Lung Disease in Primary Antibody Deficiencies

Edith Schussler, MD[a], Mary B. Beasley, MD[b], and Paul J. Maglione, MD, PhD[a] *New York, NY*

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Edith Schussler, MD, Mary B. Beasley, MD, and Paul J. Maglione, MD, PhD.

Learning objectives:

1. To review and distinguish among pulmonary complications associated with primary antibody deficiency (PAD).

2. To use a framework for evaluation and management of PAD associated lung disease.

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Primary antibody deficiencies (PADs) are the most common form of primary immunodeficiency and predispose to severe and recurrent pulmonary infections, which can result in chronic lung disease including bronchiectasis. Chronic lung disease is among the most common complications of PAD and a significant source of morbidity and mortality for these patients. However, the development of lung disease in PAD may not be solely the result of recurrent bacterial infection or a consequence of bronchiectasis. Recent characterization of monogenic immune dysregulation disorders and more extensive study of common

[a]Division of Clinical Immunology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

[b]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY

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Corresponding author: Paul J. Maglione, MD, PhD, Department of Medicine, Icahn School of Medicine at Mount Sinai, 1425 Madison Ave, New York, NY 10029. E-mail: paul.maglione@mssm.edu.

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Abbreviations used
AR- Autosomal recessive
CT- Computed tomography
CTLA-4- Cytotoxic T lymphocyte—associated protein 4
CVID- Common variable immunodeficiency
GOF- Gain-of-function
HIGM- Hyper-IgM
IgAD- Selective IgA deficiency
ILD- Interstitial lung disease
LIP- Lymphocytic interstitial pneumonia
LRBA- Lipopolysaccharide-responsive and beige-like anchor protein
PAD- Primary antibody deficiency
PI3Kδ- Phosphoinositide 3-kinase
STAT3- Signal transducer and activator of transcription 3
XLA- X-linked agammaglobulinemia

variable immunodeficiency have demonstrated that interstitial lung disease (ILD) in PAD can result from generalized immune dysregulation and frequently occurs in the absence of pneumonia history or bronchiectasis. This distinction between bronchiectasis and ILD has important consequences in the evaluation and management of lung disease in PAD. For example, treatment of ILD in PAD typically uses immunomodulatory approaches in addition to immunoglobulin replacement and antibiotic prophylaxis, which are the stalwarts of bronchiectasis management in these patients. Although all antibody-deficient patients are at risk of developing bronchiectasis, ILD occurs in some forms of PAD much more commonly than in others, suggesting that distinct but poorly understood immunological factors underlie the development of this complication. Importantly, ILD can have earlier onset and may worsen survival more than bronchiectasis. Further efforts to understand the pathogenesis of lung disease in PAD will provide vital information for the most effective methods of diagnosis, surveillance, and treatment of these patients. **(J Allergy Clin Immunol Pract 2016;4:1039-52)**

Key words: *Common variable immunodeficiency; CVID; Granulomatous interstitial lung disease; Interstitial lung disease; Bronchiectasis; Primary antibody deficiency*

Primary antibody deficiency (PAD) is the most common form of primary immunodeficiency and consists of a group of disorders with impaired antibody production.[1] Yet, even though PADs account for more than half of all primary immunodeficiencies,[2,3] the genetic basis for most PAD cases remains undefined.[4] PAD continues to be underrecognized by physicians and diagnostic delays of many years remain common.[5] Delayed diagnosis can have significant consequences, including risk of severe acute infections and sequelae of inadequately controlled chronic infections. Respiratory symptoms including productive cough, wheeze, recurrent respiratory infections, and rhinosinusitus are the most common presenting features of PAD.[6] Notably, worsening of chronic lung disease due to structural damage from severe or chronic infections is a paramount concern for patients with PAD.[7]

Perhaps because of the prominent role of bacteria in lung diseases such as bronchiectasis and pneumonia and the importance of antibodies in protection against bacteria, lung disease is a frequent issue for patients with PAD. In addition to bacterial infection, respiratory viruses may lead to pulmonary exacerbations,[8] yet there is a paucity of data regarding the role of viruses in bronchiectasis or other forms of chronic lung disease in PAD. Increased recognition and usage of appropriate therapy in patients with PAD has reduced the incidence of severe infections, including pneumonia, and improved survival.[9,10] However, lung disease can progress in patients with PAD despite conventional treatment with IgG replacement therapy, antibiotic prophylaxis, or both.[7] Importantly, interstitial lung disease (ILD) and other pulmonary complications may not simply be the result of inadequately treated antibody deficiency or infection, but may actually be a consequence of immune dysfunction inherent to these patients.

OVERVIEW OF PAD SYNDROMES

PAD consists of a diverse group of disorders resulting from fundamental defects in the ability to produce effective antibody responses against pathogens. This antibody deficiency may be due to intrinsic B-cell defects, but can also involve functional impairments of other immune cells that promote antibody responses. Because these numerous types of PAD each have differing degrees of immunological compromise, noninfectious sequelae such as chronic lung disease, much like susceptibility to infection, varies by specific disorder. To aid in understanding the pulmonary complications that can emerge in PAD, it is helpful to briefly review different etiologies of PAD commonly affected by lung disease.

Congenital agammaglobulinemia

Congenital agammaglobulinemia results in profound absence of antibody, with marked reduction in all immunoglobulin isotypes. This typically results from a genetic defect impairing the expression or signaling of the pre—B-cell receptor, leading to arrest of B-cell development. X-linked agammaglobulinemia (XLA) accounts for approximately 85% of patients with congenital agammaglobulinemia and is due to mutations in the Bruton's tyrosine kinase gene, which is carried on the X chromosome.[11] Most Bruton's tyrosine kinase mutations result in a lack of Bruton's tyrosine kinase protein expression and a severe block in B-cell differentiation, though there is some variability of presentation with a genotype-phenotype correlation.[12] Autosomal-recessive (AR) forms of congenital agammaglobulinemia have also been described, and the block in B-cell development can be more severe than in XLA.[13] In those with congenital agammaglobulinemia, the onset of bacterial infections is typically after the first 6 months of life when maternal antibody acquired through the placenta has waned. The sinopulmonary tract is the site of infection in 60% of patients, but pyoderma, chronic conjunctivitis, gastroenteritis, arthritis, meningitis, osteomyelitis, and septicemia are also seen.[14] Although infections with encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* are the most frequent concern for these patients, susceptibility to certain viral infections, such as hepatitis and enteroviruses, may also be increased. Diagnostic delay in congenital agammaglobulinemia is significant, with average age of diagnosis being 2.6 years in those with family history and 5.4 years in those without.[14]

Hyper-IgM syndrome

Hyper-IgM (HIGM) syndrome includes a group of disorders with defective B-cell isotype class switching, resulting in low concentrations of IgG and IgA with normal to increased levels of