In children, endobronchial, transbronchial, and imaging-guided needle biopsies are less commonly performed than in adults; the majority being surgical wedge biopsies. The approach to the lung biopsy depends on the immunocompetence of the patient. For immunosuppressed patients, infection is high on the differential diagnosis for both diffuse and focal disease, but entities to consider, depending on clinical history, include drug or radiation reaction, aspiration, lung transplant rejection, graft-versus-host disease, and posttransplant lymphoproliferative disease (PTLD). A specific diagnosis can be found in 50% of cases, with fungal infections being the most common.1 Lung biopsy for diffuse disease in immunocompetent children is rare and is done most frequently in infants or very young children. Although some interstitial lung diseases that occur in adults can be seen in children (particularly older adolescents), we emphasize those specific to or more common to pediatrics. Mass lesions include tumors (predominantly metastatic, primary tumors being extremely rare) and congenital lesions (such as pulmonary adenomatoid malformations and sequestrations). These are typically removed by wedge resection or lobectomy and are rarely biopsied.

INFECTIONS

Patterns of inflammatory response to common organisms are well described and considered in the following sections, but immunosuppressed patients may lack a robust inflammatory response or present with atypical histologic patterns or have multiple organisms, and special stains should be performed to rule out infection in most cases, especially those with granulomas.

Fungal Infections

Although many molds and yeast are visible with hematoxylin and eosin (H&E) (viable hyphae are basophilic, whereas degenerating forms are eosinophilic), special stains such as Gomori methenamine-silver (GMS) or periodic acid–Schiff (PAS) are almost always essential for diagnosis. GMS is preferred because it stains both viable and nonviable fungus; Pneumocystis; and many bacteria including Actinomyces, Nocardia, and mycobacteria, as well as amoeba and parasites.
Molds

Diagnosis of specific molds is only possible when fruiting heads are present, which is rare; however, a distinction between septate and aseptate molds is generally possible (eTable 9.1). Degenerative changes in septate molds, especially in fungal balls, may lead to hyphal swelling and confusion with aseptate species. Polymerase chain reaction (PCR) can be performed on paraffin-embedded tissue for speciation. In immuno suppressed patients, *Aspergillus* is the most common opportunistic organism. In neutropenic patients, invasive pulmonary aspergillosis is characterized by an angioinvasive pattern with accompanying hemorrhagic infarction. There is typically a minimal or absent inflammatory reaction. A similar angioinvasive pattern is seen with other septate molds as well as zygomycosis. Less profoundly, immunosuppressed patients may have inflammation and necrosis with or without granulomas involving either the airways or lung parenchyma termed chronic necrotizing pulmonary or chronic necrotizing bronchial aspergillosis. The invasion and tissue destruction is more limited and lacks vascular invasion. Simple colonization seen in immunocompetent patients does not require treatment. The differential diagnosis for *Aspergillus* includes other rarer septate molds such as *Fusarium* and *Pseudallescheria*. These have less regular branching patterns but are difficult to distinguish. Dematiaceous (brown pigment on H&E) molds are another rare cause of pulmonary infection with septate hyphae. Pulmonary *zygomycosis* occurs exclusively in immunosuppressed patients, particularly those with hematopoietic neoplasms. Examples of the genera include *Rhizopus*, *Absidia*, *Mucor*, and *Rhizomucor* and cannot be distinguished histologically.

Yeasts

Differentiating features of yeasts in tissue include size (including size variability), shape of budding, formation of pseudohyphae, and pattern of inflammatory response (eTable 9.2). If only a few organisms are present, diagnostic features may be absent. The differential diagnosis for small yeasts (several μm) includes *Histoplasma*, *Pneumocystis*, *Cryptococcus*, and endosporas of *Coccidioides* and for larger organisms (10 μm or more) includes immature *Coccidioides* spherules without endospores, blastomycosis (Fig. 9.1), and larger forms of *Cryptococcus*. When interpreting special stains, care must be taken to avoid artifacts (Fig. 9.2).

Malnourished infants with *Pneumocystis* may present as interstitial plasma cell pneumonia, but this is rare in developed countries. The classic histology in immuno suppressed patients is a foamy intraalveolar exudate with numerous organisms in which small dots (nuclei) can be seen on H&E (Fig. 9.3). This is often accompanied by interstitial lymphocytes, plasma cells, and type 2 pneumocyte hyperplasia. Necrotizing, granulomatous, fibrosing, and calcifying forms of disease may occur. Two main forms can be identified in tissue: the cyst form containing daughter sporozoites and the trophozoites. Only the cyst walls are positive with GMS (Fig. 9.4).
FIGURE 9.1  Blastomycosis elicits a mixed granulomatous and neutrophilic inflammation with budding yeasts within macrophages and multinucleated giant cells (PAS stain).

FIGURE 9.2  Artifacts can resemble fungus as seen here on GMS stain. The positive round structures are staining uniformly black as opposed to yeasts where only the wall should stain. These are likely to be pollen.
Both the trophozoites (the majority of the organisms) and intracystic sporozoites are negative on GMS, but their nuclear material can be seen in touch preparations stained with Romanowsky stains. On H&E, the differential diagnosis includes pulmonary edema and pulmonary alveolar proteinosis (PAP). Pulmonary edema is less eosinophilic with a smooth

![Image](image1.png)

**FIGURE 9.3** *Pneumocystis jiroveci* pneumonia is seen here with the typical finding of intraalveolar frothy pink material within which small dots are identified on H&E.

![Image](image2.png)

**FIGURE 9.4** *Pneumocystis* organisms are stained black in this patient with a granulomatous response to the infection. The organisms are seen clustered together in the middle of the granuloma (GMS stain).
texture. Secondary PAP is due to defective macrophage clearance of surfactant, resulting in the accumulation of “grungy” material in the alveolar space. Both PAP and *Pneumocystis* are PAS positive; however, only *Pneumocystis* is positive on GMS. If in doubt on frozen section, a Romanowsky stain (such as Giemsa) could be performed on a touch preparation.

**Viral Infections**

Viral infections are seen in the immunocompromised biopsy. The most common patterns are bronchiolitis, diffuse alveolar damage, or interstitial pneumonitis. Aspiration of oral secretions may lead to herpes-related tracheobronchial ulcers. Definitive viral identification is possible by morphology alone or with immunohistochemistry (IHC) for adenovirus, cytomegalovirus (CMV), and herpesvirus (eTable 9.3). The differential diagnosis for multinucleated cells in a viral infection includes measles, parainfluenza virus, and herpes/varicella-zoster virus. Other techniques include culture, electron microscopy, and molecular methods.

**Mycobacterial Infections**

The host response to tuberculosis classically results in granulomas with caseous necrosis. Rare, acid-fast, short, slender rods can be found in the center of the necrotic debris, but tissue processing may alter the cell wall components resulting in low sensitivity of the acid-fast stain. In the most profoundly immunodeficient patients, a granulomatous reaction may be entirely absent, and instead, large numbers of organisms may be present in the midst of necrotic debris with a mixed inflammatory infiltrate, including prominent neutrophils. If stains are negative and the suspicion is high, stains should be repeated on multiple sections, or molecular testing should be considered.

*Nocardia* is a gram-positive, weakly acid-fast bacterium characterized by thin-branching filaments best seen with GMS. It is associated with necrosis and inflammation with abscess formation and poorly formed granulomas.

**NONINFECTIOUS CAUSES OF DIFFUSE LUNG DISEASE IN IMMUNOSUPPRESSED PATIENTS**

Diffuse lung disease in immunosuppressed patients may have nonspecific patterns of reaction including bronchiolitis obliterans, organizing pneumonia, diffuse alveolar damage, interstitial pneumonia, pulmonary fibrosis, or pulmonary hemorrhage (Table 9.1).

In *bronchiolitis obliterans (BO)* (constrictive bronchiolitis, obliterative bronchiolitis), increased fibrous tissue, with or without a chronic inflammatory component, separates the airway epithelium from the smooth muscle, partially or completely obstructing the airway. The bronchiole may be completely replaced by fibrous tissue, resulting in an apparently unpaired pulmonary artery. Because involvement is patchy, the severity of findings in a biopsy does not necessarily correlate with clinical severity. Secondary changes suggestive of obstruction include mucostasis with
foamy macrophages and cholesterol clefts. BO may be seen in immunocompetent patients, and the most common overall etiology is postinfectious, particularly following adenoviral infection. BO is also seen in graft-versus-host disease and chronic rejection in lung transplants, in both cases due to infiltration of inflammatory cells recognizing foreign epithelial antigen. It is less commonly seen in other conditions including collagen vascular disease, drug reaction (busulfan), microaspiration, or inhaled toxins.

Organizing pneumonia (OP) and diffuse alveolar damage (DAD) have similar underlying etiologies (see Table 9.1), and both OP and the organizing stage of DAD have loose connective tissue and reactive fibroblasts. OP is characterized by Masson bodies: balls of loose fibrous tissue and fibroblasts filling alveolar spaces and sometimes extending into distal airways (Fig. 9.5). It is easiest to recognize when flowing between alveoli and is important to diagnose because it may respond to steroid treatment. In early stages, DAD is easy to recognize due to its bright, eosinophilic hyaline membranes lining the alveolar walls. Despite the name, the hyaline membranes may be focal. As fibroblasts begin to organize the membranes (after approximately 5 days), loose connective tissue and fibroblasts accumulate close to the alveolar walls and within the interstitium. Remnants of the hyaline membranes formed in early DAD and the peripheral distribution of fibroblasts distinguish this from OP.

<table>
<thead>
<tr>
<th>Bronchiolitis Obliterans</th>
<th>Diffuse Alveolar Damage</th>
<th>Organizing Pneumonia</th>
<th>Interstitial Pneumonitis</th>
<th>Pulmonary Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postviral infection</td>
<td>Infection</td>
<td>Infection</td>
<td>Pneumocystis</td>
<td>Radiation</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Drug</td>
<td>Drug reaction</td>
<td>LIP</td>
<td>Drug</td>
</tr>
<tr>
<td>Drug</td>
<td>GVHD</td>
<td>GVHD</td>
<td>Viral infection</td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Rejection of lung transplant</td>
<td>Aspiration</td>
<td>Radiation therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
<td>Idiopathic pneumonia syndrome</td>
<td>Aspiration</td>
<td>Idiopathic pneumonia syndrome</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>Aspiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GVHD, graft-versus-host disease; LIP, lymphocytic interstitial pneumonia.
Interstitial pneumonitis and interstitial fibrosis result in widening of the alveolar septa with a spectrum of cellular to fibrous tissue. In interstitial pneumonitis, the alveolar septa are thickened by an influx of lymphocytes, plasma cells, and histiocytes. Common infectious causes of interstitial pneumonitis include Pneumocystis and viral infection. It can also be seen in drug reaction and idiopathic pneumonia syndrome (IPS), which occurs post–hematopoietic stem cell transplant (HSCT). IPS typically occurs in the first 3 months after transplant and is a clinical diagnosis of exclusion when no infectious source can be identified to explain the diffuse pulmonary findings. It is thought to be a reaction to pretransplant conditioning regimens and may present as either interstitial pneumonia or DAD. Interstitial fibrosis widens the alveolar septa with a paucicellular accumulation of collagen, commonly due to radiation therapy or drug effect. Drugs associated with fibrosis include, but are not limited to, busulfan, carmustine, cyclophosphamide, and mitomycin-C.

**LUNG TRANSPLANT EVALUATION**

Transbronchial biopsies may be performed either for surveillance or to evaluate symptoms. Because findings may be focal, an adequate biopsy is considered to be one with at least five fragments of alveolated tissue, each with at least 100 alveoli. A revised consensus guideline for grading lung rejection was published in 2007 (eTable 9.4); however, some centers still prefer the 1996 classification. Acute cellular rejection is characterized by a typical

FIGURE 9.5  OP is characterized by intraalveolar Masson bodies, which often contain a few chronic inflammatory cells in the middle of whorls of fibroblasts as seen here.
mixed inflammatory infiltrate with activated lymphocytes, eosinophils and few neutrophils, and plasma cells. When involving veins, arteries, or lymphatics, this is referred to as acute cellular rejection. When involving the submucosa, it is called airway rejection. The most severe findings should be graded. As the grade increases, eosinophils, neutrophils, and endothelialitis increase. The differential includes PTLD and infection. Airway inflammation may be a component of rejection but can also be seen in infection, especially if neutrophils are predominant and perivascular inflammation is absent. Airway inflammation should also be distinguished from bronchus-associated lymphoid tissue (BALT), which is circumscribed, predominantly B cells, and has CD21-positive follicular dendritic cells. Chronic rejection is manifested by BO with or without active inflammation. A morphologic equivalent of antibody-mediated rejection is not well defined in the lung and is not included in the current grading recommendations. Positive staining for C4d by IHC is extremely rare. Microaspiration with macrophages with large vacuoles, foreign body reaction, or granulomas is common in transplant recipients and may precipitate acute rejection.

**Graft-versus-host disease (GVHD)** of the lung is rare in the absence of involvement of other organ systems. The most typical pattern is airway centered with increased subepithelial and intraepithelial lymphocytes or BO (Fig. 9.6) (see Table 9.1).

**Hematopoietic disorders** affecting the immunosuppressed pediatric lung include lymphocytic interstitial pneumonia (LIP), PTLD, lymphomatoid granulomatosis (LG), and recurrent leukemia. Primary lung lymphomas are rare and are usually mucosa-associated lymphoid tissue (MALT)
or Hodgkin lymphomas. LIP is almost always seen in immunodeficient patients, particularly in young children with perinatally acquired HIV infection, in whom it is considered an AIDS-defining illness. A diffuse, benign, polyclonal proliferation of lymphocytes and plasma cells distend the alveolar septa (Fig. 9.7), and germinal centers and occasional poorly formed granulomas may be identified. The airways and vessels are not involved. LG is characterized by an angiocentric proliferation of Epstein-Barr virus (EBV)-positive large B cells accompanied by reactive smaller T cells. PTLD may present in the lungs in either lung transplant patients or in those with hematopoietic or other solid organ transplants. The incidence of PTLD in children is relatively high due to primary EBV infection, and most pediatric PTLDs are EBV-related B-cell proliferations (see Chapter 7).

**NONIMMUNOCOMPROMISED LUNG BIOPSY**

Overall, diffuse lung diseases in children are quite rare and most commonly present in the first year of life. The most common entities identified are surfactant disorders, hemosiderosis, sarcoidosis, and hypersensitivity pneumonitis, there being no specific diagnosis in up to a quarter of patients (Fig. 9.8). In smaller series of infant lung biopsies, a subset (8%) also could not be definitively classified. An unrecognized genetic or acquired immunodeficiency first presenting with pulmonary involvement is also possible, for example, chronic granulomatous disease (CGD) (Fig. 9.9). The majority of diffuse lung diseases in children are distinct from those in adults. A relatively recent classification scheme for children younger than 2 years of age...
FIGURE 9.8  Chronic interstitial lung disease is the diagnosis that could be made in this 2-year-old, full-term gestation, who had been respirator dependent since birth. There is nonspecific interstitial fibrosis.

FIGURE 9.9  CGD is seen in the lung in this 6-week-old with recurrent infections. There is granulomatous inflammation with neutrophils and fungal hyphae, which can easily be seen with H&E in the center of the granulomas. This finding in the lung biopsy prompted the workup for CGD.
age divides these disorders into clinically related etiologies with two broad categories: those presenting primarily in infancy and those nonspecific to infancy. Categories specific to infancy include diffuse developmental disorders (eTable 9.6), growth abnormalities with deficient alveolarization, neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis, and surfactant dysfunction disorders (eTable 9.7). Conditions that are not specific to infancy include systemic disease processes, disorders of immunosuppressed patients (infections, transplant, drug/radiation induced), vascular disorders, and the wide array of pulmonary disorders seen at any age (i.e., hypersensitivity, aspiration). Some of these disorders have overlapping histologic features (eTable 9.5) and require clinicopathologic correlation for diagnosis. Consensus guidelines recommend saving tissue for special testing including electron microscopy, molecular testing, immunofluorescence, or genetic testing.

**Diseases of Infancy**

**Diffuse developmental disorders** present in term infants and have essentially 100% mortality without lung transplant. Most are extremely rare and are more frequently seen at autopsy rather than biopsy (eTable 9.6). Alveolar growth abnormalities is one of the more common diagnoses in infants but is commonly overlooked. It is often due to known lung disease of prematurity, pulmonary hypoplasia, congenital heart disease, or chromosomal disorders and may be seen when biopsy occurs for unexpectedly severe symptoms. The lobules are simplified with fewer alveoli, the airspaces are large and round (particularly in the subpleural areas), and mild interstitial fibrosis may be present. Comparison with normal lung from an infant of the same age is helpful to appreciate normal alveolar size and shape.

**Pulmonary interstitial glycogenosis** (PIG), also referred to as infantile cellular interstitial pneumonitis, is a poorly understood finding often present in conjunction with other growth abnormalities or meconium aspiration, but it may present on its own within hours to weeks of life. There are patchy areas of alveolar wall thickening with mesenchymal cells with pale or bubbly cytoplasm. Electron microscopy demonstrates glycogen within the cells, which may be PAS positive. The pathophysiology of PIG, its significance, and appropriate treatments are still a matter of debate, although it may respond to steroid therapy and is generally thought to have a relatively good prognosis.

**Neuroendocrine cell hyperplasia** is an important diagnosis to consider in the “normal” or “near normal” lung biopsy of infants and requires IHC to demonstrate increased neuroendocrine cells. It usually presents in the first few months of life, often after a viral infection, and correlates with the clinical diagnosis of persistent tachypnea of infancy. Suggested parameters include neuroendocrine cells in 70% of bronchioles or comprising 10% of cells in a single airway; however, the increase can be patchy, and neuroendocrine cells may be increased in other disorders, so there is no specific cutoff number. Additional nonspecific changes include patchy, mild, chronic inflammation or fibrosis of the airways.
Surfactant-related diseases may be divided into two main groups: those with genetic defects in surfactant or related genes (surfactant dysfunction disorders [SDD]) and those with abnormalities in macrophage function (PAP). Genetic deficiencies in surfactant production may be due to mutations in surfactant protein genes (SPB, SPC—second most common) or those involved in their expression (TTF-1—rare) or processing (ABCA3—most common) (Fig. 9.10). Although classically presenting in infancy, some surfactant mutations may present later in childhood or early adulthood as interstitial lung disease (eTable 9.7). The clinical and histologic picture is variable even with mutations in the same gene and may reflect the age at which the patient is biopsied (Table 9.2). IHC may be useful to show loss of surfactant proteins in some subtypes (SPB), but abnormal protein may still accumulate, and a normal IHC pattern does not exclude the diagnosis. Both electron microscopy (Fig. 9.11) and molecular testing are important in providing a specific diagnosis. In the absence of a demonstrated gene mutation, some patterns of lung disease (Table 9.2) are suggestive of surfactant deficiency in as yet unidentified genes. Recently, rare mutations in genes such as TTF1 (NKX2-1) involved in lung development have been described to result in alveolar proteinosis combined with defects in alveolar development.13,14

In contrast to surfactant deficiencies, PAP is secondary to defective macrophage clearance of surfactant. Extremely rare congenital mutations in the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor have been described, but the majority of PAP cases in children are secondary (Fig. 9.12). In adults, PAP is usually due to antibodies against

FIGURE 9.10  Surfactant dysfunction disorder was suggested as the diagnosis in this 4-week-old term baby who presented with increasing respiratory insufficiency. The biopsy shows only small amount of intraalveolar eosinophilic material with type II pneumocyte hyperplasia and interstitial inflammation.
### TABLE 9.2 Patterns of Tissue Reaction in Surfactant-Related Disorders

<table>
<thead>
<tr>
<th>Pattern Name</th>
<th>Alveolar Space</th>
<th>Alveolar Walls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary alveolar proteinosis (PAP)</td>
<td>PAS-positive surfactant material</td>
<td>Architectural preservation of alveolar septa</td>
</tr>
<tr>
<td></td>
<td>Foamy macrophages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholesterol clefts</td>
<td></td>
</tr>
<tr>
<td>Congenital alveolar proteinosis (CAP)</td>
<td>PAS-positive surfactant material</td>
<td>Type II pneumocyte hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Foamy macrophages</td>
<td>Interstitial fibrosis</td>
</tr>
<tr>
<td></td>
<td>Cholesterol clefts</td>
<td></td>
</tr>
<tr>
<td>Chronic pneumonitis of infancy²¹,²² (CPI)</td>
<td>Patchy surfactant material, foamy macrophages</td>
<td>Type II pneumocyte hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial widened with bland mesenchymal cells</td>
</tr>
<tr>
<td>Desquamative interstitial pneumonia²³ (DIP)</td>
<td>Macrophages filling airspaces diffusely</td>
<td>Minimal thickening</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia (NSIP)</td>
<td></td>
<td>Mixed lymphocytes, histiocytes, plasma cells</td>
</tr>
</tbody>
</table>

PAS, periodic acid–Schiff.

**FIGURE 9.11** ABCA3 mutation was subsequently confirmed in the case illustrated in Figure 9.10 both by the finding of electron-dense cores in lamellar bodies by electron microscopy as shown here and by genetic testing.
FIGURE 9.12  PAP, secondary, in a 4-year-old undergoing treatment for acute promyelocytic leukemia. The alveoli are filled with pink granular material.  

A: Touch preparation demonstrating globules of surfactant material.  
B: Frozen section with filling of alveoli and preservation of alveolar septa.  
C: Permanent section shows dense eosinophilic material, scattered macrophages, and cholesterol clefts filling the airspaces with preservation of the underlying alveolar architecture.
GM-CSF, but in children it is often due to profound immunodeficiency resulting in defective macrophage activity and is often accompanied by fungal infection.

**Diseases Not Specific to Infancy**

**Connective tissue diseases** are rare in children; however, lung involvement may be seen in diseases such as juvenile rheumatoid arthritis (eTable 9.8).

**Sarcoidosis** is also rare, but pulmonary involvement does occur in children, usually in older children and teenagers. It is characterized by well-formed, nonnecrotizing granulomas that follow a lymphatic distribution. Occasional necrotizing granulomas can be seen. Older lesions may become fibrotic, beginning with a concentric rim of fibrosis around the granulomas.

**Hypersensitivity pneumonitis** due to inhaled antigens is relatively rare in children. The histologic features are similar to those in adults, including a bronchiolocentric pattern of inflammation with chronic bronchiolitis, interstitial inflammation near the bronchioles, and poorly formed nonnecrotizing granulomas and occasional giant cells.

**Alveolar hemorrhage disorders** with or without capillaritis present with hypoxemia, diffuse alveolar infiltrates, and hemoptysis, often with anemia. In the absence of capillaritis, causes include cardiac diseases, reaction to cow’s milk in infants (Heiner syndrome), and idiopathic pulmonary hemosiderosis (IPH). Biopsy demonstrates iron in macrophages, pneumocytes, encrusting elastic fibers, and free in the interstitium (Fig. 9.15). Interstitial fibrosis occurs in long-standing cases.

![Figure 9.13](image-url) **Figure 9.13** IPH in a 2-year-old who presented with hemoptyis and anemia. There is extensive hemosiderin within macrophages and in the interstitium (Prussian blue stain).
Capillaritis is defined by fibrinoid necrosis of vessel walls accompanied by a neutrophilic infiltrate and when identified requires more aggressive treatment. It may be an isolated finding, part of a connective tissue disease, or part of a specific vasculitic disease (Goodpasture disease, Wegener granulomatosis, microscopic polyangiitis); however, these are rare in children. A clinical history of autoantibodies including c- or p-antineutrophil cytoplasmic antibody (ANCA) or anti–glioblastoma multiforme (GBM) antibodies should raise the suspicion of a vasculitic disease.

**Langerhans cell histiocytosis (LCH)** in children is a neoplastic process. Unlike the adult form of pulmonary LCH, which is a smoking-related disease, involvement of the pediatric lung is almost always a component of diffuse or multisystemic LCH involving the bone and other organ systems. The lesions have CD1a, S100, and langerin-positive Langerhans cells with grooved nuclei and a mixed inflammatory infiltrate often including eosinophils.

**Storage diseases** such as Gaucher and Niemann-Pick disease may present with pulmonary symptoms, although this is rare. Foamy macrophages or Gaucher cells are present in the alveolar spaces and interstitium. The differential diagnosis includes endogenous lipid pneumonia due to airway obstruction, aspiration, or drug reaction.

**Chronic microaspiration** may be a cause of diffuse lung disease, particularly in patients with neurologic defects and may precipitate acute rejection in lung transplant patients. Histologic features include exogenous lipid pneumonia, multinucleated giant cells, and nonnecrotizing granulomas, with or without foreign particles. Chronic bronchiolitis or obliterator bronchiolitis may also be present.

**PULMONARY VASCULAR DISORDERS**

Although biopsies are no longer performed to evaluate reversibility of pulmonary arterial hypertension (grades 1 to 3 of 6), vascular changes may still be graded in any lung biopsy (eTable 9.9). Secondary pulmonary hypertensive changes similar to the first three grades may be seen in left heart failure, chronic hypoxia, and chronic thromboembolic disease. Pulmonary lymphangiectasis usually occurs in association with congenital heart defects but may rarely be sporadic. Dilated lymphatic spaces are seen in association with bronchovascular bundles and in the pleura. It should be distinguished from interstitial pulmonary emphysema (IPE), which is due to air dissection creating cyst-like spaces without an epithelial or lymphatic lining and may have foreign body giant cells in chronic lesions.

**BIOPSY DIAGNOSIS OF MASS LESIONS**

Although rare, endobronchial biopsy may be performed for inflammatory conditions or mass lesions arising within the tracheobronchial tree, whereas transbronchial or imaging-guided needle biopsies sample masses
in the parenchyma. Most metastatic tumors are surgically excised. Primary lung tumors in children are rare, with carcinoid tumors, pleuropulmonary blastoma, and inflammatory myofibroblastic tumor being most common. Endobronchial mass lesions include hamartomas, carcinoid tumors, and mucoepidermoid carcinoma. Most hamartomas are composed of a mixture of benign fat, cartilage, and fibrous tissue, although any single component can predominate, and there is usually entrapment of adjacent lung. Pulmonary chondromas arise in association with airway cartilage with a pushing border and are associated with Carney triad. In young children, respiratory papillomatosis is characterized by recurrent squamous papillomas which rarely involve not only the larynx and trachea but also distal bronchioles and lung. The histology is similar to human papillomavirus (HPV)–associated squamous papillomas elsewhere. It is commonly associated with low-risk HPV subtypes 6 and 11 and very rarely progresses to squamous cell carcinoma of the lung.

REFERENCES