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Case Reports

A case of haemophagocytic syndrome in HIV-associated disseminated histoplasmosis

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Key Points
- In immunosuppressed patients, a lifetime travel history can be vital in making a diagnosis.
- Differential diagnoses should not exclude diagnoses that one would not expect to see at higher CD4 counts; CD4 counts should only be used as a guide in conjunction with viral load.
- Reactive haemophagocytic syndrome carries a high mortality. A high index of suspicion based on diagnostic criteria, early diagnosis and treatment of the underlying condition are paramount in preventing fatalities.

Abstract
Disseminated histoplasmosis is an opportunistic infection which is commonly associated with HIV. Haemophagocytic lymphohistiocytosis (HLH) has been described as a secondary phenomenon to infection, collagen – vascular disorders and malignancies. In patients with HIV, cases of reactive haemophagocytic syndrome associated with disseminated histoplasmosis have been reported with CD4 counts of less than 50 cells/µl (450-1660 cells/µl). We report a case of a 25 year old man with HIV who presented with a CD4 count of 153 cells/µl and would suggest that this diagnosis should be considered at higher CD4 counts than previously reported.

Keywords
HIV, AIDS, haemophagocytic syndrome, histoplasmosis

Case
A 25 year old man presented to a West London hospital with a short history of fevers, night sweats and weight loss of approximately 10kg. There was no significant past medical history but he admitted to drinking alcohol to excess for several years whilst in the Carribean as well as occasionally smoking cigarettes. On admission, the patient was afebrile but tachypnoeic and tachycardic with a respiratory rate of 26, oxygen saturations of 96% on room air, a heart rate of 142 and a blood pressure of 122/85 mm Hg. Further examination revealed cervical and inguinal lymphadenopathy and moderate splenomegaly. Blood tests revealed a haemoglobin of 11.7g/dL (13-18g/dL) and a platelet count of 127 $x10^9$/L (150-400$x10^9$/L) together with a normal white cell count of 9.6 $x10^9$/L (4-11$x10^9$/L). Abnormal biochemistry included hyponatraemia of 125 mmol/l (135-145mmol/l), lactate dehydrogenase of 4136 iu/l (70-250iu/L) and a grossly elevated ferritin of over 40,000 µg/L (12-200µg/L). His renal and liver function were normal apart from a mildly elevated alanine transaminase. He was born in the United Kingdom but lived in the Carribean between 1995-2002. He denied intravenous drug abuse and was heterosexual with one sexual partner in the preceding 18 months.

Chest x-ray on admission was normal. Sputum was negative for acid-fast bacilli as was PCR (Elispot) testing for tuberculosis but HIV type 1 was detected with a CD4 count of 153/µL (500-1500/µL) and a viral load of over 500,000 copies/ml. Blood and sputum cultures grew *Streptococcus pneumoniae* and the patient was treated with intravenous ceftriaxone and vancomycin.

Despite antibiotics, his condition deteriorated necessitating ITU admission for inotropic and ventilatory support. 4 days after commencing antibiotic therapy, the patient developed a widespread papular rash (Figure1). This was initially thought to be drug-related and the ceftriaxone was discontinued; however the rash progressed to involve palmar and plantar surfaces. Antimicrobial therapy was changed to include imipenem, clarithromycin, vancomycin, co-trimoxazole and caspofungin.

The patient was also noted to have a friable intraoral lesion which on initial inspection was thought to be consistent with Kaposi's sarcoma, however, skin and oral biopsies showed *histoplasma capsulatum*. A bone marrow biopsy was consistent with disseminated *histoplasma capsulatum* infection and CD68 staining showed multiple phagocytic histiocytes. Macroscopic bronchoscopic appearances (Figure 2) were also suggestive of histoplamosis. Broncho alveolar lavage (BAL) was performed which revealed abundant macrophages containing fungal organisms which were positive for Grocott and PAS stains, consistent with histoplamosis. No malignant cells were seen on BAL and no other fungi were isolated after long term culture. Sputum testing for *pneumocystis* was negative. A diagnosis of AIDS with disseminated histoplasmosis and HLH was made. As well as anti-fungal therapy, the patient was commenced on highly active antiretroviral

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Figure 1: Maculopapular rash on lower leg.



Figure 2:
choscopic imaging showing Histoplasma capsulata infection.

treatment (HAART) but despite maximal supportive therapy, the patient died 35 days after admission.

Discussion

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum* and is prevalent worldwide but endemic in the Americas. Infection is often asymptomatic but may present acutely as a self-limiting illness with fever, cough, myalgia and malaise; a chronic pulmonary form that most often occurs in the presence of underlying pulmonary disease, and a more severe disseminated form which usually only occurs in children, debilitated or immunocompromised patients and is commonly seen as an opportunistic infection in AIDS. Disseminated histoplasmosis is characterised by fungal multiplication in both the lungs and extra-pulmonary sites and can occur as a primary infection or as reactivation of latent infection, often in those living in endemic regions. Although the patient's initial presentation may have been due to a *Streptococcus pneumoniae* bacteraemia, there were no pneumonic changes on the admission chest x-ray and he deteriorated rapidly with widespread disseminated histoplasmosis.

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon disorder characterized by the pathological findings of activated macrophages engulfing erythrocytes, leucocytes and platelets and their precursor cells, together with clinical findings including fever and hepatosplenomegaly. The syndrome was first described in 1939[1] and was initially thought to be due to a neoplastic proliferation of histiocytes. However, in 1979, virus-associated haemophagocytic syndrome was proposed as a distinct clinical entity.[2] It has subsequently been described as a response to infection, collagen-vascular disorders and malignancies; HLH as a secondary phenomenon is known as reactive haemophagocytic syndrome[3] and carries a high mortality.[4-7]

The proposed diagnostic criteria of reactive HLH consist are outlined in Table 1[8]

Clinical criteria	Histological criteria
• Fever • Splenomegaly • Cytopenia affecting 2 of 3 cell lines • Hypertriglyceridaemia	• Haemophagocytosis in bone marrow, spleen or lymph nodes

Table 1. Diagnostic criteria of reactive HLH.[8]

We describe a case of haemophagocytic syndrome in a patient with HIV-associated histoplasmosis. There have previously been 18 cases of histoplasmosis associated haemophagocytic syndrome reported, of which 12 have occurred in HIV positive patients. Of those with documented CD4 counts, all had counts of less than 50.[9] Acute HIV infection is also a recognised cause of HLH [10, 11] but to date, only 7 cases have been described in the literature.[12, 13]

Although disseminated histoplasmosis should be considered at CD4 counts under 200,[14-16] all cases of disseminated histoplasmosis associated with HLH have reported CD4 counts of less than 50. Our patient had a CD4 count of 153 at presentation and had disseminated histoplasmosis with bone marrow evidence of HLH. It is well recognised that CD4 counts in acute infection can be temporarily decreased and therefore should not be used as a surrogate marker for HIV RNA viral load. However as far as we are aware, this is the only case of histoplasmosis associated HLH reported in the literature with a CD4 count greater than 50. We suggest that this diagnosis should be considered at higher CD4 counts than previous reports have indicated and that viral load is a more accurate guide of HIV activity and degree of immunosuppression than CD4 count.

Diagnosis is suspected on the basis of clinical features, endemnicity and CD4 counts. In areas where an infection is not endemic, it may be neglected in the differential diagnoses, therefore a diagnosis should be considered after taking an accurate travel history as immunocompromised individuals can demonstrate reactivation of latent disease.

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