Pulmonary Alveolar Proteinosis in Association with Fanconi’s Anemia and Psoriasis

A Possible Common Pathogenetic Mechanism

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We report a case of PAP which proved to be fatal despite whole lung lavage. The need for early BAL and transbronchial biopsies in diffuse infiltrative lung disorders of unknown etiology is highlighted. The occurrence of PAP in association with Fanconi’s anemia and psoriasis raises the possibility of a common pathogenetic defect which may be related to abnormal cytokine metabolism. Investigation of cytokine metabolism in PAP is warranted.

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Pulmonary alveolar proteinosis is an uncommon diffuse lung disease of unknown etiology which is characterized by the dense accumulation of lipoproteinaceous material in the alveolar spaces. This material is similar to surfactant and stains positively with PAS. We report a patient with PAP associated with Fanconi’s anemia and psoriasis, which was fatal despite whole lung lavage, and postulate a common pathogenetic basis for the concurrence of these disorders.

CASE REPORT

A 28-year-old woman with Fanconi’s congenital hypoplastic anemia and psoriasis (with arthropathy) was admitted to another hospital with a diagnosis of “atypical pneumonia.” She gave a two-week history of fever, dry cough, exertional dyspnea, myalgia, general malaise, anorexia and weight loss. She smoked 10 cigarettes daily.

A chest x-ray film showed diffuse bilateral symmetrical reticular and alveolar infiltrates most concentrated in the mid-zones without lymphadenopathy or cardiomegaly. She was treated with antibiotics (initially erythromycin and then doxycycline) for a month. There was minimal symptomatic improvement and no change in the radiographs. During the ensuing month she deteriorated and was transferred to our institution.

On transfer, two and a half months following onset of her illness, she weighed 35 kg. She had widespread psoriatic plaques, had cyanosis and was dyspneic on speaking. There was no clubbing or lymphadenopathy. She had a temperature of 38°C, respiratory rate of 26 breaths per minute, a pulse rate of 130 beats per minute and blood pressure of 110/80 mm Hg. There were profuse fine bilateral mid-zone end-inspiratory crackles. The remainder of the examination disclosed no other abnormalities.

Arterial blood gas values while she was breathing room air revealed pH = 7.45; PaCO₂ = 37 mm Hg; PaO₂ = 46 mm Hg; and the alveolar-arterial oxygen gradient was 72 mm Hg (normal, <15). The hemoglobin level was 105 g/L; MCV = 119 fl; MCH = 39.0 pg; white blood cell count, 6.9 x 10³/L; neutrophils, 5.52; lymphocytes, 1.17; monocytes, 0.13; and eosinophils, 0.06, and the platelet count was normal. The ESR was 100 mm/hr. Electrolyte levels, creatinine and liver function tests were normal. A chest x-ray film showed some increase in the right mid-zone infiltrate in comparison with previous films. Lung function testing revealed an FEV₁ of 1.40 L (predicted, 2.89 ± 0.47; FVC, 1.85 L (3.62 ± 0.52); FRC, 1.96 L (3.00 ± 0.47); TLC, 2.82 L (4.74 ± 0.55); Dco, 6.6 ml/min/mm Hg (26.3 ± 3.6); and Kco 2.4 (5.6 ± 0.6).

One and a half weeks following transfer, spatum and blood cultures showed no growth and paired serologic titers for atypical organisms were negative. There had been no response to a course of broad-spectrum antibiotics (cefamandol, sulfamethoxazole-trimethoprim and doxycycline). Bronchoscopy was performed and was anatomically normal. The BAL fluid was grossly opaque and contained profuse lipoproteinaceous material but no organisms or malignant cells. Culture of BAL fluid was negative. Light microscopic examination of transbronchial biopsies showed copious PAS-positive material in the interstitium and alveoli both free and within macrophages, with minimal fibrosis. Subsequent electron microscopy revealed that these PAS-positive areas comprised the typical concentric lamellar bodies seen in PAP.

At 2½ and 3½ weeks following transfer, right lung and sequential segmental left lung lavage were attempted in succession but were both abandoned prematurely (after only 0.85 and 2 L were instilled, respectively) because of arterial oxygen desaturation and hypotension. After the second procedure there was some symptomatic improvement but the degree of hypoxemia and the chest x-ray film findings were unchanged. Her clinical condition stabilized for the next 11 days but deteriorated in sudden deterioration in the form of respiratory and asystolic cardiac arrests from which the patient was successfully resuscitated.

At this time (now five weeks after transfer), whole lung lavage (left lung, 10 L; right lung, 13 L) was performed under cardiopulmonary bypass. Subsequently the patient required ventilatory and isotropic support but died five days later. Tracheal aspirates and blood cultures taken prior to death subsequently grew an opportunistic fungus, Pseudallescheria boydii. Postmortem examination confirmed the presence of widespread fungal infection and PAP.

DISCUSSION

The utility of various diagnostic procedures in PAP recently has been reviewed and it is apparent that BAL with or without transbronchial biopsies examined by light microscopy, with electron microscopy if necessary, would be sufficient in most cases. In our patient, recourse to open-lung biopsy and its attendant risks was not necessary. Given the relative ease with which this diagnosis can be made, and the fact that the diagnosis of PAP frequently is significantly delayed, clinicians should consider the use of BAL and transbronchial biopsies early in the course of diffuse infiltrative lung disorders without apparent etiology.

To our knowledge, only one case of PAP associated with Fanconi’s anemia has been reported previously. We estimate that the probability of these two uncommon disorders occurring in one patient by chance alone is of the order of 1 in 2 x 10¹⁰. This figure is based upon estimates of the prevalence of Fanconi’s anemia being 1 in 348,000 and the frequency of PAP being 5,000 in 250,000,000. The occurrence of PAP in a patient with Fanconi’s anemia and psoriasis raises the possibility of a common pathogenetic defect in these disorders. Psoriasis is characterized by keratinocyte hyperplasia, and disturbances in cytokine production are recognized. Although cytokine abnormalities are also well described in aplastic anemia, and there is now evidence of defective monocyte-to-macrophage maturation in this disorder, we have not found studies addressing these aspects in Fanconi’s anemia. There are no data on cytokine metabolism in PAP, but impaired alveolar macrophage function

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has been documented\(^{10-12}\) and is thought to be a major feature in the pathophysiology of this disorder.\(^{10-13}\) Various cytokines not only stimulate the proliferation of phagocyte precursors in bone marrow, but also probably enhance monocyte-to-macrophage maturation and activation of these cells.\(^{13}\) A primary defect in cytokine metabolism might explain the concurrence of these three disorders or, alternatively, may represent a common feature in the pathophysiologic process in each disorder. Further investigation of cytokine metabolism in PAP is warranted.

Bronchoalveolar lavage is of proven value in the treatment of PAP,\(^{16,17}\) and alveolar macrophage function improves after such therapy.\(^{16}\) A primary monocytic defect, whether or not related to cytokine abnormality, in Fanconi’s anemia could account for the lack of response to therapeutic lavage in our patient and may have predisposed to the occurrence of septicemia with an opportunistic fungus infection.

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Periodic Breathing Imitating Hyperventilation Syndrome*  
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We report a male patient who developed an unusual periodic breathing. At presentation, the differential diagnosis at bedside between Cheyne-Stokes and primary hyperventilation syndrome was laborious, and the final verification was based on the result of capnography.  
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An inappropriate increase of alveolar ventilation followed by a reduction of PaCO\(_2\) to a subnormal level is called hyperventilation. The primary hyperventilation syndrome is an event with a variety of symptoms caused by increased alveolar ventilation with no known organic or metabolic cause. The nonpulmonary form of hyperventilation with subsequent periods of apnea or hypopnea is called Cheyne-Stokes breathing. This form of periodic respiration is seen most frequently in patients with left ventricular failure or impaired cerebrovascular circulation.\(^{1,2}\) Cheyne-Stokes breathing is possibly caused by a phase-lag between the changes in PaCO\(_2\) resulting from variation of ventilation and detection of blood gas alternation by central chemoreceptors. Such a phase-lag is generally due to prolongation of the circulation time and occurs most commonly in left ventricular failure or cerebrovascular disease.\(^{1}\)

CASE REPORT

A 64-year-old man with a history of peripheral facial paralysis treated with surgery in 1974 and rheumatoid arthritis was diagnosed in the 1970s and treated with oral corticosteroids and oxchlorine for five years. Since the early 1980s, the rheumatic signs and symptoms have disappeared. Hypertension has been diagnosed and treated for 20 years with thiazide diuretics and metoprolol. The patient has occasionally suffered from dizziness and deterioration of memory.

In March 1984, an acute anteroseptal myocardial infarction and subsequent cardiac insufficiency was diagnosed. The left ventricle dysfunction and scar formation were detected by ultrasound. It was not possible to measure the ejection fraction due to the abnormal motion of the left ventricle wall. The daily medication of the patient comprised digoxin 0.125 mg, furosemide 20 mg, prazosin 1 mg, verapamil 80 mg, theophylline 200 mg, and nicotinic acid 50 mg.

In 1986, a gradual increase in shortness of breath was observed and nocturnal central apneic periods were noted with a duration of 7 percent of the total sleep. The ECG was normal. The patient was admitted to the chest department due to the high breathing

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