Inflammatory ascending aortic disease: Perspectives from pathology

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Inflammatory diseases of the aorta comprise a spectrum of disease with diverse clinical and histopathologic presentations. Broadly, they may be dichotomized into infectious and noninfectious varieties. Although uncommon, infectious forms, caused by bacteria, fungi, or mycobacteria, may result from hematogenous seeding of the aorta or direct spread from a contiguous infectious source. The noninfectious forms include a number of entities, the most common of which is atherosclerosis, a disease that primarily affects the aortic intima but has important secondary effects on the media and adventitia that may result in aneurysm formation. Other important noninfectious inflammatory diseases include giant cell arteritis, Takayasu arteritis, granulomatosis with polyangiitis (Wegener granulomatosis), sarcoidosis, and lymphoplasmacytic aortitis. Importantly, there is increasing recognition that there is a subset of cases of lymphoplasmacytic aortitis perhaps better classified under the spectrum of so-called IgG4-related sclerosing disease, with important clinical and therapeutic ramifications. This review focuses on the variable and defining characteristics of the inflammatory aortopathies, specifically those affecting the ascending aorta, and discusses areas of important clinical and pathological distinction between them. (J Thorac Cardiovasc Surg 2015;149:S176-83)

AORTIC ANATOMY

The aorta is the largest elastic artery in the body. Elastic arteries are defined by the presence of concentrically arranged lamellar units forming their media. A lamellar unit consists of collagen fibers, smooth muscle myocytes, and ground substance sandwiched between the concentric elastic lamella (plates).[1] The elastic lamellae are anchored to one another by smaller elastic fibers.[2]

There are important structural differences between the thoracic and abdominal aortic regions.[3] In fact, there are even structural differences that have been noted between different regions of the ascending aorta, specifically the sinus and tubular portions.[4] These differences are likely related to the different embryologic origins of the aorta, with the root being derived primarily from second heart field (lateral plate mesoderm), the ascending aorta and arch from the neural crest, and the descending aorta from paraxial mesoderm (Figure 1).[5] This regional heterogeneity in aortic structure is undoubtedly an important determinant of how the aorta responds to injury or degeneration.

SPECIMEN HANDLING

Surgical ascending aortic specimens are received in the pathology laboratory in 1 of 2 varieties: an unopened segmental resection (Figure 2, *A*) including a full-circumference portion of the aorta, or an opened specimen in which either a full- or partial-circumference portion of aorta has been removed (Figure 2, *B*). Once it has been received by the pathology laboratory, the specimen is measured, oriented, and described. In the event that the specimen either is noncircumferential or was previously opened, orientation may be facilitated by placement of a marker suture in the sinus portion of the aorta. Such orientation allows for appropriate sampling and evaluation, specifically because of the aforementioned differences in regional histologic properties.

The adventitia, media, and intima are carefully examined and described in the gross pathology report. From 6 to 8 full-thickness sections of aortic wall are then typically procured for paraffin embedding and sectioning (Figure 3).[6] Tissue sections are then stained with hematoxylin and eosin as well as an elastic stain (eg, Verhoeff-van Gieson stain; Figure 4) for review by the pathologist.

INFLAMMATORY AORTIC DISEASE

Aortitis is broadly defined as inflammation of the aortic wall. In general, conditions that result in secondary inflammation are not considered aortitis. Atherosclerosis, an inflammatory aortic disease primarily affecting the intima, is also typically not considered aortitis as such. Nevertheless, it is an important inflammatory disease that may occasionally have a very prominent inflammatory component. Although it more commonly affects the descending aorta, the infrarenal component in particular, it may be encountered in the ascending aorta. In the ascending aorta, the sinotubular junction and the minor curvature are more commonly involved.[7] Branch points such as the coronary ostia and arch vessels are also particularly vulnerable, presumably because of endothelial dysfunction in regions of hemodynamic instability.[8]

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Abbreviations and Acronyms
GCA = giant cell arteritis
GPA = granulomatosis with polyangiitis
IgG4-RSD = IgG4-related sclerosing disease–associated aortitis
TA = Takayasu aortitis

Grossly, atherosclerosis may manifest along a spectrum from a yellow-white, irregular endothelial lesion known as a *streak* to large, variegated, and ulcerated plaques. Ulcerated areas may have a sparkling appearance, which results from the reflection of light off of the cholesterol crystals contained within the lesion. Areas of calcification may be present to varying degrees throughout the involved areas. Luminal thrombus may also be seen along regions of the intimal lesion.

Histologically, atherosclerosis is characterized by an admixture of variable degrees of histiocytes (including so-called foam cells), lymphocytes, and usually cholesterol clefts within intimal plaques. The inflammatory infiltrate may become particularly intense (Figure 5, *A*) in regions of recent plaque disruption, even producing lymphoid follicles. Neutrophilic inflammation may also be seen, causing concern regarding an underlying infectious process.

Although the aforementioned gross and histologic features are rather specific for atherosclerosis, they do not preclude the presence of an underlying disease that may, in fact, be primary. Because endothelial injury is a common phenomenon in many aortic diseases, the development of secondary atherosclerosis is not uncommon.

So-called inflammatory abdominal aortic aneurysm was historically though to be related to severe atherosclerosis; however, the atherosclerotic process is now believed more likely to be a secondary phenomenon arising out of an underlying issue, such as IgG4-related sclerosing disease.[9]

Noninfectious Aortitis

Noninfectious aortitis includes a wide array of diseases, including giant cell arteritis (GCA) involving the aorta, Takayasu aortitis (TA), granulomatosis with polyangiitis (GPA), lymphoplasmacytic aortitis, Behçet disease, sarcoidosis, Cogan syndrome, and aortitis associated with other rheumatologic diseases (eg, rheumatoid arthritis and systemic lupus erythematosus). A thorough discussion of each of these entities is beyond the scope of this review. Prototypical diseases with important clinical points are therefore the focus in this section.

GCA involving the aorta. GCA (formerly Horton disease), a vasculitis that may involve the aorta, its branches, and smaller muscular vessels, is the most common systemic vasculitis to involve the aorta.[10] Such aortic involvement in GCA is relatively common, ranging from 10% to 40% in most series.[11-13] It is usually encountered in individuals older than 50 years and affects women 3 to 5 times more commonly than men. There is also an association with polymyalgia rheumatica.[14] Nonaortic symptoms include headache, jaw claudication, or visual changes. Alternatively, the disease may manifest as an asymptomatic isolated aortic process, usually presenting as an aneurysm. In fact, most cases of aortic GCA appear to be such isolated involvement.[15]

Grossly, the aortic intima frequently exhibits a wrinkled "tree bark" appearance (Figure 3). This character is imparted by a combination of medial damage, tissue edema, and the elastic properties of the vessel itself. Accordingly, this finding may be encountered in virtually any form of aortitis. Secondary atherosclerosis may also be seen as a result of altered hemodynamics and endothelial dysfunction; however, this finding also is not specific for GCA.

Histologically, GCA is characterized by a granulomatous inflammatory infiltrate, involving the media, with a variable number of multinucleated giant cells (Figure 5, *B*). A lymphoplasmacytic infiltrate may be present as well. The vessel frequently exhibits a "moth-eaten" appearance on elastic stain as a result of the medial injury (Figure 5, *C*). The inflammation may involve vasa vasora and may even produce regional bandlike infarction of the media (Figure 5, *D*).[16] This is among the mechanisms of formation of so-called laminar medial necrosis. It is important to note, however, that laminar medial necrosis is neither specific for GCA nor an inflammatory process and may be seen in noninflammatory aneurysms as well.

Takayasu aortitis. TA is the prototypical inflammatory aortic disease of the young. Typically presenting in those younger than 50 years, it often manifests in young women (female to male ratio of 8:1) of Asian descent. As with other forms of aortitis, the disease may be asymptomatic or present with catastrophic complications such as stroke. Its obstructive involvement of the arch vessels may result in loss of circulation to the upper extremities, earning the TA its nickname of "pulseless disease."

Aortic specimens from individuals with TA exhibit variable changes, depending on the phase of the disease at the time of resection. Acute phase disease may appear similar to other cases of aortitis, with areas of wall thinning and intimal wrinkling. Chronic or late phase disease may manifest as mural thickening (sometimes striking), which may involve any of the layers of the vessel but most notably the intima and adventitia. The thickening is often circumferential, producing regions of stenosis in the aortic branches.

Histopathologic features are also dependent on the phase of the disease, although the late phase is more commonly encountered. Acutely, the disease may look identical to GCA, and only the age of the patient can be used to reliably distinguish between these disease processes. In the chronic