Idiopathic Pulmonary Hemosiderosis*

Electron Microscopic, Immunofluorescent, and Iron Kinetic Studies

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The clinical course of a 37-year-old white man with idiopathic pulmonary hemosiderosis is presented. This patient is unusual in that he has had repeated exacerbations and remissions over a period of seven years and remains currently in spontaneous remission with no therapy. Routine sections of the lung biopsy revealed characteristic findings. Immunofluorescence staining of the lung was negative, and electron microscopic studies showed only nonspecific findings. While in remission, $^{51}$chromium-labelled red-blood-cell survival studies and $^{59}$iron kinetic studies were performed; the results were normal.

Idiopathic pulmonary hemosiderosis (IPH) is an uncommon disease characterized by hemoptysis, pulmonary infiltrates, and iron-deficiency anemia. The course of the disease is unpredictable, and patients may die shortly after onset of symptoms or live for many years. The patient reported herein has had repeated relapses and spontaneous remissions over a period of approximately seven years.

**Case Report**

A 37-year-old white man experienced episodes of hemoptysis in 1967 and 1968 not associated with anemia or radiologic pulmonary abnormalities. In 1970 he was hospitalized with hemoptysis and dyspnea. A chest x-ray film revealed extensive bilateral infiltrates, and the hematocrit reading was 31 percent. The patient gradually improved, and the anemia responded to oral administration of ferrous sulfate. In 1971 he was hospitalized with hemoptysis, anemia, and an abnormal chest x-ray film and again improved spontaneously. He then remained asymptomatic until August 1973 when he was admitted for the first time to the Portsmouth (Va) Naval Hospital with a history of fatigue, fever, and hemoptysis of four weeks' duration. He has been a 1½ pack-per-day smoker for many years.

Physical examination was normal except for pallor. The stool was negative for occult blood.

The hematocrit reading was 27 percent, and the mean corpuscular volume was 82 cu μm. The peripheral blood smear showed striking hypochromia, microcytosis, anisocytosis, poikilocytosis, and polychromasia. The results of the white blood cell count and the differential leukocyte count were normal, and the platelet count was 500,000/cu mm. The reticulocyte count was 6 percent. The serum iron level was 46 μg/dl.

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μg/100 ml, and the total iron binding capacity was 340 μg/100 ml. The plasma hemoglobin level was less than 0.9 mg/100 ml, and the results of haptoglobin determinations were repeatedly normal. The bone marrow showed marked erythroid hyperplasia with absent iron stores. A direct Coombs' test was slightly positive, but subsequent determinations were negative. The total bilirubin level was 1.4 mg/100 ml, with a direct fraction of 0.25 mg/100 ml, and the lactic dehydrogenase level was 325 international units. The results of electrocardiogram, urinalysis, and protein electrophoresis, as well as the levels of blood urea nitrogen, creatinine, serum glutamic oxaloacetic transaminase, alkaline phosphatase, and immunoglobulins were all normal. The chest x-ray film revealed bilateral lower lung field infiltrates (Fig 1). Arterial blood gas studies on room air revealed P O₂ 58 mm Hg, P CO₂ 33 mm Hg, and pH 7.45. Pulmonary function tests showed no definite obstruction or restrictive impairment. The sputum was positive for hemosiderin-laden macrophages.

An open lung biopsy performed during a period of hemoptysis revealed hyperplasia of the alveolar lining cells with hemosiderin-laden macrophages within the alveolar spaces (Fig 2). Fluorescein-conjugated antisera to human IgG, IgM, IgA, complement (β₁C₃/β₁A-globulin), fibrin, and albumin were obtained from a commercial supplier,* and staining was done by a modification of the Coons and Kaplan method. The antisera gave a single line on immuneelectrophoresis and double diffusion in agar. The lung sections were stained in parallel with positive controls consisting of renal tissue with established immunopathologic patterns. The lung tissue was negative for all immunofluorescent stains, and absorption studies therefore were not done. Electron microscopic studies revealed abundant alveolar macrophages with hemosiderin deposits (Fig 3), focal increase and deposition

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Figure 1. Posteroanterior chest x-ray film showing bilateral infiltrates.

Figure 2. Lung biopsy. Dilated alveoli contain large numbers of hemosiderin-laden macrophages and RBC. Alveolar septae are focally thickened and fibrotic (hematoxylin-eosin, original magnification × 100).

Figure 3. Alveolar macrophages contain hemosiderin deposits (D) within cytoplasmic lysosomes (uranyl acetate and lead citrate, original magnification × 12,400).

Figure 4. Alveolar macrophages (M) with prominent lysosomes within alveolar spaces (A). Interstitium (I) contains increased collagen deposition. Capillaries (C) are lined by normal-appearing endothelium (uranyl acetate and lead citrate, original magnification × 8,600).
of collagen and elastic fibers in the interstitium (Fig 4), and focal hyperplasia of the alveolar type 2 cells. There were no immune complexes noted in the endothelial or epithelial basement membranes nor were there any breaks in the capillary basement membrane (Fig 5).

The patient's hospital course was one of gradual improvement, with cessation of the hemoptysis and response of the anemia to ferrous sulfate therapy. While in clinical remission 51chromium-labelled red-blood-cell (RBC) survival studies and 59iron kinetic studies were performed. The 51chromium-labeled RBC half-life was 30 days (normal, 25 to 33 days). The plasma iron turnover was 0.9 mg of iron per 100 ml of whole blood per day (normal, 0.4 to 0.9),14 and the half-life was 60 minutes.

**DISCUSSION**

The etiology and pathogenesis of IPH are unknown. Although no pathognomonic marker allows certainty of diagnosis, the association of iron deficiency anemia with a compatible history and lung biopsy, along with absence of renal findings usually associated with Goodpasture's syndrome, strongly supports the diagnosis of IPH. The negative results of immunofluorescent studies of the lung biopsy specimen are in agreement with those of Irwin et al.5

Electron microscopic studies of two cases of IPH have previously been reported. Hyatt et al.6 described a break in the alveolar capillary basement membrane of a three-year-old with IPH. Irwin et al.7 studied a 21-year-old man with IPH and found no specific abnormalities. The increased fibrosis and hyperplasia of the alveolar type 2 cells found in our patient are nonspecific. The lack of subendothelial immune-complex deposits is in agreement with the findings of Hyatt et al.6 and Irwin et al.7 Breaks in the continuity of the capillary basement membrane, as reported by Hyatt et al.,6 were not seen in this study.

The pathogenesis of the anemia of IPH has been studied, and there is clear evidence1,2,7 that iron deficiency secondary to the loss of erythrocytes within the lung plays a central role. Apt et al.1 showed an increased uptake of radioactive iron within the lung during an exacerbation of IPH, associated with a corresponding decrease in the circulating radioactive iron. Iron thus sequestered in the lung parenchyma is reutilized poorly, if at all, leading to the paradox of iron deficiency anemia with iron excess in the lungs.

It has been noted that reticulocytosis in the face of iron deficiency is usually seen in IPH,1 and there has been one other adult patient reported with a positive Coombs' test.9 Indeed, our patient had some features suggestive of hemolysis: his reticulocytosis, increased lactic dehydrogenase and mildly elevated indirect bilirubin levels; and a positive direct Coombs' test. However, the most sensitive indications of recent or ongoing hemolysis, ie, the levels of plasma hemoglobin, serum haptoglobin, and urine hemosiderin, were normal. There is no evidence that hemolysis plays a significant role in the anemia of IPH, and the hematologic abnormalities simulating hemolysis have other explanations. Swallowed blood resulting from the hemoptysis could provide a ready source of iron for small intestinal absorption and subsequent reticulocytosis. The transiently positive Coombs' test could be attributed to transferrin-coated reticulocytes,10 and the bilirubin elevation is most likely a manifestation of the reabsorption of hemoglobin pigments from pulmonary alveoli.2

One month after normalization of the hematocrit reading (45 percent), 51chromium-labelled RBC survival curves and iron kinetic studies were within normal limits. There was no evidence of hemoptysis during this period. Attempts to show increased accumulation over the lungs with rectilinear scanning for radioactive iron at the time of the plasma iron turnover, one week and four weeks later, showed no increase compared to the precordium.

As the etiology of IPH is unknown, definitive therapy is lacking. Corticosteroid and immunosuppressive therapy have been advocated, mainly on the basis of a suspected autoimmune mechanism for the disease. Soergel and Sommers,4 in their review of IPH, concluded that steroid therapy was helpful in the treatment of acute bleeding episodes, but that long-term therapy did not alter the disease. Recently, Byrd and Gracey11 reported the induction of a prolonged remission in a 22-year-old patient with azathioprine.

Objective evaluation of drug therapy in IPH is difficult, however, because the disease is characterized by relapses and remissions, and prolonged remissions for years are documented.

Our patient did not receive steroids or immunosuppressive drugs, but apparently underwent a spontaneous remission, in which he now remains.

ACKNOWLEDGMENTS: The authors wish to thank Dr. Melvin Schwartz, Pathology Department, Portsmouth (Va) Naval Hospital for carrying out the immunofluorescence staining; Dr. Jacqueline J. Coalon, Department of Pathology, University of Oklahoma, for performing the electron microscopic analysis; and Dr. Richard Daly, Portsmouth (Va) Naval Hospital for assistance in the iron kinetic studies.

**Figure 5.** Capillary (C) is lined by normal endothelium. There are no subendothelial dense deposits. Type 1 epithelium, which is normal in content and width, lines alveolar spaces (A). Interstitium (I) does not show significant increase in collagen deposition (uranyl acetate and lead citrate, original magnification x 18,000).

**Chest, 68: 4, October, 1975**
Acute Pulmonary Hypersensitivity to Carbamazepine*

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Acute pulmonary hypersensitivity to carbamazepine (Tegretol) is reported, manifested by diffuse pulmonary infiltrates, skin rash, and eosinophilia. The reaction cleared on cessation of the drug. A lymphocyte transformation test was reactive to carbamazepine.

Carbamazepine (Tegretol), an iminostilbene derivative, is the medical treatment of choice for trigeminal and glossopharyngeal neuralgia; it is now gaining acceptance as a therapeutic agent in the control of psychomotor seizures.1 Coincident with its use has been an increase in reported side effects; some of the more important are aplastic anemia, leukopenia, psychosis, and skin rash.2 Drug-induced lung disease has been the subject of several recent reviews and classifications, usually based on the type of response manifested in the lung.3,4 A case of acute pulmonary hypersensitivity with eosinophilia believed to have been caused by carbamazepine is described.

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Case Report

A 55-year-old black woman was referred on October 19, 1973, for evaluation and treatment of right-sided trigeminal neuralgia. Treatment was begun with carbamazepine, 100 mg twice daily, after hepatic and hematologic profiles were reported as normal. The patient improved symptomatically; three weeks later the dosage was raised to 200 mg twice daily. Hepatic and hematologic studies were again normal.

Two weeks after this, she came to the emergency room with a three-day history of cough, shortness of breath, and skin rash which had started on the forearms and thighs and later spread to the trunk. She denied any drug ingestion other than carbamazepine during the preceding 25 days.

Physical examination disclosed a febrile hypertensive woman who appeared to be moderately ill. A striking, generalized, maculopapular, erythematous skin eruption was noted, with minimal involvement of the face and sparing the palms and soles. Blood pressure was 140/90 mm Hg, pulse was 100 beats per minute, and the temperature was 38.1°C (100.6°F). Shotty cervical, axillary, and inguinal nodes were palpable. Auscultation of the chest disclosed crackling rales throughout both lung fields. The findings from cardiac examination were normal, and neither liver nor spleen was enlarged. Blood gas analyses showed an oxygen pressure (P O₂) of 71 mm Hg, an SO₂ level of 94 percent, carbon dioxide pressure (P CO₂) of 30 mm Hg, and pH of 7.41. The initial hemoglobin level was 13.3 gm/100 ml, and the white blood cell count (WBC) was 17,400/cu mm with 22 percent polymorphonuclear leukocytes, 4 percent bands cells, 10 percent lymphocytes, 6 percent monocytes, and 58 percent eosinophils. The results of liver and renal function studies were normal. A chest x-ray film (Fig 1) showed a diffuse nodular and reticular pattern in both lungs with prominence of the hila suggesting adenopathy.

Initial therapy included discontinuation of carbamazepine therapy, topical application of hydrocortisone for the skin rash, and administration of diphenhydramine, 25 mg every six hours. On the following day, pulmonary function studies revealed a forced vital capacity (FVC) of 1.83 L (51 percent of predicted), a forced expiratory volume (FEV₁₀) of 1.36 L (45 percent of predicted and 74 percent of the FVC), peak

Figure 1. Chest x-ray film (Nov. 21, 1973) showing diffuse reticular-nodular pattern and prominent hilar structures.