interstitial and intra-alveolar accumulation of eosinophils, macrophages, and edema. The syndrome may be idiopathic or caused by parasitic infections (e.g., *Ascaris* species, *Strongyloides* species, hookworms) or drugs (e.g., nitrofurantoin, minocycline, sulfonamides, penicillin, nonsteroidal anti-inflammatory drugs). Treatment requires removal of the offending agent or treatment of the parasitic infection. In idiopathic cases, corticosteroids may be used.

Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction that occurs when *Aspergillus* species colonizes the airways in patients with asthma or cystic fibrosis. Patients may have fever; malaise; a cough productive of thick, brown mucous plugs; and occasionally hemoptysis. On the chest radiograph, pulmonary infiltrates, which are often transient and migratory, and central bronchiectasis may be seen. Peripheral eosinophilia of greater than 10%, elevated immunoglobulin E (IgE) levels (and *Aspergillus*-specific IgE), and precipitating antibodies to *Aspergillus* are among the laboratory abnormalities seen in allergic bronchopulmonary aspergillosis. Response to corticosteroids is good. Itraconazole can be added to the treatment regimen.

Pulmonary Alveolar Proteinosis

Definition and Epidemiology

Pulmonary alveolar proteinosis (PAP) is a rare disorder in which surfactant accumulates within the alveoli. PAP occurs more frequently in middle-aged patients and in smokers.

Pathology

PAP results from impaired surfactant clearance by alveolar macrophages. PAP has a congenital form, characterized most commonly by mutations of the genes encoding surfactant proteins or for the receptor for granulocyte-macrophage colony-stimulating factor (GM-CSF). Secondary PAP occurs in conditions in which there is a functional impairment or decrease in the number of alveolar macrophages, as seen in various hematologic malignancies (e.g., leukemia), infections (e.g., pneumocystis pneumonia), and inhalation of toxic dusts (e.g., silica, aluminum) or after allogeneic bone marrow transplantation. The acquired or idiopathic form of PAP is an autoimmune disease, with neutralizing antibodies directly targeting GM-CSF, resulting in abnormal surfactant metabolism by alveolar macrophages. Lung biopsy in PAP shows intra-alveolar accumulation of eosinophilic, acellular material staining positive with the periodic acid–Schiff (PAS) stain, which is consistent with surfactant.

Clinical Presentation

Patients with PAP may be asymptomatic, or they may have progressive dyspnea on exertion, malaise, low-grade fever, and cough. Examination may reveal clubbing. The chest radiograph typically shows bilateral perihilar opacities. The CT scan may show thickening of the intralobular and interlobular septa, creating a pattern called *crazy paving*, which is a nonspecific finding because it is seen in many other diseases of the lung. The course of PAP may be complicated by opportunistic lung infection.

Diagnosis

BAL fluid can establish the diagnosis because it has a milky, opaque appearance. The fluid contains large, foamy alveolar macrophages and extracellular surfactant material that stains positive with PAS. Surgical or transbronchial lung biopsy may also be performed to establish the diagnosis if the BAL is nondiagnostic.

Treatment

Asymptomatic patients and those with mild symptoms require no immediate treatment. Sequential whole lung lavage with warmed saline (level 3 evidence) is indicated for patients with hypoxemia or severe dyspnea, and in up to 40% of patients, it may be required only one time. Limited lobar lavage may be performed in milder disease (level 3). GM-CSF administration in patients with acquired PAP may be beneficial (level 2). Rituximab has been used in refractory PAP (level 2).

Prognosis

The prognosis of autoimmune PAP is good, with excellent survival since the introduction of whole lung lavage.

PROSPECTUS FOR THE FUTURE

IPF, the most common of the IIPs, is usually fatal, and current treatment strategies are ineffective. The National Institutes of Health have established the Idiopathic Pulmonary Fibrosis Clinical Research Network to accelerate clinical research trials. These trials have demonstrated the ineffectiveness or even hazard of proposed or commonly used therapies, such as the triple-therapy regimen of prednisone, azathioprine, and *N*-acetylcysteine. A deeper understanding of the pathogenesis of IPF is needed to implement more effective therapies.

The advent of technology able to evaluate genetic abnormalities related to disease has unveiled mutations associated with IPF, sarcoidosis, and other ILDs, with the prospect for further insights into disease pathogenesis. The use of mTOR inhibitors in lymphangioleiomyomatosis, which affects women of childbearing age, is an example of the successful translation of the molecular pathobiology of a specific interstitial lung disease into effective therapy.

Further work linking basic science and clinical therapeutics is needed in other ILDs. Until new and effective treatment strategies are generated, lung transplantation represents the only hope for an increasing number of patients with fibrosing ILDs, and efforts to better allocate donors and decrease complications from lung transplantation remain priorities.

SUGGESTED READINGS

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