

# Lymphocytic interstitial pneumonitis (pneumonia) in HIV-positive adults

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## Introduction

Lymphocytic interstitial pneumonitis (LIP) is an interstitial pneumonia, recently included in the radiological/histopathological classification of the interstitial pneumonias.<sup>1,2</sup> Although known to be AIDS-defining in children, LIP is still thought to be unusual in HIV-positive adults.

## Materials and methods

Between 1996 and 2003, 93 HIV-positive patients with indeterminate chest pathology at Helen Joseph Hospital, Johannesburg were subjected to diagnostic bronchoscopy. Wherever possible, biopsies were taken. The only selection criterion, was an inability to arrive at a diagnosis either clinically or radiologically. Helen Joseph Hospital admits a cross-section of the South African population, namely black, white and Asian patients. A high percentage of admissions are HIV-positive.

The findings were evaluated retrospectively.

## Results

Thirteen of the 93 patient were found to have LIP. Where the diagnosis came back as LIP histopathologically, the slides were then sent for review to the Pathology Department. Of the 15 cases of LIP originally diagnosed, 13 were confirmed to be LIP, 1 was tuberculosis (TB) and the other was nonspecific interstitial pneumonitis.

## Discussion

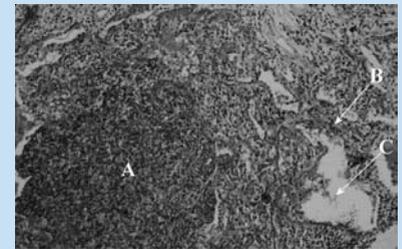
LIP is an inflammatory, lymphoproliferative non-neoplastic process representing a pulmonary reaction to various external stimuli or systemic diseases.<sup>2,3</sup> In 1969, Liebow and Carrington<sup>1</sup> classified LIP together with the other interstitial pneumonias.

Subsequently, however, a number of the lesions were found to be low-grade malignant lymphoproliferative diseases. LIP was then excluded from the classification of interstitial pneumonias. Recently, LIP has been reincluded in the American Thoracic Society and European Respiratory Society 2002 classification of idiopathic interstitial pneumonia.<sup>1</sup>

Pathologically, LIP is a diffuse pulmonary lymphoid proliferation, predominantly in the interstitium, in an alveolar septal distribution.<sup>1-3</sup> It appears that a transient lymphocytic alveolitis may develop in some HIV-positive patients, as an immune response to the HIV virus which, in a certain percentage of individuals, evolves into LIP.

Both B and T-cells, plasma cells and macrophages are present within the interstitial infiltrate. Lymphoid follicles with germinal centres occur. Lung architecture is preserved (Fig.1). Pertinent negative features are the absence of cell atypia and air-space disease. The lack of tracking along lymphatic routes in the pleura, bronchovascular bundles and interlobular septae, helps to differentiate LIP from lym-

phomas. Lymph node involvement in LIP is now more often recognised than it was in the past.



*Fig. 1. A lymphoplasmacytic cellular infiltrate is present in the interstitium forming nodules (A) and expanding the alveolar walls (B). Alveolar spaces (C) are compressed.*

LIP is associated with a number of systemic conditions, typically Sjogren's syndrome and autoimmune diseases. It also occurs post bone marrow transplantation, may be drug induced, e.g. after phenytoin exposure, and may rarely be idiopathic.<sup>3</sup> It is twice as common in women. Recently, it has become an AIDS-defining condition in children<sup>6,7</sup>, but it has been described as being uncommon or infrequently associated with HIV-positive adults. It was first described in HIV-positive adults, in the Haitian, Afro-Caribbean/Afro-American population in AIDS-related literature between 1983 and 1985.<sup>8,9</sup> Sporadic reports of LIP in HIV-positive adults have been published since then.<sup>3</sup>

Clinically, patients present with progressive cough and dyspnoea. They may, however, remain stable without significant deterioration. Spontaneous resolution may occur. The disease usually follows an indolent course and is often an incidental finding rather than the patient's presenting complaint. The mortality of HIV-positive patients afflicted with LIP is not adversely affected.<sup>2</sup>

LIP is variable in its course. It usually occurs in patients whose CD4 T-cell counts are within the normal range. HIV-positive patients with nonspecific interstitial pneumonitis usually have lower CD4 T-cell counts, around 200 cells x 10<sup>6</sup>/l,<sup>5</sup> but both conditions are reported in patients with normal range CD4 counts.

The outcome and prognosis of LIP is significantly affected by its natural history and response to antiretroviral treatment of

TYPE 1. Fine reticulamodular opacities, nodules, &lt; 3 mm.



Fig. 2. Fifty-year-old female patient, relatively well, with a non-productive cough of some months' duration.

TYPE II. Coarse reticulamodular opacities, nodules, &lt; 3 - 5 mm.



Fig. 3. Twenty-five-year-old female patient, presented with dysphagia due to oral candidiasis. She was on anti-TB treatment for 2 months. No respiratory symptoms.

the underlying HIV infection. In most cases, LIP in HIV-infected patients improves in response to corticosteroids. The literature also suggests that improvement of LIP occurs in parallel to a decrease of HIV viral load and with an increase in CD4 cell count.<sup>3</sup> Paradoxically, however, the stronger the immune system the more severe the interstitial infiltration is likely to be.<sup>3,8</sup> Thus resolution in the absence of antiretroviral or corticosteroid therapy can herald a worsening of immune suppression. It should be noted, however, that spontaneous clinical and radiographic resolution without immune deterioration can also occur.<sup>2,3,5</sup>

The classical chest radiograph presentation is of bilateral, predominantly lower-zone nodular or reticular-nodular opacities. Four radiographic categories have been most recently described (Figs 2-5).<sup>3</sup>

These presenting histories are typical for HIV-positive adults with LIP. The respiratory symptomatology is minimal and the disease process is indolent.

The chest X-ray opacities are confirmed on high-resolution computed tomography (HRCT) to be centrilobular and subpleural nodules of various sizes. Patchy bilateral and diffuse ground glass opacities on HRCT contribute to the infiltrates seen on chest X-ray, and represent a summation of lymphoid cellular infiltrates within the interstitium, rather than air space disease. CT also helps identify hilar and mediastinal lymphadenopathy, both of which have been found to be more common than previously thought. The high frequency of cysts noted on CT in LIP patients is a consequence of post-obstructive bronchiolar ectasia from infiltrate compressing the bronchioles.<sup>1,3,4,5</sup>

The differential diagnosis of the radiographic findings and patterns of LIP includes infection with *Pneumocystis carinii* and special stains are done to exclude the presence of the microorganism.<sup>2,4</sup> Viral diseases such as infectious mononucleosis, fungal pneumonias and TB may mimic LIP, as does post-transplant lymphoproliferative disorder. Nonspecific interstitial pneumonia is described more commonly in HIV-positive adults, and other benign lymphoproliferative disorders such as follicular

TYPE III. Findings of either type I or type II plus at least one patchy opacity.



Fig. 4. Forty-year-old female patient. No history available.

TYPE IV. Findings of either type I or type II with focal alveolar consolidation resembling pneumonia.



Fig. 5. Thirty-five-year-old male patient. Treated for bacterial infection for 1 month. A febrile, persistent non-productive cough. Chest X-ray was done for follow-up of his pneumonia.

grade lymphoma, where tracking along lymphoid routes, invasion of parietal pleura and lymph nodes are present, together with destruction of lung architecture and the presence of intranuclear inclusions in B-lymphocytes. In HIV-positive patients LIP is not considered pre-lymphomatous.<sup>2,6</sup> In most cases where LIP was followed by the development of lymphoma in an individual patient, the lesion was subsequently thought to have represented malignant lymphoma from the beginning, rather than LIP.

## Conclusion

Our observation leads us to believe that at least in the South African context, LIP in HIV-positive adults is more common than reports in the world literature suggest.

We believe that LIP should be included in the differential diagnosis in an interstitial pneumonitis presenting in the HIV-positive adult population.

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broncholitis are considered together with LIP to be along the same morphological spectrum, with some overlap.<sup>3</sup> Differentiation from hypersensitivity pneu-

monitis, organising pneumonia and usual interstitial pneumonia needs to be considered. Importantly, the major differential diagnosis is the separation of LIP from low-