PULMONARY ALVEOLAR PROTEINOSIS - A CASE REPORT

B S P Ang, W T Poh, Y Y Ong, G S C Chiang

ABSTRACT

Pulmonary alveolar proteinosis is a relatively rare disease. Its etiology is unknown but it has been found associated with various opportunistic infections as well as immunological conditions.

The clinical and radiological features may be indistinguishable from other respiratory disorders and diagnosis is often dependent on histology. Its course can vary from progressive deterioration to spontaneous improvement and treatment with bronchopulmonary lavage may not always be necessary.

Many theories regarding pathogenesis have been put forward and most of these centre upon the roles of alveolar macrophages. We describe a case of Pulmonary Alveolar Proteinosis in a local Oriental male and reviewed the current understanding of its pathogenesis.

Keywords: Alveolar, proteinosis, interstitial.

SINGAPORE MED J 1991; Vol 32: 454 - 456

INTRODUCTION

The first case of Pulmonary Alveolar Proteinosis was described by Rosen in 1958[1]. Since then more cases have been described but it still remains a rare disease.

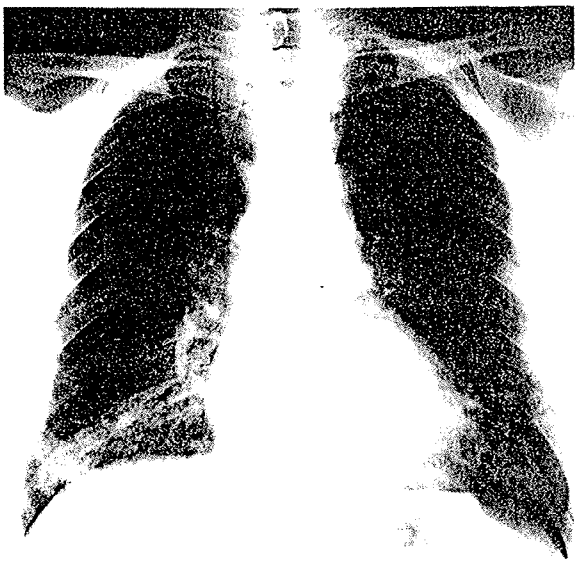
CASE REPORT

HKY, a Chinese male, was 49 years old when first seen in November 1984. He presented with a history of mild cough and breathlessness for two weeks and fever for one day. There was no history of weight loss, sputum, haemoptysis or night sweats. He worked as a controller in a power station and was not in contact with any animals. His last chest X-ray two years prior had been normal.

On clinical examination, he had occasional crepitations in the left lung base. There was no cyanosis or clubbing. Laboratory investigations showed normal blood gases, urea and electrolytes. His haemoglobin was 14.9g/dl, total white 12,800 per mm^3 with a normal differential count, and ESR 11mm/hour. His chest X-ray showed multiple small fluffy shadows in both lung bases. He was treated as for atypical pneumonia with erythromycin but there was no improvement. Further investigations were done. His LE cells, rheumatoid factor, anti-nuclear factor, mycoplasma antigen, and mycobacterium tuberculosis culture were all negative. A bronchoscopy done showed a normal bronchial tree, and the transbronchial biopsy showed normal lung tissue. Lung function studies including spirometry, static lung volumes and diffusion capacity were all within normal limits.

The patient remained stable clinically with no change in chest X-ray findings for a period of seven months. He then developed a dry cough and his Mantoux test was strongly positive. A therapeutic trial of anti-tuberculous therapy for six months was given but stopped when the patient failed to improve clinically and radiologically. A year later, he complained of weight loss of about two kilograms, painful fingers and exertional dyspnoea. Chest X-ray at that time showed honeycombing (Fig 1). He refused an open lung biopsy. Based on a working diagnosis of fibrosing alveolitis, he was started on steroids.

Fig 1
Chest X-ray of Patient (August 1985)
Showing Extensive Honeycombing



His chest X-ray continued to show honeycombing but the patient remained relatively asymptomatic except for mild

Department of Medicine III
Singapore General Hospital
Outram Road
Singapore 0316

B S P Ang , M Med (Int Med)
Registrar

Y Y Ong, M Med (Int Med) (S'pore), FRACP
Senior Consultant

Department of Pathology
Singapore General Hospital

W T Poh, FRCPA
Senior Registrar

G S C Chiang, DPath, DCP (Lond), FRCPath, FCAP, AM
Senior Consultant

Correspondence to: Dr B S P Ang

breathlessness after walking half a mile. Objectively, his lung function test did show a fall in the Forced Vital Capacity (from 2.42 litres in February 1985 to 2.16 litres in January 1987). The patient finally agreed to a repeat transbronchial biopsy in March 1987.

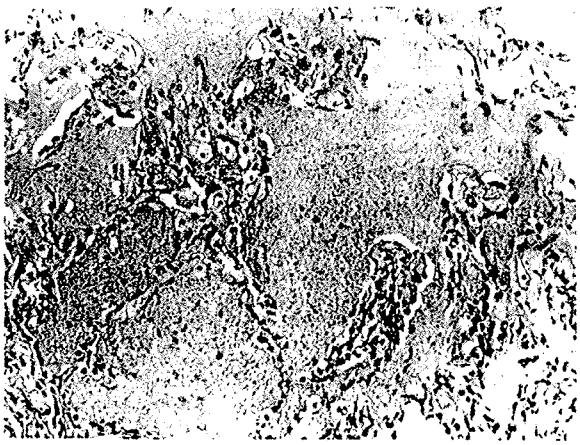
On subsequent reviews, he remained quite well up to four and a half years after the onset of his illness. Broncho-alveolar lavage was not performed as he remained clinically stable. In May 1988, his chest X-ray showed marked reduction in infiltrates.

HISTOLOGY

The histology of the repeat transbronchial biopsy done in March 1987 showed the alveolar spaces expanded and filled with granular eosinophilic material which were Periodic acid-Schiff (PAS) positive and diastase resistant (Fig 2). The alveolar septae were normal except for an increased numbers of cuboidal "septal cells" (Type 2 alveolar pneumocytes) in the alveolar lining. There was little inflammatory response. A few macrophages were present in the alveolar spaces together with ghost-like cell remnants. Special stains for acid fast bacilli and fungi were negative.

Fig 2

Alveolar Proteinosis. Alveoli are Filled with Flocculent Exudate With a Few Nuclei, Remnants of Degenerate Cells and Granular Eosinophilic Material. H&E x 200.



DISCUSSION

PAP is a condition characterised by the accumulation of lipo-proteinaceous material and cellular debris within alveolar spaces. The disease was first described by Rosen in 1958[1], who thought that exposure to wood products might play an etiological role. This, however, has never been established. The etiology of this condition remains unknown but it has been found associated with opportunistic infections such as tuberculosis[2,3], cryptococcosis[4], Nocardiosis[5,6] and conditions where there is immunosuppression[7,8] such as AIDS[9] and haematologic disorders[10].

Clinical Features

Most patients present with slowly increasing pulmonary infiltrates, productive cough and progressively decreasing effort tolerance. A few are asymptomatic. Most cases are adults, but infants and adolescents are also affected. In Rosen's first description of 27 cases, two were children, aged 2 years 4 months and 15 years respectively. Pulmonary function tests usually show a reduced vital capacity. A large pulmonary right to left shunt may be present and serial LDH may also be elevated[11]. The chest X-ray often gives an 'interstitial' pattern[12] to the extent of 'honeycombing' , rather than the 'alveolar' pattern expected of a condition showing predominantly intra-alveolar accumulation of material. This is thought to be due to hydrolysis of the alveolar material which gives rise to an inflammatory reaction in the alveolar wall. However, as Ramirez[13] noted, there is no roentgenographic pattern that is characteristic of PAP.

Pathology

Macroscopically the lungs are described as having a firm, yellow-tan appearance. The striking feature histologically is the filling of the alveolar spaces by PAS positive, diastase resistant material which are at times, granular. The pulmonary architecture is intact with normal alveolar septae except for the slight increase in Type 2 alveolar pneumocytes. Hardly any inflammatory infiltrate is present, except for an occasional macrophage.

Electron microscopy of the alveolar contents show numerous concentric and lamellar bodies that are similar to the cytoplasmic inclusions normally found in Type 2 pneumocytes. Alveolar macrophages containing these bodies are also seen[14].

Biochemistry studies on lavage fluid from patients with PAP show the presence of protein, cholesterol and a phospholipid fraction that is similar in composition to pulmonary surfactant[15-17]. In fact, surfactant specific proteins are invariably present and antibodies have been developed against a surfactant specific apoprotein. This antibody has been found to stain specifically Type 2 pneumocytes and the intra-alveolar material of lungs affected by alveolar proteinosis[18,19]. Besides surfactant, the accumulated fluid in alveolar proteinosis also contains plasma proteins, other glycoproteins and cellular debris[20].

Primary and Secondary PAP

Alveolar accumulation of proteinaceous fluid rich in phospholipids have been found in association with other diseases eg tuberculosis[2,3], cryptococcosis[4], nocardiosis[5,6], lymphomas[8,10], leukemias[8,10], pulmonary interstitial fibrosis[21,22], AIDS[9] and other immune suppressed subjects[7]. The alveolar proteinosis present in these patients are considered secondary and appears to be confined to a more localised area of the lung.

Diagnosis

The diagnosis is usually arrived at by examination of the intra-alveolar material, obtained either by biopsy specimen or by segmental lavage. Positive staining by PAS method has been considered characteristic enough to be diagnostic in the past. However, with the use of specific immunologic staining of surfactant apoprotein, Singh et al[18,19] demonstrated that the histologic appearance and the PAS staining of intra-alveolar granular material are not sufficient to establish the diagnosis of PAP. The intra-alveolar proteinaceous material from patients with PAP and no other associated diseases (ie primary PAP) stained densely and uniformly for surfactant apoprotein, whereas the intra-alveolar material of patients with PAP-like histologic appearance (secondary PAP) did not. This finding suggests that PAP may be a more specific condition than has generally been thought[23].

Pathogenesis (Singh et al)

Surfactant, under physiologic conditions, appears to be cleared by:

(a) re-uptake by alveolar cells;
(b) centripetal movement along the mucociliary escalator;
(c) lymphatics; and
(d) macrophages[25,26].

In theory, excessive accumulation of surfactant could occur either due to excessive production or deficient removal or both. Earlier studies indicate that the rate of synthesis of surfactant in patients with alveolar proteinosis is not increased[16]. Even though hypertrophy and hyperplasia of Type 2 cells are seen in patients with alveolar proteinosis, such changes are focal and appear to be secondary. It is quite conceivable that all modes of surfactant removal are defective in alveolar proteinosis. However, a deficiency in one of the mechanisms may be sufficient to explain the lesion.

It appears that pulmonary macrophage function may be defective in patients with alveolar proteinosis[20]. Even more impressive is the lack of macrophages in a tissue with as much debris as seen in a lung with alveolar proteinosis. It is possible that accumulated material in itself may be inhibitory to the function of macrophages. The evidence in support of this notion comes from the finding of defective pulmonary macrophages while circulating monocytes are normal. The alveolar proteinosis material may be hindering the migration of macrophages into the lungs. This is indicated by the changes following the removal of accumulated material by lavage. As seen in the lavage material and sections of the tissue, few macrophages are present in the involved areas of alveolar proteinosis. However, a greater than normal number of macrophages can be recovered by lavage from areas that had been lavaged a week earlier to remove alveolar proteinosis material. Surfactant has been shown to be immunosuppressive and it could exert a suppressive effect on macrophages.

The sum of clinical and experimental observation suggests that the following sequence of events, in genetically susceptible persons, could result in alveolar proteinosis:

(a) pulmonary injury leading to inflammatory exudate and transient impairment of mucociliary clearance (infection could provide such a state);
(b) with the removal of the noxious agent, the inflammatory exudate subsides and is cleared in part by the lymphatics, macrophages, and the mucociliary escalator;
(c) during the brief period of deficient clearance, surfactant accumulates with the exudate and surfactant-associated apoproteins aggregate due to their hydrophobic nature and are not cleared[27];
(d) accumulated surfactant material inhibits the macrophage function and/or their migration from the vascular to the intra-alveolar compartment, and
(e) this may create a vicious cycle leading to excessive accumulation of surfactant and surfactant apoprotein; and other surfactant associated proteins. The situation may sometimes be worsened by the active hyperplasia and hypertrophy of Type 2 pneumocytes, though that is probably a minor and secondary component. Pulmonary lavage may be acting by removing the accumulated material and restoring the clearance mechanism, especially the re-entry of macrophages into the involved areas.

Treatment

This involves repeated bronchopulmonary lavage[28] which may affect prolonged clinical remission. Both spontaneous remission and progressive respiratory failure have been described in untreated patients[29].

ACKNOWLEDGEMENT

The authors would like to thank the following people for their help. Dr Chan Tiong Beng who performed the transbronchial biopsy, Dr D Thiagaraj and Dr Anjula Thomas for reporting the histology, Dr Yeoh Swee Imm for proof-reading and Mrs T H Koh for typing the manuscript.

REFERENCES

1. Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958; 258:1123-42.
2. Ramirez RJ. Pulmonary alveolar proteinosis: Treatment in a case complicated by tuberculosis. Am Rev Respir Dis 1967; 95:491-5.
3. Lathaw SR, Williams JD Jr, McLean RL, Ramirez RJ. Pulmonary alveolar proteinosis: Treatment of a case complicated by Tuberculosis. Chest 1971; 9:452-4.
4. Sunderland WA, Campbell RA, Edward MJ. Pulmonary alveolar proteinosis and pulmonary cryptococcosis in an adolescent boy. J Paed 1972; 80:450.
5. Burbank B, Morrione TG, Cutler SS. Pulmonary alveolar proteinosis and norcardiosis. Am J Med 1960; 28:1002-7.
6. Andriole JT, Ballas M, Wilson GL. The association of Norcardiosis and pulmonary alveolar proteinosis. Ann Intern Med 1964; 60:266-75.
7. Webster JR Jr, Battifora H, Puvey C et al. Pulmonary alveolar proteinosis in two siblings with decreased immunoglobulin A. Am J Med 1980; 69:786-9.
8. Bedrossian CWM, Luna MA, Conklin RH, Miller WC. Alveolar proteinosis as a consequence of immune suppression. Hum Pathol II Suppl 1980; 527-34.
9. Ruben FL, Talano TS. Secondary pulmonary alveolar proteinosis occurring in two patients with Acquired Immune Deficiency Syndrome. Am J Med 1986; 80:1187-90.
10. Carnovale R, Zornoza J, Goldman AM, Luna M. Pulmonary alveolar proteinosis: its association with haematologic malignancy and lymphoma. Radiology 1977; 123:303-6.
11. Martin RJ, Coalson JJ, Rogers RM, Houton FO, Manous LE. Pulmonary alveolar proteinosis: the diagnosis by segmental lavage. Am Rev Respir Dis 1980; 121:819-25.
12. Miller A, Ravin E, Smith CTW. Pulmonary alveolar proteinosis with interstitial involvement. Am J Roentgenology 1981;137:1069-71.
13. Ramirez RJ. Pulmonary alveolar proteinosis: A roentgenolgic analysis. Am J Roentgenology 1964; 92:571-7.
14. Costello JF, Moriarity DC, Branthwaite MA, Turner-Warwick M, Corrin B. Diagnosis and management of alveolar proteinosis: the role of electron microscopy. Thorax 1975; 30:121-32.
15. Kuhn C, Gyorkey F, Levine BE, Ramirez RJ. Pulmonary alveolar proteinosis: a study using enzyme histochemistry, electron microscopy and surface tension measurement. Lab Invest 1966; 15:492-509.
16. Ramirez RJ, Harlen WR. Pulmonary alveolar proteinosis: Nature and origin of alveolar lipid. Am J Med 1968; 45:12-20.
17. Bell DY, Hook GER. Pulmonary alveolar proteinosis: Analysis of airway and alveolar proteins. Am Rev Respir Dis 1979; 119:979-90.
18. Katyal SL, Singh G. An immunologic study of the apoproteins of rat lung surfactant. Lab Inv 1979; 40:562-7.
19. Singh G, Katyal SL. Surfactant apoprotein in non malignant pulmonary disorders. Am J Pathol 1980; 101:51-62.
20. Sahu S, Lynn WS. Characterisation of high molecular weight glycoproteins isolated from the pulmonary secretions of patients with alveolar proteinosis. Biochem 1979; 177:153-8.
21. Hudson AR, Halprin GM, Miller JA, Kilburn KM. Pulmonary interstitial fibrosis following alveolar proteinosis . Chest 1974; 65:700.
22. Clague HW, Wallace AC, Morgan WKC. Pulmonary interstitial fibrosis associated with alveolar proteinosis. Thorax 1983; 38:865-6.
23. Harris JO. Pulmonary alveolar proteinosis: Specific or non-specific response. Chest 1983; 84(1):1-2.
24. Cline MJ, Lehrer RI, Territo MC, Golde DW. Monocytes and macrophages: function and diseases. Ann Intern Med 1978; 88:78-88.
25. Harris JO. Pulmonary alveolar proteinosis: Abnormal in-vitro function of alveolar macrophages. Chest 1979;76:156-9.
26. Golde DW, Territo M, Finley TN, Cline MJ. Defective lung macrophages in pulmonary alveolar proteinosis. Ann Intern Med 1976; 85:304-9.
27. Katyal SL, Singh G. Analysis of pulmonary surfactant apoproteins by electrophoresis. Biochem Biophys Acta 1981; 670:323-31.
28. Ramirez RJ. Alveolar Proteinosis: Importance of pulmonary lavage. Am Rev Respir Dis 1971; 103:666-78.
29. Wilson DO, Rogers RM. Prolonged spontaneous remission in a patient with increased pulmonary alveolar proteinosis. Am J Med 1987; 82 (suppl): 1014-6.