CASE STUDY

EVALUATION OF FEVER OF UNKNOWN ORIGIN BEFORE STARTING ANTIRETROVIRAL THERAPY

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A 34-year-old woman tested HIV-positive in December 2005, and was referred to a specialist HIV unit in mid-January 2006. She had presented to her general practitioner with oesophageal candidiasis and a history of a cough and occasional loose stools since November 2005, with an 8 kg weight loss over the past 6 months. She had no history of other opportunistic infections or HIV-related conditions. On examination her temperature was 38.5°C and she had sinus tachycardia. Wasting, pallor and severe oral thrush were noted. There was no lymphadenopathy, hepatomegaly or splenomegaly, and the findings on respiratory examination were normal.

The patient refused admission and results of the following investigations were obtained as an outpatient: haemoglobin 6.9 g/dl (normocytic, normochromic), white cell count 5.56×10^9/l and platelet count 88×10^{11}/l. The CD4 count was 27 cells/µl (4.32%) and the viral load > 750 000 copies/ml. The serum albumin level was 22 g/l and the lactate dehydrogenase (LDH) level 3 116 U/l; levels of alanine aminotransferase (ALT), alkaline leucocyte phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) were within normal limits. Aerobic, anaerobic and mycobacterial blood cultures were negative. A bone marrow aspirate and trephine showed disordered erythropoiesis in keeping with retroviral disease. Histological examination of the trephine biopsy specimen showed no granulomas or signs of malignancy. The Coombs test was negative and the haptoglobin level was in the normal range. The chest radiograph was normal. The patient was given a blood transfusion which brought the haemoglobin level to 9.2 g/dl, and was treated with fluconazole.

Antiretroviral therapy (ART) was commenced with stavudine, lamivudine and efavirenz. Symptomatic peripheral neuropathy was detected 2 weeks later and the stavudine was replaced with tenofovir. Four weeks after starting ART the patient's condition deteriorated and she was found to be mildly confused, apyrexial and pale. A right-sided pleural effusion had developed. Aspiration of the effusion returned bloodstained fluid, cytological examination of which showed a high-grade plasma blastic non-Hodgkin's lymphoma. The patient was assessed by an oncologist but refused further treatment and subsequently died.

COMMENT

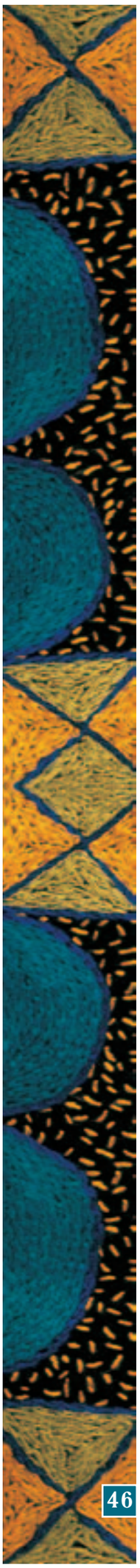
This case study encapsulates a clinical dilemma frequently encountered by South African HIV clinicians: a patient with advanced HIV disease presents for the first time with prominent constitutional symptoms; a careful evaluation for opportunistic infections is unrevealing; and ART is commenced. Within a few weeks of initiating ART a focal (and in this case fatal) disease process becomes apparent.

At issue here is how far the evaluation should be taken before ART is begun. The question becomes especially relevant in resource-constrained environments.

Diagnosing and treating opportunistic infections before starting ART is essential in order to reduce the possibility of immune reconstitution disease, and the likelihood of significant drug interactions.

Advanced HIV infection can cause fever and weight loss (constitutional symptoms) without underlying opportunistic infection. This is, however, a diagnosis of exclusion. The evaluation is best approached by considering the patient under the diagnostic label of fever of unknown origin (FUO). Typically, FUO is diagnosed using Durack's and Street's criteria:[1] temperature of 38.3°C or higher on multiple occasions over 3 days for inpatients or for more than 4 weeks for outpatients; failure to identify infectious organisms after at least 2 days of incubation of microbiological cultures; and a diagnosis that remains uncertain after 3 days despite appropriate investigation. In the South African context repeated temperature measurements can be difficult to obtain, and a history of fevers and chills or drenching night sweats persisting for more than 2 - 4 weeks is highly suggestive of FUO. Acute bacterial infections are unlikely to be confused with FUO owing to the abrupt onset of symptoms, presence of focal pain, and body fluids containing a predominance of neutrophils.

Various forms of tuberculosis are probably the most common cause of FUO in HIV-infected adults.[2] If cough is a prominent symptom at least 2 - 3 sputum specimens should be sent for staining for acid-fast bacilli.[3,4] The yield can be improved by



inducing sputum using an ultrasonic nebuliser and hypertonic saline[5,6] – if at all possible this specimen should be sent for mycobacterial culture. Other appropriate initial investigations would include a full blood count and white cell differential count, measurement of liver enzymes and C-reactive protein, urine analysis and a chest radiograph. Ultrasound of the abdomen and pericardial space is a useful technique with the potential to identify pericardial effusions, intra-abdominal lymph nodes, hepatic and splenic lesions, ascites and pelvic masses. The aim of the initial set of investigations is to detect a focal process that could potentially be the site of an opportunistic infection. Tuberculosis is compatible with pulmonary infiltrates (including micronodular, interstitial and airspace disease), pleural or ascetic exudates, pericardial effusion, mediastinal or intra-abdominal lymph nodes, or hypoechoic splenic lesions. Unfortunately, other infections and malignancies can present in a similar manner.

Mycobacterial blood culture is highly desirable if resources permit[7] (for example using the Bactec Myco/F Lytic bottle), as the technique has the potential to isolate bacteria, fungi and *Nocardia* as well as *Mycobacterium tuberculosis* and *M. avium* complex. However, the yield from urine culture in the context of advanced HIV can be as good as mycobacterial blood culture, and is less expensive.[6] If a blood or urine culture is requested the laboratory should be asked to use standard tuberculosis culture techniques for up to 6 weeks and to discuss all positive cultures with the clinician as 'contaminants' may be significant. The cryptococcal latex agglutination test performed on serum or cerebrospinal fluid rapidly confirms the diagnosis of *Cryptococcus neoformans* infection. Bone marrow biopsy is appropriate if a full blood count reveals bicytopenia or pancytopenia[8] and liver biopsy is appropriate if the cannalicular enzymes (ALP and GGT) are elevated. Biopsy of enlarged peripheral lymph nodes using either fine-needle aspiration or needle core can be helpful.[9] Biopsy specimens should be divided equally between normal saline for culture and formalin for histology.

It may be necessary to commence antituberculosis therapy without a definitive diagnosis being made. If this route is chosen a focal disease process compatible with tuberculosis must have been clearly identified and every effort should be made to send mycobacterial cultures before commencing therapy. Should the patient not show an objective response to therapy by 8 weeks an alternative diagnosis should be sought.[6]

The case study illustrates the propensity of ART-induced immune reconstitution to provoke diseases mediated by viral infections. Shingles (varicella zoster virus), condyloma accuminata (human papillomavirus), hepatitis due to the hepatitis B virus, and Kaposi's sarcoma (human herpes virus 8) can flare up in the months following successful initiation of ART.[10-12] In HIV-infected patients non-Hodgkin's lymphoma is closely associated with the Epstein-Barr virus and diagnosis shortly after ART has been initiated has been described.[13] Lymphoma-related B symptoms may have contributed to the patient's weight loss and fever. The management of HIV-associated malignancies differs from that of opportunistic infections as ART should be initiated as soon as the diagnosis is made in order to allow significant immune recovery before chemotherapy is started.

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