Clinico-pathological conference

Fever, weight loss, and night sweats: infection or malignancy?

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Case report (Dr A Winter)

A Peruvian man in his 30s was admitted as an emergency with a 3 week history of fluctuating temperatures and rigors, a worsening sore throat, and a 4 day history of non-bloody diarrhoea without significant abdominal pain. On further inquiry he denied respiratory, neurological, or urinary symptoms, but admitted to night sweats for the past 4 months and some 20 kg weight loss in the past year.

The patient had lived in the United Kingdom for 10 years. He had just arrived back from a 1 week cruise around the coast of Spain. He could not recall any insect bites and had not slept on land. Nine months before admission he had visited the coastal region of northern Peru and had made several previous visits to the Amazon basin without adequate antimalarial prophylaxis. He denied previous exposure to tuberculosis, smoked 20 cigarettes a day, and drank about 20 units of alcohol weekly. He lived with his regular male sexual partner of 5 years, but admitted to multiple male sexual partners in Spain in the 1980s. Ten months before admission he had presented to the genitourinary clinic with perianal warts but after counselling had declined an HIV test. He did not know the HIV status of any of his previous partners. Nine months before admission he had presented to his general practitioner with indigestion and was found to be seropositive for *Helicobacter pylori* with a normal upper gastrointestinal endoscopy.

Four months before this admission he had presented with an ischiorectal abscess which had required incision and drainage twice, yielding *Escherichia coli* on the first occasion, and a mixed growth of *Staphylococcus aureus* and *Bacteroides* on the second. A sterile pyuria had been noted on both occasions but had not been further investigated. Two weeks before admission he had undergone an anal stretch procedure for a fistula in ano and had subsequently received courses of flucloxacillin, ciprofloxacin, co-amoxiclav, and metronidazole.

On examination he was surprisingly well in spite of intermittent rigors. The temperature was 38°C, the pulse 100/min, and the blood pressure 140/75 mm Hg. He had mild oral candidiasis and oral hairy leucoplakia. There was a soft systolic ejection murmur. The liver was palpable 3 cm below the costal margin. The spleen and lymph nodes were impalpable. The perianal area was intact with no sign of an abscess. The respiratory and neurological systems were normal and there was no rash. Funduscopy revealed a small (and transient)

flame haemorrhage in the right eye but was otherwise normal. Oxygen saturation was 98% and did not fall on exercise.

The haemoglobin was 11.0 g/dl, total leucocyte count $2.9 \times 10^9/l$ (neutrophils $1.7 \times 10^9/l$, lymphocytes $1.0 \times 10^9/l$), and platelet count $144 \times 10^9/l$. The erythrocyte sedimentation rate was 99 mm in the first hour. The serum albumin was 28 g/l, and the alkaline phosphatase (ALP) was 482 IU/ml (normal 70–320) but the bilirubin and transaminases were normal. Serum creatinine was 84 ($\mu\text{mol/l}$). The urine contained more than 100 leucocytes/ml, red cells, and casts but was sterile.

The patient agreed to HIV testing and was found to be HIV seropositive. He was naturally immune to hepatitis B (HBsAg negative and total anti-HB core antibody positive) and seropositive for cytomegalovirus (CMV) IgG. Anti-CMV-IgM was detected but CMV DNA could not be amplified from the blood by polymerase chain reaction (PCR). Serological tests for toxoplasma (IgG and IgM), hepatitis C, hepatitis A IgM, syphilis, and parvovirus IgM were negative. He had serological evidence of past Epstein-Barr virus (EBV) infection, but was negative for IgM EBV viral capsid antibody and a Paul Bunnell test was negative. A test for serum cryptococcal antigen was negative.

No malaria parasites were found in multiple thin and thick blood films. The chest radiograph was normal. Nine sets of aerobic and anaerobic blood cultures were sterile. Five stool cultures were negative for pathogenic bacteria, cysts, and parasites (including cryptosporidium) and *C difficile* toxin. A perianal swab grew *Staphylococcus aureus* and *Candida*. The sputum grew *Candida* but no acid fast bacilli were seen. No pathogenic bacteria or viruses were isolated from a throat swab. Blood and urine was sent for mycobacterial culture. The patient was anergic to tuberculin. There was hypergammaglobulinaemia but complement levels were normal. An autoantibody screen revealed antineutrophil cytoplasmic antibody (ANCA) at a titre of 1:25 with a cytoplasmic pattern and antismooth muscle antibodies. Hepatosplenomegaly was demonstrated by ultrasound which also revealed two nodules near the femoral vessels. By computed tomography the liver measured 21 cm, the spleen 14 cm, and a few paracaval and aortic lymph nodes up to 1 cm diameter were noted. The mediastinum and chest were normal. Although there was thickening of the rectal wall no perianal abscess was seen.

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On the seventh hospital day *Staphylococcus aureus* was isolated from a single blood culture. A spiking fever was accompanied by further rigors. Intravenous flucloxacillin was commenced. An echocardiogram was normal and there were no stigmata of endocarditis. On day 11 a bone marrow aspirate and trephine were obtained and sent for mycobacterial culture, leishmania stain, and cytogenetic analysis. The aspirate was haemodilute but showed marrow dysplasia with reduced erythropoiesis and myelopoiesis. The trephine biopsy (reported on day 27) revealed marrow of increased cellularity with no granulomata, bacteria, fungi, or malignancy demonstrated.

On day 12 the CD4 cell count was reported as $0.05 \times 10^9/l$ and fortnightly pneumocystis prophylaxis with inhaled pentamidine was commenced. The flucloxacillin was stopped because the fever persisted. The haemoglobin had fallen to 8.1 g/dl and the blood film revealed target cells and schistocytes. Four units of packed cells were transfused. A direct Coombs' test was positive but haptoglobins were greater than 3.1 g/l (normal 0.4–3.0) ruling out haemolysis. Iron, transferrin, B12, and folate were normal. The ALP had risen to 1333 IU/ml and the albumin had fallen to 24 g/l.

Over the next 10 days the alkaline phosphatase rose to 2265 IU/ml and the platelet count fell inexorably to $44 \times 10^9/l$ by day 22. The pyuria persisted and several more early morning urine samples were sent for mycobacterial culture. Amplification of *Mycobacterium tuberculosis* DNA by PCR from blood was attempted. Further investigation of the anaemia revealed a negative sickle test and normal haemoglobin electrophoresis. Urine was negative for haemosiderin. A ^{99}Tc labelled leucocyte scan showed uptake confined to the spleen. A buffy coat stain for leishmaniasis was negative. Serological tests for leishmania (DAT and latex), *Brucella* (DAT, IgG, IgM), *Mycoplasma*, *Chlamydia*, influenza A and B, *Coxiella*, respiratory syncytial virus, and adenovirus were all negative.

Staphylococcus aureus was isolated from the sputum on day 21 but in the absence of chest signs treatment was deferred. A repeat computed tomograph (CT) scan of the abdomen (fig 1) demonstrated multiple para-aortic lymph nodes, enlargement of the liver and spleen without bile duct dilatation, and a right pleural effusion, and consolidation at the right lung base. A biopsy of the abnormal para-aortic lymph nodes was arranged.

Unfortunately just before the biopsy was performed, the patient passed a large amount of melaena, and required urgent resuscitation. Upper gastrointestinal endoscopy revealed two gastric ulcers with bleeding vessels which were injected. A surgical opinion was against immediate surgery. Bleeding continued and the patient developed hepatic decompensation and evidence of disseminated intravascular coagulation (APTT ratio 2.1; D-dimers 1000 ng/ml (normal <250)). Fresh frozen plasma (FFP), intravenous vitamin K, and oral neomycin were given. Endoscopy was repeated the next day but further injection failed to control the

Figure 1 Computed tomographic images taken 21 days after admission showing (A) enlarged liver (L) and spleen (S) and (B) para-aortic lymphadenopathy (arrow).

bleeding. Intravenous immunoglobulin was administered on the assumption of immune mediated thrombocytopenia and the surgeons agreed to operate. The ulcers were oversewn, and a wedge biopsy of liver together with a small para-aortic lymph node was sent for histology and culture.

The patient was admitted to intensive care but could not be permanently extubated and died the following day. He had received a total of 24 units of packed cells, 13 units of FFP, and 32 units of platelets. A coroner's necropsy was performed.

Discussion (Dr M Wiselka)

In summary, this was a Peruvian man in his 30s with advanced HIV who had lived in Spain in the 1980s and travelled to Peru 8 months before admission. The history of fever, sweats, and weight loss appears to have been present for several weeks or months and was initially associated with recurrent perianal and rectal infections. The other important clinical features include sterile pyuria, hepatosplenomegaly, and para-aortic lymphadenopathy. The liver function tests showed a pronounced obstructive pattern; however, bile ducts were not dilated indicating intrahepatic cholestasis. In addition he had anaemia and thrombocytopenia. Although the direct Coombs' test was positive there was no indication of gross haemolysis and the haptoglobins were elevated. Death followed abdominal surgery for uncontrolled bleeding from gastric ulceration.

The differential diagnosis is complicated by the travel history and the possibility that he was

suffering from a tropical infection. It is also important to consider that the interpretation of diagnostic tests, particularly serological testing, can be misleading in advanced HIV infection.

Causes of pyrexia of unknown origin (PUO) in HIV positive patients seen in the United Kingdom include tuberculosis, other bacterial infections, *Mycobacterium avium* complex (MAC) infection, lymphoma, and cytomegalovirus infection.¹ In other countries different patterns of disease are seen. A recent study of PUO in Spanish patients with HIV found that disseminated leishmania infection was the most common diagnosis.²

I shall begin by discussing the HIV related and medical conditions that are commonly seen in the United Kingdom, then consider diseases which could have been acquired abroad.

Tuberculosis should always be considered in any patient with PUO and is more frequently seen in immigrants and patients who are immunocompromised. The presentation of tuberculosis in patients with advanced HIV is often atypical and extrapulmonary so that a normal chest x ray does not exclude tuberculous infection. A trial of antituberculous therapy might have been considered in this patient. The presence of sterile pyuria, which was noted on several occasions, is consistent with tuberculous infection of the genitourinary tract and, although microscopy was negative for acid/alkaline fast bacilli, conventional cultures usually take several weeks and would not have been available at the time of death. The obstructive liver function tests and haematological abnormalities are rather unusual for tuberculosis but might be seen in advanced disease. Disseminated MAC infection could give all the clinical features described; however, this is usually associated with a very high bacterial load in patients with advanced HIV infection and positive blood cultures or evidence of MAC in the bone marrow would have been expected.

Lymphomas are increasingly common in patients with HIV as patients live longer with more effective prophylaxis and antiviral treatment. Over 90% are B cell non-Hodgkin's lymphomas, although Hodgkin's lymphoma has also been described in association with HIV. Lymphomas are frequently EBV related and this patient had evidence of previous EBV infection. Presentation may be unusual and lymphomas of the gut and liver are relatively frequent in patients with HIV. Lymphoma is an important cause of PUO in advanced HIV infection and could explain the clinical features including splenomegaly, lymphadenopathy, and positive Coombs' test. The negative bone marrow examination does not exclude lymphoma and a liver or lymph node biopsy would probably be more informative.

Cytomegalovirus infection may present as PUO and can commonly affect the eyes, liver and gastrointestinal tract. Gastrointestinal involvement may also be associated with obstructive liver function tests due to an associated sclerosing cholangitis. The flame haemorrhage may have been an indication of early CMV

retinitis but no other fundal changes were documented. The CMV PCR was negative and this makes the diagnosis less likely as recent studies have indicated that active CMV disease is usually associated with detectable viraemia.³

Medical conditions which could have caused PUO in this patient include subacute bacterial endocarditis (SBE) and vasculitis. Although the patient had a soft systolic murmur there were no cutaneous stigmata of SBE and a transthoracic echocardiogram was unremarkable, although this is less sensitive than transoesophageal echocardiography. More importantly repeated blood cultures were negative apart from *Staphylococcus aureus* on one occasion.

The patient had a relatively low titre of cANCA and a positive antismooth muscle antibody titre raising the possibility of a vasculitis. Renal involvement could explain the abnormal urinary findings. In addition there was evidence of previous hepatitis B infection which is associated with polyarteritis nodosa, although at the time of presentation he was negative for HBsAg. Although the cANCA was positive there were no abnormalities in the chest or upper respiratory tract to suggest Wegener's granulomatosis and this is likely to have been a non-specific laboratory finding.⁴ Nevertheless, vasculitis may be a cause of PUO which can be difficult to diagnose without radiological evidence or histological material.

Other possible causes of PUO arising from the lower bowel include inflammatory bowel disease, possibly with associated sclerosing cholangitis or a diverticular abscess.

I will now turn to infections normally acquired overseas. Malaria and enteric fever are common causes of fever in returning travellers but usually present as a more acute illness and should have been diagnosed on blood films and cultures respectively. Brucellosis can present with a prolonged PUO and hepatosplenomegaly but organisms should again have been cultured from the blood or bone marrow.

Leishmania infection has already been mentioned as a common cause of PUO in the Mediterranean region where infection is caused by *L. donovani* or *L. infantum*.^{5,6} *Leishmania* infection usually presents with a prolonged PUO associated with hepatosplenomegaly and pancytopenia and serological tests are only positive in about a third of infected HIV positive patients. Nevertheless bone marrow examination is positive in over 80% of cases but was negative here.

Other tropical conditions include rickettsial infection, trypanosomiasis, ehrlichiosis,⁷ and disseminated fungal infections. Although these conditions can cause multisystem disease there was no evidence of them on blood films, blood culture, or bone marrow examination.

Bartonella infection has recently been identified as an important complication of advanced HIV infection and is associated with cutaneous and systemic manifestations. *Bartonella* are Gram negative intracellular rods which parasitise red blood cells and endothelial cells. Clinically important species include *B. henselae* which is spread through contact with cats and

Figure 2 Section of liver obtained 25 days after admission. (A) Portal tract expanded by a destructive lymphoid infiltrate containing many large atypical cells (arrow) (haematoxylin and eosin); (B) CD30 immunostain demonstrating these large cells are positive for CD30. Some have the morphology of Reed–Sternberg cells consistent with Hodgkin's disease (arrow).

is the cause of cat scratch fever and bacillary angiomatosis; *B quintana* which is carried by the body louse and is responsible for trench fever; and *B bacilliformis* which is spread by the sandfly and may present with an acute febrile illness (Oroya fever) leading to a chronic papillomatous eruption on the legs known as verruga peruana. Oroya fever is endemic to Peru and is seen in the foothills of the Andes at an elevation of over 500 metres. There is a possible association with non-Hodgkin's lymphoma in HIV infected patients.⁸ Bartonellosis causes mucosal lesions in the small and large bowel and widespread lesions elsewhere in the body.^{9–10} Funduscopy may show evidence of stellate neuroretinitis and liver infection gives rise to the condition known as peliosis hepatis which is characterised by a markedly elevated alkaline phosphatase and mild or moderately raised liver enzymes. Diagnosis of *Bartonella* infection may be made on the peripheral blood film in around half of cases or may be confirmed by culture, serology, or PCR. However, most cases are diagnosed after histological examination of affected tissues, which contain cystic blood filled spaces with foci of bacteria and necrosis. All of the clinical

features would be consistent with bartonella infection and a careful review of the travel history would indicate whether this patient was at risk of bartonellosis.

Although a large number of medical conditions could have caused a pyrexial illness in this patient my clinical differential diagnosis is:

- (1) tuberculosis
- (2) disseminated *Mycobacterium avium* complex infection
- (3) visceral leishmaniasis
- (4) lymphoma
- (5) disseminated *Bartonella* infection.

Pathological findings (Dr A J Winter and Dr J Wilde)

Necropsy findings were augmented by examination of the biopsy samples obtained before death. In the stomach there was a benign active chronic ulcer in the pre-pylorus with no evidence of malignant or lymphomatous infiltration. The liver was greatly enlarged at 2000 g, with focal areas of necrosis, although the architecture was maintained. There was severe hepatocyte degeneration. The portal tracts were expanded by an infiltrate of CD30+ CD15– anaplastic lymphoid blasts and occasional Reed-Sternberg cells consistent with Hodgkin's disease (fig 2). Cytogenetic analysis of antemortem peripheral blood revealed normal male karyotype. The retroperitoneal lymph node contained a similar lymphocytic infiltrate. The spleen was enlarged (500 g) but badly autolysed. The appearance of the lungs was consistent with adult respiratory distress syndrome. There was consolidation of the left lower lobe where many Gram positive cocci were identified suggesting staphylococcal infection. The renal tract was normal. No acid-alcohol fast bacilli or granulomata could be found in any histological specimen.

Culture of the antemortem liver biopsy yielded a fully sensitive isolate of *Mycobacterium tuberculosis*. *M tuberculosis* was also isolated from the final two early morning urines, but not from any previous specimens. Bone marrow, blood, and sputum were sterile after prolonged incubation. Culture of the antemortem lymph node biopsy yielded a slight growth of *Staphylococcus aureus*. A final surprise was the isolation of *Aspergillus fumigatus* from the antemortem liver biopsy. However, *Aspergillus* antigen could not be detected by the Pasteurex test in three stored serum specimens taken at intervals throughout the final illness and no fungal elements could be identified histologically.

PATHOLOGICAL DIAGNOSES

- (1) Gastrointestinal haemorrhage due to bleeding benign chronic active ulcer of the stomach
- (2) Respiratory failure due to adult respiratory distress syndrome and *Staphylococcus aureus* pneumonia
- (3) Disseminated infection with *Mycobacterium tuberculosis* affecting liver and possibly renal tract
- (4) Hodgkin's disease of the liver
- (5) AIDS.

Discussion of pathological diagnosis (Dr A Winter and Dr K W Radcliffe)

This was a difficult case in which no clear diagnosis was reached before death. Massive gastrointestinal haemorrhage pre-empted attempts to obtain biopsy material and aborted planned empirical antituberculous therapy. As far as we can ascertain this is the first reported case of dual presentation with hepatic Hodgkin's disease and hepatic tuberculosis, although Hayes *et al* reported a lymph node biopsy in a case of suspected AIDS which contained Hodgkin's disease, tuberculosis, and Kaposi's sarcoma.¹¹ There is insufficient evidence for true *Aspergillus* infection and we suggest this isolate resulted from contamination. Two questions to consider are (i) should we have performed a liver biopsy earlier and (ii) would it have made a difference? Cappell *et al* reviewed 36 consecutive liver biopsies in HIV seropositive patients, 30 of which were performed for unexplained fever; 15 cases of mycobacterial infection were detected in 18 diagnostic biopsies. They attributed their high diagnostic yield to strict criteria for biopsy which in the absence of a focal hepatic lesion exclude isolated hepatomegaly or fever without raised alkaline phosphatase.¹² In the patient reported here, focal lesions were not demonstrated on imaging but the alkaline phosphatase at admission was moderately raised. Additional information might have been obtained with high frequency (5 MHz linear array) ultrasonography, which can better detect hepatic and splenic microabscesses,¹³ or gallium-67 imaging.¹⁴ Even had an earlier liver biopsy revealed Hodgkin's disease, we might have missed the diagnosis of hepatic tuberculosis, given the paucity of granulomata and acid-alcohol fast bacilli. Indeed, the definitive diagnosis of Hodgkin's disease might have persuaded us against starting empirical antituberculous therapy. PCR amplification of mycobacterial DNA in biopsy material may be of use in this situation. Diaz *et al* investigated paraffin embedded liver biopsy material from 64 (non-AIDS) patients who had hepatic granulomata with a PCR assay based on amplification of the IS6110 insertion sequence. Their assay was 100% sensitive in the presence of culture positive tuberculosis of the lung, liver, or lymph node, but only 58% sensitive when responders to antituberculosis therapy were included.¹⁵

We could not have predicted the massive gastrointestinal haemorrhage due to a chronic active stomach ulcer. Torrential bleeding was complicated by a coagulopathy resulting from the combination of massive transfusion, liver failure, and underlying malignancy. Tuberculosis alone has also been implicated in disseminated intravascular coagulation.¹⁶

The prognosis of Hodgkin's disease with HIV infection is almost certainly worse than for those without HIV, although published comparisons fail to match patients for age and disease stage. HIV seropositive patients present with more advanced disease than Hodgkin's disease patients without HIV infection. Fifty two per cent of a large Italian cohort of 114 Hodgkin's disease patients with HIV infection

Key points

- Late diagnosis of HIV infection contributes greatly to preventable AIDS related morbidity and death.
- Fever in late stage HIV infection can be due to multiple causes. Tuberculosis should always be considered.
- Focal lesions in the liver can still be missed by conventional non-invasive imaging

presented with stage IV disease, compared with 15% of a "similar" HIV negative cohort. Among HIV infected patients median survival was just 13 months. Poor outcome was predicted by a CD4 count below $250 \times 10^9/\text{ml}$, prior AIDS diagnosis, and failure to achieve complete remission.¹⁷ Of 45 Hodgkin's disease patients notified to the French registry of HIV associated tumours between May 1987 and July 1990, 34 (76%) had stage III or IV disease.¹⁸ The median CD4 count at presentation was $304 \times 10^9/\text{l}$. No patient presenting with a CD4 count below $300 \times 10^9/\text{l}$ survived for 2 years. As both these cohorts date from before the advent of highly active antiretroviral therapy, such survival data may be overpessimistic. HIV seropositive patients with Hodgkin's disease also tend to have unfavourable histological subtypes. Bellas *et al* compared 24 HIV positive Hodgkin's disease cases with 55 non-HIV infected Hodgkin's disease cases, and found that all the tumours from HIV seropositives expressed latent membrane protein-1 (LMP-1) compared with 57% of the non-HIV patients, suggesting that EBV more commonly plays an aetiological role in HIV associated Hodgkin's disease than in non-HIV associated disease.¹⁹ Whether HIV infection itself is a risk factor for Hodgkin's disease remains unclear. Biggar *et al* conducted a detailed review of American data and found a "possible" association with Hodgkin's disease, noting that surveillance bias tends to favour reporting of spurious associations.²⁰ To aid surveillance, and in view of the poor prognosis of Hodgkin's disease in HIV infection, others support adding Hodgkin's disease to the list of AIDS defining conditions.^{21 22}

In summary, this is the first description of dual presentation of tuberculosis and Hodgkin's disease affecting the liver in a patient with AIDS. Although death was due to unexpected gastrointestinal haemorrhage the prognosis in this case would have been very poor.

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