Immunoglobulin G4-Related Disease and the Lung

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KEYWORDS

• Immunoglobulin G4 • Fibroinflammatory • Pseudotumor • Interstitial lung disease • Pleuritis • Lymphadenopathy

KEY POINTS

- Immunoglobulin (Ig)G4-related disease (RD) is an immune-mediated fibroinflammatory disorder that can affect virtually any organ or tissue in the body.
- Any compartment in the thorax can be involved in IgG4-RD, with or without associated extrathoracic manifestations.
- In patients presenting with fibroinflammatory disease of obscure cause, the possibility of IgG4-RD should be considered.
- Although the etiology of IgG4-RD remains unclear, early diagnosis and treatment can effectively manage most patients with this corticosteroid-responsive disorder.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized systemic fibroinflammatory disease with protean manifestations involving virtually any organ in the body. IgG4-RD has been previously referred to as "IgG4-related sclerosing disease" or "hyper-IgG4 disease."[1,2] At initial clinical presentation, 1 or multiple organs may be involved with the disease process. It has become apparent in recent years that many disorders previously considered idiopathic (eg, inflammatory pseudotumors, Mikulicz's syndrome, Küttner's tumor, Riedel's thyroiditis) belong, at least in part, under the spectrum of IgG4-RD.[3,4]

Initial descriptions of IgG4-RD focused on pancreatic disease. For example, Hamano and colleagues[5] described in 2001 the association of high serum IgG4 levels with a form of sclerosing pancreatitis characterized by lymphoplasmacytic infiltrates containing $IgG4^+$ plasma cells (currently named type 1 autoimmune pancreatitis). It has since become clear that IgG4-RD can cause an immune-mediated fibroinflammatory process, commonly manifesting as mass-like lesions, in various regions of the body including intrathoracic structures.[2,4,6,7] This pathologic process is characterized by infiltration of $IgG4^+$ plasma cells and a propensity to fibrosis leading to organ dysfunction.

EPIDEMIOLOGY

Although the majority of earlier reports described IgG4-RD in the Japanese population, it is clear that those in the Western hemisphere are affected as well.[3,4,8–10] It is a rare disease with an annual incidence in Japan estimated to be approximately 1 per 100,000.[11] An increasing number of cases are being recognized in recent years with true

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incidence and prevalence figures remaining to be defined. It affects mainly adults who are more commonly men (60%–80%) than women.[4,7] The median age at diagnosis is 60 to 65 years.[7,12]

PATHOGENESIS

Immunologic Mechanisms

The etiology of IgG4-RD remains obscure. Immunologic mechanisms are likely involved in the pathogenesis of this disorder, but the target antigens and the exact role of IgG4 (the smallest subclass of IgG) remain to be defined. The immunologic profile of IgG4-RD manifests characteristics of a predominantly type 2 helper cell immune response and infiltration by regulatory T cells, which produce interleukin-10.[13–15] This cytokine imbalance is thought to potentiate IgG4 production and promote IgG4-RD. There is also evidence of expanded plasmablast (stage of B lymphocyte development between activated B cell and plasma cell) population that is oligoclonal in nature.[16]

Immunoglobulin G4

High serum levels of IgG4 are found commonly in patients with IgG4-RD. However, IgG4 is generally thought to function as an antiinflammatory antibody. Thus, the elevated serum IgG4 level may reflect a response to the inflammatory process rather than a pathogenic role. Similarly, various forms of circulating autoantibodies that are found in some patients with IgG4-RD are considered nonspecific, with no direct role in the pathogenesis of IgG4-RD.[13,15]

Genetic Predisposition

In genetic association studies, some susceptibility genes for IgG4-RD have been identified. For example, studies in Japanese and Korean patients with type 1 autoimmune pancreatitis have implicated several HLA haplotypes and non-HLA genes, for example, *CTLA4*.[13,17] These findings implicate genes related to immune response in susceptibility to IgG4-RD.

Microorganisms

Microorganisms, such as *Helicobacter pylori*, have been investigated as potential triggers for immune processes in IgG4-RD.[4,13] However, the potential role of microorganisms in inciting IgG4-RD remains speculative.

PATHOLOGY

IgG4-RD is associated with tumefactive (swelling) lesions in various organs, such as renal mass in IgG4-related kidney disease. Similarly, there are histopathologic features that are characteristic of IgG4-RD. These are dense lymphoplasmacytic infiltrate, fibrosis (often in storiform pattern), and obliterative phlebitis (**Fig. 1**). Immunohistochemical staining identifies elevated numbers of $IgG4^+$ plasma cells within the fibroinflammatory infiltrate (**Fig. 2**). Increased numbers of eosinophils and obliterative arteritis may also be seen (see **Fig. 1**D). However, as discussed elsewhere in this paper, none of these findings is specific for IgG4-RD diagnosis.

Although there are general similarities in histopathologic findings, site-specific features have also been noted for some organs including the lung, which often does not show distinct storiform fibrosis when involved with IgG4-RD.[18,19] Similarly, the density of $IgG4^+$ plasma cells in involved organs varies and influences the quantitative cutoff values used for number of $IgG4^+$ plasma cell per high-power field and $IgG4^+/IgG^+$ cell ratio in the histopathologic diagnosis of IgG4-RD.[20,21]

Clinical Manifestations

Although the initial description of IgG4-RD focused on its presentation as a pancreatic disease, it is now apparent that affected patients can present with a wide array of extrapancreatic manifestations. Aside from the pancreas, other sites commonly involved include the hepatobiliary tract, salivary and lacrimal glands, lymph nodes, orbital tissues, retroperitoneum, kidney, and lung.[1,7,11,12]

Clinical manifestations attributable to this disorder continue to expand. Patients with IgG4-RD commonly present with multiorgan manifestations, although single-organ involvement is noted in approximately 40% of patients.[3,4,7,8,12,21,22] During the clinical course of active IgG4-RD, various organs may become involved metachronously.

Symptoms

Symptoms associated with IgG4-related lung disease are nonspecific and include cough (most common), chest pain, and dyspnea. Systemic symptoms such as low-grade fever and weight loss may be present, but are uncommon. In patients presenting with symptomatic extrapulmonary IgG4-RD, asymptomatic lung involvement may be detected on imaging studies. Overall, approximately one-half of patients with IgG4-related lung disease will manifest respiratory symptoms.[2,22–25]

Immunoglobulin G4-Related Lung Disease

Pulmonary involvement (excluding intrathoracic lymphadenopathy) in IgG4-RD is reported to