CASE REPORT

Cryptococcal lymphadenitis: an unusual initial presentation of HIV infection

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SUMMARY

Lymphadenopathy can occur at any stage of HIV infection, with multiple aetiologies including reactive, infectious and malignant. An accurate and timely diagnosis has obvious implications for treatment. We report cryptococcal lymphadenitis as the presenting manifestation of HIV infection. The diagnosis in our patient was eventually confirmed with a lymph node biopsy. Fine needle aspiration cytology has been shown to be a rapid and cost-effective method, which has been used in the diagnosis of lymphadenopathy in HIV infection, and could have been used to make an earlier diagnosis in our patient.

BACKGROUND

Cryptococcus neoformans is an opportunistic fungus that causes meningitis and pneumonia in patients with HIV infection. Dissemination may cause disease in multiple sites. Cryptococcal lymphadenitis accompanies immune reconstitution syndrome but is uncommonly described in disseminated disease. We report cryptococcal lymphadenitis as the presenting manifestation of HIV infection in a patient who was found to have disseminated disease, but required a lymph node biopsy to establish the cause. The literature suggests that fine needle aspiration cytology (FNAC) of peripheral lymph nodes is a rapid and safe method to make the diagnosis in HIV-associated lymphadenopathy.

CASE PRESENTATION

A 38-year-old African-American woman presented to our outpatient clinic with fever, chills, night sweats, headache, mild haemoptysis and progressive neck swelling of 2 weeks duration. She had failed to respond to empiric treatment with azithromycin and prednisone, and reported a 30 pound weight loss.

The patient's medical history was notable for migraine headaches and hypertension. There was no history of tobacco, alcohol or injection drug use. She was monogamous with a male partner and reported consistent use of barrier protection. Her last sexual intercourse had reportedly been 1 year ago. She had two teenage children who were healthy.

On examination, she was ill-appearing and febrile to 38.5°C. Her blood pressure was 133/80 mm Hg, pulse 95/min, respiratory rate of 18/min with an O₂ saturation of 100% on room air. Head and neck examination revealed enlarged right posterior cervical lymph nodes which were firm, but non-tender and freely mobile. Smaller

submandibular and supraclavicular nodes were palpated bilaterally. Examination of the oropharynx showed no pharyngeal oedema or exudate, and mucous membranes were moist. There was no evidence of oral thrush. Neck was supple. Her cardiovascular examination was normal, lungs were clear to auscultation, and abdominal examination was unremarkable with no hepatosplenomegaly. Neurological examination was completely unremarkable and no skin lesions were appreciated.

INVESTIGATIONS

Initial laboratory data showed a white cell count of 3.9 K/ μ L (4–10.5), with an absolute neutrophil count of 2800 (1400–6500), absolute lymphocyte count of 600 (1200–3400), and 3% band forms. Haemoglobin was 9 g/dL (12.5–16) with a mean corpuscular volume of 68 (78–100). The platelet count, creatinine and liver functions tests, including bilirubin, were all within normal limits.

CT scan of the neck and chest was obtained which revealed prominent bilateral posterior cervical, supraclavicular, axillary and mediastinal adenopathy, as well as nodular pleural thickening in the posterior aspect of the lungs.

HIV ELISA and western blot were positive. A CD4 count was profoundly depressed at 18/ μ L. HIV viral load, measured by branched DNA testing was 6696 copies (Bayer, Tarrytown, New York). Blood cultures grew yeast, subsequently identified as *Cryptococcus neoformans*. Serum cryptococcal antigen was positive at 1:512. Lumbar puncture revealed 11 white , and 7 red blood cells. Cerebrospinal fluid (CSF) India ink stain was negative, cryptococcal antigen in CSF was positive at 1:4 and CSF culture grew few *Cryptococcus neoformans*, sensitive to fluconazole and voriconazole.

On hospital day 6, the patient underwent a lymph node biopsy, which showed necrotising granulomas with evidence of numerous cryptococci on H&E and Gomori's methenamine silver stain. (The patient's lymph node histopathology is shown in figure 1.) Lymph node fungal culture grew many *Cryptococcus neoformans* organisms. Acid-fast bacilli smear and culture of a specimen of expectorated sputum as well as the lymph node were negative. There was no pathological evidence of malignancy in the lymph node.

DIFFERENTIAL DIAGNOSIS

Our patient was diagnosed with disseminated cryptococcal infection with fungaemia, central nervous system and lymph node involvement.

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Figure 1 Microscopic images of cryptococcal organisms within a lymph node. Gomori's methenamine silver stain (x40 magnification).

Other infectious aetiologies were excluded by positive blood cultures for *Cryptococcus*, as well as lymph node biopsy, which also excluded malignancy as a cause of lymphadenitis in this immunocompromised host.

TREATMENT

The patient was initially treated with liposomal amphotericin B and 5-flucytosine for 2 weeks, followed by 8 weeks of oral fluconazole. The hospital course was complicated by acute kidney injury secondary to amphotericin. Her discharge medications included fluconazole 400 mg daily, as well as dapsone 100 mg daily and azithromycin 1200 mg/week for *Pneumocystis jiroveci* and *Mycobacterium avium-intracellulare* complex prophylaxis, respectively.

OUTCOME AND FOLLOW-UP

The patient was discharged after 18 days in the hospital.

Highly active antiretroviral therapy (HAART) was initiated 2 months after initial diagnosis with efavirenz/emtricitabine/tenofovir. Her CD4 count at that time was 19 cells/ μ L, with a viral load of 30 650 copies, and serum cryptococcal antigen titer of 1 : 1024. She tolerated therapy well with a few gastrointestinal side effects.

She returned to work, and lymphadenopathy was absent at her 3 month follow-up. At her 8 month follow-up CD4 count was 204 cells/ μ L, HIV viral load was undetectable (<75 copies) and cryptococcal antigen in the serum was 1 : 256. There was no evidence of immune reconstitution inflammatory syndrome (IRIS).

DISCUSSION

Lymphadenopathy is a common finding in HIV infection, and is often one of the earliest manifestations of HIV infection. Causes of HIV-associated lymphadenopathy include non-specific follicular hyperplasia, opportunistic infection and malignancy. It is critical to establish the cause(s) of lymphadenopathy in patients infected with HIV. Various researchers have reported on different causes of lymphadenopathy worldwide. With the advent of HAART, the incidence of cryptococcal disease has declined, from 24 to 66 cases/1000 persons in the USA in 1992 to 2–7/1000 in 2000.¹

In a large Indian study, Kamana *et al*² analysed lymph node specimen from 300 HIV-infected individuals. Most patients had tuberculosis or reactive lymphadenitis; cryptococcus was found

in only 4/300 lymph node samples (1.3%). Studies from India and Thailand have had similar findings. Not surprisingly, there are epidemiological variations in the aetiology of neck masses between developing and developed countries.³

Numerous case reports describe the importance of cryptococcus in the IRIS associated with the initiation of HAART.⁴ Typical presentations include lymphadenitis, central nervous system infection and pulmonary disease.^{5–7} Srinivasan *et al* reviewed 15 cases of cryptococcal lymphadenitis, all diagnosed by FNAC. In their review, 8 of the 15 patients had HIV infection, and 5/8 biopsies showed necrotising granulomas as was observed in our patient.⁸

We present this case to remind clinicians of the importance of establishing a diagnosis when patients present with unexplained adenopathy. FNAC has been shown to be a safe and effective tool even in the presence of HIV infection.^{9–10} It has also been shown to be valuable in diagnosing cryptococcal lymphadenitis, even in patients with a negative latex agglutination test,¹¹ and is safe for patients with malignancy.¹² FNAC is more cost-effective than excisional biopsy (\$75–\$350 vs \$1200–\$2500). The primary drawback is the risk of sampling error, which can contribute to false-negative results.

Learning points

- ▶ Cryptococcal infection should be a diagnostic consideration for lymphadenopathy in any patient, regardless of known HIV infection.
- ▶ This case highlights the importance of maintaining a high index of suspicion in order to diagnose and treat in a timely manner.
- ▶ Fine needle aspiration remains a rapid, accurate and cost-effective tool in the diagnosis of lymphadenopathy. It is likely that this patient would have been diagnosed sooner had an FNAC been performed earlier.

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Competing interests None.

Patient consent Obtained.

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