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Pyrexia of undetermined origin in the era of HAART

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Case presentation (Dr W Whitley, Dr R F Miller)
A 30 year old white homosexual male presented to the outpatient clinic and was admitted to hospital in early March 2000. He reported an 8 week history of dry cough, 6 weeks of diarrhoea with occasional vomiting, increasing anorexia and malaise associated with weight loss of 8 kg, and night sweats. Ten days before admission he had noted fever and mild bifrontal headaches and for 4 days both he and his partner observed a change in his personality. The patient’s symptoms had persisted despite empirical ciprofloxacin prescribed by his primary care physician. In the past the patient had had hepatitis A in 1990 and was first found to be HIV-1 antibody positive in April 1999, at which time the CD4+ T lymphocyte count was 220 cells x10^3/l and HIV viral load was 421 400 copies/ml (Chiron quantiplex b DNA assay v 3.0). An STD screen was negative and he was hepatitis B immune. At the time of diagnosis of HIV infection he had declined HAART as he was asymptomatic but had started co-trimoxazole as primary prophylaxis against Pneumocystis carinii pneumonia. He was subsequently monitored in the outpatient clinic on a regular basis. In late 1999 his CD4+ T lymphocyte count began to fall. By early February 2000 it was 70 cells x10^3/l and the HIV viral load was 308 900 copies/ml. The patient began zidovudine 250 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg at night, 10 days before admission to hospital.

The patient worked in the media, was a non-smoker, and drank alcohol occasionally. He had travelled widely within Europe. Systematic review was non-contributory. Examination on admission showed the patient to be unwell, his body temperature varied between 38.2°C and 40°C over the first few hours. The mucosae were pale and oral candida was present. There was a single shotty left supraclavicular lymph node, 0.5 cm in diameter, and multiple similar sized glands in both inguinal regions. The pulse was 110 and regular, blood pressure 115/60, and night sweats. Ten days before admission he had noted fever and mild bifrontal headaches and for 4 days both he and his partner observed a change in his personality. The patient’s symptoms had persisted despite empirical ciprofloxacin prescribed by his primary care physician. In the past the patient had had hepatitis A in 1990 and was first found to be HIV-1 antibody positive in April 1999, at which time the CD4+ T lymphocyte count was 220 cells x10^3/l and HIV viral load was 421 400 copies/ml (Chiron quantiplex b DNA assay v 3.0). An STD screen was negative and he was hepatitis B immune. At the time of diagnosis of HIV infection he had declined HAART as he was asymptomatic but had started co-trimoxazole as primary prophylaxis against Pneumocystis carinii pneumonia. He was subsequently monitored in the outpatient clinic on a regular basis. In late 1999 his CD4+ T lymphocyte count began to fall. By early February 2000 it was 70 cells x10^3/l and the HIV viral load was 308 900 copies/ml. The patient began zidovudine 250 mg twice daily, lamivudine 150 mg twice daily, and efavirenz 600 mg at night, 10 days before admission to hospital.

The patient was admitted to hospital. On admission investigations showed haemoglobin 7.4 g/dl and mean cell volume 74. The serum ferritin was markedly raised at 2796 µg/l (normal 16–323 µg/l and the serum iron was low at 4.4 µmol/l (normal 0–12 µmol/l); the TIBC was normal. The reticulocyte count was 1.2%, serum B12 and red cell folate were normal. A peripheral blood film showed anisocytosis, poikilocytosis, and occasional burr cells. The erythrocyte sedimentation rate was 24 mm in the first hour. The total white blood count was 6.2 (neutrophils 5.6) x10^9/l and platelets 183 x10^9/l. A clotting screen was normal. There was evidence of previous but not current parvovirus infection—lgG was positive and IgM was negative; parvovirus DNA was not detected using dot/blot analysis. The urea and electrolytes were normal apart from the serum sodium which was 124 mmol/l (normal 137–145 mmol/l). Liver function tests were normal. The C reactive protein (CRP) was 148 mg/ml (normal 0–12 mg/ml). The serum osmolality was low, 266 mmol/kg water (normal 280–300 mmol/kg water). Urine analysis showed protein+, and was otherwise normal; the urine osmolality was normal. Urine microscopy was negative, as was culture for bacteria. Three early morning urines were obtained and set up for mycobacterial culture. Three stool
samples were negative for bacterial pathogens, including *Clostridium difficile*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp and *Escherichia coli*. Three “hot” stools for ova, cysts, and parasites revealed no cryptosporidia or microsporidia. Three stool samples for faecal occult bloods were negative.

A chest radiograph was abnormal (fig 1) showing bilateral hilar and right paratracheal lymphadenopathy with diffuse reticular infiltrates and mild focal infiltrates at the left costophrenic angle and within the right mid-zone. A sputum sample was negative on Gram and auramine staining and was sent for culture for bacteria, mycobacteria, and fungi. An ultrasound scan of the abdomen confirmed hepatosplenomegaly but showed no ascites or intra-abdominal lymphadenopathy. Admission blood cultures were reported as negative. Blood serology, including toxoplasma latex and negative syphilis TPHA/RPR; however, the CSF CRAG was positive at a dilution of 1 in 128. Further investigations included a CT scan of the head with contrast which was normal. At lumbar puncture clear colourless cerebrospinal fluid (CSF) was obtained with an opening pressure of 13 cm H₂O. Analysis gave a CSF glucose of 2.5 mmol/l (simultaneous blood glucose 7.0 mmol/l). The CSF protein was 1.2 g/l, and WBC 2/mm³. An Indian ink stain was negative and cytology revealed no cells. Culture of the CSF was negative for bacteria; ongoing culture was set up for both fungi and mycobacteria. CSF serology showed a negative toxoplasma latex and negative syphilis TPHA/RPR; however, the CSF CRAG was positive with a dilution of 1 in 2000. The polymerase chain reaction on cell-free CSF was negative for herpes simplex virus 1 and 2, *Epstein–Barr* virus, *cytomegalovirus*, *varicella zoster* virus, and *JC* virus. A bone marrow aspirate and trephine showed a normocellular marrow with dysplastic megakaryocytes. The myeloid series showed a left shift and these findings were interpreted as showing a reactive marrow consistent with HIV associated changes. Routine staining for bacteria, mycobacteria, and fungi was negative. A sample of bone marrow aspirate was cultured for these pathogens. Two days after admission a repeat CD4+ T lymphocyte count was 190 cells ×10⁹/l and repeat HIV viral load was 500 copies/ml. The patient was thought to have disseminated cryptococcosis together with poor prognostic signs, including poor mentation and hyponatraemia. The HAART was continued and he was treated with intravenous amphotericin B and also transfused with whole blood. An upper gastrointestinal endoscopy was performed in order to investigate further the cause of his iron deficiency anaemia. This revealed only candida in the oesophagus and stomach. Biopsies of the duodenum were normal.

After 1 week in hospital the patient remained pyrexial and had persistent headache which was attributed to the lumbar puncture. However, his mentation had improved. At this point *Streptococcus pneumoniae* was cultured from blood. This was treated initially with intravenous benzyl penicillin and subsequently oral amoxycillin. Over the next week there was a marked clinical improvement with a reduction in fever being associated with a reduction in CRP levels. The serum CRAG remained positive. The patient received a total of 2 weeks of amphotericin B and then treatment was changed to oral fluconazole 600 mg once daily. At this time the patient reported an increase in size and tenderness of the lymph node in the left cervical chain. Over a period of 4 days the lymph node enlarged to a size of 10 × 12 cm and was excruciatingly painful. This was accompa-
nied by a recrudescence in fever. Repeat cultures of urine, stool, and blood were negative. An ultrasound of the neck revealed multiple homogeneous lymph nodes. A CT scan of the neck revealed multiple highly vascular lymph nodes (fig 2) and a repeat chest radiograph showed normal lung fields but persistent lymphadenopathy (fig 3). Four days after the onset of increasing cervical lymphadenopathy a fine needle aspirate (FNA) was performed. This was initially reported as showing only red blood cells, polymorphs, neutrophils, and necrotic debris.

Discussion (Dr Peters)
I wonder what further analysis of the lymph node FNA showed? I am particularly keen to know what the special stains showed? Were any infections identified? If the lymph node FNA was really non-diagnostic it might have been necessary to proceed to a surgical excision biopsy. Given the initial response to amphotericin B documented both clinically and by reductions in CRP, I think it is unlikely that the lymphadenopathy is due to cryptococcus. Rapidly enlarging lymph nodes in the HIV infected immunosuppressed patient may be caused by malignancy, including Kaposi’s sarcoma, non-Hodgkin’s lymphoma, and by mycobacteria, both typical and atypical. I do not think that we can assume that what is happening in the lymph nodes is cryptococcal infection. Occam’s razor—of diagnostic parsimony—often does not apply in this patient population and I think we need to consider a second pathology. The rise in CD4+ T lymphocyte count and fall in viral load has occurred in a very short interval and I just wonder if this is an immune reconstitution phenomenon—caused by Mycobacterium avium complex.

Pathology (Dr G Kocjan)
The lymph node FNA smears contained red cells, polymorphs, necrotic debris, and granulomatous inflammation, including epithelioid cells. A Ziehl–Neelsen stain for acid fast bacilli was positive (fig 4). A Grocott methenamine silver stain was negative for Cryptococcus neoformans and other fungi. No malignant cells were identified.

Case presentation (Dr Whitely, Dr Miller)
The HAART was continued and treatment was begun with rifabutin, isoniazid, ethambutol, and clarithromycin. This combination was chosen in order to cover both M avium complex and also M tuberculosis. At the same time, to compensate for the cytochrome P 450 inducing effects of rifabutin, the dose of fluconazole was increased to 800 mg once daily and also the dose of efavirenz was increased from 600 to 800 mg at night.

Seven weeks after commencing HAART, just before starting antimycobacterial therapy, the patient’s CD4+ T lymphocyte count was 490 cells ×10⁶/l and HIV viral load 100 copies/ml. At this time culture of peripheral blood obtained at the time of the admission, and the bone marrow aspirate, revealed Cryptococcus neoformans.

After 4 weeks of antimycobacterial therapy there had been little impact on the patient’s symptoms and no reduction in the size of the lymphadenopathy. Further lymph nodes had enlarged and some began to discharge (fig 5).
In addition to identifying mycobacteria by staining and microscopy, culture is mandatory in order to speciate the organisms.

Excluding intercurrent (opportunistic) infection when diagnosing/treating immune reconstitution inflammatory syndrome (IRIS).

In addition to antimycobacterial therapy for IRIS lymphadenitis, it may also be necessary to give glucocorticoids and/or non-steroidal anti-inflammatory.