.K. Klein et al: Is chronic HIV infection associated with venous thrombotic disease? A systematic review, Netherlands J Med (2005) 63, 129

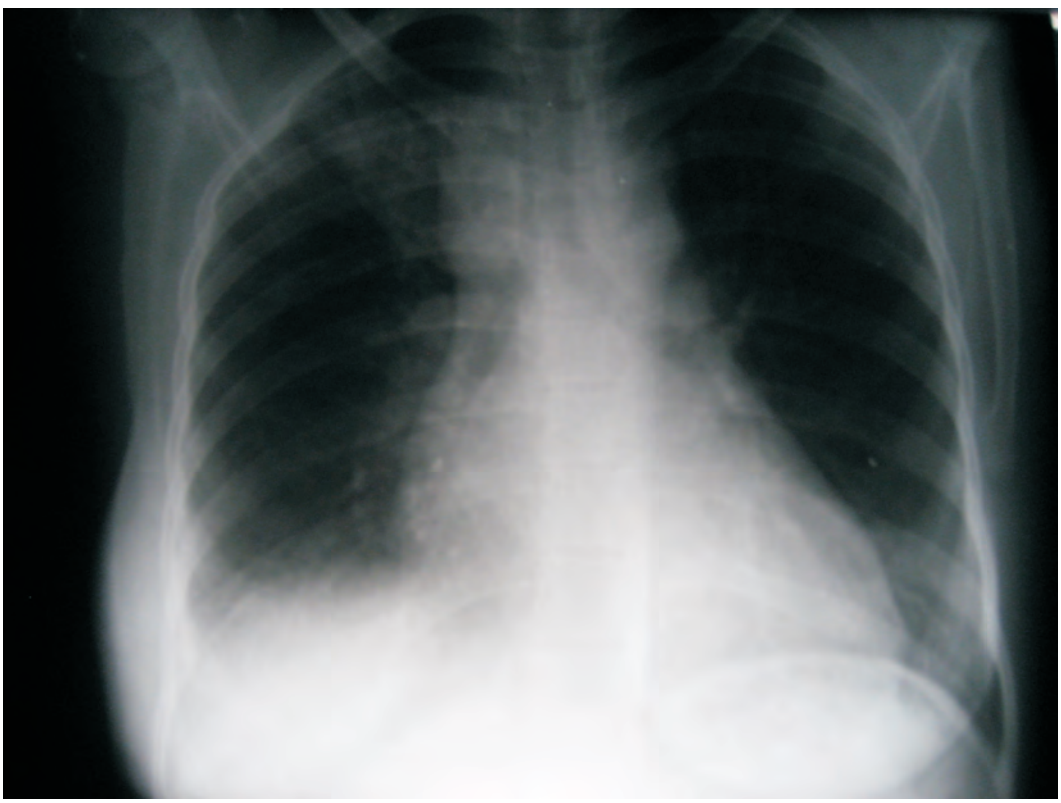
Case 34

Case presentation

A 32-year old woman who recently tested HIV positive, was seen in the clinic. Her CD4 count was 23 cells/μl. Baseline LFT, U&E and FBC were normal, sputum was negative for AFB. She was fast tracked for initiation and started D4T/3TC/EFV, CTX 2 tabs od and multivitamins.

2 weeks later she presented with a rash on the 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 in 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 have rash. Desensitization 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 2 ½ months after initiating ART, she complained of new chest pain, cough and haemoptosis. A CXR was performed.



Questions

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

Diagnosis: CTX hypersensitivity, TB-IRIS after starting ART

Answers

1) The patient started to have TB symptoms after 10 weeks of ART. This is suggestive of an immune reconstitution inflammatory syndrome (IRIS) to TB. With the slowly improving immune function, the body starts to actively fight the tuberculosis 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 commonly done by AFB smears. Nevertheless it is well known that TB in HIV patients is often smear negative and a negative smear cannot rule out tuberculosis. It is not uncommon therefore to see "unmasking" of undiagnosed TB.

3) CTX is a very effective prophylactic drug which reduces not only the rate of pneumocystis pneumonia but also bacterial infections, especially with enteric bacteria. It is therefore preferable to other drugs (like e.g. dapsone 100 mg, which can be used as a second line prophylaxis). According to WHO guidelines desensitization can be attempted 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 single strength tablet (400/80 mg), day 6 onwards 2 single strength tablet (800/160 mg). Desensitization 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, the cough and chest pain had 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, the reaction is called IRIS. Tuberculosis is the most frequent presentation of IRIS, but cryptococcal meningitis, Kaposi's 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, rarely steroids have to be administered (in 9% of patients according to a study from Cape Town). Death is rare and most commonly due to intracerebral IRIS.
The fear of IRIS should not prevent patients from being started on ART!Whilst still awaiting clinical trial data we follow national guidelines on the timing of initiation of ART in patients taking TB treatment. In TB patients with CD4 counts between 50 and 200 cells/μl it is recommended that ART be started after 2 months of TB treatment; patients with CD4 count below 50 cells/μl should start after 2 weeks as the risk of severe immunosuppression outweighs the risk of IRIS.

Key learning point

Desensitisation is difficult to perform in this setting and should only be performed 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
WHO: Guidelines on co-trimoxatole prophylaxis for HIV-related infections among children, adolescents and adults. www.who.int/hiv/pub/guidelines/ctx/en/index.html

Case 35

Case presentation

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

The patient looked otherwise 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 investigate the patient?
3) Which anticonvulsants can be used in this setting?

Diagnosis: Cerebral toxoplasmosis with new onset seizures

Answers

1) The most common causes for new onset seizures in a 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 CT scan is warranted. If there is no improvement the patient can be sent for 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 commonly available drugs to control seizures. They are started at low dose and titrated up in two-weekly intervals to reach effective levels. In patients receiving ART, it must be considered that both drugs are strong liver enzyme inducers and may 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. 1200 mg bd.

Outcome and follow up:

Cerebral toxopasmosis was considered as the most probable diagnosis and was treated with CTX 4 tbl bd. He was seen after 2 weeks and reported that he had no more episodes of fits and his headache had disappeared. His CD4 count was 239 cells/μl. The treatment was continued and after 4 weeks was reduced to 2 tabs bd. As toxoplasmosis is a stage 4 disease, 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.

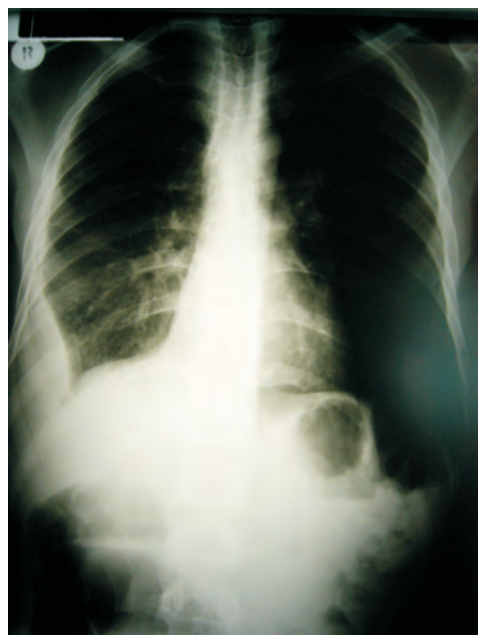
He was started on RHZE and ART was delayed for further 4 weeks.

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 and 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 and further investigation was felt not to be warranted.

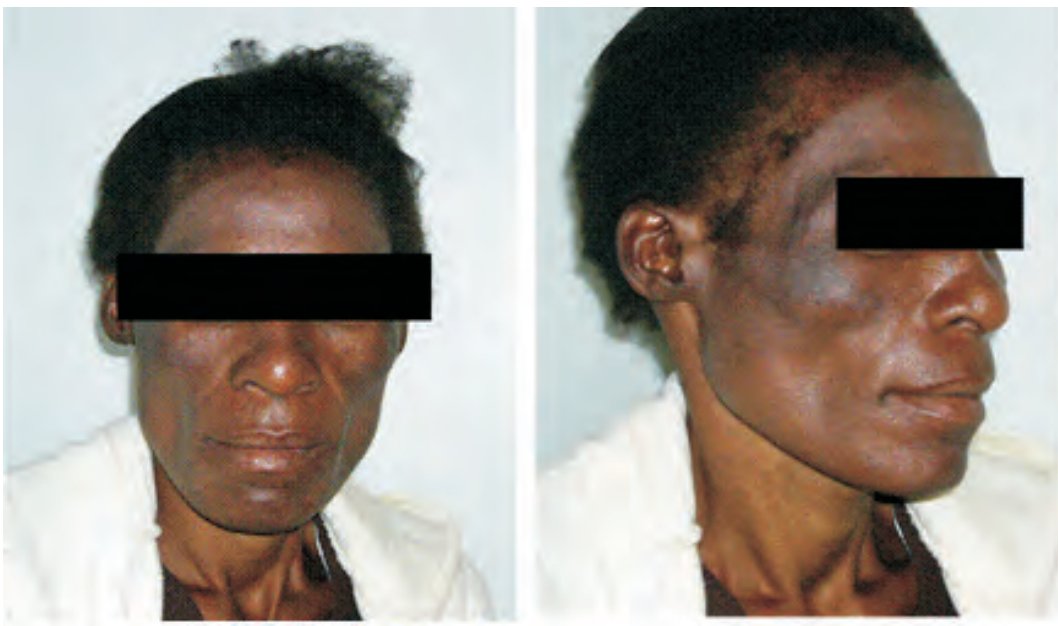
CTX 4 tabs bd for 1 month, followed by 2 tabs bd for three months, is the treatment of choice for cerebral toxoplasmosis. In patients not tolerating CTX, clindamycin 600 mg tds and pyrimethamine 100 mg bd for 1 day, than followed by 50 mg od should be given for 3-6 weeks (add 15 mg of folinic acid initially to avoid marrow toxicity of pyrimethamine).



Case 36

Case presentation

A 46-year old patient was seen in the staff clinic. She was diagnosed HIV positive in 2002 and was started on DDI/D4T/ EFV in 2003 in the private sector covered through her medical insurance. Her CD4 count at this time was 180 cells/μl. She developed diabetes mellitus in the following year and metformin 500 mg bd and glibenclamide 5 mg od were prescribed. In 2006, she had entered the public ART programme. The ART drugs were changed to AZT/3TC/EFV. She complained now (2008) only 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/μl and viral load was <25 copies/ml.



Questions

1) What is the most probable cause of her complaints?
2) How would you treat her?
3) Which other side effects would you expect in the above mentioned drug combination?

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) caused by protease inhibitors is maybe the best known form of lipohypertrophy.
The metabolic complications occur with many of the antiretroviral drugs. Nucleoside reverse transcriptase inhibitors, especially D4T, DDI but also to a lesser extend 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 might have added to the fat reduction in this patient.

2) Given the limited availability of alternative drugs the decision to change to other antiretrovirals is difficult, especially as her HIV disease seems well controlled. Even after changing the drugs, the fat changes are not necessarily reversible.
Metformin should be stopped and alternative anti-diabetic agents, even insulin if needed, should be given. The patient needs to be counseled 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 had still a sufficient blood sugar control with glibenclamide 5mg daily alone.

The changes in body fat were explained to her, the ART regimen was left unchanged. She was seen after 3 month, her compliance was still good, her facial appearance had not change.

Comments:

Change of antiretrovirals due to side effects are desirable, but difficult in face of the limited drug choice available. The possibility of reduced or absent further future treatment options has to be balanced against the severity of side effects and a decision has to be made including the patients opinion, as side effects might impair adherence and thus endanger treatment success. Abacavir and tenofovir are the least likely agents to cause lipodystrophy but are not currently not available in our setting.

Key learning point

Changing antiretrovirals for lipodystrophy is not always necessary given the limited drug options. Education and reassurance are vital.

Suggested reading

Christopher Behrens: Metabolic Complications of HIV infection and antiretroviral therapy, 2006, Northwest AETC, accessed: http://www.aids-ed.org/aidsetc?page=etres-display&resource=etres-10

Case 37

Case 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 and he 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 of the body is most commonly affected by herpes zoster?
3) Name 3 complications?

Diagnosis: Herpes zoster

Answers

1) Aciclovir is the drug of choice and should be started as soon as possible. Ideally the drug should be available at the clinic level to prevent delay in treatment.

2) Thoracic (>50%), trigeminal (10-20%) lumbosacral and cervical (10%)

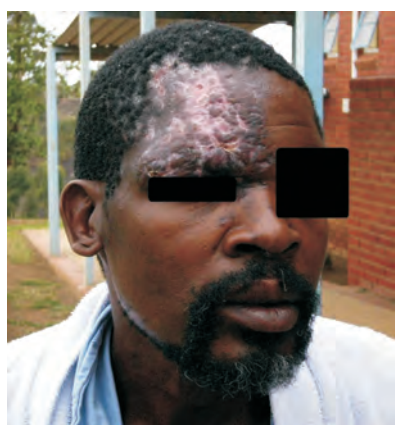
3) a) Bacterial superinfection-local antiseptic solutions might prevent this complication, if indicated systemic antibiotics need to be given
   b) Scarring-herpes zoster scars are a disfiguring (and as associated with HIV often stigmatizing) complication. Early aciclovir treatment seems the only possible preventive strategy.
   c) Ophthalmic complications if the ophthalmic nerve is affected then the eye might be involved and sight might be at risk. Keratitis, iridocyclitis and secondary glaucoma as well as ophthalmic nerve paralysis are seen. Involvement of the nasocilliary 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 is seen in more than half of the patients for one month but even after 6 months approx. 10% complain of pain. Treatment options include carbamazepine and sodium valproate (preferable in patients receiving ART) as well as tricyclic antidepressants (e.g. amitryptiline 25 -75 mg nocte)
   e) Dissemination- cutaneous dissemination as well as involvement of organs like lung, liver and pancreas is seen, especially in immune-compromised patients.
   f) Neurological disease meningitis, encephalitis, myelopathy and radiculitis have been reported and are not necessarily associated temporally with the cutaneous disease.

Outcome and follow up:

The patient was admitted and aciclovir 800 mg 5 times per day po was given. After 2 days no improvement was seen and the drug was changed to aciclovir 10 mg/kg IV. Additionally an antibiotic (amoxicillin) as well as antibiotic eye drops were added to treat secondary bacterial super-infection in the eye. The patient complained about severe sharp pain, so diclofenac and amytriptiline were given. The skin lesions healed with substantial scarring but the vision remained completely normal.

Comments:

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



Key learning point

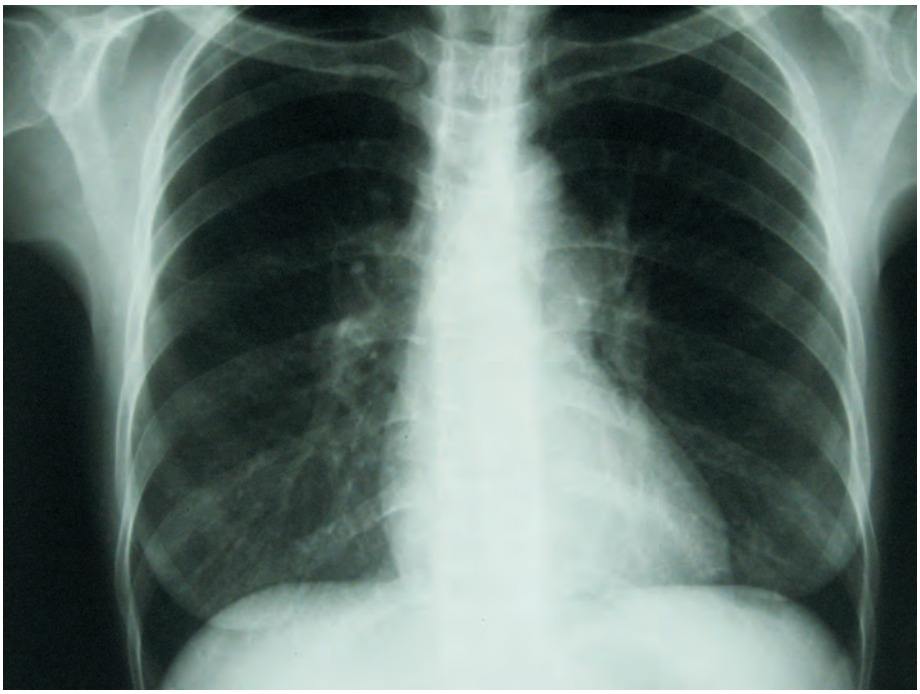
Intravenous aciclovir is often indicated for herpes zoster in HIV infection, particularly if there is ophthalmic involvement, or other organ disease

Case 38

Case presentation

A 22-year old woman was seen in the clinic complaining of cough. She reported a dry cough of 3 week duration 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, more pronounced on the left, suggestive of lymphadenopathy. This is likely to be due to TB in a high prevalence setting. Other differential diagnoses are lymphoma, carcinoma, other infections and sarcoidosis

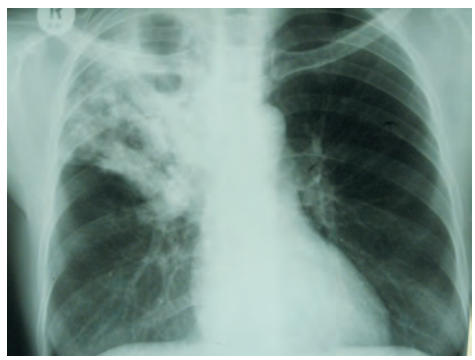
2) The patient should be sent for an HIV test.

Outcome and follow up:

Amoxicillin 500 mg tds plus erythromycin 500 mg tds were prescribed and the patient was informed to come back if no improvement was seen after 2 weeks. She did not return for follow up.

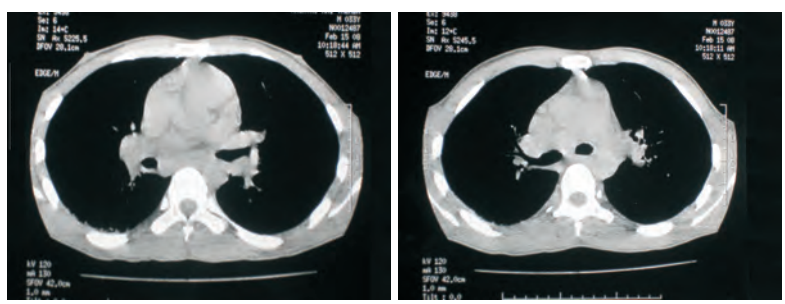
She was seen again after 5 months, then complaining of productive cough and weight loss. A severe right upper lobe infiltrate with cavities was seen on the CXR. She was started on RHZE. Additionally, she went for VCT and was found to be HIV positive. Her CD4 count was 178 cells/μl and D4T/3TC/EFV were started after completing 2 months of TB treatment.

Further images



CXR after 5 month

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.



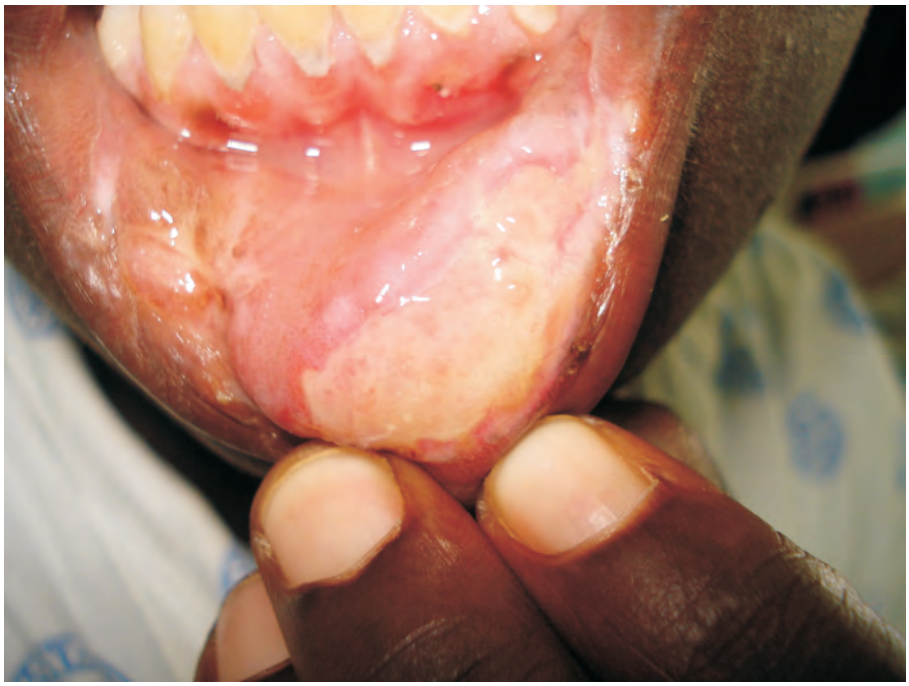
Key learning point

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

Case 39

Case presentation

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



(Courtesy of Dr. Dedicoat, Ngwelezane Hospital)

Questions

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

Diagnosis: Herpes simplex mouth ulcer and oesophagitis

Answers

1) Herpes simpex virus causes ulcers in the mouth of HIV patients which are more severe and more frequently recurring than in non-HIV patients. A differential diagnosis 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.

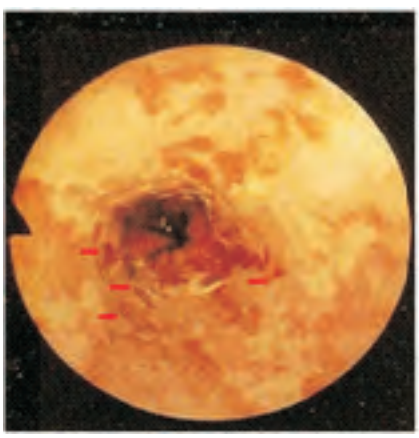
2) Oesophagitis can occur frequently in HIV patients. When associated with ulcerations (if an oesophagoscopy is performed, rarely indicated in our setting) HSV and CMV infections are the most commonly found causes. Aphthous ulceration can also affect the oesophagus.

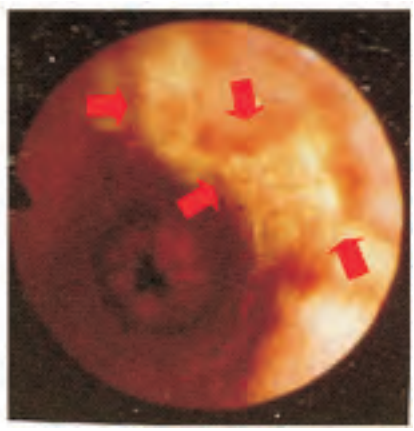
3) Acyclovir is the treatment of choice for ulcers associated with HSV. Recurrent aphthous ulcers are more difficult to treat. Antiseptic mouthwash (chlorhexidine 0.2% or polyvidone-iodine 1%) might be helpful. Local steroids (in form of cream or as puffs from a inhaler) can be used. It is recommended to treat first with acyclovir to rule out HSV infection as this exacerbates with steroid use.

Outcome and follow up:

The patient received acyclovir 400 mg tds po. The chest pain quickly improved, also the ulcerations on tongue and lip improved over the course of a 2 weeks. The patient was discharged to the clinic and ART was initiated.

Further images





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

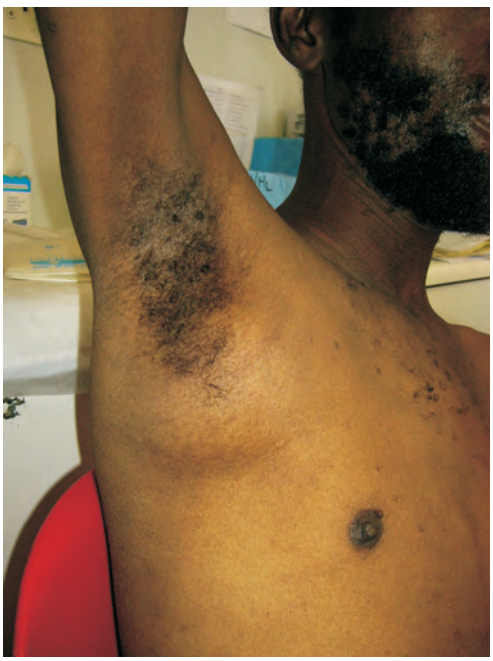
Key learning point

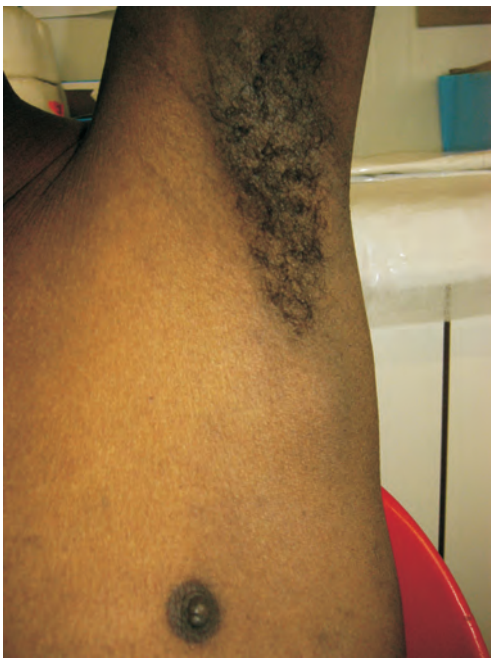
Aciclovir is indicated if there are severe mucosal ulcers and particularly if there are symptoms of more extensive GI tract involvement

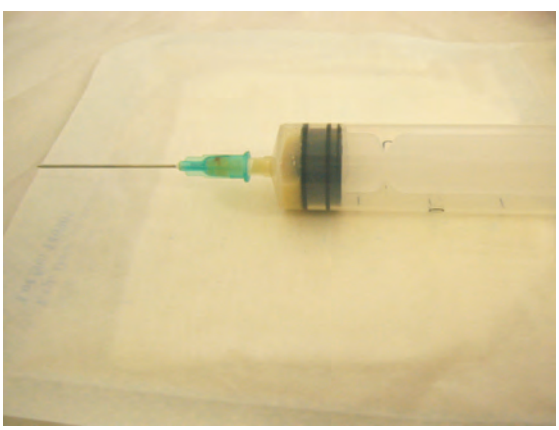
Case 40

Case presentation

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







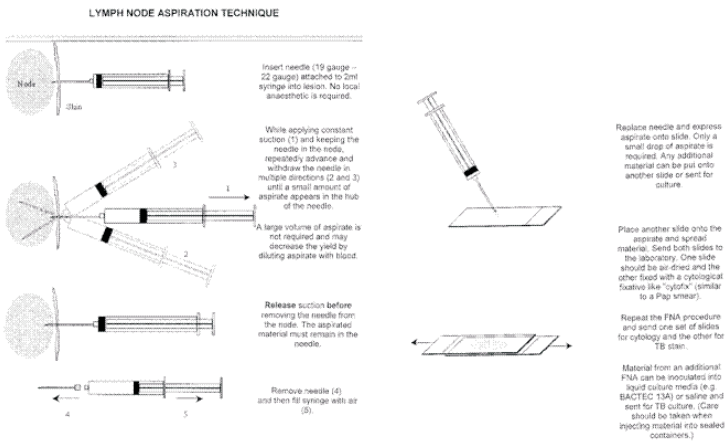
Questions

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

Diagnosis: TB lymphadnitis

Answers

1)



(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 differentials of TB:
   - Kaposi's sarcoma (watch for lesion in skin or mouth)
   - Lymphoma (symmetrical often larger nodes)
   - HIV lymphadenopathy (PGL) (symmetrical, generalized)
   - Local bacterial and fungal infections (tender, inflamed, purulent LN, local infections visible); this contrasts with the "cold abscess" of TB

3) TB lymphadenitis is treated with the same 6 month regimen as other forms of TB. Longer (9 month) treatment was recommended previously, but recent studies showed it to be no more effective. WHO guidelines recommend 6 month regimens for "virtually all forms of EPTB".

Outcome and follow up:

The pus was sent to the lab and was found to be positive for AFB. Additional material was sent for TB culture which was positive and the strain was sensitive to isoniazid and rifampicin. The further course of the patient was uneventful, the swellings subsided with therapy and he started ART after 2 months.

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 only very rarely) the case.

Key learning point

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

Suggested reading

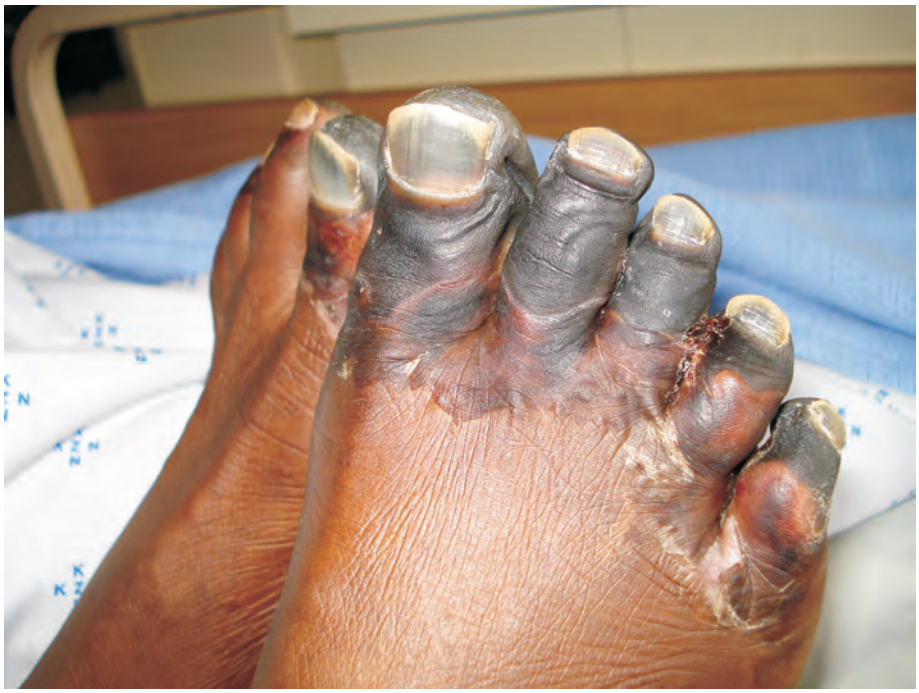
1) Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary Tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings, WHO 2007, WHO /HTM /TB /2007.379
2) Treatment of tuberculosis WHO 2003, WHO/CDS/TB/2003.313

Case 41

Case presentation

A 34-year old male patient came was admitted to the ward due to painful feet for a few weeks. All toes of his right foot as well as the big toe of his left foot had turned black.

He was HIV positive and his last CD4 count was 231 cells/μl. He was a non-smoker and had no diabetes, hypertension or other cardio-vascular disorders.



(Courtesy of Dr Declieoat, Ngwelezane Hospital)

Questions

1) What is shown in the picture and 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 described, 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, steroids are an option but frequently the patient requires amputation.

2) *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 as well as regional lymphadenitis is found.

Outcome and follow up

Low dose heparin and aspirin were prescribed. The patient additionally 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 and a fever was recorded. Antibiotic therapy was started and eventually he required an amputation.

Comments

Almost every pattern and type of vasculitis of small, medium and large vessels has been encountered in the setting of HIV. It is not fully clear whether HIV and vasculitis are causally or coincidentally related. A polyarteritis nodosa (PAN) like necrotizing vasculitis is described to involve 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 and in the absence of specific therapy amputation might be required

Suggested reading

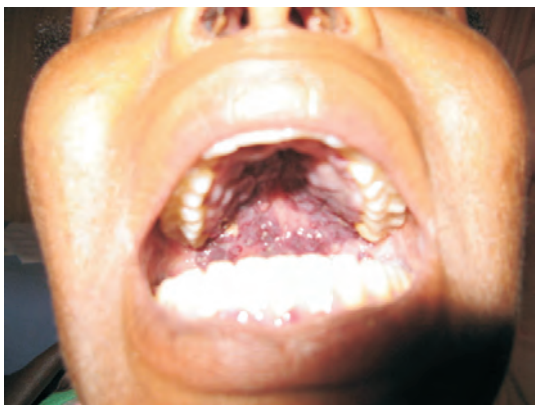
R Chetty: Vasculitides associated with HIV infection. J Clin Pathol 2001;54:275-278
Dube et al: Effects of HIV and antiretroviral therapy on the heart and vasculature. Circulation 2008, 118:e36

Case 42

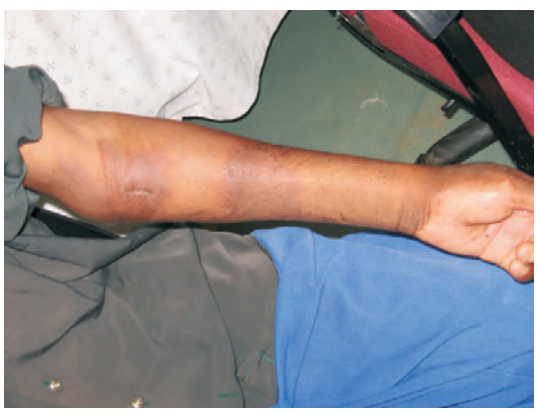
Case presentation

A 28-year old woman was seen in the cough clinic. She complained of haemoptysis for three months, fevers and night sweats. She was losing weight and this was clearly documented on her clinic card. 6 weeks ago she was started on TB treatment. She was HIV positive but has a CD4 of 272 cells/µl and was considered non-eligible for ARVs. She had TB in 2002.

Her mouth was examined and the following was seen:



She goes on to have a biopsy of another lesion which confirms the diagnosis



Questions

1) What is the most likely diagnosis?
2) What is the aetiology?
3) What implications are there for her HIV management?
4) What is the prognosis?

Diagnosis: Kaposi's sarcoma

Answers

1+2) Kaposi's sarcoma is associated with human herpes virus 8 (HHV-8). In South African adults the seroprevalence approaches 40%. In Europe the seroprevalence is significantly lower at 5%. Modes of transmission are still to be fully elucidated. The incidence of clinical disease has increased dramatically in the face of the HIV epidemic and KS is now the most common cancer in men in Africa.

3) KS is a WHO stage 4 condition and the patient requires ART irrespective of CD4 count. ART is also an essential part of treatment for KS

4) Patients with biopsy confirmed KS (lymph node, skin, palatal etc) are referred to a tertiary referral centre for treatment. Patients can be treated with radiotherapy irrespective of their CD4 if they have severe obstructive lesions, sight threatening lesions or isolated fungating lesions.

However, if the patient has skin lesions the CD4 must be over 180 before they will be considered for chemotherapy. Current treatment in KZN is with ABV (doxorubicin, bleomycin and vincristine infusions) once a month for 3 to 6 month months and oral etoposide.

The following table indicates completion and response rates

	Response	Complete	Partial	Progressive
HAART	77 %	17 %	59 %	24 %
HAART + ABV	88 %	44 %	44 %	12 %

Key learning point

KS may be revealed, or may become worse with immune constitution after starting ART

Suggested reading

Dedicoat M, Vaithilingum M, Newton RR: Treatment of Kaposis sarcoma in HIV-1 infected individuals with emphasis on resource poor settings Dedicoat Cochrane Database 2001
HATIP #102 Kaposi's Sarcoma: A clinical review. www.aidsmap.com/cms1262263

Case 43

Case 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 frequency and duration during the course of the day. His HIV status was unknown.

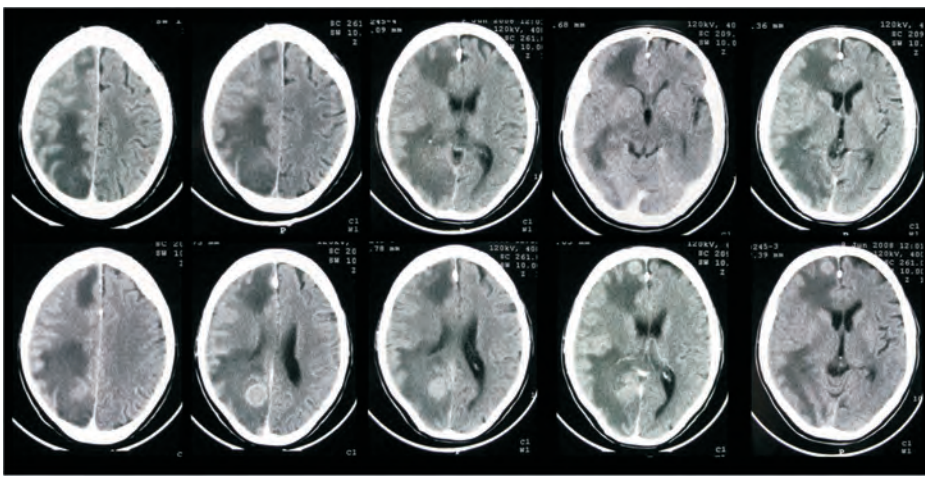
On examination he had persistent left upper limb and facial seizure activity and did not appear to be aware of his surroundings. He had nuchal rigidity but was afebrile and haemodynamically stable. The remainder of his physical examination was unremarkable. His blood sugar was normal.

The diagnosis of focal status epilepticus was made and three separate doses of 10mg 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 co-trimoxazole and fluconazole. A lumbar puncture was performed.

CSF- polymorphs	0 cells/μl	(normal <5)
CSF-lymphocytes	0 cells/μl	(normal <5)
CSF-protein	1.13 g/L	(normal 0.15-0.4)
CSF-glucose	2.58 mmol/L	(normal 2.7-4.1)
Crypto Ag and India Ink: negative		(normal negative)

An HIV test was positive and 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 investigations 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 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 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. They 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 and 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 3 months of 2 tabs bd. Patients usually respond to treatment within 2 weeks, 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 and is available in the public sector.

Outcome and follow up

He was transferred to the high care unit. The following day he was alert, with a GCS of 15, and was requesting discharge but he was kept in the ward. He remained stable and subsequently had a CT scan. It demonstrated two round ring-enhancing lesions in the right parietal and frontal lobes with marked associated oedema. The presumed diagnosis was toxoplasmosis, although tuberculomas remained 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 suspected toxoplasmosis

Case 44

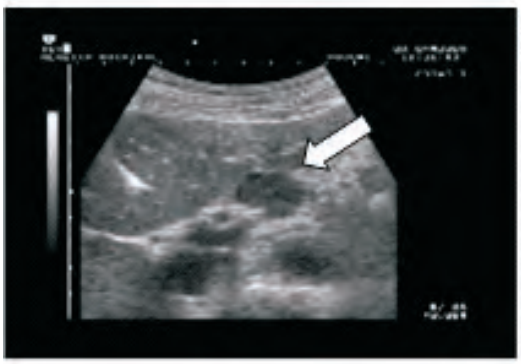
Case presentation

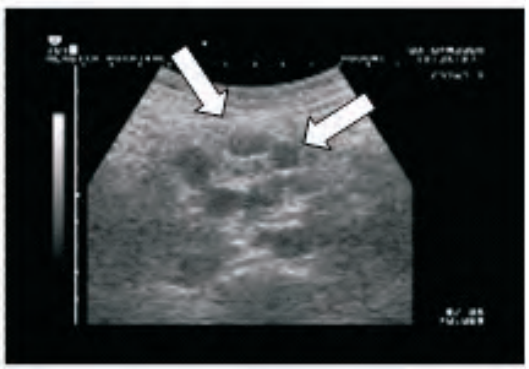
A 22-year old female patient was admitted to the medical ward with abdominal pain and distention. Additionally she complained about hiccups. She reported intermittent diarrhoea and to have lost “a lot of weight”.

On examination, her abdomen was tender without peritonitis. Her blood investigations were normal except for anemia (Hb 7.1 g/dL).

She tested HIV positive and her CD4 count was 23 cells/μl.

She was sent for abdominal ultrasound: a small amount of ascites and multiple enlarged lymph nodes (max. 3.5 cm) were found in the periportal and para-aortic area.





Questions

1) What is the most probable diagnosis? What are the differential diagnoses?
2) Which further diagnostic steps would you attempt?
3) How would you treat her?

Diagnosis: Abdominal Tuberculosis

Answers

1) *Mycobacterium tuberculosis* infection is by far the most common cause of abdominal lymphadenopathy in HIV infected patients in our setting. Alternative diagnoses include lymphoma, infections with Mycobacteria other than tuberculosis (MOTT) and Kaposi's sarcoma.

2) In a high prevalence setting no further diagnostic steps need to be taken and patients can be treated with anti-TB treatment and followed clinically, including monitoring weight gain. In case of doubt, and if no clinical improvement is observed, ultrasound guided biopsy of the nodes is the easiest 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 month of four anti-tuberculosis drugs (RHZE) followed by four month of two drugs (RH) additionally pyridoxine should be given. In this patient it is important to start her additionally on CTX prophylaxis and multivitamins.

Outcome and follow up:

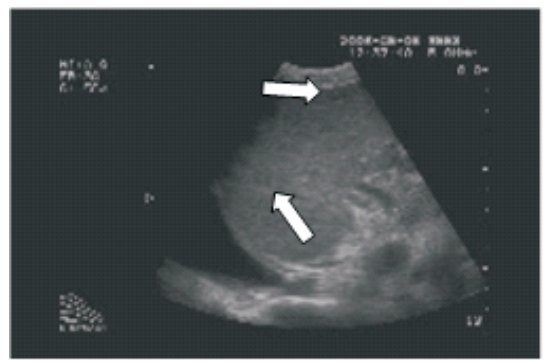
The patient was started on RHZE and CTX prophylaxis which she tolerated well. She was discharged after 3 days and was referred to her nearest clinic were she started ART treatment lessons and initiated D4T/3TC/EFV after 4 weeks. Her abdominal pain and tenderness had subsided; she still reported intermittent diarrhoea which was treated symptomatically.

Comments

Ultrasound is the fastest and easiest way to diagnose abdominal lymphadenopathy. As most HIV patients, especially with abdominal or disseminated TB are slim, the image quality is usually very good. Typically free abdominal fluid is found, the spleen might be mildly enlarged and show hypoechoic (2-10mm sized) lesions. Larger lymph nodes (>5 cm) as well as infiltrations into the liver point more towards lymphoma and should be biopsied initially.

Small hypoechoic lesions in the spleen are frequently seen in patients with disseminated TB. In this case a pleural effusion on the right is noted.

The free fluid can be aspirated and usually shows an exudate with lymphocytic predominance. AFB stain of the ascites is usually negative, culture may grow mycobacteria, but it is positive in only a minority (approx 20%) of cases.



Key learning point

Significant weight loss (in the absence of pulmonary symptoms) should prompt abdominal ultrasound, as abdominal TB is a frequent finding in HIV patients

Suggested reading

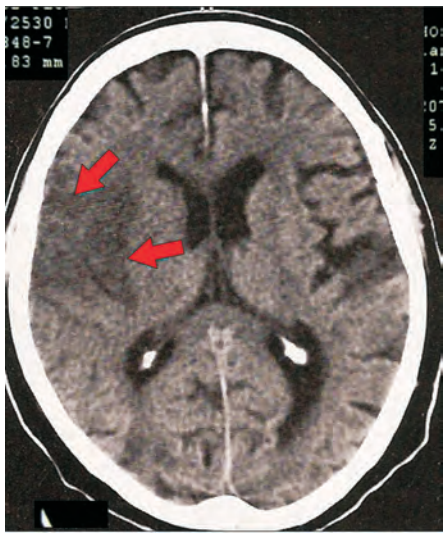
Monill-Serra JM et al.: Abdominal ultrasound findings of disseminated tuberculosis in AIDS. J Clin Ultrasound 25 (1997):16

Case 45

Case presentation

A 23-year old HIV positive patient was seen in the clinic with a left hemiparesis affecting mainly her face and arm. She had normal blood pressure, normal blood sugar and was overweight. Her CD4 count was 59 cells/μl and she was ART naive. She was transferred to hospital. A lumbar puncture revealed a minimally elevated protein but was otherwise unremarkable.

She 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 she be treated?

Diagnosis: Stroke in HIV patient, presumably HIV vasculopathy

Answers

1) A hypodense lesion 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 summarizes the causes of ischemic strokes in HIV patients in South Africa:

Opportunistic infections	28%
Tuberculous meningitis	*15 %*
Meningovascular syphilis	*5%*
Varicella zoster vasculitis	*5%*
Cryptococcal meningitis	*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 compared to HIV negative stroke patients. Intracerebral haemorrhages are rare and are mainly due to hypertension.

3) Antiplatelet therapy (aspirin 150 mg od) is indicated as in other cases of ischemic stroke. Additionally the patient needs to be started on ART as the CD4 count is low. We would also consider initiation in patients with CD4 counts higher than 200 cells/μl as many of the causative infections are HIV stage 4 diseases. Additionally ART might reduce the extent of the vasculopathy.

Outcome and follow up:

There was no sign of toxoplasma infection, syphilis serology was negative and she was diagnosed as a case of ischemic stroke due to presumed HIV vasculopathy. Aspirin 150 mg od was prescribed, additionally she was started on D4T/3TC/EFV. The neurological deficit improved but a facial paralysis remained visible even after a few months.

Comments

HIV associated cerebral vasculopathy has been reported as 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%). This is often asymptomatic and 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 in non HIV infected patients

Suggested reading

Tipping B et al: Stroke in patients with human immunodeficiency virus infection. J. Neurol. Neurosurg. Psychiatry 2007;78;1320-13

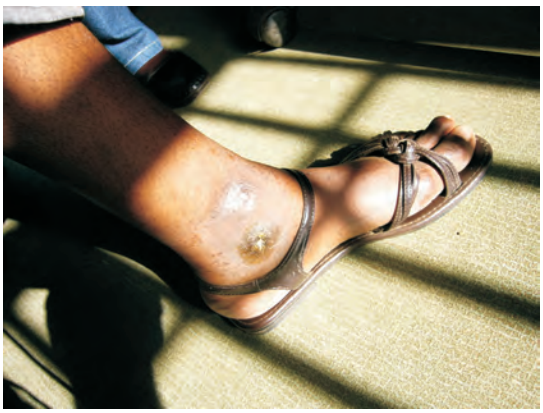
Case 46

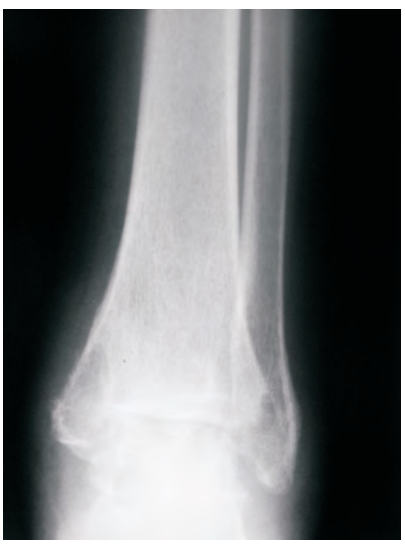
Case presentation

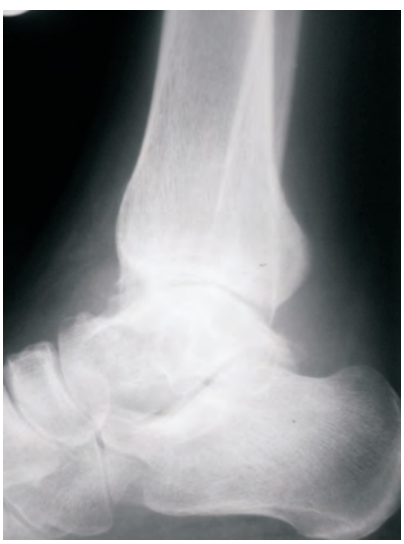
A 36-year old patient presented in the clinic with longstanding pain in the left ankle which prevented her from walking normally.

The ankle was slightly warmer than the contralateral joint and swollen without overlying erythema. The skin showed signs of a previous fistula and she reported that pus-like discharge had come out a few months previously. She was HIV positive and her last CD4 count was 787 cell/μl. She was not taking ART.

She was sent to the hospital for an x-ray of the ankle.







Questions

1) What does the x-ray show and what is the differential diagnosis?
2) What would be your next diagnostic steps?

Diagnosis: Osteomyelitis, most probably caused by TB

Answers

1) The x-rays of the ankle show demineralization in the distal area of the tibia as well as the fibula. This suggests a chronic pathological process, most probably infectious osteomyelitis. Neoplastic growth could be an alternative explanation but the distribution in two bones makes it improbable.

2) A diagnostic biopsy (bone biopsy) should be performed and sent for histology as well as for bacterial and mycobacterial culture.

Outcome and follow up:

The patient had a bone biopsy. The sample was sent for histology; the microbiology sample was lost during transport. Histology showed necrotizing 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 6 weeks. The patient improved substantially after 2 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 till diagnosis is long and ranges from 12 to 36 months. Limitation of movement and joint swelling are commonly seen. Chronic sinus formation is reported in 25-50% of patients. Constitutional symptoms are absent in more than half of the patients. RHZE for two months followed by RH for 4 months is standard treatment.

In this case the patient was not initiated 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.

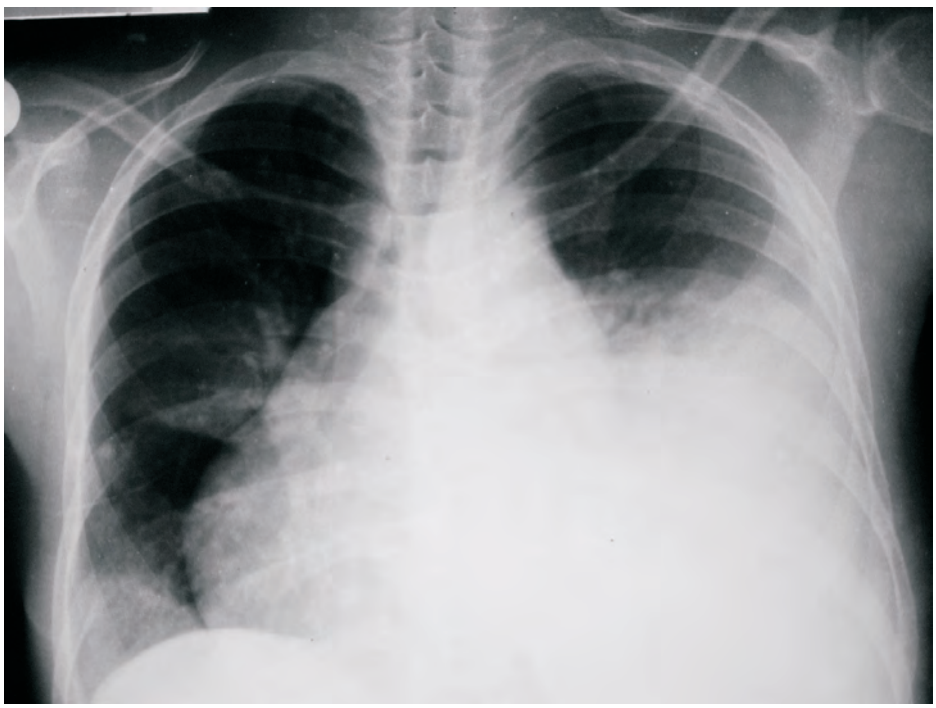
Key learning point

In this setting extrapulmonary TB is common and can be seen in patients with relatively well preserved CD4 counts and also in HIV-negative patients

Case 47

Case presentation

A 26-year old woman presented to hospital with a three week history of progressive dyspnoea on exertion, and lower limb oedema. She denied cough, fevers, night sweats or loss of appetite. She had no previous history of TB or TB contact at home. She had tested HIV positive during her recent pregnancy and had a CD4 count of 356 cells/μl. She was four weeks post-partum. On examination, she was not unwell looking and 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 probable diagnosis?
2) What other readily available investigation would be useful in this setting?
3) How should this patient be managed?
4) What is the prognosis of this condition?

Diagnosis: Postpartum cardiomyopathy (PPCM)

Answers

1) Postpartum cardiomyopathy is the most likely diagnosis given that she is 4 weeks post partum. Other possibilities include HIV cardiomyopathy, autoimmune disease, alcohol and other infections.

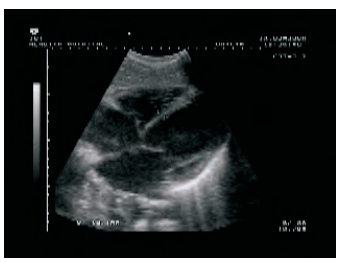
2) An ultrasound of the heart is the most important investigation to rule out pericardial effusion as a cause of cardiomegaly and increasing cardiac failure. The ultrasound in her case showed a grossly dilated heart, the left ventricle showed only minimal contraction (extremely reduced left ventricular function).

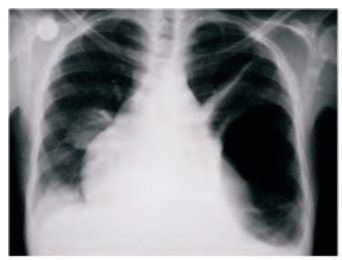
3) The medical management of patients with PPCM is similar to that for other forms of heart failure. ACE-I are usually used to reduce afterload by vasodilation; during pregnancy hydralazine is used instead. ß blockers are used to prevent arhythmmias and sudden death. Digoxin, is safe during pregnancy and may help to maximise contractility. Diuretics are used to reduce the preload as needed. Because of the high risk of thromboembolism the use of heparin is indicated.

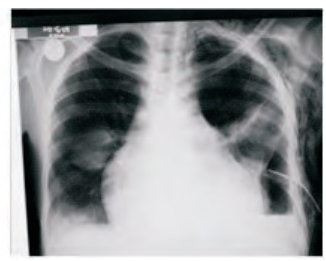
4) In a single centre prospective study of 100 South African patients with the condition, 15% died, and only 23% recovered normal left ventricular function after 6 months of treatment. Subsequent pregnancy after a diagnosis of PPCM carries high risk of relapse.

Outcome and follow up:

The pleural effusion was tapped and sent for routine biochemistry showing a transudate. The patient was then sent home with furosemide 20 mg od (which in retrospect was a low dose). One month later the patient re-presented with worsening shortness of breath. A repeat CXR showed a large pneumothorax most probably secondary to the pleural tap, and a chest drain was inserted. The pneumothorax resolved, however the patient developed significant sub-cutaneous emphysema which caused her considerable pain. She was commenced on enalapril and increasing doses of furosemide. In the following period, despite increasing doses of furosemide and added spironolactone, the patient continued to suffer from increasing peripheral oedema and shortness of breath. She became progressively hypotensive and died 3 weeks after admission.







Ultrasound of the heart: all four chambers massively dilated

Comments:

Risk factors associated with postpartum 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 reading

Sliwa K et al: Peripartum cardiomyopathy, Lancet 2006, Vol 368: 687

Case 48

Case 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. She had been treated for TB 2 years previously. A CXR showed bilateral patchy changes consistent with active TB and she commenced RHZES. She had an HIV test which was positive. Two weeks later she returned to the staff clinic complaining of increasing fatigue, lethargy, ongoing fevers and a tremor. She denied headache at this stage. Her CXR was unchanged, and it was felt she may have had a superimposed pneumonia. She was admitted to the TB ward. Her CD4 count result was 42 cells/μl. Whilst on the ward, she complained of dizziness and hearing loss, which was presumed to be a side effect of streptomycin and the dose frequency 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 denied headache.

Her CSF revealed

CSF-lymphocytes	88 cells/μl	(normal <5)
CSF-chloride	105 mmol/L	(normal >120)
CSF-protein	2.16 g/L	(normal 0.15-0.4)
CSF-glucose	1.94 mmol/L	(normal 2.7-4.1)
Crypto Ag and India Ink: negative		(normal negative)

She was prescribed steroids in addition to TB treatment. Unfortunately, she did not receive them, as all forms of steroid were out of stock. Two days later the doctor was called to the ward because she was having seizures. She was given diazepam, 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 in the early hours of the following morning. One month later her sputum culture and sensitivity results returned, showing 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 which may have contributed. Firstly, she lived and worked a high risk environment in an area with extreme high TB and HIV prevalence. She did not know her HIV status prior to becoming ill, and even then was extremely reluctant to test. 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 and therefore the results were only received after she had died. Steroids are an integral part of management of TB meningitis but stock outs of essential medications are a frequent issue in resource poor settings.

   When the seizures started there was a long delay in the administration of diazepam, as many wards are not equipped and trained to respond quickly to emergencies. The recommended management for status epilepticus is to anaesthetise and ventilate the patient, a management that is not possible in our setting.

2) Health care workers must be encouraged to know their HIV status and seek prompt medical care. This will remain a challenge while the fear and stigma associated with HIV persist. Strategies to reduce occupational exposure to TB must be employed. These include prompt identification and treatment of TB cases, maintaining good ventilation on wards, and personal protective equipment for staff.

3) All TB re-treatment cases and poor responders to first treatment should have sputum sent for TB culture and sensitivity. South African national guidelines suggest that also all HIV positive patients with suspected TB should have sputum culture and sensitivity. Current laboratory techniques mean that it will take approximately 6 weeks to have sensitivity results. New PCR methods exist and are able to speed this process up, but they are not yet widely available.

Comments:

TB is probably the most common acquired occupational illness in health care professionals. Nursing students have an extremely high tuberculin skin test conversion rate (12.5 conversions per 100 person years in a study from Zimbabwe). This underlines the importance of a practical infection control plan that should be 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 of 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 to protect them as much as possible from nosocomial TB. Some institutions have expanded access to ART to their positive staff by initiating treatment at higher CD4 counts.

Key learning point

Every health care worker should be encouraged to know and regularly check their HIV status

Suggested reading

WHO: Tuberculosis infection control in the era of expanding HIV care and treatment 2007, Addendum to "WHO guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings", 1999. http://whqlibdoc.who.int/hq/1999/WHO_TB_99.269_ADD_eng.pdf

Case 49

Case presentation

A 45-year old HIV positive man presented to clinic having been on ART (D4T/3TC/EFV) for one year. His baseline viral load was 1,500,000 copies/ml and CD4 count was 33 cells/μl. He had made a significant improvement clinically and his recent viral load was <25 copies/ml. He came into clinic limping in pain.

For the past three months he 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 finger tips.

On examination, glove-and-stocking distribution of sensory neuropathy was found. There was also reduced joint position sensation to the ankles but otherwise 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: 1) Sensory peripheral neuropathy most likely caused by stavudine

Answers

1) PNP most likely due to D4T

2) In addition to what is given in the history, you should establish whether the symptoms started prior or after ART to establish HIV related polyneuropathy.
se of other concurrent medications should be investigated.
soniazid 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 it 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 also cause it and is the alternative drug to co-trimoxazole used in opportunistic infection prophylaxis. The composition of traditional medications is not known but heavy metal ingestion can cause neuropathy and 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 can cause polyneuropathy.
Vitamin B12 deficiency is frequent and 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 of Vitamin B12 (high cell turnover). IM vitamin B12 injections are available. Finally, history of other concomitant illnesses should be sought especially diabetes mellitus.

3) A full blood count revealing a macrocytic anaemia can indicate vitamin B 12 or folate deficiency, though it should be noted that antiretroviral therapy (mainly AZT, to a lesser extent d4T) can cause a macrocytosis. Random or fasting glucose can be checked to screen for diabetes.

Comments

Stavudine therapy 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 with gradual increase up to 100 mg at night until symptom relief.

If symptoms cause grade 3 or 4 toxicity (see table) and other potential causes of neuropathy have been excluded, an application for replacement of D4T can be made. It is important to remind the patient that they should not stop their current therapy whilst waiting for the replacement. The replacement drug available at present is AZT. FBC should be monitored whilst the patient takes this drug. Incidence of AZT associated anaemia, however is less frequent than D4T associated sensory neuropathy.

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 unless necessary.

Key learning point

Peripheral neuropathy is extremely common and is often multifactorial. Treatment is essentially symptomatic and switching of ART should be reserved for severe cases.

Suggested reading

National Department of Health South Africa: National antiretroviral treatment guidelines 2004

Case 50

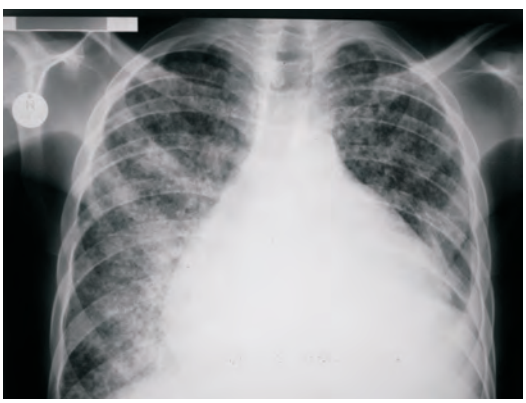
Case presentation

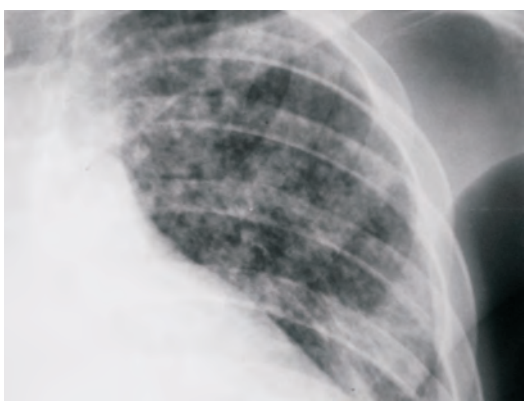
A 23-year old male patient was admitted to the ward with progressive loss of weight, fatigue and increasing shortness of breath.

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.

FBC:		
Hb	10.8 g/dL	(normal 11.5-16.5)
WBC	5.6 $10^3/mm^3$	(normal 4.0-11.0)
Plt	220 $10^3/mm^3$	(normal 150-500)
U&E and LFT:		
Na	135 mmol/L	(normal 133-153)
K	3.8 mmol/L	(normal 3.0-5.0)
CO2	25 mmol/L	(normal 22-33)
Crea	60 μmol/L	(normal 62-120)
BUN	5.1 mmol/L	(normal 3.5-6.5)
TBIL	16.2 μmol/L	(normal 3.0-17)
DBIL	1.0 μmol/L	(normal 0.0-3.0)
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 for AFB stain and TB culture. The diagnostic yield of AFB is low in patients with miliary TB (around 25%), but culture is positive in a bigger proportion (approx. 2/3 of patients). The differential diagnosis of a miliary pattern includes other infections and malignancies. Histoplasmosis, PCP, as well as hematogenous 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 profit 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 by ultrasound steroids (prednisolone 60mg for one week followed by 30 mg, 15 mg and 5 mg for the consecutive weeks) were added. The patient improved clinically surprisingly quickly. His HIV test was positive and his CD4 count was 122 cells/μl. He was discharged and started ART in the clinic after 2 month of TB treatment.

Comments:

Classically miliary nodules are approx 1-2 mm in diameter, are numerous and diffusely distributed. It is more frequently seen in HIV positive patients. To confirm the diagnosis microbiologically is often difficult, sputum cultures might be used. Bronchoscopy with lavage is an option, which 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.

If the patient has hematological changes (cytopenias) bone marrow aspiration and culture has a good diagnostic yield. Liver biopsy for culture is another option, although invasive and thus not done regularily.

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

Key learning point

Miliary TB involves haematogenius spread of mycobacteria and is therefore a multi system disease.

Case 51

Case presentation

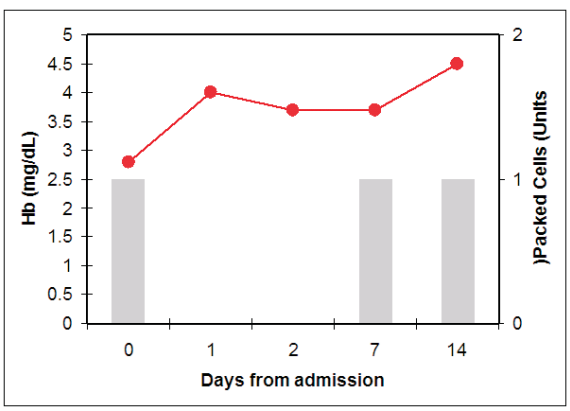
A 36-year old woman was referred from her GP with profound anaemia. She was HIV positive and had commenced ART 3 months previously. She was on D4T/3TC/EFV and had also been taking CTX. She complained of a severe frontal and occipital headache which had commenced 2 weeks prior to admission. She was comfortable 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	31pg	(normal 27-32)
WBC	12.2 $10^3/mm^3$	(normal 4.0-11.0)
Plt	308 $10^3/mm^3$	(normal 150-500)

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



Questions

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

Diagnosis: Severe anemia 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 might even have negative effects!)
-sideroblastic anaemia (mainly caused by INH in the absence of Vit. 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 anemia (malaria, autoimmune hemolytic anemia due to drugs or infection, microangiopathic anemia (thrombotic thrombocytopaenia purpura-TTP and hemolytic uremic syndrome-HUS). Inherited haemolytic anaemias like 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) Drug history. Lab investigations including as appropriate: FBC and blood film, vitamin B12, folate, iron, ferritin, malaria screen, faecal occult blood test, parvovirus B19 serology. If all these investigations show no explanation it is advisable to contact a haematology department and do a bone marrow aspiration (often EBV, CMV and HBV serology will be requested by the haematologist so this might be done before contacting them). Available imaging studies will include a CXR and ultrasound.
If a bone marrow aspiration is done, additional material should be taken for parvovirus B19 PCR and mycobacterial culture.

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 1g/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 an elevated ferritin and reduced iron, so iron supplements were stopped. Vitamin B12 and folate levels were normal. She received transfusions over the following period, her ART was continued. She left the hospital before a bone marrow examination could be done and was lost to follow up.

Comments:

Thrombocytopaenia is another frequent hematological abnormality which occurs in 5-40 % of patients. It is important to consider impaired thrombopoiesis due to bone marrow infiltration (e.g. TB) or drug toxicities.

Key learning point

Anaemia of chronic disease is characterised by low iron and raised ferritin and is unresponsive to iron supplementation

Case 52

Case presentation

A 35-year old female patient came to the clinic for a disability grant form. She reported that she was weak and tired and had been vomiting and nauseated for the past four weeks. On examination she had severe oral candidiasis. On reviewing her file it was found that she started ART in June 2005 and had been taking TB treatment at the time of ART initiation. Her CD4 counts and viral loads are as shown;

Date	03/04/2005	03/12/2005	12/07/2006	01/05/2007	22/01/2008
CD4	98	159	161	183	66
Viral Load	530,000	950	No result	8,000	50,000

Questions

1) What do these results and the 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 suggest abovementioned diagnosis. Current opportunistic infection should be treated (probably oesophageal candidiasis, treated with 2 week of oral fluconazole 200mg). Step-up adherence counselling should be initiated and second-line ART should be ordered (AZT/DDI/LPV/r).

Outcome and follow up:

This patient was treated for oesophageal candidiasis, which improved her vomiting. She was well at the time of starting AZT/DDI/LPV/r and after 3 months had a suppressed viral load (<25copies/ml).

Comments

Treatment failure is defined as failure to suppress viral load to undetectable levels in spite of adequate levels of antiretroviral drugs in the blood. This has to be carefully differentiated from poor compliance, where there is a detectable viral load because the patient either takes the treatment 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 the development of OI or malignancy occurring 3 or more months after initiation

The department of health guidelines on testing of viral loads and identification of those who should be switched to second-line therapy are as follows

- **VL rebound 400-5000copies/ml, step up adherence and repeat in 6 months.**
  - If still 400-5000 continue adherence and repeat in 6 months
  - If >5000 and adherence > 80%, switch to second line
- **VL >5000copies/ml repeat in 3 months after step up adherence**
  - If <400 return to 6monthly monitoring
  - If 400-5000 continue stepped up adherence and repeat in 6 months
  - If >5000 despite stepped up adherence switch to second line therapy if adherence >80%

HIV produces 10 billion viral copies of itself per day in untreated individuals. The replication process is prone to errors and 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 develop. Development of resistance to some drugs is relatively easy (mutation to allow class resistance to the NNRTIs requires only one base pair substitution). Adherence to lifelong antiretrovirals is difficult and often poor adherence is poorly recognised and 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 resistance

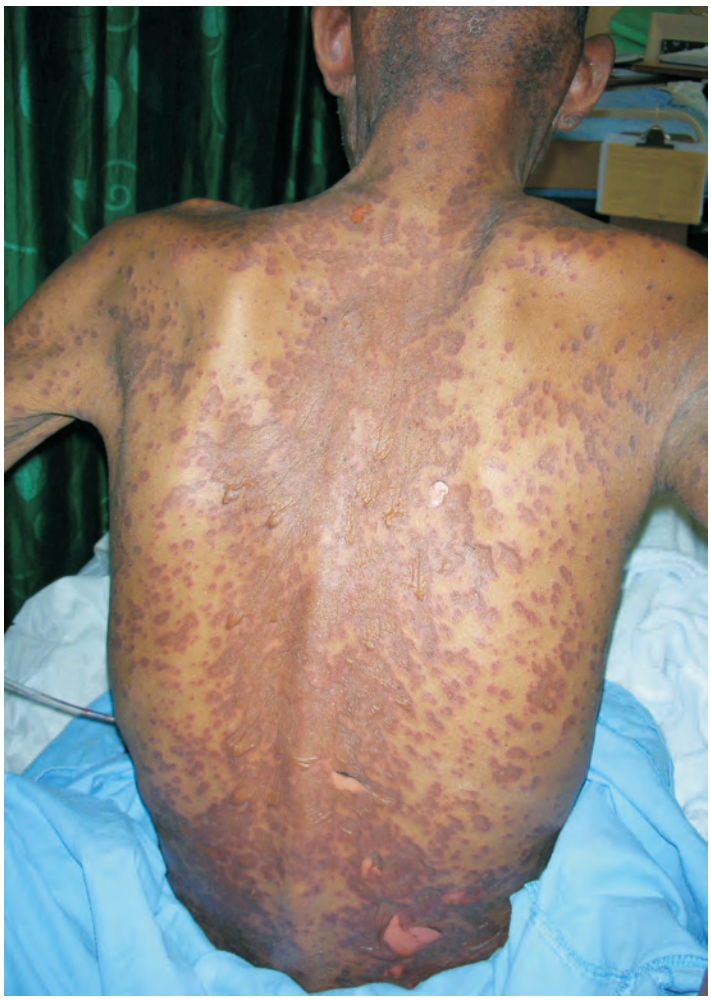
Key learning point

Laboratory monitoring is important: detectable viral load whilst on ART needs to be acted upon

Case 53

Case presentation

A 43-year old man presented to OPD with a few day history of a blistering rash which began on his face, then spread to his torso, arms and legs. The rash was neither painful nor pruritic. He did however report painful eyes with discharge. The patient was HIV positive, with an unknown CD4 count. Four months prior to presentation he had been diagnosed with TB on clinical grounds and was commenced on RHZE. He 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: Toxic epidermal necrolysis (TEN)

Answers

1) Fixed drug eruption or toxic epidermal necrolysis (TEN). TEN produces large area of skin necrosis followed by blistering and stripping of the skin layers as seen in severe burns. If mucosal surface are involved the term Stevens-Johnson Syndrome (SJS) is used.

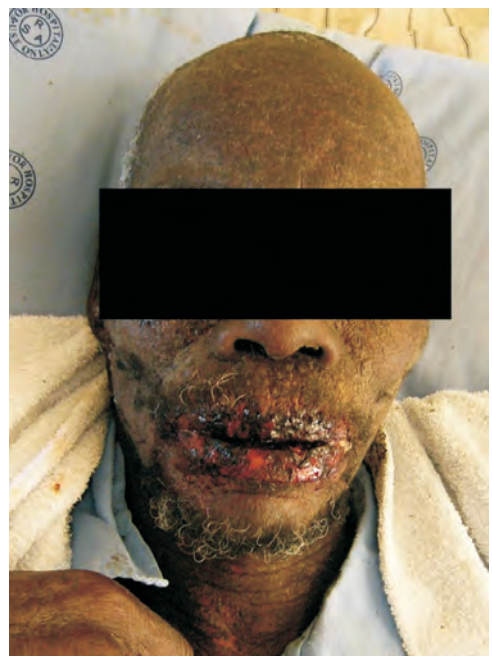
2) The most common causes of drug rashes are CTX, penicillin, anti-TB drugs and ART, especially NVP and EFV. Non-steroidal analgesics as well as antiepileptic drugs should also be considered as possible cause. Most cases occur within the first two months of therapy; this case was unusual in that it developed after four months but no other cause could be identified.

3) Stop all medications !! Careful fluid management If possible oral fluid replacement is preferable as it prevents adhesions in the oropharynx, consider eye care with ointments and saline eye washes. Analgesia before daily bathing and dressing change (non-stick dressings or dressing towels and soft barrier cream, soaking off in bath). Antibiotics are not used prophylactically but are used if signs of infection appear. Routine use of steroids is not recommended.

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 occur.

Outcome and follow up:

The patient was managed on the ward, and recovered slowly. A decision was made not to recommence the TB therapy as it was felt that the risks of a repeated reaction out-weighed the benefits of treating a TB infection diagnosed on soft clinical indicators.
The patient's CD4 count was found to be below 50 and prior to discharge he had commenced ART (D4T/3TC/EFV) as well as prophylactic CTX, with no complications. He was discharged 3 weeks later to be followed up in the clinic; he did not develop TB symptoms.



Comments

Drug reactions are far more common in HIV infected patients than in the general population, in particular reactions to TB drugs. 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 and, in this setting, CTX is the most common cause followed by TB drugs and ART

Case 54

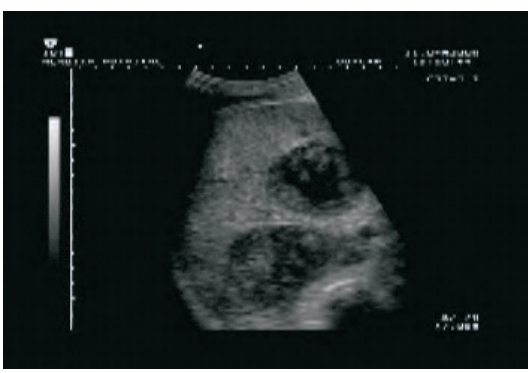
Case presentation

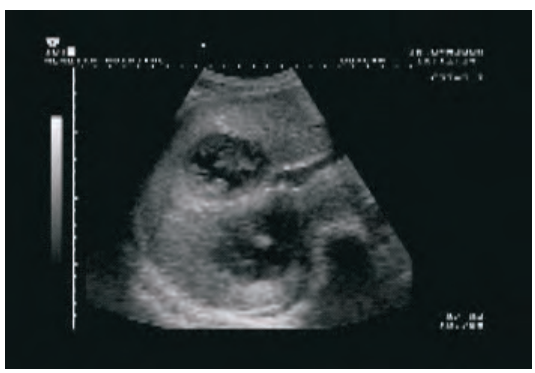
A 40-year old HIV negative man was seen in the hospital with right upper quadrant pain. He had no fever, no diarrhoea, and no other complaints.

On examination the patient looked generally unwell; diffuse abdominal tenderness without peritonism was found. The liver seemed enlarged on palpation.

FBC:		
Hb	13,1 g/dl	(normal 11.5-16.5)
WBC	12.2 10^3/mm^3	(normal 4.0-11.0)
Plt	308 10^3/mm^3	(normal 150-500)
U&E and LFT:		
Na	138 mmol/L	(normal 133-153)
K	3.4 mmol/L	(normal 3.0-5.0)
CO2	28 mmol/L	(normal 22-33)
Creat	75 μmol/L	(normal 62-120)
Urea	5.2 mmol/L	(normal 3.5-6.5)
TBIL	7.2 μmol/L	(normal 3.0-17)
DBIL	1.2 μmol/L	(normal 0.0-3.0)
GGT	112 U/L	(normal 7-62)
ALP	231 U/lL	(normal 42-121)
ALT	58 U/L	(normal 10-60)

An abdominal ultrasound was performed:





Questions

1) What do you see on the ultrasound images and what is the differential diagnosis?
2) What would you expect to find in the CXR?
3) Which tests would you order and 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 probable diagnoses are amoebic and pyogenic liver abscess. Echinoccocal cysts and necrotic liver tumors (necrotic metastases) are far less probable differential diagnoses.

2) An elevated right hemi-diaphragm, possibly with a small (sympathetic) pleural effusion are compatible with a liver abscess.

3) One option is to aspirate 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 and enthusiastic search might produce a result which 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 the patients 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 than came back to hospital and reported felling better but still had mild pain. In the follow up ultrasound the abscesses appeared similar in size, the content was found to be less echogenic. To rule out other diseases one of the collections was punctured and aspirated, anchovy-sauce material was found which was found sterile on bacterial culture. The metronidazole treatment was continued for two further weeks. Diloxanide furoate or paromomycin were not available at this time, so no bowel eradication treatment was 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, they are more common in adults than in children, more common in males than females. In animals substantial necrosis is induced 5 to 7 days after arrival of the amoeba in the liver, explaining the abrupt onset in previously healthy individuals. The abscesses are round shaped and more commonly in the dorsal segments of the right lobe of the liver.

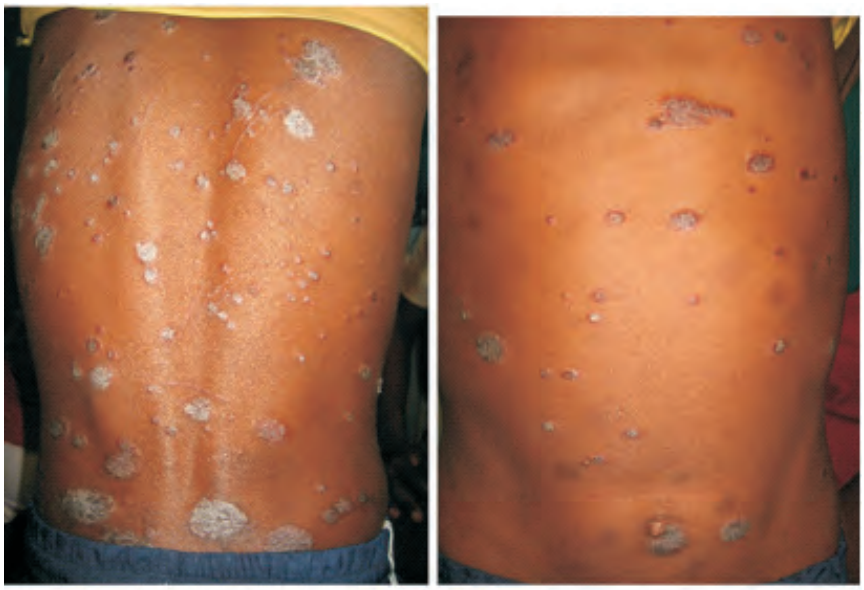
Key learning point

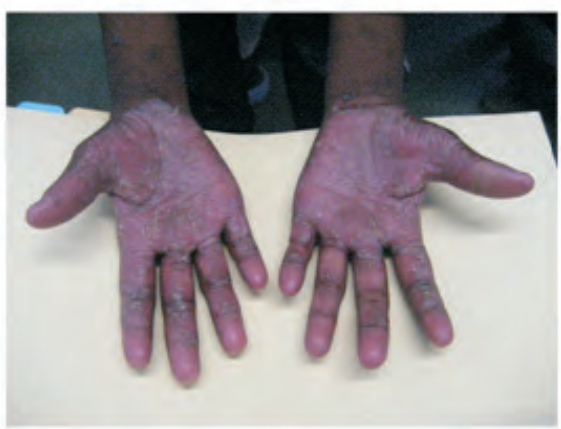
If an elevated right hemi-diaphragm or small right pleural effusion are found, an abdominal ultrasound should be performed to look for liver (or subphrenic) pathology

Case 55

Case presentation

A 12-year old boy, who was recently diagnosed with HIV was brought to the clinic by his grandmother with itching skin lesions. The lesions were most pronounced on the patient's back as well as on the palms, but other areas were also affected. The scaly lesions were slightly elevated and showed erythematous borders. He was otherwise healthy and his CD4 count was 138 cells/μl.





Questions

1) What is the diagnosis?
2) What is the differential diagnosis of scaling itching skin lesions in an HIV positive patient?
3) How can they be treated?

Diagnosis: De-novo psoriasis in HIV infection

Answers

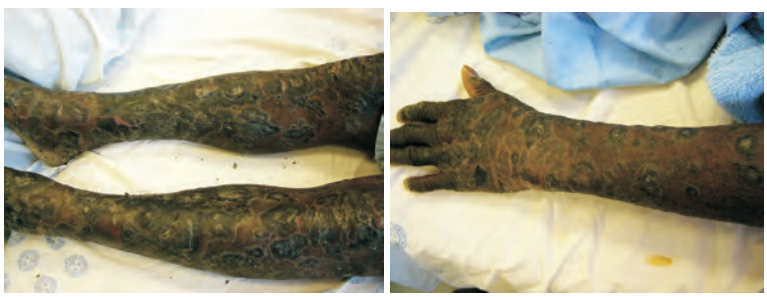
1) Psoriasis

2+3) The most frequent itching, scaling skin diseases in HIV patients and their treatment are

a) Tinea (fungal infection): clotrimazole topical tid for 2 weeks (or nystatin or Whitfield's ointment as available), if extensive griseofulvin 0.5-1g od for 3 weeks can be given
b) Psoriasis: 2% salicylic acid cream topical, alternatively steroid cream (e.g. hydrocortisone cream)
c) Seborrhoeic dermatitis: often no treatment indicated if mild disease. In severe cases use steroid cream (e.g. bethamethasone valproate)
d) Scabies: 25% benzyl benzoate lotion for 24 h, might be repeated after 72 h with washing of bed linen
e) Ichthyosis: skin moisturisers, if available urea 5% preparations, vaseline

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. Additionally baseline FBC, U&E and LFT were ordered with the aim of starting the on ART (his CD4 was < 200 cells/μl). After 2 weeks he returned to the clinic, the lesions were unchanged and treatment for psoriasis with salicylic acid cream was started. At the same time D4T/3TC/EFV were initiated. The boy was seen a few weeks later when he applied for a social grant, the lesion had substantially improved and he did not complain about itchiness.



Pre-existing psoriasis can deteriorate in HIV infection as seen in this different patient with severe generalised psoriasis.

Comments

The prevalence of psoriasis in HIV disease has been reported as approximately 13% of HIV-positive individuals. Associated arthritis seems to be more common and in general the disease is more severe than in non-infected persons (Fig 2). Guttate psoriasis, in form of multiple rain-drop 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. Preexisting psoriasis may undergo severe exacerbation in HIV disease, and psoriasis is reported to become more severe with progression to AIDS. HIV associated psoriasis was found to respond to ART.

Key learning point

Fungal skin infections are by far the most common disease and should be considered as the first and most probable diagnosis.

Suggested reading

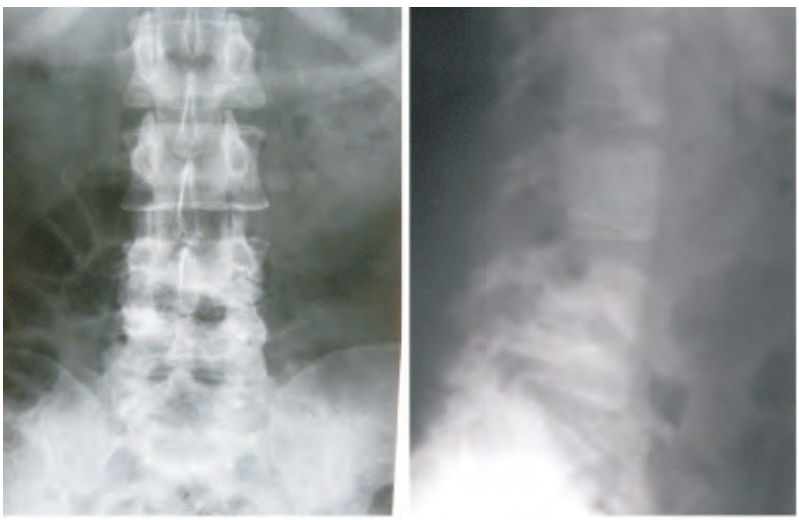
Mallon E, Bunker CB: HIV-associated psoriasis. AIDS Patient Care STDS 2000, 14(5): 239-46

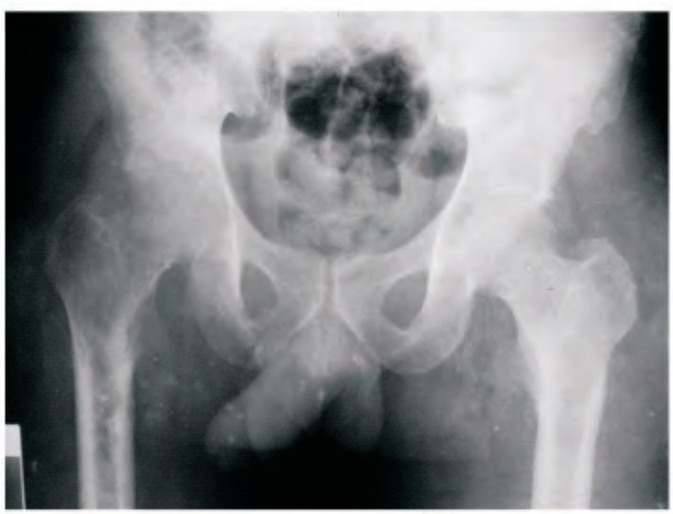
Case 56

Case presentation

A 34-year old HIV negative man presented with 2 weeks of worsening right hip pain and increasing inability to walk, on a background of one year of hip pain. He had been diagnosed with spinal TB 4 years previously.

X-rays of his pelvis and his spine were done.





Questions

1) What do the X-rays show?
2) Which further investigations would you order?
3) How would you treat the patient, especially with respect to his former episode of TB spine?

Diagnosis: TB of the spine and right hip

Answers

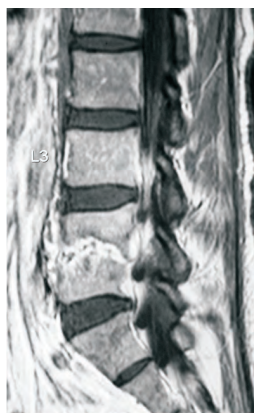
1) Spine: destruction of L4/L5 vertebrae with osteolysis and reactive osteosclerotic changes in the vertebrae
   Pelvis: destructive arthropathy of the right hip joint with obliteration of the hip joint space and associated severe osteopaenia of the femur.

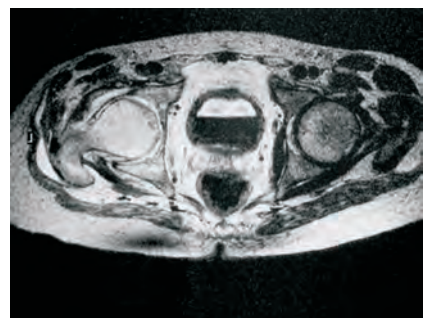
2) As it is unclear to what extent the changes are a consequence of the former TB infection or active disease (no previous x-rays available) an MRI might be helpful to differentiate. In case of doubt it may be necessary to perform a biopsy.

3) The patient should be started on TB treatment as he has clinically signs of progressing TB disease, compared to the relatively stable period during 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 five months of RH.

Outcome and follow up

A diagnosis of TB spine and hip was made and RHZES was started. He responded quickly to TB treatment and simple analgesia (NSAIDs), and was walking with the aid of a walking stick within two weeks. An MRI of his lumbar spine and left femur confirmed the active TB infection.





Comments

This case demonstrates the difficulty to assess radiological changes if 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 has often to be based on the clinical presentation.

In extrapulmonary TB, a further problem is the difficulty in obtaining samples for microbiological investigation. Most cases have to be treated empirically without mycobacterial culture posing a difficulty 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 57

Case presentation

A 31-year old male patient was brought to the clinic in a wheelbarrow by his relatives. He was unable to walk due to progressive weakness of his lower limbs. He was cachectic and HIV infection was suspected.

On examination he 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 for further investigations and treatment to the hospital ward.

Questions

1) What is the differential diagnosis of paresis of the legs, especially considering his absent reflexes?
2) What investigations should be done?

Diagnosis: Inflammatory demyelinating polyneuropathy

Answers

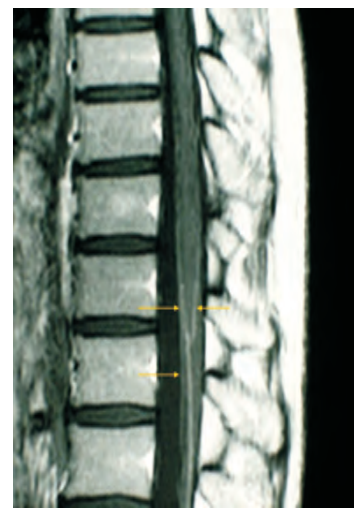
1) Tuberculosis of the spine is in our experience the most common cause of paresis of the legs in HIV patients. Due to pressure on the spinal cord it frequently shows spastic features and increased reflexes.
Human T-cell lymphotrophic virus 1 (HTLV -1), a retrovirus similar to HIV, causes a chronic spastic 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 causes spinal syndromes/ progressive polyradiculopathy. It 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 a 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 as well as the loss of sensations (temperature, touch) dominates 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 investigations, imaging (MRI) of the spine

Outcome and follow up

The patient was admitted and a conventional x-ray of his lumbar spine was done which showed no abnormality. His FBC showed a mild normocytic anemia, his U&E and LFTs were normal. A lumbar puncture was done which showed a mildly elevated protein only (CSF-protein 0.51 g/l, normal 0.15-0.4)

Empirical therapy with vitamin B complex and vitamin B1 was started. Additionally he started prophylactic CTX (2 tabs od) as his CD4 count was found to be 37 cells/µl. An MRI of the spine was done, it showed signs of leptomenigeal enhancement characteristic of inflammatory demyelinating polyneuropathy. Steroids were prescribed (60 mg od for 1 week, then 40 mg od, 20 mg od, 10 mg od for the consecutive weeks). He was discharged and seen 2 weeks later in the clinic. By this time he was able to walk with a stick and reported general improvement. ART was initiated.



MRI shows 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 diagnosis

Suggested reading

McGuire D: Neurologic Manifestations of HIV, HIV InSite knowledge base chapter, June 2003 http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-04-01-02

Case 58

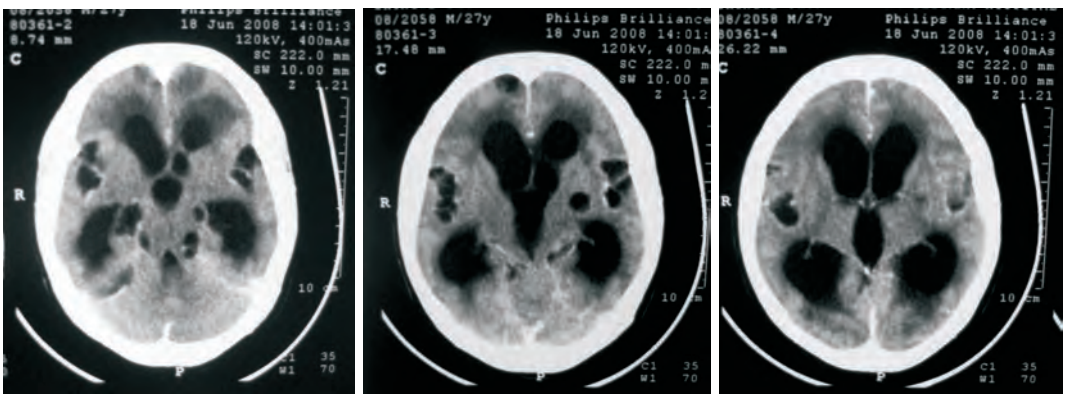
Case presentation

A 30-year old woman presented with a 2 week history of confusion, headache and seizures. Her HIV status was unknown. As no family was available to consent no HIV test was performed but there was concern that she might have HIV infection.

A lumbar puncture revealed:

CSF- polymorphs	0 cells/μl	(normal <5)
CSF-lymphocytes	18 cells/μl	(normal <5)
CSF-protein	0.9 g/L	(normal 0.15-0.4)
CSF-glucose	1.3 mmol/L	(normal 2.7-4.1)
Crypto Ag and India Ink:	negative	(normal negative)

The presumptive diagnosis of TB meningitis was made and she was commenced on RHZE, in addition to prednisolone and anticonvulsants. She failed to improve and CTX was added to cover for Toxoplasma infection. Eventually the family was reached and consented to HIV testing, which was negative. A CT brain was ordered, which revealed multiple cystic lesions.



Questions

1) What is the likely diagnosis and what is the pathophysiology?
2) 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, and 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) Cysticercosis can be treated with albendazole 15 mg/kg od for 30 days or praziquantel 15 mg/kg tds for 21 days. During treatment and for a week or two after there might be increased headache due to the immune reaction around the dying cysts. Dexamethasone is an adjunctive treatment to control the inflammatory reaction and can be routinely given for two weeks. Neurosurgical assistance should be sought in hydrocephalus.

Outcome and follow up:

The patient was diagnosed with neurocysticercosis and commenced high dose steroids and albendazole. Neurosurgical intervention was planned to relieve her obstructing hydrocephalus but she died before transfer.

Comments

Humans can be the intermediate host of *Taenia solium*. Light peripheral infections causes few symptoms. The worm encysts in muscle and subcutaneous tissue. Small swellings (< 1cm) beneath the skin and calcified nodules in the skeletal muscle (years later) are the findings.

Key learning point

In an HIV-negative individual with focal neurological symptoms or signs, the threshold for brain imaging should be low

Suggested reading

Carpio A. Neurocysticercosis: an update. Lancet Infect Dis 2002; 2: 751

Case 59

Case presentation

A 42-year old female HIV positive patient with a CD4 of 201cells/μl, presented with jaundice and anorexia, without abdominal pain or vomiting.

Three weeks previously she had been diagnosed with pleural TB and had been commenced on RHZE. She was also taking CTX but no other medications.

Prior to commencement of TB treatment her baseline creatinine was 68 μmol/L(normal 62-120) and ALT was 16 U/l (normal 42-121).

On admission, investigations revealed acute renal failure, hyperbilirubinaemia, mild hepatic injury and normal INR. Her hemoglobin was low 6.3 g/dl (normal 11.5-16.5). HBsAg was negative. The liver appeared normal at ultrasound.

Creat	213 μmol/L	(normal 62-120)
TBIL	297.7 μmol/L	(normal 3.0-17)
DBIL	178 μmol/L	(normal 0.0-3.0)
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 hyperbilurubinaemia)

Answers

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 is also well described.

Immune mediated complications including haemolytic anemia, acute interstitial nephritis and glomerulonephritis with renal failure and respiratory failure (often together) have been described with rifampicin. Immune-mediated thrombocytopaenia has also been reported.

Fortunately these complications are rare but mandate immediate discontinuation 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 hemoglobin) due to rifampicin was suspected. All medications were stopped and IV fluids were given. The hyperbilirubinaemia rapidly resolved, but renal function remained impaired until discharge. She was discharged and it was planned to see her in the clinic but the patient was lost to follow up.

Summary table of investigations

Day	Creat	Urea	TBIL	DBIL	ALT
0	68	3.4	13.4	3.4	16
21	213	13.2	292.7	178.8	87
27	404	18.4	140.9	80.6	40
29	441	21.6	129.1	71.2	32
34	514	29.2	84.6	44.4	25
38	329	22.9	53.1	28.9	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 described. 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

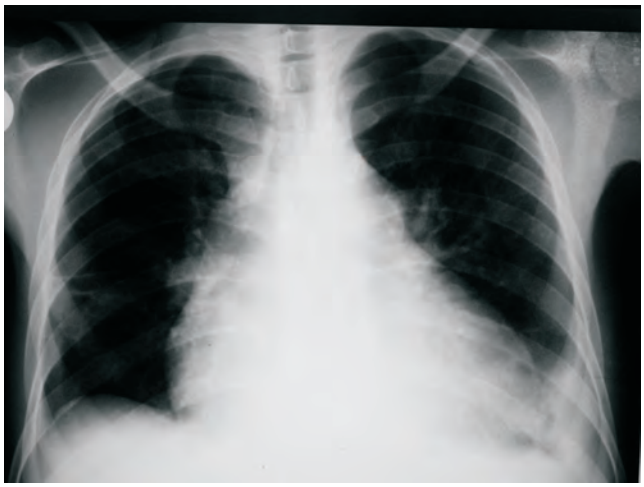
Suggested reading

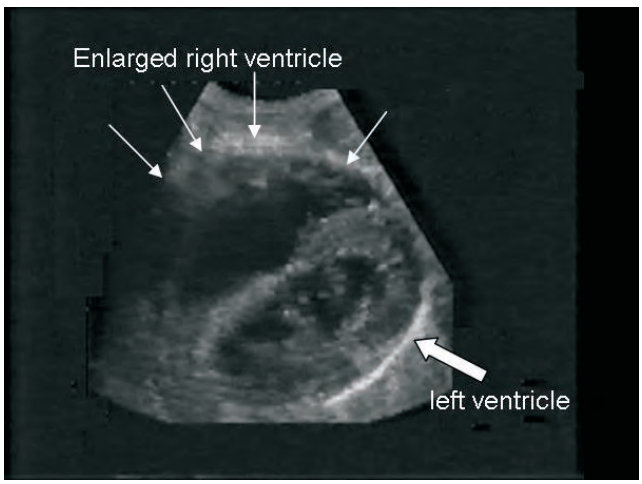
Covic et al. Rifampicin-induced acute renal failure: a series of 60 patients. Nephrol Dial Transpl 1998; 13: 924

Case 60

Case presentation

A 28-year old man who had recently tested positive for HIV with a CD4 count of 149 cells/μl, presented with shortness of breath, abdominal distension, and swollen legs. On examination he was tachypnoeic, with distended jugular veins, loud pan-systolic murmur loudest over the tricuspid valve, ascites, pulsatile hepatomegaly and peripheral oedema. CXR showed 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 investigated and treated further?

Diagnosis: Right heart failure due to pulmonary hypertension secondary to chronic thromboembolic disease

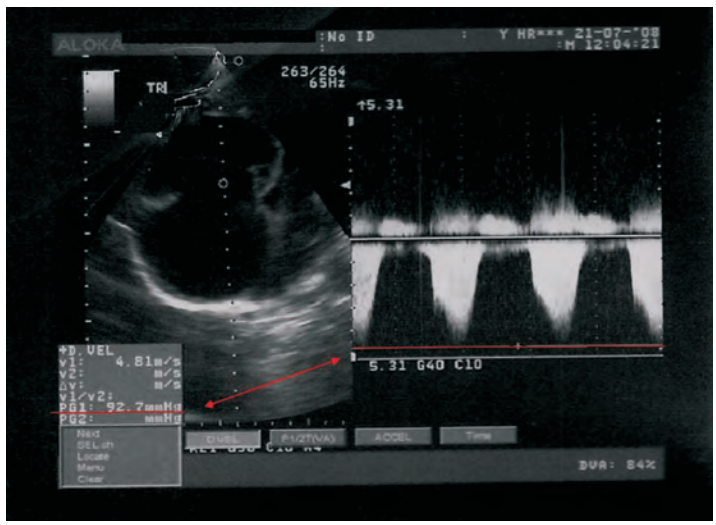
Answers

1) The causes of pulmonary hypertension and right sided heart failure are many and varied, but can be grouped into (not specific to HIV positive patients):
   a) Group 1 PH "Pulmonary arterial hypertension (PAH)". Idiopathic pulmonary hypertension and diseases of the pulmonary muscular arterioles, including HIV
   b) Group 2 PH "Pulmonary venous hypertension". PH due to left atrial, left ventricular, or left valvular heart disease.
   c) Group 3 PH "Pulmonary hypertension associated with disorders of the respiratory system or hypoxemia", e.g. interstitial lung disease and chronic obstructive pulmonary disorder.
   d) Group 4 PH "Pulmonary hypertension caused by chronic thrombotic or embolic disease".
   e) Group 5 PH PH caused by inflammation, mechanical obstruction, or extrinsic compression of the pulmonary vasculature (eg, sarcoidosis)

2) As mentioned above, HIV per se is a cause of pulmonary hypertension, nonetheless it is important to exclude reversible causes.

Outcome and follow up:

The patient was sent for a formal echocardiogram at our referral hospital, which confirmed the findings. His pulmonary pressure was measured 102 mmHg (!). He was then referred for high resolution chest CT scan. This revealed multiple small pulmonary emboli. He was commenced on warfarin, additionally ART was started.



Comments:

The incidence of thromboembolic disease is higher in HIV infected individuals, particularly in more advanced disease

Suggested reading

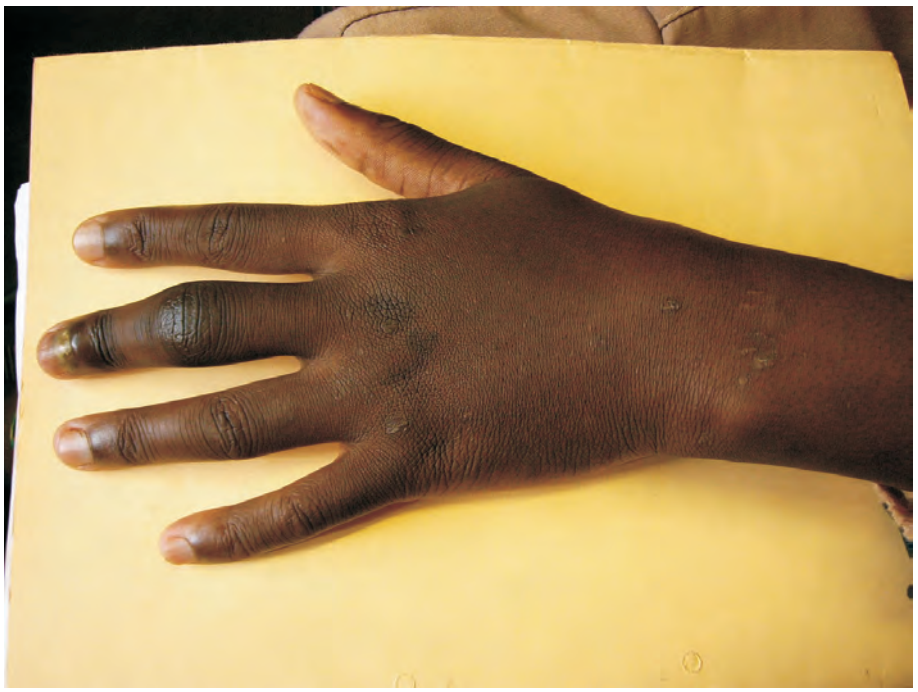
Barbarinia, G, Barbaro, G. Incidence of the involvement of the cardiovascular system in HIV infection. AIDS 2003; 17 Suppl 1:S46.

Case 61

Case presentation

A 16-year old woman who was recently diagnosed HIV positive was seen in the clinic complaining of painful joints. Her CD4 count was 120 cells/μl and she had started training sessions before 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 on 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 pains with signs of inflammation (swollen, warm joints) can be due to infectious or inflammatory causes. Mono-articular involvement points more towards infectious causes, oligo- and polyarticular disease more towards inflammatory diseases.
   Main causes of oligo/polyarthritis are:
   - Reiter's syndrome
   - Psoriatic arthritis
   - HIV associated arthritis
   - Rheumatoid arthritis
   - Gout (can be secondary to pyrazinamide)

2) Dactylitis = sausage finger frequently seen in reactive forms of arthritis

3) Psoriatic arthritis: change of skin and nails
   Reiter's syndrome: Urethritis and conjunctivitis

4) Symptomatic treatment with nonsteroidal antiinflamatory drugs (NSAIDs) is the approach of choice in this patient. Disease modifying drugs (e.g. methotrexate) are rarely indicated and anyway difficult to provide in a rural setting. In severe cases temporary treatment with steroids might be indicated, carefully balancing the immuno-compromising effect of the drug in already immunosupressed patients with the treatment benefits.

Outcome and follow up:

Diclofenac 25 mg bd and paracetamol 1g qds were prescribed for the patient. After 1 week the arthritis had not improved and the patient became unable to walk so the diclofenac dose was increased to 25 mg tds. After another week the patient used a wheelchair due to the pain in the ankle. A course of prednisolone (40 mg od for 1 week, then tapered to 10 mg over the next 2 weeks) was administered. She significantly improved with this treatment and was kept on prednisolone 10 mg od plus diclofenac 25 mg bd which was issued for 4 weeks. She initiated ART (D4T/3TC/EFV) and collected her ART in the following months but did not seek attention for further arthritis treatment.

Comments:

A seronegative arthritis distinct from 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 seen. 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, and should not be withheld even in HIV patients with low CD4 counts.

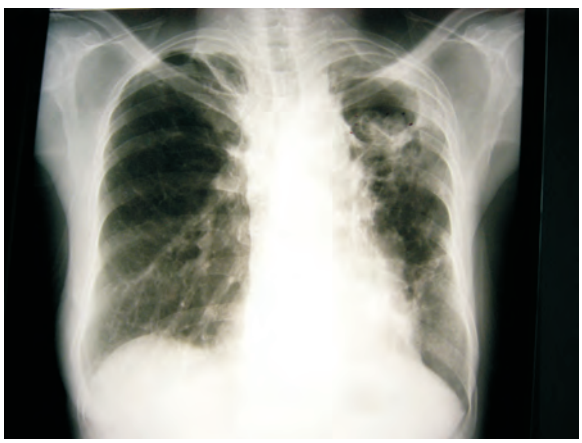
Suggested reading

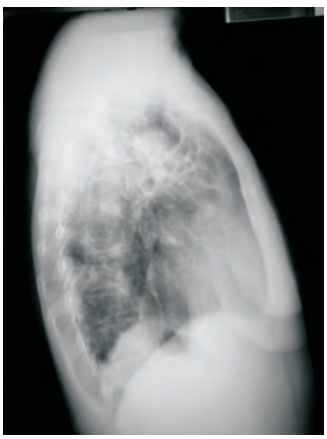
Reveille JD The changing spectrum of rheumatic disease in human immunodeficiency virus infection. Semin Arthritis Rheum, 2000, 30: 47-66

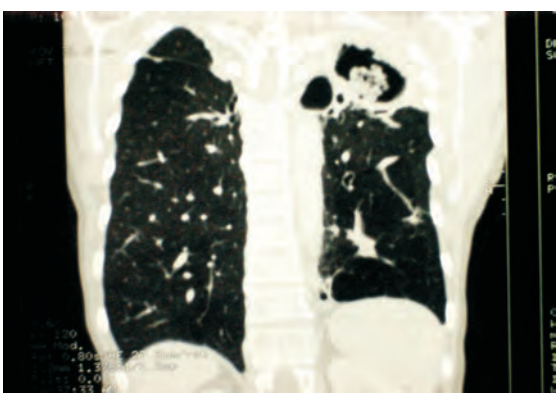
Case 62

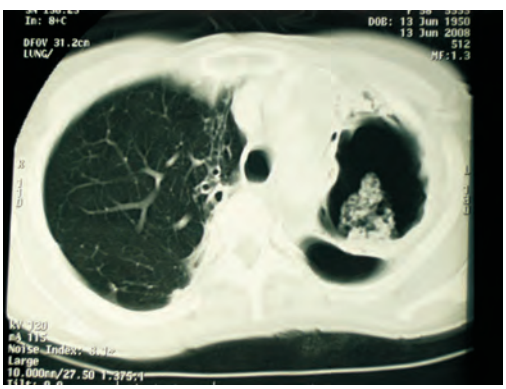
Case presentation

A 57-year old female presented with a 6 week history of cough, haemoptysis, and chest pain. She had no significant weight loss or night sweats. She had been diagnosed HIV positive in 2006 and a recent CD4 count was 563 cells/μl. Her relevant past medical history included pulmonary tuberculosis treated in 1999 and treated hypertension. Sputum microscopy for AFB was negative and she had no improvement with a course of amoxicillin. CXR and subsequently CT thorax were performed.









Questions

1) Describe the appearances on 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 (as *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 this condition.

Outcome and follow up:

Sputum culture for TB was negative. However, having seen a private physician, she was commenced on RHZE to treat possible chronic pulmonary TB. Her family then requested a second opinion from another private physician and 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 past history of pulmonary tuberculosis. Common sequelae of pulmonary TB included 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. 25-50% of patients with pulmonary aspergilloma have a past history of pulmonary tuberculosis. Often the mycetoma is asymptomatic but chronic cough and haemoptysis 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 had a high rate of morbidity and mortality attached 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

1) Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest* 2002; 121:1988-1999

2) Kim HY, Song K, Goo JS et al. Thoracic sequelae and complications of tuberculosis. *Radiographics* 2001; 21: 839-858

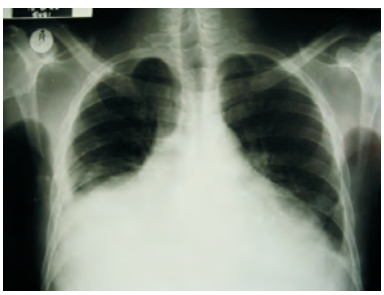
Case 63

Case presentation

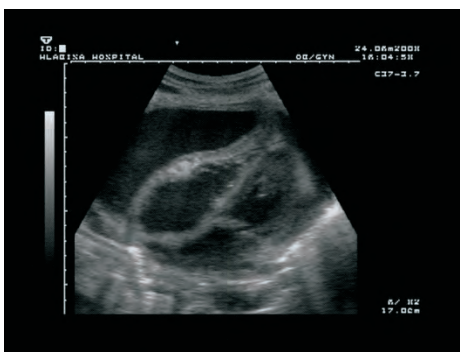
A 38-year old was referred from clinic with a 2-week history of being generally unwell with cough, dyspnoea, chest pain, fever and weight loss. He was newly diagnosed with HIV and his CD4 count was 55 cells/μl. He had no previous history of TB and no household contacts. A course of amoxicillin from the GP had not alleviated his symptoms. On examination he was distressed with a respiratory rate of 36/min, BP of 109/75 mmHg, and heart rate of 109/min, temperature of 37.4C. Breath sounds were diminished at both lung bases, the right base was dull to percussion to the midzone, heart sounds were muffled, and abdomen was soft and non-tender.

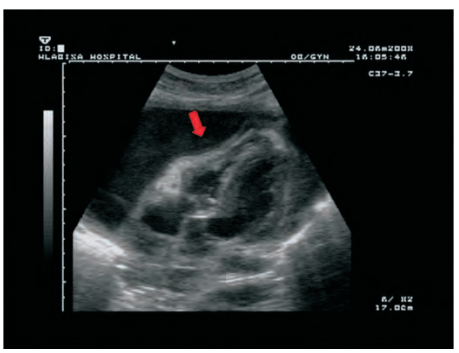
He had several raised tender violaceous plaques on his legs and trunk, and a purple plaque on his hard palate.

Presumptive diagnosis of disseminated Kaposi Sarcoma had been made in the clinic, with possible superimposed bacterial infection, and/or PCP. He had been commenced on ceftriaxone and high-dose CTX.



CXR demonstrating 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 abdominal free 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 ?HHV-8) superinfected with *S. typhi*

Answers

1) Tuberculosis, HHV-8 disease, lymphoma, viral infection

2) Pericardiocentesis is an invasive procedure and should be reserved for cases with large effusions (to make it safe) and hemodynamic 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 to use ultrasound to guide the procedure (if available).
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:

He was transferred to the high care unit and emergeny pericardiocentesis was performed using a conventional central IV line. 1200 ml of green-brown thick fluid with a sulphurous odour was aspirated and sent for cytology, microscopy, AFB stain, 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. He was continued on high dose ceftriaxone, and commenced on TB treatment and metronidazole to provide anaerobe cover. PCP treatment was stopped. The right pleural effusion was drained of 1.3 l of bloodstained serous fluid.

He 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 atrium or ventricle collapse. Bacterial culture on the pericardial fluid grew *Salmonella typhi*, antibiotics were changed (after 14 days of ceftriaxone) to ciprofloxacin 750mg twice daily. He remained on TB treatment. The patient requested discharge two weeks later and was followed at the clinic. Over the next weeks his general state deteriorated and he was eventually lost to follow up and presumed dead.

Footnote: Results for investigations on the pericardial and pleural fluids eventually returned, but showed no evidence of malignancy, the pericardial fluid consisted of an acute inflammatory milieu. AFB stains and TB cultures were negative. Skin biopsy from the leg showed Kaposi's Sacoma.

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.

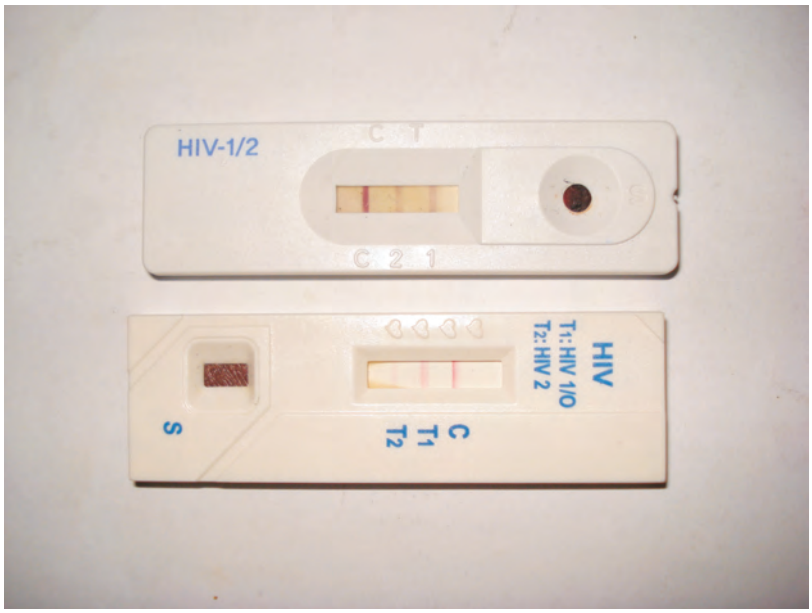
Key learning point

Bacterial superinfection of fluid collections is common and cover with broad spectrum antibiotics is indicated

Case 64

Case presentation

A 40-year old lady was seen accompanied by the HIV counsellor. The counsellor was confused and upset by the VCT results and presented the rapid tests.



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 faint band in 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 and can 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 centered around West Africa; cases are rare in South Africa where HIV-1 predominates. Countries with links 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 to AIDS defining illness (some suggest 10-20 years). Dual infection has also been reported, and these patients need to be treated for HIV-1 and 2. HIV-2 has a different structure to HIV-1 in 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 reading

British HIV Association: Guidelines for Antiretroviral Treatment of HIV-2 Positive Individuals, July 2008, http://www.bhiva.org/cms1222603.asp

Epilogue (for the overwhelmed doctor)

To correct a natural indifference I was placed half-way 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 at the same time.

Additionally, he 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 tuberculosis, incurable at this time, as he was bedridden for long periods. His plans, aspirations, dreams were changed by a disease and it moved him to embrace theatre and literature (thank tuberculosis for that). It is this same necessity to constantly adapt life according to your diseases and diseases of your family, that is exemplary for so many of our patients.

When working in the middle of a combined HIV/TB epidemic, definitely one of Camus' major works "The plague" comes to mind. In this he describes the Algerian city of Oran that is befallen by an epidemic of plague. "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 look at 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 he refuses "to surrender to a destiny that kills innocent children"(3).

The other of his books that needs mentioning is "The Myth of Sisyphus". It is a short philosophical essay which was 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 the final chapter he compares the absurdity of our life with the situation of Sisyphus, from the 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 of missing drugs, lacking equipment and missing administrative support, repeating the same advices and warnings over and over again and still see them suffering and dying might be overwhelming. Nevertheless we continue, also we might seem like Sisyphus. But as Camus concludes his essay, "the struggle itself toward the heights is enough to fill a man's heart. One must imagine Sisyphus happy."(2)

«Il faut se imaginer le docteur comme heureux».

1) www.wikipedia.com on Albert Camus accessed 10/7/2008
2) Albert Camus: Le mythe de sisyphe, Gallimard Paris 1942
3) Albert Camus: La peste, Gallimard Paris 1947

Abbreviations

3TC	lamivudine
ABC	abacavir
ACE-I	angiotensin converting enzyme inhibitor
AFB	acid fast bacilli
Ag	antigen
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
bd	two times per day
BMI	body-mass index
CMV	cytomegalovirus
CSF	cerebrospinal fluid
CTX	cotrimoxazole
CXR	chest x-ray
D4T	stavudine
DBIL	direct bilirubin
DDI	didanosine
DVT	deep vein thrombosis
EBV	Epstein-Barr virus
EFV	efavirenz
FBC	full blood count
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HIVAN	HIV associated nephropathy
HPV	human papilloma virus
HSV	herpes simplex virus
IM	intramuscular
INR	international normalized ratio
IV	intravenous
KS	Kaposi's sarcoma

LFT	liver function test
LP	lumbar puncture
LPV/r	lopinavir/ritonavir
MAC	mycobacterium avium complex
MDR-TB	multi-drug resistant tuberculosis
NHL	Non-Hodgkin's lymphoma
NVP	nevirapine
od	once per day
PCP	pneumocytis pnemonia
PHC	primary health care
PI	protease inhibitor
PMTCT	prevention of mother to child transmission
qid	four times per day
RH	rifampicin/isoniazid
RHZE	rifampicin/isoniazid/pyrazinamide/ethambutol
RHZES	rifampicin/isoniazid/pyrazinamide/ethambutol/streptomycin
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
VZV	varicella zoster virus
XDR-TB	extensively-drug resistant tuberculosis

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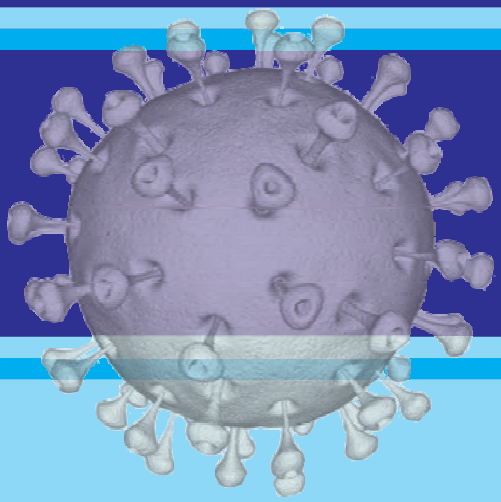

Supporting organisations

Centre for International Migration and Development

a joint operation of GTZ and the German Federal Employment Agency

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