Interstitial pneumonitis in patients infected with the human immunodeficiency virus

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Abstract

Background — A study was performed to identify the clinical, radiographic, and histopathological features of interstitial pneumonitis in patients infected with the human immunodeficiency virus.

Methods — A retrospective review was made of the case notes, chest radiographs, and histopathological results of seven HIV-1 antibody positive patients with symptomatic diffuse pulmonary disease and a pathological diagnosis of non-specific interstitial pneumonitis.

Results — All patients had dyspnoea, with or without cough, and chest radiographs showing diffuse infiltrates. The arterial oxygen tension ranged widely from 5.9 to 13.1 kPa. The initial clinical diagnosis was Pneumocystis carinii pneumonia in most cases. The pathological diagnosis was made by transbronchial biopsy in one case and by open lung biopsy in six cases. The interstitial pneumonitis consisted of a patchy lymphocytic infiltrate composed of B cells in focal aggregates and T cells in a more diffuse distribution. The T cell population was a mixture of CD4+ and CD8+ cells. The histological findings contrast with the more extensive infiltrate of predominantly CD8+ lymphocytes seen in HIV-associated lymphocytic interstitial pneumonitis which occurs mainly in children. The condition ran a subacute course. Three patients spontaneously improved and three improved with steroid therapy. Long term survival was less than three years, the prognosis being determined by other infective or neoplastic complications.

Conclusions — Non-specific interstitial pneumonitis usually presents with an illness resembling Pneumocystis carinii pneumonia but occurs when the CD4 and total lymphocyte counts are still preserved. The pneumonitis resolves spontaneously or responds to steroids, and does not itself lead directly to the patient’s death. It does, however, appear to mark a downturn in the course of HIV infection.

Keywords: interstitial pneumonitis, non-specific interstitial pneumonitis, HIV, AIDS.

Pulmonary disease is a common feature of HIV infection and is often the first indication of the onset of AIDS. The clinical differential diagnosis in a patient presenting with dyspnoea who has diffuse radiological pulmonary infiltrates includes bacterial infection, pneumocystis pneumonia, cryptococcal pneumonia, and pulmonary Kaposi’s sarcoma, all of which are life-threatening conditions for which specific forms of therapy are appropriate. Bacterial, pneumocystis, and cryptococcal pneumonia are usually diagnosed by examination of sputum, induced sputum, or bronchoalveolar lavage fluid. If these investigations fail to yield a diagnosis it may be necessary to proceed to open lung biopsy as some conditions, such as atypical pneumocystis infection and Kaposi’s sarcoma, may only be diagnosed by this procedure. It was in this clinical setting that our seven patients presented.

Methods

The seven patients were all homosexual Caucasian men of mean age 41 years (range 35–56). Two patients had cutaneous Kaposi’s sarcoma. The remainder had none of the criteria for a diagnosis of AIDS but all were known to be HIV antibody positive for periods ranging from 12 to 53 months before their hospital admission for diagnosis. All seven patients complained of breathlessness; five also complained of cough (table 1). The duration of the symptoms was, in most cases, only a few weeks but, in two patients, the duration was three and seven months. Three of the patients were non-smokers. Crackles on auscultation of the chest was the only abnormal physical sign elicited.

Table 1: Clinical features

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>Duration (weeks)</th>
<th>Initial clinical diagnosis</th>
<th>Prior AIDS diagnosis</th>
<th>Duration known to be HIV antibody+ve (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>PCP</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>+</td>
<td>12</td>
<td>PCP</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>2</td>
<td>PCP</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>3</td>
<td>PCP</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>+</td>
<td>3</td>
<td>Pulmonary KS</td>
<td>Cutaneous and nodal KS</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>PCP</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>4</td>
<td>PCP</td>
<td>Cutaneous KS</td>
</tr>
</tbody>
</table>

PCP = Pneumocystis carinii pneumonia; KS = Kaposi’s sarcoma.
except in one patient (no. 5) who had a pleural effusion.

Routine haematological and biochemical blood tests and chest radiographs were performed on all patients on admission. In addition, all patients had induced sputum examinations and fibreoptic bronchoscopy with bronchoalveolar lavage. None of these investigations established a diagnosis and, in particular, no evidence of Pneumocystis carinii infection or endobronchial Kaposi’s sarcoma was found. Every patient had an abnormal chest radiograph but the changes were usually slight and non-specific (table 2) with two main patterns of abnormality – reticular nodular, and a fine perihilar generalised loss of translucency with loss of the normal lung markings. Comparison with the descriptive terms used in much of the radiological literature suggests that the term “reticular nodular shadowing” used in this paper would be termed “interstitial infiltrates”, and “diffuse loss of translucency with loss of lung markings” would be “alveolar infiltrates (grade I or II)”. Most of the radiographs were compatible with a diagnosis of pneumocystis pneumonia. Additional findings were a mass at the right hilum (patient 3), mediastinal hilar gland enlargement (patient 6), and a left pleural effusion (patient 5).

The arterial gas tensions were either normal or showed mild hypoxaemia while breathing air. The exception was a patient admitted with an exacerbation of longstanding asthma who was severely hypoxaemic with an abnormal arterial carbon dioxide tension (patient 2). Treatment with bronchodilators and prednisolone partially corrected the hypoxaemia.

In three patients the CD4 lymphocyte count was measured and was found to be normal in two cases and modestly reduced in the third (table 2). The total lymphocyte count was within the normal range for all patients except one in whom it was just below the normal range.

In five patients the initial clinical diagnosis was pneumocystis pneumonia, though it was appreciated that the normal or near normal CD4 count or total lymphocyte count was atypical for that diagnosis. Two of the patients had an empirical course of treatment for pneumocystis pneumonia with no improvement before lung biopsy.

Four of the seven patients had transbronchial biopsies and in one (patient 4) the diagnosis of non-specific interstitial pneumonitis was made. In the other three the histological findings were inconclusive. These three, together with the remaining patients with negative bronchoscopic investigations, proceeded to open lung biopsy. The lung tissue in all cases was processed, paraffin embedded in routine fashion, and stained by conventional techniques which included Ziehl-Neelsen, PAS, and Grocott’s silver methenamine for acid fast bacilli and fungi, respectively. Immunoperoxidase preparations on paraffin sections were performed for the following leucocyte markers: CD20 for B lymphocytes, CD3 and CD45 RO (UCHL1) for T cells, CD4 for T helper/inducer cells, CD8 for T cytotoxic/suppressor cells, CD21 for dendritic reticulum cells, and CD28 for macrophages. Immunostaining was also performed for cytomegalovirus (CMV) and herpes simplex viruses (HSV) 1 and 2. Epstein-Barr virus (EBV) was sought by immunostaining for latent membrane protein and, in three cases, by in situ hybridisation using an EBER oligonucleotide on paraffin sections. Studies for HIV were not undertaken on tissue sections for technical reasons.

Results
The lung pathology was characterised by an interstitial infiltrate of mature lymphocytes, plasma cells, and macrophages (table 3). In two cases (nos 2 and 3) there were also scattered eosinophils in the infiltrate. The lymphocytes

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Severity of infiltrate (grades 1–3)</th>
<th>B cells (CD20)</th>
<th>Germinatal centres (CD21)</th>
<th>T cells (CD3 and CD45 RO)</th>
<th>Ratio of CD8 to CD4 cells</th>
<th>Other histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Focal</td>
<td>ND</td>
<td>Diffuse</td>
<td>1:0</td>
<td>Patchy intra-alveolar haemorrhage</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>ND</td>
<td>ND</td>
<td>Diffuse</td>
<td>ND</td>
<td>Focal BOOP</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Focal</td>
<td>Present</td>
<td>Diffuse</td>
<td>3:2</td>
<td>BOOP</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Focal</td>
<td>Absent</td>
<td>Diffuse</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Focal</td>
<td>Present</td>
<td>Diffuse</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Focal</td>
<td>Present</td>
<td>Diffuse</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>Focal</td>
<td>Present</td>
<td>Diffuse</td>
<td>3:2</td>
<td></td>
</tr>
</tbody>
</table>

ND = not done; BOOP = bronchiolitis obliterans organising pneumonia.
Interstitial pneumonitis in patients infected with the human immunodeficiency virus

Figure 1  Lung biopsy specimen showing mild non-specific interstitial pneumonitis at low power. Aggregates of lymphocytes are found in the interstitium, especially around vessels, and there are collections of macrophages in alveolar spaces. Magnification × 100.

Figure 2  (A) Lung biopsy specimen showing non-specific interstitial pneumonitis at higher power stained with antibody CD20 showing a peribronchiolar, perivascular aggregate of B cells. (B) Same field as in (A) stained with CD3 showing a more diffuse infiltrate of T cells. Magnification × 250.

were found in aggregates in bronchiolar walls and perivascular areas (fig 1) and in interlobular and subpleural connective tissue. When the infiltrate was more extensive it extended into the alveolar septa. Approximately 50% of the cells within these aggregates were CD20 + B lymphocytes (fig 2A). Follicles, identified by the presence of clusters of CD21 + dendritic reticulum cells, had formed in some of these aggregates. Mixed with the B cell aggregates and extending from them was a more diffuse infiltrate of T cells (fig 2B) which were CD4 + and CD8 + in approximately equal numbers. In two cases there was a slight preponderance of CD8 cells over CD4 cells, and in one case (no. 1) no CD4 + cells were found. The severity of the infiltrate varied from mild and patchy (nos 5 and 6) to severe (no. 3), but was never as extensive or as dense as is seen in lymphocytic interstitial pneumonia. There was no cytological atypia which might have suggested the presence of lymphoma. Oedema fluid and collections of macrophages had accumulated in the alveoli in the vicinity of the interstitial infiltrates and in the bronchioles. Pigment was often present in the cytoplasm of the macrophages and some had formed giant cells. In patient no. 3 there was patchy intra-alveolar organisation of the type seen in bronchiolitis obliterans with organising pneumonia (BOOP). This was also present focally in patient no. 2. Type II pneumocyte hyperplasia was often seen where the alveolar interstitium was expanded by oedema or cellular infiltrates. There were no granulomas. Stains for acid fast bacilli, pneumocystis, and other fungi were negative.

No CMV or HSV was detected immuno-histochemically in the six cases examined. In one case there was insufficient tissue for viral studies. EBV latent membrane protein was negative in six cases but EBV was detected in one of the three cases examined by in situ hybridisation (no. 7), a few scattered positive cells being present in the lymphocytic infiltrate.

Three patients received prednisolone and in two there was an apparent rapid beneficial response to treatment with clearing of the chest radiographs (table 4). In one of these two (no. 6) the Tlco and Kco (which had been 64% and 56% of predicted) rose to normal levels, and that patient remains alive 29 months later. The third patient who received prednisolone (no. 2) had long term asthma. There was an initial improvement after which his condition remained stable for a few weeks; thereafter he pursued a relentlessly downhill course with increasing respiratory failure and recurrent bacterial chest infections.

In two patients (nos 3 and 4) their condition resolved spontaneously, whilst in a third patient (no. 1) there was a reduction in the severity of his dyspnoea and the frequency of his cough but he remained mildly symptomatic. In one patient (no. 5) the course of the illness and the cause of death was attributed to pulmonary and pleural Kaposi's sarcoma. This was not proven as a necropsy was not performed, but he had widespread cutaneous Kaposi's sarcoma and extensive bilateral leg oedema secondary
to Kaposi's sarcoma of the inguinal lymph glands. These findings, together with that of a large left pleural effusion, make it likely that the patient's dyspnoea and his subsequent respiratory failure and death were due to pulmonary Kaposi's sarcoma rather than non-specific interstitial pneumonitis.

The subsequent illness and cause of death in five of the six patients who died (nos 1, 3, 4, 5, and 7) was plainly due to one or more of the complications of AIDS. This includes patient no. 3 who later developed disseminated high grade non-Hodgkin's lymphoma which presented as a mass in the right iliac fossa. There is no evidence that non-specific interstitial pneumonitis contributed to their deaths or to the subsequent course of their illnesses following biopsy. It is possible that the deterioration of respiratory function in patient no. 2 was caused by non-specific interstitial pneumonitis, but the clinical course of the other patients suggests that this is improbable and a more likely explanation is repeated chest infections in a patient with severe long standing asthma.

Although non-specific interstitial pneumonitis did not appear to contribute directly to death in our patients, their survival was, in fact, very poor given that none had significantly reduced CD4 or total lymphocyte counts at the time of diagnosis. No patient has survived longer than 32 months. The patient who is still alive has survived 29 months to date.

**Discussion**

There are a number of conditions reported in patients infected with HIV where there is an infiltration and/or proliferation of mononuclear cells within the lung. These cells, when identified, are predominantly lymphocytes and plasma cells which are polyclonal in origin. These conditions are variously described as lymphocytic interstitial pneumonia, non-specific interstitial pneumonitis, pulmonary lymphoid hyperplasia, lymphocytic bronchiolitis, and follicular bronchitis/bronchiolitis.

Non-malignant lymphocytic infiltration of the lung is not common in adults, whether infected by HIV or not. The two conditions most frequently described in association with HIV infection are lymphocytic interstitial pneumonitis and non-specific interstitial pneumonitis. Lymphocytic interstitial pneumonitis is common in children and rare in adults, whilst non-specific interstitial pneumonitis has only been well characterised in adults. In non-specific interstitial pneumonitis there are few or no symptoms, the radiographic changes are often minimal or non-existent, and any symptoms or radiographic changes which are present either remain unchanged or regress, the subsequent course of their illness being dominated by the development of other complications of HIV disease. In contrast, in lymphocytic interstitial pneumonitis symptoms are usually moderate to severe, reticulonodular shadows, sometimes with a pleural effusion, are seen on the chest radiograph, and extra-pulmonary involvement including generalised and mediastinal lymphadenopathy, parotid enlargement and lymphocytic infiltration of the liver, bone marrow, and gastrointestinal tract is common. Before the advent of AIDS, lymphocytic interstitial pneumonitis was most commonly seen in middle aged women associated with Sjögren's syndrome. It has also been described in children with hypogammaglobulinaemia. A very similar clinical picture is seen in young children less than two years of age infected by HIV. These children also have salivary gland and lymph node enlargement and lymphocytic infiltration of other organs, and there is evidence that the Epstein-Barr virus may play a part in the development of this condition. Lymphocytic interstitial pneumonitis is rarely seen in HIV infected adults, except in a group of Afro-Caribbean patients particularly from Haiti. Some patients with lymphocytic interstitial pneumonitis have been referred to as having the diffuse infiltrative CD8 lymphocytosis syndrome. The condition described in young children with HIV infection referred to as pulmonary lymphoid hyperplasia (PLH) appears to form part of a pathological and clinical spectrum with lymphocytic interstitial pneumonitis (LIP) which is referred to by some as the PLH/LIP complex. There are isolated reports of lymphocytic bronchiolitis and follicular bronchitis/bronchiolitis. The pathological changes observed in lymphocytic

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**Table 4 Clinical outcome**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Treatied with prednisolone</th>
<th>Follow up</th>
<th>Time to death after biopsy (months)</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Improved, then PCP and HIV encephalopathy</td>
<td>26</td>
<td>HIV encephalopathy.</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Stable for several weeks, then progressive respiratory failure</td>
<td>9</td>
<td>Sepicemia.</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Spontaneous resolution, later developed generalised high grade B cell lymphoma</td>
<td>32</td>
<td>Respiratory failure.</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>Spontaneous resolution, then MAI, PCP, CMV infections</td>
<td>32</td>
<td><em>Right carotid artery thrombosis.</em></td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>Increasing dyspnoea due to pulmonary KS</td>
<td>2</td>
<td>Cerebral infarction.</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>Improved, Alive 29 months later</td>
<td>2</td>
<td>No residual lymphoma.</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>Rapid response then cerebral toxoplasmosis</td>
<td>2</td>
<td>No pneumonitis.</td>
</tr>
</tbody>
</table>

PCP = Pneumocystis carinii pneumonia; CMV = cytomegalovirus; MAI = Mycobacterium avium intracellulare; KS = Kaposi's sarcoma.

* Necropsic findings.
Interstitial pneumonitis in patients infected with the human immunodeficiency virus


Joshi, VV, Oleaje, JM. Pulmonary lesions in children with the acquired immunodeficiency syndrome: a reappraisal based on data in additional cases and follow up study of previously reported cases (letter). Hum Pathol 1986;17:641-2.
Griffiths, Miller, Semple


