Circulating Immune Complexes with Pulmonary Hemorrhage During Pregnancy in Idiopathic Pulmonary Hemosiderosis*

Samuel Louie, M.D., F.C.C.P.; Lisa A. Russell, M.D.; Robert B. Richeson III, M.D.; and Carroll F. Cross, M.D., F.C.C.P.

Circulating immune complexes occurred during pulmonary hemorrhage in a pregnant patient with idiopathic pulmonary hemosiderosis, an association not previously reported. The patient required mechanical ventilation, but recovered; after a prolonged hospitalization, she was delivered of a healthy infant without further complications.

(IPH = idiopathic pulmonary hemosiderosis)

Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder recognized by the clinical triad of recurrent hemoptysis, iron deficiency anemia, and diffuse pulmonary infiltrates on the chest radiograph.1,2 It is often suspected that IPH has an immune etiology.3,4 Since IPH is a diagnosis of exclusion, the presence of unusual clinical features may make diagnosis more difficult to establish.4,5 Rarely, it is associated with rheumatoid-like arthritis,6 and its occurrence in pregnancy has been reported twice.6,7 We report a case of acute pulmonary hemorrhage with circulating immune complexes in a pregnant 19-year-old patient with chronic IPH who later developed clinical manifestations of rheumatoid arthritis, including subcutaneous nodules.

Case Report

A 19-year-old black woman was hospitalized at age 2 years with hemoptysis, a hemoglobin level of 3.9 g/dl and a hematocrit value of 12 percent. Hemoglobin electrophoresis, glucose-6 phosphate dehydrogenase levels, and Coombs' test results were normal. Transfusions were given. She was hospitalized at age 3 years for hypoxemic respiratory failure and diffuse alveolar densities shown on the chest radiograph. Hemosiderin-laden macrophages were demonstrated on gastric lavage, and a bone marrow biopsy showed iron deficiency. She required mechanical ventilation and was treated with intravenous corticosteroids and deferoxamine. The patient gradually improved and was discharged on a regimen of prednisone, 1 mg/kg every other day.

One month after hospital discharge, she returned for open biopsy of the right lung. Sections of lung parenchyma revealed dense accumulations of hemosiderin-laden intra-alveolar macrophages distending individual alveoli and diffuse pulmonary fibrosis involving the walls of the respiratory ducts and terminal bronchioles as well as focally in association with individual alveolar septa. No evidence of an organizing alveolitis, interstitial granulomatous pneumonitis, or vasculitis was seen on light microscopy. This was considered to be consistent with the diagnosis of IPH. Immunofluorescent stains were indeterminate for fibrinogen, IgG, and C3 and absent for IgA, IgM, and C4. Electron microscopy demonstrated thickened endothelial component of the alveolar basement membrane and focal areas of alveolar epithelial disruption with hydropic pneumocytes. No electron-dense immune complex-like deposits were noted in any area of the alveolar basement membrane.

The patient continued to experience recurrent hemoptysis three to four times yearly during adolescence. She continued to take prednisone, 1 mg/kg every other day, with pulse steroids for recurrent hemoptysis. She became oxygen-dependent, receiving 4 L/min, by age 17 years. In May 1990, 10 weeks pregnant, she presented to the hospital with fever and cough, and a diagnosis of probable viral pneumonia was made. Studies included an erythrocyte sedimentation rate of 17 mm/h, antinuclear antibody, positive at a titer of 1:80 with a nucleolar pattern; IgG and IgA anticardiolipin antibodies positive; C2 and C3 levels, normal. The rheumatoid factor titer was positive at 1:5,120; Sjogren's antibodies SS-A, negative; and anti-DNA antibody, negative. Antiglomerular basement membrane antibodies were not detected in plasma. She was treated with acyclovir for suspected Varicella pneumonia and improved after a ten-day hospitalization.

In August 1990, now 21 weeks pregnant, she was again hospitalized with progressive dyspnea and scanty hemoptysis. Examination revealed a gravid, dyspneic female with a blood pressure of 100/70 mm Hg; heart rate, 100 beats per minute; respiratory rate, 26 breaths per minute, central cyanosis, wheezes, and inspiratory crackles; clubbing; no evidence of synovitis, and minimal lower extremity edema. Admission arterial blood gas levels with the patient receiving oxygen, 4 L/min, revealed a Po2 of 43 mm Hg; Pco2, 30 mm Hg; and pH, 7.48. With the patient receiving 10 L/min, the Po2 increased to 67 mm Hg. A chest radiograph demonstrated bilateral diffuse interstitial and alveolar densities greater in the lower lung fields. She was treated with ampicillin empirically and continued to receive prednisone, 20 mg daily. The ECG showed right ventricular hypertrophy, and an echocardiogram demonstrated a dilated right ventricle with normal left ventricular function.

On the third hospital day, she developed severe dyspnea and fever, prompting transfer to the ICU. Mechanical ventilation and positive end-expiratory pressure (10 cm H2O) were initiated for acute hypoxemic respiratory failure. No hemoptysis was found. A chest radiograph showed increased bilateral alveolar infiltrates (Fig 1). The hematocrit level decreased from 45 to 36 percent. Renal function and urinalysis were normal. Ceftizoxime and erythromycin were given. A chest radiograph on day 4 revealed improved bilateral alveolar infiltrates. A bronchoscopy on day 6 revealed diffusely hyperemic bronchi and alveoli. A modified barium-swallow examination demonstrated pooling of barium in the esophagus (Fig 1).

Figure 1. Modified barium-swallow examination demonstrates pooling of barium in the esophagus.

*From the Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of California, Davis Medical Center, Sacramento.

Reprint requests: Dr. Louie, University of California, 2601 Stockton Blvd, Sacramento, CA 95817
were started empirically. Right heart catheterization revealed a right atrial pressure of 10 mm Hg; pulmonary artery pressure, 47/31 Hg; pulmonary artery occlusion pressure, 15 mm Hg; cardiac index, 4.8 L/min/m²; and systemic vascular resistance, 891 dynes/sec.cm⁻⁵.

Fiberoptic bronchoscopy demonstrated normal tracheobronchial mucosa and anatomy. Bronchoalveolar lavage of the right middle lobe returned bloody fluid. She was treated with methylprednisolone, 60 mg intravenously every 6 h. Bronchoalveolar lavage cytology revealed numerous RBC and multinucleated giant histiocytes with hemosiderin-ladened macrophages by Prussian blue staining. Studies done the same day revealed an erythrocyte sedimentation rate of 86 mm/h; no cryoglobulin; CH₅₀, 237 U/ml (normal, 97 to 292 U/ml); C₃, 118 mg/dl (normal 88 to 186 mg/dl); C₄, 28 (normal, 14 to 54 mg/dl); rheumatoid factor titer, positive; 1:1280; Sjogren's antibodies SS-A and SS-B, not detected; antibody to native DNA detected by immunofluorescence, negative; and a Raji cell assay, 28 µg Eq/ml (normal, less than 15 µg Eq/ml), consistent with the presence of circulating immune complexes. Antinuclear and antiglomerular basement membrane antibodies in plasma were not detectable. Cultures of blood, urine, and bronchoscopic aspirate samples for pathogenic bacteria, fungi, and viruses were all eventually negative.

Mechanical ventilation was withdrawn on the seventh hospital day, and the prednisone dosage was tapered to 25 mg daily. On the 23rd hospital day, the patient noted wrist and shoulder pain and the appearance of small, nontender 1-cm subcutaneous nodules over the extensor surface of her right elbow. Articular films of the hands and shoulders were normal. Biopsy of one nodule revealed granulomatous inflammation characterized by central necrosis and surrounding epithelioid histiocytes and occasional lymphocytes consistent with a rheumatoid nodule (Fig 2).

On the 93rd hospital day, the patient went into labor and had a spontaneous vaginal delivery of a healthy infant without major complications. Intrapartum oxygen saturation levels with the patient receiving 10 L/min of oxygen was 93 to 95 percent. A room air PO₂ level was 39 mm Hg prior to discharge. She continues to receive 5 L/min O₂ and 25 mg of prednisone daily without further episodes of life-threatening pulmonary hemorrhage.

**DISCUSSION**

Idiopathic pulmonary hemosiderosis is diagnosed by the clinical triad of hemoptysis, pulmonary infiltrates, and anemia in the absence of renal disease and other disorders that might be considered in the differential diagnosis. Although the median survival is three years after diagnosis, some patients do survive longer with recurrent episodes of hemoptysis between periods of spontaneous remission that lead to eventual pulmonary hypertension and iron-deficiency anemia. The quantity of hemoptysis can be variable and is not a reliable index of the degree of pulmonary hemorrhage because alveolar bleeding does not readily reach the central airways.¹¹ The original open-lung biopsy in this patient showed focal rupture of the capillary basement membrane and swelling of alveolar epithelial cells on electron microscopy, findings reported previously in IPH that suggest a primary pneumocyte injury.¹²-¹⁴ Apart from one report,¹⁵ no subsequent study has described electron-dense immune complex-like deposits within the basement membrane, and no study utilizing immunofluorescent staining described any localization of complement, immunoglobulin, or immune complexes within the alveolar septa.¹²-¹⁴ The ultrastructural findings of IPH differ considerably from Goodpasture's syndrome in which wide endothelial gaps and diffuse fragmentation of the basement membrane are characteristic.¹⁶,¹⁷

While several risk factors may be involved in IPH, its pathogenesis remains speculative at present. Hereditary factors may predispose families to IPH.¹⁸-²⁰ Autoimmune hemolytic anemia,²¹ autoimmune thyrotoxicosis,²² celiac disease,²³ rheumatoid arthritis,²⁴ and IgA monoclonal gammapathy²⁵ have been reported with IPH.

However, an immunologic marker unique to IPH remains elusive. Immune complexes may mediate pulmonary hemorrhage during penicillamine treatment and in systemic lupus erythematosus by causing type 3 immune reactions, with or without complement.²⁶,²⁷ The presence of circulating immune complexes in our case during pulmonary hemorrhage suggests an analogous process. The antigen inducing the immune complex remains unknown. Whether immune deposits in the lung are necessary for pulmonary hemorrhage is controversial. Pulmonary hemorrhage can develop with no detectable immune complex deposits in the lung.²⁸ Open-lung biopsy to provide ultrastructural correlation was not done in our case because of the pregnancy and the favorable response to corticosteroids.

In two previous case reports, IPH was exacerbated at the seventh month of pregnancy.²⁹,³⁰ a time when gestational increase in plasma volume reaches its peak. Our patient presented with pulmonary hemorrhage during the fifth month of pregnancy, and pulmonary artery pressures, measured during mechanical ventilation were moderately increased. It is debatable whether rises in pulmonary artery pressures in IPH are primary or secondary events.

Corticosteroids are probably beneficial for acute exacerbations of IPH but do not affect the long-term prognosis.¹³ Recurrent pulmonary hemorrhage may cause iron overload within the lung and predispose generation of tissue-damaging reactive oxygen species, such as hydroxyl radical.³¹ Present evidence, though suggestive, does not rigorously prove that reactive oxygen species are involved in IPH. However, the use of an iron chelating agent like deferoxamine may be an area for clinical investigation in this rare disease.
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REFERENCES

Esophageal Obstruction in a Tracheostomized Infant*

Bruce M. Schnupp, D.O., F.C.C.P.; Jeanne Ravert, M.D.; and Stephanie Dodson, M.S.

Partial esophageal obstruction was an unusual complication of tracheostomy in an infant. Esesmes and failure to thrive prompted a modified barium-swallow study, which revealed that the tracheostomy tube was causing an obstruction in the proximal esophagus. Use of a shorter, customized tube eliminated the esophageal obstruction, allowing normal feeding and weight gain. (Chest 1993; 104:1909-10)

A review of the literature on pediatric tracheotomies found complication rates as high as 46.5 percent.1 Complication rates in children are directly related to the age of the patient, with an incidence of 67 percent in those less than 1 year.2 Although aspiration has been described as a posttracheotomy complication,3 it has not been described in a child without a cuffed tracheostomy tube. We report the case of a young infant in whom feeding intolerance and aspiration were complications related to a tracheostomy tube.

CASE REPORT

The patient is a black female infant who was born after a 26-week pregnancy to a 17-year-old primigravida woman. The infant was treated for respiratory distress syndrome and required mechanical ventilator support for the first 2 weeks of life. The baby was noted to have intermittent stridor but was without significant respiratory compromise. She was discharged at 2 months of age without medications or oxygen. Oral feedings were well tolerated.

Ten days after discharge from the hospital, she presented to the emergency room with worsening stridor and severe respiratory distress. Her arterial oxygen saturation, as measured by pulse oximetry while breathing room air, was 94 percent. In addition, the patient was noted to have lost weight and was not tolerating feedings at home. A flexible bronchoscopic examination revealed severe laryngomalacia. No subglottic stenosis or tracheal narrowing was evident. Because of the severe airway obstruction, hypoxia, and compromised growth, a No. 00 neonatal tracheostomy tube (Shiley, Irvine, Calif) was inserted 12 h after presentation to the hospital. Feedings were not attempted prior to the tracheostomy while the infant was in the hospital.

The infant's postoperative course was uneventful until shortly after oral feedings were resumed. Although she maintained a vigorous suck and swallow, esesmes was noted with most feedings, and little gain in weight occurred. No improvement was noted

*From the Pulmonary Division, Department of Pediatrics, University of South Florida College of Medicine, Tampa.