bodies (composed of surfactant) within phagocytic vacuoles, presumably derived from necrotic type II pneumocytes. The alveolar septa are thickened by a sparse inflammatory infiltrate of lymphocytes, plasma cells, and occasional eosinophils. The septa are lined by plump, cuboidal pneumocytes. Interstitial fibrosis, when present, is mild. Emphysema is often present.

Desquamative interstitial pneumonia usually presents in the fourth or fifth decade of life, and is now equally common in men and women. Virtually all patients are cigarette smokers. Presenting symptoms include an insidious onset of dyspnea and dry cough over weeks or months, often associated with clubbing of digits. Pulmonary function tests usually show a mild restrictive abnormality with a moderate reduction of the diffusing capacity of carbon dioxide. Patients with desquamative interstitial pneumonia typically have an excellent response to steroid therapy and cessation of smoking but occasional patients may progress to interstitial fibrosis.

### *Respiratory Bronchiolitis-Associated Interstitial Lung Disease*

Respiratory bronchiolitis-associated interstitial lung disease is marked by chronic inflammation and peribronchiolar fibrosis. It is a common histologic lesion in cigarette smokers. It is characterized by the presence of pigmented intraluminal macrophages within first- and second-order respiratory bronchioles. In its mildest form, it is most often an incidental finding in the lungs of smokers or ex-smokers. The term *respiratory bronchiolitis-associated interstitial lung disease* is used for patients who develop significant pulmonary symptoms, abnormal pulmonary function, and imaging abnormalities.

#### MORPHOLOGY

The changes are patchy at low magnification and have a bronchiolocentric distribution. Respiratory bronchioles, alveolar ducts, and peribronchiolar spaces contain aggregates of dusty brown macrophages **(smokers' macrophages)** similar to those seen in desquamative interstitial pneumonia. There is a patchy submucosal and peribronchiolar infiltrate of lymphocytes and histiocytes. Mild peribronchiolar fibrosis is also seen, which expands contiguous alveolar septa. Centrilobular emphysema is common but not severe. Desquamative interstitial pneumonia is often found in different parts of the same lung.

Symptoms are usually mild, consisting of gradual onset of dyspnea and cough in patients who are typically current smokers in the fourth or fifth decade of life with average exposures of over 30 pack-years of cigarette smoking. Cessation of smoking usually results in improvement.

## Pulmonary Langerhans Cell Histiocytosis

Pulmonary Langerhans cell histiocytosis is a rare disease characterized by focal collections of Langerhans cells (often accompanied by eosinophils). As these lesions progress scarring occurs, leading to airway destruction and alveolar damage that result in the appearance of irregular cystic spaces. Imaging of the chest shows characteristic cystic and nodular abnormalities. Langerhans cells are immature dendritic cells with grooved, indented nuclei and abundant cytoplasm. They are positive for S100, CD1a, and CD207 (langerin) and are negative for CD68.

More than 95% of affected patients are relatively young adult smokers who get better after smoking cessation, suggesting that in some cases the lesions are a reactive inflammatory process. However, in other cases the Langerhans cells have acquired activating mutations in the serine/threonine kinase BRAF, a feature consistent with a neoplastic process that is also commonly seen in Langerhans cell proliferations involving other tissues (Chapter 13). A neoplastic basis may explain why the disease progresses in some patients, sometimes even necessitating lung transplantation.

## Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare disease caused by defects related to granulocyte-macrophage colony-stimulating factor (GM-CSF) or pulmonary macrophage dysfunction that results in the accumulation of surfactant in the intra-alveolar and bronchiolar spaces. PAP is characterized radiologically by bilateral patchy asymmetric pulmonary opacifications. There are three distinct classes of disease—autoimmune (formerly called acquired), secondary, and congenital—each with a similar spectrum of histologic changes.

- *Autoimmune PAP* is caused by circulating neutralizing antibodies specific for GM-CSF. It occurs primarily in adults, represents 90% of all cases of PAP, and lacks any familial predisposition. Knockout of the GM-CSF gene in mice induces PAP, and these mice are "cured" by treatment with GM-CSF. Loss of GM-CSF signaling blocks the terminal differentiation of alveolar macrophages impairing their ability to catabolize surfactant.
- *Secondary PAP* is uncommon and is associated with diverse diseases, including hematopoietic disorders, malignancies, immunodeficiency disorders, lysinuric protein intolerance (an inborn error of amino acid metabolism), and acute silicosis and other inhalational syndromes. It is speculated that these diseases somehow impair macrophage maturation or function, again leading to inadequate clearance of surfactant from alveolar spaces.
- *Hereditary PAP* is extremely rare, occurs in neonates and is caused by mutations that disrupt genes involved in GM-CSF signaling (GM-CSF and GM-CSF receptor gene mutations).

#### MORPHOLOGY

The disease is characterized by a peculiar homogeneous, granular precipitate containing surfactant proteins within the alveoli, causing focal-to-confluent consolidation of large areas of the lungs with minimal inflammatory reaction (Fig. 15-25). As a consequence there is a marked increase in the size and weight of the lung. The alveolar precipitate is periodic acid-Schiff positive, and contains cholesterol clefts and surfactant proteins (which can be demonstrated by immunohistochemical stains). Ultrastructurally, the surfactant lamellae in type II pneumocytes are normal.