Eur Respir J 1999; 13: 207–209
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European Respiratory Journal
ISSN 0903-1936

CASE FOR DIAGNOSIS

A breathless female

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A 67-yr-old female was admitted with a two week history of dry cough, cold sores and progressive breathlessness. Her exercise tolerance had gradually reduced over 3 yrs from 3 miles to half a mile. Three years previously she was diagnosed as having chronic myeloid leukaemia for which she received a total of 1.3 g busulphan, producing remission for the last 2 yrs. She was an exsmoker with a 40 pack-yr history. There was no relevant occupational history. The only regular medication was allopurinol.

On examination she was breathless at rest, cyanosed but afebrile, pulse rate 110 beats·min^{-1}, respiratory rate 24 beats·min^{-1}, blood pressure 120/70, normal jugular venous pressure and heart sounds. On examination of the chest, percussion notes were normal and auscultation revealed bilateral basal crackles. The remainder of the examination was normal.

Full blood count showed normocytic normochromic anaemia with haemoglobin (Hb) 88 g·L^{-1} and leukocytosis with white blood cell (WBC) count 17.2×10^9 cells·L^{-1}, erythrocyte sedimentation rate (ESR) was raised to 80 (normal 0–20) and C-reative protein (CRP) was raised to 164 mg·L^{-1} (normal range 0–9). The chest radiograph on admission is shown in figure 1. Autoimmune profile, blood culture, sputum culture, urine culture, viral serology and protein electrophoresis were normal. Arterial blood gas analysis on air showed arterial oxygen tension (P_{a,O_2}) 3.5 kPa and arterial carbon dioxide tension (P_{a,CO_2}) 3.3 kPa, the P_{a,O_2} increasing to 11.7 kPa on 50% oxygen. Dynamic spirometry showed a restrictive ventilatory defect forced expiratory volume in one second (FEV_1) 0.95 (61% pred), forced vital capacity (FVC) 0.97 (51% pred), FEV_1/FVC ratio 98%. Shunt fraction determined by breathing 100% oxygen was grossly elevated at 40%.

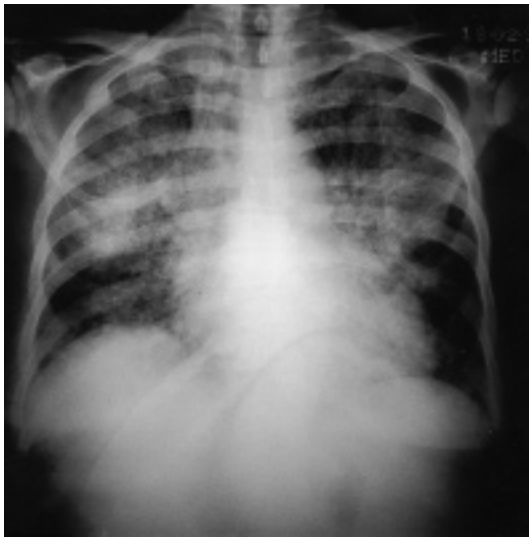

Fig. 1. – Chest radiograph on admission.

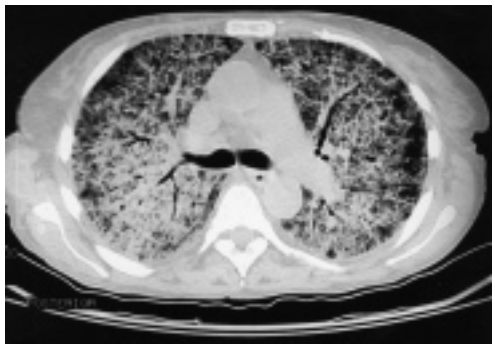

Fig. 2. – High-resolution computed tomography scan of the thorax at the level of carina.

High-resolution computed tomography (HRCT) was performed (fig. 2). Fibreoptic bronchoscopy showed normal endobronchial anatomy. Owing to severe hypoxia, bronchoalveolar lavage (BAL) was not performed. Fluid obtained from bronchial washing was colourless and was negative for *Pneumocystis carinii* pneumonia (PCP). Transbronchial biopsy concluded at the same time confirmed the diagnosis (fig. 3).

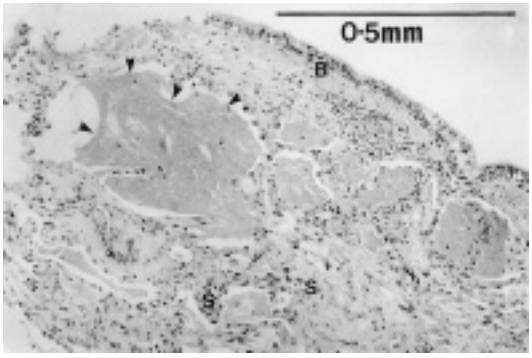

Fig. 3. – A section of the transbronchial biopsy, haematoxylin and eosin stained. B: bronchus; S: alveolar septa; Arrowheads: intra-alveolar space.

BEFORE TURNING THE PAGE, INTERPRET THE RADIOGRAPH, CT SCAN AND HISTOLOGICAL SAMPLE, AND SUGGEST DIAGNOSIS, ALTERNATIVE DIAGNOSIS AND TREATMENT.

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Interpretation

The frontal chest radiograph demonstrates bilateral, perihilar airspace consolidation with some basal sparing.

HRCT at the level of carina shows there is extensive ground-glass opacity and consolidation with air bronchograms. Background reticular opacities and thickened interlobular septae are present in the affected lung. Areas of well demarcated lung can be identified peripherally.

Histological examination of the transbronchial biopsy showed alveoli filled with granular pink material which was periodic acid-Schiff (PAS) positive. There were cholesterol clefts and a few foamy histiocytes. The pulmonary interstitium was thickened but there was no evidence of capillaritis or haemorrhage. No organisms were seen on special stains.

Diagnosis "Pulmonary alveolar proteinosis"

Treatment and clinical course

The patient was initially treated with *i.v.* ceftazidime, gentamicin, high-dose cotrimoxazole and prednisolone 40 mg orally daily. Steroids were reduced and the antibiotics stopped after the diagnosis was confirmed. She initially improved but remained oxygen dependent. In view of her poor general state and persistent hypoxaemia, therapeutic bronchoalveolar lavage was not possible and she died peacefully. Permission for autopsy was not obtained.

Discussion

Pulmonary alveolar proteinosis (PAP) was first described in 1958 by ROSEN *et al.* [1]. It is a diffuse lung disorder characterized by the accumulation of large amounts of phospholipids and proteinaceous material in the alveoli and distal airway with preservation of the pulmonary interstitium.

PAP is classified into either primary or idiopathic, occurring in the absence of any identifiable cause, and secondary. The latter is associated with three pathological processes [2]: 1) infections of the lung; 2) haematological malignancies; and 3) exposure to inhaled chemical and minerals [3].

Infections associated with PAP are mainly PCP seen in both human immunodeficiency virus (HIV) and non-HIV immunosuppressed patients, *Nocardia asteroides*, *Mycobacterium tuberculosis* and *M. aviam-intracellularae.*

The associations with haematological malignancies include lymphoma, leukaemia, particularly acute and chronic myeloid and multiple myeloma [4, 5]. Finally, exposure to inorganic dust or fumes particularly silica, aluminium dust, insecticides and titanium is reported to induce PAP [2].

Normal lung surfactant and its corresponding apoproteins are synthesized and released by alveolar type II cells in the alveolar lumen. Spent surfactant is taken up by the type II cells again. This recycling involves 90% of surfactant in the developing lung and 50% in the adult lung. The rest is cleared either through phagocytosis and degradation by macrophages or to a lesser degree *via* the lymphatics or the airways mucociliary apparatus [6]. The exact mechanism of excess surfactant accumulation in alveolar spaces in PAP is not clear. Derangement in the normal pathways of surfactant secretion, metabolism and reuse or degradation seems most likely.

The main presenting symptoms are breathlessness on exertion and cough. Occasionally chest pain, fatigue, weight loss and haemoptysis can occur. Physical examination can be normal, but basal inspiratory crackles are heard in 40–80% and clubbing is reported in 30–50% of patients [2].

Chest radiographs typically show diffuse, bilateral, perihilar, ill-defined nodular or confluent airspace disease. HRCT more clearly demonstrates the extent and distribution of the airspace disease, which appears as ground-glass opacity and sometimes consolidation. Areas of normal lung are often very clearly demarcated giving the disease a geographic appearance. Computed tomography and HRCT reveal additional interstitial abnormalities with smooth thickening of the interlobular septae that are not appreciable on the plain radiographs [7]. The presence of sharply demarcated areas of ground-glass opacity with superimposed reticular interstitial opacities ("crazy-paving" appearance) is strongly suggestive of PAP although it has been described in PCP and cytomegalovirus infections.

Pulmonary function testing in PAP shows a restrictive ventilatory defect with reduced gas transfer. The shunt fraction measured while breathing 100% oxygen is a reliable index of gas exchange efficiency and is typically elevated in PAP. In 12 patients with PAP, the average shunt fraction was 20%, significantly higher than 35 patients with other forms of diffuse lung diseases who had an average shunt fraction of around 9% [8].

Diagnosis is usually established by BAL, obviating the need for transbronchial biopsy or open lung biopsy in the majority of cases. On gross examination BAL fluid shows a characteristic milky appearance. On light microscopy the striking features are the presence of acellular granules that are basophilic on Giemsa and positive with PAS staining. Recently, immunological studies performed on the serum and BAL from a small number of patients with PAP showed a marked (10–50-fold) elevation in levels of surfactant protein (SP)-A, SP-D, carcinoembryonic antigen and CA19-9. However, the specificity of these findings for PAP as opposed to other diffuse lung disorders remains to be determined [9, 10].

The histological characteristic of PAP is the accumulation of granular, PAS-positive, lipoproteinaceous material within the air spaces of otherwise preserved alveolar tissue with few inflammatory cells and normal alveolar septa [11].

Presentation of PAP in our patient was atypical. Although history and examination are compatible with PAP, the patient's chest radiograph showed upper and mid zone shadowing, as compared with classical PAP where it is mainly perihilar and basal. The markedly raised shunt fraction (40%) and restrictive ventilatory defect raised the suspicion of PAP. Although BAL could not be performed in our case, fluid obtained from bronchial washing was colourless. This is in contrast to classical PAP where BAL fluid has a characteristic milky appearance. Transbronchial biopsy confirmed the diagnosis of PAP and also showed thickened interalveolar septa.

Haematological malignancies in remission, complicated by pulmonary alveolar proteinosis, have been well described and all previously reported cases of chronic myeloid leukaemia in association with pulmonary alveolar

proteinosis had received busulphan [12]. Bulsulphan not only induces pulmonary fibrosis but also produces dysplastic abnormalities in the alveolar lining cells, so-called "busulphan cells" [13]. Whether or not this structural alteration in alveolar lining cells leads to impairment of surfactant metabolism and thus predisposes the development of pulmonary alveolar proteinosis is not clear. In a previous review, YAMAMOTO *et al.* [14] suggested that busulphan therapy might increase the susceptibility of the lung to the development of pulmonary alveolar proteinosis. Interlobular septal thickenings are often seen in conjunction with air space filling both on high-resolution computed tomography scans and on histological examination of the lung parenchyma in pulmonary alveolar proteinosis. However, alveolar septa are often normal on histology [2]. With the presence of alveolar septal thickening we believe that busulphan was the likely cause of pulmonary alveolar proteinosis in this case.

Acknowledgement. The authors thank M. Greaves for her interpretation of chest radiographs and computed tomography thorax and C. Scott and E. Renaudon for their help in the preparation of medical photographs.

Keywords: Busulphan, chronic myeloid leukaemia, *Pneumocystic carinii* pneumonia, pulmonary alveolar proteinosis, surfactant

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