Pulmonary alveolar proteinosis in an AIDS patient without concurrent pulmonary infection

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AT LIU, LJ MIEDZINSKI, E VALLIERES, DC RAYNER, DC LIEN. Pulmonary alveolar proteinosis in an AIDS patient without concurrent pulmonary infection. *Can Respir J* 1995;2(3):183-186.

Patients with acquired immunodeficiency syndrome (AIDS) are potentially at increased risk for developing secondary pulmonary alveolar proteinosis because of underlying immunosuppression and frequent opportunistic lung infections. This condition, however, has been diagnosed uncommonly in these patients and, with the exception of one previously reported case, only in the presence of concurrent pulmonary infection. The case of a 35-year-old male with AIDS who was found on open lung biopsy to have pulmonary alveolar proteinosis without evidence of associated lung infection is presented.

Key Words: *Acquired immune deficiency syndrome, Pneumocystis carinii pneumonia, Pulmonary alveolar proteinosis*

Protéinose alvéolaire sans infection pulmonaire concomitante chez un patient sidatique

RÉSUMÉ : Les patients souffrant du syndrome d'immuno-déficience acquise (SIDA) sont potentiellement à plus grand risque de développer une protéinose alvéolaire secondaire à cause d'une immunodépression sous-jacente et de fréquentes infections pulmonaires opportunistes. Cependant, cette affection a rarement été diagnostiquée chez ces patients et, à l'exception d'un cas précédemment rapporté, seulement en présence d'une infection pulmonaire concomitante. Le cas d'un homme de 35 ans atteint du SIDA dont la biopsie pulmonaire ouverte a révélé une protéinose alvéolaire sans évidence d'une infection pulmonaire concomitante est présenté.

PULMONARY ALVEOLAR PROTEINOSIS (PAP) IS AN UNCOMMON condition that may be either primary (idiopathic), arising in an otherwise healthy patient, or secondary, where it occurs in a setting of altered immunity or concurrent lung infections. Patients with acquired immunodeficiency syndrome (AIDS) should be at risk for this disorder al-

though it has rarely been reported in this population (1). Previous reports of PAP in AIDS patients have usually been in the presence of an active or recent infection. We present a case without an associated lung infection which, to our knowledge, has been reported only once previously (2).

Figure 1) Chest radiograph showing poorly defined airspace consolidative changes in both lung fields, more predominant in the left mid-lung zone. The radiographic results remained unchanged from December 1992 to February 1993

CASE PRESENTATION

A 35-year-old homosexual male was found to be positive for the human immunodeficiency virus (HIV) in 1987. He had documented *Pneumocystis carinii* pneumonia (PCP) in March 1991 and again in April 1992. Because of adverse effects from pentamidine and sulpha, he was maintained on dapsone as prophylaxis against PCP. In addition, he had previously developed cutaneous Kaposi's sarcoma, which was treated with local irradiation, esophageal candidiasis treated with fluconazole, and cutaneous herpes simplex infection for which acyclovir was prescribed. In July 1992, because of a two-week history of mild dyspnea and nonproductive cough without significant radiographic change, a bronchoalveolar lavage (BAL) was performed which failed to demonstrate any bacterial, viral or fungal organisms, including *P. carinii*. These symptoms subsided spontaneously without specific treatment.

He presented again in December 1992 with a four-month history of progressive dyspnea on exertion, nonproductive cough, fever, anorexia and fatigue. His chest radiograph and computerized tomographic (CT) scan are shown in Figures 1 and 2, respectively. He underwent fiberoptic bronchoscopy with BAL and transbronchial lung biopsies from the lingula. No endobronchial Kaposi's sarcoma was seen and there was no evidence of bacterial, viral, fungal, mycobacterial or pneumocystis organisms in the BAL fluid. Analysis of the differential cell count of the BAL showed greater than 80% macrophages and the biopsies failed to reveal any inflammatory or neoplastic changes.

Figure 2) Computerized tomographic section showing patchy airspace consolidation. The mediastinum and hila were free of lymphadenopathy

Figure 3) Open lung biopsy stained with hematoxylin and eosin. Airspaces are obliterated by amorphous eosinophilic material with no cellular infiltrate. Magnification X13.6

His symptoms and radiographic changes persisted unaltered and in February 1993 an open biopsy of the lingula was performed. Paraffin sections showed obliteration of the distal airspaces by eosinophilic amorphous material which stained variably positive with periodic acid-Schiff (PAS) (Figure 3). No inflammatory infiltrate, no specific viral changes and no interstitial process was seen. Multiple sections examined with Gomori's methenamine silver (GMS), Ziehl-Neelsen, Fite and Gram stains revealed no pathogenic organisms and an immunoperoxidase stain for cytomegalovirus (Chemicon, California) was negative. In addition, routine cultures of the biopsy tissue for bacteria, viruses, fungi and mycobacteria were negative.

No active treatment was instituted and at his follow-up two months later, he reported no new symptoms but was still dyspneic after walking one block. Six weeks later he was readmitted to hospital because of increasing dyspnea, cough and hypoxemia. Chest radiograph revealed airspace disease in upper lung zones bilaterally. Bronchoscopy with BAL was undertaken and the results were diagnostic of PCP on this

occasion. The patient initially improved with treatment and was discharged, but one week later required readmission due to worsening dyspnea, cough and hypoxemia. Chest radiograph demonstrated more dense consolidation diffusely. His condition deteriorated rapidly and he subsequently died. An autopsy was not performed.

DISCUSSION

PAP was initially described in 1958 by Rosen et al (3). Pathologically, the characteristic change is an accumulation of amorphous PAS-positive phospholipids and proteins in the alveoli, with preservation of the interstitium. Various theories of its pathogenesis have been proposed that revolve around a disturbance of alveolar surfactant homeostasis, with a defect in the removal or resorption of surfactant being the most favoured (4). The two classical symptoms are chronic cough, which is usually nonproductive, and progressive dyspnea on exertion. Less common symptoms include fever, weight loss, fatigue, chest pain and hemoptysis. Chest radiographs show nonspecific alveolar infiltrates without mediastinal lymphadenopathy. CT scans characteristically demonstrate a grey homogeneous appearance of the lungs related to the underlying consolidative process. Overlying this is a branching pattern of white linear structures representing the thickened interlobular septa between the secondary lobules. This results in an overall 'crazy paving' appearance typical of alveolar proteinosis (5). In contrast, PCP is a diffuse airspace disease that appears as focal areas of ground glass opacification on CT through which pulmonary vessels can still be identified. Kaposi's sarcoma classically takes on a nodular pattern in the perivascular and peribronchial regions (6). Gallium scan is negative in PAP. Pulmonary function testing typically demonstrates a restrictive defect with decreased total lung capacity and vital capacity, along with a low diffusing capacity. The diagnosis may be made on BAL specimens due to the presence of granular acidophilic phospholipid material, which stains positively with PAS and has a characteristic ultrastructural appearance (7). Transbronchial or open lung biopsy may be required for diagnosis. Biopsy may also be required when the possibility of a concurrent process, particularly infection, remains in the differential diagnosis. PAS staining was not performed on the BAL fluid in this patient because the diagnosis was not suspected.

Two forms of this pulmonary disorder have been described, with primary or classic PAP occurring without an associated cause, while secondary PAP (or alveolar phospholipidosis) is reported to be linked to certain conditions, most importantly lung infections (8-10) and immunodeficiency states (11). It seems that AIDS patients should be at risk for this latter form of PAP (1). However, to our knowledge, only nine cases of PAP have been reported in this patient population, in eight of whom it was associated with a simultaneous opportunistic lung infection. PCP was found in six cases (7), tuberculosis in one case (12), and PCP together with disseminated cytomegalovirus in one case (12).

The relationship between lung infection and PAP in AIDS

patients remains unclear. It is still possible that infection may have been an important part of the pathogenetic process in our patient. Although we were unable to demonstrate an associated infection, our patient did have previous PCP, which could have an unknown pathogenetic role. Of further concern is that our patient relied on a less effective agent, dapsone, as prophylaxis against PCP.

Dapsone is used for both primary and secondary PCP prophylaxis, especially in those who are intolerant of trimethoprim-sulfamethoxazole, as was the case in our patient. Dapsone is felt to be as effective as aerosolized pentamidine, which is also used as prophylaxis against PCP and may be associated with a lower diagnostic yield for *P. carinii* on BAL (13), but this issue has not been studied with dapsone. However, the diagnostic gold standard is a lung biopsy and our patient did have transbronchial and open lung biopsies while he was on dapsone, but neither demonstrated *P. carinii* or any other microorganisms. To ensure this, we carefully examined approximately 8 cm² of GMS stained tissue from several blocks of the open lung biopsy and found no organisms. We therefore believe that our patient is the second reported case of PAP described in an AIDS patient without a concurrent or recent pulmonary infection.

Furthermore, superinfections are known complications of PAP (4). Our patient was found to have PCP 3.5 months after the diagnosis of PAP, with progressive deterioration until his demise. Indeed, superimposed infections and respiratory failure from the proteinosis are the two major causes of death from this disorder.

In spite of a 30% mortality from PAP noted before the era of lung lavage, spontaneous and complete remission is known to occur in 20 to 25% of patients (14). However, there are no factors that accurately predict which patient will succumb, remit or respond to treatment. This uncertainty in the natural course of PAP in any given patient serves to account for the lack of a specific and well-defined set of indications for therapeutic intervention. Various objective criteria have been proposed, including arterial PO_2 less than 65 mmHg, difference in partial pressures of oxygen in mixed alveolar gas and mixed arterial blood greater than 40 mmHg, shunt fraction greater than 10 to 12%, and all confirmed histological diagnosis (15,16). However, the decision to recommend treatment is generally based on the extent to which PAP affects the patient in relation to his or her exercise tolerance, lifestyle and occupation. That is, if the patient's daily activities are limited by the symptoms, treatment may be appropriate (4).

Various treatment options were used in the past, including systemic corticosteroids and inhalational therapy with heparin, trypsin or acetylcysteine, but they have largely been abandoned due to their side effects and lack of proven efficacy. Whole lung lavage is currently the therapy of choice and functions by mechanically removing the intra-alveolar phospholipids. It is safe and effective in the majority of patients if performed by an experienced multidisciplinary team (4). However, secondary PAP, as seen with concurrent pulmonary infection and/or underlying immunodeficiency, may not

have as favourable a response to whole lung lavage as primary PAP. Therefore it may be important that the diagnosis of primary PAP not be made unless the possible secondary causes have been excluded because therapy may be best directed at these causes initially. This underlies the need for histological examination of lung tissues in certain cases to obtain an accurate diagnosis, thus allowing appropriate therapy to be given.

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CONCLUSIONS

This case should alert clinicians to include PAP in their differential diagnosis in an AIDS patient who presents with an alveolar infiltrate accompanied by a nonproductive cough and exertional dyspnea. Although PAP is often associated with a pulmonary infection in patients with AIDS, the absence of an identifiable organism does not appear to preclude its diagnosis.