Pulmonary Langerhans Cell Histiocytosis and Other Pulmonary Histiocytic Diseases
A Review

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Objective.—To review pulmonary Langerhans cell histiocytosis and other pulmonary histiocytoses to better ensure correct diagnosis and optimal assessment of prognosis and treatment.

Putnam Langerhans cell histiocytosis (PLCH) is the most common and best known pulmonary histiocytic lesion; however, the realm of pulmonary histiocytic lesions also includes an assortment of uncommon diseases that may exhibit pulmonary involvement. This review discusses the most common pulmonary histiocytosis, PLCH, and also reviews the uncommon pulmonary histiocytic lesions that are distinct from PLCH.

The pulmonary histiocytoses are diseases characterized by the accumulation of histiocytes within the airspaces or parenchyma of the lung. This diverse group of disorders includes dendritic cell disorders, macrophage diseases, and storage diseases. The Histocyte Society classifies histiocytic diseases as dendritic cell–related disorders such as Langerhans cell histiocytosis, xanthogranulomatous disorders such as Erdheim-Chester disease, macrophage–related disorders such as Rosai-Dorfman disease, and malignant disorders such as dendritic cell–related histiocytic sarcoma. Langerhans cell histiocytosis is a term for a variety of diseases characterized by the proliferation and infiltration of Langerhans cells into various organs. Several terms have been used in the past to denote multisystem lesions predominantly arising in children, including Letterer-Siwe disease, Hand-Schüller-Christian syndrome, histiocytosis X, and Hashimoto Pritzker syndrome. Multisystem Langerhans cell histiocytosis may exhibit lung involvement. Eosinophilic granuloma and histiocytosis X are terms that have frequently been used in the past to designate localized pulmonary lesions. The characteristic feature of all lesions designated Langerhans cell histiocytosis, from any site, is the infiltration Langerhans cells—CD1a-positive histiocytes of dendritic lineage derived from CD34-positive bone marrow stem cells. Langerhans cells play a role in the induction of primary antigen-specific immune reactions, play a key role in immunity, and are found in many tissues. These pulmonary dendritic cells are leukocytes that have been found to play a key role in immune response in the lung. Pulmonary Langerhans cell histiocytosis, in contrast to the systemic Langerhans cell histiocytoses typically found in childhood that are clonal neoplastic diseases, consists of nonneoplastic collections of reactive Langerhans cells.

Pulmonary Langerhans cell histiocytosis is an interstitial lung disease occurring predominantly in adult cigarette smokers. Smokers have been shown to have an increased total number of T lymphocytes and a decreased helper-induced–suppressor-cytotoxic T lymphocyte (T4/T8) ratio compared with nonsmokers, potentially reducing helper-inducer lymphocytes that facilitate B-lymphocyte proliferation. Alveolar macrophages in smokers may be activated by materials in tobacco smoke causing them to release chemotactic factors with a resultant increase in peripheral blood monocytes within the lung. Pulmonary neuroendocrine cell stimulation by cigarette smoke may cause neuroendocrine cell hyperplasia in some smokers, with resultant increased recruitment of monocyte differentiation into Langerhans cells and associated fibroblast stimulation by bombesin-like peptides. Macrophage colony-stimulating factor and platelet-derived growth factor may also play a role in initiating and maintaining PLCH pathology. Langerhans cells in PLCH are phenotypically similar to mature lymphostimulatory dendritic cells within lymphoid organs, and the pathogenesis of PLCH may be related to an abnormal immune response by these Langerhans cells.

Data Sources.—Literature review and primary material from the author’s institution.

Conclusions.—This review discusses the most common pulmonary histiocytosis, pulmonary Langerhans cell histiocytosis, and also reviews the uncommon pulmonary histiocytic lesions, which are distinct from pulmonary Langerhans cell histiocytosis.

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Clinically, PLCH is uncommon, comprising approximately 5% of all interstitial lung disease cases, generally occurring in middle-aged men and women. Presenting symptoms are variable and include dyspnea, nonproductive cough, malaise, fever, weight loss, and night sweats. Patients may present with hemoptysis. Patients may be asymptomatic and be identified radiographically. Pulmonary fibrosis, sometimes recurrent, occurs in one fourth of patients during their disease course. Physical examination may also show variable features, including pulmonary ronchi, rales, and wheezes, as well as decreased breath sounds. With increasing severity of disease, patients typically exhibit decreased diffusing capacity. Radiographically, most patients have x-ray abnormalities of varying degrees. Reticular changes, micronodules measuring 2 to 5 mm, and cysts measuring up to 1 cm have been commonly observed in PLCH patients.

Pulmonary Langerhans cell histiocytosis is typically diagnosed from open lung biopsy, and gross appearance varies according to disease progression. Wedge biopsies of early lesions show multiple well-demarcated grey-white to tan-white irregular, stellate nodules ranging from less than 1 cm to about 2 cm. With evolution of PLCH, lesions show increasing amounts of stellate fibrosis and cyst formation. Pathologically, early PLCH lesions consist of discrete bronchiole-centric stellate nodules (Figures 1 and 2). Early lesions are more cellular and less fibrotic than more mature lesions and consist of a variable mix of Langerhans cells, lymphocytes, eosinophils, and plasma cells with a background of generally mild fibrosis (Figures 3 through 5). Fibrosis replaces the cellular nodules as disease progresses, and less cellular stellate nodules are formed (Figure 6). Few Langerhans cell histiocytes and variable numbers of eosinophils may be found in these more fibrotic nodules. Surrounding lung may contain smoker’s pigment-laden alveolar macrophages arranged in a desquamative interstitial pneumonia–like pattern (Figure 7). Surrounding lung may retract with resultant airspace enlargement (Figure 8). Coalescence of nodules and the formation of large cysts are later occurrences, with some cases progressing to end-stage lung changes with honeycombing (Figure 9). Pulmonary Langerhans cell histiocytosis patients frequently have changes of early to late stage disease, both of which may be identifiable in a wedge biopsy. Langerhans cells usually are immunopositive with CD1a, Langerin, E-cadherin, and S100. Birbeck granules, also termed Langerhans cell granules, pentalaminar rod-shaped cytoplasmic organelles with a racket- or rod-shaped appearance, are found ultrastructurally.

The primary therapy for PLCH is smoking cessation. Anecdotal reports have shown patient improvement from corticosteroid therapy, and patients with progressive disease have been treated with chemotherapy such as cyclophosphamide and methotrexate; however, no randomized study has been performed to assess the benefit of these therapies. Pulmonary Langerhans cell histiocytosis patients have variable prognoses. About one fourth of patients will regress spontaneously whether or not they stop smoking, about half of patients will stabilize but not regress spontaneously, and about one fourth of patients will exhibit progressive disease that may ultimately cause honeycombing. The differential diagnosis of PLCH varies depending on whether early PLCH lesions or late lesions, or both, are present in the biopsy. Early, cellular PLCH nodules containing many eosinophils are suggestive of eosinophilic pneumonia; however, in contrast to PLCH, eosinophilic pneumonia generally is composed of collections of eosinophils and macrophages lying within alveolar spaces, as well as an interstitial infiltrate of variable degree made up of lymphocytes, macrophages, and eosinophils. Desquamative interstitial pneumonia should be considered in the differential diagnosis when the biopsy predominantly contains smoker’s pigment-laden macrophages lying within alveolar spaces. It is important to consider that respiratory bronchiolitis-associated interstitial lung disease/desquamative interstitial pneumonia is another smoking-related disease and may occasionally coexist with PLCH. In later stage PLCH, with its more fibrotic and scarred lesions, ultimately causing honeycombing, usual interstitial pneumonia becomes a differential diagnosis. Usual interstitial pneumonia is predominantly a subpleural disease usually involving the lower zones of the lungs. Pulmonary Erdheim-Chester disease is a differential diagnosis that is discussed later.

**ROSAI-DORFMAN DISEASE**

Sinus histiocytosis with massive lymphadenopathy, also termed Rosai-Dorfman disease, is a rare nonmalignant proliferation of histiocytic/phagocytic cells of unknown etiology occurring within lymph node sinuses, lymphatics, and various extranodal sites. It typically occurs in children and young adults. No clinical response with antibacterial or antitubercular therapies have been documented, and viral infection and disordered immune regulation have been hypothesized as possible etiologies. An exuberant hematopoietic system response to an unknown immunologic trigger has been considered a possible cause. The association of Rosai-Dorfman disease with autoimmune lymphoproliferative syndrome, an inherited disorder of lymphocyte programmed cell death primarily occurring in early childhood, and the identification of mutations of the *Fas* gene in a small subset of Rosai-Dorfman disease patients suggests that Rosai-Dorfman disease is a member of a spectrum of disorders that includes autoimmune lymphoproliferative syndrome.

**Figure 1.** Typical stellate nodules of pulmonary Langerhans cell histiocytosis within lung parenchyma (hematoxylin-eosin, original magnification ×2).

**Figure 2.** Cellular early stellate nodule of pulmonary Langerhans cell histiocytosis adjacent to bronchiole (hematoxylin-eosin, original magnification ×4).

**Figure 3.** A mixture of inflammatory cells, including Langerhans cells, within an early nodule, with associated early fibrosis (hematoxylin-eosin, original magnification ×10).
Figure 4. High-power image of Langerhans cells, scattered lymphocytes, and pigmented macrophages, without abundant eosinophils (hematoxylin-eosin, original magnification ×40).

Figure 5. High-power image showing an admixture of Langerhans cells and eosinophils (hematoxylin-eosin, original magnification ×40).

Figure 6. Low-power image showing a predominantly fibrotic stellate nodule of pulmonary Langerhans cell histiocytosis (hematoxylin-eosin, original magnification ×2).
Figure 7. Desquamative interstitial pneumonia–like pattern of interstitial fibrosis and pigmented alveolar macrophages adjacent to a stellate nodule of pulmonary Langerhans cell histiocytosis (hematoxylin-eosin, original magnification ×10).

Figure 8. Retraction of lung parenchyma surrounding a stellate nodule of pulmonary Langerhans cell histiocytosis produces adjacent airway enlargement (hematoxylin-eosin, original magnification ×4).

Figure 9. Coalescence of adjacent stellate nodules of pulmonary Langerhans cell histiocytosis leads to end-stage lung changes (hematoxylin-eosin, original magnification ×2).
man disease may represent an acquired disorder of apoptotic signaling pathway regulation.36,39–42

Rosai-Dorfman disease most frequently presents as painless massive, often cervical, lymphadenopathy.36,43

Nodal disease is frequently self-limited.43 Extramedullary involvement of various sites including bone, retro-orbital tissue, skin, lung, and kidneys occurs in approximately 20% to 40% of patients.38,44 Skin and soft tissue, nasal and paranasal sinuses, the eye and ocular adnexa, and bone are the most common extranodal sites of involvement.36 Pulmonary involvement is rare and occurs in approximately 2% to 3% of cases with extranodal disease.36,45,46 It usually presents as solitary or multiple mass lesions in the lung, bronchi, or trachea, typically with coexisting nodal and extranodal disease.45–49 The tracheobronchial tree is most commonly involved with pulmonary Rosai-Dorfman disease, presenting as large single or multiple airway masses; however, diffuse interstitial lung involvement may rarely occur, and primarily pleural disease has been reported.45 Radiographically, mediastinal fullness or nodal enlargement or hilar or perihilar masses may be present.46–49 Diffuse lung involvement may present radiographically as bilateral reticulonodular infiltrates.

Histologically, pulmonary Rosai-Dorfman disease exhibits an infiltrate of faintly staining histiocytes with oval nuclei that may contain mild atypia, one or more nucleoli, and abundant pale eosinophilic cytoplasm.36 The histiocytes lie in an inflammatory background of scattered plasma cells and lymphocytes. Lymphocytes within histiocyte cytoplasm, termed lymphophagocytosis or emperipolesis, is a distinctive feature of Rosai-Dorfman disease.46,49 (Figures 12 and 13). Usually located within cytoplasmic vacuoles, these lymphocytes avoid degradation as they transit through the histiocyte.46 Surrounding lung parenchyma generally contains a mixture of inflammatory cells, fibrosis, foamy alveolar macrophages, and a proliferation of type II pneumocytes. Immunopositivity with S100 is the most useful immunomarker for Rosai-Dorfman disease.46,49 Histiocytes in Rosai-Dorfman disease also typically show immunopositivity with CD68, CD14, CD15, CD163, and α1-antichymotrypsin and immunonegativity with CD1a and factor XIIIa.36,37

Most cases of Rosai-Dorfman disease limited to nodal disease exhibit spontaneous resolution.36 Pulmonary disease, renal disease, and hepatic disease with associated immunogenic dysfunction frequently show persistent lymphadenopathy or disease dissemination.36 Treatment for Rosai-Dorfman disease varies with disease severity. Uncomplicated cases may be observed; however, disease that is widely disseminated, which manifests organ compression, may require surgical debulking, radiation therapy, or both.36 Chemotherapy has not shown obvious benefit and is not a primary treatment.36 Prognosis varies, but for patients with pulmonary Rosai-Dorfman disease, prognosis is guarded.45 Patient mortality of 45% has been reported, with 33% of patients exhibiting persistent or progressive disease.35,46 The differential diagnosis of pulmonary involvement with Rosai-Dorfman disease includes PLCH, Erdheim-Chester disease, carcinoma, Hodgkin lymphoma, Gaucher disease, and mycobacterial and fungal infections, among others.6 The eosinophils often present in lesions of PLCH are not a usual feature of pulmonary Rosai-Dorfman disease.36 The characteristic bilateral and symmetric osteosclerosis of long bones present with Erdheim-Chester disease is helpful in differentiating it from Rosai-Dorfman disease, as is its lack of emperipolesis. Indeed, emperipolesis is rarely a feature seen outside of the setting of Rosai-Dorfman disease.36

**ERDHEIM-CHESTER DISEASE**

Erdheim-Chester disease, identified by William Chester in 1930, is a rare, systemic, nonfamilial non-Langerhans cell histiocytosis of unclear, but possibly clonal, etiology that occurs predominantly in middle-aged and older adults.33–35,50–53 Bone pain is the typical presenting complaint, and the disease is characterized clinically and radiographically by symmetric osteosclerosis that involves the metaphyses and diaphyses of long bones.33,35,52 Almost pathognomonic, symmetrical sclerotic or mixed sclerotic and lytic lesions involving the metaphyseal and diaphyseal regions of long bones can be seen on skeletal radiographs.35 Approximately half of Erdheim-Chester disease patients exhibit extraskeletal disease, including lung, heart, skin, kidney, retroperitoneum, retro-orbital and periorbital tissues, breast, pituitary-hypothalamic axis, sinonasal mucosa, and skeletal muscle.35,53 Twenty percent to 35% of patients exhibit pulmonary involvement.32,33,35,50,54

Patients having lung involvement typically present with cough and progressive dyspnea, and decreased diffusing capacity is frequently a feature.35,52,55 A pleural effusion may be present.35,52 Chest x-ray often exhibits diffuse interstitial infiltrates with pleural and interlobular septal thickening and may show a relatively nonspecific pattern of interstitial opacities, generally in the upper lung zones.35 Pleural thickening may occur, occasionally being the prevalent radiographic change.35 Interlobular and visceral pleural thickening with patchy reticular and centrilobular opacities, areas of ground glass attenuation, and pleural effusion are frequent findings on chest computed tomography scan.33 Combined with the typical clinical and radiographic skeletal findings, the radiographic findings of smooth interlobular septal thickening and centrilobular nodular opacities, fissural thickening, and pleural effusions are highly suggestive of Erdheim-Chester disease.36

Transbronchial biopsies of Erdheim-Chester disease are unhelpful in showing the distribution of this interstitial lung disease, but wedge biopsy specimens are able to exhibit diagnostic features.51 Histologically, lung involvement with Erdheim-Chester disease generally shows a his-

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**Figure 10.** Abundant immunopositivity within Langerhans cells with CD1a in a cellular stellate nodule of pulmonary Langerhans cell histiocytosis (original magnification ×10).

**Figure 11.** Less obvious CD1a immunopositivity within Langerhans cells in a more advanced, fibrotic stellate nodule (original magnification ×40).

**Figure 12.** Medium-power image showing a mixture of lymphocytes, plasma cells, and histiocytes in the lung in Rosai-Dorfman disease (hematoxylin-eosin, original magnification ×10).
Figure 13. High-power image showing emperipolesis in the lung in Rosai-Dorfman disease (hematoxylin-eosin, original magnification ×40).

Figure 14. Low-power image of lung in Erdheim-Chester disease showing lymphangitic pattern of disease (hematoxylin-eosin, original magnification ×1).

Figure 15. Subpleural fibrosis in the lung in Erdheim-Chester disease (hematoxylin-eosin, original magnification ×2).

Figure 16. Pulmonary nodules in Erdheim-Chester disease may mimic early lesions of pulmonary Langerhans cell histiocytosis (hematoxylin-eosin, original magnification ×20).
tiocytic and lymphocytic infiltrate arranged in a lymphangitic pattern, as well as diffuse interstitial thickening and variable fibrosis, and the accumulation of foamy to clear histiocytes within alveolar spaces. Approximately two thirds of patients with lung involvement have a bronchovascular, subpleural, and/or interlobar septal distribution of the lymphangitic infiltrate. Pleural and subpleural fibrosis may be identified extending into underlying lung parenchyma along the interlobular septa. The histiocytes within the inflammatory infiltrate in Erdheim-Chester disease have abundant pale staining cytoplasm; however, they do not exhibit nuclear folding or eosinophilic cytoplasm that characterize the Langerhans histiocytes of PLCH (Figures 16 and 17). The histiocytes in Erdheim-Chester disease characteristically exhibit CD68 and factor XIIIa immunopositivity and CD1a immunonegativity (Figure 18). Immunostain with S100 is variably positive, possibly because of the presence of S100-positive reactive histiocytes within the fibrohistiocytic areas. Birbeck granules are not present ultrastructurally within Erdheim-Chester disease histiocytes, in contrast to PLCH Langerhans histiocytes.

Differential diagnosis of Erdheim-Chester disease in the lung includes other interstitial lung diseases such as usual interstitial pneumonia and other differential diagnoses. The characteristic lymphangitic distribution of Erdheim-Chester disease, as well as CD1a immunonegativity and absence of Birbeck granules in histiocytes, are helpful in distinguishing it from PLCH, usual interstitial pneumonia, and other differential diagnoses.

**GAUCHER DISEASE**

Gaucher disease, the most prevalent lysosomal storage disorder, is an autosomal recessive lipid storage disease caused by glucocerebrosidase deficiency. The adult form of the disease, type I, typically involves bone, spleen, and liver, and pulmonary involvement is uncommon and generally exhibited only in association with disease in the more common organs. Type I disease is especially prevalent in the Ashkenazi Jew population and is much more common than type II and type III disease, differing from those types by sparing of the central nervous system. Type II disease, also termed acute neuropathic type, is generally found in children by age 6 months, and type III disease is a juvenile form of disease also termed the subacute neuropathic form. A glucocerebrosidase gene mutation with resultant diminished enzymatic activity causes increased accumulation of glucocerebroside in lysosomes of phagocytic Gaucher cells. Hepatosplenomegaly, bone pain and pathologic fractures, anemia, and easy bruising are frequently identified symptoms. Patients with severe disease, especially in disease with neuropathic changes, are more likely to exhibit pulmonary disease.

Histologically, lung involvement with Gaucher disease may be multifaceted. Gaucher cells may fill alveolar spaces, as well as septa, with resultant interstitial lung disease. Pulmonary hypertension may occur, with or without the involvement and subsequent occlusion of alveolar septal capillaries or other vessels with Gaucher cells. Gaucher cells exhibit a "wrinkled paper" appearance, highlighted with periodic acid–Schiff stain (Figure 19). In contrast to alveolar macrophages, Gaucher cells usually exhibit relatively light CD68 immunopositivity. Enzyme replacement therapy has been found to be safe and effective in reducing hepatosplenomegaly and improving hematologic parameters; however, pulmonary manifestations of Gaucher disease have not shown a similar response to such therapy. Bilateral lung transplant has been reported. Research positing that glucocerebrosidase secretion is related to its delivery to lysosomes by interaction with transmembrane protein LIMP-2 suggests the potential for improved future therapy for Gaucher disease patients.

**FABRY DISEASE**

Fabry disease is an X-linked metabolic disease caused by α-galactosidase A deficiency, with resultant accumulation of glycosphingolipids, predominantly globotriaosylceramide, throughout the body, including the lungs. Patients with Fabry disease can exhibit a variety of pulmonary signs and symptoms including dyspnea, wheezing, pneumothorax, airway obstruction, and hemoptysis. Airway obstruction is more common in older patients, many of whom are smokers. Frameshift mutations as well as the missense mutation D24V are also associated with airway obstruction. Chest x-ray is frequently normal; however, airflow limitation may be demonstrated by pulmonary function studies. Chest computed tomography may show ground glass opacities, possibly representing alveolar filling by glycosphingolipid. Histologically, diagnostic laminated inclusions can be found in capillary endothelium; type II pneumocytes, ciliated bronchial mu-

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**Figure 17.** High-power image of Erdheim-Chester disease showing histiocytes with abundant, pale cytoplasm (hematoxylin-eosin, original magnification ×40).

**Figure 18.** CD68 immunopositivity within Erdheim-Chester disease histiocytes (original magnification ×20).
Figure 19.  High-power image of lung with Gaucher cells (hematoxylin-eosin, original magnification ×40).

Figure 20.  Medium-power image of lung in Niemann-Pick disease showing interstitial fibrosis and inflammation and Niemann-Pick histiocytes in airspaces and septa (hematoxylin-eosin, original magnification ×10).

Figure 21.  High-power image of Niemann-Pick histiocytes within airspaces, showing abundant finely vacuolated cytoplasm (hematoxylin-eosin, original magnification ×40).

Figure 22.  Lung in Hermansky-Pudlak syndrome showing septal thickening and fibrosis and ceroid-filled histiocytes within septa and airspaces (hematoxylin-eosin, original magnification ×2).
cosal cells, and goblet cells are generally found in bronchial biopsy specimens, brushings, or lavage fluid. Diagnosis via sputum cytology has been reported. Enzyme replacement therapy using enzymatically active human α-galactosidase A became available in 2003 and has been shown to alleviate pulmonary dysfunction in some patients.

NIEMANN-PICK DISEASE

Niemann-Pick disease is a term used to describe rare, inherited autosomal recessive disorders characterized by an absence or deficiency of the enzyme acid sphingomyelinase and resulting in increased sphingomyelin deposition within reticuloendothelial cells. Types A and B Niemann-Pick disease are lysosomal storage disorders showing symptoms caused by the accumulations of lipid laden macrophages, called Niemann-Pick cells, in a variety of organs, specifically spleen and liver. Type C disease is a complex lipid storage disorder caused by cholesterol trafficking defects because of mutations in the NPC1 and NPC2 genes. Type A disease usually causes death by about age 3 years; however, patients with type B disease show phenotypic variability and some residual enzymatic activity, with patients frequently living into adulthood. Lung involvement is relatively frequent in infantile forms of Niemann-Pick disease but is an uncommon finding in adult forms.

Lung disease may be present in patients with type A disease; however, the lungs are typically spared in patients with type C disease, especially in adults. Lung involvement in patients with type C Niemann-Pick disease has been reported. Lung involvement is a common finding in patients with type B disease. Adult patients with type B disease frequently exhibit hepatosplenomegaly, but lung involvement may be asymptomatic and detected only on chest x-ray. Mild, recurrent cough or dyspnea on exertion may be present. Chest x-ray and computed tomography scan often show nonspecific bilateral interstitial reticulonodular changes, sometimes with diffuse honeycomb lung bases, establishing the presence of interstitial lung disease. Radiologic studies do not assist in determining the severity of disease or predicting clinical outcome.

Grossly, the lung in Niemann-Pick disease is often heavy and pale. Histologically, the lungs frequently show endogenous lipid pneumonia consisting of alveolar filling by Niemann-Pick cells. Areas of interstitial foamy macrophages, variable interstitial fibrosis, and often foamy change within ciliated mucosal epithelium are found. Pleura and lymphatics may also be involved. Niemann-Pick histiocytes are generally enlarged with abundant finely vacuolated cytoplasm and eccentric nuclei (Figures 20 and 21). The cells are usually immunopositive with CD68. Strong blue staining of Niemann-Pick cells with May-Grunwald Giemsa stain, called "sea blue histiocytes," is a nonspecific feature. Concentric lamellar myelin-like lysosomal inclusions are an ultrastructural feature of the disease. Treatment by whole lung lavage has been described, and bone marrow transplantation has been attempted in some patients. Differential diagnosis includes other causes of endogenous lipid pneumonia, including peritumoral disease, and drug therapy, specifically amiodarone therapy with associated toxicity. Progression of lung disease is generally slow and unremitting, but cases of rapidly fatal lung disease have been reported.

HERMANSKY-PUDLAK SYNDROME

Hermansky-Pudlak syndrome, also termed oculocutaneous albinism syndrome, is a rare heterogeneous inherited autosomal recessive disease characterized by the systemic accumulation of ceroid-filled histiocytes, considered to be a consequence of disturbed formation or trafficking of intracellular vesicles, specifically melanosomes, platelet dense granules, and lysosomes. Patients frequently have oculocutaneous albinism, with associated decreased visual acuity, congenital nystagmus, and iris transillumination; variable skin and hair hypopigmentation; and bruising. Patients may have prolonged bleeding time caused by platelet aggregation defects. Ceroid deposition involves many organs and causes increased morbidity in the lungs, often leading to death in patients’ fourth or fifth decades of life because of pulmonary fibrosis. Pulmonary macrophages are abnormal, and type II pneumocytes are disrupted. The gene mutation causing Hermansky-Pudlak syndrome is one of the most prevalent single-gene disorders in northwest Puerto Rico. Clinical and radiologic features of interstitial lung disease may occur, usually causing disease by the patients’ fourth or fifth decade of life and death by the fifth decade. Approximately 50% of patient deaths are because of pulmonary fibrosis. The pathogenesis of pulmonary fibrosis is uncertain; however, intracellular disruption of type II pneumocytes by ceroid, causing a cascade of inflammation, cytokine reduction, and fibroblast proliferation, may ultimately cause the development of pulmonary fibrosis. A usual interstitial pneumonia–like pattern or a nonspecific interstitial pneumonia–like pattern of fibrosis is seen in the lung histologically. Ceroid-filled histiocytes are usually located within air spaces and interstitial septa (Figures 22 and 23). Prevention or minimization of bleeding is an important therapeutic goal, as is the prevention or minimization of lung fibrosis. Therapies such as corticosteroids, cyclophosphamide, cyclosporine, and azathioprine often cause deleterious side effects such as myelosuppression, oncogenesis, and lung toxicity, without inhibiting disease progression. Pirfenidone, with anti-inflammatory, antioxidant, and antifibrotic properties, has been investigated with a randomized placebo-controlled trial and has shown an approximately 8% slower decline in pulmonary function in patients compared with a control group. Bilateral lung transplantation has been reported, with the patient stable at 12 months posttransplant.
DIABETIC XANTHROGRANULOMA

Reinilä, in a study of 339 autopsy lung samples, found perivascular collections of foamy histiocytes in 20 (5.9%) lung samples from diabetic patients versus 3 (1.9%) samples of control patients. The perivascular collections measured an average of 176 μm, and periodic acid–Schiff and iron stains were negative. The author hypothesized that some dysfunction in lipid transport through the vessel wall might be causative.

CHOLESTERYL ESTER STORAGE DISEASE

Cholestereryl ester storage disease is an autosomal recessive storage disease that typically results in chronic liver disease. It is caused by partial lysosomal acid lipase/cholestereryl ester hydrolase deficiency because of mutation of the gene encoding for lysosomal acid lipase, located on chromosome 10q23.2-q23.3. Wolman disease, in which there is complete enzyme deficiency, is typically fatal within the first 6 months of life. Most patients are carriers of exon 8 splice junction mutation, leading to an in-frame deletion of exon 8 with the resultant protein having no residual lysosomal acid lipase activity. Disease usually begins in childhood or adolescence, and both males and females are equally affected. Survival to age 30 years is rare. Deposition of cholestereryl ester usually occurs within the spleen, liver, bone marrow, and intestine. Lung involvement is rare. Intracytoplasmic accumulation of cholesterol esters within alveolar macrophages, fibroblasts, and interstitial cells occurs histologically, and pulmonary arteries may contain focal concentric intimal deposits of foam cells and extracellular lipid.

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