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STUDENTS' CORNER

LETTERS

Immune reconstitution inflammatory syndrome in a patient with cryptococcal lymphadenitis as the first presentation of acquired immunodeficiency syndrome

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ABSTRACT

Immune reconstitution inflammatory syndrome is commonly seen in acquired immunodeficiency syndrome (AIDS) patients having concomitant opportunistic infection, following initiation of highly active anti-retroviral therapy (HAART). We describe IRIS in a young man with unknown human immunodeficiency virus (HIV) status who presented with cryptococcal lymphadenitis as the first manifestation of AIDS. At presentation the patient had features overlapping with tuberculosis (TB) lymphadenitis which was ruled out by fine needle aspiration cytology. The patient responded to antifungal treatment but following the start of HAART, symptoms recurred which were managed conservatively. Though TB is common in India, a thorough workup including histopathology of lymph node should be done before the patient is started on anti-tuberculosis treatment. HIV infected patients having opportunistic co-infection should be closely monitored following initiation of HAART.

KEY WORDS: Acquired immunodeficiency syndrome, cryptococcus, cryptococcus lymphadenitis, highly active anti-retroviral therapy, immune reconstitution inflammatory syndrome

Human immunodeficiency virus (HIV) infection has emerged as a global epidemic and India contributes significantly to this global burden.[1] Highly active anti-retroviral therapy (HAART) has brought a revolution in the management of HIV/AIDS associated morbidity and mortality. In addition, it has given rise to a new entity: immune reconstitution inflammatory syndrome (IRIS) in HIV/AIDS patients. Immune reconstitution inflammatory syndrome has been defined as appearance of new/ worsening of existing symptoms, following initiation of HAART despite improvement of immune function documented by increase in CD4+ cell count or decreasing plasma HIV RNA load.[2] Immune reconstitution inflammatory syndrome commonly occurs in HIV/AIDS patients having concomitant opportunistic infections.[3,4] *Cryptococcus neoformans* infection has been frequently associated with IRIS.[3,5]

We hereby present a case of cryptococcal IRIS in a patient who presented to us with cryptococcal lymphadenitis as the first manifestation of AIDS. Though cryptococcal lymphadenitis has been described from India,[6-8] there is paucity of reports on cryptococcal IRIS following HAART.

Case History

In February 2006, a 27-year-old man with unknown HIV status presented to us with low-grade fever (100.0 F), weight loss and anorexia, for six months and right submandibular lymph node (LN) swelling (2.5×2 cm) for three weeks. Following clinical suspicion of TB, he was started on anti-tuberculosis treatment (ATT) by a private physician five days ago.

Mild dry cough was present. No evidence of expectoration, hemoptysis, chest pain or neurological involvement was present. Radiograph and computerized tomography (CT) scan of chest showed bilateral hilar lymphadenopathy (BHL) with normal lung parenchyma. Ultrasonography of abdomen was normal. Fine needle aspiration cytology (FNAC) from cervical LN showed *Cryptococcus neoformans*, yeast cells with unstained capsule and magenta-colored cell wall on May-Grünwald-Giemsa stain and refractile organisms with narrow based budding on Papanicolaou stain. No *Mycobacterium tuberculosis* (*Mtb*) or caseating granulomas were seen. Fungal culture of the LN aspirate was not done. No *Mtb* or *Cryptococcus neoformans* was seen in sputum (produced by sputum induction), smear examination as well as culture. Tuberculin skin test measured 7 mm at 48h. HIV ELISA in serum was positive. The ATT was discontinued and the patient was started on intravenous amphoterecin-B at a dose of 1 mg/kg daily. Following CD4+ count report of 13 cells/mm^3, he was started on standard *Pneumocystis jirovecii* and *Mycobacterium avium-intracellulare* complex (MAC) prophylaxis. After two weeks, amphoterecin-B was changed to oral fluconazole 400 mg/day. Patient showed

marked improvement. His appetite improved and he became afebrile after two weeks. The size of the LN reduced to 1.0×1.0 cm. HAART consisting of lamivudine (150 mg) stavudine (40 mg) and nevirapine (200 mg), twice daily.

Two weeks following HAART, he developed high-grade fever (103.0 F), malaise, dizziness and increase in the size of previous LN along with appearance of two new LNs in the right supraclavicular (1.5×1.5 cm) and submandibular (3×2 cm) areas. Chest CT scan and radiograph were suggestive of BHL along with necrotic mediastinal LNs. Ultrasonography of abdomen revealed multiple enlarged retroperitoneal LNs which on FNAC showed reactive lymphadenitis. Magnetic resonance imaging (MRI) of brain and spinal cord was normal. Fine needle aspiration cytology of right supraclavicualr LN showed numerous cells of *Cryptococcus neoformans* [Figure 1] and culture of aspirate grew *Cryptococcus neoformans*. Repeat CD4+ count was 105 cells/mm^3.

Keeping with good initial response to initial antifungal therapy and worsening of the symptoms following HAART despite a rise in CD4+ count, a diagnosis of *Cryptococcus neoformans* infection flare-up owing to immune reconstitution inflammatory syndrome (IRIS) was made. Patient was treated with non-steroidal anti-inflammatory drugs (NSAIDS) with fluconazole continued and was closely monitored for any deterioration

Patient became afebrile after three weeks. Size of the LNs decreased (1.0×1.0 cm) and follow-up FNAC after four weeks did not show any evidence of active disease. The NSAIDS were discontinued after four weeks.

The patient received fluconazole 400 mg/day for 10 weeks (total duration) and was later switched to fluconazole 200 mg once daily. Highly active anti-retroviral therapy and PCP as well as MAC prophylaxis were continued. At six months follow-up, CD4+ cell count was 125 cells/ mm^3. The MAC prophylaxis was discontinued whereas HAART, PCP prophylaxis and fluconazole 200 mg once daily were continued. Patient is continuing follow-up and there is no episode of recurrence.

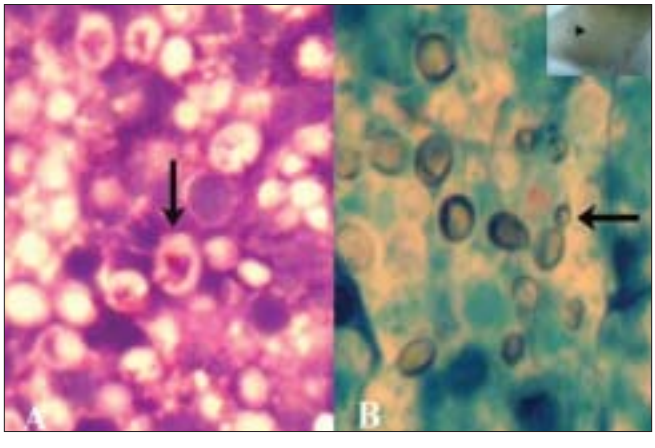

Figure 1: Aspirate from right cervical lymph node (inset: arrow head) showing yeast form of *Cryptococcus neoformans* having unstained capsule with magenta-colored cell wall in the middle (Panel A: May-Grünwald-Giemsa x400, arrow) and refractile organism showing narrow based budding (Panel B: Papanicolaou x400, arrow)

Discussion

Cryptococcal lymphadenitis is an uncommon form of extrapulmonary cryptococcosis which is one of the AIDS defining criteria according to the Center for Disease Control and Prevention (CDC), Atlanta, Georgia, USA guidelines. *Cryptococcus neoformans* infection is associated with high risk of developing IRIS following HAART.

Incidence of IRIS varies, Lortholary *et al*. have reported an incidence of be 4.2/100 person-years of all HAART-treated patients.[9] Whereas, Shelbourne *et al*. have reported an incidence of 15.1/100 person-years of HAART in their cohort.[2]

Reports of IRIS from India are sparse[10] and to best of our knowledge, this is the first report of cryptococcal IRIS from the Indian subcontinent. Patients having a low CD4$^+$ count and active or sub-clinical opportunistic infections at presentation are at increased risk of developing IRIS following HAART.[2]

The clinical presentation described above makes TB the first differential diagnosis, especially in a country like India with a high prevalence of TB and may prompt for starting ATT empirically. Though empirical therapy may be beneficial to patients in many cases, confirmation of diagnosis by histopathological/ microbiological evidence should always be looked for. The same has to be followed during disease flare-up/IRIS, following initiation of HAART so as to rule out development of new infection along with close monitoring of patient. Patients developing IRIS because of flare-up of previous infection can be managed symptomatically and conservatively.[4]

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