IgG4-Related Disease
A Reminder for Practicing Pathologists
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IgG4-related disease (IgG4-RD) is a systemic autoimmune fibroinflammatory disease that produces sclerotic, tumefactive masses containing dense lymphoplasmacytic infiltrates rich in immunoglobulin (Ig) G4+ plasma cells. Initially characterized as a form of autoimmune pancreatitis, the distinctive histopathology of IgG4-RD has now been described in almost every organ system. However, because the clinical manifestations of IgG4-RD are diverse and nonspecific, the disease may go unsuspected until a biopsy or resection specimen is obtained to diagnose a presumed malignancy. Pathologists thus play a key role in the diagnosis of IgG4-RD, and familiarity with its histopathologic features is essential to preventing the irreversible comorbidities associated with this treatable disease. This brief review outlines the epidemiology, clinical manifestations, and histopathology of IgG4-RD, with the aim of furthering pathologists’ awareness of and ability to diagnose this disorder.


IgG4-related disease (IgG4-RD) is a systemic autoimmune disorder characterized by elevated serum immunoglobulin (Ig) G4 levels and tumorlike fibroinflammatory masses with distinctive histopathologic features that almost always include infiltrates of IgG4+ plasma cells. Described initially as a form of sclerosing autoimmune pancreatitis (now designated as type I autoimmune pancreatitis),1–3 the disease has since been recognized as having the capacity to affect nearly every organ system. Indeed, IgG4-RD is notable for unifying several historical and seemingly organ-specific fibrosing diseases into a single process (Figure 1).

The designation of IgG4-RD as a distinct disease entity was proposed in 2003.3 Much literature has been published since then (Figure 2), including many recommendations regarding its diagnosis and management.4,5 Despite these advances, however, the pathophysiology of IgG4-RD remains poorly understood. Moreover, as some6,7 have observed, diagnosis of the disease suffers from a paradoxical combination of underrecognition and overrecognition—underrecognition due to unfamiliarity, and overrecognition due to overeagerness to demonstrate familiarity. Accurate and timely recognition of the characteristic histopathologic features of IgG4-RD, and differentiation from its mimics, is important because it is eminently treatable, yet debilitating and potential deadly if left unchecked. Pathologists in particular play a crucial role by alerting clinicians to the possibility of a diagnosis of IgG4-RD, since it may be unsuspected clinically until a resection specimen arrives (Figure 3, A through H). This brief review will summarize the clinical features, histopathology, and differential diagnosis of IgG4-RD, with an eye toward increasing pathologists’ awareness of this unique disorder.

EPIDEMIOLOGY AND CLINICAL FEATURES

The incidence of IgG4-RD across all organ systems is difficult to determine, since the disease has only recently been described and global population-based data are lacking. In Japan, where the disease has been characterized extensively, one study examining the incidence of autoimmune pancreatitis reported a rate of 0.8 per 100 000 individuals.8 More recently, a rate for all forms of IgG4-RD of 0.28 to 1.08 per 100 000 individuals was estimated in Japan from the number of patients with IgG4-RD who presented to 2 hospitals within a single prefecture over the course of several years.9 These rates may rise as additional data accumulate and physicians become more familiar with and able to recognize the disease.10

Unlike most autoimmune diseases, IgG4-RD is more prevalent in middle-aged and elderly males, although the extent of this male predominance varies with the anatomic site of involvement. At least in Japanese populations, IgG4-related autoimmune pancreatitis has a male to female ratio of 3–4:1,11 but this ratio decreases nearly to unity in the context of head and neck disease.12 The most common clinical manifestation is the development of a mass lesion that produces site-specific symptoms and raises suspicion for malignancy. The effects range from simple swelling of the affected organs (salivary and lacrimal glands, lymph nodes) to obstruction (pancreaticobiliary, ureteral), organ dysfunction (pituitary insufficiency secondary to hypophysitis, kidney disease), and even frank medical emergency (aortic dissection, pachypleuritis, pancreatitis). Apart from the mass effects, a small number of patients may experience constitutional symptoms such as fever and weight loss.10
Figure 1. Some of the many clinical manifestations of IgG4-related disease, including the names of historic fibrosing diseases (italicized) subsequently linked to the disorder. Abbreviation: IgG4, immunoglobulin G4.

Figure 2. The yearly number of PubMed citations since 2000 containing the search term IgG4-related. Abbreviation: IgG4, immunoglobulin G4.
Figure 3. IgG4-related disease involving the submandibular gland. The specimen was taken from a 46-year-old woman with a 3-month history of a right submandibular gland mass and mild regional neck lymphadenopathy. Her medical history included Graves disease and asthma. Nineteen months earlier she underwent a lacrimal gland biopsy for periorbital swelling. Lymphoma had been suspected, but flow cytometry was negative, and the biopsy was interpreted as sclerosing inflammatory pseudotumor with numerous active lymphoid follicles. Sections of the excised right submandibular gland mass (A) show serous salivary gland tissue and adjacent nodular lymphoid tissue consisting of reactive germinal centers (B).
Other patients are asymptomatic, and a mass lesion is only found incidentally on imaging. With such diverse clinical presentations, it is perhaps not surprising that the possibility of a systemic autoimmune disease may be overlooked in favor of alternative diagnoses during initial or even subsequent evaluations.

**PATHOPHYSIOLOGY**

The etiology of IgG4-RD remains obscure, and it is easier to describe the inflammatory response in affected patients than to identify definitive causative mechanisms. Evidence suggests that the disease is associated with both T helper 2 (Th2) and regulatory T-cell (Treg) immune responses. Th2 responses are linked to the development of allergies and bronchial asthma, conditions that are more prevalent in patients with IgG4-RD.13,14 They are characterized by CD4+ T cells secreting the cytokines interleukin (IL)-4, IL-5, and IL-13, and they promote class switching to IgG4, increased IgE synthesis, and eosinophilia. Regulatory CD4+ T cells (Tregs), in contrast, secrete cytokines such as IL-10 and transforming growth factor β (TGF-β), leading to immunomodulatory or immunosuppressive effects. Serum from patients with IgG4-RD shows elevated mRNA expression of IL-4, IL-5, and IL-10, as well as increased concentrations of IgG4 and IgE.15 Tissue sections of salivary glands,16 lacrimal glands,16 and pancreas17 from patients with IgG4-RD show high mRNA expression of Th2- and Treg-associated cytokines. Circulating Treg-type CD4+ T cells are increased in the peripheral blood of patients with IgG4-related autoimmune pancreatitis.18 Treg cells (as defined by immunohistochemical expression of the Treg-related transcription factor Foxp3) are also increased in liver biopsies from patients with IgG4-RD.19 These findings suggest a possible model10,20 in which an unknown immunomodulator triggers an aberrant Th2-type immune response leading to peripheral blood and tissue eosinophilia and increased IgE production. At the same time, Treg cells, perhaps to ameliorate the Th2 response, are stimulated to secrete IL-10, which (along with IL-4) induces class switching to IgG4, and TGF-β, a known stimulator of fibroblast activity. Repeated cycles of antigenic stimulation and cytokine secretion then produce the histopathologic findings of tissue fibrosis and a lymphoplasmacytic infiltrate rich in IgG4+ plasma cells. However, direct evidence that Th2-associated cytokines truly drive the inflammation in IgG4-RD is still lacking, and no convincing environmental trigger (infectious or otherwise) or autoantigen has been identified. Other possible predisposing conditions or contributors to IgG4-RD pathogenesis include specific human leukocyte antigen (HLA) alleles and single-nucleotide polymorphisms within some non-HLA genes.21,22

Also puzzling is the precise role of IgG4 in the disease. IgG4 is the least common IgG subtype, comprising less than 5% of total IgG,23 and is usually viewed as an anti-inflammatory molecule. IgG4 binds C1q and the Fcγ receptor with relatively low affinity,24,25 and consequently is not expected to be as effective as other IgG subclasses at activating complement or promoting phagocytosis. In addition, owing to unstable inter-heavy chain disulfide bonds,26 IgG4 can exchange its Fab arms with other IgG molecules, rendering it functionally monovalent. Because IL-10, a cytokine produced by Treg cells, promotes class switching to IgG4, one possibility is that the infiltrates of IgG4+ plasma cells in IgG4-RD result from Treg cells attempting to dampen the immune response. However, whether the IgG4+ plasma cells damage tissue directly or represent the byproduct of an exaggerated immune response remains unclear.

**HISTOPATHOLOGY**

For several reasons, histopathologic evaluation of affected tissues remains a critical component in the diagnosis of IgG4-RD. The histologic pattern is highly characteristic (with certain caveats described below), and immunohistochemistry demonstrating increased IgG4+ plasma cells is important and necessary confirmatory evidence. Moreover, considering the diverse clinical presentations associated with IgG4-RD, histopathology can both exclude malignancy and alert clinicians to the presence of a separate (and treatable) disease that may have been unsuspected. The major histologic features associated with IgG4-RD have been well described5,10,27,28 and include (1) a dense lymphoplasmacytic inflammatory infiltrate with increased numbers of IgG4+ plasma cells and often increased eosinophils; (2) a storiform pattern of fibrosis; and (3) obliterative vasculitis.

**The Inflammatory Infiltrate**

While IgG4-RD is usually described in terms of increased IgG4+ plasma cells, T cells (predominantly CD4+) actually comprise the bulk of the inflammatory infiltrate (Figure 4, A and B). Other components include small aggregates of B cells (which may be distributed in germinal centers, depending on anatomic location), along with interspersed macrophages and the requisite IgG4+ plasma cells (Figure 4, C and D). These may be diffusely increased (Figure 3, E and H) or distributed in variably dense patches (Figure 4, D). Tissue eosinophilia is usually present (Figure 3, C). Not characteristic are epithelioid granulomas, multinucleated giant cells, overt necrosis, and neutrophilic infiltrates in sites other than the lung (see below). If present, these findings should prompt consideration of alternative diagnoses.

The number of IgG4+ plasma cells should be quantified in some manner, either as the number per high-power field or as the IgG4+/IgG+ plasma cell ratio. The absolute number of IgG4+ plasma cells often varies with anatomic site, and many organ-specific cutoff values of IgG4+ plasma cells per high-power field have been proposed.3,27 These range from greater than 10 to greater than 200 IgG4+ plasma cells, with values in most sites falling somewhere between 10 and 50.
Alternatively, an elevated IgG4+:IgG+ plasma cell ratio may be more specific for IgG4-RD, with most authors recommending a ratio greater than 40% as characteristic.5,27–30 The ratio may be especially useful in evaluating specimens that lack large absolute numbers of IgG4+ plasma cells, such as small needle biopsy samples or specimens consisting predominantly of paucicellular fibrosis.

**Storiform Fibrosis**

This pattern is defined by dense, wirelike strands of fibrotic collagen deposition radiating outward from a central point (Figure 3, A and F; Figure 5, A and B). The collagen fibers contain fibroblasts and myofibroblasts, and may resemble similar arrangements associated with fibrohistiocytic malignancies. In cases of long-standing fibrosis, a sparsely cellular or acellular fibrotic pattern may predominate (Figure 5, B).

**Obliterative Vasculitis**

Inflammatory infiltrates fill both the walls and lumina of the affected vessels, producing partial or complete obliteration (Figure 6, A and B). Veins are most often involved, and fully obliterated veins may sometimes be identified by their proximity to adjacent arteries, which are usually spared. However, arteritis is sometimes observed, especially in the lung, and elastic stains may be required to highlight the residual vessel walls (Figure 6, B). Despite the dense inflammatory infiltrate, necrotizing vasculitis is not characteristic.

**Caveats and Differential Diagnosis**

While the histopathologic and immunohistochemical findings are distinctive, they are not always present to the same extent within each affected organ. Salivary and lacrimal glands, for example, may show more of a thick, collagenous pattern of fibrosis (Figure 3, A and F). These organs are also less likely to feature obliterative vasculitis, and the inflammatory infiltrates may manifest instead as many lymphoid follicles, albeit with increased numbers of IgG4+ plasma cells. In the lung,31 plasma cell–rich infiltrates are often distributed along vessels and lymphatic channels, and may surround bronchioles concentrically. In contrast to other tissues, the infiltrates may include small neutrophilic aggregates within alveolar spaces, although abscess formation and necrosis are not characteristic. Typical storiform fibrosis may be absent, and obliterative vasculitis affects.
both pulmonary arteries and veins. Some of the most variable IgG4-related morphologies occur in lymph nodes, in which 5 separate patterns are recognized and typical storiform fibrosis is again often absent.\(^7\) Since not all histologic features may be present within a given specimen, core needle biopsies may not sample the most important diagnostic areas, and therefore larger specimens should be obtained whenever possible. In addition, owing to their highly variable patterns of involvement, enlarged lymph nodes may not be optimal specimens for diagnosing IgG4-RD prospectively.\(^32,33\)

Further complicating interpretation is the observation that increased numbers of IgG4\(^+\) plasma cells is not a finding specific to IgG4-RD. Many other benign and malignant processes may also feature increased IgG4\(^+\) plasma cells,\(^27,34\) including granulomatosis with polyangiitis,\(^35\) multicentric Castleman disease,\(^36\) Rosai-Dorfman disease,\(^37\) marginal zone lymphoma,\(^38-41\) pancreatic adenocarcinoma,\(^32,42\) and even reactive lymphadenopathy,\(^44\) to name just a few. Additionally, the histologic patterns of both these and other entities sometimes overlap with that of true IgG4-RD. These mimics include lymphoproliferative/histiocytic disorders (multicentric Castleman disease, Rosai-Dorfman disease, lymphoma), autoimmune disorders (Sjögren syndrome in salivary and lacrimal glands, primary sclerosing cholangitis in the liver), spindle cell neoplasms (inflammatory myofibroblastic tumor, desmoid fibromatosis), and infections (especially within the lung). Thus, a specimen with increased IgG4\(^+\) plasma cells and IgG4-RD–like histology must also be interpreted within the context of the associated clinical history. In some cases, judicious use of additional immunohistochemical or special stains may also provide important diagnostic clues.

**CLINICAL DIAGNOSIS, TREATMENT, AND THE ROLE OF THE PATHOLOGIST**

Beyond the histologic findings, the clinical diagnosis of IgG4-RD requires additional correlation with laboratory and radiologic evaluations. According to the proposed Comprehensive Diagnostic Criteria for IgG4-RD,\(^29\) a definite
diagnosis of IgG4-RD may be made by demonstrating (1) organ involvement; (2) a serum IgG4 level exceeding 135 mg/dL; and (3) greater than 10 IgG4+ plasma cells per high-power field and an IgG4+/IgG+ plasma cell ratio of at least 40% on histologic tissue sections. In contrast, if organ involvement is present along with only 1 of the remaining 2 criteria, a diagnosis of IgG4-RD is considered “possible” or “probable.” Confirmation then depends upon the radiologic appearance of the affected organ or organs, organ-specific histologic criteria, or the responsiveness of patient symptoms to a trial of steroids. An elevated serum IgG4 level (>135 mg/dL) is suggestive of IgG4-RD but is not specific, and may be found in patients with chronic sinusitis, pneumonia, other autoimmune diseases, and certain malignancies. Moreover, although the negative predictive value for an elevated serum IgG4 is high (96%), occasional patients will have a normal level despite characteristic IgG4-RD histology on a tissue biopsy.

Once the diagnosis of IgG4-RD has been established, most patients’ symptoms respond within several weeks to treatment and helps to avoid both complications and unnecessary surgical procedures (such as the Whipple resection) that furnished so many autoimmune pancreatitis specimens before IgG4-RD was recognized). The chief responsibilities of the pathologist are awareness of the disease, recognition of its characteristic histology, and appropriate communication with the clinical team. Because histology constitutes only a part of the diagnostic criteria (albeit a major one), one consensus statement recommends a 3-tiered approach to reporting on suspected IgG4-RD specimens. Cases “histologically highly suggestive of IgG4-RD” show, in addition to increased IgG4+ plasma cells, at least 2 of the following: a dense lymphoplasmacytic infiltrate, fibrosis (usually storiform), and obliterator vasculitis (usually phlebitis). Cases showing “probable histologic features of IgG4-RD” may show only 1 of these features, may be insufficiently large (needle cores), or may derive from an anatomic site not typically associated with IgG4-RD. The remaining cases may be described as having “insufficient histopathologic evidence of IgG4-RD,” with the caveat that the diagnosis is not excluded. While not providing a definitive diagnosis, these designations at a minimum alert the clinical team to the possibility of IgG4-RD, which may prompt further diagnostic laboratory and radiologic evaluations.

CONCLUSIONS

IgG4-RD is a systemic autoimmune disease with distinctive histopathology and protean clinical implications. Histopathologic examination of affected tissues is crucial for diagnosis, partly because the pattern is so distinctive, but also because the disease may be unsuspected owing to its diverse and nonspecific clinical presentations. Pathologists’ familiarity with and prompt recognition of the features of IgG4-RD allows clinicians to institute proper treatment and avoid unnecessary comorbidities.

References