Extreme hypoxemia may produce pulmonary edema by injuring smaller vessels.15 Moss et al16 produced pulmonary edema in animals by selective cerebral perfusion with the hypoxic blood, and suggested that hypoxemia may lead to autonomically mediated pulmonary edema.

This case suggests that another feature should be added to the increasingly different presentations of the sleep apnea syndrome.

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Usual Interstitial Pneumonitis in Infancy*

Clinical and Pathologic Evolution

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Interstitial lung disease is uncommon in infancy and childhood, and the long-term clinical and pathologic evolution of this entity in infants has not been published previously. We describe an infant with a steroid-sensitive chronic interstitial pneumonitis for which the clinical and histopathologic progression of the disease are presented. A family history of interstitial pneumonitis consistent with an autosomal dominant trait was present, and Pneumocystis carinii were found in the lung biopsy specimen.

Since Hamman and Rich1 originally described cases of diffuse fibrosis of the lungs in 1935, a variety of acute and chronic interstitial inflammatory diseases of the lung have been reported. Terminology for such diseases has included interstitial pneumonia, fibrosing alveolitis, idiopathic pulmonary fibrosis, usual interstitial pneumonia (UIP), and desquamative interstitial pneumonitis (DIP), the last described by Liebow et al2 as histologically distinct from the former four entities. Very few children have been well described in the literature with any of these processes. While some had been clinically followed up after biopsy-proved histologic diagnosis, only one case in an older child had long-term follow-up biopsy evaluation of the histopathologic changes in the lung.3 We describe an infant with a steroid sensitive chronic interstitial lung disease with clinical signs presenting at five months of age, a lung biopsy at seven months of age, and a repeated lung biopsy one year later. There was a family history of interstitial pneumonitis consistent with an autosomal dominant trait.

CASE REPORT

This 2,948-g, full-term female infant did well until five months of age, when she was admitted to the Bethesda Naval Hospital because of congestive heart failure. Cardiac catheterization revealed a small atrial septal defect with elevated pulmonary arterial pressures. Despite vigorous treatment with digoxin and diuretics, she showed no clinical improvement and was transferred to the Johns Hopkins Hospital for further evaluation.

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The family history was remarkable for death in a maternal great-uncle at one year of age from an unknown pulmonary disease. Another maternal great uncle was found to have DIP at Jefferson Medical College in 1966 and required long-term steroid administration for clinical management. This case was previously published by Patchefsky et al.4

Physical examination on admission at seven months of age showed this infant to be pale and malnourished, with intercostal retractions and a respiratory rate of 75. Diffuse coarse crackling rales were present, and there was a grade 2-3/6 systolic ejection murmur at the left sternal border with fixed splitting of S2 and accentuation of P2. The liver was 2.5 cm below the right costal margin, and the spleen tip was palpable. Arterial blood gas in room air revealed a PaO2 of 58 mm Hg, Pco2 of 31 mm Hg, and a pH of 7.48. Chest roentgenograms showed diffuse interstitial and intra-alveolar infiltrates (Fig 1). Subsequent evaluation of her pulmonary disease included the following negative findings: nonreactive PPD, normal sweat chloride, normal esophagogram with no reflux or tracheo-esophageal fistula, normal s-antitrypsin with Pi type MM, normal quantitative immunoglobulins, C3 and C4, normal T cell functions as assessed by response to mixed lymphocyte culture and phytohemaglutinins, and negative antinuclear antibody and rheumatoid factor. An open lung biopsy showed an interstitial pneumonitis with a desquamative component and the presence of scattered Pneumocystis carinii cysts. Bacterial, viral, mycobacterial, and chlamydial cultures of the biopsy specimen were sterile. Despite a three-week course of Bactrim (combination of 20 mg/kg of trimethoprim and 100 mg/kg of sulfamethoxazole), no significant clinical change was noted. Prednisone therapy at 2.0 mg/kg was started, and within 72 hours marked clinical improvement was observed. The patient did relatively well over the next 12 months, and the prednisone dosage was gradually reduced to 1.0 mg/kg every other day. However, she received maintenance prophylactic therapy with Bactrim, since several attempts

Figure 1. Initial chest roentgenogram taken at time of first lung biopsy. Diffuse bilateral intra-alveolar and interstitial infiltrates with air bronchograms.

Figure 2. Follow-up chest roentgenogram when second lung biopsy was taken. Diffuse bilateral interstitial infiltrates, with upper lobes more severely involved.

to discontinue giving the antibiotic resulted in fever and respiratory distress.

Fifteen months after the initial diagnosis, the patient became ill with tachypnea, fever, and weight loss and was admitted to Wilford Hall USAF Medical Center. At that time, her steroid dosage had been reduced to 0.5 mg/kg. She had a prolonged and complicated hospital course marked by spiking temperatures, hypoxia, and requirement for mechanical ventilation. A chest roentgenogram showed diffuse bilateral interstitial infiltrates (Fig 2). Repeated open lung biopsy showed usual interstitial pneumonitis with mild interstitial fibrosis and no evidence of Pneumocystis. All bacterial and viral cultures were sterile. The patient gradually responded to reinstitution of high-dose corticosteroid and Bactrim. Since then she has remained well with alternate-day therapy of low-dose prednisone and Bactrim.

Histopathology

The first lung biopsy obtained at seven months of age showed active interstitial inflammation with lymphocytes, plasma cells, and scattered polymorphonuclear leukocytes diffusely infiltrating the alveolar walls. Marked alveolar cell hyperplasia, desquamation, and focal epithelial necrosis were present. The alveoli contained numerous macrophages and a few foci of polymorphonuclear leukocytes (Fig 3). A few scattered P carinii cysts were demonstrated in the alveoli by the Gram-Weigert stain (Fig 3, inset). These changes were consistent with an active phase of usual interstitial pneumonitis.

Results of the second lung biopsy, at 22 months of age, showed considerably less activity than that of the previous biopsy, with only a minimal interstitial infiltrate of lymphocytes accompanied by a mild degree of interstitial fibrosis. Epithelial desquamation and necrosis were absent. P carinii could not be demonstrated by special stains (Fig 4).
Fibrosing alveolitis, DIP, and UIP are rare, diffuse lung diseases, usually of unknown etiology, that may occur in infancy and childhood. The clinical manifestations are similar to those in adults, but the onset may be more acute. The major signs and symptoms in children include tachypnea, dyspnea, hypoxia, cough, and failure to thrive. Superimposed infections, pulmonary hypertension, and respiratory and cardiac failure are some of the major complications.5

This case documents the clinical, roentgenographic, and pathologic progression of an unusual and severe lung disease in early childhood and raises the question of a local pulmonary immune defect, potentially familial, as an underlying etiologic factor. A maternal-uncle had been found at age 42 to have DIP on lung biopsy examination, but remained steroid-dependent until his death 14 years later. One other infant on the maternal side also had died of pulmonary disease. Such data would be consistent with prior reports of familial aggregation of interstitial pneumonitis consistent with an autosomal dominant trait.6,7 The uncle with DIP, however, was steroid-dependent for the remainder of his life, suggesting that the initial diagnosis of DIP may have reflected simply the early findings of the disease process that in fact progressed, as it did in this child, to a pathologic picture consistent with UIP. Although we failed to demonstrate any immune or autoimmune defects from studies of peripheral blood in this patient, the early presence of P carinii, while clearly not of primary importance, was essentially consistent with the suppression of local immune mechanisms that would normally clear such organisms. The role of antibiotics in further modifying the evolution of this disease process by controlling secondary infections may be part of the long-term care of such patients.

This case demonstrates the progression from the initial roentgenographic findings of diffuse intra-alveolar infiltrates to a more focal interstitial disease. This can be correlated with the histopathologic evolution of the disease from one with active interstitial inflammation with a significant intra-alveolar desquamative element, to the diffuse fibrosis with little interstitial inflammation and no intra-alveolar desquamation one year later. It is clear that the lung biopsy picture in this disease is dynamic and that consultation and interpretation of the lung biopsy specimen from any child with interstitial pneumonitis should be obtained from those most familiar with the wide spectrum of histopathologic findings.

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