IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells; a typical pattern of sclerosis that is termed “storiform fibrosis”; a tendency to form tumefactive lesions; and the capability of involving multiple organs either simultaneously or metachronously. A majority of patients with IgG4-RD have elevated serum IgG4 concentrations. However, some patients have diagnostic histopathologic and immunostaining features on organ biopsies yet normal serum IgG4 concentrations.

IgG4-RD can affect essentially any organ system [1]. The pancreas was the first organ recognized in this context, in the form of an entity once termed “lymphoplasmacytic sclerosing pancreatitis”, now called type 1 (IgG4-related) autoimmune pancreatitis. The biliary tree, salivary glands, periportal tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid gland, pericardium, and skin are also known to be involved [2]. Regardless of the site of disease, the histopathologic features are strikingly similar.

A high percentage of plasma cells within the lesion stain for IgG4. More specifically, ratio of IgG4-positive plasma cells to the total number of plasma cells – the IgG4:total IgG ratio – is elevated, typically on the order of more than 0.3 but often much higher. Elevations of IgG4 in both tissue and serum are helpful diagnostic markers when IgG4-RD is a consideration, but neither tissue nor serum IgG4 levels are entirely specific for this condition [3,4]. Correlation with specific histopathologic findings as well as the clinical presentation is essential, regardless of the serum IgG4 concentration, the number of IgG4-positive plasma cells in tissue, or the tissue IgG4:IgG ratio.

Although IgG4-RD was identified initially in glands such as the pancreas and salivary glands [5], reports since 2008 have indicated that this disease can affect the full extent of the aorta as well as surrounding tissues; for example, the retroperitoneum [6–15]. A significant minority of thoracic and abdominal aortic aneurysms, in fact, are associated with inflammatory disease that has no association with any primary form of vasculitis (e.g., giant cell arteritis, Takayasu arteritis). The relevant entity has been termed “isolated aortitis” when found in the thoracic aorta and “inflammatory abdominal aortic aneurysm” when involving the abdominal segment.

The ability of IgG4-RD to affect blood vessels of a wide range in size, with not only large-vessel involvement but also microscopic findings of obliteratorive phlebitis and arteritis, warrants consideration of this condition as a primary form of systemic vasculitis. For most organs affected by IgG4-RD, veins tend to be involved to a greater extent than arteries (figure 1). Arterial inflammation is also well described, however, particularly in the lung [16]. Veins and arteries are classically affected by an obliteratorive process. Necrosis, especially fibrinoid necrosis, is not characteristic of IgG4-RD.

Recognition of the vascular nature of IgG4-RD has caused a re-consideration of the classification of both thoracic and abdominal aortitis and triggered a re-examination of the disorders known as inflammatory abdominal aortic aneurysm (IAAA) and retroperitoneal fibrosis (RPF). This review will focus


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Attributed to “isolated aortitis”. Despite careful searches of ascending aorta surgeries, where 9% of the cases were found to have IgG4-related aortitis, IAAA, and RPF. Similar findings were reported in another study of 513 ascending aorta surgeries, where 9% of the cases were found to have IgG4-related aortitis, IAAA, and RPF. IgG4 was not performed because IgG4-RD was still unknown. Plasmacytic inflammation. These lymphoplasmacytic infiltrates were viewed as being non-specific, but immunostaining for IgG4-positive plasma cells per high-power field and the IgG4:total IgG ratio was 0.75. Storiform fibrosis was also present. Obliterative phlebitis, depicted in this figure, was shown in a vein running adjacent to an artery (top of figure). The vein is cut transversely in this image and the walls of the vessel are outlined by arrows.

**Figure 1** Obliterative phlebitis in a case of retroperitoneal fibrosis. A 54-year-old man presented with right lower abdominal and upper thigh pain. Cross-sectional imaging of the abdomen revealed right hydronephrosis caused by a mass adjacent to the bladder. Following stent placement, a fine-needle biopsy of the mass revealed a lymphoplasmacytic infiltrate with more than 100 IgG4-positive plasma cells per high-power field and the IgG4:total IgG ratio was 0.75. Storiform fibrosis was also present. Obliterative phlebitis, depicted in this figure, was shown in a vein running adjacent to an artery (top of figure). The vein is cut transversely in this image and the walls of the vessel are outlined by arrows.

More critical than the number of IgG4-positive plasma cells in tissue is not diagnostic for IgG4-RD. However, the finding of increased serum IgG4 concentrations. Similarly, the finding of increased IgG4-positive plasma cells in tissue of 0.6 to 0.9 are not unusual. Obliterative phlebitis within the adventitia is another hallmark finding, as is storiform fibrosis similar to that reported in type 1 (IgG4-related) autoimmune pancreatitis and other organs involved in classic IgG4-RD. Neither obliterative phlebitis nor storiform fibrosis is found in every aortitis case. The potential for sampling variability dictates the importance of thorough evaluations of all available aortic segments. The absence of granulomatous inflammation in IgG4-related aortitis is critical in distinguishing this entity from giant cell aortitis, Takayasu arteritis, sarcoidaortitis, and rheumatoid aortitis. Serum IgG4 concentrations are often elevated in patients with IgG4-related aortitis but the relatively small numbers of patients with this entity reported to date do not permit confident reporting of the sensitivity, specificity, and positive and negative predictive values of elevated serum concentrations. For IgG4-RD in general, a study from the Massachusetts General Hospital reported the sensitivity of serum IgG4 concentration elevation as being 90%, the specificity as 59%, the positive predictive value as 34%, and the negative predictive value as 96% [20]. Some patients with the classic histopathologic and immunostaining features of IgG4-RD in tissue have normal serum IgG4 concentrations. Similarly, the finding of increased numbers of IgG4-positive plasma cells in tissue is not diagnostic of IgG4-RD [3]. More critical than the number of IgG4-positive plasma cells per high-power field are the findings on histopathology (lymphoplasmacytic as opposed to granulomatous
infiltrate, storiform fibrosis, obliterative phlebitis, mild tissue eosinophilia); the IgG4:total IgG ratio within tissue; and careful clinicopathologic correlation, to ensure that the pathology features reported are consistent with the clinical findings and pattern of organ involvement.

IgG4-RD appears to be approximately as common a cause of thoracic aortitis as more traditional disorders such as giant cell arteritis and Takayasu arteritis [17,18]. Assessment of all thoracic aortitis cases encountered from 2003 to 2008 at the Massachusetts General Hospital revealed that IgG4-RD was responsible for 9% of all cases of thoracic aortitis [13]. IgG4-related aortitis was present in 0.5% of all thoracic aorta resections. A subsequent study from Japan identified two cases of IgG4 aortitis/periaortitis in 125 thoracic aorta resections, accounting for 1.6% of all such cases [19].

**Inflammatory aortic aneurysm and periaortitis**

Abdominal aortic aneurysms with severe atherosclerosis that contain more chronic inflammation and scarring in the adventitia than typical atherosclerotic aneurysms have often been termed “IAAA” or “periaortitis” [21–23]. Approximately 2–15% of all abdominal aortic aneurysms are thought to be inflammatory aneurysms. The entity of IAAA was first described in 1972 [21]. The classic IAAA patient is a middle-aged to elderly man with a history of smoking and the clinical triad of abdominal or back pain, an elevated erythrocyte sedimentation rate, and weight loss [23]. The gross anatomic features of IAAA differ substantially from those of atherosclerotic AAA. A thick, dense, glistening white layer of fibrous tissue is often found over the anterior and lateral walls of the aneurysm [24], and the wall of the aneurysm in IAAA is 3–4 times the thickness of a normal aortic wall. The histopathology of IAAA is also distinct from atherosclerotic aneurysms, with an overall picture of lymphocytic aortitis and extensive adventitial fibrosis [23]. Clusters of inflammatory infiltrates are present through the media and adventitia, consisting predominantly of lymphocytes and plasma cells. This histopathology, of course, is strongly reminiscent of IgG4-RD occurring in other organ systems.

Surgical lore holds that aneurysms of this nature are less likely to rupture than are those associated with atherosclerosis. The IAAA is frequently surrounded by perianeurysmal fibrosis (“desmoplasia”), and RPF frequently accompanies this condition. Surrounding structures such as the duodenum, inferior vena cava, left renal vein, and ureters often adhere to the aneurysm wall [25].

**Retroperitoneal fibrosis**

IgG4-RD also accounts for a substantial subset – perhaps the majority – of cases of “idiopathic” RPF. The association of autoimmune pancreatitis with inflammatory masses in the retroperitoneum was described as early as 2002 [26]. RPF tends to affect the periaortic region and often occurs – as implied by the discussion above pertaining to IAAA – in the setting of an abdominal aortic aneurysm. The kidneys, ureters, and other retroperitoneal structures can also be involved, and ureteral obstruction with hydronephrosis is a common presentation. Pathological examination of the inflammatory masses, important to exclude malignancy, reveals lymphoplasmacytic inflammation and fibrosis with a substantial number of IgG4-positive plasma cells.

IgG4-related RPF occurs predominantly in men. Extra-retroperitoneal disease is common and includes autoimmune pancreatitis, chronic sclerosing sialadenitis, diffuse lymphadenopathy, orbital pseudotumor, Riedel’s thyroiditis, and other conditions now recognized as part of IgG4-RD. Zen and colleagues reported that among 17 cases of “idiopathic” RPF, 10 were associated with IgG4-RD [14]. All 10 patients with IgG4-related RPF were men, but six of the other seven patients were women. The cases of IgG4-related RPF were separated readily from their non-IgG4-RD counterparts by the percentage of plasma cells that stained positively for IgG4. The mean IgG4:IgG ratios ranged from 0.35–0.76 in the IgG4-RD group to 0.0–0.1 among patients in the other group. The mean serum IgG4 concentration was also higher in the IgG4-RD group: 695 mg/dL (range 154–2330 mg/dL; upper limit of normal: <135 mg/dL) versus 30 mg/dL (range 10–53 mg/dL).

Some RPF cases do not come to medical attention until the retroperitoneal tissues are highly fibrotic. In such cases, the size of the cellular inflammatory infiltrate may be small; large numbers of plasma cells are absent, replaced by fibroblasts. The correct diagnosis can be established in such cases by careful interpretation of the pattern of fibrosis (storiform as opposed to matted), the identification of obliterative vasculopathy, and evaluation of the IgG4:total IgG ratio. Even if there are only 15 plasma cells per high-power field in such a sample, for example, the diagnosis of IgG4-RD is likely if a high percentage of these cells are IgG4-positive and the other histopathology findings and the rest of the clinicopathologic picture is compatible with that conclusion. Clinicopathologic correlation is essential and it is particularly important to examine the patient’s history for manifestations of IgG4-RD in other organs.

**Conclusion**

IgG4-RD is a new cause of thoracic aortitis, IAAA, and RPF recognized only in recent years. Effective therapies for these disease entities (and their underlying disease) exist, making precise diagnosis crucial to appropriate management. The simple observation of IgG4-positive plasma cells does not necessarily clinch the diagnosis of IgG4-RD. Rather, representation of the hallmark histopathologic criteria is essential to the diagnosis, as is rigorous clinicopathologic confirmation. A reasonably high absolute number of IgG4-positive plasma cells relative to the total number of plasma cells is also crucial.
References


L46. Novel forms of clinical vasculitis: Anti-GBM vasculitis (Goodpasture’s disease)

Introduction

Anti-glomerular basement membrane (GBM) vasculitis, whilst new to the International Chapel Hill Consensus on Nomenclature of Vasculitides [1,2], is hardly a novel disease. The first case of ‘Goodpasture’s syndrome’ dates as far back as 1919, to the description of a fatal case of lung haemorrhage accompanied by glomerulonephritis, that at the time was attributed to an atypical influenza infection [3]. The eponymous label was bestowed almost 40 years later, when Australians Stanton and Tange [4], in a report describing nine similar cases of lung haemorrhage and glomerulonephritis, attributed Ernest Goodpasture with the first description of the syndrome in his 1919 paper. It is unclear, however, if any of these patients had anti-GBM antibodies, as it was not until the 1960s that immunoglobulins were first visualized by immunofluorescence in the typical linear pattern along the GBM that is seen in this condition [5], allowing their subsequent elucidation and characterisation. Circulating anti-GBM