CASE REPORT

Disseminated histoplasmosis in an HIV patient with CD4 count of 1 cell/ μ L

Sri Harsha Tella, Ahmed Abuzaid

Department of Internal Medicine, Creighton University, Omaha, Nebraska, USA

Correspondence to
Dr Sri Harsha Tella,
drsriharshatella@gmail.com

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SUMMARY

We report a case of a young woman with advanced HIV/AIDS who presented with a short duration of fever and shortness of breath, with no recent travel history or previous hospitalisation, accompanied by non-specific abdominal symptoms and suspicious upper gastrointestinal bleed. Her CD4 count was 1 cell/ μ L raising the suspicion for various opportunistic aetiologies. The initial suspicion was for pneumocystis pneumonia (PCP) and the patient was treated empirically with antimicrobials. Peripheral smear findings, urinary antigen tests and bronchoalveolar lavage (BAL) were suggestive of disseminated histoplasmosis. PCP was ruled out in BAL. Transabdominal imaging was concerning for periaortic lymphadenopathy raising the suspicion of occult malignancy. Endoscopic evaluation of her digestive tract was unrevealing. Endoscopic ultrasound fine-needle aspiration (EUS-FNA) confirmed histoplasmosis. She received a liposomal amphotericin B for 10 days followed by itraconazole with significant improvement. Her CD4 count was found to be the lowest reported count with a single opportunistic pathogen.

BACKGROUND

Gastrointestinal histoplasmosis may have either vague or no symptoms. Together with respiratory compromise this represents the vast majority of suspected cases of disseminated histoplasmosis, largely in the HIV/AIDS population. Upper and/or lower endoscopy with biopsy is an essential diagnostic tool. Regional lymphadenopathy can add to the diagnostic accuracy while ruling out other life-threatening non-infectious aetiologies. Disseminated histoplasmosis occurs predominantly in elderly persons, infants and persons with defective cell-mediated immunity including HIV/AIDS population and in patients who are on immunosuppressive agents.^{1 2} Respiratory and digestive tract involvement has significant morbidity.³ Clinical manifestations of disseminated histoplasmosis include fever, fatigue, nausea, vomiting, weight loss and anorexia.¹ Physical examination may reveal hepatosplenomegaly, lymphadenopathy, or both and laboratory studies may reveal pancytopenia, abnormal liver function, and in severe cases, renal failure or coagulopathy.^{4 5} Uveitis has been described rarely. The urinary histoplasma antigen test has emerged as a non-invasive assay that can be used to detect disseminated disease. The test has a sensitivity of more than 90% in patients with HIV infection and other conditions that compromise the immune system, but false-positive results of tests

for other endemic mycoses are possible owing to antigenic cross-reactivity. Peripheral or deep-seated lymphadenopathy has been found in a great proportion of the affected patients with high-yield material for microbial and cytological evaluation.⁶ We report a young woman with advanced HIV/AIDS who presented with a short duration of fever and shortness of breath, with no recent travel history, no exposure to infected soil of birds/bats or pets and no previous hospitalisation, accompanied by non-specific abdominal symptoms and suspicious upper gastrointestinal bleed. The patient's CD4 count was found to be the lowest reported count with a single opportunistic pathogen.

CASE PRESENTATION

A 29-year-old HIV-positive African-American woman presented with fatigue for 1 month associated with night sweats, chills and unintentional weight loss for the same duration. Review of symptoms been noticeable for colicky abdominal pain, not related to meals, located mainly in the epigastrium, radiating to the lower chest and upper right quadrant and associated with one episode of bloody tinged vomitus. She recently has been experiencing exertional shortness of breath associated and productive cough with clear whitish phlegm.

Her medical history is significant for HIV/AIDS known for 3 years with poor adherence to her HAART and frequent emergency room visits for outpatient symptomatic urinary infections. On physical examination: vitals are temperature 98.3, BP 105/70, HR 103/min, regular, RR 22/min, oxygen saturation was 90–92% on 2 L oxygen. There was no oral thrush or lymphadenopathy. The rest of the general physical examination was unremarkable. Chest examination was notable for clear lung fields with no rales or wheeze. Abdominal examination revealed mild epigastric tenderness. Liver and spleen were not palpable.

INVESTIGATIONS

Laboratory evaluation showed haemoglobin 7.5 g/dL with mean cell volume 83 fL, platelet count 78 000/mL, total white cell count 10 000 cells/ μ L (absolute neutrophil count 1000 cells/ μ L) and absolute lymphocytic count 700 cells/ μ L. Comprehensive metabolic profile was as follows: sodium 135 mmol/L, potassium 4.1 mmol/L, chloride 110 mmol/L, serum bicarbonate 22 mmol/L, blood urea nitrogen 12 mg/dL, serum creatinine 1 mg/dL, alkaline phosphatase 267 units/L, aspartate aminotransferase 466 units/L, alanine aminotransferase 80 units/L, direct bilirubin 2.6 mg/dL.

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Arterial blood gas: pH 7.49, PCO₂ 27.4, PO₂ 58.4, oxygen saturation 93%. Urine analysis was normal. Chest X-ray did not reveal any cardiopulmonary abnormalities. Her most recent CD4 count was 21 cells/ μ L 7 months before hospitalisation.

DIFFERENTIAL DIAGNOSIS

Given the significant respiratory compromise in the context of uncontrolled HIV before, she was empirically treated for pneumocystis pneumonia. We ruled out tuberculosis by three negative acid-fast bacillus (AFB) strains and quantiferon test. The patient was enquired about the exposure to infected soil by birds and bats and she replied in negative. Meanwhile, abdominal ultrasound was significant for acute cholecystitis which was managed conservatively. CT of the abdomen/pelvis with contrast was significant for diffuse ground glass and peripheral tree in bud opacities in the lower lung zones consistent with inflammatory process, together with extensive non-specific periaortic lymphadenopathy (figure 1).

Her peripheral smear was significant for normocytic normochromic anaemia with 21% bands, absolute neutropenia with rare intracytoplasmic inclusion bodies suggestive of yeast infection. Her urine histoplasma antigen was positive. The patient was started on broad-spectrum antifungal for possible systemic histoplasmosis.

TREATMENT

Follow-up of her laboratory work up was notable for CD4 count 1 cell/ μ L, CD8 64 cells/ μ L, CD19 112 cells/ μ L and CD56 21 cells/ μ L. Ferritin level 27 960 ng/mL, increased total iron-binding capacity with normal free iron. Lactate dehydrogenase (LDH) 724 units/L. Hepatitis B, C, influenza PCR, MONOSPOT, urine GC PCR, together with blood cultures were negative. Her bronchoalveolar lavage Gram stain and bacterial cultures were negative. However, a multiple budding yeast-like structures been noticed consistent with *Histoplasma capsulatum*. The diagnosis of systemic histoplasmosis was confirmed. Treatment was initiated with itaconazole and her symptoms resolved over the next 5 days. One week later, the patient was started back on HAART therapy.

Given the very low CD4 count, marked mesenteric lymphadenopathy on transabdominal imaging studies and deranged liver function tests, the patient was scheduled for endoscopic ultrasound (EUS) and fine-needle aspiration (FNA) to rule out other possible infectious aetiologies or intra-abdominal malignancy. EUS was consistent with multiple enlarged groups of

hypoechoic lymph nodes in the periportal, coeliac and periduodenal areas with unremarkable hepatic parenchyma and common bile duct. FNA result was suggestive of reactive lymph node pathology with abundant fungal organisms, histologically consistent with histoplasma. No evidence of MAI, cytomegalovirus or AFB.

Flow cytometer did not show any evidence of monoclonal B-cell or aberrant T-cell population. Gastric, small and large intestine biopsies did not show any significant findings and no AFBs or fungi were seen.

DISCUSSION

H. capsulatum is an intracellular pathogen. The infectious spores usually are spread by the air-borne route. Disseminated histoplasmosis occurs predominantly in elderly persons, infants and persons with defective cell-mediated immunity including advanced HIV/AIDS population and patients receiving immunosuppressive agents.⁷ Clinical manifestations of disseminated histoplasmosis include fever, fatigue, nausea, vomiting, weight loss and anorexia. Physical examination may reveal hepatosplenomegaly, lymphadenopathy, or both, and laboratory studies may reveal pancytopenia, abnormal liver function and in severe cases, renal failure or coagulopathy.^{4 5}

Cellular immunity plays crucial role in disease progression. Immunocompromised hosts, like those with HIV/AIDS, are more susceptible to symptomatic infection and have a greater chance of developing disseminated disease. Disseminated histoplasmosis in HIV-infected patients is usually associated with advanced immunosuppression⁷ with CD4+ lymphocyte counts of $<50/\text{mm}^3$. Disseminated histoplasmosis is an AIDS-defining illness which usually presents as non-specific systemic illness with varying degrees of respiratory, digestive tract and reticulo-endothelial system involvement.¹

The diagnosis of gastrointestinal histoplasmosis with or without mesenteric lymphadenopathy may be confused with inflammatory bowel disease, malignancy or other intestinal diseases leading to inappropriate therapies and unnecessary surgical interventions.

Despite the fact that abdominal histoplasmosis is uncommon, clinicians should be suspicious in patients with low CD4 counts or in patients who are non-compliant with their antiretroviral therapy. Elevated LDH and serum ferritin levels may prompt the physician to look for a diagnosis early in the course of the illness.^{8–10}

In the disseminated form of histoplasmosis, isolation and further identification of *H. capsulatum* can be performed by several methods, namely, bone-marrow aspiration, blood culture and liver biopsy. Lymph node disease is common and provides a substantial clue to confirm the diagnosis with proper fungal stains and specific antigen immunohistochemistry assays.^{11 12}

HIV infection is associated with a number of opportunistic infections and malignancies frequently involving the lymph nodes at variable stages of the disease with a wide spectrum of differential diagnoses. Lymph node biopsy can diagnose opportunistic diseases in HIV-infected patients, including histoplasmosis, mycobacteriosis and cryptococcosis and other rare causes of systemic mycosis together with excluding haematological malignancies in peripheral and deep seated groups of lymph nodes. The role of EUS-FNA can help to establish the diagnosis and to aid the disease prognosis since the method was able to assess the general anatomy of hepatic parenchyma and biliary radicles better than other imaging modalities due to its proximity and direct visualisation. EUS-FNA is superior in evaluating para-aortic and mesenteric lymphadenopathy in cases needing a tissue diagnosis entailing an easy, reliable and safe outcomes.

Figure 1 CT of the abdomen showing para-aortic lymphadenopathy.

Patient's perspective

During the hospital course the patient was frustrated due to overwhelming diagnostic tests but later she realised that all the symptoms are due to an infection secondary to non-compliance to her medications. She said that she will be compliant to HAART therapy and medications for histoplasmosis.

Learning points

- ▶ Clinicians should broaden the differential with opportunistic infections while dealing with immunocompromised patients.
- ▶ Patients are to be educated about the opportunistic infections that are caused by exposure to the infected soil by bird or bat droppings, contact with pets (dogs/cats) and physicians should get this history in immunocompromised cases.
- ▶ In developing countries, one should not forget to rule out tuberculosis while evaluating for opportunistic infections in immunocompromised person.
- ▶ Diagnosis of gastrointestinal histoplasmosis with or without mesenteric lymphadenopathy may be confused with inflammatory bowel disease, malignancy or other intestinal diseases leading to inappropriate therapies and unnecessary surgical interventions.
- ▶ Elevated lactate dehydrogenase and serum ferritin levels may prompt the physician to look for a diagnosis early in the course of the illness; as long as wide spectrum of opportunistic infections can delay the proper treatment modalities which improves outcome for >80% of AIDS patients with histoplasmosis with proper antifungal regimens.

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Competing interests None.

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