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Retroperitoneal and aortic manifestations of immunoglobulin G4-related disease

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Retroperitoneal fibrosis is one of the prototypic manifestations of immunoglobulin G4 (IgG4)-related disease (IgG4-RD), but there is growing evidence that the aorta is also involved. These 2 conditions are closely linked, and based on the epicenter of the disease, the clinical manifestations can be classified as retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm (including a combination of the 2), and thoracic aortitis. IgG4-RD is responsible for only a subset (~50%) of cases of retroperitoneal fibrosis and inflammatory aortic aneurysms. Histological features include an extensive lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, fibrosis arranged in a storiform pattern, moderate tissue eosinophilia, and partially or completely obliterated veins. Among the 3 layers comprising the aorta, the adventitia is most susceptible to IgG4-related inflammation. The inflammatory process can also disrupt the lamellar elastic fibers in the media, which is seemingly a critical event leading to aneurysmal transformation. Steroid therapy is effective for both retroperitoneal and aortic lesions, as it is for the other manifestations of IgG4-RD. The risk of rupture appears to be low in patients with IgG4-related aortic aneurysms, but immunosuppressive therapy may trigger this critical complication by reducing the wall thickness.

Retroperitoneal fibrosis, one of the major manifestations of immunoglobulin G4 (IgG4)-related disease (IgG4-RD),[1] was first described in the French literature in 1905.[2] Because Ormond[3] reported the condition in the English literature in 1948, retroperitoneal fibrosis has also been known as Ormond disease. Although a century has passed, the disorder remains poorly understood.[4,5] One reason for this is its rarity, with an incidence estimated to be 1/1,000,000 person-years based on a Finnish retrospective case-control study,[6] although given the widespread use of cross-sectional imaging, this figure is likely to increase in the near future.[5] Another reason is that most studies on retroperitoneal fibrosis have examined heterogeneous patient populations, which has led to controversial and less reproducible results.

Because IgG4-RD was proposed in the last decade,[7,8] retroperitoneal inflammatory conditions have been reassessed in terms of tissue infiltration by IgG4-positive plasma cells.[9] In addition, the fact that IgG4-related retroperitoneal fibrosis commonly involves the abdominal aorta raised the possibility that the aorta itself may be another target of IgG4-RD, and this led to the recognition that some forms of inflammatory aortic aneurysm belong to the spectrum of IgG4-RD.[10]

In this article, we review our current understanding of IgG4-related retroperitoneal and aortic disease, particularly in terms of the disease spectrum and histopathological features.

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Table 1 A list of arteries that have been confirmed to be involved in IgG4-related disease

Thoracic aorta
Abdominal aorta, most commonly infrarenal segment
Left common carotid artery
Left subclavian artery
Superior mesenteric artery
Splenic artery
Common iliac artery
Internal iliac artery
Coronary artery

IgG4, immunoglobulin G4.

Spectrum of IgG4-RD in the retroperitoneum and aorta

IgG4-RD involving the retroperitoneum and aorta exhibits variable macroscopic changes. The formation of a mass can be a feature in some patients, whereas a plaque-like infiltrative process may predominate in others. The degree of aortic involvement also varies among patients. Based on the epicenter of the disease, IgG4-RD of these anatomical sites can be classified into: (1) retroperitoneal fibrosis, (2) inflammatory abdominal aortic aneurysm, (3) a combination of retroperitoneal and aortic involvement, (4) thoracic aortitis. "IgG4-related retroperitoneal fibrosis" and "IgG4-related aortitis" are now the terms of choice for describing these variations of the disease.[11]

Retroperitoneal fibrosis

"Idiopathic" retroperitoneal fibrosis is not always IgG4 related. The proportion of IgG4-related cases among patients with idiopathic retroperitoneal fibrosis is approximately 55% according to pathological studies,[12,13] but the real percentage remains unclear given that retroperitoneal fibrosis is not always biopsied. For example, in a patient with type 1 autoimmune pancreatitis and retroperitoneal fibrosis, steroid therapy would be commenced without a tissue diagnosis of the retroperitoneal lesion. In terms of the predominant location, periaortic/periarterial involvement was most common (~80%) in our cohort, followed by ureteral involvement and plaque-like lesions.[12] Another study, which examined both IgG4-related and nonrelated cases in a single group, described ureteral involvement as most frequent.[13]

Mediastinal fibrosis

A similar inflammatory process can develop in the mediastinum, namely mediastinal fibrosis.[14,15] This disease is exceptionally rare, but may be associated with IgG4-related thoracic aortitis. A mass in the retromediastinal/paravertebral region is another manifestation of IgG4-RD.

Inflammatory abdominal aortic aneurysm

IgG4-related abdominal aortic aneurysm was first reported in 2008.[10] All cases fulfilled the criteria of an "inflammatory" aneurysm (ie, extensive inflammatory cell infiltration and severe thickening of the wall), leading to the hypothesis that IgG4-RD could be responsible for a subset of inflammatory abdominal aneurysms. Eventually, IgG4-related aneurysm was found to account for some 40% of all inflammatory aneurysms at this location.[10] Given that approximately 2%-15% of all abdominal aortic aneurysms are thought to be inflammatory in nature, 1%-6% of abdominal aortic aneurysms are estimated to be IgG4 related.[16] Controversy remains over the ideal term to describe aortic-centric disease that lacks aneurysm formation. "Retroperitoneal fibrosis" has been traditionally used to describe this disease; however, this term overlooks the aortic disease. Periaortitis is a potential alternative that would include periaortic retroperitoneal disease, aortitis including aneurys-

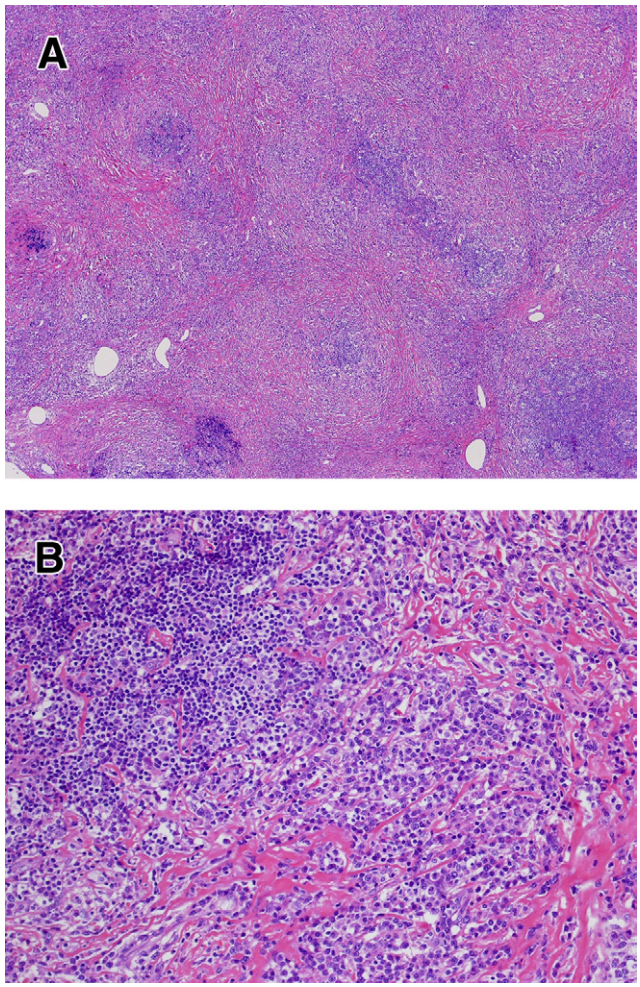

Figure 1 Immunoglobulin G4 (IgG4)-related retroperitoneal fibrosis. (A) The fibroinflammatory process extensively involves the retroperitoneal soft tissue. Hematoxylin and eosin stain (H&E), ×40. (B) Infiltrating inflammatory cells consist of predominantly lymphocytes and plasma cells. H&E, ×200. (Color version of figure is available online.)