IgG4 Aortitis: A Case Report

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ABSTRACT

IgG4 aortitis is one of the entities seen in the spectrum of IgG4-related disease (IgG4-RD). It is characterized by serologic (elevated serum IgG4) and histologic features including a lymphoplasmacytic infiltrate with increased numbers of IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis. Some studies have described a correlation between infections and IgG4 aortitis. We describe a patient with an aneurysm of the infrarenal descending abdominal aorta with features of IgG4-RD, as well as culture evidence of *Streptococcus sanguis*.

KEYWORDS: IgG4, aortitis, plasma cells

CASE REPORT

History

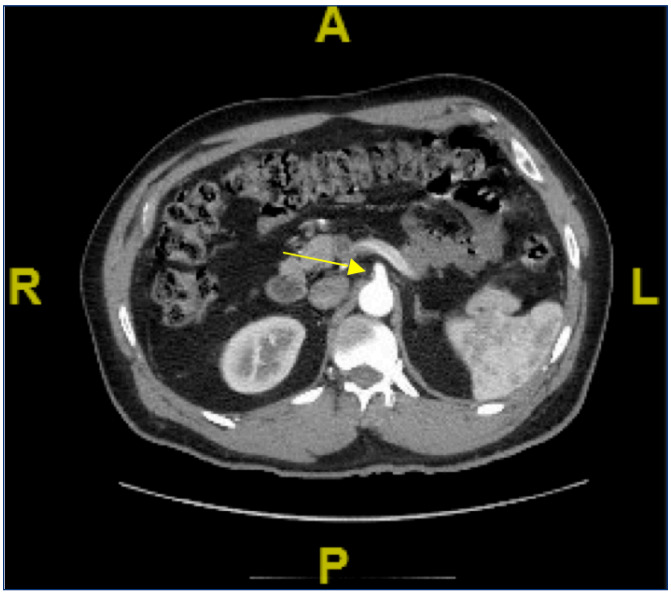
Our patient is a 50-year-old veterinarian from the Dominican Republic who presented as an outpatient with the complaint of intermittent periumbilical pain for two years. The pain radiated to his back and to his groin bilaterally and lasted for 2-3 hours. It occurred a few times a week and was self-subsiding. The patient denied any fever or symptoms suggestive of an underlying infection. The physical examination apart from abdominal tenderness was unremarkable. The labs were significant for positive c –ANCA. The WBC count, ESR and CRP were within normal limits. A CT of the abdomen was then performed, which demonstrated a saccular aneurysm of the abdominal aorta measuring 1.2x1.8 cm beginning infrarenally and encasing the inferior mesenteric artery. Radiology favored a mycotic aneurysm due to the site, appearance and surrounding retroperitoneal fat stranding. (**Figure 1**)

The patient subsequently underwent surgical resection of the aneurysm, was prescribed ceftriaxone for six weeks and tapering doses of prednisolone for three months post- surgery. He followed up with urology for testicular pain in 2014 and was subsequently lost to follow-up.

Pathology Findings

The aneurysm was received as multiple tan-yellow tissue fragments measuring 4.5 x 3.5 x 2.0 cm. Retroperitoneal tissue was sent separately as multiple tan-red soft tissue fragments measuring 1.5 x 1.0 x 0.5 cm. Microscopically on H &E stain the retroperitoneal soft tissue and aortic wall demonstrated bands of storiform fibrosis, a lymphoplasmacytic infiltrate and obliterative phlebitis. (**Figure A**)

Figure 1. CT scan showing aortic aneurysm.



The lymphoplasmacytic infiltrate was composed predominantly of sheets of polyclonal plasma cells (Kappa/lambda staining.) The plasma cells stained for CD138 and equivocally for Kappa/lambda. (**Figure B**)

They were IgG positive with predominant IgG4 positivity (>60/hpf). (**Figures C and D**) Steiner's stain and gram stain were negative for spirochetes and bacteria respectively. A flow cytometry performed on the tissue identified 51% CD5+ T cells and 48% polytypic CD19+ B cells, with a surface Ig kappa to surface Ig lambda cell ratio of 1.5.

Serology

The patient had persistently raised serum IgG4 at 199mg/dl prior to aneurysm resection and this value dropped to 114mg/dl once he was started on steroids (N: 4.0-86.0), subsequently lost to follow-up.

Microbiology

Streptococcus sanguis was isolated from the broth of retroperitoneal tissue and in spite of antibiotic therapy the patient's serum still showed elevated IgG4 levels.

Figure A. H/Ex10X showing diffuse lymphoplasmacytic infiltrate with obliterative phlebitis and fibrosis.

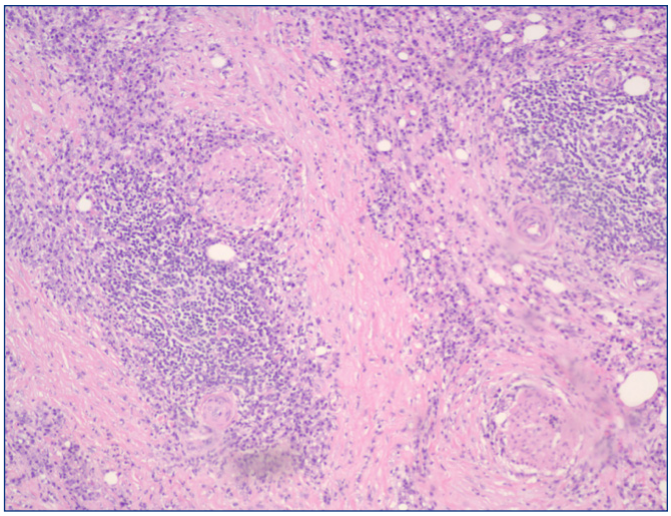


Figure B. CD 138 staining showing increased number of plasma cells.

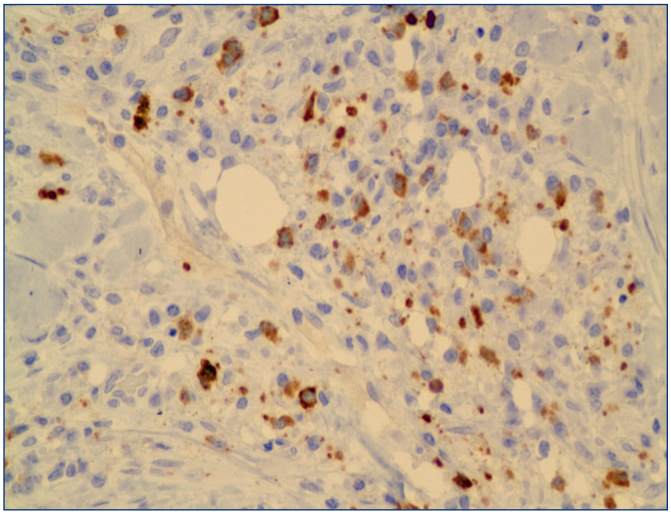


Figure C. IgG staining showing increased number of IgG positive plasma cells.

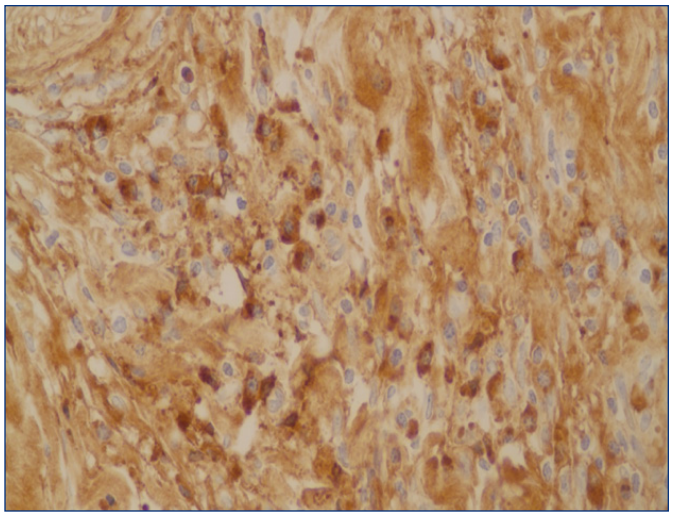
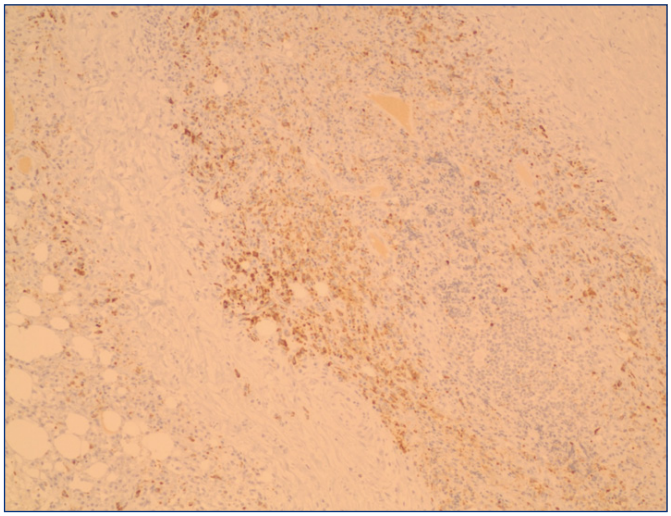


Figure D. Increased IgG4 positive plasma cells by immunostain.



DISCUSSION

Clinical features

IgG4-RD usually presents subacutely and the majority of patients are not constitutionally ill. Fevers and elevated C-reactive proteins are unusual. It is incidentally detected through histology or radiology.[1] The presentation can range, depending on the site of involvement, and usually presents with pain or swelling of the particular site. Multiorgan disease may be evident at diagnosis but can evolve metachronously over months to years.[1] Spontaneous improvement, sometimes leading to clinical resolution of certain organ system manifestations, is reported in a minority of patients.[2] Common findings in IgG4-RD are tumefactive lesions and allergic disease.[1] Many patients with IgG4 disease have allergic features like atopy, asthma, eczema and modest peripheral blood eosinophilia.[3] Up to 40 % of patients with IgG4-related diseases have allergic diseases like bronchial asthma or chronic sinusitis.[3]

DIFFERENTIAL DIAGNOSIS

Diseases such as giant cell aortitis, Takayusu arteritis, rheumatoid arthritis, and syphilis should be considered in the differential diagnosis when an aortic lesion is found. Differentiating between a chronic infectious aneurysm and IgG4-related aortitis may have some overlap; however, when a diffuse lymphoplasmacytic infiltrate with obliterative phlebitis and keloidal fibrosis is found, IgG4-related disease is high on the index of suspicion. It is confirmed by immunohistochemistry. Some studies have noted the plasma cell

response in infectious aortitis is focal as opposed to the diffuse response in IgG4 disease. Occasional granulomas found in IgG4 related disease may sometimes confound the diagnosis, hence staining of the plasma cells for IgG4 is necessary for definitive diagnosis.[4-5]

IgG4-RD as is it now known is a multisystemic disease with more than one organ being involved. IgG4-RD should be considered in any patient found to have aortitis or periaortitis. There can be different epicenters of the disease, based on which it can be classified, including retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, a combination of retroperitoneal and aortic involvement (as seen in our case) and thoracic aorta.[6] Recently reported data indicate that IgG4-related aortic disease may be more common than previously realized.[7] It has been shown that a significant percentage of thoracic lymphoplasmacytic aortitis cases, 40% of inflammatory abdominal aortic aneurysms/abdominal periaortitis cases, and a portion of retroperitoneal fibrosis cases are all caused by IgG4-RD.[7] A national study of autoimmune pancreatitis in Japan suggested a male-to-female ratio of 2.8/:1.[8]

Characteristic pathologic features of this condition are the involvement of blood vessels by the lymphoplasmacytic infiltrate and disruption of the elastic lamina causing obliteration of the blood vessels known as obliterative phlebitis. Fibroblastic proliferation due to release of TGF-B by the plasma cells is seen leading to florid fibrosis. Sometimes eosinophils are seen admixed with the lymphoplasmacytic infiltrate as IL-5 is also released in the process.[9] Granulocytic epithelial lesions and rare granulomas have been associated mostly with autoimmune pancreatitis.

The majority of patients are men and older than 50 years of age.[1,9,10,11,12] The disease is difficult to diagnose in the later phases of organ involvement, when fewer plasma cells are present and fibrosis may predominate in some tissues.[1] Serum IgG4 may not always be elevated; in such cases the histology plays an important role in diagnosis. Sometimes misdiagnosis may occur due to moderate elevation of serum IgG4 concentration and the finding of occasional IgG4 positive cells in the tissues. This dilemma can be resolved by the ratio between IgG positive cells and IgG4 positive cells in the tissue and the overall morphology.[1] Serum IgG4 values may not always correlate; according to a multicenter study from Japan, IgG4 levels failed to normalize in 115 of 182 patients treated with glucocorticoids.[13] The same study showed that the majority of patients with high levels of IgG4 were in remission and about 30% of them relapsed eventually.[13] **Table 1** from the 2011 study[4] defines the criteria for diagnosis of IgG4-RD.

Various pathophysiological mechanisms have been proposed for the disease including genetic risk factors, bacterial infection and molecular mimicry and autoimmunity.[1] Although various inciting factors have been hypothesized, the definitive cause is still elusive. No specific autoantibody has been consistently described in patients with IgG4-RD,

Table 1.

Comprehensive diagnostic criteria for IgG4-RD, 2011 4
1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs.
2. Hematological examination shows increased serum IgG4 concentrations (≥135 mg dl-1).
3. Histopathologic examination shows (i) Marked lymphocyte and plasmacyte infiltration and fibrosis. (ii) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per HPF.
Definite: 1 + 2 + 3
Probable: 1 + 3
Possible: 1 + 2
However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. SS, primary sclerosing cholangitis, Castleman's disease, secondary RPF, Wegener's granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

but nonspecific antibodies to other immune mediated conditions is common.[14] It has been proposed that infection may be a causal factor.[15] According to recent reports, it has been found that increased IgG4 is due to Th-2 dominated cytokine production due to increased T cells which can be upregulated due to bacterial infection.[16] However, these are just a few studies and there is no convincing evidence for the role of infection in the IgG4-RD, as the majority of cases are not associated with infection.

CONCLUSION

Our patient demonstrates a rare case of IgG4 aortitis which was correlated with increased serum IgG4 and IgG4/IgG ratio. In spite of the finding of *streptococcus sanguis* in the retroperitoneum and the possibility of an infectious etiology, the classical histological findings of storiform fibrosis obliterative phlebitis and increased plasma cells along with immunohistochemistry showing increased IgG4 plasma cells should prompt us towards the diagnosis of IgG4 aortitis.

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