CLINICAL VIGNETTE

A Cough Productive of White Flecks

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Case Presentation

A 43-year-old male veteran presented to pulmonary for evaluation of cough, and shortness of breath. He reports symptoms started about 8 months ago and have been slowly progressive. The cough is productive of white flecks and he denies fever, chills, night sweats, nausea, vomiting. He has no recent travel or any sick household contacts. He has no chronic medical problems and takes no medications. He unemployed, but previously worked as a waiter and has lived in Los Angeles for most of his adult life. He denies smoking, alcohol use, or intravenous or inhaled drug use. His vital signs are remarkable for room air oxygen saturation of 92%. His physical exam is significant for fine bibasilar inspiratory crackles, and no clubbing or cyanosis. A non-contrast computerized tomography (CT) scan of his chest is remarkable for diffuse ground glass opacities accompanied by thickened intralobular and interlobular septa in polygonal shapes (Figure 1). Labs including complete blood count, infectious and rheumatologic serologies, and quantitative antibodies, were nonrevealing. Given concern for pulmonary alveolar proteinosis based on chest imaging, serum anti-GM-CSF antibodies were obtained, which returned positive.

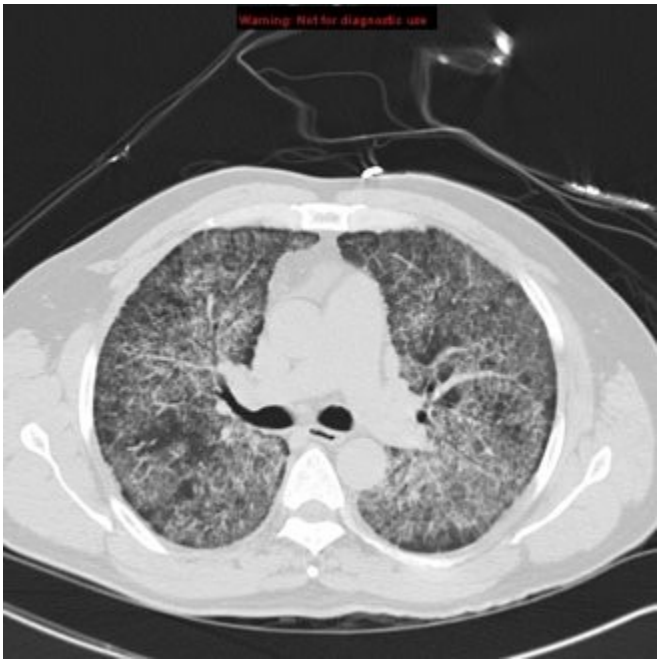

Figure 1: Non-contrast computerized tomography (CT) scan of his chest which is remarkable for diffuse ground glass opacities accompanied by thickened intralobular and interlobular septa in polygonal shapes.

Pulmonary alveolar proteinosis (PAP) is a rare parenchymal lung disease characterized by accumulation of lipoproteinaceous material in the alveoli.

Pathogenesis

PAP is a result of reduced granulocyte-macrophage colony-stimulating factor (GM-CSF) levels or function, and impaired processing of surfactant by alveolar macrophages.[1] GM-CSF regulates clearance of surfactant by alveolar macrophages.[1] Some evidence suggests that reduced GM-CSF protein or function is likely responsible for impairment in surfactant processing.[2] Other human and mice studies also suggest that macrophage dysfunction (either primary or acquired) contributes to impaired processing of surfactant and contributes to the pathogenesis of PAP.[3-5]

Classification

PAP can be classified based on its cause[1]:

PAP	Characteristics
Primary PAP	-90% of cases -Autoimmune PAP due to anti-GM-CSF autoantibodies prevents binding of GM-CSF to GM-CSF receptors on macrophages and impairs terminal differentiation and function (most common PAP in adults) -Hereditary PAP due to genetic variants of GM-CSF receptor that impair signaling by intact GM-CSF
Secondary PAP	-<10% of cases -Impaired function, or reduced number of alveolar macrophages ---> Systemic inflammatory disease or hematologic malignancies ---> Inhalation of silica, aluminum dust, titanium dioxide, etc ---> Immune defects such as Fanconi syndrome, severe combined immunodeficiency, etc ----> Infections such as Nocardia, Pneumocystic Jirovecii, etc
Congenital PAP	-2% of cases -Deficiency of surfactant protein B or, abnormalities in beta chain of receptor for GM-CSF

Figure 2: Classification of PAP and characteristics

Clinical Manifestations

Age of presentation is generally 40 to 50years, with a male to female ratio of 2:1.[6,7] Patients typically present with an insidious onset of symptoms including dyspnea on exertion, cough, sputum production, fatigue, weight loss, low grade fevers.[7,8] On physical exam, crackles are present in about 50 percent of patients,[6] and clubbing and cyanosis in about 25 percent of patients.[7]

Laboratory abnormalities are dependent on the etiology of the PAP. Patients with autoimmune PAP will be positive for serum anti-GM-CSF antibodies, which are 100 percent sensitive and specific.[8] For patients with secondary PAP, laboratory evaluation is done directed at the probable etiologies including, infections, inhalational exposures, and hematological malignancies among others. Hereditary PAP due to dysfunctional GM-CSF receptor is evaluated with GM-CSF levels, which will be elevated due to abnormal receptor function.[8] Patients with congenital PAP due to surfactant production and metabolism disorders typically present in childhood, and adults generally do not require testing for these gene variants.[1]

Imaging

Chest radiographs shows bilateral centrally located alveolar opacities in the mid and lower lung zones in a “bat wing” pattern. Patients with chronic PAP may develop pulmonary fibrosis. On computed tomography (CT), homogenous ground glass opacification may be apparent, accompanied by thickened intralobular and interlobular septa in polygonal shapes and superimposed on the ground glass opacities. This pattern is referred to as “crazy-paving”.[9] Crazy-paving, however, is not specific for PAP and can be observed in multiple other pulmonary disorders including acute respiratory distress syndrome, organizing pneumonia, lipoid pneumonia, and others.[10]

Diagnostic Evaluation

In patients with imaging suggestive of PAP, assessment of respiratory impairment with pulmonary function tests is important to determine the pace of evaluation. Secondary causes of PAP should be evaluated by reviewing history of exposures, infections, and assessing for hematologic malignancies or myelodysplastic syndrome.[1] Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies should be performed next, along with laboratory evaluation for antibodies to GM-CSF. In patients with PAP, bronchoalveolar lavage yields a milky effluent, with periodic acid-Schiff stain (PAS)-positive lipoproteinaceous material. Transbronchial biopsy reveals granular, PAS-positive lipoproteinaceous material within alveolar spaces, with preservation of alveolar architecture.[11] Elevated serum anti-GM-CSF antibody is 100 percent sensitive and 91 to 98 percent specific for the diagnosis of autoimmune PAP.[12,13]

A confident diagnosis of autoimmune PAP can be made based on typical CT imaging characteristics, bronchoalveolar lavage features, and positive serological testing for anti-GM-CSF antibodies. Diagnosis of secondary PAP is based on typical CT and BAL findings, and a positive history of inhalational exposure, or hematologic abnormalities, or malignancy, or infections. Hereditary PAP diagnosis is based on typical BAL and CT findings, with abnormal GM-CSF receptor function and gene sequencing.[1] Surgical lung biopsy is needed to establish a diagnosis of PAP in 10 to 20 percent of patients due to nondiagnostic findings on CT and BAL.[8]

Differential Diagnosis

These include disorders with similar imaging findings of crazy paving such as infections such as Pneumocystis Jirovecii or Mycoplasma, pulmonary edema, organizing pneumonia, lipoid pneumonia, drug-related hypersensitivity reactions, acute interstitial pneumonia, and diffuse alveolar damage.[1]

Treatment

Treatment for PAP is based on the etiology, severity of symptoms, and gas exchange derangements.

Treatment of autoimmune PAP

Mild disease: Patients who are asymptomatic, or mildly symptomatic with little or no physiologic impairment may be observed untreated with interval reevaluation of symptoms, oxygen saturation, pulmonary function tests, and chest imaging. Spontaneous remission may occasionally occur.[8,14]

Moderate to severe disease: Whole lung lavage (WLL) under general anesthesia with a double-lumen endotracheal tube is the most accepted and effective form of treatment.[14,15] Repeated whole lung lavage with 20 – 30L of isotonic fluid is done for removal of the lipoproteinaceous material. The initial lavage effluent appears thick and milky, while the final lavage appears clear.[16] Often patients feel dramatically improved after WLL, with improvement in oxygenation despite only small changes in pulmonary function.[17] The clinical course is variable with about 50 percent requiring only one lavage while others require repeated lavages every 6 to 12months.[14,18,19]

If there is progression of disease with whole lung lavage, inhaled recombinant GM-CSF may moderately improve lung function and facilitate clearance of GM-CSF antibody complex from the lung.[20,21] Subcutaneous GM-CSF is also available as monthly injections with a response rate of about 50 percent.[22]

Refractory disease: In patients with refractory disease, therapies including Rituximab and plasma exchange may be tried, though there are limited data on efficacy.

Treatment of other types of PAP

Treatment of secondary PAP due to hematologic defects involves treating the underlying disease. WLL generally has mixed success in this group of patients.[23,24] In patients with secondary PAP due to inhalational exposures, discontinuation of exposure is paramount. WLL in these patients have mixed success.[25,26] In patients with congenital PAP, depending on the deficiency, some can be managed with dietary modification and occasionally WLL.[27]

Prognosis

About 30 percent of patients may achieve remission or stability without treatment. Seventy to 90 percent achieve remission or stability with one or more whole lung lavages.[8,14] Patients who develop pulmonary fibrosis have a poor prognosis.[28]

Case Outcome

This patient underwent whole lung lavage once about 12 months ago. He had dramatic improvement of his symptoms and oxygen saturation and has not required another whole lung lavage. He continues to be followed every six months with symptom check, and oximetry. His yearly CT chest have been stable.

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