

Pulmonary Disease in Primary Immunodeficiency Disorders

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Pulmonary complications are an extremely common manifestation of primary immunodeficiency disorders (PIDD). Infections are the most common abnormality and can lead to specific pulmonary complications. Patients with PIDD can present with a variety of manifestations such as recurrent bacterial, viral, or fungal pneumonia, bronchiectasis, granulomatous disease, and obstructive or restrictive lung disease. Some of the PIDDs can have unique lung abnormalities seen with specific defects. This review covers the respiratory manifestations seen in patients with a variety of primary immunodeficiencies. This recognition is important to reduce morbidity and mortality in these patients and possibly prevent the occurrence of chronic lung damage.

Introduction

THERE ARE CURRENTLY more than 170 different forms of primary immunodeficiency disorders (PIDD) that affect components of the innate and adaptive immune system.¹ Primary immunodeficiencies are classified into broad categories according to the portion of the immune system that is most affected. These categories include antibody deficiencies, combined T- and B-cell immunodeficiencies, diseases of immune dysregulation, disorders of phagocytes, defects of innate immunity, autoinflammatory disorders, complement deficiencies, and a group composed of other well-defined immunodeficiency syndromes.^{1–3} A global study characterizing primary immunodeficiency patients followed at 192 centers of the Jeffrey Model Centers Network was collected on a total of 60,364 patients. The patients were categorized into 8 major subgroups of the International Union Immunologic Society (IUIS) classification and revealed 51.62% with antibody deficiencies, 15.62% with other well-defined immunodeficiencies, 6.05% with complement deficiencies, 5.96% with autoinflammatory disorders, 5.28% with disorders of phagocytes, 5.24% with combined T- and B-cell immunodeficiencies, 2.57% with diseases of immune dysregulation, and 0.54% with defects in innate immunity.^{3,4} Pulmonary complications are one of the most common manifestations of primary immunodeficiencies. This article will cover the pulmonary complications of some of these immunodeficiencies including infections, characteristic findings secondary to infectious processes, and lung abnormalities seen in specific defects.

Antibody Deficiency Syndromes

X-linked agammaglobulinemia (XLA), also called Bruton's agammaglobulinemia, is caused by mutations in the

gene encoding an enzyme called Bruton tyrosine kinase. This mutation results in the failure of B-cells to mature beyond the pre-B-cell stage in the bone marrow. There are also autosomal recessive (AR) forms of B negative agammaglobulinemia. The disorder is characterized by decreased to absent serum immunoglobulins and reduced/absent B-cell numbers. These patients have increased risk of developing infections secondary to polysaccharide encapsulated bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Neisseria meningitidis*, and *Mycoplasma pneumoniae* (Table 1). In addition, patients with XLA are susceptible to enteroviruses.^{5,6} Infections typically occur after the first 6 months of life once maternally derived IgG begins to diminish. Data collected from a U.S. registry of 201 patients with XLA showed that pneumonia occurred in 62% of the individuals.⁷ A study looking at 39 XLA patients showed that 82% experienced at least 1 episode of pneumonia before diagnosis.⁵ The treatment for agammaglobulinemia is immunoglobulin replacement therapy. Delayed diagnosis of this immunodeficiency can lead to structural damage of the lungs such as bronchiectasis.⁸ Bronchiectasis is an irreversible dilatation of the bronchial airways caused by inflammatory destruction of the airway walls. It has been shown that the most common site of bronchiectasis tends to be the middle lobe, followed by the lower lobes and the lingula.⁸ Patients with bronchiectasis can present with shortness of breath, chronic cough with purulent sputum, clubbing, and occasionally hemoptysis. These patients can also develop fibrotic lung changes, bronchial wall thickening, atelectasis, and consolidation as shown in Fig. 1.

The standard treatment of B-cell immunodeficiency is immunoglobulin replacement therapy, which is typically

TABLE 1. INFECTIONS ASSOCIATED WITH PRIMARY IMMUNODEFICIENCY DISORDERS

Organisms	Antibody deficiencies	Combined T- & B-cell deficiencies	Disorders of phagocytes	Complement deficiencies
Viruses	Enteroviruses	All, especially CMV, RSV, PI3, EBV, adenovirus, influenza	HPV	No
Bacteria	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> <i>Neisseria meningitidis</i> <i>Mycoplasma pneumoniae</i>	Same as B-cell; <i>Salmonella typhi</i> , <i>Listeria monocytogenes</i> , enteric flora	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Serratia marcescens</i> , <i>Nocardia asteroides</i> , <i>S. typhi</i>	Same as B-cell; esp <i>N. meningitidis</i>
Mycobacteria	No	MAI, BCG	MAI, BCG	No
Fungi	No	<i>Canadia</i> , <i>Aspergillus</i> , <i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i>	<i>Canadia</i> , <i>Aspergillus</i>	No
Protozoa	<i>Giardia lamblia</i>	PJP, <i>Toxoplasma gondii</i> , <i>Cryptosporidium parvum</i>	No	No

CMV, cytomegalovirus; RSV, respiratory syncytial virus; PI3, parainfluenza virus type 3; EBV, Epstein-Barr virus; MAI, Mycobacterium avium-intracellulare; BCG, Bacillus Calmette-Guerin; PJP, *Pneumocystis jirovecii* pneumonia.

started at 400 to 600 mg/kg given intravenously every 3 to 4 weeks or subcutaneously at 100 to 200 mg/kg on a weekly basis. It has been recommended that the patient's serum IgG level should be based on a "biologic IgG level", which is an individualized level that prevents recurrent bacterial infections.⁹ One study looked at 90 patients with common variable immunodeficiency (CVID) over a 22-year period and provided evidence that the goal of immunoglobulin replacement therapy should be to reduce breakthrough infections rather than focus on achieving a particular trough IgG level.¹⁰ The trough IgG levels were found to be unique to the individual with protective trough IgG levels achieved with a large range of immunoglobulin doses (0.2–1.2 g/kg/month).¹⁰ A meta-analysis of 17 studies investigated the impact on trough IgG on pneumonia incidence in patients with antibody deficiencies and provided evidence that higher trough IgG levels up to at least 1,000 mg/dL can reduce the risk of developing pneumonia.¹¹ It has also been shown that patients with bronchiectasis require higher doses of immunoglobulin up to twice as much to achieve the same IgG level when compared to patients without bronchiectasis.¹⁰

CVID is a group of heterogeneous disorders defined by reduced levels of at least 2 of the 3 serum immunoglobulins, typically IgG and IgA, and impaired antibody responses to protein and polysaccharide antigens. Both infectious and noninfectious pulmonary complications are common in patients with CVID. Patients with CVID are prone to recurrent respiratory tract infections, which over time can result in pulmonary damage.^{5,12} Prominent infections include recurrent pyogenic sinopulmonary infections, particularly pneumonia, bronchitis, rhinosinusitis, and otitis media. The typical bacterial organisms causing these infections tend to include *S. pneumoniae*, *H. influenzae*, *Mycoplasma pneumoniae*, and *P. aeruginosa*. In a cohort of 248 patients with CVID, 78% had pneumonia at least once prior to diagnosis.¹³ Onset of infections may occur in early childhood, late childhood, or adulthood. Forty-two of 47 patients (89%) with CVID in a retrospective case study had respiratory symptoms mostly due to bronchiectasis, asthma, and recurrent chest infections.¹⁴ Chronic lung disease, including bronchiectasis, is also a com-

mon problem amongst this group of patients, as seen in Fig. 2.^{5,13,14} The development of bronchiectasis can lead to frequent hospitalizations and severe respiratory impairment. Patients with CVID appear to have a greater likelihood of developing chronic lung disease when compared to XLA patients. This is thought to be secondary to both delayed diagnosis of CVID and T-cell defects that may occur in CVID but not XLA.¹⁵ The most common lung findings in CVID patients are bronchiectasis, bronchial wall thickening, atelectasis, and air trapping.^{14,16} Since significant pulmonary disease can occur in patients with CVID, the evaluation of patients with CVID should include a high resolution CT (HRCT) scan of the chest and a full pulmonary function test.^{12,17}

There are a variety of noninfectious pulmonary diseases that also occur in CVID. These patients are prone to develop lymphoid interstitial pneumonitis (LIP).^{18–20} LIP is the development of diffuse or multifocal reactive lymphoid infiltrates in the alveolar interstitium.^{18,21} Histologically, it is characterized by infiltration of the alveolar interstitium largely by T lymphocytes and also by plasma cells, fibroblasts, and scattered macrophages.¹⁸ HRCT findings in 22 patients with LIP were characterized by the presence of ground-glass attenuation, poorly defined centrilobular nodules, and thickening of perilymphatic interstitium.²² These features on HRCT are usually bilateral and involve all lung zones.²² LIP is primarily treated and responds well to corticosteroids.^{19,20} One case report also describes successful use of cyclosporine A in the treatment of a patient with CVID and LIP.¹⁸ Another interstitial lung disease that has been described in CVID is bronchiolitis with organizing pneumonia (BOOP).^{23,24} Patients with BOOP, show patchy infiltrates on chest radiograph and typically present with cough, dyspnea, inspiratory crackles, low lung volumes, and decreased diffusing capacity on physiologic testing. They generally respond well to corticosteroids.²⁴

Granulomatous infiltration is another entity seen in patients with CVID.^{21,25–27} These infiltrates can be confused with sarcoidosis.^{25,26} In a case series of 17 patients with CVID and granulomas on biopsy, 7 of the 17 patients were diagnosed with sarcoidosis before CVID was diagnosed.²⁶ The pathogenesis of the granulomas is unknown, but it is

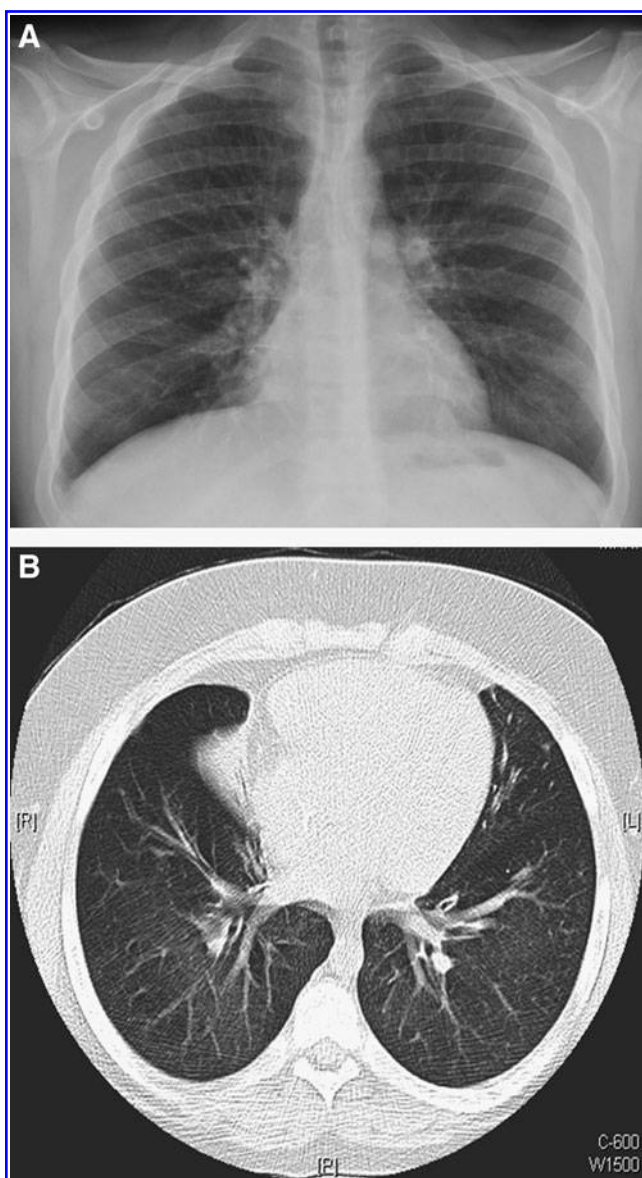


FIG. 1. Airway disease in a boy with X-linked agammaglobulinemia. Pulmonary function testing demonstrated fixed obstruction with FVC 50%, FEV₁ 42%, and FEF₂₅₋₇₅ 25% predicted. (A) chest radiograph demonstrated bilateral central peribronchial thickening and subsegmental atelectasis at both lung bases. (B) chest computerized tomography demonstrated bronchial wall thickening; fibrotic changes in the lingula and consolidation of the medial right middle lobe. FVC, forced vital capacity; FEV, forced expiratory volume; FEF, forced expiratory flow.

thought to arise from unregulated inflammation and impaired T-cell function in CVID.^{26,27} Patients with CVID and granulomas or autoimmunity are also likely to have a significant deficiency of switched memory B-cells, which is thought to be associated with the abnormal genetic, cellular, or cytokine environment that supports granuloma formation.²⁸ Patients can also develop granulomatous lymphocytic interstitial lung disease (GLILD), which is a combination of granulomatous and lymphoproliferative airway changes (LIP, follicular bronchiolitis, and lymphoid hyperplasia).^{27,29} A retrospective analysis of 69 patients with CVID found 13

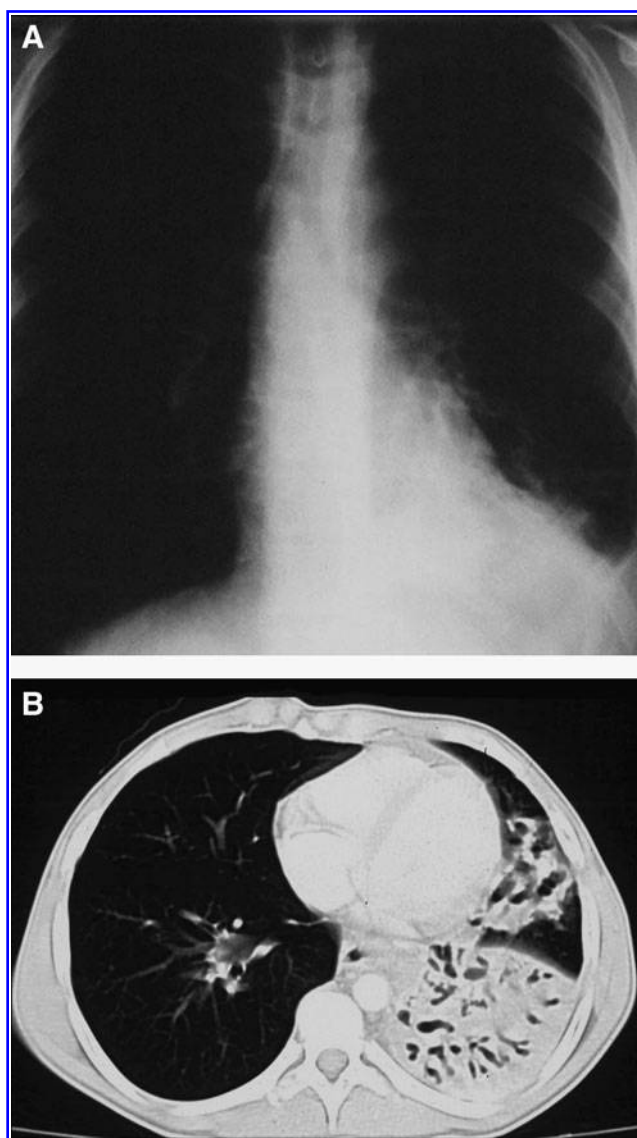


FIG. 2. Bronchiectasis in a 14-year-old boy with common variable immunodeficiency. (A) The patient had a history of 5 pneumonias, recurrent otitis media, and sinusitis. The patient was referred to Pulmonary Clinic for evaluation of persistent left lower lobe infiltrate. (B), CT scan demonstrated bronchiectasis in the left lower and lingular lobes.

(19%) of the patients to have GLILD.²⁹ The analysis showed a marked difference in survival from the date of CVID diagnosis comparing CVID patients with and without GLILD (13.7 years vs. 28.8 years).²⁹ They reported that GLILD was associated with the presence of dyspnea, splenomegaly, and decreased CD3+ and CD8+ cell populations. Pulmonary function data showed a restrictive pattern with a low normal DLco.²⁹ The pulmonary parenchymal involvement in GLILD tends to slowly progress, showing a decline in pulmonary function over several years.¹⁷ The predominant HRCT findings of GLILD are consolidation, ground-glass abnormality, reticular abnormality, hilar and mediastinal lymphadenopathy, and scattered nodules.^{16,17,29} Currently, there are no established treatment guidelines for GLILD. Corticosteroids have been used to treat patients with GLILD but there is no established dosage or treatment duration and prolonged use

can lead to significant morbidities.²⁷ Two case reports noted improvement in granulomatous disease in CVID with the use of infliximab after the patients failed to improve with corticosteroids.^{30,31} A retrospective study with 7 patients with CVID and GLILD discussed treatment with chemotherapy that showed improved pulmonary function and improvement of radiographic abnormalities.³² These 7 patients were treated with weekly doses of rituximab (375 mg/M²/infusion) for 4 weeks with repeated doses at 4–6 month intervals for 3 or 4 total courses and oral azathioprine (1–2 mg/kg/day) for 18 months.³² Patients who were unable to tolerate azathioprine secondary to gastrointestinal side effects were treated with 6-mercaptopurine (1–1.5 mg/kg/day) and 1 patient who was unable to tolerate either azathioprine or 6-MP was treated with mycophenolate mofetil (1,000 mg BID).³²

Mucosal-associated lymphoid tissue (MALT) lymphomas have also been described in CVID.^{21,33} MALT lymphomas are a subset of B-cell non-Hodgkin's lymphoma that are low grade malignancies composed of neoplastic marginal zone-related cells of lymphoid tissue. In a study looking at 5 patients with CVID and MALT lymphoma, it was found that 3 of the patients had lymphoma located in the lung.³³ Two of the patients underwent treatment with chemotherapy and rituximab, and the rituximab treatment resulted in resolution of the lung nodules.³³ Lymphoma was found to be the second most common cause of death after lung failure in a cohort of 473 subjects with CVID.³⁴

Specific antibody deficiency (SAD) is a disorder in which patients have normal immunoglobulin levels but are unable to develop an immune response to bacterial polysaccharide antigens, such as *S. pneumoniae*. These patients are susceptible to recurrent upper and lower respiratory tract infections, which include rhinosinusitis, otitis media, and pneumonia. These patients can also demonstrate symptoms compatible with reactive airway disease (eg, asthma), which is often exacerbated by recurrent sinobronchitis. In a retrospective series of 75 patients with SAD, 36 patients (52%) had a documented episode of pneumonia.³⁵ Nine of these patients were found to have bronchiectasis documented on chest HRCT and these patients tended to have fewer responses to Pneumovax immunization.³⁵ Another series of 120 patients diagnosed with SAD reported pneumonia in 57% of the patients.³⁶

Thymoma with immunodeficiency, also known as Good syndrome, is a syndrome associated with thymoma and adult-onset immunodeficiency.^{37,38} It is commonly seen between the ages of 40 to 70 years. The immunodeficiency is characterized by low or absent B-cells, hypogammaglobulinemia, variable defects in cell-mediated immunity with CD4 lymphopenia, and reduced T-cell mitogen proliferative responses.^{37,38} Immunodeficiency typically develops in 3%–6% of patients with thymoma.³⁸ On CT of the chest a thymoma appears as a well-delimited mass in the anterior mediastinum.³⁹ The thymoma alone can cause symptoms of cough, dysphagia, and hoarseness depending on the size. These patients are at risk for bacterial, fungal, viral, and opportunistic infections.^{3,37} The most common infectious complications are recurrent sinopulmonary infections with *H. influenzae* and *Pseudomonas* being the most common identified pathogens.^{37,38} Other infectious pathogens include *Klebsiella*, *S. pneumoniae*, *S. aureus*, *M. catarrhalis*, *Serratia*, *S. viridans*, *Salmonella*, *Enterobacter*, *Acinetobacter baumannii*, *M. pneumoniae*, *Candida*, cytomegalovirus (CMV), *Pneumocystis jirovecii*, and *Aspergillus*.³⁷ Patients have also been found to

have necrotizing pneumonia with lung abscess, mediastinitis, empyema, and bronchiectasis.³⁷

Other antibody deficiencies that can present with recurrent pulmonary infections include myelodysplasia with hypogammaglobulinemia, and IgA with IgG subclass deficiency.³

Combined T- and B-Cell Immunodeficiencies

Severe combined immunodeficiency (SCID) is caused by multiple genetic defects that result in deficiencies of T-cell and B-cell number/function.¹ Natural killer cell numbers and/or function may also be decreased. SCID is estimated to occur in 1 per 50,000 to 1 per 100,000 births.⁴⁰ It is typically characterized by decreased thymopoiesis, decreased CD3+ T-cells, anergy, decreased T-cell function *in vitro*, hypogammaglobulinemia, and decreased antibody responses. SCID and other conditions with low/absent T lymphocytes can be identified by testing for T-cell receptor excision circles (TRECs), which are now recommended on newborn screening studies.⁴¹ This screening is lifesaving and allows for identification of diseases that would have otherwise been missed or delayed in diagnosis. TRECs are a biomarker of normal T-cell development and can be measured in DNA isolated from the dried blood spots routinely obtained for newborn screening.^{40,41}

Patients with SCID present early in life with infections of bacterial, viral, and/or fungal etiology (Table 1). Pulmonary manifestations in patients with SCID include recurrent severe pneumonias, which may be due to *Pneumocystis jirovecii*. *P. jirovecii* pneumonia (PJP) causes an interstitial pneumonitis, characterized by tachypnea and hypoxia. Figure 2 demonstrates the progression of PJP from early to severe. Pathophysiologically, PJP is characterized by interstitial infiltrates and proteinous exudate into the alveoli (Fig. 3). Pneumonia caused by *P. jirovecii* is common and may occur in combination with viral pneumonias. Pneumonias caused by viruses, such as CMV, adenovirus, respiratory syncytial virus (RSV), influenza, parainfluenza type 3, also cause interstitial pneumonias that are radiographically indistinguishable from PJP (Fig. 4). Patients with SCID are also susceptible to develop pneumonia due to both Gram-negative and Gram-positive bacteria, such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, *P. aeruginosa*, *Legionella* sp, *Listeria monocytogenes*, *Salmonella* species, and enteric bacteria (Fig. 5). In addition, patients with SCID are susceptible to develop pneumonia due to fungi, in particular, *Candida albicans* and *Aspergillus fumigatus*. The pneumonia is typically a lobar lobular bronchopneumonia. It is important to note that chest radiographs of patients with SCID will be remarkable for an absent thymic shadow (Fig. 6). A retrospective series of 15 children with SCID showed 13 of the 15 (87%) developing pulmonary disease; the other 2 children were diagnosed at birth and transplanted before infections occurred.⁴² The median age for the development of pulmonary manifestations in the 13 children was 4 months (range 3 to 9 months).⁴² Ten of the 15 children (67%) had pulmonary illness as their presenting symptom, which included chronic cough from persistent respiratory tract infections or as respiratory distress from acute pneumonia.⁴²

Noninfectious lung disease may occur in adenosine deaminase-deficient (ADA) SCID.^{43,44} One group compared respiratory symptoms, radiological findings, and microbiological findings in a cohort of 21 patients with ADA-SCID to 19 patients with X-linked SCID. They found that both groups

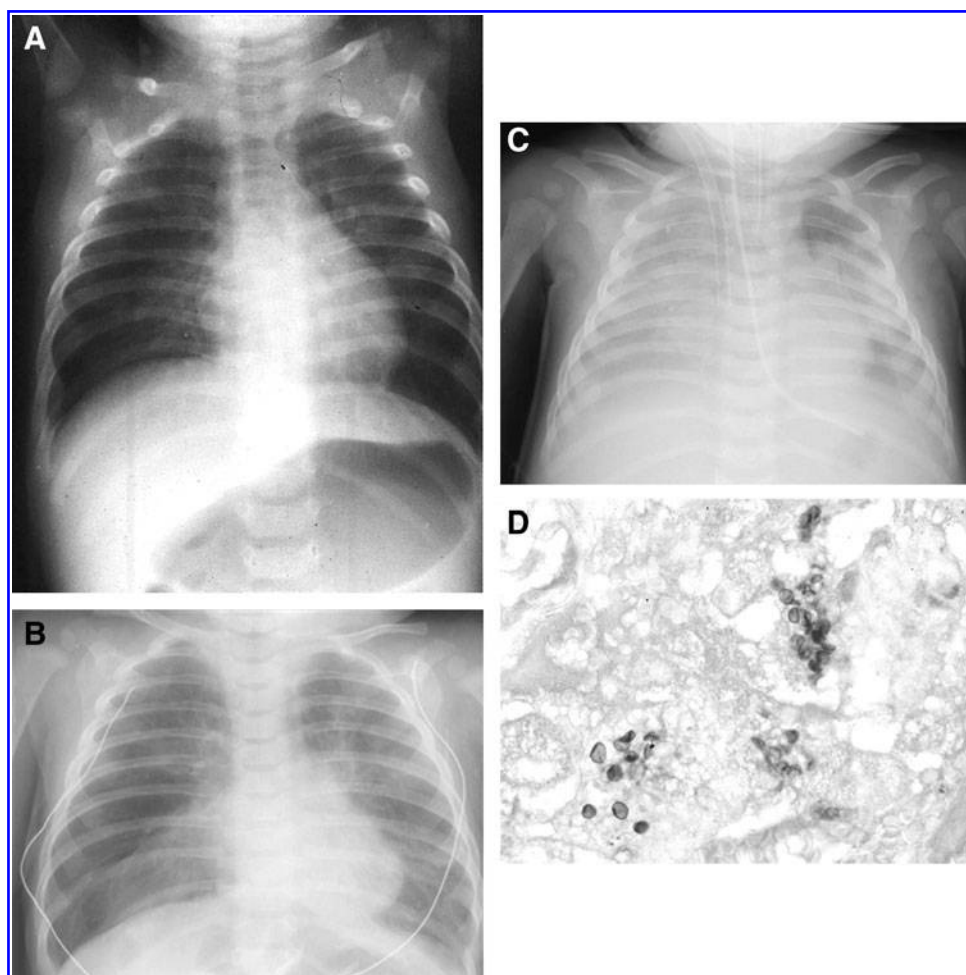


FIG. 3. Radiographic patterns of *Pneumocystis jirovecii* pneumonia in infants with severe combined immunodeficiency (SCID). (A) 5-month-old male: X-SCID with early PJP. There are bilateral perihilar infiltrates; the patient was tachypneic but there was no O₂ Requirement. (B) A 6-month-old female: IL7RA SCID diffuse bilateral interstitial infiltrates. The patient was tachypneic, hypoxic, and required O₂. (C) A 6-month-old female with T-B- SCID. There are marked diffuse bilateral interstitial infiltrates. The patient developed respiratory failure requiring mechanical ventilation and ECMO. Both PJP and Influenza A were isolated. (D) Lung biopsy demonstrating *Pneumocystis jirovecii* pneumonia in a patient with SCID. *Pneumocystis jirovecii* stains as dark trophocytes or fungi with Giemsa stain. Note the interstitial thickening and exudative fluid in the alveoli. PJP, *Pneumocystis jirovecii* pneumonia.

had similar respiratory symptoms and radiological findings, but positive respiratory cultures were significantly less frequent in the ADA-SCID group ($P=0.0004$).⁴³ Given these findings, the authors suggest that a possible metabolic abnormality may be contributing to the lung pathology when

no infectious cause is discovered.⁴³ Pulmonary alveolar proteinosis (PAP) has recently been described in a group of 7 out of 16 patients with ADA-SCID.⁴⁴ The 16 patients with ADA-SCID were compared to a control group of 22 patients with SCID secondary to other genetic defects, and PAP was

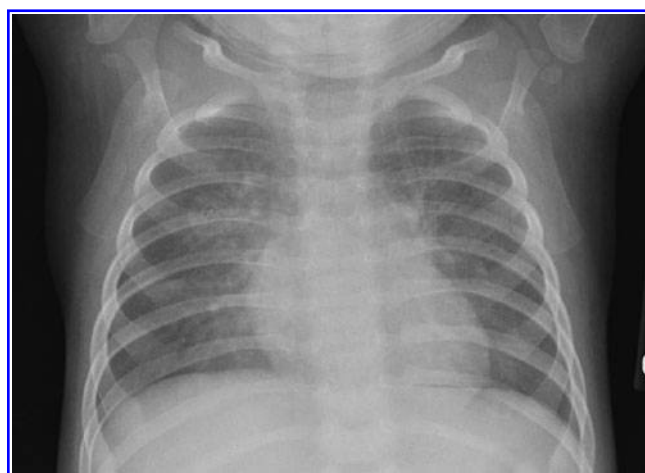


FIG. 4. Five-month-old female with RAG1 atypical SCID and viral pneumonia. She developed diffuse interstitial infiltrates caused by parainfluenzae type 3. She was tachypneic and hypoxic. This was successfully treated with PI3 interstitial pneumonia O₂ and ribavirin.

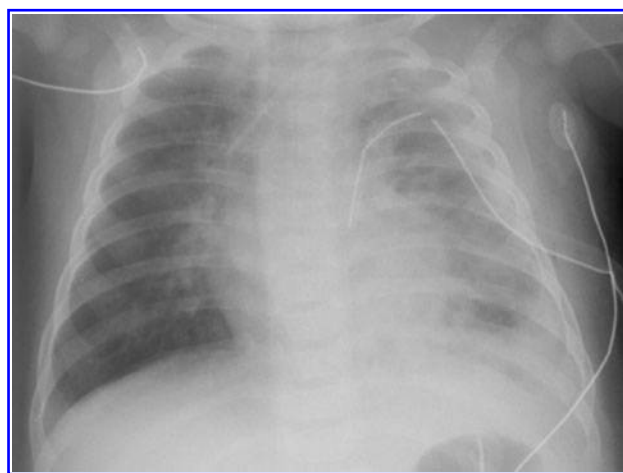


FIG. 5. Six-month-old female with Jak-3 SCID developed necrotizing pneumonia in the left lower and lingular lobes due to *Pseudomonas aeruginosa*. She was treated with antibiotics and the necrotic lung tissue was surgically removed. She was successfully reconstituted with an umbilical cord transplant.

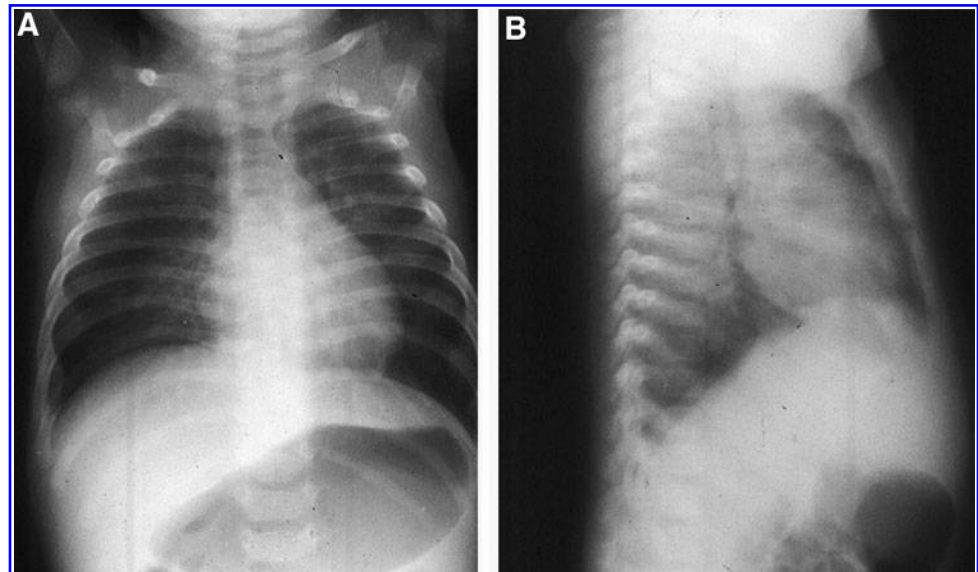


FIG. 6. (A) Absent thymic shadow as seen on chest radiograph in a patient with SCID. (B) There is absence of thymic shadow in the anterior mediastinum, best observed on lateral view.

found only in the ADA-SCID group.⁴⁴ PAP is a rare lung disease caused by abnormal surfactant accumulation resulting in respiratory insufficiency/failure.^{45,46} PAP is characterized by the accumulation of surfactant-derived lipoproteins within pulmonary alveolar macrophages and alveoli due to a disruption of GM-CSF signaling.^{45,46} PAP is classified as autoimmune, hereditary, or secondary. Clinically, patients present with progressive respiratory distress with hypoxia as surfactant accumulates. Spirometry most often shows a restrictive defect with decreased vital capacity and lung volume.⁴⁷ Chest X-ray typically reveals a bilateral ill-defined nodular or confluent alveolar filling pattern with a perihilar or basal distribution.⁴⁷ Chest HRCT shows congestion of the alveoli demonstrated by smooth interlobular and intralobular septal thickening superimposed on a background of ground-glass opacities; this finding has been described as the “crazy paving pattern”.^{46,47} Thick proteinaceous material and foamy macrophages are found on bronchoalveolar lavage (BAL). PAP on lung biopsy typically presents as well-preserved alveoli with granular, eosinophilic, periodic acid-Schiff-positive lipoproteinaceous material.^{45,46} The patients with ADA-SCID and PAP were treated with PEG-ADA enzyme replacement, allogeneic HSCT, or both. Six of the 7 patients showed rapid (2 to 4 weeks) and complete clinical and radiological resolution of PAP.⁴⁴

DiGeorge anomaly (DGA) is a genetic disorder leading to defective development of the third and fourth pharyngeal pouches. This field defect can result in facial dysmorphism characterized by posteriorly rotated ears, malformed pinnae, micrognathia, hooded eyelid, bulbous tip of the nose, velopharyngeal defects, conotruncal heart defects, hypocalcemia secondary to hypoparathyroidism, and T- and B-cell defects secondary to hypoplasia or aplasia of the thymus gland.^{1,48,49} The T-cell deficiency is variable. When there is thymic aplasia, naïve (CD45RA+CD62L+) T-cells are absent resulting in severe T-cell immunodeficiency (complete DGA). Patients with complete DGA resemble patients with SCID in relation to their susceptibility to infections. There are 2 phenotypes of complete DGA described as typical or atypical.⁴⁸ The “typical” phenotype is characterized by <50 naïve T-cells/mm³, no rash, and no lymphadenopathy. The

“atypical” phenotype, which can be considered a subgroup of Omenn syndrome, is characterized by <50 naïve T-cells/mm³, a rash associated with T-cell infiltration of the skin, lymphadenopathy, and circulating oligoclonal T-cells.⁴⁸ Most children with clinical findings of DGA have a small thymus with low T-cell numbers but relatively normal function (partial DGA).⁴⁸ Fortunately, $>95\%$ of patients with DGA have some thymic tissue, which allows for the maturation of stem cells into mature functioning T-cells that can be protective of opportunistic and viral infection. In partial DGA, there is a variable antibody dysfunction ranging from IgA deficiency, impaired responses to vaccines, transient hypogammaglobulinemia of infancy, to rare patients that are indistinguishable from CVID.⁴⁹ These patients are susceptible to recurrent sinopulmonary bacterial infections. A retrospective series of 19 children with DGA looked at the occurrence of pulmonary manifestations. These patients were divided into 3 groups: DGA with a T-cell defect (4/19), DGA with normal T-cells (10/19), or unknown T-cell status (5/19).⁴² Two out of the 4 patients with DGA with T-cell defects were noted to have recurrent pulmonary infections with resulting lung fibrosis. The organisms isolated were *Klebsiella*, *Corynebacterium*, *rhinovirus*, RSV, parainfluenza type 3, and CMV.⁴² One of these patients was also noted to have bronchomalacia. Two of the 10 patients with normal T-cell function and one of the 5 with unknown T-cell status were reported to have both bronchomalacia and recurrent pulmonary infections. The organisms isolated were *P. aeruginosa*, *Escherichia coli*, *H. influenzae*, adenovirus, RSV, and *Flavibacterium*.⁴² Besides respiratory infections associated with T-cell deficiency, this series of patients and other case reports have described structural airway abnormalities in patients with DGA.^{42,50–53} One report describes 2 patients with DGA with recurring respiratory difficulties secondary to airway abnormalities that were initially attributed to other associated conditions or complications of DGA. Patient 1 had an anatomic abnormality of the larynx characterized by malposition of the epiglottis, laryngeal torsion, and laryngomalacia.⁵³ Patient 2 had moderate laryngomalacia, moderate tracheomalacia, and moderate right bronchomalacia.⁵³ Pulmonary agenesis or aplasia has also been

described in 3 separate case reports in patients with DGA.^{50–52} One case describes a 22-day-old female who had central cyanosis and decreased breath sounds over her left hemithorax and was found to have left pulmonary artery agenesis and left lung aplasia.⁵² The second case describes a newborn who was found to have left pulmonary artery and lung agenesis.⁵⁰ The third case describes a 2-month-old female who was found to have severe hypoplasia of her left pulmonary artery and lung.⁵¹ Although not common, structural abnormalities of the respiratory system should be considered in patients with DGA who present with significant or recurrent respiratory difficulty.

Hyper-IgM (HIGM) is a heterogeneous group characterized by recurrent infections associated with decreased serum IgG, IgA, and IgE and normal to increased levels of serum IgM.⁵⁴ There is an X-linked and 3 AR forms of HIGM caused by mutations in genes that lead to immunoglobulin class switch recombination defects. The X-linked form of HIGM is caused by mutations in CD40L (CD154) on T-cells. The ligand for CD40L is CD40 on B-cells and monocytes. Mutations of CD40L on T-cells (X-linked) and CD40 on B-cells (AR) also lead to a combined T- and B-cell immunodeficiency. These patients are susceptible to infections with opportunistic microorganisms, such as *P. jirovecii* pneumonia and *Cryptosporidium*, enteritis, liver disease, and pyogenic infections. The AR forms of HIGM caused by activation-induced cytidine deaminase and uracil-DNA glycosylase have a similar phenotype to patients with CVID.

A registry of 79 patients with X-linked hyper-IgM revealed pneumonia as the most prominent clinical infection occurring in 81% of the patients.⁵⁴ *P. jirovecii* pneumonia occurred in 32 of the 79 (41%) patients prior to or at the time of diagnosis.⁵⁴ Other etiologies of pneumonia included CMV, adenovirus, *Pseudomonas*, HSV type 1, RSV, Histoplasmosis, *S. pneumoniae*, *S. aureus*, and *H. influenzae* type B.⁵⁴ A cohort of 23 patients with HIGM reported 18 of the 23 (78%) developing recurrent pneumonia during the course of the disease.⁵⁵ Three of the 23 patients developed bronchiectasis secondary to recurrent pneumonia and long delay of diagnosis.⁵⁵

Other combined immunodeficiencies that can be associated with respiratory complications include MHC class II deficiency, STAT5b deficiency, and MAGT1 deficiency.³

Disorders of Phagocytes

Chronic granulomatous disease (CGD) is a disorder characterized by defects in the NADPH oxidase system of phagocytes, leading to the defective killing of phagocytosed microbes.⁵⁶ The disease is characterized by recurrent infections with catalase-producing intracellular bacteria and fungi (Table 1). Approximately two-thirds of cases show an X-linked recessive pattern of inheritance, and the remainders are AR. These patients suffer from recurrent life-threatening bacterial and fungal infections and from abnormal inflammatory responses that lead to formation of granulomas in tissue. Information from a national registry of 368 patients with CGD reported pneumonia occurring at least once in 79% of the patients and lung abscess occurring in 16% of the patients.⁵⁷ A cohort of 60 patients with CGD reported lung infections (pneumonia/lung abscess) as the most prominent clinical problem occurring in 50% of the patients.⁵⁸ *Aspergillus* species were the most frequent isolated organism amongst the patients with pneumonia in both groups (Fig. 7).^{57,58} Other organisms isolated from CGD patients with pneumonia are *Burkholderia* and *Pseudomonas*, *Nocardia*, *Serratia*, *Candida*, *Paecilomyces*, *Actinomyces israelii*, *S. aureus*, *Mycobacterium tuberculosis*, atypical mycobacteria, *Klebsiella*, *Trichosporon*, *Acremonium kiliense*, *Absidia corymbifera*, and *Francisella philomiragia*.^{57–64} Infections of *Aspergillus* were the most common cause of death and were characterized by pneumonia with direct extension to the chest wall and vertebrae and dissemination to the central nervous system.⁵⁷ High level exposure to aerosolized fungi, such as with mulching, can lead to an acute fulminant presentation, with fever, dyspnea, pulmonary infiltrates, and possibly death.⁶⁵ One case series reported 9 patients with CGD who developed fulminant mulch pneumonitis after mulching, playing in a moldy garden shed, cleaning up dead leaves, chipping wood in a forest, or working in a lawn mower repair shop.⁶⁵

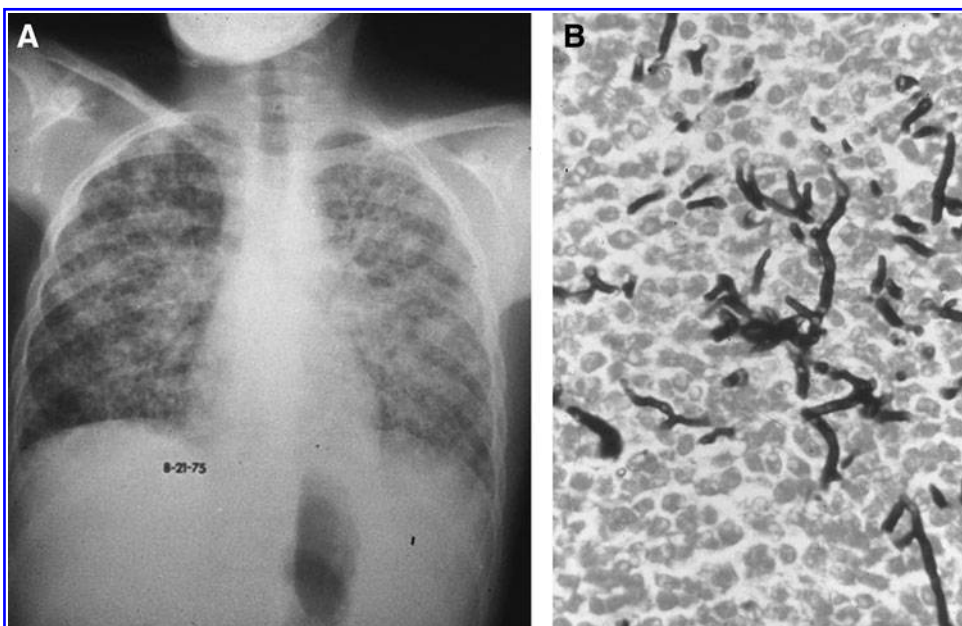
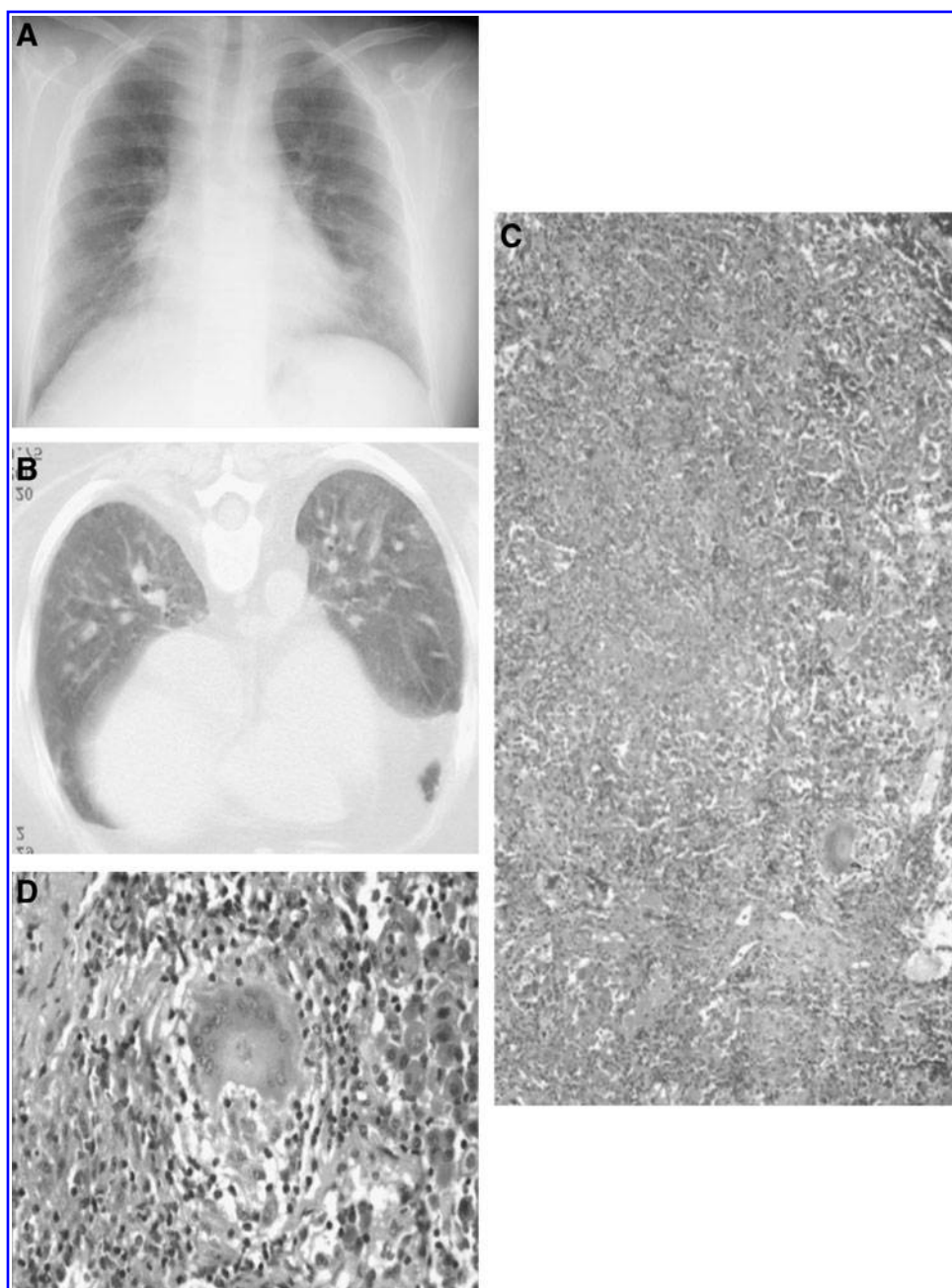


FIG. 7. *Aspergillus fumigatus* in a patient with chronic granulomatous disease. (A) There are diffuse nodular infiltrates. (B) Lung biopsy demonstrated the branching hyphae of *A. fumigatus*.

All patients presented within 10 days after exposure to mold with flu-like symptoms and had bilateral diffuse infiltrates on chest radiograph.⁶⁵ Another case report describes a 23-year-old female who presented with similar findings after working with compost. She was initially diagnosed with acute eosinophilic pneumonia due to the finding of 67% eosinophils on BAL and a biopsy demonstrating extensive eosinophilic infiltrates. She was started on steroids with worsening of symptoms and further work up lead to a diagnosis of CGD and invasive pulmonary aspergillosis.⁶⁶ These case reports emphasize the importance of maintaining a high index of suspicion for possible immunodeficiency in an adult patient and obtaining a careful history of recent activities and environmental exposures. Pulmonary disease in CGD patients can present on chest radiograph as focal

consolidation, miliary pattern secondary to hematogenous spread, diffuse bilateral reticulonodular opacities, pleural effusion, abscess formation, or empyema.^{67,68} HRCT findings of the chest include consolidation, pulmonary nodules in a random distribution, areas of scarring, traction bronchiectasis, ground-glass opacities, and emphysematous changes (Fig. 8).^{67,68} Protracted infections in the lung and chronic inflammation may lead to granulomatous inflammation, persistent hilar and mediastinal lymphadenopathy, pulmonary fibrosis, pulmonary hypertension, and honeycomb lung.^{56,67,69,70} Treatment of patients with CGD should include antibiotic prophylaxis with trimethoprim-sulfamethoxazole (5 mg/kg/day based on trimethoprim), itraconazole (5 mg/kg/day), and recombinant interferon- γ (50 μ g/m² 3 times a week or 1.5 μ g/kg 3 times a week for children <0.5 m²) to

FIG. 8. (A) Twenty-year-old male with X-chronic granulomatous disease demonstrating on chest radiograph bilateral diffuse interstitial infiltrates in the right middle and lingular lobes. (B), Chest high-resolution CT demonstrated diffuse pulmonary nodules. Lung biopsy demonstrated diffuse mononuclear cell inflammation with granulomata formations, (C) and giant cells (D).



help reduce the infections.^{56,70} Stem cell transplantation should be considered in patients with an available HLA-identical donor.^{56,70}

INF- γ /IL-12 defects lead to mendelian susceptibility to mycobacterial disease (MSMD). All forms of MSMD are characterized by increased infections to environmental mycobacteria such as *M. avium*, *M. kansasii*, *M. fortuitum*, *M. chelonae*, *M. smegmatis*, *M. abscessus*, *M. tuberculosis*, and the BCG vaccine strain.^{1,71} Rather than presenting with pulmonary manifestations, these patients typically present with disseminated mycobacterial infections.^{71–73} However, there have been reports of patients developing pneumonia from viral pathogens such as CMV, varicella zoster virus, RSV, and parainfluenza virus type 3.⁷¹

GATA2 deficiency, also known as MonoMac syndrome, is characterized by susceptibility to disseminated non-tuberculous mycobacterial infections, disseminated human papilloma virus infections, histoplasmosis, opportunistic fungal infections, and PAP.⁷⁴ These patients are found to have monocytopenia, B-cell and NK-cell lymphopenia, and they can develop myelodysplasia, acute myeloid leukemia, or chronic myelomonocytic leukemia. It is inherited as autosomal dominant or occurs as sporadic cases.⁷⁴ This immunodeficiency has some overlap in infections with IFN- γ /IL-12 defects but IFN- γ /IL-12 defects are not associated with PAP or myelodysplasia. PAP is a common occurrence in GATA2 deficiency and is thought to be secondary to the role GATA2 plays in regulating phagocytosis by pulmonary alveolar macrophages.⁷⁴

Other Well-Defined Immunodeficiency Syndromes

Hyper-IgE syndrome (HIES) is characterized by elevated serum IgE, eczema, and recurrent infections.⁷⁵ It is inherited as either an autosomal dominant or recessive form. AD-HIES is caused by mutations in STAT3 while the AR form is caused by mutations in TYK2 or DOCK8 deficiency.³ AD-HIES is characterized by coarse facial features, skeletal/connective tissue abnormalities, and pulmonary abnormalities. The pulmonary abnormalities include recurrent pneumonia, pneumatocele formation, empyema, and lung abscesses caused by bacterial and fungal infections.^{75–77} Patients with AD-HIES are susceptible to a variety of bacteria and fungi, including *S. aureus*, *C. albicans*, *H. influenza B*, *P. aeruginosa*, *Aspergillus fumigatus*, *M. catarrhalis*, *K. pneumoniae*, *Stenotrophomonas maltophilia*, *M. intracellulare*, *Alcaligenes xylosoxidans*, and *S. pneumoniae*. *S. aureus* is the most frequent cause of pneumonia in patients with AD-HIES.^{75,76} *S. pneumoniae* and *Haemophilus* species are also common causes of pneumonia.^{75,76} Pneumatocèles, bullae, and bronchiectasis frequently develop as a complication of recurrent pneumonias (Fig. 9).^{75,76} The parenchymal damage can then lead to chronic infections with *Aspergillus*, *Scedosporium*, *Histoplasmosis*, *Pseudomonas*, and nontuberculous mycobacteria.^{75,76,78,79} In a group of 64 patients with AD-HIES, 41 of the patients (64%) were noted to have parenchymal lung defects. Amongst these 41 patients, 18 (44%) had a history of invasive fungal disease.⁷⁸ These chronic lung infections have been associated with mortality secondary to vascular invasion into the pulmonary vessels causing life-threatening hemoptysis and fungal dissemination to the brain.^{75,80} A retrospective review was completed on 6 patients with HIES to identify causes of

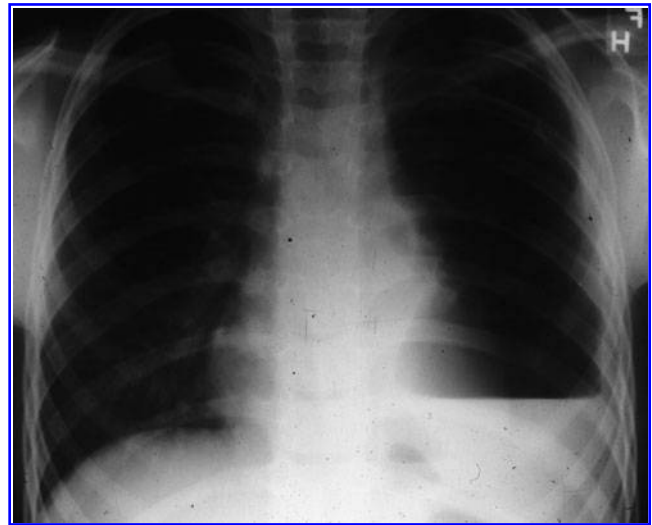


FIG. 9. Giant pneumatocele in a patient with AD hyper-IgE syndrome. *Streptococcus Pneumoniae* was isolated from the fluid in the bulla.

death.⁸⁰ All 6 patients had cystic lung disease and pneumonia caused by *Scedosporium*, *Aspergillus*, and/or *Pseudomonas* at the time of their death.⁸⁰ On autopsy 3 of the patients were found to have pulmonary vascular invasion with fatal hemorrhage and 2 of the patients had metastatic fungal disease to the brain.⁸⁰ One case report describes a 30-year-old man with AD-HIES who developed recurrent pneumonia, lung abscesses, and multiple pneumatoceles from *S. maltophilia* and *Penicillium marneffei* complicated by life-threatening hemoptysis.⁷⁷ *P. jirovecii* has also been reported as a cause of pneumonia in these patients.^{75,76,81} Patient with AD-HIES should be treated with prophylactic antibiotics such as trimethoprim-sulfamethoxazole to prevent *S. aureus* and other organisms.^{75,76} Antifungal prophylaxis should be considered in patients with recurrent candida or *Aspergillus* infections.^{75,76} Immunoglobulin replacement therapy has also been used in patients who continue to develop infections while on prophylactic antibiotics.^{75,76}

Other well-defined syndromes with immunodeficiency that have been associated with respiratory complications include ataxia-telangiectasia, Schimke syndrome, hepatic veno-occlusive disease with immunodeficiency, and X-linked dyskeratosis congenital.³

Conclusion

Patients often present first to their primary care physician when respiratory infections occur. Therefore, a primary immunodeficiency should be considered in patients who present with recurrent infections, opportunistic or unusual infections, frequent antibiotic use, and/or a positive family history. Early diagnosis and treatment of PID can help reduce morbidity and mortality in these patients and possibly prevent chronic lung damage. In patients with a PID, it is also important to consider noninfectious pulmonary complications when a patient presents with lung disease.

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