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CLINICAL UPDATE

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Beyond Infection: The Realities of Primary Immunodeficiency

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Pulmonary complications of primary immunodeficiency

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OBJECTIVES

1. **Understand key aspects of the pathogenesis and clinical presentation of pulmonary disease in primary immunodeficiency.**
2. **Summarize our understanding of asthma and chronic obstructive pulmonary disease in primary immunodeficiency.**
3. **Recognize the physiology, clinical presentation, and therapeutic approach to bronchiectasis in primary immunodeficiency.**
4. **Identify distinct forms of interstitial lung disease occurring in primary immunodeficiency.**

Pulmonary complications occur frequently in primary immunodeficiency (PI). In the United States Immunodeficiency Network (USIDNET), the largest PI research consortium in the United States with nearly 5500 patient participants, 39.3% were reported to have a history of pulmonary disease.[1] These complications often result from increased susceptibility to recurrent or severe respiratory infections due to immune system impairment. However, in many instances the etiology of pulmonary disease may be more complex and result, at least in part, from immune dysregulation inherent to some patients with PI. The goal of this review is to present an overview of pulmonary manifestations of PI, those with either a presumed infectious or non-infectious cause, as well as outline our current knowledge gaps for which continued research efforts aim for advancements in the future.

Respiratory Infections in PI

Infection is a frequent pulmonary complication of PI. An Immune Deficiency Foundation patient survey found that 68% reported a history of sinusitis, 55% reported bronchitis, and 51% reported a history of pneumonia. Along with ear infections (51%), these respiratory infections were by far the most common infectious complications of PI (https://primaryimmune.org/idf-surveys). One study of 252 patients with common variable immunodeficiency (CVID), the most frequently diagnosed symptomatic primary immunodeficiency, found 84% had a history of respiratory tract infection, 69% bronchitis, 63% sinusitis, and 58% pneumonia, with gastrointestinal tract involvement the next most common infection at 27% of subjects.[2] Similarly, in another form of severe primary antibody deficiency, X-linked agammaglobulinemia (XLA), a study leveraging the Italian Primary Immunodeficiency Network registry found respiratory infections to be the most frequent clinical feature.[3] Respiratory infections are also frequent in those with PIs that are not predominately antibody deficiencies, with viral respiratory infections reported in 56% of those with severe combined immunodeficiency and organisms identified from the respiratory tract accounting for 80% or more of infections in patients with chronic granulomatous disease (CGD).[4, 5]

Severe pulmonary infections, including pneumonia, lung abscess, and/or empyema, account for 29% to 44% of deaths in those with PI.[6] In those with autosomal dominant hyper IgE syndrome due to loss-of-function mutations in STAT3 in the USIDNET registry, 19.5% have a history of lung abscess.[7] Collectively, pneumonia and pulmonary abscesses are likely to be the greatest cause of death in those with CGD.[8] One study of over 400 CGD patients reported lung abscess in over 5%.[9] Thus, severe pulmonary infections are a major concern in those with PI, accounting for much of the morbidity and mortality affecting these patients.

Medical interventions are available to limit or prevent pulmonary infections in PI. Immunoglobulin replacement therapy (IRT) has been shown to reduce the incidence of pneumonia in PI patients with antibody deficiency, including one study focusing on CVID patients.[10, 11] IgG trough levels may need to be higher for some patients in order to achieve optimal efficacy.[12] In addition to IRT, or instead of this therapy in those for which it is not indicated, prophylaxis with antimicrobial agents can aid with management of respiratory infections. Prophylaxis with 250 mg of azithromycin daily three times weekly for two years was found to reduce respiratory exacerbations and hospitalizations in CVID and XLA patients with chronic infection-related pulmonary disease (asthma, bronchiectasis, and chronic obstructive pulmonary disease).[13] While this study did not find an increase in patients colonized by macrolide-resistant strains of bacteria as a result of azithromycin prophylaxis, they did report high levels of macrolide resistance in bacteria isolated from sputum, including 86% of *Streptococcus pneumoniae* and 79% of *Hemophilus influenzae* isolates. Together, IRT and antibiotic prophylaxis form the basis of respiratory infection management in PI.

Asthma and Chronic Obstructive Pulmonary Disease in PI

Asthma and chronic obstructive pulmonary disease (COPD) are frequent respiratory complications of PI. This is particularly the case for patients with CVID, the type of PI in which most of the research on respiratory disease has been conducted. Obstructive lung disease or bronchial hyperresponsiveness has been reported in 15% to 50% of CVID patients in numerous studies.[14] However, it is important to note that many cases of obstructive lung disease or other pulmonary complications may be misdiagnosed as asthma. In one study of 29 CVID patients with obstructive lung disease, only 9 were confirmed to have asthma.[15] Further complicating the evaluation of obstructive lung disease in PI, airway bronchoconstriction in response to allergens can occur even when allergy testing is negative.[15, 16] Moreover, there is frequently no difference in peripheral eosinophil counts or serum IgE in PI patients with or without airway hyperreactivity, limiting the utility of these measurements for diagnosis of asthma in these patients.[17] Notably, there is increased incidence of asthma in CVID patients compared with XLA, highlighting the fact that factors other than antibody deficiency underlie the pathogenesis of respiratory complications in PI.[18]

There have been strikingly few studies of mechanisms and treatment of asthma and COPD in PI despite the fact that such respiratory complications are common. Primary antibody deficiency is associated with more frequent COPD exacerbations, and low levels of IgA have

been proposed to underlie COPD exacerbation and/or progression.[19-21] Asthma has been associated with lower levels of IgA and IgM in CVID.[18] Other than provision of immunoglobulin replacement therapy, management of asthma and COPD in CVID follows standard diagnostic treatment guidelines. However, it is unknown whether there should be alterations to the clinical approach of PI patients with asthma and COPD. No studies have been conducted to determine whether changes in conventional management of asthma or COPD are warranted in CVID, or whether specific biologic therapies have more or less efficacy in these patients.

There can be significant overlap of features often thought of as distinct to asthma or COPD, such as elevation of eosinophils in COPD or neutrophilic asthma.[22] This asthma-COPD overlap may be more pronounced in PI given the immunological complexity of these patients. Furthermore, asthma and COPD exist in distinct forms or endotypes with specific immunological characteristics. Asthma can present with an eosinophilic endotype that renders it more susceptible to therapies targeting eosinophil biology.[23] COPD can manifest as chronic bronchitis, in which thick and narrow bronchioles are filled with excess mucus, or emphysema, defined by destruction of the alveolar walls. How the clinical and immunological complexity of asthma and COPD is shaped by PI remains a major knowledge gap.

There are several key concepts of COPD pathogenesis particularly relevant to PI. Tobacco smoking is the key risk factor for COPD, however, about one-third of those with COPD are nonsmokers.[24] This demonstrates that there are other key determinants of COPD susceptibility which may include infection or chronic pulmonary inflammation resulting from PI. COPD is thought to result from an imbalance of protease and antiprotease activity. The cardinal example of this being that α1-antitrypsin deficiency due to mutation of *SERPINA1* predisposes to COPD.[25] However, supported by studies identifying genetic polymorphisms associated with COPD, additional mechanisms can contribute, including apoptosis, oxidative stress response, and inflammation, which may be of particular relevance to PI.[26] B cell infiltration of terminal bronchioles and alveolar tissue with formation of lymphoid follicles has been described in COPD.[27] Similar pulmonary pathology also occurs in CVID patients, even in the absence of apparent COPD.[28] Study of respiratory complications, like COPD, in PI patients will not only provide insight for pulmonary disease in these patients, but may provide model human systems to elucidate pathogenic mechanisms relevant to broader patient populations.

Bronchiectasis

PI patients are particularly susceptible to developing bronchiectasis and this pulmonary complication may develop as a consequence of delayed diagnosis or inadequate treatment of immune deficiency. Patients with bronchiectasis will often present with chronic cough associated with mucus hypersecretion that is exacerbated by infection. Bronchiectasis is defined as permanent airway dilation due to chronic inflammation, recurrent infection, and/or mucus hypersecretion.[29] Bronchiectasis can be a complication of recurrent pneumonia and PI can increase the frequency of pulmonary infections that drive the inflammation and fixed changes of the airway that define bronchiectasis.[30, 31] Chronic or recurrent damage to the bronchial epithelium results in what is considered to be the vicious cycle of bronchiectasis: airway inflammation, alteration of the microbiome, and failure to resolve the infection.[32] Unsurprisingly, PI causes alterations in all three aspects of this bronchiectasis cycle. Bronchiectasis is often divided into disease that is associated with cystic fibrosis or disease that is not. Immune deficiency is among the most typical causes of non-cystic fibrosis bronchiectasis, along with aspiration, primary ciliary dyskinesia, and recurrent lung infections due to other causes.

There is evidence for numerous ways by which PI can predispose to bronchiectasis. In addition to being associated with recurrent pneumonia, as already mentioned, other respiratory infections may promote bronchiectasis. In a large study of 900 bronchiectasis patients at a United States tertiary care center, chronic rhinosinusitis was found in nearly half of subjects and was significantly associated with antibody deficiency.[33] In CVID patients, bronchiectasis has been associated with diagnostic delay, older age, pneumonia, and reduced levels of CD4+ T cells as well as IgM.[34-37] Other forms of primary antibody deficiency also predispose to bronchiectasis, including IgG subclass deficiency, selective IgA deficiency, and specific antibody deficiency.[38-42] IgA and IgM at mucosal surfaces are thought to be key aspects of pulmonary immunity, and reduced IgA and/or IgM are associated with bronchiectasis in primary antibody deficiency.[43, 44] Time is also a factor in bronchiectasis pathogenesis as this complication is more common in older PI patients.[34, 35] Clinical approaches targeting these determinants of bronchiectasis may improve care of PI.

Diagnosis of bronchiectasis may employ imaging and pulmonary function testing (PFT). Airflow obstruction is often evident on PFT. Regarding imaging, chest radiographs are often inadequate and CT scan of the chest is usually needed to confirm the diagnosis. Chest CT scan also has the sensitivity to pick up precursors of bronchiectasis, such as early bronchial wall thickening. Sputum culture is often included as part of the clinical evaluation of bronchiectasis as it can help with antibiotic selection as well as identify colonization with nontuberculous mycobacteria or *Pseudomonas* species. It is useful to rule out bacterial colonization when selecting antibiotics to reduce antimicrobial resistance.[45]

Bronchiectasis treatment in PI is multi-faceted. The first major component of management is optimization of IRT (if indicated in the particular form of PI). This typically includes a high IgG trough goal of 1000 mg/dL. Once sputum culture rules out nontuberculous mycobacteria, extended course macrolide therapy can be initiated. Efficacy of macrolide therapy for non-cystic fibrosis bronchiectasis has been demonstrated in numerous studies from 8 weeks to 24 months in duration, typically 250 or 500 mg of azithromycin 3 days per week, though not in PI patients specifically.[46-48] Other possible treatment options for bronchiectasis include inhaled antibiotics and mucolytics, though these have only been studied on a limited basis.[49, 50] Inhaled corticosteroids and β2-agonists are used in bronchiectasis management as is pulmonary rehabilitation.[14] Other than IRT, none of these therapeutic approaches have been specifically evaluated in PI. Thus, it remains to be determined whether one of the bronchiectasis interventions is superior to another for these patients.

Interstitial Lung Disease

Interstitial lung disease (ILD) significantly impacts morbidity and mortality, but disproportionately affects certain types of PI with particularly high occurrence in CVID at an estimated 5%-20% of patients.[18, 51] Unlike bronchiectasis, which is associated with older age and improves with antibiotics and IRT, ILD occurs in younger patients (typically present at PI diagnosis) and usually does not improve with antibiotics or IRT. Though both are forms of severe primary antibody deficiency, ILD occurs about 10-fold more frequently in CVID than XLA, indicating that antibody deficiency does not tell the whole story.[18] ILD is also less common in X-linked and autosomal recessive hyper IgM syndrome compared to CVID.[52, 53] Some monogenic immune dysregulation disorders associated with immune deficiency appear to have ILD frequently, including gain-of-function mutations of *PI3KD* and *STAT3* as well as genetic deficiency of *CTLA4* and *LRBA*. Numerous factors have been postulated to promote ILD in PI, including deficiency of regulatory T cells, increased inflammatory T cells, pathogenic B-cell activation, as well as other mechanisms of

systemic immune dysregulation that drive concurrent autoimmunity, lymphadenopathy, and splenomegaly.[54]

Of all forms of PI, ILD has been most extensively studied in CVID. CT findings consistent with ILD (ground glass opacity, pulmonary nodules) were found in 64% of CVID patients with respiratory symptoms at a tertiary referral center.[35] However, not all CT findings in CVID are clinically significant as they may not be associated with clinical symptoms or compromised pulmonary function.[55] Pulmonary nodules are not infrequent findings in CVID and need not be indicative of progressive ILD.[56] When pulmonary nodules do warrant additional work-up, lung biopsy is vital to confirming a diagnosis of ILD and can rule-out malignancy.[57] PI-associated ILD typically manifests within the spectrum of benign pulmonary lymphoproliferative lung disease which includes follicular bronchiolitis, peribronchial disease, and lymphocytic interstitial pneumonia, when there is broader interstitial involvement.[35, 58, 59] Granulomatous lymphocytic interstitial lung disease (GLILD) is frequently used to describe ILD in PI, as pulmonary pathology demonstrates both granulomatous and lymphocytic inflammation in these patients.[60-62]

CVID ILD may be incorrectly diagnosed as sarcoidosis due to radiologic similarities and shared associations with granulomatous inflammation. However, there are clear distinctions between these conditions. In addition to being differentiated by biopsy, CVID ILD has larger pulmonary nodules with a more generalized lung distribution than sarcoidosis.[63] Also, clinical history that includes recurrent infections, autoimmune cytopenias, benign lymph node hyperplasia, and other cardinal features of PI can aid the diagnosis.

Management of symptomatic ILD begins with optimization of IgG replacement therapy (if appropriate for the particular form of PI), with goal troughs of 1000 mg/dL or greater being typical.[56, 64] For those with mild to moderate symptoms, inhaled corticosteroids, with or without long-acting beta agonists, and/or prophylactic macrolides may be beneficial.[65-67] Systemic corticosteroid treatment may be effective in the short-term, but is not a viable long-term answer.[68] Numerous immunomodulators have been used to manage ILD in CVID, not much data exists for ILD in other PIs.[69-72] Rituximab (Rituxan) is a staple of therapy and may not heighten immunodeficiency in those already antibody deficient as much as broader immunosuppressants, and has a preferable safety profile.[73, 74] Following rituximab with azathioprine or mycophenolate mofetil (Cellcept) may induce longer remission after B-cell depletion[75]

In PI patients with known genetic etiologies, precision therapeutic approaches may be available. In those with genetic deficiency of the immune regulatory molecule CTLA-4 or a protein involved in the surface expression of CTLA-4, lipopolysaccharide responsive and beige-like anchor protein (LRBA), provision of CTLA-4-Ig (abatacept [Actemra]) is efficacious.[76] Likewise, gain-of-function mutation of *PI3KD* can be treated with leniolisib, an inhibitor of phosphoinositide 3-kinase **δ**.[77] Amelioration of gain-of-function mutations in STAT3 with jakinibs or IL-6R antagonists (as IL-6 signals via STAT3) have also been reported.[78, 79] Continued application of genomics to PI evaluation will undoubtedly reveal more opportunities for precision therapy.

Conclusion

Pulmonary complications can be the initial and/or primary complication of PI patients. One study found that the most common presenting feature among CVID patients was respiratory tract infections (29% lower respiratory tract infection, 27% upper respiratory tract infection).[80] Another found that sinopulmonary manifestations were the presenting symptoms of more than half of PI patients.[81] Consequently, earlier diagnosis of PI may limit resultant pulmonary complications. Delay in diagnosis of Pulmonary Arterial DIsease is associated with progression to obstructive airway disease, chronic atelectasis, bronchiectasis, and pulmonary fibrosis. Importantly however, lung disease occurs in many with PI diagnoses despite usage of immunoglobulin replacement therapy (IRT). Thus, some forms of chronic lung disease occurring in PI may develop because of immune dysregulation independent of infection or deficiencies in host defense that are not alleviated by IRT and/or antibiotic prophylaxis.

Even though diagnosis and treatment of PI has improved over the years, pulmonary complications remain common in these patients. There are several fundamental concepts that form the core of clinical management of respiratory disease in PI. Of paramount importance is the fact that infections of the upper and lower respiratory tract are principal clinical manifestations of PI. Accordingly, timely diagnosis and treatment may limit the progression of certain forms of chronic lung disease. While PI may increase the risk of obstructive lung disease, asthma may be frequently misdiagnosed as patients are often incompletely evaluated for their pulmonary disease. CT is often needed to diagnose bronchiectasis and sputum culture can shape appropriate management. ILD is associated with increased morbidity and mortality in CVID and results from pulmonary lymphoproliferative pathology that is responsive to immunomodulatory therapy. Clinical surveillance, lung biopsy, and genetic evaluation can be helpful to identify patients that should be treated and aid in selection of therapy. Further research is needed to expand the impact of genomics and build upon our recent advancements in diagnosis and treatment of PI-associated lung disease.

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