CASE REPORT

'Occam's Scissors': opportunistic infections in advanced HIV infection

Nirav Shah,¹ Leah Owen,² Sanjay Bhagani²¹Department of HIV/Thoracic Medicine, Royal Free Hospital, London, UK²Department of HIV Medicine, Royal Free Hospital, London, UK

Correspondence to

Dr Nirav Shah,
nirav.shah1@nhs.net

SUMMARY

The authors report the case of a new diagnosis of advanced HIV-1 infection with a blood CD4 cell count of $0.003 \times 10^9/L$ (2%), presenting with weight loss, night sweats, diarrhoea and anorexia. Symptoms were due to disseminated histoplasmosis (confirmed pulmonary and colonic disease), *Pneumocystis* pneumonia and oral candidiasis highlighting the limitations of 'Occam's razor' with advanced HIV infection.

BACKGROUND

Patients with advanced HIV infection are predisposed to develop a multitude of infectious and neoplastic multisystem complications. To minimise drug toxicities, excess cost and inconvenience of unnecessary drugs, it is ideal to establish a diagnosis and specific pathogen to offer targeted therapy. We report a new diagnosis of AIDS and advanced HIV infection to highlight an important lesson in investigating the immunocompromised host. Clinical and radiological features were thought to be caused by mycobacterial disease and possibly *Pneumocystis* pneumonia (PCP) but, upon reflection of subsequent investigations, were found to be secondary to disseminated histoplasmosis and *Pneumocystis* allowing discontinuation of antituberculous medications.

CASE PRESENTATION

A 54-year-old woman born in Eastern Africa, in the UK for over 10 years, presented as an acute admission to a district general hospital with a 2-month history of diarrhoea, nausea, weight loss, anorexia, lower abdominal pain and dysphagia on the background of a 6-month history of drenching night sweats and intermittent dry cough. She denied intravenous drug use, smoking or alcohol intake and had a male partner for over 10 years with no unprotected intercourse for 6 years. Her medical history included Bell's palsy 6 years prior, with some residual motor weakness in the face and menorrhagia secondary to uterine fibroids. Examination was notable for oral candidiasis, subcentimetre left supraclavicular and right axillary lymphadenopathy and fullness in the right iliac fossa. Neurological investigation was notable for a subtle right lower motor neurone cranial nerve VII palsy, while respiratory and cardiovascular examinations were unremarkable.

INVESTIGATIONS

Full blood count revealed low haemoglobin 6.5 g/dL, white blood cell $8.02 \times 10^9/L$, platelets $237 \times 10^9/L$,

low mean corpuscular volume 72.0 fL and low lymphocytes $0.17 \times 10^9/L$ (2.1%), CD4 count $0.003 \times 10^9/L$ (2%) and the film revealed microcytosis, hypochromasia, polychromasia and target cells with iron studies and haematinics suggestive of mixed iron and folate deficiency. Biochemistry revealed sodium 137 mmol/L, potassium 4.0 mmol/L, urea 6.1 mmol/L, creatine 57 $\mu\text{mol/L}$, total bilirubin 4 $\mu\text{mol/L}$, alkaline phosphatase 78 IU/L, alanine aminotransferase 14 IU/L γ -glutamyl transpeptidase 20 IU/L, low-serum albumin 18 g/L and elevated serum lactate dehydrogenase 834 IU/L.

HIV 1 and 2 antibodies were positive with a high avidity index 0.8, HIV-1 subtype A, HIV-1 viral load PCR 309 688 copies/mL (log 10:5.5 copies/mL) with no major resistances detected at baseline. Subsequent testing revealed normal G6PD and negative HLAB5701.

In addition, serum galactomannan antigen ELISA was positive, Index 13.966, cryptococcal latex antigen test negative, syphilis total antibody negative, toxoplasma ELISA negative. Hepatitis screening revealed hepatitis A IgG antibody positive, hepatitis B 's' antigen negative, hepatitis B 's' antibody negative, hepatitis B core total antibody negative and hepatitis C IgG antibody negative. Urine protein/creatinine ratio at presentation was raised at 195 mg/mmol suggesting proteinuria with negative serum antinuclear body, extractable nuclear antigen, dsDNA, antineutrophil cytoplasmic antibody and normal C3 and C4 levels.

Chest radiograph showed widespread reticular-nodular shadowing (figure 1) and subsequent thoracic CT (figure 2) confirmed extensive pan-lobe interstitial nodular miliary shadowing with basal

Figure 1 Chest radiograph at presentation.

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Figure 2 Thoracic CT at presentation.

predominance, but no significant mediastinal lymphadenopathy. Note was made of multiple thin-walled pneumatoceles with a maximum diameter of 17 mm. CT of the abdomen and pelvis (figure 3) showed abnormal transmural thickening of the ascending colon and caecum to the hepatic flexure. There was small volume para-aortic and retroperitoneal lymphadenopathy and a large fibroid uterus, confirmed on subsequent MRI of the pelvis.

Diagnostic bronchoscopy was macroscopically normal and a bronchoalveolar lavage (BAL) was collected. Pulmonary and abdominal features were initially believed to be secondary to mycobacterial infection and PCP. A subsequent CT scan of the brain revealed subtle periventricular white matter low-attenuation change in keeping with small vessel disease and diagnostic lumbar puncture indicated normal opening pressure with normal cerebrospinal fluid biochemistry, which was acellular and did not stain for fungi or bacterial pathogens and importantly PCR negative for JC virus and *Mycobacterium tuberculosis* as well as Epstein Barr virus, varicella zoster virus and herpes simplex virus.

BAL cytopathology initially revealed benign respiratory epithelial cells, numerous alveolar macrophages and mixed inflammatory cells. In addition, several alveolar proteinaceous casts comprising cysts showing typical dot-like staining consistent with *Pneumocystis jirovecii* infection were seen. Samples were culture negative for bacterial pathogens, PCR negative for respiratory viruses, tuberculosis (TB) PCR negative, Ziehl-Neelsen (ZN) stain negative for mycobacteria and mycobacterial culture negative.

Oesophagogastrroduodenoscopy revealed no oesophageal candidiasis and duodenal biopsies showed normal villous

Figure 3 A CT of the abdomen at presentation.

Figure 4 Macroscopic appearance of caecal ulcer taken at colonoscopy.

architecture, with no excess inflammatory cells in the lamina propria, there were no organisms or granulomas seen, no evidence of dysplasia or malignancy. Periodic acid Shieff (PAS) and Grocott stains were negative for fungal organisms; ZN stain was negative for mycobacteria and cytomegalovirus (CMV) immunostaining was also negative. Colonoscopy revealed a grossly distended, inflamed and ulcerated ileocaecal valve where multiple biopsies were taken (figure 4). Caecal biopsies revealed normal crypt architecture with no significant inflammation; however, within lamina propria, there were scattered macrophages containing small cytoplasmic dot-like organisms that stained positive for diastase-resistance (DPAS), characteristic of *Histoplasma capsulatum* (figure 5). No granulomas or viral inclusions were seen and PAS, Grocott stains were negative for fungal organisms, ZN stain negative for mycobacteria and CMV immunostaining was also negative.

On re-review of the BAL at our tertiary referral HIV-unit, unstained intracellular yeasts were noted within-macrophages

Figure 5 Biopsies of large bowel mucosa revealing small cytoplasmic dot-like organisms which stain positive for diastase-resistance, characteristic of *Histoplasma capsulatum*.

and polymorphs. Similar yeast and budding forms stained strongly with Grocott, consistent with *H encapsulatum* infection. Short-'Synacthen' testing of adrenal corticosteroid function showed a normal response with a baseline early morning cortisol ($t=0$) 606 nmol/L, 30 min post synthetic adrenocorticotrophic hormone injection cortisol of 916 nmol/L and 1000 nmol/L for 30 min ($t=30$) and 60 min ($t=60$), respectively. Serological histoplasma testing was negative by complement fixation test for mycelial phase and yeast phase and also negative by double diffusion.

TREATMENT

Immediately postbronchoscopy, the patient was started on empirical treatment for oral candidiasis (fluconazole 50 mg once daily), PCP (intravenous trimethoprim-sulfamethoxazole (TMP-SMZ) 120 mg/kg daily in divided doses), miliary *M tuberculosis* (rifampicin 600 mg once daily, isoniazid 300 mg once daily, ethambutol 900 mg once daily and pyrazinamide 2 g once daily) and community-acquired broad-spectrum antibacterial cover (intravenous piperacillin and tazobactam 4.5 g thrice daily). Following the caecal histological confirmation of *H encapsulatum* infection, the patient completed a 14-day induction phase of intravenous liposomal amphotericin B (3 mg/kg once daily) followed by oral itraconazole (200 mg twice daily) for at least 12 months.

Given the lack of evidence for mycobacterial disease, antituberculous treatment was stopped after 13 days. Treatment dose TMP-SMZ was also stopped due to evidence of drug-induced myelosuppression after 14 days, but the patient completed a 21 day course of treatment for PCP with oral clindamycin (450 mg four times a day) and primaquine (30 mg once daily). *Pneumocystis* prophylaxis with low-dose TMP-SMZ (480 mg once daily) was subsequently well tolerated.

HIV antiviral medication was started on day 24 with a combination of emtricitabine, boosted atazanvir with low-dose ritonavir and raltegravir.

OUTCOME AND FOLLOW-UP

The patient was discharged home after a 32-day inpatient admission with the diagnoses of advanced HIV infection, oral candidiasis, *Pneumocystis jirovecii* pneumonia (PCP) and disseminated histoplasmosis. Serial galactomannan antigen index measurements revealed a reduction from 13.966 at presentation to 5.836 on day 7 of amphotericin and 3.664 on day 29. On review, a fortnight after discharge, she had gained 8.7 kg, serum albumin was 35 g/L and urine protein/creatinine ratio 38 mg/mmol with a complete resolution of all symptoms including diarrhoea, night sweats and respiratory symptoms.

DISCUSSION

The differential diagnosis of miliary pattern on thoracic imaging in HIV-infected patients includes miliary TB, histoplasmosis, cryptococcosis, bronchoalveolar carcinoma, haematogenous metastases from a non-pulmonary source as well as primary lung cancers.

Pneumocystis accounts for a significant burden of respiratory disease in those with a low CD4 cell count. *Pneumocystis (jirovecii)* pneumonia (PCP) is diagnosed definitively on the identification of the organism on histopathology utilising periodic-acid-Schiff positivity and DPAS as well as Grocott's methenamine silver stain. Untreated PCP is almost always fatal and (TMP-SMZ) is widely recommended as the first line therapy internationally.^{1 2}

The diagnosis of disseminated histoplasmosis requires a high index of suspicion. The causative organism is the dimorphic

fungus *H capsulatum*, which can also stain positive with Grocott's methenamine silver stain. This highlights the importance in the limitations of mycological and serological tests in HIV-infected patients. In immunocompetent patients, antibodies are thought to develop within 4–6 weeks in symptomatic histoplasmosis. However, as with our case, serology is not always useful in advanced HIV infection and AIDS. Chest imaging may reveal widespread interstitial, nodular and miliary infiltrates or more focal disease². Severe disease is treated with induction therapy of intravenous liposomal amphotericin B followed by itraconazole monotherapy.² Adrenal involvement is a common finding in disseminated disease postmortem (80–90%), but clinical adrenal insufficiency is reported in less than 10% of cases.³ Adrenal insufficiency should be suspected in patients who present with electrolyte abnormalities, postural hypotension, hypoglycaemia, cardiovascular collapse and those found to have a radiographic adrenal abnormality.

The investigation of advanced HIV disease and its associated opportunistic infections poses a diagnostic dilemma to the clinician. Clinical and radiographic manifestations can be difficult to accurately identify given the severity of disease due to an altered immunological response by the host.⁴ Occam's razor, by William of Ockham (1285–1347/49), stated that '*Pluralitas non est ponenda sine necessitate*', 'plurality should not be posited without necessity'. This principle has been applied to diagnostic uncertainty in the field of medicine in order to limit to multiple aetiologies to a single unifying diagnosis. Although the limitations of this principle have been discussed previously with Hickam's dictum and Saint's triad,⁵ we emphasise this when investigating patients for opportunistic infections with advanced HIV infection.

Learning points

- ▶ The differential diagnosis of miliary shadowing in advanced HIV infection is wide.
- ▶ Interpretation of serological and mycological testing in HIV requires caution to make an accurate diagnosis.
- ▶ When investigating opportunistic infections in HIV-infected patients, it is important to consider multiple pathologies.

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Competing interests None.

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