Pulmonary pathology in AIDS: atypical *Pneumocystis carinii* infection and lymphoid interstitial pneumonia

Mario J Saldana, Joan M Mones

It is generally agreed that the acquired immunodeficiency syndrome (AIDS) results from infection by the human immunodeficiency virus (HIV). The latter agent destroys primarily T helper lymphocytes and produces a progressive impairment of cell mediated immunity with increased susceptibility to various opportunistic infections and malignant tumours. The accepted definition of AIDS, as of 1 January 1993, includes all HIV-infected individuals with severe immunosuppression—that is, less than $200 \times 10^3/\ell$ CD4+ T lymphocytes, or a percentage of CD4+ T lymphocytes below 14% of the total count of lymphocytes. The definition also includes the presence of tuberculosis, recurrent pneumonia, or invasive cervical cancer.

The lung is a major target of disease and the cause of death in most patients with AIDS. About 80% of children infected with AIDS develop pulmonary problems and, if left untreated, 70% will die within two years of diagnosis.

The purpose of this paper is to review and illustrate two lesser known areas of pulmonary disease in AIDS, namely (1) atypical *Pneumocystis carinii* infection; and (2) lymphoid interstitial pneumonia.

**Atypical Pneumocystis carinii pneumonia**

Over the years the taxonomy of *Pneumocystis carinii* has been a matter of controversy. However, recent evidence using RNA probes and Southern blot analysis indicates that it is probably a fungus with a unique unicellular mycelial phase. Vanek and Jirovec in 1952 identified *Pn carinii* as the agent in outbreaks of pneumonia in malnourished infants and children in European orphanages after World War II. It has since become a well recognised pathogen in patients immunocompromised by malignancies, prolonged corticosteroid therapy, and organ transplantation.

The incidence of *Pneumocystis carinii* pneumonia (PCP) has risen dramatically in developed nations since the advent of AIDS. It is often the initial presentation of the disease and will affect eventually 60–80% of these patients. The risk of developing PCP in HIV positive adults increases significantly as the CD4 (helper) T lymphocyte count falls below $200 \times 10^3/\ell$.

The prognosis of PCP in children is much poorer than in adults, and the initial infection is often fatal even though their CD4 T lymphocyte count may be higher. PCP is relatively rare in Africa and has not been reported in Uganda, a country with the highest number of AIDS patients in the world. This surprising finding is probably due to the fact that *Pn carinii* is not indigenous to that part of the world.

The typical patient with PCP develops fever, cough, and shortness of breath. The chest radiograph varies considerably from normal, to relatively mild involvement with interstitial or reticulonodular infiltrates throughout both lungs, to more severe disease with patchy areas of alveolar consolidation. When the alveolar disease becomes extensive and confluent there is respiratory insufficiency, frequently followed by death of the patient. The duration of symptoms of PCP is longer in patients with AIDS than in non-AIDS patients, and the clinical manifestations are somewhat different in the two groups.

The pathological manifestation of early (“incipient”) PCP is characterised by empty alveoli; however, with special stains individual cysts and trophozoites can be seen attached to the alveolar septae (fig. 1). As the infection proceeds the alveoli become progressively filled by masses of exudative material with a characteristic “foamy” or “honeycomb” appearance. Ultrastructurally, the “foamy” exudates of *Pn carinii* consist of large numbers of trophozoites with their microtubular extensions, the parasite cysts, fibrin, and cellular debris. The trophozoites are well demonstrated with Romanovsky type stains such as.
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Giemsa, Wright–Giemsa and Diffquick. The cytoplasm appears blue and the nucleus red surrounded by a pale halo. The cysts are best demonstrated by Grocott's modification of Gomori's methenamine silver (GMS) stain. Cysts and trophozoites can be stained in the same preparation with AFIP light silver/haematoxylin and eosin stain, and Shiota's combined GMS/Giemsa method.14

We have studied the pulmonary pathology in AIDS patients with severe PCP requiring assisted ventilation.15 Patients dying within the first two weeks on the respirator had heavy lungs, usually more than 2000 g in combined weight. The pleura was frequently smooth and shiny. On cut section the lungs were airless, pale grey, and frequently slimy in consistence. Microscopically there was extensive filling of alveoli with proteinaceous exudate (fig 2). Eight patients dying within one week on the respirator had the "exudative" stage of "diffuse alveolar damage" including hyaline membranes and reactive, atypical alveolar lining cells (fig 3a). In nine patients surviving more than one week changes of "proliferative" diffuse alveolar damage were observed, including the presence of intra-alveolar fibroblastic proliferation extending to alveolar ducts and bronchioli (fig 3b). Eleven cases of PCP of a relatively lesser severity responded to treatment but recurrence of the infection on two, three or more occasions was noted in the following months or years; some patients died of other causes.

With the large number of cases of PCP seen in the AIDS epidemic it has been possible to appreciate several atypical manifestations of this infection and these include: (1) interstitial lung disease; (2) lymphoplasmacytic interstitial infiltrates; (3) nodular and granulomatous PCP; (4) cavitary PCP; and (5) extrapulmonary PCP.

INTERSTITIAL LUNG DISEASE

Diffuse alveolar damage is a well recognised, non-specific reaction of alveolar tissue to several injurious agents of a physical, chemical, and biological nature. The development of diffuse alveolar damage in PCP has been the subject of several studies.10–23 In the study by Nash and Fligel15 15 of 17 homosexual males (88%) studied at post mortem examination had PCP. Of these 15 patients 12 (71%) had manifestations of diffuse alveolar damage in the "exudative" and "proliferative" stages. These investigators showed that, while cytomegalovirus (CMV) infection or Pn carinii may be the cause of diffuse alveolar damage, the contribution of other factors such as oxygen toxicity could not be excluded. This is a problem inherent to post mortem studies; it is only when PCP is diagnosed by biopsy and before oxygen administration that a direct relationship between Pn carinii and diffuse alveolar damage can be ascertained. In a study by Ramaswany et al23 diffuse alveolar damage was described in 12 patients with no concurrent infections in the lung biopsy sample; however, some of these patients were receiving treatment for PCP, including oxygen administration.

The mechanisms by which Pn carinii produces diffuse alveolar damage are not clear, although considerable insight has been gained from studies in both humans and animals. Price and Hughes14 described the early stages of PCP, with no clinical manifestations (infestation) and noted that the cysts first attach to the inner lining of the alveolus. In rats developing PCP after the administration of cortisone acetate,
Barton and Campbell, and Lanken et al. also described the attachment of trophozoites to type I pneumocytes. The latter eventually died, leaving a gap in the epithelial lining of the alveolus which was soon repaired by proliferating type II pneumocytes. Observations of the Pneumocystis cycle in vitro corroborated that trophozoites initially attach to type I pneumocytes and later evolve into cysts. After the cysts were released the host cells underwent degeneration and death. It is probable that the breakdown of the alveolar capillary membrane is the mechanism of production of protein-rich oedema fluid that underlies the production of diffuse alveolar damage. Damage to the air-blood barrier probably allows irritants, chemotactic factors, and fibrogenic substances to reach the interstitial space.

Lesions of bronchiolitis obliterans are frequently seen in PCP associated diffuse alveolar damage and may contribute to the respiratory insufficiency. Interstitial fibrosis (“mural” or “septal”) and “honeycombing” as the end stage of diffuse alveolar damage have been described, but they are rare in our experience because most of these patients either recover completely or die before such changes can occur.

Why most patients with PCP develop the “classic” form of the infection with characteristic intra-alveolar foamy exudates while others develop diffuse alveolar damage and other interstitial responses remains unknown. It is possible that in the latter group a much more severe infection with massive numbers of trophozoites diffusely attacking the alveolar capillary membrane underlies the production of the lesions. A different strain of Pneumocystis, or an idiosyncratic host response, are also possibilities to be considered.

LYMPHOPLASMACYTIC INTERSTITIAL INFILTRATES

Pneumocystis carinii may also produce a significant lymphoplasmacytic interstitial infiltrate more striking in children than adults. It is of historical interest that, because of this feature, the disease was originally termed “lymphoid interstitial pneumonia” in 1952. The same designation, however, was later used by Liebow and Carrington in a totally different context. Ironically, a true form of lymphoid interstitial pneumonia unrelated to PCP has become recognised as a major pulmonary process in patients with AIDS (see later).

NODULAR AND GRANULOMATOUS PCP

PCP can present as a localised process in up to 33.7% of patients. Unilateral and lobar distribution have also been reported, and the disease may mimic tuberculosis. Less frequently PCP may present as a nodule simulating a carcinoma or a granuloma. In the case described by Cross and Steigbigel, a 28 year old renal transplant patient on prednisone presented with two nodules in the right lower lobe. Rodriguez-Servera and colleagues reported the case of a 28 year old woman with systemic lupus erythematosus, treated with cyclophosphamide, who developed two masses in the left lung measuring 7 cm and 3 cm in diameter. Hartz et al. described a 57 year old woman with two contiguous nodules of necrotising PCP associated with granulomatous inflammation and fibrosis. In the case described by Bier et al. a nodule lesion also had granulomatous features. Two patients described by Barrio and colleagues had nodular lesions of PCP, in one case associated with central cavitation. Two other patients exhibiting nodular lesions with granulomatous features were reported by Bleiweiss et al., but a third patient with granulomatous features had bilateral and diffuse PCP.

Based on the above information it seems that about half the patients with nodular PCP will exhibit granuloma formation. One can speculate that perhaps the immunosuppressed state of these patients is relatively less profound, hence their ability to mount a localised and granulomatous response. The presence of granulomatous features is rare, yet it is one of the most striking histological findings in PCP (fig 4). Many cases of extrapulmonary spread of Pneumocystis infection are also accompanied by granuloma formation, probably because such lesions occur in organs rich in reticuloendothelial tissue (lymph nodes, spleen, liver). The two patients with diffuse PCP and granulomas described by Blumenfeld and colleagues had received aerosolised pentamidine and zidovudine, so a possible association between the granulomatous response and the inhaled agent (pentamidine) deserves further attention. Ill defined granulomas composed of scattered histiocytes and multinucleated giant cells of foreign body type represent peculiar variations in the spectrum of histiocytic granulomatous responses. They are often seen in treated patients and in

Figure 4 Granulomatous PCP mimicking tuberculosis. The centre of the granuloma contains the foamy exudate characteristic of PCP and later confirmed by silver stain. Stain: haematoxylin and eosin, original magnification × 200 reduced to 90% in origination.
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Figure 5 (a) Chest radiograph of a 32 year old homosexual male with bilateral, confluent reticulonodular infiltrates and extensive cavitation of both apices. (b) Section of the lung at post mortem examination showing extensive cavitation at the left upper lobe lesion with surrounding PCP consolidation.

association with masses of degenerated and calcified PCP exudate.

CAVITARY PCP
For many years it was believed that *Pn carinii* was unable to elicit tissue necrosis in the lung but recently this has been contradicted.43,44 Five cases of PCP with cavitary lesions, some presenting with pneumothoraces, were described by Eng and colleagues.45 These investigators thought that the chronicity of PCP in AIDS patients was responsible for the accumulation of many activated macrophages with production of elastase and subsequent digestion of lung tissue. Mark44 and Liu et al45 proposed that arterial invasion by the organisms leads to thrombosis and secondary necrosis and cavitation of lung tissue. *Pneumocystis carinii* could be identified within the vascular lumina,44,45 and the authors described severe necrotising vasculitis with lymphocytes, immunoblasts, and plasma cells. In 1989 we described a peculiar invasion of the pulmonary interstitium and pulmonary vessels by *Pn carinii* in a case of cavitary pneumonia (figs 5 and 6).46

Travis et al47 reviewed 123 lung biopsy specimens from 76 patients with PCP and reported one case of vascular invasion with associated vasculitis; several of their cases had intraparenchymal cysts probably representing cavitation with septal invasion. In a recent study Murry and Schmidt48 described tissue invasion in seven patients with AIDS and two with leukaemia. Invasion of *Pn carinii* into the interstitial compartment was present in eight of their nine patients. Organisms were demonstrated in alveolar septa (eight cases), pleura (six cases), and vessel walls (two cases). Pulmonary cavitation occurred in seven of eight cases with tissue invasion, and six of these patients developed pneumothoraces. Ultrastructurally, both the tissue invasive and the intra-alveolar organisms were predominantly of the trophozoite form; they were present in greater numbers than suggested by the routine silver stain which detects only cysts. Immunocytochemical techniques which demonstrate both trophozoite and cyst forms were much more sensitive than silver stains for the detection of *Pn carinii*.

Murry and Schmidt48 addressed the problem of how tissue invasion causes necrosis in PCP. The possibility of a host inflammatory response was ruled out in view of the distinct paucity of inflammation in these cases. A second mechanism – direct tissue injury by toxins or hydrolytic enzymes which might be elaborated by the organism – cannot be accepted or rejected since so little is known about the biology of *Pn carinii*. A third possibility – vascular invasion with secondary infarction – seems unlikely since six patients with cavitation in their study46 did not show vascular invasion and, when present, the latter was not quantitatively sufficient to explain the extent of the necrosis. Nevertheless, the possibility of collapse of pulmonary capillaries within the distended alveolar septa producing ischaemia and necrosis is an attractive hypothesis to be explored further.48

The role of a coinfection in the cavitary phenomenon in patients with PCP also deserves attention since many of these patients do have mixed infections. As noted by Murry and Schmidt,48 however, the strongest evidence supporting a primary role for *Pn carinii* was that two patients with cavitation had no documented coinfections, and a third patient had cytomegalovirus isolated from the urine only. The possibility of a necrotising concomitant infection should, however, be carefully ruled out when examining cases of cavitary PCP.
EXTRAPULMONARY PCP

Extrapulmonary spread of *Pn carinii* infection does occur in patients without as well as with AIDS.49-58 Favoured sites of spread include the regional lymph nodes and other organs rich in reticuloendothelial tissue such as liver and spleen. Unusual presentations include polypoid lesions of the ear,5091 and spread to the hard palate, pericardium, and thymic capsule.52 Pavlica53 reported a remarkable case of transplacental spread of the organism via haematogenous pathways. Eye involvement has been documented.44-56 Unger et al46 described the presence of *Pn carinii* in Virchow-Robin spaces surrounding cortical arterioles. Macher56 believes that splenomegaly and lymphadenopathy, not infrequent clinical findings in patients with AIDS, may be caused by disseminated *Pn carinii* infection. A remarkable example of *Pn carinii* infection presenting as a small intestinal mass causing an acute abdomen, in the absence of pulmonary involvement, was reported by Carter et al.59 Regardless of location, the presence of *Pn carinii* in organs other than the lung can be recognised by the same characteristic eosinophilic “honeycomb” exudates.

Lymphoid interstitial pneumonia

Lymphoid interstitial pneumonia was described by Carrington and Liebow60 in an abstract, in 1966, based on four adults and one child who exhibited massive lymphoid infiltrates of the lung, bilateral in four patients and unilateral in one. The definitive description,70 published seven years later, was based on 17 patients and appeared under the title “diffuse pulmonary lymphoreticular infiltrates associated with dysproteinenaemia.” This remarkable feature of the disease has since been corroborated by other investigators.39-49 We estimate that about 80% of patients with lymphoid interstitial pneumonia will present with dysgammaglobulinaemia.

Lymphoid interstitial pneumonia has been described in association with Sjögren’s syndrome,70-72 primary biliary cirrhosis,73 pernicious anaemia and agammaglobulinaemia,74 chronic active hepatitis with renal tubular acidosis,75 and allogenic bone marrow transplantation.76 Familial occurrence has been described.77 Whether it represents an inflammatory (“reactive”) process or a malignant lymphoma was a question already posed by Liebow and Carrington.80-81 Observations over the past two decades indicate that most examples of lymphoid interstitial pneumonia are initially low grade lymphomas and later evolve into aggressive lymphomas in the lung and elsewhere.78-80 This transition may take many years. It might never become manifest in adult patients with short follow up studies. It is therefore convenient to state80 that lymphoid interstitial pneumonia is best considered “a prelymphomatous state frequently associated with other features of immune dysregulation.”

In 1983 we described a form of lymphoid interstitial pneumonia occurring almost exclusively among Haitian adults and children.
living in Miami, Florida, who also had HIV infection. At about the time of the original description Oleske et al and Rubinstein et al also noted the same process in their series of children with AIDS living in the north-eastern USA. Kradin and Mark, also in 1983, in their papers on benign lymphoid disorders of the lung included two Haitian adult patients with the same disease. Subsequent papers have described in greater detail the clinical manifestations, radiological features, and aetio-pathogenesis of this pulmonary condition of HIV infected individuals.

Most of the adults in our study (81%) had HIV infection only at the time of diagnosis. Fifteen of these patients (43%) progressed to AIDS during the course of their disease, while 20 (57%) did not evolve into full blown AIDS. Only eight patients (19%) had AIDS at diagnosis and remained so until death. By definition, all children in this study had AIDS.

Chest radiographs taken at the time of diagnosis and during the evolution of the disease were classified into four grades: 0, normal chest radiograph; I, reticulonodular infiltrates with nodules up to 5 mm in diameter, frequently referred to as “miliary”; II, grade I plus one or more patchy areas of alveolar consolidation; III, one or more areas of alveolar consolidation and little or no interstitial component of significance (“atypical” lymphoid interstitial pneumonia). In adults grades I (39%) and II (54%) occurred most frequently. In children grade I was the most common pattern at presentation (67%), to be superseded by grade II (67%) at later stages of the disease.

Pathologically the mildest or earliest forms of lymphoid interstitial pneumonia represents hyperplasia of bronchial associated lymphoid tissue (BALT) with little interstitial involvement (fig 7). Aggregates of lymphocytes and plasma cells form around airways and blood vessels. As the disease progresses they extend along the alveolar septae (fig 8). In later stages large confluent nodules often measure up to 2-5 cm in diameter. The lung parenchyma in these areas is solid and resembles a lymph node. Lymphoid interstitial pneumonia has not been noted to progress to interstitial fibrosis of the lung in either children or adults; progression to Kaposi's sarcoma has been noted in adults only. In children it can be a debilitating disease producing respiratory insufficiency with severe hypoxaemia and digital clubbing. In adults it is usually asymptomatic but its radiographic features mimic PCP.

The composition of the lymphocytic population was studied in two children and one adult by monoclonal antibodies applied to frozen sections of the lesions. The results were comparable in all three cases and were characterised by: (1) positivity for both kappa and lambda light chains (polyclonality); (2) distinct predominance of T lymphocytes (CD3/Leu3) over B lymphocytes (CD22/Leu4); and (3) T suppressor lymphocytes (CD8/Leu2) in significantly greater numbers than T helper lymphocytes (CD4/Leu3).

Bronchiolitis obliterans consisting of polypoid structures of loose myxoid connective tis-
sue occluding respiratory bronchioles was seen. Distally, there was atelecasis with accumulation of “foamy” histiocytes, a picture characteristic of “endogenous” lipid pneumonia. The presence of bronchiolitis obliterans was frequently seen in association with the most severe degrees of lymphoid interstitial pneumonia and probably accounts for the areas of alveolar disease.

The pathological evolution of lymphoid interstitial pneumonia from the time of diagnosis to death was studied in a group of eight adults and five children at post mortem examination. In three adults the process had resolved completely, in four it remained unchanged, and in the remaining patient it showed signs of slight regression. The striking nodular component of the lesions was markedly diminished or had vanished altogether in most children studied at post mortem. On the other hand, the diffuse component of lymphoid interstitial pneumonia remained unchanged in four patients and actually increased in one. In none of the patients, adults or children, was there evidence of diffuse interstitial fibrosis of the lung, but increased amounts of reticulin fibres and loose fibroblastic as well as capillary proliferation were present at sites of previously hyperplastic BALT.

Unusual associations of lymphoid interstitial pneumonia infected individuals include the remarkable transformation of infiltrates of lymphoid interstitial pneumonia into Kaposi’s sarcoma in two cases (fig 9); the development of multiple vascular leiomyomas in one child (fig 10); and lymphocytic arteritis associated with plexiform structures and a picture of “primary” pulmonary hypertension in another adult (fig 11).

The pathogenesis of lymphoid interstitial pneumonia remains to be clarified. The recovery of HIV from bronchoalveolar lavage fluid in these patients, as well as in situ hybridisation studies by Chayt et al. and Travis et al. support the role of this virus as the cause of lymphoid interstitial pneumonia. In five of our cases, however, the presence of HIV was investigated by the avidin-biotin immunoperoxidase technique using p24 antibody (Du Pont Laboratories, Wilmington, Delaware, USA) in formalin fixed, paraffin embedded tissue, with negative results.

A second line of thinking suggests that, following infection of T lymphocytes by HIV, Epstein-Barr virus (EBV) containing B lymphocytes proliferates leading to a polyclonal B cell population in the lungs and other tissues. The role of EBV in our patient population was investigated several times. Two of the seven
children had negative serological evidence of prior EBV infection, a finding that mitigates strongly against a primary role for EBV. Only one child had serological evidence of acute infection at the time of diagnosis of lymphoid interstitial pneumonia. This child exhibited the most florid example of lymphoid proliferation, including germinal centres with tingible body macrophages in the lung and regional lymph nodes. In situ hybridisation of the lung biopsy material for EBV showed only a rare positive cell. Four adults in whom in situ hybridisation for EBV was carried out were negative. We conclude that, although HIV is probably the main cause of lymphoid interstitial pneumonia, it is also possible that in some patients EBV might be a coexistent factor in triggering the lymphoproliferative response. A possible link between lymphoid interstitial pneumonia and the HTLV-I or HTLV-II viruses has recently been suggested, but the results are still inconclusive.109

Figure 11  (a) Necrotising lymphocytic vasculitis in a young Haitian patient with AIDS, lymphoid interstitial pneumonia, and pulmonary hypertension. The arrow indicates the remains of the arterial wall, much of which is totally destroyed and infiltrated by lymphocytes. A muscular artery adjacent to a bronchile shows marked medial hypertrophy (two arrows). (b) Same case as in (a) showing a well developed "plexiform" structure. The parent artery shows marked medial hypertrophy and a cushion of fibrous tissue at the origin of the "plexiform" lesion (arrow). Note the adjacent "dilatation" lesions and the absence of angitis at this stage. Stain: elastic tissue. Original magnification × 80 reduced to × 57% in origination. Reproduced from ref 88 with permission.


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