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A histologically proven case of lymphocytic interstitial pneumonia in a HIV infected adult with an undetectable viral load

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ABSTRACT

Lymphocytic interstitial pneumonia (LIP) is on the spectrum of lymphoproliferative diseases that can affect the lungs. Although common in human immunodeficiency virus (HIV) infected children, it is rarely reported in adults. A 51-year-old HIV infected female patient presented with worsening dyspnea over five months. She had radiological findings of bilateral lung nodular infiltrates. Her CD4 count was 835 cells/uL and her HIV viral load was undetectable. Bronchoalveolar lavage did not yield any infectious pathogen. The pathology on an open lung biopsy revealed marked lymphocytic infiltrates and widening of alveolar septa consistent with the diagnosis of LIP. LIP is a rare entity in adults. Previously reported cases in HIV infected adults were associated with a high HIV viral load at the time of diagnosis. Here we present the first case of LIP in an HIV infected adult with an undetectable viral load.

1. Introduction

Non-malignant lymphoproliferative diseases in human immunodeficiency virus (HIV) infected patients include non-specific interstitial pneumonia (NSIP) and lymphocytic interstitial pneumonia (LIP). Whilst the former is described in adults, the latter is more commonly reported in children with few cases described in adults with AIDS before the advent of antiretroviral therapy. LIP is a great clinical and radiological mimicker of opportunistic infections. Tissue biopsy remains the gold standard for diagnosis [1,2].

All previous LIP cases were noted in patients with high HIV viral load at the time of diagnosis (Table 1) [3–9]. We hereby, present the first case of an HIV infected adult receiving treatment with highly active antiretroviral therapy (HAART) and who had an undetectable viral load at the time of diagnosis.

2. Case report

A 51-year-old HIV infected African American female patient presented to our hospital with worsening dyspnea over the last 5 months. Her review of systems was negative for cough or fever. She had been on Abacavir, Tenofovir and Dolutegravir and had an undetectable HIV viral load for the past 7 years. She had no other medical problems.

Upon presentation, she was not able to complete full sentences and her oxygen saturation was 93% on room air, for which she was placed on 4 L of nasal cannula oxygen. Her lung examination revealed equal bilateral air movement with no crackles or wheezes. The rest of her physical examination was unremarkable.

Diagnostic work up revealed normal basic laboratory tests, a CD4 count of 835 cells/uL and an undetectable HIV viral load. An ABG unveiled hypoxemia with a partial pressure of arterial oxygen (PaO_2) of 62 mmHg and an elevated A-a gradient of 33 mmHg. A chest radiograph showed bilateral infiltrates. A chest computed tomography (CT) revealed multiple bilateral pulmonary nodules with ground glass attenuation; a pattern not as often seen in LIP as reticulonodular involvement (Fig. 1). The patient was started on empiric treatment for community acquired pneumonia and was started on trimethoprim-sulfamethoxazole to cover for possible *Pneumocystis jiroveci* pneumonia (PJP).

A diagnostic bronchoscopy was performed and the bronchoalveolar lavage (BAL) return yielded 485 white blood cells of which 10% were lymphocytes. Gram stain, acid fast stain, and Grocott's methenamine silver stain were negative. Bacterial, mycobacterial, fungal and viral cultures were also negative. The lack of symptomatic improvement despite antibiotics prompted a decision to obtain an open lung biopsy. Pathology revealed marked

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Table 1
A summary of case reports and case series of HIV infected adults with a diagnosis of LIP.

Reference	CD-4 count/cells/uL	HIV viral load/copies	Management	Outcome
Ripamonti et al. [3] Case report	228	379 670	Initiation of anti-retroviral symptoms	CT findings improved after 6 months, symptoms resolved
Innes et al. [4] Case report	198	>290 000	Initiation of anti-retroviral therapy	CT findings improved after 3 months
Lujan et al. [5] Case report (article in Spanish)	281	26 788	Initiation of anti-retroviral therapy	Resolution of symptoms
Hanlyn et al. [6] Case report	108	22 400	Initiation of anti-retroviral therapy delayed as patient lost to follow up	Resolution of symptoms during pregnancy
Van Zyl et al. [7] Case series	Median CD4 194	Not available	Not available	Not available
Saito et al. [8] Case report	380	510 000	Treated initially with methyl prednisone (tapered over a month) then HAART was initiated	Disease well controlled without progression over 3 years follow up
Dufour et al. [9] Case series	Median 269	Median 92 000	Initiation of anti-retroviral therapy	Improvement in symptoms in 2 patients and 3 patients were cured

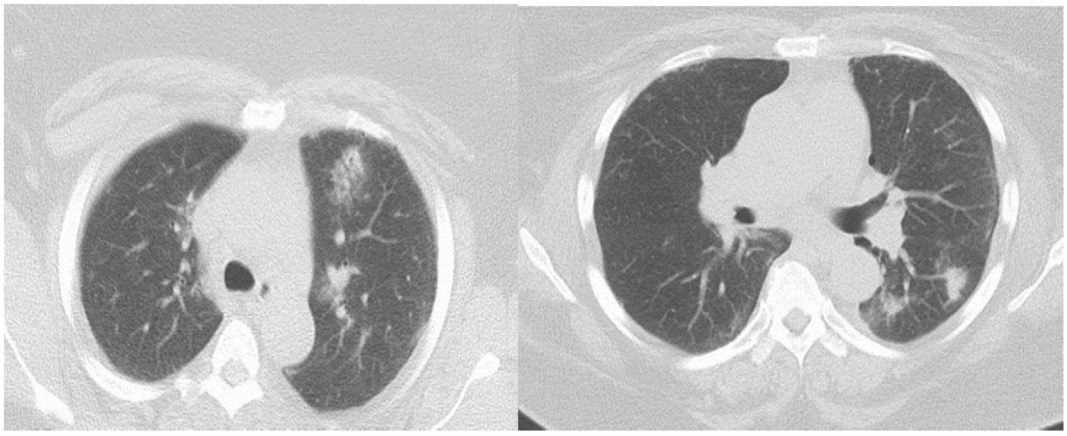

Fig. 1. Computed tomography (CT) scan of the chest, showing multiple pulmonary nodules at presentation.

widening of alveolar septa and infiltration with lymphocytes consistent with a diagnosis of LIP (Fig. 2). Stains and cultures on the tissue biopsy did not yield any infectious pathogen. Immunohistochemistry testing demonstrated poly-clonality of the lymphocytic infiltrates. A rheumatological work up including Anti- SSA, Anti-SSB, rheumatoid factor and antinuclear antibodies was negative. In retrospect, our patient denied any history of keratoconjunctivitis sicca or xerostomia.

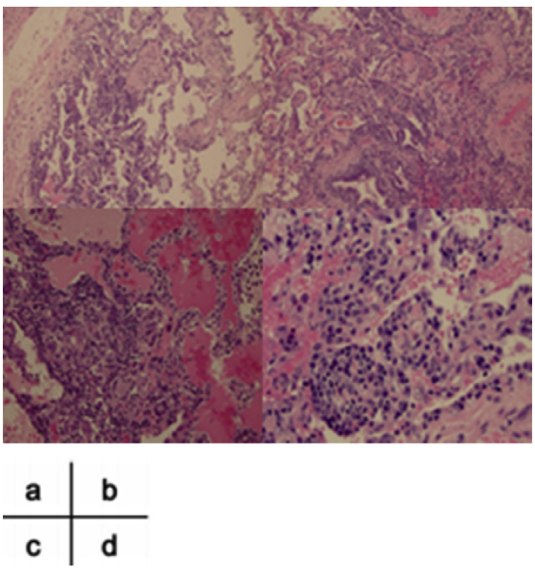

Fig. 2. A–D: Pathologic changes in the lung wedge biopsy. A: A lung section showing diffuse lymphocytic infiltrates in the alveolar septa under Hematoxylin- Eosin stain. B–D: Non caseating granulomas seen on higher power.

Given that our patient developed LIP on optimal HAART regimen and with undetectable viral load, initiation of steroids was entertained but deferred at this time in view of scarce data supporting their use in LIP and the resolution of our patient's symptoms with the administration of oxygen therapy.

3. Discussion

LIP is seen in patient with HIV and other systemic diseases. A case series of HIV infected adults with a tissue diagnosis of LIP had a median viral load of 92,000 copies/mL at the time of diagnosis. Patients with elevated viral loads are more likely to have lymphocytes, mainly CD8 T-cells, recruited to the lungs leading to the histological changes of LIP. Given that our patient had undetectable plasma viral loads, it would suggest that mechanisms other than HIV viral replication can be implicated in the etiology of LIP. In HIV infected persons, one other possible hypothesis is the reactivation of viruses like Epstein Barr Virus (EBV) or human T-lymphotropic virus type I (HTLV-1) that leads to a lymphoproliferative response [10–12]. The viral polymerase chain reaction (PCR) panel obtained in our patient was negative. Furthermore, autoimmune dysregulation might play a

role in the pathogenesis of LIP. In fact, 25% of LIP cases are associated with Sjögren's disease. Other autoimmune diseases associated with LIP include systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia and autoimmune thyroiditis.

The histopathological differential diagnoses of LIP includes: small lymphocytic lymphoma, MALToma and lymphomatoid granulomatosis. Lymphocytes in LIP are polyclonal in contrary to the monoclonal ones found in lymphomas. Immunohistochemistry testing is therefore key to help differentiating lymphomas from LIP.

Treatment is mostly based on anecdotal reports as no clinical trials exist. Initiation of HAART therapy to control viremia remains the mainstay of intervention. In cases refractory to HAART, steroids have been reported to be used with clinical and radiological response (8). In cases of underlying autoimmune diseases, other immunosuppressive therapies have been tried including cyclophosphamide, azathioprine and chlorambucil and some patients improve without any therapy [4,8,13].

Our patient was already optimized on HAART therapy and the decision to start steroids was yet to be made after discussion with infectious disease consultants.

Although commonly described as a complication of HIV in infected children, LIP remains a rare entity in adults. To our knowledge (Table 1), we presented the first case of LIP in an HIV infected adult with an undetectable viral load and without an underlying autoimmune disease.

Authorship statement

All authors are responsible for the conception of this case report and participated in its draft. All authors read and approved the final manuscript. As this is a case report without patient identifiers, approval from Ethical Committee is not required at our Institution.

Conflict of interest

The authors have no conflict of interest to declare.

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