A 40 YEAR OLD WOMAN WITH COUGH, PROGRESSIVE DYSPNEA AND BILATERAL LUNG OPACITIES

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A 40 year old lady was admitted to TUTH because of persistent cough, dyspnea and bilateral perihilar opacities.

The patient had been unwell since 15 years. Her illness began with cough, which was mostly non productive. There was no diurnal or seasonal variation in cough, and she never coughed up blood.

Breathlessness started 5 years ago, initially only on exertion, and it increased in severity over the years. There was no history of wheezy breathing. She had recently been orthopnic, but there was no history of Paroxysmal Nocturnal Dyspnea. Since the last 1 1/2 months, both cough and breathlessness had increased in severity, and on admission she was breathless at rest and had intractable cough.

She did not give any history of fever, chest pain, joint pain, skin rash, bleeding episodes or weight loss.

She was treated for tuberculosis 10 years ago, and retreated in 1997 (on both occasions sputum was not examined for AFB). Since one month she was on bronchodilators and inhaled steroids. She was a house wife with no history of exposure to organic or inorganic dust. She was a non smoker and had no risk factors for HIV infection. There was no significant family history. She had a history of skin allergy and had undergone desensitization, which was unrewarding.

EXAMINATION:

She was conscious, cooperative and oriented. Tachypnea was present- respiratory rate 35per minute, laboured.

Temperature 99°F, pulse 130/min, regular. BP 140/70 mmhg

Marked central cyanosis was present.

There was no pallor, clubbing, edema, icterus, lymphadenopathy and JVP was not raised.

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There were few fine basal crepitations on auscultation of the chest. No other abnormality was detected. Cardiovascular, Gastrointestinal and Central nervous system examination were normal.

The patient was started on prednisolone 40mg/day.

INVESTIGATIONS:

Hb. - 15.5gm%, PCV - 53.5%, RBC morphology- Normochromic Normocytic.

TLC - 13,200/cumm, - Neutrophils - 70%, Lymphocytes - 22%, Monocytes - 4%, Eosinophils - 2% and Atypical cells- 2%.

ESR-8mm/h.

The values for Blood Urea, Creatinine, Glucose, Electrolytes, Bilirubin, SGOT and SGPT were normal.

Sputum gram stain no organism isolated
AFB not found in two occasions

HIV -negative, ANA and Ra factor - Negative.

ABG - without oxygen supplementation

PH 7.43
PO₂ 35mmhg
PCO₂ 36mmhg
HCO₃ 26.1mmol/l
TCO₂ 26.1mmol/l
BEV 0.6
O₂ Sat 73.4%

(O₂ Saturation after O₂ supplementation @ 4 l/minute = 89%).

ECG was normal.

Radiograph of the chest showed bilateral blotchy

and wooly opacities, mainly perihilar region(acinar pattern). There was no loss of lung volume, and the costo-phrenic angles were normal. The heart and mediastinum were normal. Serial chest X- rays over the last two years showed an increase in the opacities in both lungs with confluent and acinar appearance.

Fig. 1

HRCT(high resolution computer tomography)-revealed extensive patchy and confluent ground glass opacities in both lung fields. Peripheral sparing was seen in most of the scan except for posterior basal segments. Some of the lobules also contained ground glass opacity in a geographical pattern. Interlobular septa were also thickened, with areas of consolidation producing a “crazy paving” appearance. These findings were highly suggestive of Alveolar Proteinosis.

Fig. 2

Oral steroid was discontinued after the HRCT, which was highly suggestive of ALVEOLAR PROTEINOSIS. A transbronchial lung biopsy was

planned to confirm this diagnosis. The patient was stable on continuous oxygen supplementation and was discharged with advise to come back after two weeks for Transbronchial lung biopsy. She however came back in a week with complaints of fever, cough with mucoid expectoration and increased breathlessness. This time sputum was examined for PAS staining material, which came strongly positive, however, it contained mainly mucoid material and lacked the granularity, typical of alveolar proteinosis.

Thus, considering the clinical features, HRCT, and sputum findings, the diagnosis of Alveolar proteinosis was strongly suggestive.

Subsequently, a Transbronchial Lung Biopsy was done, which showed several alveolar spaces filled by eosinophilic, granular and acellular material that was Periodic Acid Schiff (PAS) positive. The interstitium showed mild inflammatory cell infiltration, thus confirming the diagnosis. Tests for pneumocystis carinii, AFB, Candida, and Nocardia were negative.

Fig. 3

The treatment of Pulmonary Alveolar Proteinosis (PAP) is Total Lung Lavage, which is not available in Nepal. Our patient while awaiting treatment underwent spontaneous remission in May 2000. (see X-ray). She has no breathlessness or cough at present. Follow up with x-ray chest is planned every year.

Fig. 4

DISCUSSION:

PULMONARY ALVEOLAR PROTEINOSIS

It is a disease of the lungs resulting from the accumulation of a Periodic Acid Schiff (PAS) - positive proteinaceous material rich in phospholipids in the alveolar air spaces. Primary PAP is a rare disorder of unknown etiology first described by Rosen et al in 1958.¹ Congenital PAP affecting neonates has also been reported, in which a subset of the infants have been shown to be deficient in surfactant-associated protein B(SP-B).² Secondary PAP is a similar accumulation of lipoproteinaceous material in the distal air space, observed with increased frequency in association with a limited set of diverse pathological processes, implying the existence of causal relationships. Beuchner and Ansari in 1969 first described PAP associated with inhalation of Silica dust.³ It occurred as a response to inhaled silica and comparable illnesses can be seen on ex

posure to aluminum dust,⁴ titanium dioxide,⁵ and other organic dusts. Secondary PAP is also seen with increased frequency in association with hematologic malignancies and myeloid disorders, suggesting a relationship between PAP and immune dysfunction.⁶ Parto et al, have reported PAP in patients with Lysinuric protein intolerance.⁷ In acquired immunodeficiency syndrome(AIDS), varying degree of accumulation of the lipoproteinaceous materials in association with pneumocystis carinii are recognized.⁸ Infection with *Nocardia asteroides* has been frequently noted in patients with PAP⁹ although this association is decreasing in recent years.¹⁰ There have been reports of PAP associated with *Mycobacterium tuberculosis* infection.¹¹ Recently, a high incidence of isolation of *Mycobacterium avium-intracellulare* was found in patients with PAP.¹² *Pneumocystis carinii* pneumonia (PCP) has been associated with PAP, in both HIV and non HIV immunosuppressed patients.¹³

Analysis of the lipoproteinaceous materials accumulating in the air spaces demonstrates that they represent an abnormal accumulation of the normal constituents of surfactant.¹⁴ Surfactant is a mixture of lipids and surfactant associated proteins (SP-A, SP-B, SP-C, SP-D), which serve to reduce surface tension and thereby maintain the patency of the distal air spaces. The homeostatic mechanisms affecting the quantity and quality of surfactant in the distal air spaces involve the regulation of the synthesis and secretion of surfactant by type II epithelial cells and the clearance of lipids and surfactant associated proteins from the air spaces.¹⁵ A significant proportion of surfactant is recycled by the type II epithelial cell. PAP has been postulated to have a relationship to impaired macrophage maturation or function because of its increased frequency in association with hematologic malignancies and the unusual spectrum of organisms associated with it. Claypool and colleagues have suggested that alveolar macrophages in PAP

are defective in the process of clearing of surfactant.¹⁵ It has been shown that experimental mice, deficient in the gene for GM-CSF, develop alveolar accumulations of surfactant substances similar to that seen in PAP.¹⁶ The absence of macrophage activation for surfactant clearance by locally synthesized GM-CSF could be the mechanism involved.¹⁷

CLINICAL FEATURES:

Primary PAP is a rare disorder with an estimated prevalence of 1 per 100,000. Its peak incidence is between the ages 20 and 50 years, although it has been reported in a wide range of ages, from neonatal onset to a 72-year-old-patient.¹⁸ The male to female ratio is around 2:1 to 4:1.¹⁹ The primary symptom is shortness of breath with exertion, with a slowly progressive course. Cough is a common symptom usually non-productive, but occasionally with sputum described as "White" and "Gummy" in consistency.¹⁹

Hemoptysis and chest pain are rare.¹⁸ Other less frequent features are weight loss, malaise, fatigue and intermittent low grade fever. Clubbing is sometimes observed and it may regress if the PAP undergoes remission. Auscultation of the lungs reveals fine end inspiratory crackles. Rarely, there may be pulmonary hypertension and cor-pulmonale.

The usual radiographic manifestation of PAP are those of air-space consolidation or ground glass opacity; air bronchograms are rare. The typical radiograph shows a bilateral, patchy, diffuse or perihilar ill-defined nodular or confluent air space pattern suggestive of the "butterfly" or "bat wing" appearance of pulmonary edema, except for absence of cardiomegaly. Lymphadenopathy is rare.²⁰

CT with high resolution techniques(HRCT) more

precisely describes the morphologic features of this lung disease. Godwin et al showed the air-space disease to have a variable appearance, which ranged from ill-defined nodular opacities (air-space nodules) to large area of confluent air-space consolidation. The areas of ground glass opacity or consolidation are often sharply demarcated from surrounding normal parenchyma, giving the abnormal areas a "geographic" appearance. HRCT commonly shows smooth thickening of intralobar and interlobar septa, often in polygonal shapes that have been called "crazy paving". The distribution of the disease is variable, sometimes being mainly central and sometimes peripheral. HRCT pattern can however be similar to that found in certain cases of PCP and Sarcoidosis.

The sputum of patients with PAP may contain PAS positive material. The diagnosis of PAP by sputum examination was suggested by Vidone and colleagues.²¹ They noted, however, that the sputum could lead to false negative conclusions. PAS positive sputum is also found in chronic bronchitis, bronchiectasis, pneumonia and primary and secondary malignancies. On light microscopic examination of the pulmonary parenchyma, the alveoli are filled with a granular, PAS base reactive and diastase-resistant eosinophilic material. The classic pathologic description of PAP does not include the interstitial changes and fibrosis that may develop in the course of this disease. Alveolar septa are normal except for reactive type II pneumocytes; secondary lobar septa may be thickened owing to reactive fibroblasts.

The basic pathologic characteristic of PAP, as seen in tissue from transbronchial or open lung biopsy specimens, is the accumulation of granular, PAS-positive, lipoproteinaceous material within the air-spaces of otherwise preserved alveolar lung tissue. In our case the diagnosis was confirmed by transbronchial biopsy.

PROGNOSIS:

Some patients with primary PAP undergo spontaneous remission. There has been a report of prolonged spontaneous recovery in two cases by Martin RJ et al. The response to whole lung lavage can be quite dramatic, and some patients appear to have subsequent complete remission. Most patients require repeated lavages to maintain adequate gas exchange, and a significant number have accompanying fibrosis, which worsens the prognosis.

CONCLUSION:

This is the first case report of primary pulmonary alveolar proteinosis from Nepal. Although cough and breathlessness are common symptoms of many respiratory diseases, not all cases are due to tuberculosis or COPD. There is a tendency to over-diagnose both these conditions in Nepal. The slow progressive nature of the disease and presence of acinar shadows in both lung fields gave a clue towards alveolar origin of the disease. HRCT has helped tremendously in the diagnosis of this case, and should be used more frequently for a more accurate diagnosis of pulmonary diseases. Confirmation of the diagnosis requires PAS positive proteinaceous material in the lung biopsy. Therapeutic lavage is the only hope of treatment of this disease in majority of the patients. Though rare, this patient was fortunate to undergo remission spontaneously.

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