Rosen et al. first described pulmonary alveolar proteinosis (PAP) in 1958. PAP is characterized by the accumulation of phospholipoproteinaceous material in alveolar spaces. The prevalence of PAP is difficult to determine from the literature, however, it is rare. The etiology of this disorder is not yet known. There are two types of PAP based on associated disorders: primary (idiopathic) type, in the absence of identifiable coexisting abnormalities, and secondary type, when conditions including infection, malignant hematologic disease and inorganic dust exposure coexist.

In Saudi Arabia there is only one previous report of PAP in a Saudi pregnant female who presented with respiratory failure, and was found to have pulmonary Mycobacterium tuberculosis infection, i.e., the secondary form of PAP. In this communication, we report the first adult Saudi male patient with primary pulmonary alveolar proteinosis, followed by an updated literature review of disease etiology, clinical manifestations, diagnosis, natural history, and treatment.

Case Report

A 29-year-old male who was a 15-pack-per-year smoker presented with a one-year history of progressive shortness of breath on exertion. His exercise tolerance was finally limited to one flight of stairs. He had no history of cough, chest pain, palpitations, orthopnea, paroxysmal nocturnal dyspnea or wheezes. He denied any previous medical illnesses and was not taking any medications. There was no history of fever, weight loss or night sweats. The rest of the systemic review was unremarkable. The patient, who works as a public relations representative, denied any possible exposure to occupational hazards or toxic fumes. He had no risk factors for human immunodeficiency virus (HIV) or other infections.

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sounds. Cardiovascular, abdominal and CNS examinations were normal. Investigations revealed a normal complete blood count and peripheral blood morphology. Coagulation profile, urea and electrolytes were normal. Liver function tests were normal, except for alanine transaminase and aspartate transaminase, both of which were slightly raised at 50 and 43 units/L, respectively. His lactic acid dehydrogenase (LDH) was slightly elevated at 499 units/L. Total cholesterol was 6.7 mmol/L (3.5-5.2) and triglycerides were 2.80 mmol/L (<2.3). The patient’s hepatitis B surface antigen, hepatitis C antibody, HIV antibody, and antinuclear antibodies were negative.

Pulmonary function test revealed a restrictive pattern of moderate severity with total lung capacity of 61%, vital capacity of 71% and transfer factor of 32% of predicted values. Arterial blood gases revealed hypoxia of 8.9 kpa and the alveolar-arterial oxygen gradient was increased to 37.7 mm Hg. A six-minute walk test demonstrated significant oxygen desaturation from 95% at rest down to 83%. His chest radiograph (Figure 1) showed diffuse bilateral opacities with ill-defined nodular infiltrates. Computed tomographic (CT) scan of the chest with high-resolution techniques (Figure 2) revealed ground glass opacities affecting both lungs in a “geographic pattern.” There was a remarkable smooth thickening of intralobular structures and interlobular septa, but no architectural distortion. No mediastinal or hilar lymphadenopathy was noted.

A diagnostic bronchoscopy and transbronchial biopsy were done. The bronchial alveolar lavage fluid was a cream-white color. Microscopic examination of the lavage fluid was negative for acid-fast bacilli, fungal organisms, and gram-staining organisms. Cultures for *Mycobacterium*, fungus, and bacteria were all negative.

Cytology of the bronchial lavage revealed a few normal respiratory epithelial cells with a background of proteinaceous acellular material and cellular debris.

Histological examination of the transbronchial biopsy revealed a granular eosinophilic acellular material distending the alveolar spaces. Mild pneumocyte type II hyperplasia was seen. The proteinaceous material was strongly positive for periodic acid-Schiff (PAS) (Figure 3). Ultrastructural examination of the bronchoalveolar lavage fluid demonstrated lamellar bodies at various stages of fragmentation mixed with cellular debris (Figure 4).

Ultrasound of abdomen revealed only fatty infiltration of the liver. Based on the above clinical, microbiological and pathological findings, and in the absence of identifiable associated diseases, including infections of the lung, hematologic malignancies, or exposure to inorganic dust and chemicals, the diagnosis of primary pulmonary alveolar proteinosis was made.

The patient’s dyspnea progressed and he started to have a productive cough with expectoration of thick white cement-like material. His gas exchange deteriorated further, with an arterial oxygen tension at room air decreased to 6.3 Kp and the six-minute walk test showing a nadir oxygen saturation of 62%.

Due to the significant deterioration of his condition, bilateral whole-lung lavage was performed. Under general anesthesia in the operating room, and using a left double-lumen endobronchial tube, whole-lung lavages of the right and then the left lung were performed. The total volume of saline used for each lung lavage was 16 and 17 L, with 15.5 and 16.7 L being drained respectively. The initial drain fluid was thick and creamy to muddy in color. The procedure was completed when the drain fluid became clear. The patient’s oxygenation, end-tidal carbon dioxide, lung-thorax compliance, blood pressure and pulse rate remained stable throughout the procedure.
Post whole-lung lavage procedure, the patient had no dyspnea or cough. His diffusing capacity improved from 32% to 50% of predicted values, with mild improvement in lung volumes. Arterial oxygen tension and saturation at room air improved remarkably (Table 1). Chest radiograph revealed remarkable regression of the diffuse opacities.

**Discussion**

Although the etiology of PAP remains unknown, a number of hypotheses have been made to explain its pathogenesis. Alveolar proteinosis has been reported as a response to infection (e.g., Pneumocystis carinii), to inhaled foreign agents (e.g., silica), and in immuno-deficiency states (e.g., hematologic malignancies). These are considered causes for secondary PAP. Excessive secretion or clearance failure of surfactant by type II pneumocytes, and more recently, impaired processing and clearance of surfactant by alveolar macrophages, have all been implicated in PAP. It has been shown that mice with granulocyte-macrophage colony-stimulating factor (GM-CSF) deficiency developed an abnormality that resembles PAP. Furthermore, inserting the deficient GM-CSF gene corrected their pulmonary abnormalities. These findings suggest that impaired processing of surfactant due to defective alveolar macrophages may play a role in PAP pathogenesis. Another mouse model with a deficiency in the β-peptide chain that is shared by receptors on mononuclear cells for GM-CSF, interleukin 3, and interleukin 5, resulted in a similar disease to PAP. Absence of this β-peptide dramatically reduced the alveolar macrophages response to stimulation with GM-CSF. These findings suggest that degradation of alveolar surfactant is regulated by GM-CSF signalling of alveolar macrophages.

PAP is more frequently seen in men than women, with the reported sex ratio ranging from 2:1 to 4:1. It may occur in all age groups, but typically in the fifth decade of life. The clinical manifestations of PAP are usually insidious. The most common symptom is dyspnea on exertion, as was the case with our patient. The next most common symptom is a mild cough, which is usually dry but occasionally productive of sputum, described as “chunky or white and gummy.” More recently, cough has been reported to be an equally common presenting symptom as dyspnea. Chest pain and hemoptysis are unusual symptoms. Constitutional symptoms of weight loss and malaise are common but not fever or night sweats. The presence of fever would imply an added infection or a different diagnosis. Physical findings, including fine crackles at the lung bases, with cyanosis and finger clubbing, are seen only in severe cases.

The most common abnormal laboratory data is a modest elevation of serum LDH as in our case, in the presence of normal serum transaminases. The mild elevation in serum transaminase levels in our case was most likely secondary to fatty liver changes as a result of hyperlipidemia, rather than hepatic abnormalities related to PAP. Recently, serum levels of specific lung surfactant proteins A and D have been found to be markedly elevated in patients with PAP. This, however, is not specific for PAP, since high serum levels of surfactant proteins A and D are also present in patients with idiopathic pulmonary fibrosis, and mild elevations can be seen in patients with panbronchiolitis or infections including tuberculosis and pneumonia.

Chest radiograph typically reveals bilateral, diffuse or patchy airspace disease of a confluent pattern, and less commonly an ill-defined nodular pattern. The disease is usually worse at the bases and predominant in the perihilar regions, giving the bat-wing appearance of pulmonary edema. Interstitial pattern, lymphadenopathy and pleural involvement have also been described. High-resolution CT (HRCT) scan may further demonstrate the extent and pattern of the disease more than the routine radiograph. The main features of PAP in HRCT were present in our patient, constituting thickened intralobular structures and interlobular septa, with no architectural distortion, often with typical polygonal shapes, sometimes called “crazy-paving,” and areas of ground-glass opacification with a “geographic” pattern as the diseased lung is sharply demarcated from surrounding normal lung tissue.

The restrictive ventilatory pattern of our case, with reduced lung volumes, transfer factor and the absence of obstructive component, is typical of PAP. It is worth noting that there is a striking reduction of transfer factor when compared to lung volumes. This is possibly related to the relative absence of pulmonary fibrosis.

Arriving at the diagnosis of PAP can be a difficult task. The clinical manifestations are nonspecific, and as a result there is about a one-year delay in making the diagnosis. HRCT scan findings in this disorder are not pathognomonic, though highly suggestive. Measuring the serum levels of surfactant protein A and D may further narrow the list of differential diagnoses, however, the
definitive diagnosis of PAP is most often based on tissue
examination obtained either by transbronchial or open
lung biopsy. Although the latter remains the gold standard
for the diagnosis of PAP, more recently bronchoscopy with
bronchial lavage and transbronchial biopsy has obviated
the need for the open biopsy procedure.22,24,25 Cytology of
bronchial lavage without biopsy has been shown to be
reliable in confirming the diagnosis of PAP if the
histologic findings are considered together with the
clinical setting.22,25 Biochemical analyses of lavage fluid from
patients with PAP, for surfactant protein A and D and
tumor markers, is promising, but remains non-specific.22 A
recent report, however, has suggested that increased
bronchial lavage fluid levels of surfactant protein D may be
highly specific for PAP.21

The cytology of bronchoalveolar lavage, histology of
lung biopsy, and the ultrastructural examination in PAP
are typical of our case. The ultrastructural and immuno-
histochemical features of the amorphous material indicate
its origin from surfactant.2

The natural history of the disease is variable, making
the evaluation of the efficacy of any specific treatment
difficult. In 1965, Larson and Gordinier reported that
approximately one-third of their patients with PAP
progressively deteriorated or died, one-third appeared to be
symptomatic but stable, and the remaining one-third
appeared to improve spontaneously.26 A spontaneous
remission rate of up to 25% has been reported in one case
series.27 Pulmonary fibrosis can occur years after the
diagnosis of PAP has been established.2,28 Summers29
followed 93 patients with PAP for a period up to 17 years,
and reported a mortality rate of 39.7%, due to respiratory
failure or complicating diseases. More recent reports have
lower mortality rates, with Prakash et al.30 reporting a
mortality rate of 8.8% in the 34 patients they followed.
Recent experience from Japan reveals no deaths in 68
patients with PAP.31 Goldstein et al.32 presented a series of
24 patients with PAP, and none of these patients died as a
result of the sequelae of the disorder. On the other hand,
only 13 patients (54%) required treatment, i.e., whole-lung
lavage. In the same series, of the 15 patients followed for a
mean of 9.8 years, 9 (60%) reported persistent symptoms.
It is clear from the above data that predicting the long-
term outcome for PAP patients and the need for whole-
lung lavage are still unresolved issues.

The only consistently successful treatment for this
disorder is whole-lung lavage. This technique was first
described by Ramirez and colleagues in 1965,31 and further
modified by Wasserman and coworkers in 1968.32 After
whole-lung lavage, symptoms often improve dramatically,
however, clinical long-term follow-up is needed since the
clinical outcome is variable and unpredictable. While only
one lavage may be required for a prolonged remission, up
to 55% of cases may need repeated lavages at 6-12-month
intervals.2,16 Thus the variability of disease outcome and
the possibility of spontaneous remission has made the
evaluation of a specific treatment efficacy challenging and
requiring, ideally, a multicenter randomized trial. For the
same reasons, treatment decisions have become more
conflicting. Asymptomatic patients with minimal
impairment in pulmonary function and gas exchange,
regardless of the extent of their radiological abnormalities,
do not require immediate therapy, although these patients
require frequent follow-up because of the unpredictable
natural history of the disease. The primary current
indications for whole-lung lavage are progressive dyspnea
with objective deterioration in lung function.

Potential adjunct or alternative emerging therapies are
GM-CSF, based on the possible relation between PAP and
abnormalities of GM-CSF receptor function. Seymour et
al.33 recently reported a single case of PAP in which
administration of the growth factor was associated with
clinical improvement, and relapse with the withdrawal of
GM-CSF.

Lung transplantation has been performed in severe
cases that fail to respond to whole-lung lavage.
Unfortunately, recurrence in the allograft has also been
reported.34 Bone marrow transplantation (BMT) in
experimental mice deficient in GM-CSF receptor has
reversed PAP and so has been suggested in humans,
though not yet reported.35 It is important to emphasize that
there is no role for corticosteroids or other
immunosuppressive agents in the treatment of PAP. The
use of such agents can increase the patient’s susceptibility
to opportunistic infections and thus increase mortality.14

In conclusion, we are reporting this case to make
physicians aware of the existence of this disorder among
Saudis. Although the condition is rare, it should be
considered in the differential diagnosis in asymptomatic
patients or patients with chronic dyspnea on exertion and
diffuse lung infiltrate.

References


