

Extra-Pancreatic Features of Autoimmune Pancreatitis (IgG4-Related Disease)

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Introduction

IgG4-related disease (IgG4-RD) was identified and recognized as a multi-organ disease during the first decade of this century. The disease is characterized by histopathology and immunohistochemical staining patterns that are consistent across many organ systems (54). It is easier to indicate which organs are affected seldom (if ever) than to list all of the systems involved by this condition. To date, it has been rare to find confirmed cases of IgG4-RD affecting the brain parenchyma, muscle tissue, synovium, and bone marrow. Virtually every other organ is now known to be affected by IgG4-RD, with some organs affected more commonly than others.

IgG4-RD was first identified in the pancreas. During the 1990s, the concept of “autoimmune pancreatitis” (AIP) began to emerge from a variety of other names for a condition associated with sclerosing inflammation in that organ (68). “Sclerosing pancreatitis” was linked to elevated serum concentrations of IgG4 in 2001 (17). IgG4-RD was recognized as a systemic condition in 2003, when a variety of extra-pancreatic lesions were observed to occur in patients with AIP (20, 22).

IgG4-RD is now known to affect the pancreas, biliary tree, salivary glands, periorbital tissues

(e.g., the lacrimal gland and retro-orbital space), kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid gland, pericardium, and skin (**Table 1**) (16, 18, 15, 59, 21, 11, 50, 65, 10, 72, 46, 62, 26, 23, 52, 56, 19, 71). The general pathology findings in any organ include a lymphoplasmacytic infiltrate, fibrosis that typically has a storiform pattern, obliterative phlebitis, modest tissue eosinophilia, and the tendency to form tumefactive lesions (14). This chapter is devoted to a review of the extra-pancreatic features of IgG4-RD that can be seen in those with type 1 AIP.

Nomenclature

The Organizing Committee of the 2011 Boston International Symposium on IgG4-RD recommended names for the individual organ system manifestations of this disease (50). These are shown in **Table 2**. The nomenclature system reinforces the concept that the same fundamental pathophysiologic processes are operative across organ systems, regardless of whether the role of IgG4 is primary or secondary. Individual organ involvement is referred to in a style that employs “*IgG4-related-*” as a prefix. As examples, the most common form of kidney involvement in IgG4-RD is termed IgG4-related tubulointerstitial nephritis, and eye manifestations of this condition are regarded collectively as IgG4-related ophthalmic disease.

Table 1. Clinical Manifestations of IgG4-Related Disease by Organ System.

Organ System	Clinical Feature
Eyes	Chronic sclerosing dacryoadenitis Orbital pseudotumor Extension of pseudotumor along trigeminal nerve Orbital myositis Scleritis
Ears	Destructive disease of middle ear
Nose	Eosinophilic angiocentric fibrosis
Salivary glands	Chronic sclerosing sialadenitis (submandibular & parotid glands)
Lymph nodes	Generalized or localized lymphadenopathy
Thyroid gland	Fibrosing variant of Hashimoto's thyroiditis, Riedel's thyroiditis
Lungs and airways	Pulmonary nodules, ground-glass opacities, alveolar/interstitial inflammation, bronchovascular bundle thickening, pleural thickening, large airway disease leading to tracheobronchial stenosis
Heart	Pericarditis (sometimes with constriction)
Aorta	Thoracic aortitis, abdominal aortitis, inflammatory aortic aneurysms, aortic dissection
Retroperitoneum	Retroperitoneal fibrosis
Pancreas	Type 1 autoimmune pancreatitis
Biliary tree	Sclerosing cholangitis mimicking primary sclerosing cholangitis
Skin	Erythematous or flesh-colored papules or plaques on the face or head
Central nervous system	Hypopituitarism, hypertrophic pachymeningitis
Peripheral nervous system	Perineural inflammation
Other	Prostatism, sclerosing mesenteritis, fibrosing mediastinitis

Systemic Features

IgG4-RD typically has an indolent presentation. Features of the disease generally become manifest after months or even years. In addition, constitutional symptoms are subtle or absent in the majority of patients, who often feel relatively well even in the setting of multi-organ disease. Others, however, have anorexia and weight loss that becomes substantial over time. A minority of patients have more explosive presentations characterized by constitutional symptoms, fevers, and acute phase reactant elevations.

Tumefactive Lesions (Pseudotumors)

Patients with IgG4-RD are often suspected or even misdiagnosed initially as having a malignancy, because of the disease's predilection for causing mass-forming lesions within organs. Many patients are subjected to pancreatic resection out of concern for pancreatic cancer. In addition, pseudotumors are reported commonly in the orbital region, salivary glands, lung, kidney, lymph nodes, retroperitoneum, and other organs (72, 71, 27). Many have an indolent course, but local tissue destruction including the erosion of bone and aortic aneurysms or dissections have been reported (52, 28, 37, 48, 5, 53).

Table 2. Preferred Nomenclature for Individual Organ Manifestations of IgG4-Related Disease.

Organ System/Tissue	Preferred Name
Pancreas	Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
Eye	IgG4-related ophthalmic disease is the general term for the peri-ocular manifestations of this disease. There are several subsets, outlined below.
Lacrimal glands	IgG4-related dacryoadenitis
Orbital soft tissue (orbital inflammatory pseudotumor)	IgG4-related orbital inflammation (or IgG4-related orbital inflammatory pseudotumor)
Extra-ocular muscle disease	IgG4-related orbital myositis
Orbit with involvement of multiple anatomic structures	IgG4-related pan-orbital inflammation (includes lacrimal gland disease, extra-ocular muscle involvement, and other potential intra-orbital complications)
Salivary glands (parotid and submandibular glands)	IgG4-related sialadenitis or, more specifically, IgG4-related parotitis or IgG4-related submandibular gland disease
Pachymeninges	IgG4-related pachymeningitis
Hypophysis	IgG4-related hypophysitis
Thyroid (Riedel's thyroiditis)	IgG4-related thyroiditis
Aorta	IgG4-related aortitis/periaortitis
Arteries	IgG4-related periarteritis
Mediastinum	IgG4-related mediastinitis
Retroperitoneum	IgG4-related retroperitoneal fibrosis
Mesentery	IgG4-related mesenteritis
Skin	IgG4-related skin disease
Lymph node	IgG4-related lymphadenopathy
Bile ducts	IgG4-related sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis
Liver	IgG4-related hepatopathy (refers to liver involvement that is distinct from biliary tract involvement)
Lung	IgG4-related lung disease
Pleura	IgG4-related pleuritis
Pericardium	IgG4-related pericarditis
Kidney	IgG4-related kidney disease. The specific renal complications should be termed tubulointerstitial nephritis secondary to IgG4-RD and membranous glomerulonephritis secondary to IgG4-RD. Involvement of the renal pelvis should be termed IgG4-related renal pyelitis.
Breast	IgG4-related mastitis
Prostate	IgG4-related prostatitis

Diffuse infiltrative lesions also occur in organs such as the meninges, skin, or aorta.

Inflammatory pseudotumors have been described in IgG4-RD involving the lung and central nervous system (10, 72, 71, 32), as well as in the orbit (29), salivary gland (66), paraspinal regions (6), and other tissue and organs. Because of the tendency of IgG4-RD to cause tumefactive lesions, immunostaining should be performed on

all pseudotumors with significant infiltrates of plasma cells and fibrosis (61).

Multifocal Fibrosclerosis

A condition known as multifocal fibrosclerosis was identified first in the 1960s (9). Multifocal fibrosclerosis, often characterized by the simultaneous occurrence of other fibrotic syndromes such as Riedel's thyroiditis, hypertrophic pachymeningitis (3, 31),

retroperitoneal fibrosis, fibrosing mediastinitis (59), sclerosing mesenteritis (4), and orbital pseudotumor, is probably explained in most cases by IgG4-RD.

Allergic Disease

Allergic or atopic manifestations occur in approximately 50% of patients with IgG4-RD. Patients with IgG4-RD often have longstanding histories of allergic rhinitis, sinusitis, asthma, and other clinical features of this nature. Many patients have substantial elevations of serum IgE concentrations or peripheral eosinophilias that sometimes approach 25% of the total white blood cell count. Mild to moderate eosinophil infiltration is also typical of tissue lesions (14).

Eosinophilic angiocentric fibrosis

One subset of IgG4-RD associated with striking allergic features is eosinophilic angiocentric fibrosis (EAF), an uncommon tumefactive lesion of the orbit and the upper respiratory tract (41, 12). The histopathology of this condition is characterized by an overabundance of eosinophils as well as an admixture of lymphocytes and plasma cells. Small-caliber arterioles in EAF demonstrate “onion-skinning” – concentric layers of fibrosis – of the blood vessels. Patients with EAF share the broader tendency of IgG4-RD to form tumefactive lesions within involved organs.

Lymphadenopathy

Lymphadenopathy in IgG4-RD generally takes two forms. First, generalized lymphadenopathy can be the major or sole component of the clinical presentation. Patients with IgG4-related lymphadenopathy of this nature are often constitutionally well, at least for prolonged periods. Second, involvement of lymph nodes as localized disease adjacent to a specific organ affected by IgG4-RD (e.g., the pancreas) is common.

Patients with IgG4-related lymphadenopathy often undergo serial lymph node biopsies to exclude

lymphoma, sarcoidosis, multicentric Castleman’s disease, or disseminated malignancies. Rendering the diagnosis of IgG4-RD purely on the basis of lymph node pathology is difficult at the present time, however, because the histology of lymph nodes in this setting is remarkably variable (47). Clinicians must seek evidence of disease in other organ systems typically involved by IgG4-RD in order to be confident of the diagnosis. Increased numbers of IgG4⁺ plasma cells, of course, are universal, but the storiform fibrosis so common in other types of IgG4-RD organ involvement is unusual in IgG4-related lymphadenopathy. Lymph node biopsies in most cases are reported as “reactive follicular hyperplasia,” and specific stains for IgG4 generally not performed because the diagnosis is not considered.

Specific Organ Involvement by Body Region

The discussion of specific organ involvement is divided by the different major body regions: the head and neck, the chest, the abdomen/retroperitoneum, and miscellaneous.

Head & Neck

Meninges

A study of fifteen cases of idiopathic hypertrophic pachymeningitis found that IgG4-RD, linked to four of the cases (27%), was the most common disease association (62). Other causes in that series were granulomatosis with polyangiitis (3 cases) and miscellaneous other diagnoses including sarcoidosis, lymphoma, giant cell arteritis, and rheumatoid arthritis. This study confirmed an earlier one that had demonstrated IgG4-RD to be the cause of five out of ten cases of idiopathic lymphoplasmacytic meningeal inflammation (31).

Pituitary gland

The presence of IgG4-RD in other organs and elevated serum IgG4 concentrations are common

features of IgG4-related hypophysitis and often constitute a major clue to the diagnosis of IgG4-related hypophysitis. The radiologic findings in this entity include a pituitary mass or thickened pituitary stalk. Most IgG4-RD patients with hypophysitis are middle-aged men who present with various degrees of anterior or posterior hypopituitarism. IgG4-RD must be differentiated from sarcoidosis, granulomatosis with polyangiitis (formerly Wegener's), histiocytosis, and lymphoma as causes of hypophysitis. Both glucocorticoid therapy and rituximab can lead to resolution of imaging abnormalities and clinical signs of pituitary insufficiency.

Salivary Glands

"Küttner's tumor", another disorder described originally in the 1890s (30), consists of a tumorous swelling of the submandibular glands (**Figure 1**). Bilateral submandibular gland swelling in the absence of stones within Wharton's duct is commonly associated with IgG4-RD (16, 8). In contrast to Sjögren's syndrome (SjS), in which the degree of parotid enlargement is often dramatically out of proportion to that of the submandibular glands, the opposite pattern is more typical of IgG4-related sialadenitis. Submandibular gland disease often occurs in IgG4-RD in the absence of any clinical evidence of parotid gland enlargement, but parotid disease in IgG4-RD is also described (**Figure 2**). Salivary gland involvement consists of firm, nodular swelling that is generally symmetrical and associated with pain, tenderness, and decreased saliva production. The sublingual glands can also be affected by IgG4-RD (**Figure 2**).



Figure 1. Submandibular gland involvement.

Submandibular gland enlargement occurring during a flare of IgG4-related disease in a patient with a history of IgG4-related sclerosing cholangitis.

The triad of swelling in the submandibular, parotid, and lacrimal glands, first described in 1892, was termed "Mikulicz disease" for more than 100 years (34, 35). For decades, Mikulicz disease was believed to be a variant of SjS (35, 36), and even today patients with IgG4-RD are continually misdiagnosed with SjS. IgG4-RD can be differentiated clearly from SjS on the basis of clinical, serological, and pathological findings (67).

Minor salivary glands of the lip may be affected, as demonstrated by lip biopsy (2). Minor salivary gland disease can be present even when the glands are macroscopically normal. The sensitivity and specificity of minor salivary gland biopsy in patients with IgG4-RD have not been well defined.



Figure 2. Parotid and sublingual gland disease. Parotid and sublingual gland enlargement. The sublingual glands have herniated through the floor of the mouth.

Ophthalmic disease

The orbital tissues are perhaps the most commonly affected region of the body in IgG4-RD. IgG4-RD accounts for a substantial percentage – at least 25% – of the cases of “idiopathic” orbital inflammation, a differential diagnosis that includes lymphoma, granulomatosis with polyangiitis, Graves’ orbitopathy, and other conditions (56).

The ocular structures affected by IgG4-RD include the lacrimal glands (dacryoadenitis) (**Figure 3**), the nasolacrimal duct, and the retro-bulbar region that is frequently involved by orbital pseudotumor (**Figure 4**), and the extra-ocular muscles (a condition often termed “orbital myositis”) (64, 37, 46, 7). As noted, many cases of IgG4-related dacryoadenitis are accompanied by salivary gland disease. In some patients with IgG4-related ophthalmic disease, the process extends beyond the orbit and tracks along the course of the trigeminal nerve (37, 24).

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Figure 3. Dacryoadenitis. Lacrimal gland swelling in a patient with IgG4-related disease.

Thyroid gland

Riedel’s thyroiditis has been identified as a manifestation of IgG4-RD (11). Although thyroid gland biopsies from patients with advanced disease simply demonstrate glandular fibrosis, biopsies from early in the disease course demonstrate the classic pathologic hallmarks of IgG4-RD. The fibrosing variant of Hashimoto’s thyroiditis also appears to be part of the IgG4-RD spectrum, at least in a percentage of cases (13). Finally, it has been postulated that classic Hashimoto’s thyroiditis, distinct from the fibrosing variant discussed above, also falls within the IgG4-RD spectrum and might account for the high frequency of hypothyroidism in AIP. This putative “IgG4-related thyroiditis” is said to have a lower

likelihood of anti-thyroid autoantibodies compared with Hashimoto's thyroiditis, a low likelihood of diffuse goiter, and a favorable response to glucocorticoid treatment. However, relatively few such cases have been examined histopathologically and this hypothesis remains controversial and unconfirmed.



Figure 4. Orbital pseudotumor. Left eye proptosis caused by an orbital pseudotumor that spared the lacrimal gland.

Chest

Lung

Pulmonary involvement in IgG4-RD is protean in its scope, and understanding of the nature and extent of lung and airway disease continues to evolve. At least six major patterns of IgG4-related pulmonary disease are described on the basis of radiological and histological findings (72, 70, 58, 49): 1) nodules; 2) thickening of the bronchovascular bundle (**Figure 5**); 3) alveolar interstitial disease (with honeycombing, bronchiectasis, and diffuse ground-glass opacities); 4) rounded ground-glass opacities; 5) pleural lesions associated with severely thickened visceral or parietal pleura with diffuse sclerosing inflammation; and, 6) airway lesions leading to narrowing.

Some patients with IgG4-related lung disease experience cough, hemoptysis, dyspnea, pleural effusion, or chest discomfort (15, 56, 58). In others, however, the presence of lung disease is asymptomatic and discovered only incidentally upon imaging.

Thoracic Aorta

IgG4-RD appears to account for at least 10% of cases of inflammatory aortitis involving the thoracic aorta (51). The lymphoplasmacytic aortitis associated with IgG4-RD must be distinguished from the granulomatous inflammation that accompanies a somewhat larger subset of cases diagnosed as giant cell aortitis. The entity referred to by the descriptive pathologic term “chronic sclerosing aortitis” probably represents IgG4-RD in the great majority of cases. The term “isolated aortitis” should generally be regarded as unsatisfactory now without thorough attempts at differentiating IgG4-related aortitis from giant cell aortitis and other causes of aortic inflammation.

Retroperitoneum & Abdomen

Manifestations of IgG4-RD within many of the abdominal organs are addressed in detail in other sections of this publication; namely, those associated with pancreatic, biliary, liver, or gallbladder disease (*insert links to Chapter 5. CT and MR features of autoimmune pancreatitis, Chapter 6 ERCP features of autoimmune pancreatitis*). This section, therefore, focuses on retroperitoneal organs.

Chronic Periaortitis

Chronic periaortitis is now regarded as the umbrella term for inflammation in the retroperitoneum and peri-aortic regions that includes such entities as retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, and perianeurysmal fibrosis (39). IgG4-RD is now known to cause well over half of the cases previously regarded as “idiopathic” retroperitoneal fibrosis (**Figure 6**) (25, 73). When detected early, biopsies from patients with retroperitoneal fibrosis whose disease demonstrate histopathological and immunohistochemical features that are diagnostic of IgG4-RD (73). In contrast, biopsies performed in patients at a later phase of disease simply show fibrosis, because they represent a more advanced IgG4-RD stage in which the fibrotic features have become predominant.

Nevertheless, the storiform morphology of the fibrosis can still be highly suggestive of IgG4-RD. In such cases, the IgG4/total IgG ratio within tissue rather than the number of IgG4-positive plasma cells/high-power field is often a key to recognizing IgG4-related retroperitoneal fibrosis (25).

The first study to connect retroperitoneal fibrosis and the entity now termed IgG4-RD was that of Hamano et al. (18), who reported three patients with retroperitoneal fibrosis and elevated serum IgG4 concentrations. Zen et al. reported that 10 of 17 retroperitoneal fibrosis patients had both elevated serum IgG4 concentrations and histopathological features typical of IgG4-RD (73).

Moreover, IgG4-related retroperitoneal fibrosis had an overwhelming tendency to occur in males. This tendency was confirmed by Khosroshahi et al. (25), who identified the histopathological and immunohistochemistry signature of IgG4-RD in the biopsies of 13 of 23 cases of “idiopathic” retroperitoneal fibrosis.

Inflammatory abdominal aortic aneurysm is also associated with IgG4-RD (23,53). Patients with inflammatory abdominal aortic aneurysms have clinical, demographic, and radiologic features that are distinct from those of patients with classic atherosclerotic aortic aneurysms.



Figure 5. Pulmonary involvement in IgG4-related disease. This computed tomographic scan of the chest shows thickening of the bronchial wall and a pulmonary nodule in the anterior right upper lobe.



Figure 6. Retroperitoneal fibrosis. Computed tomographic scan of the abdomen reveals an inflammatory mass surrounding the abdominal aorta.

Kidney

The radiologic appearance of the kidneys in IgG4-related renal disease can take several forms. Diffuse enlargement accompanied by parenchymal hypodensities may occur. Focal tumefactive lesions may also develop, mimicking renal cell carcinoma (10). More than one such lesion within any kidney can occur. A thickening of the renal pelvis has also been described (40). Finally, following a period of IgG4-related renal disease, pronounced atrophy of the kidneys can ensue. This atrophy can occur even in patients whose disease has appeared to respond to therapy with glucocorticoids (42).

The most common histopathological correlate of these radiologic findings is tubulointerstitial nephritis (TIN), which consists of patchy or diffuse tubulointerstitial lymphoplasmacytic infiltrates within a fibrotic interstitium (44). The clinical manifestations of IgG4-related TIN include proteinuria, hematuria, and decreased kidney function, sometimes culminating in end-stage renal disease (58, 66).

Patients with IgG4-related renal disease are typically hypocomplementemic and often profoundly so (43). The basis for this phenomenon remains incompletely defined, because the IgG4 molecule itself does not activate complement avidly. Nevertheless, renal biopsies in IgG4-related TIN demonstrate immune complexes that consist in part of IgG4 (10). The

TIN associated with IgG4-RD can be differentiated histopathologically and immunohistochemically from other causes of TIN (40, 38). The great majority of patients with IgG4-related renal disease also have disease that is manifest in other organs, as well (42).

A second form of renal disease – membranous glomerulonephritis (MGN) – has also been described in IgG4-RD, although this lesion is decidedly less common than TIN (42, 1). Nephrotic-range proteinuria can occur in IgG4-related MGN. IgG4-related MGN comprises a disorder that is distinct from idiopathic MGN, even though the autoantibody associated with the latter disorder is also principally of the IgG4 subclass. The MGN associated with IgG4-RD is probably secondary to immune complex deposition rather than to the usual destructive inflammatory process that characterizes other organ involvement by this condition.

Miscellaneous Organ Involvement

Miscellaneous organs in which the typical histopathological features of IgG4-RD have been reported include the skin (26), prostate gland (1, 70, 61), and pericardium (55). In all of these reports, the patients' clinical features have been associated with disease in more classic IgG4-RD

organs, as well. The true frequency with which IgG4-RD affects these organs is not known for certain, because the presence of disease there can be extremely subtle. In the skin, for example, IgG4-RD causes flesh-colored or erythematous papules that are often asymptomatic. Similarly, symptoms of prostatism in middle-aged to elderly males are likely to be diagnosed as benign prostatic hypertrophy. IgG4-related prostate disease, however, is known to cause symptoms of “benign prostatic hypertrophy” in men in their 30s.

Summary

Type 1 AIP is the pancreatic manifestation of a systemic disease referred to as IgG4-RD. The current diagnostic criteria for AIP recognize typical other organ involvement including proximal biliary strictures, retroperitoneal fibrosis, symmetric enlargement of salivary/lacrimal glands, and renal disease. However, manifestations and currently is recognized to involve essentially any organ. Histology is important not only to identify diagnostic features of IgG4-RD, but also to exclude malignancy in those with mass-forming lesions.

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