Thoracic Manifestations of Systemic Diseases

David V. Holland, R. Paul Guillerman, and Alan S. Brody

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Abstract

A wide variety of systemic diseases have manifestations in the pediatric chest. Among these systemic diseases are connective tissue diseases, granulomatous diseases, immunodeficiency disorders, vasculitis, sickle cell disease, cystic fibrosis, ciliary dyskinesia, histiocytosis, phakomatoses, and storage disorders. The primary manifestations are diverse, and may include interstitial lung disease, air space disease, pleuritis, lymphadenopathy, and skeletal abnormalities. Secondary effects, such as bronchiectasis from recurrent infection, are also common. Although the underlying systemic disease has often been previously diagnosed, it is not uncommon for pulmonary manifestations to be the first signs of a systemic disease, and knowledge of the pertinent clinical and imaging features may allow the radiologist to be the first to suggest an underlying systemic disease.

1 Introduction

A wide variety of systemic diseases have primary or secondary manifestations in the pediatric chest. Although the underlying systemic disease has often been previously diagnosed, it is not uncommon for pulmonary manifestations to be the first signs of a systemic disease. This chapter has two main goals: first, to aid the reader in interpreting imaging findings of known systemic diseases in which lung

P. Garcia-Peña and R. P. Guillerman (eds.), *Pediatric Chest Imaging*, Medical Radiology. Diagnostic Imaging,
DOI: 10.1007/174_2014_965, © Springer-Verlag Berlin Heidelberg 2014
Published Online: 19 March 2014

manifestations are common; second, to provide a guide based on the imaging appearance to allow the reader to suggest the possibility of an undiagnosed systemic disease. In-depth information on the imaging techniques that are used in the evaluation of these and other pediatric thoracic diseases is provided in other chapters of this book, and only pertinent additional comments will be made in this chapter. For each condition or group of conditions, the general features of the condition will be described, followed by a review of the imaging appearance of the thoracic manifestations. Knowledge of the characteristic clinical and imaging features may allow the radiologist to be the first to suggest an underlying systemic disease in these children.

In addition to disease-specific associated thoracic abnormalities, many systemic diseases produce nonspecific secondary effects that can be reflected by thoracic findings on diagnostic imaging. Abnormal host defences frequently result in both an increased incidence of pulmonary infection and a change in the spectrum of infection. Neuromuscular abnormalities can result in aspiration with direct chemical insult to the lungs as well as infection. The likelihood of such effects should be borne in mind, as these abnormalities may be more common in certain clinical settings than the primary pathologies associated with a specific systemic disease.

It is important to note that many of the reports that form the literature in these diseases are more than 10–20-years old. Recent advances in classification, diagnosis, treatment, and complications related to treatment may not be reflected in this literature. Understanding of the spectrum of imaging findings may also be limited by the technology that was available at the time of these reports.

2 Connective Tissue Diseases

The connective tissue diseases (CTDs) are a group of diseases characterized by inflammation affecting the connective tissue of various organ systems. Common CTDs in children and adolescents include juvenile idiopathic arthritis (JIA), juvenile-onset systemic sclerosis (JSS), juvenile dermatomyositis (JDM) and systemic lupus erythematosus (SLE). In mixed connective tissue disease (MCTD) or overlap syndrome, patients may present with features of multiple CTDs.

The frequency and pattern of lung involvement vary greatly with the type of CTD (Garcia-Pena et al. 2011). Nonspecific interstitial pneumonitis (NSIP) is the most common histopathologic pattern, but pulmonary lymphoid hyperplasia, organizing pneumonia, vasculopathy and pleuritis may also occur (Dishop 2010). Clinically apparent pulmonary abnormalities are very rare in JIA, rare in JDM, and more common in JSS, SLE, and MCTD. Pulmonary function test (PFT) abnormalities are reported in the majority of children with active CTD, although abnormalities on chest radiographs (CXR) are uncommon (Cerveri et al. 1992). Due to its superior resolution, computed tomography (CT) is the primary imaging modality used for investigation of lung parenchymal involvement. Echocardiography is the preferred noninvasive method for assessing pulmonary hypertension, which can be a complication of pulmonary involvement by CTDs.

2.1 Juvenile Idiopathic Arthritis

Transient pleuritis resulting in pleural effusion is common in juvenile idiopathic arthritis (JIA) patients (Garcia-Pena et al. 2011). Clinically overt pulmonary disease is uncommon in JIA, though, occurring in only 4 % in one study (Athreya et al. 1980). However, when PFTs were performed in 16 children with JIA, 10 had abnormalities (Wagener et al. 1981). Respiratory muscle weakness may be a contributing factor in the lung function abnormalities (Knook et al. 1999). Over the last decade, children with systemic JIA (sJIA) have been reported to have a higher incidence of pulmonary complications including pulmonary hypertension, alveolar proteinosis and interstitial lung disease (ILD). This recent increase is possibly attributable to new medications being used to treat these patients, although no controlled studies are available. Macrophage activation syndrome, common in sJIA, is associated with lipoid pneumonia related to deposition of cholesterol granulomas in the interstitium and alveoli (Kimura et al. 2013).

Pleural and pericardial effusions are reported to be the most common abnormalities on chest imaging, occurring in five of 191 children in one report (Athreya et al. 1980) (Fig. 1). Lymphocytic interstitial pneumonitis (LIP) occurred in two children in this group. In two additional reports, LIP preceded other symptoms of JIA by as long as 2 years (Lovell et al. 1984; Uziel et al. 1998). These reports described nonspecific interstitial infiltrates on CXR, but no report of CT findings was given. In a report of LIP on CT, the findings were predominantly ground-glass opacity with associated consolidation, nodules, and cysts (Lynch et al. 1999). A case report describes a patient with onset of JIA at age 5 years who developed cryptogenic organizing pneumonia (COP), also known as bronchiolitis obliterans organizing pneumonia (BOOP), at 25 years of age (Sohn et al. 2007).

2.2 Juvenile Systemic Sclerosis

Scleroderma is characterized by fibrotic infiltration of connective tissues. Involvement of the skin and the gastrointestinal tract, particularly the esophagus, is most common. The term systemic sclerosis is used to describe disseminated

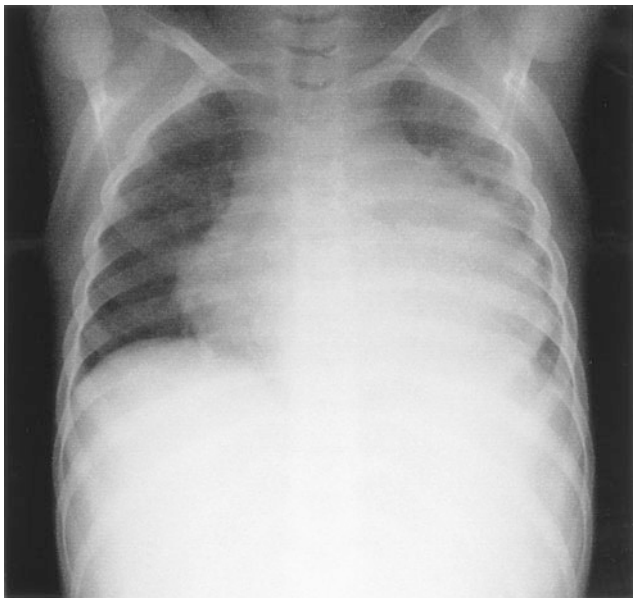

Fig. 1 Juvenile idiopathic arthritis (JIA). A frontal CXR demonstrates a large pericardial effusion and a small left pleural effusion in an 8-year-old boy with JIA

disease. Systemic sclerosis presents most commonly in adult women, but 10 % of cases present in children as juvenile systemic sclerosis (JSS). Both PFT abnormalities and lung parenchymal abnormalities on imaging are common in JSS. In a study of 11 JSS patients aged 5–19 years, 8 had ILD on CT. The most common abnormalities were peripheral ground-glass opacities in eight, subpleural nodules in seven, peripheral reticular opacities in six, and honeycombing in five (Seely et al. 1998) (Fig. 2). In a more recent and much larger study of 153 JSS patients, the prevalence of ILD on CT was 5 % at diagnosis and 23 % at some point in the overall course. Pulmonary hypertension occurred in 7 % (Martini et al. 2006). The severity of CT abnormalities correlates inversely with FEV_1 (forced expiratory volume in one second), FVC (forced vital capacity), and D_{LCO} (lung diffusion capacity for carbon monoxide) values (Panigada et al. 2009). Pulmonary hypertension can develop without lung parenchymal disease, possibly due to direct pulmonary vascular involvement (Cheema and Quismorio 2001).

Although frequently described as honeycombing, the peripheral reticular opacities and cysts that are commonly seen in JSS often do not meet strict diagnostic criteria for honeycombing, and there is poor interobserver agreement for the identification of honeycombing, even among expert thoracic radiologists. In our experience, unlike the case in idiopathic pulmonary fibrosis, these findings may remain stable for long periods of time, which is consistent with reports that there is no correlation between the duration of illness and the severity of the lung disease (Panigada et al. 2009). However, since pulmonary fibrosis is a leading cause of mortality and progression of fibrosis may be clinically silent, measuring serum levels of KL-6 (Vesely et al. 2004) or obtaining serial CT exams (Seely et al. 1998; Panigada et al. 2009) has been suggested to monitor ILD in JSS. Preliminary studies have shown that lung ultrasound findings correlate with CT findings and PFT results in adults with ILD related to systemic sclerosis (Delle Sedie et al. 2012). If validated in children, ultrasound could provide a means to monitor ILD in JSS patients without ionizing radiation exposure. Aspiration and infection must also be considered as potential causes of lung disease in JSS patients given the high rate of esophageal dysmotility and gastroesophageal reflux and the use of immunosuppressive therapy (Christmann et al. 2010).

Scleroderma sin scleroderma, a rare form of scleroderma, presents without a skin rash and may be difficult to diagnose. Usually an adult disease, it has been reported in children as young as 6 years of age. Lung involvement is reported in approximately two-thirds of these patients (Toya and Tzelepis 2009).

2.3 Juvenile Dermatomyositis

Abnormal PFTs are reported in more than more than half of patients with juvenile dermatomyositis (JDM) (Takizawa et al. 1987). In a report of five cases, interstitial pneumonia was noted in three and COP in two. All had abnormalities on physical examination or imaging studies at the time of presentation with JDM, although in two cases these abnormalities were initially mild (Kobayashi et al. 2003).

A more recent report of 21 pediatric patients found that respiratory involvement was common, occurring in 76 %, but respiratory symptoms were not the presenting symptoms in any. Respiratory muscle involvement was the most common abnormality followed by interstitial lung disease. Chest CT was abnormal in 12 of the 15 patients in whom CT was performed, with linear opacities, nodules, ground glass opacities, expiratory air trapping, and bronchial wall thickening being the most common findings (Pouessel et al. 2013). Rarely, JDM may be complicated by an acute, rapidly progressive, steroid-refractory, fatal interstitial lung disease (Lin et al. 2002).

2.4 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by persistent B-cell activation and overproduction of autoantibodies and immune complexes. Both the activity of the autoantibodies and the deposition of the immune complexes are associated with organ

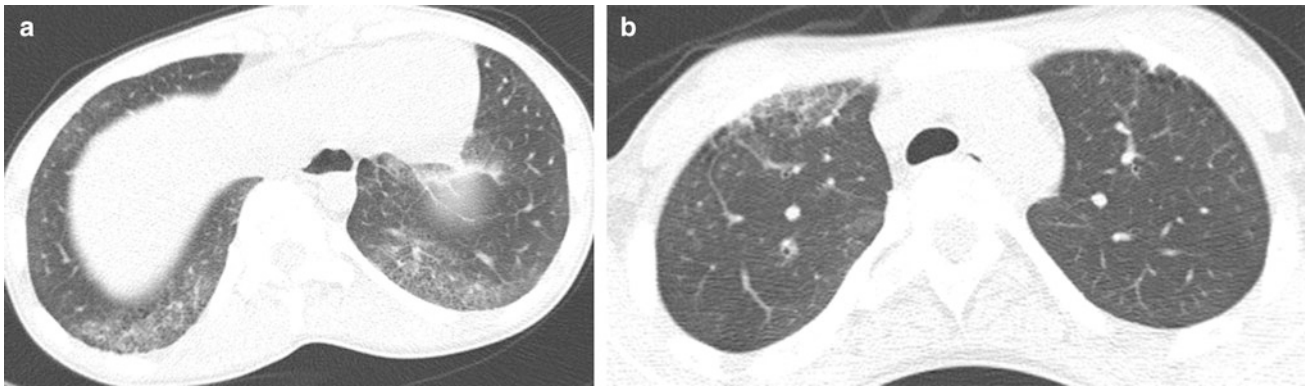

Fig. 2 Juvenile systemic sclerosis (JSS). Axial chest CT images (**a**, **b**) from a 17-year-old girl with JSS show ground-glass opacities, fine reticular opacities, and tiny cysts at the peripheral posterior lower lobes and peripheral anterior upper lobes, as well as esophageal dilation

dysfunction (Lehman 1995). SLE is more common in non-Caucasian than in Caucasian populations, and susceptibility to SLE is thought to be related to multiple genes. The number of SLE susceptibility alleles relates to the likelihood of onset in childhood in African-Americans, but not in populations of Hispanic or European origin (Webb et al. 2011). One-fifth to one-sixth of SLE patients present before the age of 16 years (Arkachaisri and Lehman 1999). A comparison of adult- and pediatric-onset SLE found that children tend to present with more acute illness and have higher mortality rates (Mina and Brunner 2010).

In 37 % of cases of childhood-onset SLE, the pulmonary function is impaired, with a reduction of D_{LCO} most commonly noted. Pulmonary abnormalities on chest CT are less common, with a prevalence of 8 %, and pulmonary function does not correlate with CT findings (Lilleby et al. 2006). Manifestations of SLE on chest imaging include pleural effusion, pericardial effusion, pneumonitis, obliterative bronchiolitis, vasculitis, pulmonary hemorrhage and pulmonary embolism (Babyn and Doria 2005). Opportunistic infections are a leading cause of death in children with SLE, so infection should be excluded before attributing respiratory signs or symptoms to primary lupus involvement (Wang et al. 2003).

Acute lupus pneumonitis is a rare, life-threatening condition related to diffuse alveolar damage. Acute lupus pneumonitis can be difficult to diagnose due to its nonspecific presentation of shortness of breath and extensive pulmonary opacification that simulates infectious pneumonia or pulmonary edema (Vece and Fan 2010) (Fig. 3).

Alveolar hemorrhage from SLE is more common in children than in adults, and the mortality is higher (Araujo et al. 2012). Patients present with a decrease in hematocrit, but hemoptysis may be absent. This condition can potentially be treated successfully with steroids and cytotoxic agents, so correct identification is important (Schwab et al. 1993). Air space opacities can be seen on CXR and CT. The imaging is not specific, as lupus pneumonitis or infection can produce the same findings. The finding of T2 shortening on magnetic resonance imaging (MRI) has been reported as a means of specifically identifying hemorrhage (Hsu et al. 1992).

"Shrinking lung syndrome" is a term used to describe a progressive decrease in lung volumes seen in some patients with SLE. This is usually identified on CXR as a progressive elevation of the diaphragm despite attempted full inspiration. The etiology is unknown, but may relate to a combination of pleural restriction due to recurrent pleural inflammation, pulmonary restriction due to pulmonary fibrosis, and weakness of the diaphragm and chest wall musculature. African-American patients are most commonly affected (Ferguson and Weinberger 2006).

3 Systemic Granulomatous Disorders

3.1 Sarcoidosis

Imaging findings of thoracic sarcoidosis in children are similar to those in adults. The most common thoracic manifestation of sarcoidosis in children is bilateral hilar lymphadenopathy. Pulmonary parenchymal disease occurs in approximately two-thirds of cases, usually in association with lymphadenopathy. Isolated pulmonary parenchymal involvement is found in only 11 % of cases (Keesling et al. 1998). Typical CT findings of pulmonary sarcoidosis in children include nodular beading and thickening of the bronchovascular bundles, interlobular septae, and fissures (Milman et al. 1998) (Fig. 4). Ground-glass opacities are also common, but parenchymal distortion and consolidation are less frequent and cysts or pleural effusions are typically not seen. Decreases in CT finding scores over time are

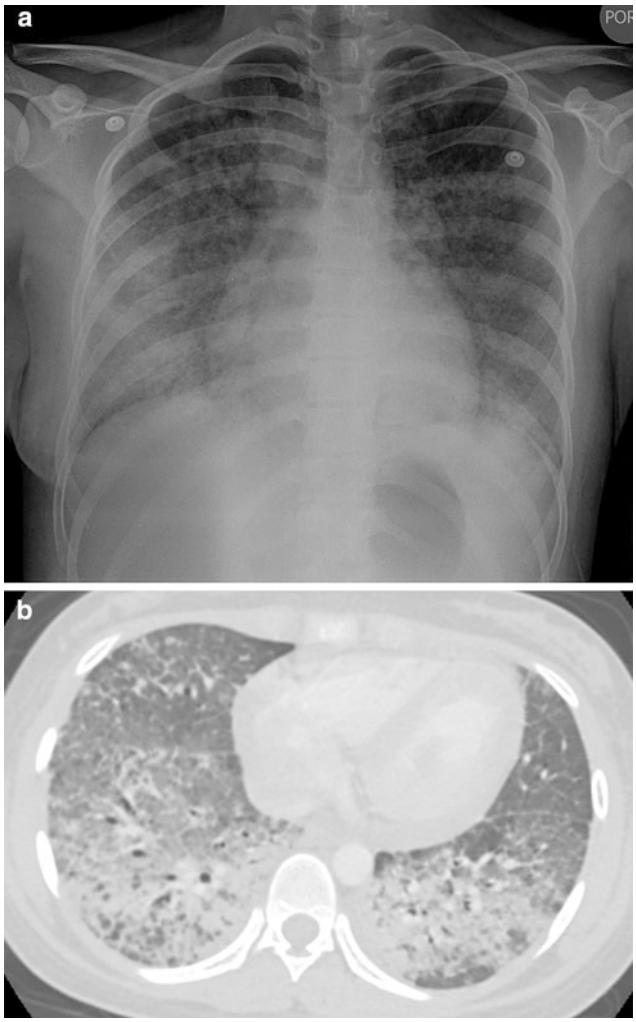

Fig. 3 Acute lupus pneumonitis. A frontal CXR (**a**) and an axial chest CT image (**b**) depict extensive bilateral pulmonary air space opacification in this 13-year-old girl with SLE and acute respiratory symptoms

associated with improvement of pulmonary function measured by FEV_1 and FVC, so that the need for follow-up CT scans may be reduced when PFT results improve over time (Sileo et al. 2013a).

3.2 Crohn Disease

Although extraintestinal manifestations of Crohn disease are well known, respiratory tract involvement is uncommon but increasingly recognized, including in children (Al-Binali et al. 2003). Involvement can range from the large central airways (bronchiectasis, chronic bronchitis), to the small airways (bronchiolitis obliterans) and lung parenchyma (eosinophilic pneumonia, organizing pneumonia, granulomatous pneumonitis, interstitial pneumonitis) (Fig. 5). Drug-induced lung disease should be considered, particularly in the setting of eosinophilic pneumonia in patients on sulfasalazine or mesalamine therapy. Infection, including tuberculosis, should also be considered given the altered immune status of many of these patients. Treatment of pulmonary involvement is usually based on discontinuation of possible inciting drugs and initiation of steroids or other immunosuppressants (Basseri et al. 2010).

4 Immunodeficiencies

Defences against infection include physical barriers, B-cells, T-cells, natural killer cells, phagocytes, and complement proteins. Defects in one or more of these components of the immune system result in an increased risk of infection. The lungs are exposed to both inhaled and circulating infectious agents and are frequently the site of infection in immunocompromised children.

Acquired immunodeficiency states are common in children, and can relate to chemotherapy for cancer, solid organ transplantation, hematopoietic stem cell transplantation (HSCT), immunosuppressive therapy for autoimmune disorders, or HIV infection. Although individually rare, the primary immunodeficiency diseases (PIDs) have a collective prevalence of 1/2,000 children in the United States (Boyle and Buckley 2007). Accumulating knowledge of the genetic and molecular basis of the immune system is providing a far more detailed understanding of PID, and specific genetic defects leading to distinct types of PID are increasingly being identified. With this increased understanding has come increased complexity in classifying PID. At least 200 inborn errors of immunity have been genetically defined, and the classification of PID is updated on a biennial basis by an expert committee of the International Union of Immunological Societies (IUIS). Based on disease mechanism, the IUIS classification groups PIDs into eight categories: predominantly antibody deficiencies, combined T-cell and B-cell immunodeficiencies, well-defined syndromes with immunodeficiency, congenital defects of phagocyte number and/or function, diseases of immune dysregulation, defects in innate immunity, auto-inflammatory disorders, and complement deficiencies. There is considerable heterogeneity, as well as overlap, in the phenotypic expression of these disorders (Al-Herz et al. 2011).

The radiologist has several roles when assessing the chest of children with an immunodeficiency. These include suggesting the possibility of an immunodeficiency, noting features characteristic of a specific immunodeficiency, evaluating infections, and detecting malignancies that can occur as a complication of certain immunodeficiencies.

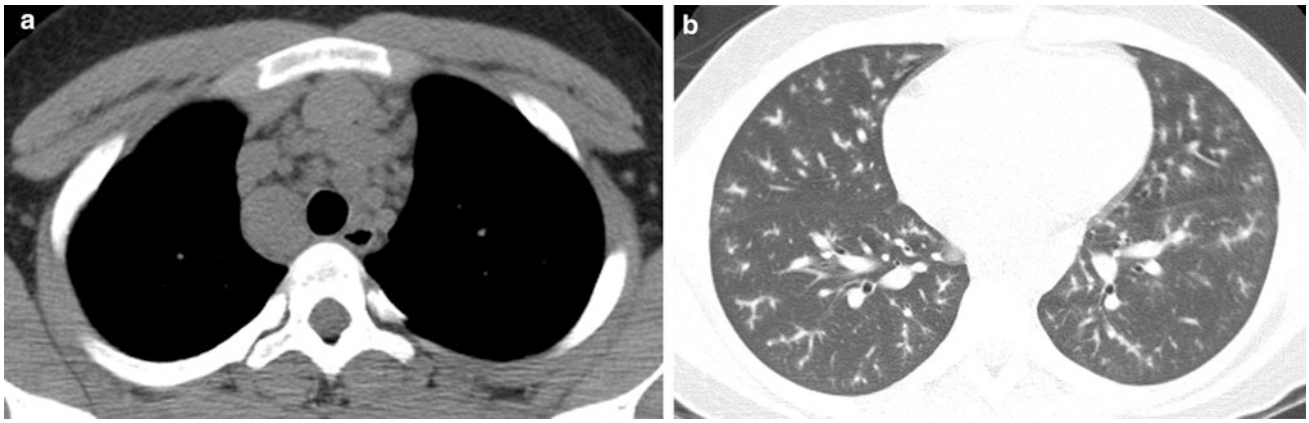

Fig. 4 Sarcoidosis. An axial chest CT image reconstructed in soft tissue windows (**a**) from a 13-year-old boy with sarcoidosis demonstrates mediastinal lymphadenopathy (**a**). An axial chest image reconstructed in lung windows (**b**) shows nodular beading of the pulmonary bronchovascular bundles

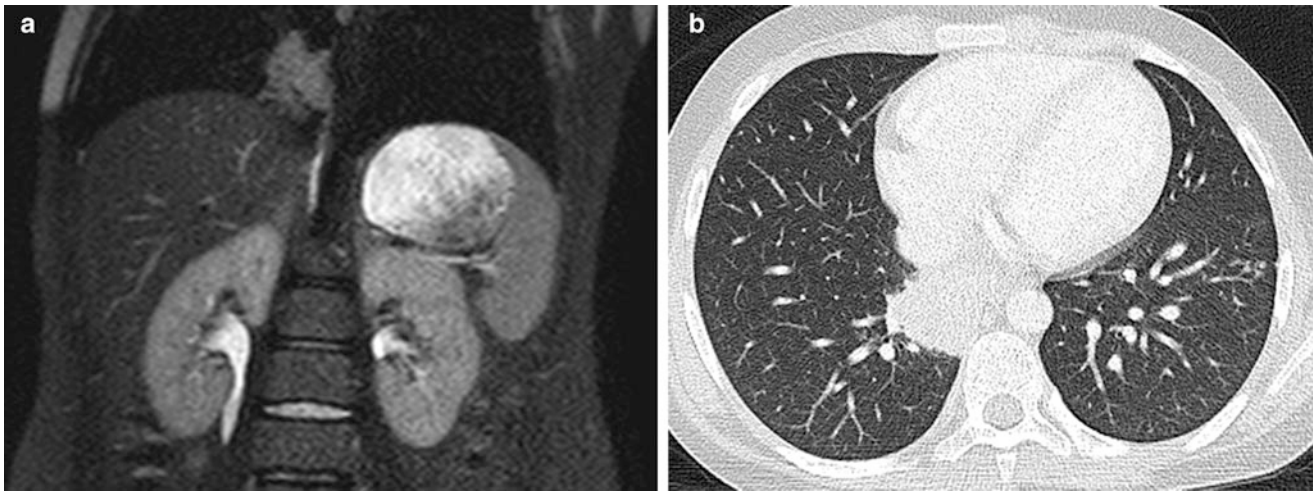

Fig. 5 Pulmonary Crohn disease. A coronal T2-weighted MR image (**a**) obtained during an MR enterography study on an 11-year-old boy with Crohn disease reveals a mass-like intermediate-to-high signal intensity lesion of the medial basilar right lower lobe. An axial chest CT image (**b**) shows a mass-like opacity of the medial basilar right lower lobe that was found to represent granulomatous inflammation on subsequent biopsy

By noting repetitive, severe, or refractory infections or recognizing certain patterns of disease, the radiologist may be the first to suggest the possibility of an immunodeficiency. In a recent study, 96 % of children with PIDs were referred to pediatric immunodeficiency centers by hospital clinicians rather than general pediatricians, illustrating the difficulty in making an early diagnosis of PID (Subbarayan et al. 2011). Early recognition of PID is important for several reasons. Bronchiectasis resulting from repeated or inadequately treated respiratory tract infection is irreversible. Outcomes are improved and treatment costs are reduced with institution of appropriate therapy, which can include immunoglobulin replacement therapy, prophylactic antimicrobials, and hematopoietic stem cell reconstitution. Avoidance of live vaccines and nonirradiated cellular blood products may be needed (Modell et al. 2009). Due to the heritable nature of many of these disorders, genetic testing and counseling may be warranted.

The primary role of thoracic imaging in children with immunodeficiencies is the detection and therapy response assessment of pulmonary infections. CXRs remain the most frequently obtained imaging study. However, CT scanning has long been recognized as both more sensitive and specific than CXR for the evaluation of diffuse infiltrative lung disease (Mathieson et al. 1989). CT is useful in children with antibody deficiency disorders to demonstrate the extent and severity of lung disease (Manson et al. 1997). Aerogenous spread of mycobacterial infection will frequently show a "tree-in-bud" appearance of infectious material filling dilated distal bronchioles (Fig. 6), although this appearance

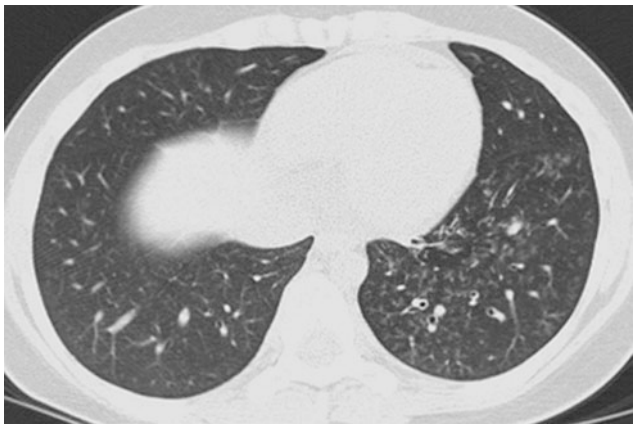

Fig. 6 Atypical mycobacterial infection. An axial chest CT image in a 14-year old with a history of large cell lymphoma and bone marrow transplantation demonstrates extensive "tree-in-bud" opacities of the left lower lobe

is far less specific than originally reported. Invasive aspergillosis may manifest as pulmonary nodules with a "halo" of ground-glass opacity (Seely et al. 1997) (Fig. 7). *Pneumocystis jirovecii* pneumonia (PCP) has a broad spectrum of findings that can include ground-glass opacities, reticulonodular opacities, septal thickening, and cysts (George et al. 2009) (Fig. 8). When identification of a specific etiology is required, CT can be used to guide bronchoscopy or needle biopsy to increase the yield of these procedures (Spencer et al. 1996).

CT scanning can be overused in children with immunodeficiencies. In one study of children with primary antibody immunodeficiencies and chronic cough, there was little disease progression on CT over 3 years and the authors suggested that annual surveillance may be more than is necessary (Rusconi et al. 2003). While MRI currently lags CT in spatial resolution, MRI has been shown to reliably identify pneumonia in immunocompromised patients when compared to CT, and is more sensitive for necrotizing pneumonia than CT (Leutner et al. 2000).

Due to the large number of types and varied phenotypic expressions of PID, only the disorders that are the most common or have the most characteristic imaging manifestations will be further discussed in this chapter.

4.1 Predominantly Antibody Deficiencies

The predominantly antibody deficiencies result from a decreased ability to produce immunoglobulins from B-cells and, in aggregate, account for more than half of all cases of PID (Buckley 2004). Genetic defects resulting in impaired immunoglobulin formation have been identified in multiple discrete steps in B-cell development (Cunningham-Rundles and Ponda 2005). Antibody deficiencies predispose to recurrent respiratory tract infection with encapsulated bacteria such as *Streptococcus* and *Haemophilus influenzae*, leading to bronchiectasis (Buckley 2004). Despite the presence of chronic respiratory symptoms, delay in diagnosis is common and can result in progressive lung damage with development of respiratory insufficiency and cor pulmonale (Wood et al. 2007).

4.1.1 IgA Deficiency

IgA deficiency is the most common PID and is noted in as many as 1 in 333 blood donors (Cunningham-Rundles 2001). IgA is secreted onto epithelial surfaces, and is present in smaller amounts in serum as well. Most individuals with IgA deficiency are asymptomatic. However, an increased propensity for infections of the respiratory, gastrointestinal, and genitourinary tracts is seen in some affected individuals. Pyogenic sinopulmonary infections are the most common (Cunningham-Rundles 2001), and the presence of IgA and IgG subclass antibody deficiencies is associated with greater pulmonary damage in children with recurrent respiratory tract infections (Ozkan et al. 2005).

4.1.2 X-Linked Agammaglobulinemia

X-linked agammaglobulinemia (XLA) is responsible for approximately 85 % of cases of childhood agammaglobulinemia (Plebani et al. 2002). There may be a family history of an affected brother, uncle, or male cousin. XLA most often results from a mutation in the X-linked gene encoding the Bruton tyrosine kinase. Deficiency of this kinase prevents precursor cells from maturing into circulating B-cells and plasma cells, resulting in impaired production of immunoglobulins of all isotypes (Buckley 2004). Infants with XLA typically present after the first several months of life coinciding the waning of maternally transmitted IgG (Fried and Bonilla 2009). Without IgG therapy, recurrent bacterial infections occur (Fig. 9). Bronchiectasis due to recurring infections usually affects the lower lungs. Similar involvement of both the right and left lungs may help differentiate these patients from those with bronchiectasis related to aspiration (Curtin et al. 1991). Pulmonary insufficiency is a common cause of death. *Streptococcus*, *H. influenzae* and Mycoplasma are the most typical cause of infections. There is an increased rate of hepatitis and enterovirus infections, but other viral infections are usually handled normally (Winkelstein et al. 2006). *Pneumocystis* and other fungal infections are rare. The adenoids, tonsils, and lymph nodes are typically small, while the thymus is usually normal in size. A lateral airway radiograph demonstrating diminutive adenoid tissue is the absence of a history of adenoidectomy can be very helpful in suggesting this diagnosis (Buckley 2004) (Fig. 9).

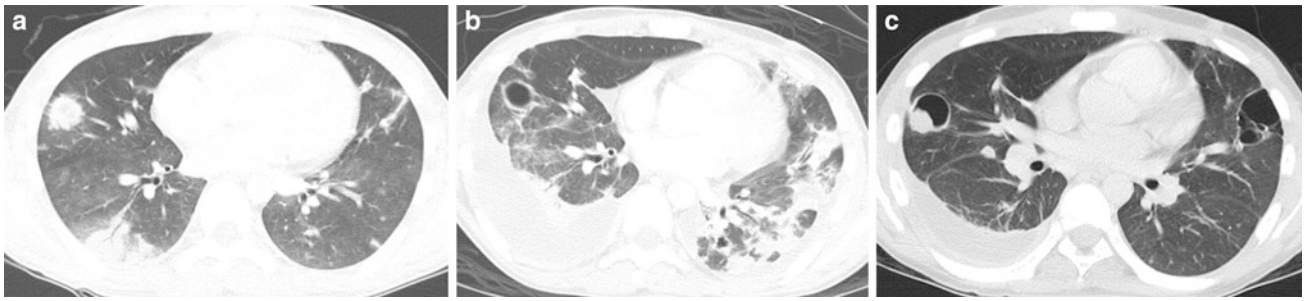

Fig. 7 Invasive aspergillosis. An axial chest CT image (**a**) in a febrile neutropenic 12-year old with acute lymphoblastic leukemia undergoing induction chemotherapy shows multiple pulmonary nodules with a ground-glass "halo" in the right lung. An axial chest CT image (**b**) obtained 19 days later after neutrophil recovery shows cavitation of the anterior right lung lesion. An axial CT chest image (**c**) obtained a further 2 weeks later reveals development of a mural nodule in the cavitary lesion that was due to cytomegalovirus superinfection

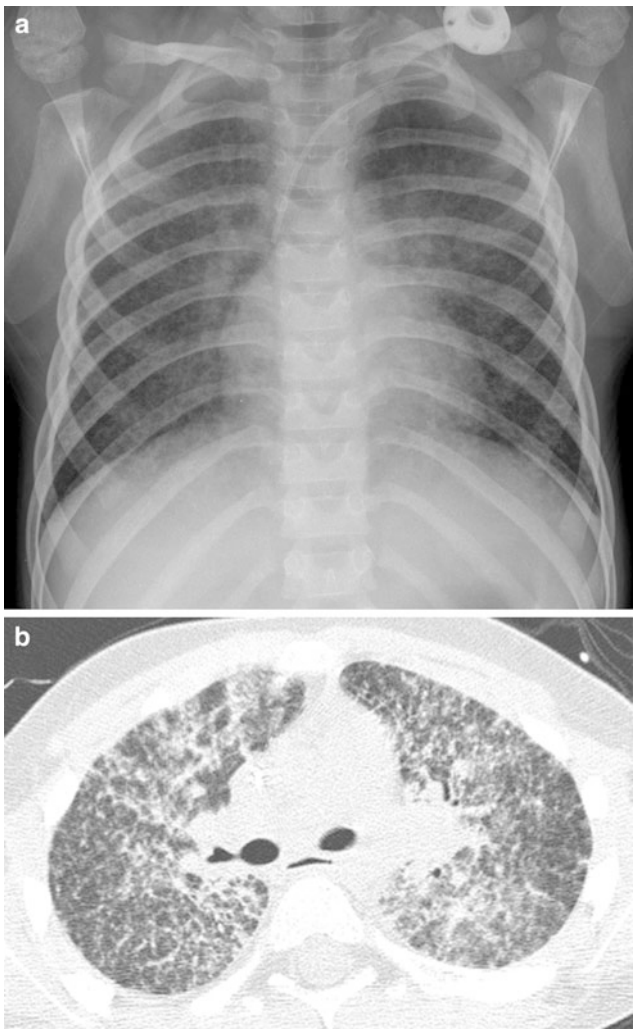

Fig. 8 *Pneumocystis jiroveci* pneumonia (PCP). A frontal CXR (**a**) and an axial chest CT image (**b**) from a 5-year old with acute lymphoblastic leukemia undergoing maintenance chemotherapy show diffuse reticulonodular opacities with a central predominance

4.1.3 Common Variable Immunodeficiency Disorder

Common variable immunodeficiency (CVID) is characterized by a failure of terminal differentiation of B-cells to plasma cells, resulting in hypogammaglobulinemia, even though B-cell number may be normal. CVID is usually less severe than agammaglobulinemia and diagnostic delay until the second decade or later is common. The infectious manifestations are otherwise similar to XLA. Unlike the case in XLA, the tonsils, adenoids, and lymph nodes are not small, and may be enlarged. Splenomegaly is seen in about 25 % of cases. Also unlike XLA, CVID is associated with an increased risk for autoimmune cytopenia, lymphoproliferative disease, lymphoma and gastric cancer. The benign lymphoproliferative disease associated with CVID can have a waxing and waning course. The associated lymphadenopathy can be difficult to discern from lymphoma (Cunningham-Rundles 2012) (Fig. 10). The word variable in this disorder refers to the variability of disease severity between patients, and not to temporal variability of disease in a single patient. There are two main phenotypes, one in which infections are characteristic and another in which inflammatory or hematologic complications are prevalent (Cunningham-Rundles 2012).

Approximately three-fourths of CVID patients develop a lung disease with air trapping, bronchiectasis, bronchial wall thickening, and endobronchial mucus plugging closely resembling cystic fibrosis (CF) (Fig. 10). Although this CF-like lung disease is associated with obstructive PFTs, it can be asymptomatic and progress silently. The degree of bronchiectasis at presentation inversely correlates with survival, and the disease can be monitored with a CF-like CT scoring system, although there is no consensus on the optimal surveillance strategy (Touw et al. 2010).

Patients with CVID can also develop granulomatous lymphocytic-interstitial lung disease (GLILD) characterized

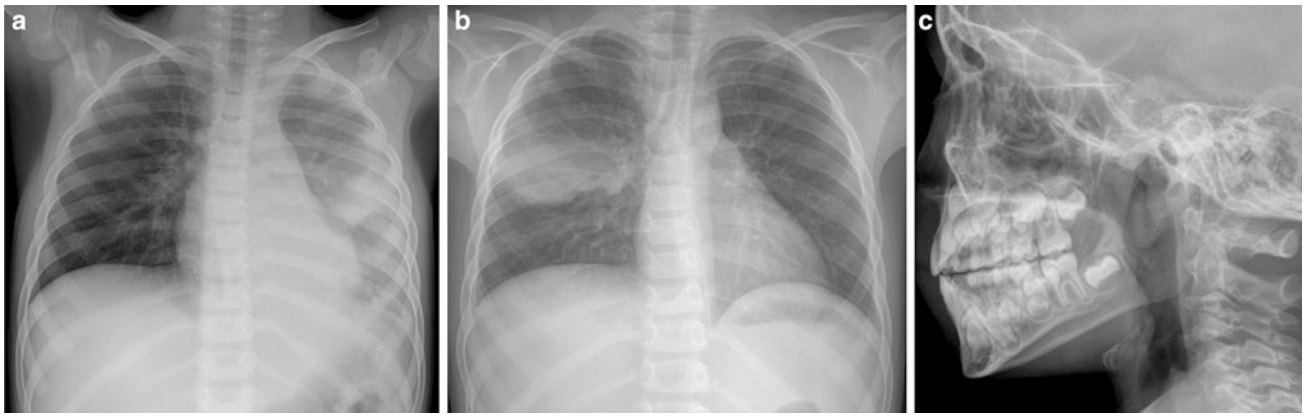

Fig. 9 X-linked agammaglobulinemia (XLA). A frontal CXR (**a**) from a 7-year-old boy with XLA depicts patchy air space opacity due to pneumococcal pneumonia. A frontal CXR (**b**) obtained 3 months later shows clearance of the previous pneumonia, but a new pneumonia of the right mid lung. A lateral upper airway radiograph (**c**) demonstrates diminutive adenoidal tissue

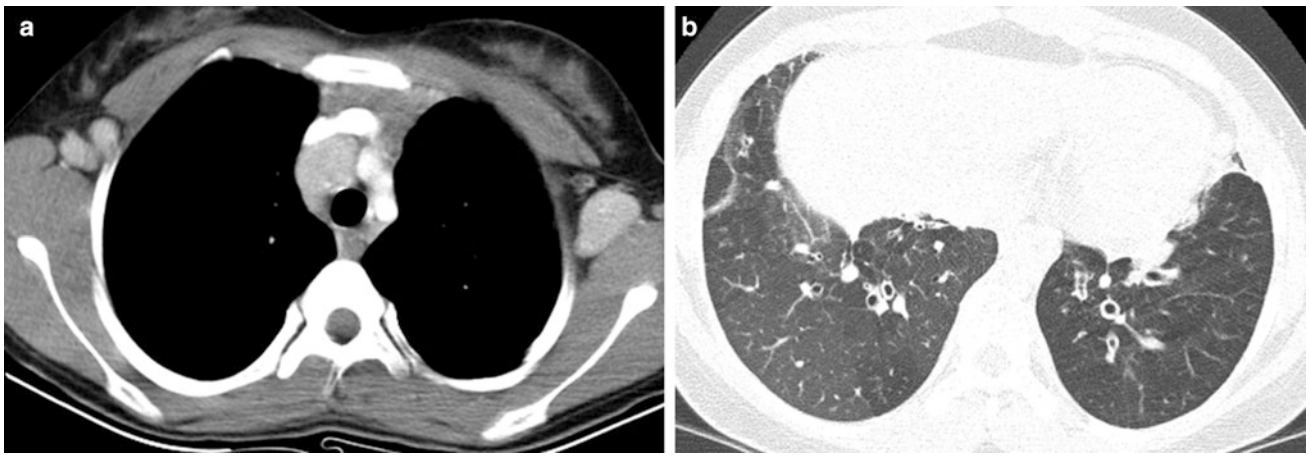

Fig. 10 Common variable immunodeficiency (CVID). An axial contrast-enhanced chest CT image (**a**) in a 12-year old demonstrates mediastinal and axillary lymphadenopathy representing CVID-associated benign lymphoproliferative disease that can simulate lymphoma. An axial chest CT image (**b**) from the same patient 2 years later shows lower lobe bronchiectasis, bronchial wall thickening, and mosaic lung attenuation from air trapping, resembling changes of cystic fibrosis

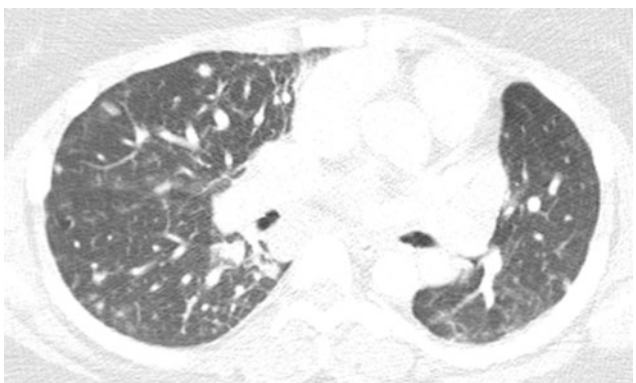

Fig. 11 Granulomatous lymphocytic-interstitial lung disease (GL-ILD). An axial chest CT image of a 21-year old with CVID shows multiple pulmonary nodules

by noncaseating granulomatous and lymphoproliferative histologic patterns. Findings on chest imaging can include pulmonary nodules, consolidation, and ground-glass or reticular opacities (Fig. 11). GLILD can precede the diagnosis of CVID and is associated with restrictive PFTs, a high prevalence of autoimmune disorders and decreased survival (Park and Levinson 2010).

4.1.4 Hyper-IgM Syndrome

Children affected by Hyper-IgM syndrome are identified by an elevated or normal IgM level and decreased IgG and IgA levels in serum. There is a normal number of circulating lymphocytes but a defect in signaling between T-cells and B-cells that prevents the switch from producing IgM to IgG or IgA. Most commonly, it is related to an X-linked

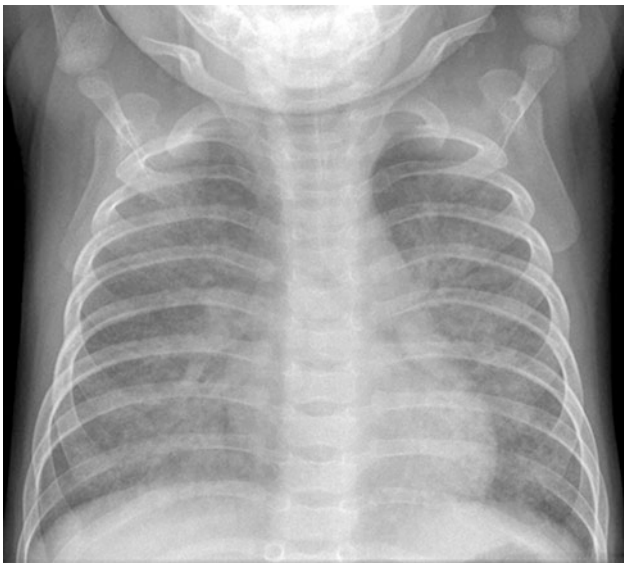

Fig. 12 X-linked hyper-IgM syndrome. A frontal CXR of a 6-year-old boy with tachypnea and hypoxemia due to *Pneumocystis jiroveci* pneumonia demonstrates diffuse bilateral nodular pulmonary opacities with central confluence of the opacities

mutation of the *CD40L* gene encoding a T-cell surface ligand. Presentation is similar to agammaglobulinemia, with recurrent respiratory and gastrointestinal tract infections by encapsulated bacteria, viruses, fungi and parasites. There is a particular susceptibility for *P. jirovecii* pneumonia (PCP) (Fig. 12). There is also a proclivity for Cryptosporidium-related diarrhea and sclerosing cholangitis, as well as an increased risk of hepatocellular carcinoma (Winkelstein et al. 2003).

4.2 Combined T-Cell and B-Cell Immunodeficiencies

T-cells function in the initial response to an antigen and in limiting the potentially harmful immune response. Because antibody production by B-cells is regulated by T-cells, T-cell immunodeficiencies may be accompanied by impaired antibody production. Children with combined T-cell and B-cell immunodeficiencies are susceptible to the same pathogens that afflict those with antibody deficiencies, as well as a variety of opportunistic infections including *Mycobacteria*, viruses, *Pneumocystis* and other fungi (Buckley 2004).

4.2.1 Severe Combined Immunodeficiency

Absence of both T-cell and B-cell function results in severe combined immunodeficiency (SCID), the most severe of the primary immunodeficiencies. A number of different genetic defects can cause SCID, including autosomal recessive and X-linked forms (Chan and Puck 2005). Most cases present between 2 and 6 months of age as protection from maternal antibodies wanes. Recurrent, persistent, severe or opportunistic respiratory infections beginning in early infancy along with thrush, dermatitis, chronic diarrhea or failure to thrive should raise suspicion of SCID. Without HSCT, gene therapy or enzyme replacement therapy, SICD is almost uniformly fatal in the first two years of life, making early diagnosis critical to prevent death from overwhelming infection (Griffith et al. 2009).

The primary role of radiology of the thorax in these children is to evaluate infections that are the main cause of mortality. While SCID patients have a diminutive thymus, physiologic thymic involution in response to stress in normal infants limits the use of this finding for suggesting a diagnosis of SCID (Manson et al. 2000) (Fig. 13). The adenosine deaminase (ADA)-deficient form of SCID is of particular note to radiologists because it is associated with a characteristic chondro-osseous dysplasia that manifests with costochondral junction cupping and splaying, concavity of the lateral margins of the vertebral transverse processes and medial margins of the posterior ribs, and thick growth arrest lines (Chakravarti et al. 1991) (Fig. 13).

4.2.2 Combined Immunodeficiency

While the susceptibility to infections may be similar to SCID, there is no lymphopenia in combined immunodeficiency (CID). Some forms of CID have distinctive clinical features. For example, signal transducer and activator of transcription 5B (STAT5b)-deficiency manifest with severe growth hormone-resistant growth failure beginning after birth, recurrent infection, dysmorphic features, atopic disease, autoimmune diatheses, and chronic lung disease beginning in infancy or childhood. The chronic lung disease is typically in the form of LIP (Fig. 14), and can lead to death from respiratory failure (Nadeau et al. 2011).

4.3 Well-defined Syndromes with Immunodeficiency

4.3.1 DiGeorge Syndrome

DiGeorge syndrome (DGS), also known as velocardiofacial syndrome, is a contiguous gene syndrome due to an inherited autosomal dominant or de novo chromosome 22q11.2 deletion. DGS is characterized by maldevelopment of the third and fourth pharyngeal pouches resulting in distinctive facial features (hypertelorism, saddle nose, short philtrum, low-set ears, cleft palate), conotruncal malformations (including tetralogy of Fallot, interrupted aortic arch, or truncus arteriosus), thymic hypoplasia (leading to immunodeficiency from T-cell lymphopenia and dysfunction) and parathyroid hypoplasia (leading to hypocalcemia from hypoparathyroidism) (Demczuk and Aurius 1995). Presentation in the

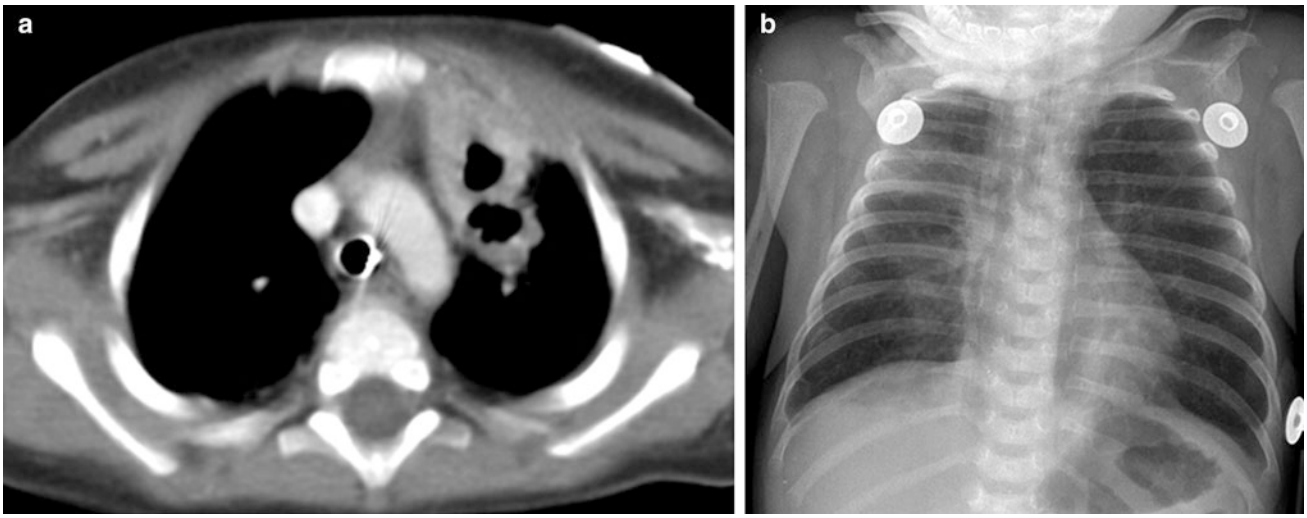

Fig. 13 Severe combined immunodeficiency (SCID). An axial contrast-enhanced chest CT image (**a**) in a 6-year old with SCID demonstrates a paucity of thymic tissue in the anterior mediastinum, along with cavitary lesions in the anterior left upper lobe related to *Nocardia* infection. A frontal CXR (**b**) in a 2-month old with adenosine deaminase (ADA)-deficient SCID shows cupping and splaying of the anterior rib costochondral junctions, a narrow superior mediastinum related to a diminutive thymus, and patchy bilateral pneumonia

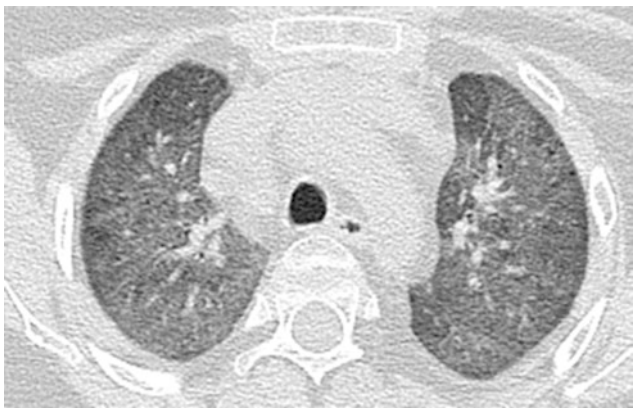

Fig. 14 Combined immunodeficiency (CID). An axial CT chest image from a 12-year old with *STAT5B* mutation-related CID and chronic respiratory symptoms depicts extensive bilateral ground-glass pulmonary opacities and scattered tiny cysts related to lymphocytic interstitial pneumonitis (LIP)

neonatal period is more often due to hypocalcemia-induced seizures than to immunodeficiency.

DGS may be partial or complete. Partial DGS is associated with mild defects in T-cell numbers and highly variable degrees of immunodeficiency. Patients with partial DGS may experience recurrent sinopulmonary infections. Complete DGS is a form of SCID and is associated with severe T-cell deficiency. Patients with complete DGS are susceptible to opportunistic infections and to graft-versus-host disease from nonirradiated blood products (Jawad et al. 2001).

Thoracic imaging findings of DGS may include an abnormal cardiac silhouette related to a conotruncal malformation, a narrow mediastinum related to a small thymus, and pneumonia (Fig. 15). Additional findings may include tracheobronchomalacia and anomalies of the ribs or vertebrae (Ryan et al. 1997).

4.3.2 Wiskott-Aldrich Syndrome

X-linked gene mutations resulting in aberrant structure of the Wiscott-Aldrich syndrome (WAS) protein are responsible for this immunodeficiency. In addition to a role in immune defense, the WAS protein functions in a pathway that protects against autoimmune disease (Notarangelo et al. 2008). Clinical manifestations of WAS include recurrent infections, eczema, elevated IgA, autoimmune disease (vasculitis, colitis, glomerulonephritis), malignancy (especially non-Hodgkin lymphoma associated with Ebstein-Barr virus), and thrombocytopenia with small platelets. Subtypes exist, with phenotypes ranging from mild intermittent thrombocytopenia to the complete syndrome (Massaad et al. 2013). The association of WAS with abnormal blood clotting that leads to bleeding in the first month of life is unique among the forms of PID. Pulmonary infections with encapsulated *Streptococcus pneumoniae* and *Pneumocystis* are common in affected children. Herpes virus infections also occur (Buckley 2004) (Fig. 16). The only curative treatment is HSCT or gene therapy (Aiuti et al. 2013).

4.3.3 Hyper-IgE syndrome

Hyper-IgE syndrome (HIES) is characterized by a reduction in CD4+ T-cells, eosinophilia and elevated IgE levels. The autosomal dominant form of HIES, also known as Job syndrome, is due to *STAT3* gene mutations (Heimall et al. 2010). Job syndrome is characterized by distinctive facial features

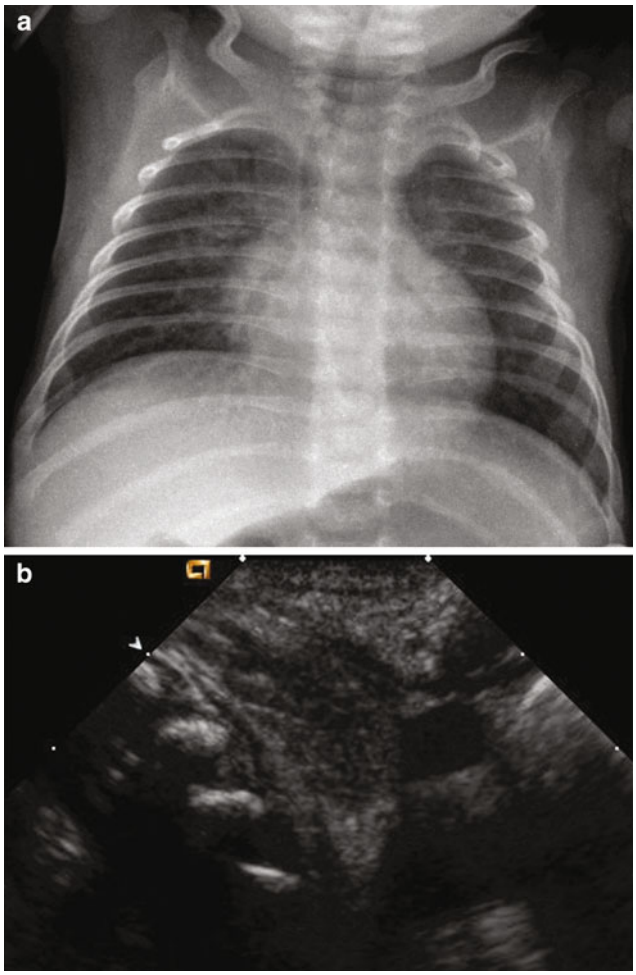

Fig. 15 DiGeorge syndrome (DGS). The thymic size is unable to be reliably assessed on the frontal CXR (**a**) of a 5-week-old boy with hypocalcemic seizures from parathyroid hypoplasia. A longitudinal chest US image (**b**) reveals a hypoplastic thymus

(broad nasal bridge, high palate, delayed shedding of primary teeth), eczematous dermatitis beginning in infancy, hyperextensible joints, osteoporosis, fractures, scoliosis, and recurrent *Staphylococcus aureus* and *Candida* infections. Skin infections often begin in infancy and can manifest as "cold" abscesses that lack classical symptoms and signs of inflammation. Sinopulmonary infections are common and can occur in patients who remain afebrile, likely due to the impaired inflammatory response. Thoracic findings include recurrent pneumonia, bronchiectasis, postinfectious pneumatoceles, lymphadenopathy, and esophagitis. Pathologic fractures incurred after mild trauma can mimic child abuse (Woellner et al. 2010; Chandesris et al. 2012) (Fig. 17).

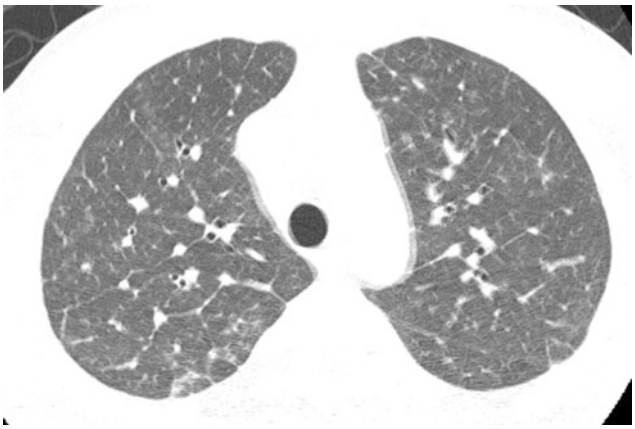

Fig. 16 Wiskott-Aldrich syndrome (WAS). An axial chest CT image from a 14-year old with a history of eczema and bloody diarrhea in infancy shows septal thickening related to herpes interstitial pneumonitis

4.3.4 Dyskeratosis Congenita

Dyskeratosis congenita (DKC) is a progressive multisystem disorder characterized by the clinical triad of nail dystrophy, lacy reticular skin pigmentation, and oral leukoplakia. Additional features may include developmental delay, short stature, cerebellar hypoplasia, esophageal stenosis, urethral stenosis, osteopenia, liver fibrosis, and pulmonary fibrosis. DKC is most often attributable to mutations in genes involved in telomere maintenance, and inheritance may follow an X-linked, autosomal dominant or autosomal recessive pattern. Patients with DKC are at very high risk of aplastic anemia, myelodysplastic syndrome, leukemia, and squamous cell carcinoma. The bone marrow failure does not respond to immunosuppressive therapy (Savage and Alter 2009). Pulmonary fibrosis is a serious complication and accounts for more than 15 % of deaths in DKC. The pulmonary fibrosis occurs earlier in DKC patients who undergo HSCT and is rapidly progressive with a median survival of less than 2 years after onset of pulmonary symptoms. The presenting features of DKC-related pulmonary fibrosis include persistent dry cough, progressive dyspnea, restrictive PFTs, markedly reduced D_{LCO}, and patchy or diffuse interstitial pulmonary opacities on CXR or CT (Giri et al. 2011) (Fig. 18).

4.3.5 Ataxia-Telangiectasia

Ataxia-telangiectasia (AT) is attributable to autosomal recessive mutations in the *ATM* gene that encodes a DNA damage response protein. Patients with AT have aberrant T-cells which results in onset of immunodeficiency in infancy. Cerebellar ataxia manifests at toddler age, and is

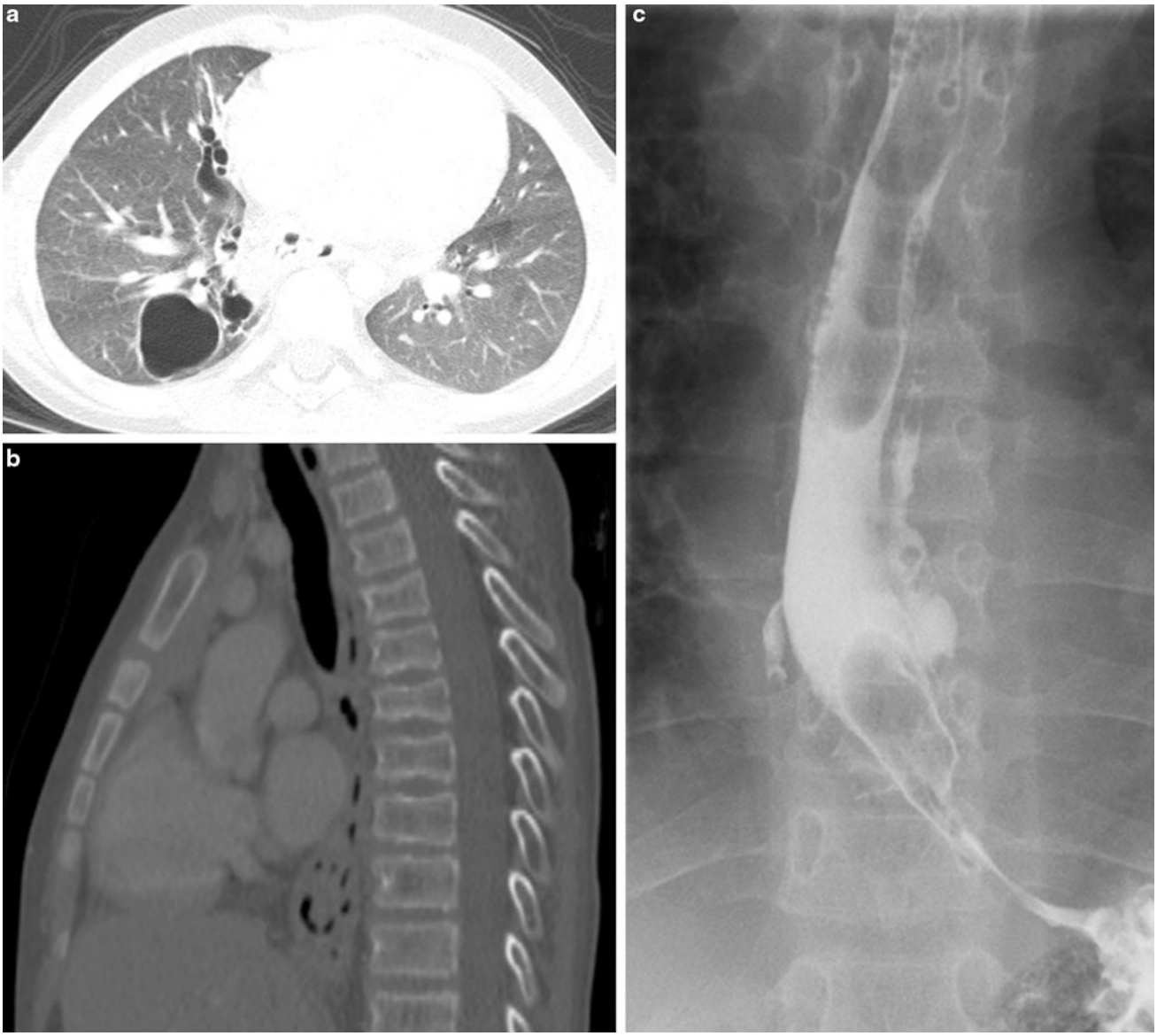

Fig. 17 Hyper-IgE syndrome (HIES). An axial chest CT image (**a**) from an 11-year old with HIES shows pneumatoceles in the right lung related to previous *Staphylococcus* infections. In the same patient, several thoracic vertebral body compression fracture deformities related to osteoporosis are revealed on a sagittal chest CT image reconstructed with bone windows (**b**). An esophagram (**c**) on the same patient demonstrates intramural tracking of contrast related to deep esophageal ulcers from *Candida* esophagitis

often misdiagnosed as cerebral palsy. Oculocutaneous telangiectasias begin to appear at 3–6 years of age, while growth retardation develops later in childhood. An elevated AFP is characteristic and AFP testing in children with persistent ataxia is advised to avoid diagnostic delay (Cabana et al. 1998). Recurrent sinopulmonary bacterial infections and noninfectious granulomatous inflammation of various tissues are typical. In children and adolescents with AT, *S. aureus*, *H. influenzae*, and *S. pneumoniae* are the predominant respiratory infectious agents, while opportunistic infections are not observed (Schroeder and Zielen 2013). There is extreme susceptibility to DNA damage from ionizing radiation and a high risk of cancer, especially lymphoma, leukemia, and leiomyosarcoma. Life expectancy is only 20–30 years due to the increased mortality from cancer and respiratory disease (Micol et al. 2011).

Thoracic imaging findings can include a small thymus, recurrent pneumonia, bronchiectasis, lymphadenopathy, and a chronic interstitial lung disease unique to ataxia-telangiectasia (AT-ILD). AT-ILD is characterized by lymphocytic infiltrate, bizarre atypical cells, and fibrosis resulting in interstitial and pleural thickening, restrictive PFTs, chronic cough, fever, dyspnea, and an inability to

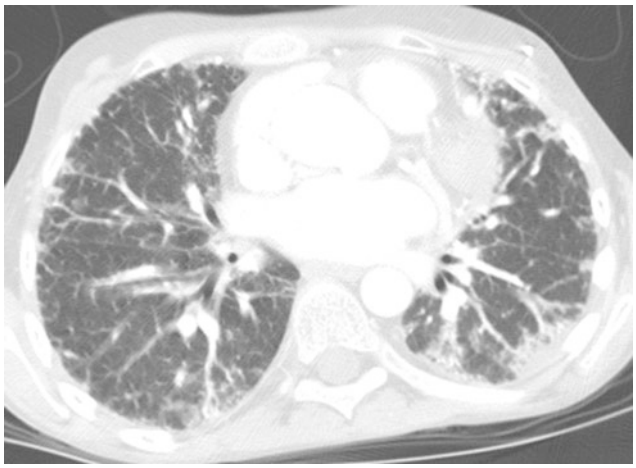

Fig. 18 Dyskeratosis congenita (DKC). An axial chest CT image of a 12-year old shows diffuse bilateral linear and patchy pulmonary opacities, predominantly in a subpleural distribution, representing DKC-related pulmonary fibrosis

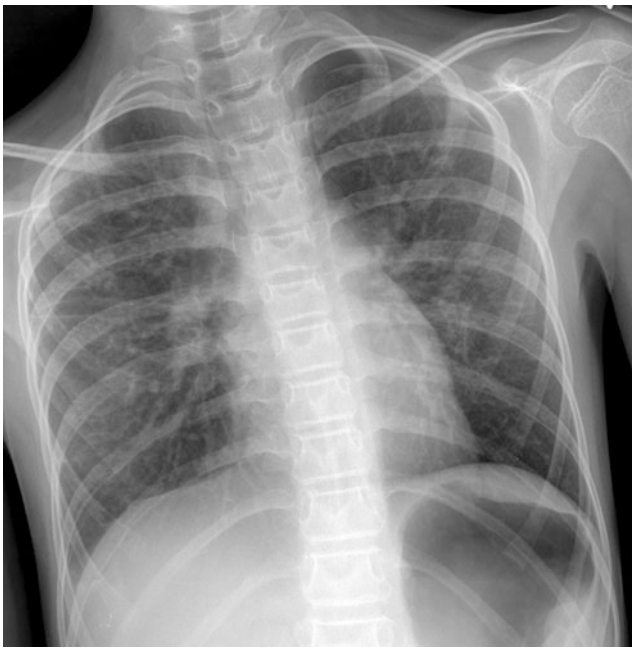

Fig. 19 Ataxia-telangiectasia (AT). A frontal CXR in a 13-year old with AT and worsening dyspnea demonstrates subtle interstitial opacities, predominantly in the mid and upper lungs, and a small left pneumothorax. These findings are manifestations of a unique interstitial lung disease (AT-ILD) associated with progressive clinical deterioration and high mortality

reinflate the lung after pneumothorax (Fig. 19). AT-ILD has a mean age of onset of 17.5 years and a prevalence of at least 25 % in AT patients (Schroeder et al. 2005). Progressive clinical deterioration and death usually ensue within 2 years of diagnosis of AT-ILD, unless steroid therapy is initiated within the first year of onset (McGrath-Morrow et al. 2010).

4.4 Congenital Defects of Phagocyte Number and/or Function

Congenital defects of phagocyte number and/or function manifest with variable susceptibility to infection and exist in neutropenic and nonneutropenic forms. The neutropenic forms can be nonsyndromic or syndromic, as in the case of Shwachman-Diamond syndrome (pancytopenia, exocrine pancreatic insufficiency, and chondrodysplasia). Nonneutropenic forms are subdivided according to the results of a dihydrorhodamine (DHR) assay. A normal DHR assay is seen in pulmonary alveolar proteinosis from alveolar macrophage dysfunction due to *CSF2*-receptor-alpha (*GM-CSF*-receptor-alpha) gene defects, and in Mendelian susceptibility to mycobacteria disease (MSMD) from an abnormal IL12-IFNgamma axis due to *IFNGR1* gene defects. An abnormal DHR assay is seen in chronic granulomatous disease (CGD) (Bousfiha et al. 2013).

4.4.1 Chronic Granulomatous Disease

Due to a defect in the nicotinamide adenine dinucleotide phosphate-oxidase (NAPDH) complex, the phagocytes in children with chronic granulomatous disease (CGD) are unable to generate the superoxide burst necessary for killing ingested micro-organisms. CGD occurs in both X-linked and autosomal recessive forms, with the former being more common and severe.

Symptoms or signs of CGD often develop in the first 2 years of life. Presentation and ongoing complications are related to granuloma and abscess formation. These manifestations are likely due to ongoing inflammatory response to viable microorganisms. Histopathologic studies have shown that the granulomas in these patients may contain relatively few organisms and that the predominant portion of the granulomas results from the exuberant inflammatory response (Moskaluk et al. 1994).

Catalase-positive *S. aureus* is the most commonly cultured organism in the granulomas. *Burkholderia* and *Serratia* are also frequently isolated, while *Streptococcus* is relatively rare. Fungi and atypical mycobacteria are other causes of infection. Children with CGD are at high risk for invasive aspergillosis, which is the most common cause of mortality (Tabone 2003).

The lungs are the most common site of involvement, with pneumonia occurring in 80 % of patients (Mahdaviani et al. 2013). Lung findings on CT vary depending on the infectious organism and disease chronicity, and may include consolidation, ground-glass opacities, centrilobular opacities, nodules, bronchiectasis, septal thickening, cysts, and parenchymal distortion (Towbin and Chaves 2010). Chronic

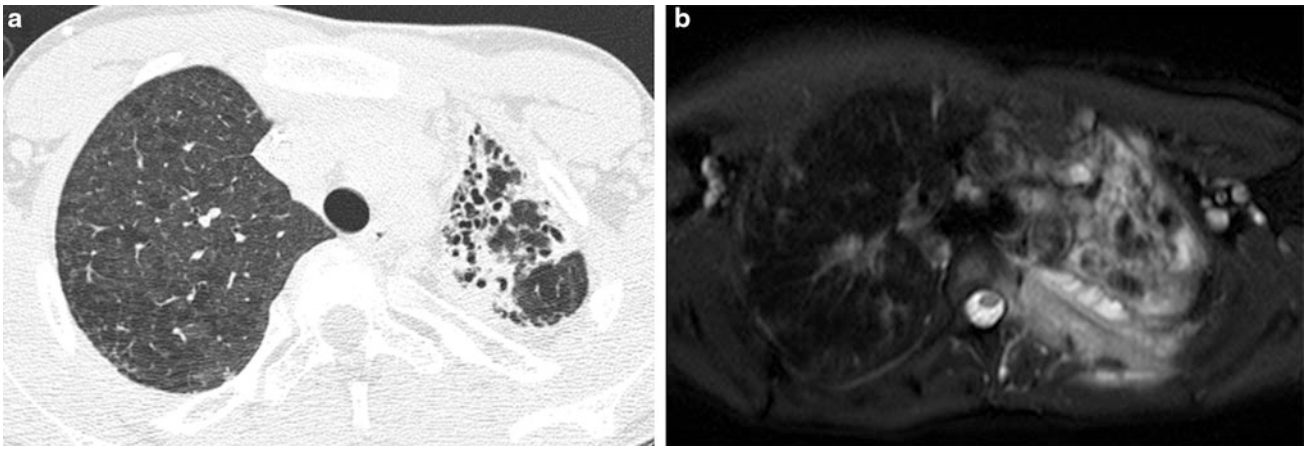

Fig. 20 Chronic granulomatous disease (CGD). An axial chest CT image (**a**) from a 13-year old shows left lung volume loss and traction bronchiectasis from fibrosis related to CGD. An axial T2-weighted fat saturated chest MR image (**b**) in the same patient at 19 years of age reveals involvement of the left pleura, ribs, and chest wall soft tissues by invasive *Aspergillus*

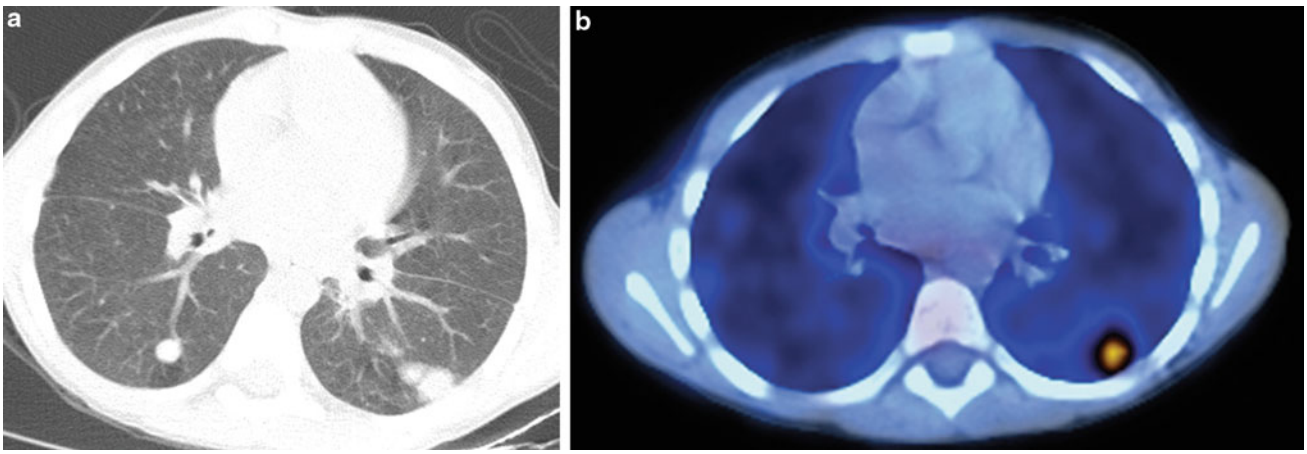

Fig. 21 Chronic granulomatous disease (CGD). An axial chest CT image (**a**) in a 6-year old undergoing evaluation for bone marrow transplantation for CGD shows multiple bilateral pulmonary nodules. An axial fused FDG–PET/CT image (**b**) reveals increased FDG uptake within only one of the nodules located in the posterior left lung. Subsequent targeted biopsy of the nodule allowed identification of active fungal infection with *Cladophialophora bantiana* that was undiagnosed by other means

lung involvement may lead to pulmonary fibrosis, honeycombing, pulmonary hypertension, and development of systemic blood supply to areas of pulmonary infection (pseudo-sequestration) (Matsuzono et al. 1995). Extrapulmonary thoracic manifestations include suppurative lymphadenopathy, pleuritis, empyema, and rib or vertebral osteomyelitis (Khanna et al. 2005). Infections involving both the lungs and the chest wall are highly suggestive of the diagnosis of CGD (Fig. 20). Fluorodeoxyglucose-positron emission tomography (FDG–PET) is more reliable than CT for distinguishing active disease from quiescent disease or scarring (Fig. 21), an important distinction for evaluating therapy response, identifying sites for biopsy or surgical debridement, and planning for HSCT (Gungor et al. 2001) (Fig. 21).

4.5 Acquired Immunodeficiency

4.5.1 Acquired Immunodeficiency Syndrome

In the Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV (P^2C^2) Study from the 1990s, pulmonary infection was the most common cause of death, especially in infants and young children (Langston et al. 2001). Since then, there has been a marked decrease in opportunistic pulmonary infections and deaths related to acquired immunodeficiency syndrome (AIDS) in developed countries as a result of the implementation of highly active antiretroviral therapy (HAART) (Gona et al. 2006). Even in developed countries, though, vigilance for opportunistic infections remains important due to noncompliance and drug resistance.

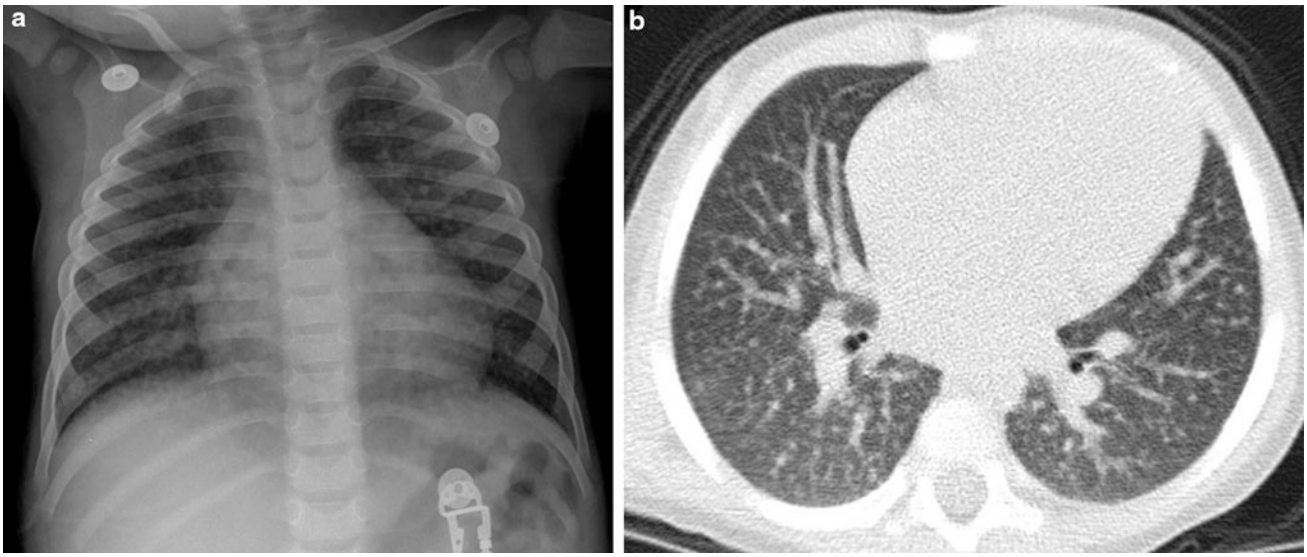

Fig. 22 Lymphocytic interstitial pneumonitis (LIP). A frontal CXR (**a**) in a 16-month-old HIV+ patient shows numerous tiny pulmonary nodules. No infectious pathogen was identified, and the nodules persisted for several months, as demonstrated on a chest CT (**b**) obtained at 21 months of age

Although HAART has reduced rates of opportunistic infection, bacterial pneumonia still tends to be more severe in HIV-infected children than in HIV-uninfected children related to a higher incidence of abscess and empyema. *Streptococcus* is the most common pathogen, and manifests as lobar or multilobar patchy consolidation. Mycobacterial infection is more likely to be multilobar or miliary, and is associated with necrotic lymphadenopathy. Pneumonias from respiratory syncytial virus (RSV), cytomegalovirus (CMV), parainfluenza, influenza, adenovirus, or human metapneumovirus infections have diverse radiographic appearances that can be indistinguishable from bacterial pneumonias. A patient age of less than 6 months, a respiratory rate >59 breaths/minute, an O_2 saturation <93 %, and an absence of vomiting are clinical features that suggest *P. jirovecii* pneumonia (PCP), which classically manifests with bilateral diffuse or patchy ground-glass or reticulonodular opacities with perihilar to peripheral progression, although this appearance overlaps with mycobacterial and viral pneumonia. PCP can also be associated with pulmonary cysts that rupture, leading to pneumothorax or pneumomediastinum (George et al. 2009).

Lymphocytic interstitial pneumonitis (LIP) is a form of pulmonary lymphoid hyperplasia characterized by infiltration of the interstitium by lymphocytes and plasma cells and classically presenting in HIV-infected children older than 2 years of age with chronic or recurrent cough and mild hypoxemia (Theron et al. 2009). The 1987 CDC criteria for a presumptive diagnosis stipulate the persistence of diffuse, symmetrical, reticulonodular or nodular pulmonary opacities for at least 2 months without an identifiable pathogen, or a response to antibiotic therapy (Pitcher et al. 2010). CT reveals nodules in a subpleural, septal, centrilobular, or peribronchial distribution, and ground-glass opacities with or without lymphadenopathy (Becciolini et al. 2001) (Fig. 22). Bronchiectasis and cystic dilated air spaces have also been described (Pitcher et al. 2010). Resolution of LIP in children can be due to response to HAART or corticosteroid therapy, or to immunologic deterioration and progression of HIV disease (Theron et al. 2009).

The immune reconstitution inflammatory syndrome (IRIS) is an exaggerated inflammatory response by the reconstituted immune system occurring 1–6 months after HAART initiation, resulting in apparent clinical worsening. "Unmasking" IRIS occurs in response to a previously unrecognized underlying infection, while "paradoxical" IRIS occurs in response to a previously treated infection. IRIS is most frequently observed in response to mycobacterial, herpes virus, JC virus, PCP, and cryptococcal infections, and can appear as new or worsening lymphadenopathy, pulmonary nodules, or pulmonary consolidation on imaging. IRIS must be distinguished from noncompliance, drug resistance, or newly acquired opportunistic infection, and is treated by NSAIDs, steroids, and discontinuation of HAART (Theron et al. 2009).

A high incidence of swallowing dysfunction and gastroesophageal reflux predisposes to aspiration pneumonia in HIV-infected children. These children may also suffer from odynophagia and dysphagia related to esophagitis caused by Candida or CMV infection. HIV-related cardiomyopathy, antiviral therapy cardiotoxicity, accelerated atherosclerosis and chronic anemia can lead to cardiac failure and

pulmonary edema that is misattributed to primary pulmonary infection (Pitcher et al. 2009). In addition, HIV infection is associated with an increased risk of thymic cysts and non-Hodgkin lymphoma, which are covered in the chapter entitled Imaging of the Pediatric Thymus and Thymic Disorders by Sams and Voss, as well as smooth muscle tumors, which are covered in the chapter entitled Pulmonary and Extra-Thymic Mediastinal Tumors by Lyons, Guillerman and McHugh.

4.5.2 Acquired Neutropenia and Invasive Fungal Disease

Neutropenia is common in children undergoing chemotherapy for cancer or allogeneic HSCT, and confers a high risk of invasive fungal disease (IFD) by mold (most frequently *Aspergillus*) or yeast (most frequently *Candida*). The lungs are the most common site of deep organ involvement by IFD. In a neutropenic patient with fever or respiratory symptoms or signs, the traditional approach has been to obtain a CXR, give early empiric broad-spectrum antibacterials, and add empiric antifungals for suspected invasive fungal disease (IFD) if the fever or respiratory symptoms or signs persist >96 h. In the presence of a deficient immune response, findings of infection are often absent or subtle and nonspecific on CXR, so that chest CT is preferred. However, even the yield of chest CT is low in this setting. In a study of 52 pediatric oncology patients with persistent febrile neutropenia, only 18 % of the initial (mean of 5 days of febrile neutropenia) CT scans were positive, and alterations in therapy were made in only 3 % based on the findings of initial CT. Repeat (mean of 17 days of febrile neutropenia) CT had a much higher yield, being positive in 52 % of cases and directing a change in therapy in 20 %. Respiratory symptoms or signs were present in only a minority of cases with a positive chest CT, while all patients with a concern for occult IFD had findings on chest CT, suggesting that initial chest CT should be limited to patients without localized signs or symptoms (Agrawal et al. 2011).

Rather than administering empiric antifungals in all patients at risk with persistent febrile neutropenia, a "preemptive" or "diagnostic-driven" approach of administering antifungals only in the setting of either microbiologic (cytology, direct microscopy, culture, ß-D-glucan or galactomannan assay of serum, or bronchoalveolar lavage fluid) or chest CT evidence of probable IFD may reduce unnecessary therapy without compromising prognosis (Castagnola et al. 2014). The European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC-MSG) chest CT criteria for probable IFD are the presence of well-circumscribed pulmonary lesions (with or without a "halo" sign), an "air-crescent" sign, or a cavity in the appropriate clinical setting (De Pauw et al. 2008).

The "halo" sign consists of a ground-glass halo of alveolar hemorrhage around a nodular or consolidative focus of infarcting lung from fungal vascular invasion and thrombosis that occurs early in IFD. A "reversed halo" sign of focal ground-glass opacity surrounded by a crescent or ring of consolidation may also be observed with early IFD (Georgiadou et al. 2011). An "air-crescent" sign or cavitation is the result of neutrophil recovery with release of proteases that resorb necrotic tissue (McAdams et al. 1995). In the course of IFD, a "halo" sign, nodule, or consolidation is typically visible on chest CT within 5 days of fever onset (Fig. 7). Early initiation of antifungals based on detection of the "halo" sign on chest CT is associated with better response to treatment and improved survival (Greene et al. 2007). Despite effective antifungal therapy, an increase in lesion number and size may be observed for 7–10 days followed by a plateau for a few days, and should not be confused for progressive disease. The "air-crescent" sign and cavitation develop in 2–3 weeks, dependent on the timing of neutrophil recovery (Caillot et al. 2001) (Fig. 7). Refractory IFD is suggested by no decrease in lesion number or size or by lack of development of an "air-crescent" sign or cavitation after 2–3 weeks, but initial or maximal lesion size or number does not impact outcome (Horger et al. 2005). After 2–3 weeks, reappearance of a "halo" sign, development of new lesions, or an increase in wall thickness of a cavitary lesion suggests relapsed or new infection (Fig. 7). Even after clinical remission, there may be fibrotic or thin-walled cavitary remnants visible on chest imaging (Gefter et al. 1985).

The chest imaging findings of IFD are not entirely specific and can also be observed in immunocompromised children with *Myobacterium*, *Nocardia*, *Pseudomonas*, or herpes virus infections (Gasparetto et al. 2008). Following allogeneic HSCT, children are susceptible not only to opportunistic pulmonary infections, but also to noninfectious pulmonary disorders such as alveolar hemorrhage, pulmonary edema, drug reaction, lymphoproliferative disease, organizing pneumonia, bronchiolitis obliterans, graft-versus-host disease, and idiopathic pneumonia syndrome. These disorders can cause considerable morbidity and mortality in the post-transplant setting, and can be difficult to distinguish on the basis of imaging findings, so that correlation with clinical features, identification of risk factors and institution of preventative measures are paramount in management (Sakaguchi et al. 2012).

5 Vasculitis

Vasculitis is an inflammatory disease of the blood vessel walls. Apart from invasive aspergillosis, infectious vasculitis is uncommon in childhood. Environmental, autoimmune

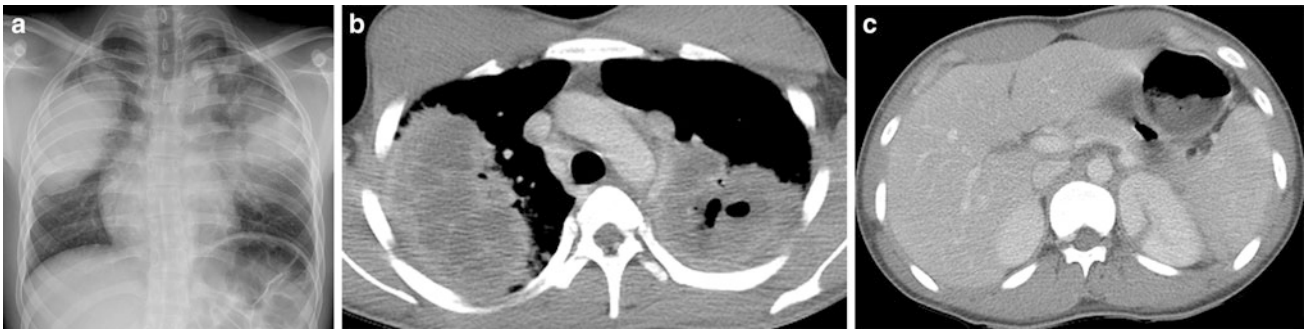

Fig. 23 Granulomatosis with polyangiitis (GPA). A frontal CXR (**a**) of a 17-year-old male with hemoptysis, hematuria and elevated anti-PR3 antibodies depicts large mass-like opacities of the mid to upper lungs bilaterally. An axial contrast-enhanced chest CT image (**b**) demonstrates low-attenuation necrosis and cavitation within the pulmonary opacities. An axial contrast-enhanced abdominal CT image (**c**) reveals a wedge-shaped lesion of the posteromedial aspect of the left kidney related to renal vasculitis

and genetic factors play a role in the pathogenesis of non-infectious vasculitis. Vasculitis can be categorized according to the predominant size of the affected vessels. Takayasu arteritis, a large vessel vasculitis, and Kawasaki disease, a medium vessel vasculitis, are covered in the chapters entitled Pediatric Cardiac CT by Sena and Goo and Pediatric Cardiac MRI by Krishnamurthy and Chung. Small vessel vasculitis affecting the pediatric lungs may be associated with a systemic disease (such as SLE), an immune complex deposition disease (such as anti-glomerular basement membrane disease), or diseases with anti-neutrophil cytoplasmic antibodies (ANCA). ANCA-associated vasculitides are characterized by necrotizing inflammation of small vessels (i.e., capillaries, venules, arterioles, small arteries) and encompass overlapping syndromes, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) (Jennette et al. 2013). ANCA directed against proteinase 3 (PR3) are predominantly associated with GPA, and ANCA directed against myeloperoxidase (MPO) are mainly associated with MPA (Millet et al. 2013).

Pediatric vasculitis affecting the lungs is often associated with diffuse pulmonary hemorrhage. This must be distinguished from nonvasculitic causes of pulmonary hemorrhage in childhood, such as idiopathic pulmonary hemosiderosis, cystic fibrosis, coagulopathy, pulmonary venoocclusive disease, and pulmonary arteriovenous malformations (Susarla and Fan 2007).

5.1 Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly known as Wegener granulomatosis, is characterized by necrotizing vasculitis predominantly affecting small to medium vessels (i.e., capillaries, venules, arterioles, arteries, and veins), usually of the upper and lower respiratory tract. Necrotizing glomerulonephritis is also common. A limited form initially confined to the lungs may occur. In the acute phase, the predominant pattern of inflammation is purulent rather than granulomatous. In the chronic phase, granulomatous and nongranulomatous extravascular inflammation is common (Jennette et al. 2013). The most common finding at presentation on chest imaging is multiple pulmonary nodules and masses. The lesions may coalesce or cavitate over a period of several days or a few weeks (Fig. 23). Consolidation and ground-glass opacities may also be noted. The airways can be affected, manifesting as tracheobronchial wall thickening, bronchial stenosis or bronchiectasis (Castaner et al. 2010).

5.2 Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is characterized by necrotizing vasculitis predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). In distinction to GPA, granulomatous and extravascular inflammation is absent. Renal and lung involvement are common.

In pulmonary capillaritis, there is inflammatory disruption of the alveolar interstitial capillary network, resulting in pulmonary hemorrhage. Although most pediatric patients with pulmonary capillaritis have dyspnea and anemia on presentation, only a minority has hemoptysis, contributing to diagnostic delay (Fullmer et al. 2005). ANCA-associated pulmonary capillaritis is an underappreciated cause of pulmonary hemorrhage and likely accounts for a substantial proportion of pulmonary hemorrhage cases attributed to idiopathic pulmonary hemosiderosis (Taytard et al. 2013).

Acute hemorrhage into the pulmonary airspaces produces ill-defined pulmonary nodules, ground-glass opacities and consolidation on CT (Fig. 24). Aggregates of hemosiderin-laden macrophages from repetitive hemorrhage result in septal thickening and crazy-paving. Parenchymal and subpleural cysts and architectural distortion may be

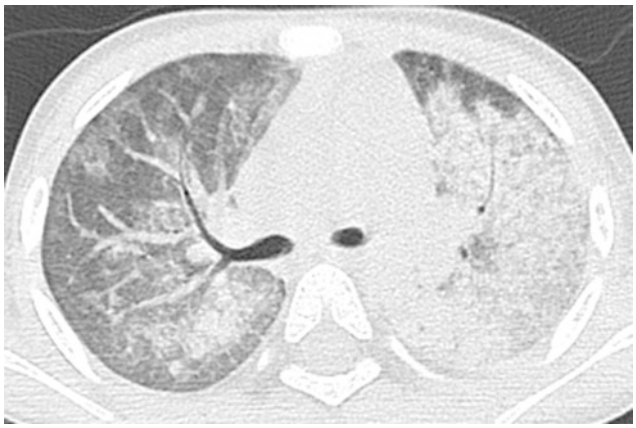

Fig. 24 Microscopic polyangiitis (MPA). An axial chest CT image of a 2-year-old girl with anemia, hypoxemia and elevated anti-MPO antibodies show patchy ground-glass opacities of the right lung and consolidative opacities of the left lung. These findings represent alveolar hemorrhage related to pulmonary capillaritis

observed on CT in the chronic setting (Connolly et al. 1996; Ravenel and McAdams 2003).

The finding of ill-defined centrilobular opacities suggest angiocentric inflammation and hemorrhage from small vessel pulmonary vasculitis, but it is not possible to reliably differentiate capillaritis from other causes of diffuse pulmonary hemorrhage on the basis of the imaging features, and lung biopsy is often required for differentiation (Guillerman and Brody 2011). Definitive diagnosis is crucial because successful treatment of pulmonary capillaritis typically requires aggressive and prolonged immunosuppressant therapy. CT can be used to help assess response to therapy (Vece and Fan 2010).

6 Sickle Cell Disease

The sickle hemoglobinopathies are autosomal recessive genetic disorders that include the presence of hemoglobin (Hgb) S within red blood cells. A substitution of valine for glutamic acid in the hemoglobin beta chain changes the structure of hemoglobin, allowing the hemoglobin to crystallize under conditions of low oxygen, dehydration, and acidosis. When the hemoglobin crystallizes, the red blood cell becomes less flexible and assumes the namesake sickle shape. These sickle cells have a decreased life span related to hemolysis and resulting in anemia. These nondeformable cells often obstruct small capillaries where slow flow promotes the conditions that encourage further sickling in a cascade effect.

Homozygous Hgb SS produces the most severe disease. Different mutations are associated with different amounts of hemoglobin F, with higher levels of Hgb F being associated with decreased disease severity. Compound heterozygous conditions occupy a spectrum of disease severity depending on the non-S hemoglobin. The most common are hemoglobin S with hemoglobin C (Hgb SC) and hemoglobin S with β^0 or β^+ thalassemia. Hgb Sβ^0 thalassemia is similar to Hgb SS, while Hgb Sβ^+ thalassemia and Hgb SC disease will often have preserved splenic function and less risk of vaso-occlusive crisis and infection. Heterozygous hemoglobin S and hemoglobin A is the asymptomatic carrier state.

Infants with sickle cell disease usually show no abnormalities, and clinical signs and symptoms develop as fetal hemoglobin is replaced by defective adult-type hemoglobin. Hand-foot syndrome, a painful swelling of the hands and feet, may be an early presentation, in which case soft tissue swelling and periosteal new bone formation are seen radiographically (Babhulkar et al. 1995). Anemia and painful crises in other locations then develop. Decreased splenic function causes an increased susceptibility to infection.

The most common cardiovascular imaging findings in children with sickle cell disease are mild cardiomegaly and pulmonary vascular plethora related to chronic anemia. Myocardial perfusion abnormalities in children have been reported (Acar et al. 2000). Bone infarctions are common. CXR may demonstrate biconcave vertebral bodies from impression of the intervertebral discs on the adjacent endplates weakened by microinfarcts.

Lung function can be abnormal from an early age. Evidence of obstructive and restrictive pulmonary disease has been shown on PFTs in infants and young children (Koumbourlis et al. 1997; Arteta et al. 2013). It is increasingly recognized that long-term adverse changes in lung function are a major cause of morbidity and mortality, even in the absence of episodes of acute lung disease (Koumbourlis 2013). Airway hyperreactivity, which is more common in individuals with sickle cell disease, is associated with obstructive physiology (Mekontso Dessap et al. 2013) and may be an additional factor in the development of both acute and chronic lung disease (Leong et al. 1997).

The two most common acute chest complications of sickle cell disease are pneumonia and the acute chest syndrome (ACS). Functional asplenia can occur as young as 6 months of age. Children are then particularly susceptible to infections caused by bacteria with polysaccharide capsules. While *S. pneumoniae* sepsis was once a common cause of death in young children with sickle cell disease, mortality has decreased dramatically in recent years related to the effectiveness of newborn screening, prophylactic penicillin, and vaccination measures (Hamideh and Alvarez 2013).

The acute chest syndrome (ACS) is a major cause of morbidity and mortality in sickle cell disease. ACS a largely descriptive term applied to the clinical situation in which a

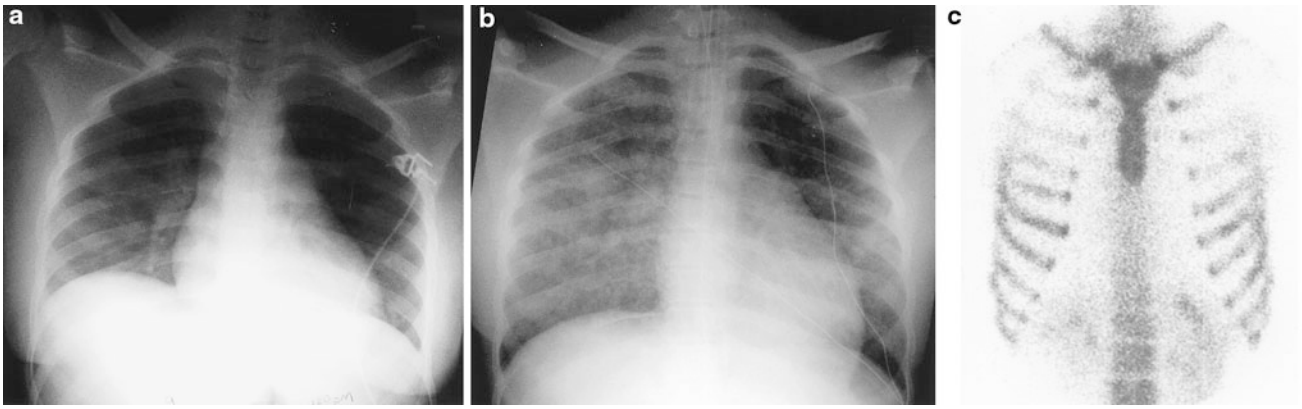

Fig. 25 Acute chest syndrome. A frontal CXR (**a**) of a 17-year old with sickle cell/β thalassemia with acute chest pain demonstrates confluent opacity in the left lower lobe and a less well-defined opacity at the right lung base. A frontal CXR (**b**) obtained 2 days later for increasing hypoxemia shows diffuse, ill-defined opacities of both lungs. A planar image of the chest from a technetium-99 m methylene diphosphonate bone scan (**c**) shows increased uptake in multiple ribs representing rib infarcts

patient with sickle cell disease develops a new infiltrate on CXR accompanied by chest pain, fever, and respiratory symptom (Fig. 25). ACS has been reported to account for 30 % of deaths in sickle cell patients under 10 years of age (Martin and Buonomo 1997), but the absolute mortality has decreased in the modern era of hydroxyurea therapy and early aggressive transfusion therapy. In a prospective study of 538 patients admitted for ACS, overall mortality was 3 % (Vichinsky et al. 2000). In adults, ACS-associated mortality is now primarily related to underlying pulmonary hypertension and acute cor pulmonale (Miller and Gladwin 2012). A specific cause can be identified in ACS in 40–70 % of cases. Etiologies include infection, pulmonary infarction, and fat embolism from vasoocclusive crises involving bone marrow (Vichinsky et al. 2000). Rib infarctions have also been identified in ACS (Gelfand et al. 1993) (Fig. 25). Asthma is associated with an increased risk of ACS in children (Boyd et al. 2006), and episodes of ACS predispose children to increased airway resistance (Sylvester et al. 2006). Repetitive episodes of ACS also lead to lung fibrosis, predominantly at the lung bases, contributing to chronic restrictive lung disease (Miller and Gladwin 2012).

By definition, infiltrates of ACS must occupy at least one complete bronchopulmonary segment on CXR without evidence of volume loss. The appearance of the infiltrates alone is not helpful in suggesting an etiology. Longitudinal evaluation may be of benefit. A lack of infiltrate resolution is associated with the presence of an infectious etiology and longer clinical course (Martin and Buonomo 1997). The presence of infiltrates in four or more lobes on the admission CXR is associated with an incidence of complications nine times that of involvement in one lobe (Vichinsky et al. 2000). Increasing infiltrates over the first days of hospitalization are also associated with an increase in complications and prolonged hospitalization.

A study of CT and bedside chest radiographs in 118 adult patients with ACS found that the sensitivity of CXR for consolidation on CT was high, but specificity was low. More than half demonstrated partial, rather than complete opacification of a segment. Presentation and course were more severe in patients with complete opacification. Consolidation was more common than atelectasis or ground glass opacity, and involvement was greatest in the lung bases, decreasing to the apices (Mekontso Dessap et al. 2013). In a 1993 CT study, Bhalla et al. found evidence of decreased peripheral pulmonary vessels in children with ACS (Bhalla et al. 1993). This decrease was not seen in children without sickle cell disease whose CT scans were used as controls. These findings suggest that there is a component of small vessel occlusion in these children.

7 Cystic Fibrosis

Within the first few months of postnatal life, the presence of airway inflammation and infection can be identified histologically in children with cystic fibrosis (CF) (Khan et al. 1995). Bronchiectasis is noted in two-thirds of children and air trapping in one-half of children with CF by the age of 5 years (Stick et al. 2009) (Fig. 26). As CF-related lung disease progresses, there is further bronchial dilation and mucous plugging, which become the distinctive features of CF-related lung disease (Fig. 27). Approximately 95 % of people with CF die of respiratory complications. The relative lack of lung disease at birth presents the opportunity to

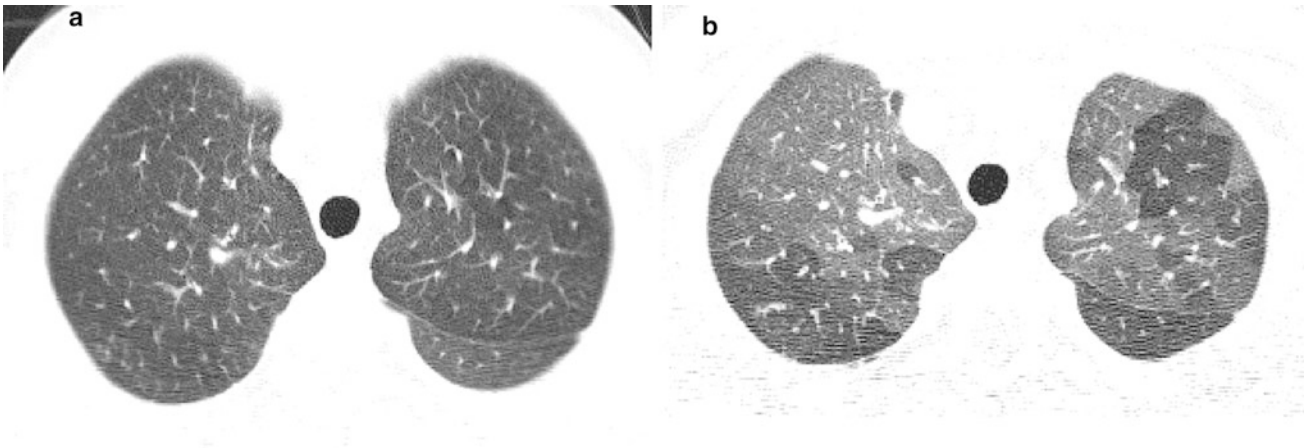

Fig. 26 Cystic fibrosis (CF). An axial chest CT image acquired at deep inspiration (**a**) in a 12-year old demonstrates no bronchiectasis and only subtle heterogeneity of lung parenchymal attenuation. A chest CT image acquired at end-expiration at the same axial level (**b**) reveals mosaic attenuation of the lungs bilaterally due to air trapping from CF-related lung disease

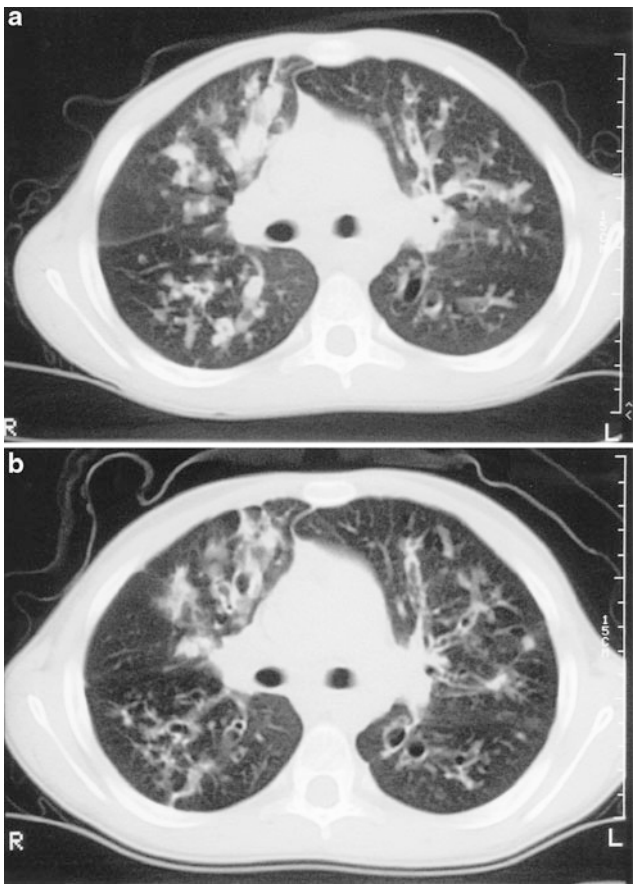

Fig. 27 Cystic fibrosis (CF). An axial chest CT image (**a**) from an 11-year-old boy with CF shows bronchiectasis, bronchial wall thickening, and multiple sites of endobronchial mucous plugging. An axial chest CT image (**b**) obtained after several months of daily therapy with human recombinant DNase shows clearing of mucous plugs from many of the ectatic bronchi

eliminate these respiratory complications if a treatment can be found. However, any treatment would need to be effective in early infancy to avoid structural lung disease. Even without a cure as yet, the history of CF is one of dramatic advances. This progress is reflected in the fact that the best predictor of life expectancy in CF is the patient's year of birth, and that the rate of improvement of life expectancy in CF patients exceeds that of the general population (Hurley et al. 2014).

Children with CF are a more heterogeneous group than originally described. Pulmonary disease and pancreatic disease are the primary abnormalities in CF, although in 15 % of patients pancreatic function is adequate. The severity of lung disease in CF is also more variable than often appreciated. In patients with homozygous ΔF508 mutations, disease ranges from the development of bronchiectasis in the first few years of life to a 20-year-old patient with normal PFTs and a normal CXR. Complete bilateral absence of the vas deferens is the mildest expression of the CF spectrum. Genotype predicts phenotype in pancreatic sufficiency, but not the severity or pattern of respiratory disease (Rowntree and Harris 2003).

7.1 Genetics

CF is an autosomal recessive disease that affects approximately 1 in 4,000 live births in the United States. CF occurs most commonly in Caucasians, in whom the incidence is 1 in 2,500 live births, with progressively lower frequency in black, Hispanic, and Asian populations. The gene for CF is located on the long arm of chromosome 7 and encodes the CF transmembrane conductance regulator (CFTR). CFTR is

a single chain protein that forms a membrane-bound regulated chloride channel activated by cyclic adenosine monophosphate (cAMP). CFTR functions primarily at the apical cell membrane where it regulates fluid balance across the cell membrane with effects on both chloride and sodium. The most common mutation is a three base pair deletion that causes omission of phenylalanine at position 508 of the protein product. This ΔF508 mutation is present in almost 90 % of those with CF (CF Foundation 2011). Homozygous ΔF508 is responsible for about one-half of cases of CF (CF Foundation 2011). More than 1,000 additional mutations of the CF gene have been identified.

7.2 Diagnosis

In 1999, 7 % of children diagnosed with CF were identified by neonatal screening (CF Foundation 2000). This has risen to almost 60 % in 2011 (CF Foundation 2011). Newborn screening for CF is now universal in many countries. Neonatal screening is most often performed by measuring the level of immunoreactive trypsinogen in a dried blood spot. Positive screening tests must be confirmed by further tests including meconium lactase, sweat chloride, or genotyping. A controlled trial of neonatal screening in Wisconsin has shown improved growth and nutritional status in children with CF identified by neonatal screening (Farrell et al. 2001). A study in Australia demonstrated improvement in both nutrition and pulmonary function in children identified by neonatal screening (Waters et al. 1999). Other studies have supported the economic benefit of a universal newborn screening program (Sims et al. 2007).

Of the children with CF, 70 % present within the first year, 80 % by the age of 4 years, and 90 % by the age of 12 years. The median age at diagnosis of patients with CF listed in the Cystic Fibrosis Patient Registry in 2004 was 6 months (CF Foundation 2004). In the first year, gastrointestinal findings are more common than respiratory disease. In North America, nearly all Caucasian infants with meconium ileus have CF. In 1999, 19 % of infants diagnosed with CF had meconium ileus (CF Foundation 2000). Gastrointestinal findings after the neonatal period and within the first year include malabsorption and failure to thrive. CF should be suspected in children with these symptoms without regard to the presence or absence of pulmonary disease.

After the first year, respiratory complaints increase, becoming the most common reason to suspect CF. Cystic fibrosis care continues to improve patient outcomes. In 1991, median FEV_1 at 13 years of age was 80 % of predicted. In 2011, median FEV_1 was 95 % of predicted at 13 years of age and did not decline to 80 % until 18 years of age (CF Foundation 2011). In the United States, for the cohort of individuals with CF born from 1985 to 1994 and surviving infancy, the median predicted life expectancy in years is in the lower 50s for males and lower 40s for females (Jackson et al. 2011).

One of the earliest recognized characteristics of a child with CF was the salty taste of the child's skin. Abnormal sweat chloride was reported in 1953 (Di Sant'Agnese et al. 1953). Sweat chloride determination remains the most common diagnostic test for CF. This test requires careful technique and should only be performed at centers with expertise in sweat chloride determination. Values greater than 60 mEq/ml are generally regarded as positive, 40–60 mEq/ml as indeterminate, and less than 40 mEq/ml as negative. Other methods of making the diagnosis include genotyping and neonatal screening.

Even in a screened population, cases of CF are still detected on clinical grounds. In this group, gastrointestinal symptoms remain more common at presentation than pulmonary symptoms. A sweat test should be requested when the clinical features suggest the diagnosis of CF, even if the child underwent a negative screening (Massie et al. 2000). Of nine children diagnosed with CF after negative neonatal screening in the study of Massie et al., eight presented with failure to thrive or steatorrhea, and one with respiratory symptoms.

7.3 Pulmonary Pathophysiology

Abnormal CFTR causes a change in the composition of the fluid lining the airways, which results in numerous alterations in the functioning of the airway epithelium. The mucous becomes abnormal, resulting in airway plugging and decreased mucociliary clearance. Abnormal mucus in CF likely results from both abnormal mucus produced by the mucous glands and the presence of degradation products from white blood cells. Deoxyribonucleic acid is a major component of the degradation products, and is a major contributor to the increased viscosity and tendency of the mucous to form long strands. Both infection and inflammation result in elaboration of proteolytic enzymes that damage the epithelium and the supporting structure of the airways.

Repeated infection and increased inflammatory response cause airway damage that makes the airways more susceptible to infection. Infection then increases in both frequency and severity, inciting greater inflammatory response. This vicious cycle results in progressive respiratory compromise. The hallmarks of CF lung disease are bronchiectasis and air trapping secondary to airway damage and obstruction by the tenacious mucus produced in CF.

Studies using CT to evaluate the onset of CF lung disease have shown that structural lung disease, particularly

bronchiectasis and air trapping, begin in infancy. In a cross-sectional study of infants diagnosed by newborn screening, bronchiectasis was seen by CT in 29 % of 3-month olds and in 62 % of 3-year olds (Sly et al. 2013). A longitudinal study comparing CT scans obtained in children with CF under 7 years of age demonstrated that bronchiectasis persisted once detected in 74 % and progressed in 63 % over a 1-year interval (Mott et al. 2012).

7.4 Lung Care

One of the most important factors improving longevity in CF patients in North America is the use of skilled care through a network of CF centers. Two important concepts of care are routine monitoring and early intervention. Pulmonary exacerbations are treated with aggressive pulmonary physiotherapy and parenteral antibiotics.

Regular pulmonary care in CF has traditionally been directed at the clearance of lower airway secretions and the treatment of infection. In the last decade, numerous new techniques have become available. In addition to manual external percussion, airway clearance techniques include airway oscillators and high frequency chest compression with an inflatable vest. The tenacity of secretions can be reduced by the administration of recombinant human deoxyribonuclease (DNase) which breaks up DNA strands (Fig. 27). Inhaled bronchodilators and hypertonic saline can also be administered. Inhaled antibiotics have been shown to improve pulmonary function in initial short term trials (Ramsey et al. 1999). Airway inflammation can also be directly treated. In a 4-year study, Konstan et al. showed that inhaled ibuprofen decreased the decline of pulmonary function in CF, an effect that was most marked in children (Konstan et al. 1995).

Systemically administered drugs such as oral and intravenous antibiotics are also an important part of CF care. Continued advances are leading to the development of new oral and intravenous therapies. In the last decade, high throughput screening has identified new compounds that can directly affect the defect caused by a specific CFTR mutation. The G551D mutation reduces the amount of time that CFTR is "open," allowing chloride to move from the cell to the airway surface liquid. Ivacaftor is a drug that increases this open time, partially restoring the normal function of the CFTR. A study of children 6–11 years of age treated with ivacaftor showed improvement in lung function by 2 weeks that was sustained over the 48 week study. In addition to pulmonary benefits, subjects taking ivacaftor gained 2.8 kg more weight on average than those taking placebo (Davies et al. 2013).

Despite advances in care, the lung disease in many patients progresses to respiratory insufficiency despite medical treatment. Lung transplantation is the treatment for end-stage CF lung disease. Both cadaveric transplantation and living donor lobe transplantation can be performed. Since 2001, more than 2,000 people with CF have undergone lung transplantation (CF Foundation 2011).

7.5 Imaging

The role of imaging in the care of children with CF is changing. Historically, care has been based on clinical evaluation, with CXR used to confirm clinical impressions and provide an indicator of overall disease severity. CXRs remain the most common imaging study performed in patients with CF. CF center directors report that CTs are frequently obtained, although little has been published on the use of CT in the routine care of patients with CF. Nuclear medicine studies of lung ventilation and perfusion and of aerosol deposition have been reported primarily as a research tool. FDG–PET scanning is currently under investigation as a means of evaluating the degree of inflammation in the CF lung. MRI is an alternative method to follow CF-related lung disease without the use of ionizing radiation.

7.5.1 Chest Radiography

CXRs obtained in the first year of life are usually normal. Abnormal CXRs will show changes typical of airways disease, with the appearance being the same as seen with viral or atypical bacterial infections. Features more characteristic of CF, including bronchiectasis and mucous plugging, are typically not seen on CXR in the first several years of life.

Scoring systems for the evaluation of lung disease on CXR include the Brasfield (Brasfield et al. 1979), Chrispin-Norman (Chrispin and Norman 1974) and NIH (Sockrider et al. 1994) scores. One CXR scoring system, the Wisconsin score, was specifically developed for use in young children with CF (Weatherly et al. 1993). Comparison between the different scoring systems shows similar results (Sawyer et al. 1994; Terheggen-Lagro et al. 2003). While these scores correlate with disease severity in older patients, they are insensitive when used in young children (Weatherly et al. 1993). Although early CXRs do not correlate well with clinical changes in young children with mild disease (Koscik et al. 2000), CXRs show a higher correlation with *Pseudomonas* acquisition than with PFTs (Kosorok et al. 2001).

In an adult study, Greene et al. (1994) found that CXRs obtained during an acute exacerbation could not be differentiated from CXRs obtained when the patients were clinically well. No pediatric study has been performed to evaluate the ability of CXRs to reflect changes due to short term treatment, but anecdotal experience suggests that this is very unlikely.

In longitudinal studies of multiple year duration, serial CXRs have been useful. Cleveland et al. developed a database of CXR scores over time to provide reference values for the progression of lung disease (Cleveland et al. 1998). Using this database, a decrease in the lung disease progression as monitored by Brasfield scores has been shown when children were treated with aerosolized tobramycin (Slattery et al. 2004). A study from the Wisconsin Randomized Control Trial of neonatal screening found that the CXR is a very sensitive means to detect the presence of lung disease as measured by CT scanning (Sanders et al. 2012). These investigators have used CXRs to assess risk factors for the development of CF-related lung disease (Sanders et al. 2014), and regional differences in the evolution of lung disease (Li et al. 2012).

7.5.2 CT

Currently, high-resolution CT is the most accurate means of evaluating the morphologic changes of CF lung disease. CT can detect and quantify the changes seen in children with CF, including bronchiectasis, peribronchial thickening, mucous plugging, parenchymal air trapping, and lung destruction.

In 1986, Jacobsen et al. compared CXR and CT in 12 adult patients with CF. The authors found that CT was more sensitive for the detection of bronchiectasis, mucous plugging, and hilar lymphadenopathy (Jacobsen et al. 1986). In 1991, Bhalla et al. described a scoring system for CT in CF (Bhalla et al. 1991). This scoring system evaluates the severity of bronchiectasis and peribronchial thickening, and the extent of bronchiectasis, mucous plugging, sacculations or abscesses, bullae, emphysema, and collapse or consolidation. The authors found again that CT was more sensitive than CXR in detecting abnormalities, and that the CT score correlated with the FEV1/FVC ratio. In the same year, Nathanson et al. published a scoring system for CF using electron beam CT in a pediatric population. This scoring system correlated well with PFT and clinical scores (Nathanson et al. 1991). A scoring system devised by Mafessanti et al. (1996) has been adopted and used by several authors.

More recent efforts have examined the ability of CT to evaluate the onset and progression of disease, and response to treatment. An adult study showed that the findings differed when CTs obtained during exacerbations were compared to those obtained when patients were at their baseline health. CT scores were higher during exacerbations. Air-fluid levels in ectatic bronchi during exacerbations resolved on follow-up scans. Centrilobular nodules and mucous plugging improved in about one-third of the cases (Shah et al. 1997).

In a pediatric study, the CT appearance was compared between admission and discharge for treatment of an acute pulmonary exacerbation (Brody et al. 1999). In this study, the CT appearance improved in 13 of 15 admissions. Peribronchial thickening, mucous plugging, and the overall appearance were all significantly improved on the discharge CT. A second study of 17 children also showed CT improvement following treatment for exacerbation (Robinson et al. 2001). A study that included patients aged between 2 and 32 years evaluated the change in CT appearance over time. The authors found that CT scores increased significantly when the interval between exams was more than 18 months, with no significant change over shorter intervals (Helbich et al. 1999). In a study of children with a mean age of 11 years, de Jong et al. found that CT scans showed progressive disease over 2 years despite stable PFT results (de Jong et al. 2004). CT scanning has been shown to be more sensitive than pulmonary function tests for the presence of lung disease. One study of children 6–10 years old found bronchiectasis in 30 % of children with normal PFTs (Brody et al. 2004). Changes on CT scanning have also been shown to correlate with the number of pulmonary exacerbations (Brody et al. 2005). A follow-up study showed that CT scores correlated with the severity of lung disease 10 years later, and that correlation was higher with CT scores than with PFTs (Sanders et al. 2011). At the time of writing, however, no studies have evaluated the impact of using CT as part of the routine clinical care of the children with CF.

7.5.3 Nuclear Medicine

The functional information provided by nuclear medicine imaging has been used to evaluate pulmonary ventilation/perfusion, aerosol deposition, and mucous clearance in patients with CF (Laube et al. 1992; Sirr et al. 1986). Regional pulmonary blood defined by perfusion scintigraphy has been shown to correlate with morphologic findings on CT (Donnelly et al. 1997). The relative sensitivities of the two modalities have not been determined.

FDG–PET scanning can detect and quantify inflammation in the lungs of CF patients. In a study of 28 adults and children with CF, FDG–PET/CT demonstrated multiple focal sites of increased FDG uptake that correlated poorly with the size of bronchiectasis, degree of peribronchial thickening, or location of structural abnormalities (Klein et al. 2009). Seven of these subjects were studied during and after a pulmonary exacerbation, and FDG uptake frequently decreased without a corresponding change in CT appearance. This and other studies suggest that FDG–PET/CT may have a role in the evaluation of interventions directed toward reducing inflammation. However, the quantitation of chronic inflammation has not been well studied, and the relatively high radiation dose of 5–7 mSv may limit the use of FDG–PET in children (Chen et al. 2006).

7.5.4 MRI

Initial attempts to use MRI to evaluate CF-related lung disease were disappointing. The relatively small number of protons in aerated lung and magnetic susceptibility artifacts from the air/soft tissue interfaces resulted in very little usable MR signal. One early study demonstrated the ability of MRI to detect hilar lymphadenopathy and bronchiectasis with mucous plugging (Fiel et al. 1987). A subsequent study in 1994 compared conventional axial CT to MRI and found that the limited resolution of MRI did not allow adequate evaluation of the gross features of CF-related lung disease (Carr et al. 1995).

Advances in MRI technology have dramatically improved the ability of MRI to demonstrate pulmonary parenchymal abnormalities. The spatial resolution of conventional proton MRI remains lower than that of CT, but MRI can now provide similar results in demonstrating bronchial wall thickening, mucous plugging, and infiltrates (Puderbach et al. 2007). Early findings of CF lung disease such as air trapping can now be identified on MRI. Currently, MRI is most limited in the detection of peripheral bronchiectasis without wall thickening (Failo et al. 2009). MRI is increasingly being advocated as a way to follow CF-related lung disease without the use of ionizing radiation. In support, a recent study showed a high correlation between MRI and CT scores for CF-related lung disease in children (Sileo et al. 2013b).

MRI using hyperpolarized helium provides very different capabilities. The high signal of the hyperpolarized gas allows single breath-hold evaluation of ventilation. Ventilated portions of the lung show high signal, and unventilated regions are seen as focal defects. The appearance is grossly similar to nuclear medicine ventilation scans, but with much higher resolution.

A preliminary report published in 1999 using hyperpolarized helium and conventional proton MRI in four patients with CF found extensive ventilation defects that were frequently much more striking than the associated morphologic abnormalities (Donnelly et al. 1999). The severity of lung disease shown by hyperpolarized helium MRI correlates with other measure of lung disease severity (van Beek et al. 2007). Other studies have demonstrated ventilation defects in CF patients with normal PFTs, and have shown that these defects improve with treatment (Mentore et al. 2005). A recent trial using hyperpolarized helium demonstrated dramatic improvement in ventilation defects following treatment with a CFTR corrector therapy in children with CF (Altes et al. 2011). This study provides the most convincing data to date on the value of imaging endpoints in CF research trials.

The limited availability of hyperpolarized helium has hampered more widespread adoption of hyperpolarized gas MRI. Hyperpolarized xenon is being studied as an alternative. Unlike helium, hyperpolarized xenon diffuses across the alveolar walls into the capillaries and allows additional physiologic measurements. The use of hyperpolarized gas MRI in CF and other pediatric pulmonary disorders is discussed more extensively in the chapter entitled Hyperpolarized Gas MRI in Pediatric Lung Disease by Komlosi, Benjamin and Altes. Several additional MR techniques, including phase-contrast (Fleck et al. 2013) and oxygen-enhanced imaging (Stadler et al. 2007), are being used to investigate the pathophysiology of CF-related lung disease.

8 Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a genetic disorder characterized by dysfunctional ciliary function resulting in impaired mucociliary clearance. Disease-causing mutations are most often autosomal recessive and may involve genes that encode axonemal motor proteins, regulatory proteins, or cytoplasmic proteins involved in ciliary assembly. To date, at least 19 different genes have been linked to PCD, but known PCD-causing mutations account for only about 60 % of PCD cases (Horani et al. 2013).

Cilia line the respiratory tract from the middle ear to the conducting bronchioles and play an important role in clearing amniotic fluid from the neonatal lungs. Neonatal respiratory distress occurs in up to 70–75 % of patients with PCD, although this is often misattributed to transient tachypnea of the newborn or neonatal pneumonia, and the diagnosis of PCD is frequently delayed until later childhood or even adulthood (Noone et al. 2004). Chronic or recurrent upper and lower respiratory tract infections begin in early childhood, most often caused by *H. influenzae*, *S. aureus*, or *S. pneumonia*, with *Pseudomonas aeruginosa* and nontuberculous *Mycobacteri*a appearing in older patients. This leads to bronchiectasis in a majority of affected children, most commonly of the right middle lobe, lingula and lower lobes, which contrasts with the upper lobe predominance of CF (Fig. 28). The extent and severity of bronchiectasis increase as age progresses. Antibiotics and physiotherapy to improve mucociliary clearance are the mainstays of therapy directed to halting the progression of bronchiectasis. In addition to bronchiectasis, other common pulmonary radiographic findings of PCD include mucus plugging, bronchial wall thickening, peribronchial consolidation, atelectasis and hyperinflation (Kennedy et al. 2007; Santamaria et al. 2008; Magnin et al. 2012).

Although both are chronic suppurative lung disorders, PCD typically shows milder lung damage on CT and a much better prognosis than CF, with many PCD patients living a near normal life span (Santamaria et al. 2008). As with CF, CT is superior to spirometry for detecting

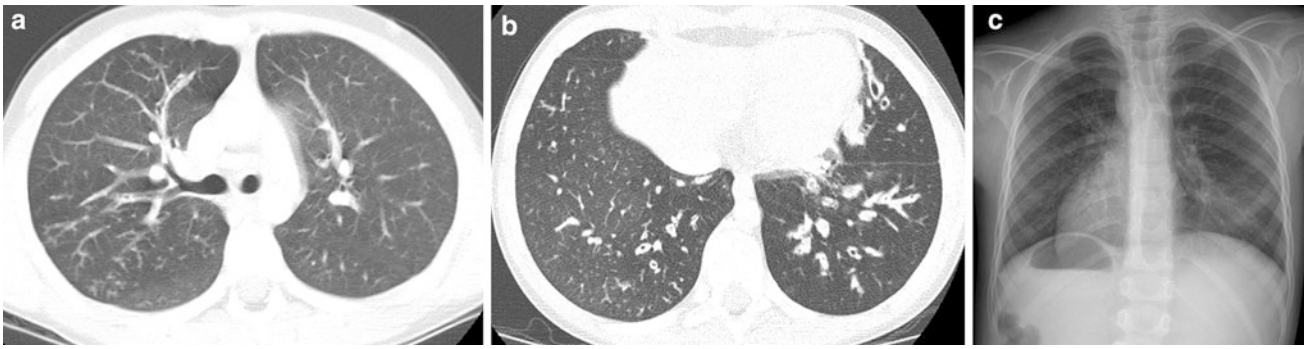

Fig. 28 Primary ciliary dyskinesia (PCD). Axial chest CT images (**a**, **b**) from a 10-year old with a history of chronic sinusitis show bronchiectasis and bronchial wall thickening that resembles CF-related lung disease, but the lower lobe and lingular predominance are more typical of PCD. A frontal CXR (**c**) in a 5-year old with a history of recurrent upper and lower respiratory tract infections related to PCD reveals situs inversus totalis and left middle lobe opacity

progression of PCD-related lung disease (Maglione et al. 2012). The degree of lung disease scored by CT in children with PCD significantly increases with age and correlates with declines in functional parameters noted on PFTs. To minimize the burden of ionizing radiation, clinicians could rely on spirometry to monitor disease progression in PCD patients with clinically stable disease, and reserve CT for suspected unstable disease (Magnin et al. 2012). As an alternative to CT, the extent and severity of lung disease in PCD may be scored comparably with MRI (Montella et al. 2009).

Situs inversus or heterotaxy occurs in approximately 50 % of PCD cases (Fig. 28), related to randomization of left-right axis asymmetry from embryonic nodal cilia dysfunction. The classic Kartagener syndrome consists of the combination of bronchiectasis, sinusitis, and situs inversus (Kartagener and Stucki 1962). Pectus excavatum develops in 5–10 % (Kennedy et al. 2007).

Recognition of clinical or imaging features suggestive of PCD should prompt confirmation of diagnosis. Nasal nitric oxide (nNO) measurement has been proposed as a screening test since low nNO is characteristic of PCD, but it is usually not technically feasible in infants or young children. Ultrastructural defects in the cilia detected by transmission electron microscopy were once considered the "gold standard" for diagnosis, but some PCD cases lack these defects and ciliary beat analysis or genetic testing is required for diagnosis (Boon et al. 2013).

9 Langerhan Cell Histiocytosis

Langerhan cell histiocytosis (LCH) is characterized by proliferation and infiltration of tissues by Langerhans cells. These cells are histiocytes identifiable by the presence of cytoplasmic Birbeck granules on electron microscopy or by CD-1a positivity on immunohistochemistry. Aggregates of these histiocytes form granulomas that may later be replaced by fibrosis and cysts. Unlike adult LCH, childhood LCH is clonal and pulmonary involvement is not associated with smoking (Seely et al. 2012).

The previous classification of LCH into eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease is no longer in favor. The current classification divides these patients into those with single organ system involvement and those with multisystem involvement. Multisystem LCH is more common in children under 2 years of age, and the younger the patient, the worse the prognosis. The presence of multisystem involvement requires more intensive therapy than single system involvement. Pulmonary involvement can be seen either in isolated (primary) pulmonary LCH or in multisystem disease. Isolated pulmonary LCH is uncommon in childhood (Chatkin et al. 1993; Al-Trabolsi et al. 2006). The most common clinical signs and symptoms suggesting pulmonary involvement are tachypnea, cyanosis, chest pain, and chronic or persistent cough.

In a study of 220 children with LCH, 36 (16 %) had pulmonary involvement. Thirty-four (94 %) of these had multisystem LCH and two had primary pulmonary LCH. In 20 (56 %) of the 36, respiratory symptoms or signs were present, and diffuse interstitial involvement was present in all of these. The presence of pulmonary disease without risk organ (liver, spleen, hematopoietic system) involvement was not an adverse prognostic factor (Braier et al. 2004). In a larger, more recent study of 420 children with multisystem LCH, pulmonary involvement was present at diagnosis in 24 %, with a median age at diagnosis of 1.3 years, and strongly correlated with liver and spleen involvement. Pulmonary involvement later developed in an additional 7 % of patients. Pulmonary involvement was not an independent prognostic variable, suggesting that pulmonary involvement should be excluded from the definition of risk organ involvement in LCH (Ronceray et al. 2012).

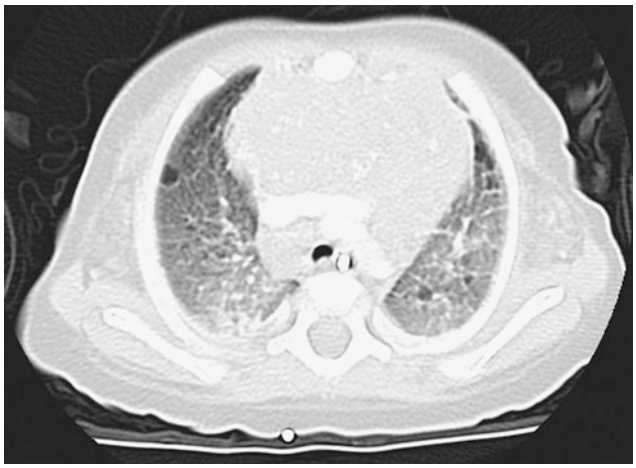

Fig. 29 Langerhans cell histiocytosis (LCH). An axial chest CT image in a 7-month old with LCH depicts multiple small pulmonary cysts, as well as an enlarged thymus with calcifications

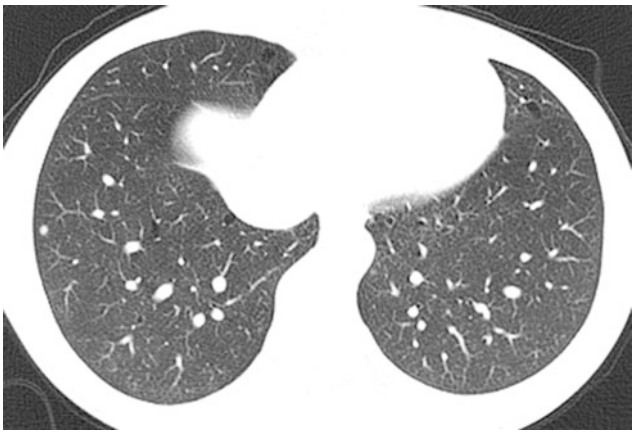

Fig. 30 Tuberous sclerosis (TS). An axial chest CT image in a 17-year-old female with TS shows several, small, round cysts of the lung bases bilaterally, consistent with lymphangioleiomyomatosis. In addition, there is a small, well-defined nodule of the peripheral lateral right lower lobe, possibly related to micronodular pneumocyte hyperplasia that occurs in the setting of TS

On CXR, the predominant finding of pulmonary LCH is reticulonodular opacities with or without cysts (Smets et al. 1997). CT depicts small cysts and nodules occult to CXR. Cysts and nodules often coexist and cavitating nodules may be seen during active stages of disease (Odame et al. 2006). The nodules and cysts in children are distributed randomly and usually involve the lung bases. This differs from adults, in whom sparing of the subpleural basilar lung parenchyma is highly characteristic of LCH (Seely et al. 2012). The cysts often have thin or imperceptible walls and may assume bizarre shapes (Fig. 29). Spontaneous pneumothorax can ensue from cyst rupture (Ha et al. 1992). The nodules typically regress, and the appearance of new nodules after cysts are well established suggests disease recurrence or progression (Bano et al. 2014). The cysts usually persist, and extensive cyst formation and surrounding fibrosis can lead to a honeycomb appearance of the lungs. Although pulmonary involvement has no independent effect on survival, it may result in lung parenchymal destruction and fibrosis severe enough to necessitate lung transplantation (Odame et al. 2006; Ronceray et al. 2012).

A recent review of the imaging features of 1,264 LCH patients demonstrated thymic involvement in 18 (14 %). Thymic involvement at presentation was limited to children less than 2-years old with multisystem disease. Patients who presented later all had active disease in at least one additional system at the time thymic involvement was identified. In cases of thymic involvement, thymic calcifications were present in all cases, thymic cysts in 80 %, and thymic enlargement in 67 % (Lakatos et al. 2013) (Fig. 29). Recognition of the characteristic pulmonary or thymic appearances of LCH involvement may allow the diagnosis to be confirmed and lung biopsy avoided by biopsy of an accompanying skin rash or by detection of elevated numbers of CD1a+ cells in bronchoalveolar lavage fluid (Crawley and Guillerman 2010).

10 Tuberous Sclerosis

Tuberous sclerosis (TS) is one of a group of genetic neurocutaneous syndromes characterized by involvement of structures that arise from the embryonic ectoderm, although other structures may be involved. TS is attributable to autosomal dominant defects of the *TSC1* or *TSC2* tumor suppressor genes.

The classic clinical triad includes mental retardation, seizures, and adenoma sebaceum. TS, however, affects multiple organ systems. In addition to the central nervous system (CNS) abnormalities of cortical tubers and subependymal nodules, abnormal cellular proliferation results in angiomyolipomas of the kidneys and liver, rhabdomyomas of the heart, and lymphangioleiomyomatosis (LAM) and multifocal micronodular pneumocyte hyperplasia (MMPH) of the lungs. There is a characteristic rash which has been described as a butterfly rash over the cheeks with a narrower affected area on the nose. In women of childbearing age, LAM is the most common thoracic manifestation of TS. In young children, CNS lesions and cardiac rhabdomyomas are by far the most common manifestations (Mettin et al. 2013). Cardiac rhabdomyomas are further discussed in the chapter entitled Pediatric Cardiac MRI by Krishnamurthy and Chung.

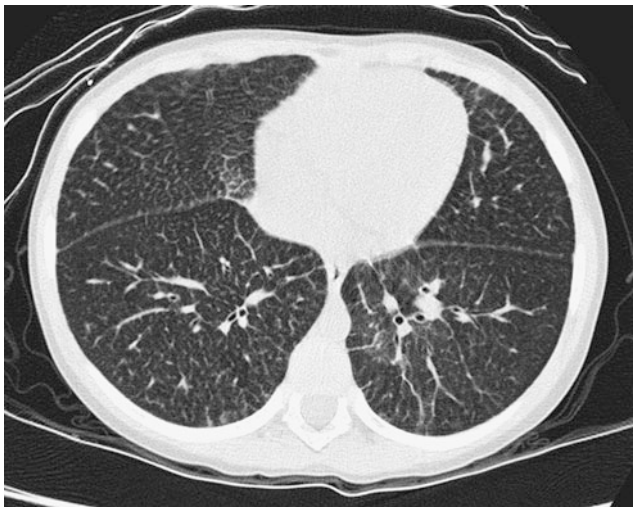

Fig. 31 Niemann–Pick disease. An axial chest CT image of a 5-year old with type B disease depicts diffuse septal thickening

LAM presents most commonly in the third decade; however, children as young as 11-years old have been diagnosed with LAM. Clinical presentation is usually with dyspnea or spontaneous pneumothorax, and there is typically a slow but inexorable progression to respiratory failure, with a median survival of 8–10 years without lung transplantation. The clinical course may also be complicated by chylous effusions. LAM is difficult to appreciate on CXRs until extensive fibrosis has developed late in the course of the disease. The early appearance of LAM is characterized by the presence of multiple small cysts with thin or imperceptible walls (Fig. 30). These cysts are evenly distributed through the lungs. Unlike the cysts in LCH, the cysts in LAM are round and usually do not coalesce. The presence of normal lung parenchyma between the cysts is useful in differentiating these cysts from other causes of destructive lung disease. In a prospective HRCT screening study of young women with TS, the incidence of lung cysts was 30 % (McCormack et al. 2002). This is much higher than earlier estimates, likely reflecting a high incidence of mild findings that do not present clinically and are not apparent on CXR.

MMPH is characterized by proliferations of enlarged type II pneumocytes that form ill-defined papillae and fill the alveolar spaces. MMPH is very rare before adulthood, and appears as multiple, well-defined pulmonary nodules resembling metastases on CT (Fig. 30). Definitive diagnosis can only be established by lung biopsy (Behnes et al. 2013).

Overactivation of the mammalian target of rapamycin (mTOR) signaling pathway as a result of *TSC1* or *TSC2* gene mutations is thought to be a mechanism of abnormal cellular proliferation in TS. Inhibitors of mTOR may provide an effective treatment for many of the manifestations of TS. For example, sirolimus has been shown to decrease the size of renal angiomyolipomas, and to improve pulmonary function and decrease chylous effusions in adult patients with LAM (Ando et al. 2013).

11 Lysosomal Storage Diseases

Lysosomal storage disorders (LSDs) are genetic diseases characterized by the absence or dysfunction of a lysosomal enzyme, with resulting accumulation of the lipid, glycoprotein or mucopolysaccharide substrate associated with the defective enzyme. The LSDs have a broad phenotypic range depending on the rate, amount and effect of substrate accumulation.

11.1 Gaucher Disease

Gaucher disease is the most common LSD and is due to a defect in β-glucocerebrosidase. This results in accumulation of glucocerebroside-laden macrophages (Gaucher cells) in various organs and tissues. The most common clinical manifestations are caused by involvement of the liver, spleen, and bone marrow. Lung involvement at presentation is uncommon, reported in only 2 % in one study (Goitein et al. 2001). Lung abnormalities may be caused by infiltration of Gaucher cells, hepatopulmonary syndrome, or aspiration secondary to neurological compromise (McHugh et al. 2004). Reticulonodular opacities can be seen on CXR, while CT findings include nodules, ground-glass opacities, and septal thickening (Tunaci et al. 1995). Enzyme replacement therapy does not consistently normalize the lung structure or function in these patients (Goitein et al. 2001).

11.2 Niemann–Pick Disease

In Niemann–Pick disease, sphingomyelin accumulates in "foamy" macrophages due to deficiency of sphingomyelinase. Pulmonary involvement is a major cause of morbidity and mortality (McGovern et al. 2013). Pulmonary involvement is greatest in Type B disease, which is characterized by lipid-laden macrophages infiltrating the pulmonary interstitium, resulting in the finding of diffuse interstitial thickening on CXR and CT (Guillemot et al. 2007) (Fig. 31). The type C2 form of the disease may present in infants or young children with failure to thrive, hepatosplenomegaly, and respiratory distress from pulmonary alveolar proteinosis

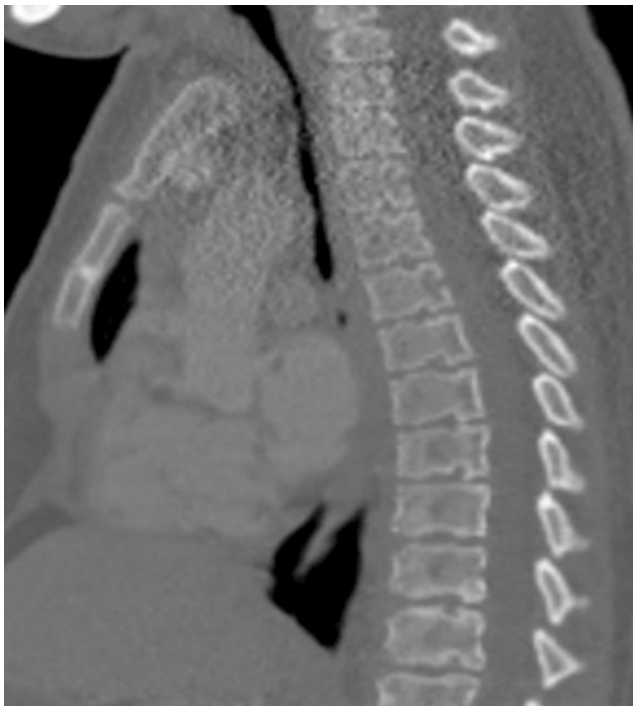

Fig. 32 Mucopolysaccharidosis (MPS). A sagittal chest CT image reconstructed with bone windows in a 16-year old with Type 2 MPS (Hunter syndrome) shows severe narrowing of the intrathoracic tracheal lumen and spinal dysostosis. Airway obstruction results from a narrowed thoracic inlet and accumulation of glycosaminoglycans in the airway wall

(Griese et al. 2010). Crazy-paving may be observed on chest CT of patients with the type C2 form (Guillerman and Brody 2011).

11.3 Mucopolysaccharidosis

The mucopolysaccharidoses (MPS) are characterized by accumulation of glycosaminoglycans in multiple organs and tissues. Eponyms for these diseases include Hurler, Hunter, Sanfilippo, Morquio, Maroteaux-Lamy, and Sly syndromes. Otolaryngological and respiratory problems are very common in patients with MPS. Typical features include upper and lower airway obstruction, restrictive pulmonary disease, and respiratory tract infections. Excess glycosaminoglycan deposition in the airway walls can result in tracheobronchomalacia, airway wall deformity, and airway luminal narrowing and contribute to a high risk of respiratory complications during sedation or anesthesia (Shih et al. 2002) (Fig. 32). Restrictive lung disease is a consequence of skeletal dysplasia limiting chest wall excursion and hepatosplenomegaly limiting diaphragmatic motion (Berger et al. 2013). Pulmonary function generally declines with age, but can be improved with enzyme replacement therapy (Lin et al. 2013).

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