be life threatening. Spontaneous pneumothorax occurs in 50% of patients; it may be bilateral and necessitate pleurodesis. Meningioma and renal angiomyolipomas (hamartomas), characteristic findings in the genetic disorder tuberous sclerosis, are also common in patients with LAM. Chylothorax, chyloperitoneum (chylous ascites), chyluria, and chylopericardium are other complications. Pulmonary function testing usually reveals an obstructive or mixed obstructive-restrictive pattern, and gas exchange is often abnormal. HRCT shows thin-walled cysts surrounded by normal lung without zonal predominance.

Histologic Findings Pathologically, LAM is characterized by the proliferation of atypical pulmonary interstitial smooth muscle and cyst formation. The immature-appearing smooth-muscle cells react with monoclonal antibody HMB45, which recognizes a 100-kDa glycoprotein (gp100) originally found in human melanoma cells.

Treatment Progression is common, with a median survival of 8–10 years from diagnosis. No therapy is of proven benefit in LAM. Sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), appears to be an active agent for LAM. After 12 months, it stabilized lung function (FVC, FEV_1, and functional residual capacity) and was associated with a reduction in symptoms and improvement in quality of life. Adverse effects (e.g., mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash, peripheral edema) were more common in the sirolimus group, but serious adverse effects were not increased. Subjects were followed off sirolimus for an additional 12 months, during which time pulmonary function declined at the same rate as in the placebo group. Progesterone and luteinizing hormone–releasing hormone analogues have been used. Oophorectomy is no longer recommended, and estrogen-containing drugs should be discontinued. Lung transplantation offers the only hope for cure despite reports of recurrent disease in the transplanted lung.

SYNDROMES OF ILD WITH DIFFUSE ALVEOLAR HEMORRHAGE

Clinical Manifestations The clinical onset is often abrupt, with cough, fever, and dyspnea. Severe respiratory distress requiring ventilatory support may be evident at initial presentation. Although hemoptysis is expected, it can be absent at the time of presentation in one-third of the cases. For patients without hemoptysis, new alveolar opacities, a falling hemoglobin level, and hemorrhagic BAL fluid point to the diagnosis. The chest radiograph is nonspecific and most commonly shows new patchy or diffuse alveolar opacities. Recurrent episodes of DAH may lead to pulmonary fibrosis, resulting in interstitial opacities on the chest radiograph. An elevated white blood cell count and falling hematocrit are common. Evidence for impaired renal function caused by focal segmental necrotizing glomerulonephritis, usually with crescent formation, also may be present. Varying degrees of hypoxemia may occur and are often severe enough to require ventilatory support. D_{LCO} may be increased, resulting from the increased hemoglobin within the alveoli compartment.

Histologic Findings Injury to arterioles, venules, and the alveolar septal (alveolar wall or interstitial) capillaries can result in hemoptysis secondary to disruption of the alveolar-capillary basement membrane. This results in bleeding into the alveolar spaces, which characterizes DAH. Pulmonary capillaritis, characterized by a neutrophilic infiltration of the alveolar septae, may lead to necrosis of these structures, loss of capillary structural integrity, and the pouring of red blood cells into the alveolar space. Fibrinoid necrosis of the interstitium and red blood cells within the interstitial space are sometimes seen. Bland pulmonary hemorrhage (i.e., DAH without inflammation of the alveolar structures) also may occur.

Evaluation of either lung or renal tissue by immunofluorescent techniques indicates an absence of immune complexes (pauci-immune) in granulomatosis with polyangiitis (Wegener), microscopic polyangiitis, pauci-immune glomerulonephritis, and isolated pulmonary capillaritis. A granular pattern is found in the CTDs, particularly SLE, and a characteristic linear deposition is found in Goodpasture syndrome. Granular deposition of IgA-containing immune complexes is present in Henoch-Schönlein purpura.

Treatment The mainstay of therapy for the DAH associated with systemic vasculitis, CTD, Goodpasture syndrome, and isolated pulmonary capillaritis is IV methylprednisolone, 0.5–2 g daily in divided doses for up to 5 days, followed by a gradual tapering, and then maintenance on an oral preparation. Prompt initiation of therapy is important, particularly in the face of renal insufficiency, because early initiation of therapy has the best chance of preserving renal function. The decision to start other immunosuppressive therapy (cyclophosphamide or azathioprine) acutely depends on the severity of illness.

Goodpasture Syndrome • *CLINICAL MANIFESTATIONS* Pulmonary hemorrhage and glomerulonephritis are features in most patients with this disease. Autoantibodies to renal glomerular and lung alveolar basement membranes are present. This syndrome can present and recur as DAH without an associated glomerulonephritis. In such cases, circulating anti-basement membrane antibody is often absent, and the only way to establish the diagnosis is by demonstrating linear immunofluorescence in lung tissue.

HISTOLOGIC FINDINGS The underlying histology may be bland hemorrhage or DAH associated with capillaritis.

TREATMENT Plasmapheresis has been recommended as adjunctive treatment.

INHERITED DISORDERS ASSOCIATED WITH ILD

Pulmonary opacities and respiratory symptoms typical of ILD can develop in related family members and in several inherited diseases. These diseases include the phakomatoses, tuberous sclerosis and neurofibromatosis (Chap. 118), and the lysosomal storage diseases, Niemann-Pick disease and Gaucher disease (Chap. 432e). The Hermansky-Pudlak syndrome is an autosomal recessive disorder in which granulomatous colitis and ILD may occur. It is characterized by oculocutaneous albinism, bleeding diathesis secondary to platelet dysfunction, and the accumulation of a chromolipid, lipofuscin material in cells of the reticuloendothelial system. A fibrotic pattern is found on lung biopsy, but the alveolar macrophages may contain cytoplasmic ceroid-like inclusions.

ILD WITH A GRANULOMATOUS RESPONSE IN LUNG TISSUE OR VASCULAR STRUCTURES

Inhalation of organic dusts, which cause hypersensitivity pneumonitis, or of inorganic dust, such as silica, which elicits a granulomatous inflammatory reaction leading to ILD, produces diseases of known etiology (Table 315-1) that are discussed in Chaps. 310 and 311. Sarcoidosis (Chap. 390) is prominent among granulomatous diseases of unknown cause in which ILD is an important feature.

Granulomatous Vasculitides (See also Chap. 385) The granulomatous vasculitides are characterized by pulmonary angiitis (i.e., inflammation and necrosis of blood vessels) with associated granuloma formation (i.e., infiltrates of lymphocytes, plasma cells, epithelioid cells, or histiocytes, with or without the presence of multinucleated giant cells, sometimes with tissue necrosis). The lungs are almost always involved, although any organ system may be affected. Granulomatosis with polyangiitis (Wegener) and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) primarily affect the lung but are associated with a systemic vasculitis as well. The granulomatous vasculitides generally limited to the lung include necrotizing sarcoid granulomatosis and benign lymphocytic angiitis and granulomatosis. Granulomatous infection and pulmonary angiitis due to irritating embolic material (e.g., talc) are important known causes of pulmonary vasculitis.

LYMPHOCYTIC INFILTRATIVE DISORDERS

This group of disorders features lymphocyte and plasma cell infiltration of the lung parenchyma. The disorders either are benign or can behave as low-grade lymphomas. Included is angioimmunoblastic lymphadenopathy with dysproteinemia, a rare lymphoproliferative disorder characterized by diffuse lymphadenopathy, fever, hepatosplenomegaly, and hemolytic anemia, with ILD in some cases.