IgG-4 related disease: A mini-review
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ABSTRACT
IgG4-related disease is a fibroinflammatory condition that mimics many malignant, infectious, and inflammatory disorders. Histopathology is key to diagnosis and is hallmarked by tumor like infiltration of IgG4 positive plasma cells in tissues, with dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis. Disease has been reported in virtually every organ system1-4. Though the underlying pathophysiology is still unclear, untreated disease ultimately leads to irreversible fibrosis. We describe the pathogenesis, diagnosis, and relevant features of IgG4-related disease and discuss current evidence regarding treatment.

The role of IgG4 in disease
IgG4 is an antibody with unique structure and function5. It is the least abundant IgG subclass, accounting for <5% of total IgG. IgG4 is a noninflammatory immunoglobulin that might function in antigen-capture, preventing the binding of yet unidentified antigens that drive inflammatory processes. Responses of IgG4 have been induced by prolonged or repeated antigen exposures (6). IgG4 production is thought to be controlled primarily by type 2 helper T (Th2) cells5,6.

The molecule of IgG4 is thought to play an important role in immune mediated conditions. IgG4 antibodies against desmoglein are responsible for the formation of cutaneous blisters in pemphigus vulgaris7. They also have been implicated in idiopathic membranous glomerulonephritis and in thrombotic thrombocytopenic purpura8,9.

Pathophysiology
The pathogenesis of IgG4-related disease is vague and still immature in scientific study. The two prevailing theories underlying observed pathology include 1) induction of a polarized CD4+ T cell that activates innate immune cells responsible for the development of fibrosis and 2) a negative feedback process involving generation of IgG4 secreting plasmablasts, plasma cells, and IgG4 antibodies responsible for preventing autoimmunity. Autoimmunity has been hypothesized to be a potential initial immunologic stimulus for the Th2-cell response in IgG4 related disease10-12.

T cells are commonly linked in disease pathogenesis due to the observation that many CD4+ T cells are present at sites of inflammation in IgG4-related disease. Recent published studies have also shown that Th2 memory cells do aggregate in a large percentage of people with IgG4-related disease if they have concomitant atopy13,14. Large clonal expansions of cytotoxic CD4+ cytotoxic...
T lymphocytes have been found in affected tissues, in addition to activated CD19+CD20-CD38^high/CD27^high B cells (called plasmablasts). The reason and nature of the disease-causing CD4+ T cells remains to be elucidated.

Eosinophilia and elevations in serum IgE levels have been found in 40% of patients with IgG4 related disease; extreme cases have been reported resembling eosinophilic organopathy. Ultimately, an encounter with a microbe likely triggers tissue damage with breaks in immunologic tolerance. Activated CD4+ T-helper cells induce a fibrosis driven cytokine pathway. These memory T cells that help coordinate disease are presumably sustained by plasmablasts, explaining potential responses to B-cell depletion.

**Pathologic features of IgG4-related disease**

Histologic examination of biopsy specimens is the gold standard in diagnosing IgG4-related disease. Even with supportive histopathology, clinical symptoms and serologic findings are needed to confirm diagnosis. Serum IgG4 is elevated in most cases, but about 30% of histologically confirmed cases have normal levels of IgG4, which can lead to false negatives. In general, the specificity and positive predictive value of serum IgG4 are low. Misdiagnosis is common due to overreliance on mild elevations of serum IgG4 or the presence of IgG4-positive plasma cells in tissue (Table 1).

The typical histologic abnormalities are a dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis. Due to patchy distribution, storiform fibrosis can escape detection due to sampling error, especially if obtained by needle biopsy (Figure 1). Fibrosis is very rare in lymph nodes; diagnosis of IgG4-related disease is therefore extremely difficult on lymph-node pathology alone. Granulomas are unusual and if found suggest alternative etiology. Though histologic features are similar for all organs, subtle pathologic variations exist among affected organ systems. Immunohistochemical confirmation with IgG4 immunostaining is required (Figure 2).

**Immunostaining**

Inflammatory infiltrates are composed of both T and B-lymphocytes. High numbers of IgG4 positive plasma cells are required for diagnosis, but are commonly found in other inflammatory infiltrates such as xanthogranulomatous disease, granulomatosis with polyangitis, Castelman’s disease, sarcoidosis and neoplastic disorders. Lymphoma is the closest histologic relative of IgG4 related disease and clonal studies should be considered to rule out malignancy. Simple presence of IgG4 positive plasma cells is insufficient to establish a diagnosis of IgG4-related disease. A variety of

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**Table 1: Diagnostic criteria for IgG4-Related Disease.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tr>
<td>A dense lymphoplasmacytic infiltrate,</td>
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<td>Storiform fibrosis, and</td>
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<tr>
<td>Obliterative phlebitis</td>
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The presence of these findings, with or without tissue eosinophilia, is strongly suggestive of IgG4-related disease. Disease is more suggestive if accompanied by increased numbers of IgG4-positive plasma cells. Sizeable minority have normal serum IgG4 despite classic histopathological changes in tissue.

The diagnosis cannot be made solely by the number of IgG4-positive plasma cells as many other disease states have similar findings. Serum IgG4 concentrations are neither sensitive nor specific for this disease. Histologic confirmation of the diagnosis by biopsy of an involved organ is necessary.
cutoff points for the number if IgG4-positive plasma cells required for diagnosis have been suggested, ranging from 10 to 50 IgG4 positive plasma cells per high-power field \(^\text{19-21}\). In addition, the ratio of IgG4/IgG positive plasma cells in tissues should be greater than 40%. Diagnosis is important to consider early in disease, as late stage is hallmarked by fibrosis and unlikely to respond to treatment. Several sets of diagnostic criteria have been devised and proposed for practical use by nonspecialists \(^\text{22-25}\).

**Epidemiologic characteristics**

Epidemiologic understanding of IgG4-related disease is limited due to insufficient awareness of the diagnosis and its only recent appearance in the medical literature. Several observations however have been noted: patients are mostly male and older than 50 years of age \(^\text{26}\). Male predominance is much more prevalent in disease involving the kidney and retroperitoneum, with reported prevalence as high as 90% \(^\text{27}\). The higher disease prevalence in men is in contrast to other autoimmune diseases hallmarked by female predominance by nine to one. The differences in expression between the two sexes are unclear.

**The role of imaging**

Although definitive diagnosis of IgG4-related disease requires histopathology analysis, radiologic imaging plays an important role in demonstrating features suggestive of the diagnosis. Imaging workup for IgG4-related disease should include a CT scan of the chest, abdomen and pelvis to detect possible multiorgan involvement, specifics of which will be further described. Cross sectional imaging can supplement diagnostic criteria for IgG4-related disease. Key features can be seen based on the involved organ. In general, imaging studies will demonstrate infiltration and enlargement of involved organs. Other general radiologic features include glandular swelling, nodularity, organ wall thickening, fibrosis, and lymphadenopathy. Familiarity with radiologic findings can help avoid delays in diagnosis, unnecessary surgical procedures, establish a biopsy site for histologic analysis, and allow for timely initiation of appropriate therapy. Use of positron emission tomography-computed tomography (PET-CT) is advocated by many. Studies have shown its utility for diagnosis, staging, and monitoring of response. This imaging method, in comparison to ultrasonography and CT has yielded better results \(^\text{28}\).

**Clinical features and organ involvement**

The clinical features of IgG4-related disease (Table 2) will be discussed in the context of the body cavities in which they occur and typical radiographic findings:

**Constitutional and musculoskeletal symptoms**

The presentation of IgG4-related disease is typically subacute. Symptoms may wax and wane with spontaneous improvement, with years of disease inactivity. Fatigue and musculoskeletal complaints are common, especially with multiorgan system involvement. Constitutional features, such as fevers and elevations of inflammatory markers, are not typical.

**Head and neck**

Salivary glands may be affected by IgG4-related disease. Submandibular gland involvement is particularly characteristic, and carries the eponym Kuttner’s tumor \(^\text{29}\). In contrast to Sjogren’s syndrome, symptoms improve with immunosuppression. Isolated enlargement of the submandibular gland, common to IgG4-related disease, is uncommon in Sjogren’s disease, which is hallmarked by parotid gland enlargement. CT imaging demonstrates homogenous attenuation and enhancement. On MRI, low signal intensity is seen on T2 imaging secondary to fibrosis \(^\text{30}\).

Allergic features are most prominent in the ears, nose,

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| Orbits & periorbital tissues: tumefactive lesions, orbital pseudotumor, dacrocystitis, orbital myositis |
| Ears, nose, sinuses: allergic phenomena, eosinophilic angiocentric fibrosis |
| Salivary glands: submandibular and/or parotid enlargement |
| Meninges: predilection for dura, formation of mass lesions |
| Lymph nodes: lymphadenopathy |
| Thyroid: Riedel’s thyroiditis (fibrosing variant of Hashimoto’s thyroiditis) |
| Lungs: inflammatory pseudotumor, central airway disease, diffuse interstitial pneumonia, pleuritis |
| Aorta: lymphoplasmacytic aortitis, periarteritis, periarteritis, inflammatory aneurysms |
| Retroperitoneum: retroperitoneal fibrosis |
| Kidneys: tubulointerstitial nephritis, asymptomatic tumoral lesions |
| Pancreas: type I autoimmune pancreatitis |
| Biliary tree: sclerosing cholangitis |
| Liver: inflammatory mass lesions (pseudotumor) |
| Gallbladder: lymphoplasmacytic sclerosing cholecystitis |
| Sclerosing mediastinitis and mesenteritis |
| Breast, prostate, skin, and peripheral nerve involvement also described |

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**Table 2: Organ Involvement in IgG4-Related Diseases (IgG4-RD).**
and throat. Presentation includes allergic rhinitis, nasal polyps, chronic sinusitis, nasal obstruction, and rhinorrhea. Mild to moderate peripheral eosinophilia and elevated serum IgE levels are common. Despite these findings, most patients with IgG4-related disease lack atopy.\textsuperscript{31}

IgG4-related disease can lead to inflammation in the pharynx, hypopharynx, and can present with mass lesions.\textsuperscript{32} Mass lesions can occur in the sinuses, middle ear, and facial bones. Tracheal inflammation and vocal cord involvement have been described, but further studies are needed to better elucidate its relationship to subglottic stenosis.\textsuperscript{33}

Thyroid gland enlargement secondary to Riedel’s thyroiditis can present with neck pain, dyspnea, dysphagia and dysphonia. They thyroid gland can become sclerotic overtime and disease extension to adjacent tissues is well documented. CT demonstrates focal or diffuse low attenuation of the thyroid.\textsuperscript{34}

**Intracranial disease**

Intracranial presentations of pachymeningitis and hypophysitis have been noted. Presentation includes headache, radiculopathy, cranial nerve palsies, or symptoms consistent with spinal cord compression. Mass lesions have also been seen, leading to the disease description of hypertrophic patchymeningitis.\textsuperscript{35} Of note, IgG4-related disease does not typically affect brain parenchyma.

**Lungs**

Lung manifestations of IgG4-related disease are diverse. The disease tracks along bronchi and blood vessels, and can be seen on imaging as pulmonary nodules, ground-glass opacities, pleural thickening or interstitial lung disease.\textsuperscript{36} Clinical symptoms include cough, hemoptysis, dyspnea, pleural effusions, and chest pain. More vascular lesions and obliterator phlebitis occur in the lungs (Figure 3). In addition, neutrophilic infiltration is more common in the lungs than in other organs.\textsuperscript{36,37} Pleural effusions can occur. On CT, findings are nonspecific, and usually appear as ground glass opacities. Honeycombing may also be seen, making it difficult to distinguish from nonspecific interstitial pneumonia.\textsuperscript{37}

**Thoracic aorta**

IgG4-related aortitis can cause aneurysms or dissections of the thoracic aorta. Arterial wall thickening and aortic dilatation can be detected on cross imaging studies.\textsuperscript{37} Coronary artery lesions are rare. Fibrosing mediastinitis has been described and can be difficult to treat as compression of mediastinal structures is not uncommon. Storiform fibrosis can be seen under the microscope.\textsuperscript{38}

**Pancreas**

The pancreas was the first organ recognized as related to IgG4 disease.\textsuperscript{4} Type 1 autoimmune pancreatitis presents with mild abdominal pain, weight loss, and painless and often obstructive jaundice. It is characterized histopathologically by lymphoplasmacytic sclerosing pancreatitis. Two main recognized patterns have been recognized: diffuse and focal. Diffuse disease is more common and is characterized by an enlarged pancreas with absence of pancreatic ducts. Focal disease has a characteristic enlargement of the pancreatic head and appears very similar to mass like lesions. International diagnostic criteria have been proposed and include imaging, serum IgG4 concentrations, pancreatic histology, extrapancreatic disease, and glucocorticoid responsiveness.\textsuperscript{22} Endoscopic ultrasound should be performed, with fine needle aspiration, to exclude pancreatic malignancy.

**Biliary tract and liver**

IgG4-related sclerosing cholangitis is commonly associated with type 1 autoimmune pancreatitis.\textsuperscript{39} If untreated, it can progress to end-stage liver disease and is extremely difficult to differentiate from primary sclerosing cholangitis. The histology includes obliterator phlebitis and transmural fibrosis. Dense infiltrates of IgG4-positive plasma cells and T cells can be seen. IgG4-related disease can similarly affect the liver. Patients present with mass lesions and clinically with obstructive jaundice. If the mass lesions occlude the bile ducts, presentation may resemble cholangiocarcinoma.\textsuperscript{40} Imaging may show focal or diffuse bile duct thickening, often associated with stenosis or upstream dilatation. These findings may similarly be depicted on ERCP or MRCP.

**Retroperitoneal fibrosis & kidney involvement**

A large percentage of idiopathic retroperitoneal fibrosis has been linked to IgG4-related disease.\textsuperscript{41} Storiform fibrosis and obliterator phlebitis are commonly identified. In the
kidney, tubulointerstitial disease is common. Although presentation is typically indolent, nephrotic syndrome and advanced renal failure can occur. Histopathology is similar to other organs. Kidney disease is differentiated from other organs by profoundly low complement levels. At this time, the cause of low complement is poorly understood. Renal lesions are usually not visible on nonenhanced CT. MR imaging show low intensity on both T1 and T2 weighted images, with mild enhancement on T1 after contrast administration.

Other organs

Many patients with IgG4-related disease have allergic features seen in atopy, eczema, chronic sinusitis and asthma. Modest elevations in eosinophils can be observed. Cutaneous disease and skin manifestations are rare, with typical lesions being erythematous, flesh colored papules on the face.

Serologic findings

Though the majority of patients with IgG4-related disease have elevations in serum IgG4 levels, 30% of patients do not, despite confirmation of tissue pathology. In addition, data regarding serial measurements of IgG4 concentrations as indicators of disease activity are mixed. IgG4 levels do decrease after initiation of glucocorticoid treatment in the majority of patients, but regularly remain above baseline weeks to months later. Identifying high numbers of circulating plasmablasts by flow cytometry is more sensitive than serum IgG4 concentrations, but testing assays are not widely accessible.

Treatment

No randomized trials exist at this time and large retrospective studies are few. Review of current literature suggests early aggressive treatment to prevent serious organ dysfunction and failure. Glucocorticoids are the first line of treatment. Unfortunately, many patients require a prolonged course. A consensus statement from Japan suggests starting with prednisolone at a dose of 0.6mg per kilogram for 2 to 4 weeks with a very slow taper, adjusted according to aggressiveness of disease. Though glucocorticoids appear to be effective in the short-term, disease flairs and relapse are common despite maintenance therapy. Glucocorticoid sparing agents and DMARDs, such as azathioprine, mycophenolate mofetil, and methotrexate, have been used, though efficacy has not been validated in clinical trials. Rigorous assessment of these treatments is needed.

Patients with refractory disease appear to respond to B-cell depletion with Rituximab, offering novel insight to the pathophysiology of this disorder. Clinical response is rapid, with correlating decreases in IgG4 concentrations. B-cell depletion targets the subset of plasma cells that produce IgG4. This is likely achieved by depleting CD20+ B cells. Some authors have suggested the role of antigen presentation by IgG4+ plasmablasts prior to a cytokine cascade driving the fibrotic process. These plasmablasts decline quickly after B-cell depletion and can be useful to know which patients should be individually targeted with Rituximab therapy. Intravenous or subcutaneous immunoglobulin treatment has been successful in treating other inflammatory or immune mediated diseases, but has not yet been trialed in IgG4-related disease. Responsiveness to medical therapy is limited in late stage disease and in the case of extensive fibrosis, though case reports have been reported.

Conclusions and future perspectives

IgG4-related disease is rare and underappreciated secondary to unawareness. Symptoms are variable and clinical presentation is reflective of affected organs. Early recognition and therapy are important to prevent serious and irreversible tissue damage. Further epidemiologic data are needed to confirm and validate early observations. Better understanding and knowledge of the dysregulation associated with IgG4-related disease will explain much about the immune system.

References


