A 74 Year-Old male with intermittent hemoptysis

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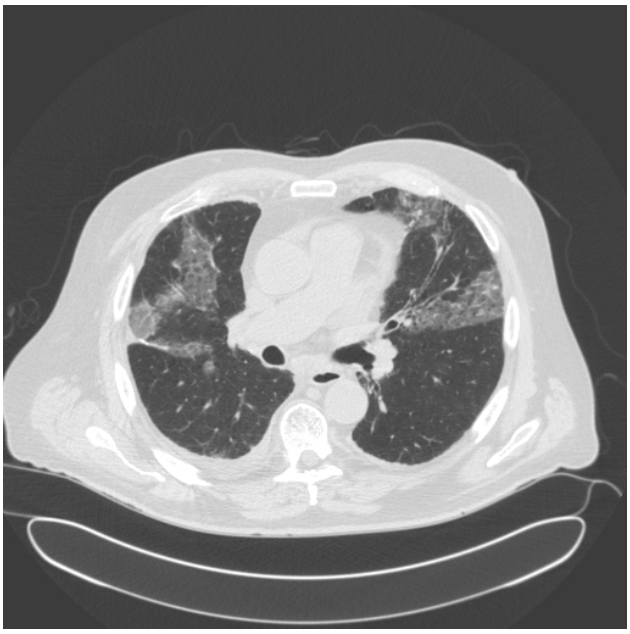
A 74 y/o male was referred for evaluation of hemoptysis. He described daily production of 6 – 8 spoonfuls of bloody sputum for 2 years. He had accompanying dyspnea on exertion and occasional shortness of breath at rest. He suffered from night sweats and daily fevers, which resolved with acetaminophen. He had lost about 20 pounds in the preceding 2 years. He complained of intermittent nausea and loss of appetite. Further review of systems was negative. His past medical history included hypertension, gastroesophageal reflux disease, benign prostatic hypertrophy, back pain, and remote pulmonary histoplasmosis and coccidiomycosis. His medications included atenolol, hydrochlorothiazide, lisinopril, trazodone, tamsulosin, omeprazole, hydrocodone with acetaminophen, guaifenesin, potassium, iron, and compazine. The patient had lived in Indiana all his life. He had been a pipe insulator and he had been exposed to asbestos and fumigating agents. His hobbies included hunting and shooting firearms, but he had to abandon them due to the dyspnea. He had smoked 50 pack-years prior to quitting tobacco use 20 years ago. He briefly resumed smoking two years ago, but stopped within two months when hemoptysis appeared. He denied alcohol or drug use. The patient's physical examination was remarkable for an oxygen saturation of 93% on room air and mild crackles in the lung bases.

The patient's prior work up had been remarkable for an erythrocyte sedimentation rate of 33, intermittent hematuria on repeated urinalyses, and normal p-ANCA, c-ANCA, myeloperoxidase, and proteinase 3 serologies. Anemia had not been present until 6 months prior to the referral. His pulmonary function tests had been significant only for a reduced diffusing capacity at 58% predicted. An echocardiogram had revealed left ventricular hypertrophy with mild left atrial and right ventricular dilation, and mild diastolic dysfunction. There had been no valvular abnormalities. Six months prior to the referral, he underwent a video-assisted thoracoscopic biopsy of the lung, which showed recent and remote intraalveolar hemorrhage, arterial mural hypertrophy, emphysematous blebs, and no vasculitis, granulomas, or thrombosis on hematoxylin and eosin stains. Immunostaining was not been performed. He has not received any treatment for the hemoptysis.

The patient's laboratory values included hemoglobin of 9.2, creatinine of 1.6, ferritin of 996, rheumatoid factor of 315, and prostate specific antigen of 11.8. The pertinent normal results included platelets, INR, iron level, iron saturation, total iron binding capacity, antinuclear, anti-glomerular basement membrane, and anti-cyclic citrullinated peptide antibodies, antiphospholipid antibody panel, and complement C3 and C4 levels. Multiple chest imaging in the preceeding two years demonstrated intermittent, migrating areas of patchy ground glass opacities superimposed on mild emphysematous changes (see figure 1). V/Q scan revealed perfusion defects which matched the areas of ground glass opacities. Bronchoscopy with bronchoalveolar lavage yielded fluid became increasingly bloodier on serial aliquots. The fluid analysis was negative for any infectious process and showed a cell differential with 80%

macrophages, 5% lymphocytes, 12% neutrophils, and 3% eosinophils. Thirty percent of cells stained with hemosiderin (see figure 2). A right heart catheterization showed a pulmonary artery pressure of 21/6 (mean 12) mmHg and a capillary wedge pressure of 5 mmHg.



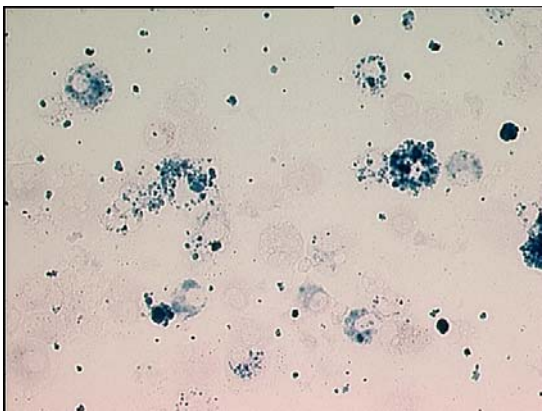


Figure 2- Bronchoalveolar lavage fluid stained for hemosiderin showing hemosiderin-laden macrophages at 20x magnification.

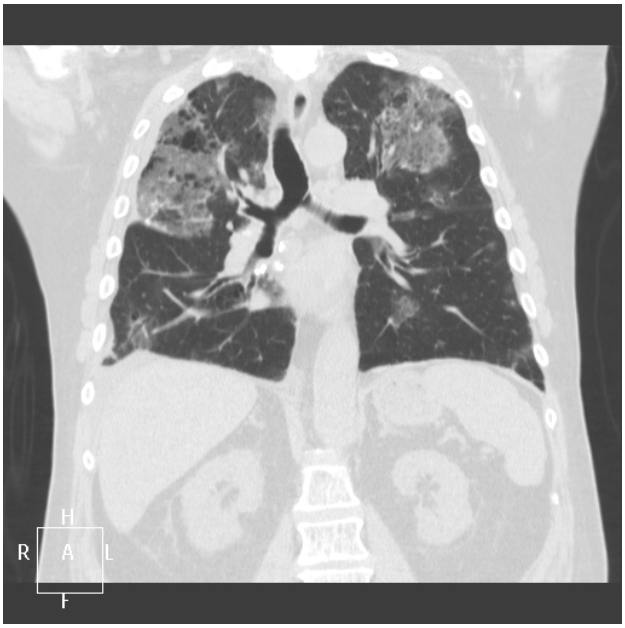


Figure 1- Chest CT upon presentation

What is the diagnosis?

Diagnosis: Diffuse alveolar hemorrhage (DAH) from idiopathic pulmonary hemosiderosis (IPH).

DAH should be suspected in patients with recurrent hemoptysis, iron deficiency anemia, and bilateral air-space opacifications. The differential diagnosis of DAH is broad and includes systemic vasculitis syndromes, connective tissue diseases, glomerulonephritis-associated disease, infections, drugs or toxic agents, primary and metastatic lung cancers, complications of transplantation, cardiac disorders, bleeding disorders, pulmonary vascular disease, and others (Table 1). The systemic vasculitides and connective-tissue diseases are the most common causes. During the workup of DAH, it is helpful to classify the underlying disorders as those with or without pulmonary capillaritis (Table 2).

The patient presented here was evaluated for the causes of DAH listed in Table 2. His lung biopsy revealed arterial mural hypertrophy, which raised a suspicion for chronic pulmonary emboli and/or pulmonary hypertension. Both of those possibilities were excluded by a V/Q scan which showed matched ventilation-perfusion defects and a normal right heart catheterization. Neither the patient's lung biopsy nor serologies were consistent with vasculutis. His intermittent hematuria and elevated creatinine were attributed to obstructive uropathy. In the absence of an identifiable cause of DAH, the patient was diagnosed with IPH. The diagnostic certainty of IPH would have been improved if immunostaining of lung tissue had been performed (see below). This test had not been done because lung specimens had been submitted to pathology in formalin alone, and not in normal saline. A negative immunostaining would have been specifically helpful in excluding anti-basement – membrane disease and Henoch-Schonlein Purpura, two diseases for which treatment is similar to that for IPH.

IPH is defined as recurrent hemoptysis, anemia, and pulmonary infiltrates without a known cause. It is a diagnosis of exclusion. Vasculitis, capillaritis, granulomas, and deposition of immunoglobulins should be ruled out by lung biopsy. IPH is a disease predominantly affecting children and young adults with a reported prevalence ranging from 0.24 to 1.23 cases per million[1]. In children, the syndrome is equally common in both genders, while in adults, it is more frequent in men than in women. Familial and geographic clustering of IPH has been described, suggesting that environmental factors may precipitate the disease in genetically predisposed individuals[2]. There are several theories about the etiology of IPH. The genetic theory is based on the observed familial clustering of cases. The allergic theory is suggested by an association between IPH and allergy to cow's milk (Heiner's syndrome) and an association between IPH and celiac disease[1]. The latter association has been further supported by an observation that gluten free diet induced remission of hemoptysis in some patients with celiac disease and IPH[3]. Of note, the patient described here tested negative for antigliadin, anti-tissue transglutaminase, and antiendomysial antibodies, although an intestinal biopsy could be considered if he has further unremitting symptoms. Environmental factors, such as insecticides or molds have also been implicated in the etiology of IPH. In this regard, it is interesting to note that the patient under discussion reported significant exposure to fumigating agents at his workplace.

The symptoms of IPH are nonspecific and include exertional dyspnea, hemoptysis, weight loss, and fever. Lymphadenopathy and hepatosplenomegaly are found in approximately

20% of patient[2]. Pulmonary function tests may reveal a restrictive ventilatory abnormality, and carbon monoxide diffusing capacity may be elevated in the hemorrhagic phase of the disease, due to increased binding of carbon monoxide by alveolar-blood hemoglobin. The diffusing capacity is typically low in the chronic phase of IPH, as was the case in this patient. During an episode of acute pulmonary bleeding, imaging abnormalities include ground grass opacities, as has been illustrated in this case. The opacities may show partial or complete regression in the symptom-free phase[4]. Iron deficiency anemia may be present, though serum ferritin may be misleadingly elevated due to large amount of immobile hemosiderin deposited in the lungs. The accumulation of hemosiderin is likely due to an impaired ability of alveolar macrophages to metabolize hemoglobin iron. However, a small proportion of iron is continuously released from the alveoli back to the circulation resulting in elevation of ferritin despite low bone marrow iron stores. Absorption of hemoglobin from the alveoli may cause a rise in serum bilirubin and the urinary excretion of urobilinogen, mimicking hemolytic anemia[4]. The deposition of iron in the lungs causes slowly progressive fibrosis, and interestingly, mild fibrotic changes have been noted on a 9 month follow up chest CT of this patient.

The course of IPH is variable and it carries a better prognosis in adults than it does in children. Patients usually succumb to acute respiratory failure due to massive DAH or chronic respiratory failure and cor pulmonale from severe pulmonary fibrosis[1]. There are no controlled studies of therapy for IPH, due to the low prevalence of the disease. Glucocorticoids at a dose equivalent to 1 mg/kg of prednisone, administered in the acute phase of alveolar hemorrhage and slowly tapered over a period of months, have been recommended based on observational data[1]. Most patients respond favorably to chronic oral corticosteroids with reduction in exacerbations and fibrosis. Other immunosuppressive agents, such as azathioprine, hydroxychloroquine, cyclophosphamide, and methotrexate have been tried with variable success. Single lung transplantation has been reported, but it was complicated by recurrence of IPH in the transplanted lung[5].

The patient described here was discharged from the hospital on prednisone at 1 mg/kg per day, with a taper of 5 mg per week. Azathioprine was subsequently added in an effort to wean him from steroids entirely. During the eight months of follow-up, he experienced recurrent hemoptysis whenever his prednisone dose was dropped below 0.1 mg/kg per day.

References:

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Table 1- Differential diagnosis of diffuse alveolar hemorrhage (adopted from reference 2).

Systemic vasculitis syndromes Wegener's granulomatosis Microscopic polyangiitis Henoch–Schönlein purpura Behçet's syndrome Mixed cryoglobulinemia Churg–Strauss syndrome **Connective-tissue diseases** Systemic lupus erythematosus Rheumatoid arthritis Scleroderma Mixed connective-tissue disease Polymyositis or dermatomyositis **Drugs or toxic agents** Penicillamine Trimellitic anhydride Isocyanates Cocaine Propylthiouracil Tirofiban Abciximab Phenytoin **Glomerulonephritis-associated alveolar hemorrhage** Immune-complex–mediated Pauci-immune IgA nephropathy **Infections** Pneumonia Angioinvasive aspergillosis Candidiasis Cytomegalovirus infection Legionellosis Herpes simplex pneumonia Acquired immunodeficiency syndrome	**Pulmonary metastasis** Metastasis of angiosarcoma Metastasis of Kaposi's sarcoma **Transplantation** Bone marrow transplantation Solid-organ transplantation **Pulmonary vascular disease** Primary pulmonary hypertension Thromboembolic disease Pulmonary-capillary hemangiomatosis **Diffuse alveolar damage or acute respiratory distress syndrome** **Cardiac disorders** Mitral stenosis Congestive heart failure Cor triatriatum **Anti–basement-membrane disease** **Bleeding disorders** Adverse effect of anticoagulation therapy Disseminated intravascular coagulation Thrombotic thrombocytopenic purpura **Other disorders** Lymphangioleiomyomatosis or tuberous sclerosis Sarcoidosis Idiopathic pulmonary fibrosis Antiphospholipid-antibody syndrome Heiner's syndrome (alveolar hemorrhage associated with allergy to milk) Isolated pauci-immune pulmonary capillaritis Idiopathic pulmonary hemosiderosis

Table 2-Disorders associated with diffuse alveaolar hemorrhage (adopted from reference 4). GN = Glomerulonephritis

Without pulmonary capillaritis	**With pulmonary capillaritis**
Bleeding disorder	Systemic vasculitis syndromes
Cardiac disorder	Connective tissue diseases
Pulmonary metastasis	Anti-basement membrane disease
Pulmonary vascular disease	GN-associated alveolar hemorrhage
Pulmonary vascular malformation	Infections
Lymphangioleyomatomatosis or tuberous sclerosis	Drugs or toxic syndromes
Idiopathic pulmonary fibrosis	Heiner's syndrome
Sarcoidosis	Antiphospholipid antibody syndrome
Drugs or toxic syndromes	Isolated pauci-immune pulmonary capillaritis
Idiopathic pulmonary hemosiderosis	Transplantation