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Review Article

Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology: I. Inflammatory diseases

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ABSTRACT

Inflammatory diseases of the aorta include routine atherosclerosis, aortitis, periaortitis, and atherosclerosis with excessive inflammatory responses, such as inflammatory atherosclerotic aneurysms. The nomenclature and histologic features of these disorders are reviewed and discussed. In addition, diagnostic criteria are provided to distinguish between these disorders in surgical pathology specimens. An initial classification scheme is provided for aortitis and periaortitis based on the pattern of the inflammatory infiltrate: granulomatous/giant cell pattern,

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lymphoplasmacytic pattern, mixed inflammatory pattern, and the suppurative pattern. These inflammatory patterns are discussed in relation to specific systemic diseases including giant cell arteritis, Takayasu arteritis, granulomatosis with polyangiitis (Wegener's), rheumatoid arthritis, sarcoidosis, ankylosing spondylitis, Cogan syndrome, Behçet's disease, relapsing polychondritis, syphilitic aortitis, and bacterial and fungal infections.

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1. Introduction

Aortic diseases cause significant morbidity and mortality through the development of aneurysm, aortic wall rupture, acute dissection, and luminal obstruction [1,2]. These phenomena can result from many distinct diseases that afflict the aorta. During surgical repair of aortic aneurysms and dissections, portions of aorta resected by surgeons contain important diagnostic information concerning these underlying diseases. To promote a better understanding of these aortic diseases and to enhance patient care, the Standards and Definitions Committee of the Society of Cardiovascular Pathology and the Association for European Cardiovascular Pathology is issuing guidelines for diagnosing aortic diseases in surgical pathology specimens. These guidelines will be issued in two consecutive reports. This first report on aortic diseases will cover inflammatory diseases of the aorta, with other aortic diseases being addressed in a second document.

This document on surgical aortic diseases will cover atherosclerosis, inflammatory atherosclerotic aneurysms (IAAs), aortitis, and periaortitis. Including atherosclerosis as an inflammatory aortic disease is not a declaration that inflammation is the underlying driving force for all atherosclerosis. It is acknowledged that atherosclerosis is usually associated with inflammation but has multiple precipitating etiological factors in addition to inflammation including age, lipid metabolism, and vascular cell activation. The influx of lipid into the vessel wall is a key feature in the development of atherosclerosis [3,4], and the inflammation present is usually a reaction to this lipid. However, in atherosclerosis, the degree of the inflammatory reaction can be substantial, and in some cases, the inflammation can contribute to complications such as aneurysm formation and surface disruption with thrombus formation, justifying the inclusion of atherosclerosis as an inflammatory aortic disease. It is acknowledged that many primarily noninflammatory aortic diseases to be covered in the subsequent report are associated with some degree of inflammation, although in those disorders, the inflammation is usually mild and occurs secondarily to some other primary pathologic process. Disorders of the aortic valve will not be covered in this report.

It is understood that precise classification of an inflammatory aortic disease may require correlation of the pathologic features with clinical features, other laboratory findings, and imaging. Thus, there are two major sections to this report. First, there is a section focusing on a histology-based classification scheme, with recommendations for nomenclature and diagnostic criteria, to aid the surgical pathologist when confronted with one of these specimens, following which there is a section discussing the pathology of the specific inflammatory aortic disorders. In both of these sections, the disorders are discussed in order of increasing amounts of inflammation, starting with atherosclerosis, which has variable amounts of inflammation, and ending with aortitis, which is defined by the presence of more extensive inflammation. The committee supports specific training in cardiovascular pathology [5] and the specific involvement of cardiovascular pathologists in the work-up of complex aortic surgical pathology specimens.

2. Methods

Consensus committee membership was solicited from members of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. This multi-institutional committee membership identified the types of inflammatory aortic diseases encountered by cardiovascular surgical pathology services, reviewed the literature on these conditions, and constructed consensus guidelines for nomenclature and diagnostic criteria. For this report, consensus is defined as being the majority of the membership of the committee and may not necessarily, in all cases, indicate a unanimous opinion. The opinions put forth here do not necessarily represent the opinions of all members of the Society for Cardiovascular Pathology or the Association for European Cardiovascular Pathology. Areas with significant dissenting opinion within the committee are indicated in the text. For the consensus opinions, an emphasis was placed on incorporating the results of relevant published peer-reviewed literature.

3. Histologic classification and diagnostic criteria of inflammatory aortic diseases

3.1. Processing of aortic surgical pathology specimens

It is recommended to examine the aortic specimen grossly and to measure both the overall dimensions of the specimen and thickness of the aortic wall. It is recommended to note the presence and extent of atherosclerotic lesions as well as features suggestive of aortitis, including thickening of the wall and cracking/wrinkling of the intima, i.e., a "tree bark" appearance. In accordance with previous consensus guidelines, it is recommended that all segments of aorta surgically resected for aneurysm or dissection be examined histologically [6]. In the absence of a clinical history of vasculitis or gross findings suggestive of aortitis, it is recommended that six pieces of aorta be submitted in a total of two cassettes for initial screening. If there is a clinical history of vasculitis, gross findings worrisome for aortitis, or histologic findings suggesting aortitis, then it is recommended to submit additional blocks of tissue for histologic examination. In these situations, it is recommended to submit up to 12 blocks of tissue, or at least 1 block of tissue per cm of tissue, to fully characterize the nature of the inflammatory infiltrate. Sections are recommended to be 1.0–1.5 cm in length and cut in cross section, i.e., perpendicular to the longitudinal axis of the aorta. If atherosclerosis is present, it is recommended to submit both areas with and without atherosclerosis. If there is a clinical history of infection or a grossly suppurative appearance, i.e., pus, and tissue was not sent for culture directly from the operating room, then it is recommended to send fresh sterile tissue for culture if possible. Fresh sterile tissue can also be frozen for potential use in identification of microorganisms by ribosomal DNA amplification and sequencing. Hematoxylin and eosin (H&E) and elastic stains should be evaluated. Trichrome (or Azan–Mallory or Sirius red), Movat, and Alcian–PAS stains are helpful to identify areas of degeneration, elastic fiber fragmentation, scarring, and accumulation of proteoglycans and mucopolysaccharides. Immunohistochemical staining for α-smooth muscle actin can also be helpful in assessing the integrity of medial smooth muscle cells.

3.2. Major diagnostic classes of inflammatory aortic diseases

The committee recognizes that there are three broad categories of inflammatory aortic disease, which in order of increasing inflammation are atherosclerosis, atherosclerosis with excessive inflammation, and aortitis/periaortitis (Table 1). Specific aortic diseases are described in more detail in Section 4. Atherosclerosis is most often associated with at least some degree of inflammation, and in some cases, the inflammation can be prominent. It is also acknowledged that some patients show

Table 1
Comparison of major diagnostic classes of inflammatory aortic diseases

Diagnostic class	Degree, location, and type of inflammation in relation to the degree of atherosclerosis present	Examples
Atherosclerosis	Routine for atherosclerosis	Atheroma, fibroatheroma, thin-cap fibroatheroma
Atherosclerosis with excessive inflammation	Uncommon for atherosclerosis but likely due to atherosclerosis	IAA, atherosclerosis with excessive neutrophilc inflammation
Aortitis/ periaortitis	Cannot be accounted for by atherosclerosis.	Infectious aortitis/ periaortitis, noninfectious aortitis/ periaortitis

signs of an unusually intense and likely localized inflammatory reaction to a vessel with atherosclerosis. Since these cases may be associated with distinct clinical features, the committee recommends highlighting these cases with the designation of atherosclerosis with excessive inflammation. The committee also recommends reserving the designations *aortitis* and *periaortitis* for inflammatory aortic conditions in which the inflammation cannot be fully accounted for solely by atherosclerosis.

3.3. Atherosclerosis

Multiple detailed classification schemes for atherosclerosis have been reported [7–11]. These schemes have much utility in research studies, particularly of the coronary arteries. However, these schemes have severe limitations in the setting of aortic surgical pathology. First, there are little to no data to indicate that all of the specific categories in these schemes have clinical significance for aortic disease. Also, these schemes are largely based on intimal changes, and many clinical complications of aortic atherosclerosis, such as aortic aneurysm formation, are largely based on changes in the media. In essence, these schemes do not readily delineate when atherosclerosis is the primary aortic pathology or when the atherosclerosis is superimposed on a more significant underlying disorder such as a connective tissue disease. Thus, it is recommended that a simplified and more directly relevant atherosclerosis classification scheme be employed for aortic surgical pathology (Table 2). This simplified scheme is based on designating atherosclerosis as mild, moderate, or severe based largely on the presence of fibrosis and the amount of medial loss or destruction due to the atherosclerosis (Fig. 1). A designation of severe atherosclerosis would indicate a degree of the disease for which the atherosclerosis may be the predominant pathologic feature in the specimen. The scheme also specifies for the pathologist to indicate the presence of plaque disruption and luminal thrombus. Such luminal thrombus can be associated with any degree of atherosclerosis, mild, moderate, or severe, and the presence of such thrombus has important clinical implications for embolic ischemic events. The scheme also allows the pathologist to designate if the plaque is calcified. The overall extent of atherosclerosis is best obtained from the gross inspection of the aorta and can be described as focal, patchy, or diffuse.

Table 2
Grading atherosclerosis in surgically resected segments of aorta

Grade/qualifier	Gross	Histology
No significant atherosclerosis	Normal or fatty streaks	Intimal thickening/hyperplasia Scattered intimal foam cells and lymphocytes
Mild atherosclerosis	Raised plaques	Extracellular lipid deposition without fibrosis (AHA grade III/IV [8,9]) Minimal to no destruction or loss of media
Moderate atherosclerosis	Raised or confluent plaques	Extracellular lipid deposition with fibrosis (AHA grade V and above [9]) Destruction or loss of less than 1/3 of the media thickness
Severe atherosclerosis	Raised or confluent plaques	Extracellular lipid deposition with fibrosis (AHA grade V and above [9]) Destruction or loss of 1/3 or more of the media thickness
Atherosclerosis with plaque disruption and surface thrombus[a]	Ulcerated plaque with surface thrombus	Atherosclerotic plaque (AHA grade III and above [8,9]) with surface disruption and surface thrombus
Calcific atherosclerosis[a]	Firm calcified plaque	Atherosclerotic plaque (AHA grade III and above [8,9]) with calcification.

AHA, American Heart Association.
[a] Used in conjunction with the grade mild, moderate, or severe.

The inflammation in atherosclerotic lesions consists primarily of macrophages in the intima. There may also be lymphocytes present in the intima, media, and/or adventitia, which are primarily CD3 + T-cells, although, in some cases, nodular aggregates of CD20 + B-cells will be present in the adventitia along with clusters of plasma cells. Disrupted plaques will show surface thrombus, and chronically disrupted or ulcerated plaques may contain organizing thrombus. Giant cells reacting to cholesterol clefts may be present. In disrupted plaques, neutrophils are often present near the site of disruption.

3.4. Atherosclerosis with excessive inflammation

In some cases, the degree of inflammatory reaction in a vessel with moderate to severe atherosclerosis is unusually intense but can still be explained as a reaction to the atherosclerotic plaque. Two major examples of this phenomenon are atherosclerosis with excessive neutrophilic inflammation and IAA (Fig. 2). Between “usual atherosclerosis” and

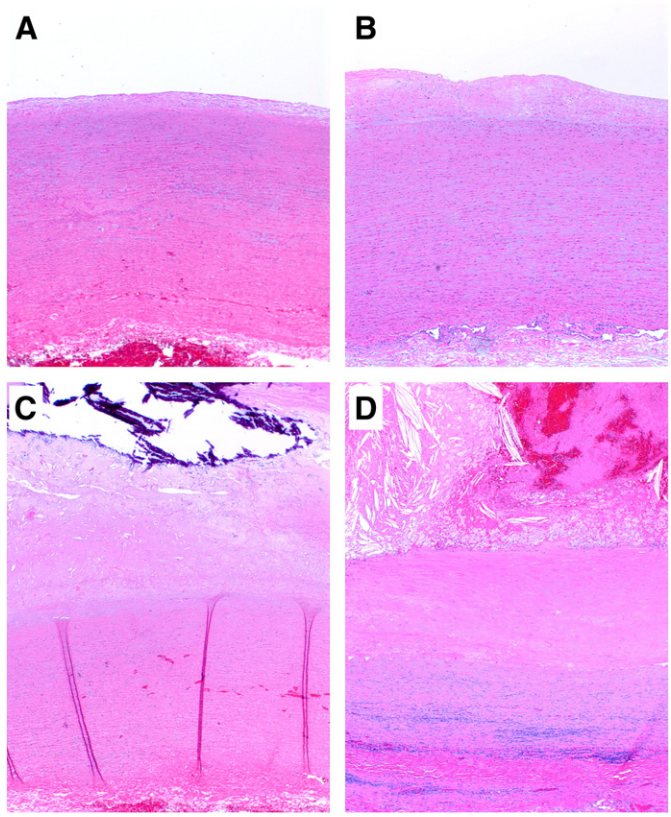

Fig. 1. Grades of Atherosclerosis. (A) No significant atherosclerosis. (B) Mild atherosclerosis. (C) Moderate calcific atherosclerosis. (D) Severe atherosclerosis with plaque disruption and surface thrombus.

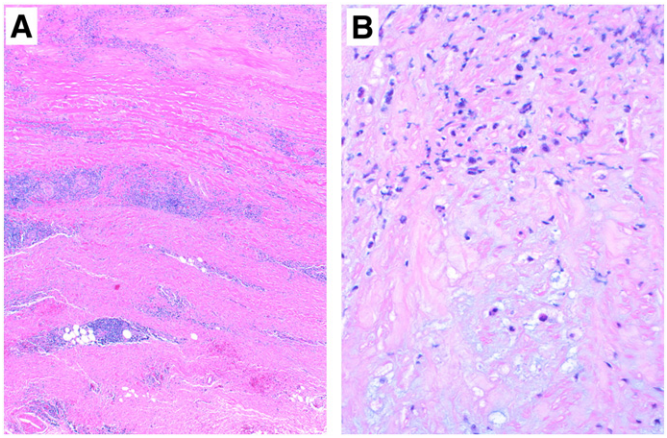

Fig. 2. Atherosclerosis with excessive inflammation. (A) IAA. (B) Atherosclerosis with excessive neutrophilic infiltrates.

"atherosclerosis with excessive inflammation," a spectrum of different degrees of inflammation may be associated with aortic atherosclerosis.

3.4.1. Atherosclerosis with excessive neutrophilic inflammation

This is an unusual condition in which there is an excessive amount of neutrophils involving an atherosclerotic plaque, often in the setting of plaque disruption and luminal thrombus formation [12]. The primary entity in the differential is suppurative aortitis due to bacterial infection. In contrast to suppurative aortitis, extensive necrosis is not present other than in the necrotic/lipid atherosclerotic core. Also, microorganisms are not present on special stains. If considering this diagnosis, it is recommended that Gram, Grocott–Gomori methenamine silver and a silver impregnation stain such as Steiner or Warthin–Starry be evaluated to assess for infectious agents. It may not be possible to definitively rule out infection in such cases.

3.4.2. Inflammatory atherosclerotic aneurysm

IAA is associated with severe atherosclerosis and is thus most common in the abdominal aorta. The committee recommends the term *inflammatory atherosclerotic aneurysm* over inflammatory aortic aneurysm to emphasize the relationship with atherosclerosis, to allow for future inclusion of similar pathologies outside of the aorta, and to promote a clearer distinction from aortitis and periaortitis. Histologically, IAA shows the features of severe atherosclerosis with an excessive degree of adventitial inflammation. The adventitial inflammation consists primarily of lymphocytes and plasma cells. Eosinophils may also be present. It is recommended that, for a pathologic diagnosis of IAA, the thickness of the aortic wall exceeds 4 mm [13]. The primary entity in the differential is periaortitis. It is acknowledged that, currently, criteria for distinguishing IAA from periaortitis have not been fully developed. However, the presence of pathologic features in the adventitial inflammation that are not typical of atherosclerosis would favor periaortitis. Such features would include compact granulomas, extensive IgG4 + plasma cells, a suppurate pattern of inflammation, or extensive necrosis. The presence of intense adventitial inflammation with no significant or mild atherosclerosis would also favor periaortitis over IAA.

3.5. Aortitis and periaortitis

With the advent of newer biologic therapies that target specific inflammatory molecules such as tumor necrosis factor-α, CD20, and interleukin (IL)-6, therapies for aortitis are becoming more tailored to the specific type of aortitis present [14,15]. Thus, correct subclassification of aortitis is becoming increasingly more important. Subclassification of aortitis often requires a combination of clinical, radiologic, laboratory, and pathologic information. Therefore, when confronted with a case of aortitis, it is recommended that the surgical pathologist review the clinical, radiologic, and laboratory findings when possible. It is recognized that, in many cases, complete classification of aortitis to a specific disease process is not possible. However, it is recommended that the aortitis be primarily subclassified pathologically based on the pattern of the inflammatory infiltrate (Table 3). The differential diagnosis concerning specific diseases can be discussed in a note or comment in the surgical pathology report. The presence of necrosis can also be indicated. It is helpful to acknowledge in the note that, in some patients with aortitis, the clinically apparent manifestations of their vasculitis may be limited to the aorta. If the inflammation is restricted to the adventitia, the term *periaortitis* is recommended. If the inflammation involves the media and/or intima to any degree, then the term *aortitis* is recommended. The committee supports the Chapel Hill consensus criteria for the general classification of vasculitis [16].

3.5.1. Aortitis/periaortitis with granulomatous/giant cell pattern

A granulomatous/giant cell pattern is the most common pattern of inflammation in aortitis. The granulomatous/giant cell pattern consists of clusters of activated epithelioid macrophages (Fig. 3). Giant cells and/or actual granulomas may also be present. A lymphoplasmacytic component will also usually be present in the adventitia and/or the media. Pathologic features of the inflammation can help delineate the underlying specific disease. The presence of extensive non-necrotizing compact/well-formed granulomas would suggest sarcoidosis. The presence of necrotizing granulomas would suggest rheumatoid vasculitis, Takayasu aortitis, mycobacterial infection, or fungal infection. It is recommended to obtain stains for microorganisms in such cases. As discussed in more detail below, compared with Takayasu arteritis, aortic involvement by giant cell arteritis (GCA) tends to show less adventitial scarring and a predilection for the inner half of the media (Fig. 4, Table 4). Extensive neutrophils and geographic necrosis would support involvement by granulomatosis with polyangiitis (GPA).

The committee recognizes that the term *giant cell aortitis* is being applied in different manners in different medical centers. It is recognized that the term is often used to suggest involvement of the aorta by GCA (Horton's disease) (Table 5). Thus, it is recommended that the term not be used liberally for any aortitis containing giant cells, particularly if there are clinical or pathologic features to suggest a disorder distinct from GCA.

Table 3
Inflammatory patterns in aortitis and periaortitis

Inflammatory pattern	Composition	Examples of specific systemic diseases
Granulomatous/ giant cell pattern	Clusters of epithelioid macrophages with or without giant cells or compact/well-formed granulomas	*Usually without compact/ well-formed granulomas:* GCA, GPA, EGPA *Sometimes with compact/ well-formed granulomas:* Rheumatoid arthritis, Takayasu arteritis *Usually with compact/well-formed granulomas:* Sarcoidosis, mycobacterial and fungal infections
Lymphoplasmacytic pattern	Lymphocytes and plasma cells without a granulomatous component	IgG4-RD, lupus, AS, syphilitic aortitis, an undersampled granulomatous aortitis
Mixed inflammatory pattern	All/most inflammatory cell types without an overt granulomatous pattern	Cogan syndrome, Behçet's disease, relapsing polychondritis
Suppurative pattern	Neutrophilic abscesses with necrosis and cell debris	*Staphylococcus*, *Streptococcus*, *Salmonella*, *Pseudomonas,* and fungal infections

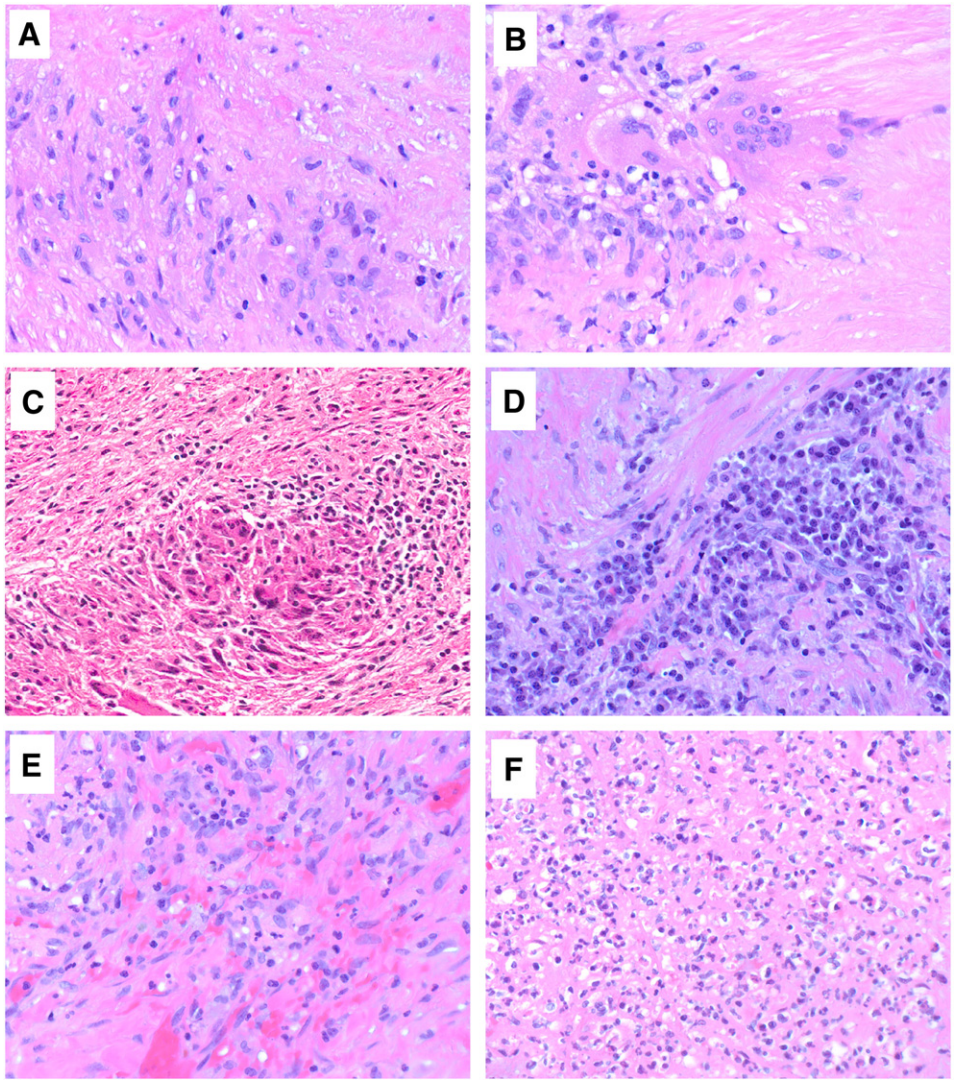

Fig. 3. Inflammatory patterns for aortitis and periaortitis. (A–C) The granulomatous/giant cell pattern is comprised of clusters of epithelioid macrophages (A), giant cells (B), and/or compact well-formed granulomas (C). (D) Lymphoplasmacytic pattern. (E) Mixed inflammatory pattern. (F) Suppurative pattern.

3.5.2. Aortitis/periaortitis with lymphoplasmacytic pattern

In the lymphoplasmacytic pattern of aortitis, the inflammation is composed of lymphocytes and plasma cells without a granulomatous component. The lymphoplasmacytic pattern is much less common than the granulomatous/giant cell pattern in most populations studied. It is recommended to stain such cases for IgG4 and either IgG or CD138. A primary specific disease to consider when confronted with this pattern of inflammation is IgG4-related disease (IgG4-RD). By international consensus criteria, the presence of more than 50 IgG4 + plasma cells per 400x high power field (HPF) with more than 50% of the IgG + plasma cells expressing IgG4 would support the presence of IgG4-related aortitis. At least three 400× HPFs should be assessed. The diagnosis of IgG4-related aortitis also requires the absence of another inflammatory process, such as infection or granulomatous inflammation. In lymphoplasmacytic aortitis cases, a special stain for spirochetes can be obtained, particularly if there is a clinical history of syphilis, but such stains are rarely rewarding in this setting.

3.5.3. Aortitis/periaortitis with mixed inflammatory pattern

The mixed inflammatory pattern is a relatively uncommon type of aortitis. The inflammatory infiltrate will contain substantial quantities of most, if not all, inflammatory cell types: macrophages, lymphocytes, plasma cells, eosinophils, mast cells, and neutrophils. An overtly granulomatous pattern of inflammation is not present in these cases, but necrosis may be present. This inflammatory pattern has been associated with aortitis in Cogan syndrome, Behçet's disease, and relapsing polychondritis. The latter two conditions have also been linked together clinically in some cases as the MAGIC (Mouth And Genital ulcers with Inflamed Cartilage) syndrome [17].

3.5.4. Aortitis/periaortitis with suppurative pattern

In the suppurative pattern of aortitis, there is a marked neutrophilic infiltrate with extensive necrosis histologically. This pattern is largely associated with bacterial infection and, in some cases, with fungal infection. Special stains for microorganisms are recommended, as discussed in detail in Section 4.3 below. Focal granulomatous reaction to the organisms may also be present. In the chronic stages, fibrosis and lymphoplasmacytic infiltrates may be present. In chronic active infections from Gram-positive bacteria, the plasma cells may show focally high expression of IgG4. However, the presence of the coexisting suppurative pattern and bacteria enables distinction from IgG4-related aortitis.

3.5.5. Unclassified aortitis/periaortitis

An aortitis/periaortitis that does not fit readily into one of the above designations can be designated as unclassified aortitis/periaortitis. In

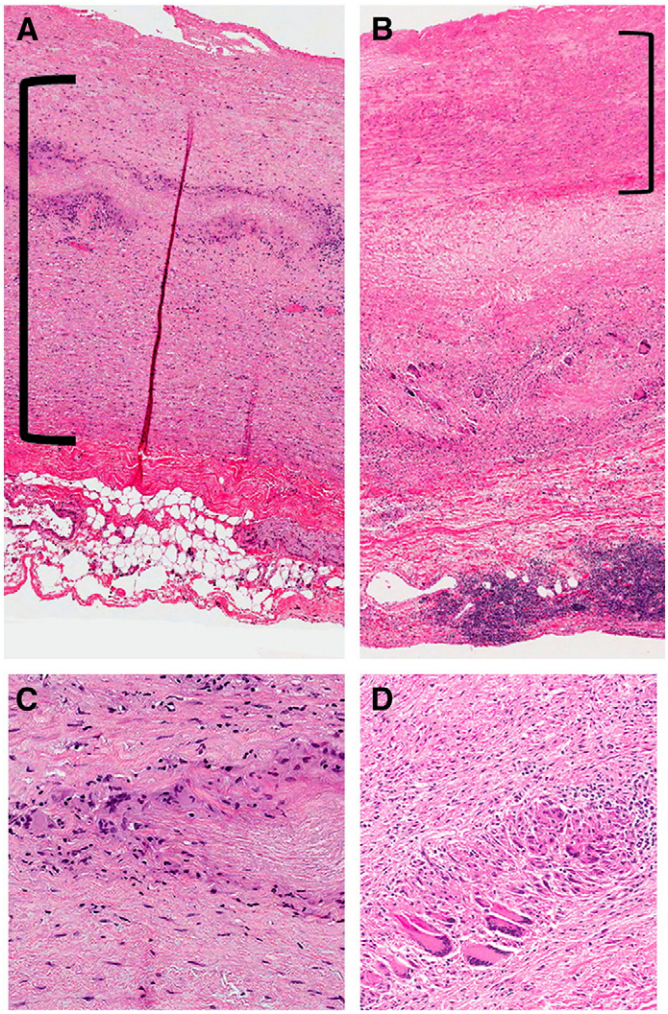

Fig. 4. Comparison of GCA with Takayasu Arteritis. The aortitis in GCA (A) tends to involve the inner half of the media most severely with less adventitial involvement and with usually no compact/well-formed granulomas. In contrast, the aortitis in Takayasu arteritis (B) tends to show more adventitial involvement and may contain compact/well-formed granulomas. At higher magnification, the aortitis in GCA contains epithelioid macrophages and often giant cells (C), while, in addition to these features, compact granulomas may also be present in Takayasu arteritis (D).

such cases, it is recommended that the features of the inflammatory infiltrate be described, including the types of inflammatory cells present and the presence and extent of necrosis and scarring.

4. Inflammatory diseases of the aorta

4.1. Atherosclerosis

Atherosclerosis is a disease characterized by the formation of intimal plaques containing smooth muscle cells, myofibroblasts, lipid, collagen, and/or calcification with variable amounts of inflammation in large and medium-sized arteries. The inflammation in atherosclerosis is composed predominantly of macrophages/foam cells, which release metalloproteinases. Atherosclerosis has several predilection sites, and the aorta, particularly the abdominal aorta, is one of the sites that is affected early and often severely during the course of the disease. The pathologic characteristics of aortic atherosclerosis have been described extensively in numerous postmortem studies [18–25]. The disease begins, often in childhood, with hyperplastic thickening of the intima due to accumulation of smooth muscle cells. Lipid is entrapped within the thickened intima and ingested by macrophages and to a lesser extent smooth muscle cells to become foam cells. Continued lipid deposition results in extracellular lipid accumulation and eventually a central necrotic/lipid core composed of lipid and debris from dead macrophages and smooth muscle cells. The development of atherosclerotic lesions is associated with varying degrees of fibrosis, calcification, and inflammatory reactions. With lesion progression, there are progressive elastic lamellae fragmentation, thinning, and fibrosis of the medial layer, with variable fibrosis and inflammation of periadventitial tissues. Severe aortic atherosclerotic plaques frequently show disruption of the plaque surface or "ulceration" with adherent organizing thrombus.

Table 4
Comparison of GCA and Takayasu arteritis

	GCA	Takayasu arteritis
Age	Usually > 50 years	Usually <50 years
Most severely afflicted race	Northern European	Asian
Arteries involved	Aorta, proximal branches, cranial arteries	Aorta, proximal branches, pulmonary arteries
Aortic layers involved	Inner media > outer media and adventitia	Outer media and adventitia > inner media
Compact granulomas	Usually absent	May be present

Table 5
Eponyms and historical nomenclature for selected inflammatory aortic diseases

Disease	Eponyms and historical nomenclature
GCA	Horton's disease, cranial arteritis, giant cell aortitis, granulomatous arteritis, polymyalgia arteritis, temporal arteritis
Takayasu arteritis	Aortic arch syndrome, idiopathic arteritis, Martorell syndrome, nonspecific aortoarteritis, obliterative brachiocephalic arteritis, occlusive thromboaortopathy, panaortitis or aortitis syndrome, pulseless disease, reversed coarctation, Takayasu's disease, Takayasu syndrome, young female arteritis
GPA	Wegener's granulomatosis, pathergic granulomatosis, ANCA-associated granulomatous vasculitis
EGPA	Churg Strauss syndrome, allergic granulomatous vasculitis
Behçet's disease	Adamantiades–Behçet's disease, Behçet's syndrome, Silk Road disease

While atherosclerosis usually starts in childhood, the rate of progression of atherosclerotic plaques depends on both genetic factors and nongenetic risk factors such as hypercholesterolemia, systemic arterial hypertension, diabetes mellitus, smoking, obesity, and aging. In the aorta, plaque formation can be seen in its earliest stages in the posterior aortic wall, especially around ostia of branch vessels. In the advanced stages, usually in the elderly population, diffuse involvement of large segments of the aorta can be seen, particularly in the infrarenal aorta. There is often a marked difference in disease severity between the highly atherosclerosis-prone abdominal aorta and the less atherosclerosis-prone thoracic aorta. In addition, the presence of atherosclerotic plaques and the relative number of complicated plaques increase substantially from the ascending aorta to the aortic arch and to the descending aorta. However, there is a relationship between the degrees of atherosclerosis in the thoracic and abdominal aortas, as patients with atherosclerotic abdominal aortic aneurysms frequently also have thoracic aortic atherosclerosis, which is typically less severe than that present in the abdominal aorta.

Complications of aortic atherosclerosis that may result in surgical correction include aneurysm formation, aneurysm rupture, occlusive aortic thrombosis, fistula formation, infection, penetrating ulcer with dissection, and distal embolization of thrombus and/or plaque material. In surgical pathology studies of aortas resected primarily for aneurysms, ruptured aneurysms, and dissections, the frequency and severity of atherosclerosis are much greater in resected abdominal aortic segments than in resected thoracic aortic segments [26–32]. In adults, prominent atherosclerosis typically involves less than 10% of resected thoracic aortic segments but usually more than 80% of resected abdominal aortic segments.

4.2. Inflammatory aortic (atherosclerotic) aneurysms

Inflammatory aortic aneurysm or IAA is a disorder identified initially based on the intraoperative gross appearance of the aorta showing thickening of the wall with fibrosis and extensive adhesions to adjacent structures [13,28,33–41]. So defined, it has been reported to be present in 2%–15% of resected abdominal aortic aneurysms, most often in men, and usually in the setting of severe aortic atherosclerosis. Histologic assessment of the thickened adventitia typically shows fibrosis with extensive inflammation, most often composed of lymphocytes and plasma cells, but less commonly, granulomatous inflammation, including giant cells and occasional compact granulomas, has been reported. There are often lymphoid follicles, as well as inflammation involving small adventitial arteries and veins. Some, but not all, studies have shown increased preoperative serum inflammatory markers.

The literature regarding IAA is difficult to interpret. Since the condition is often defined clinically or intraoperatively, these cases likely represent a mixture of diseases ranging from secondary complications of severe atherosclerosis to primary involvement by systemic rheumatologic diseases. In some series, the pathologic features of inflammatory aneurysm, as defined intraoperatively, overlap with the pathologic features of atherosclerosis [13,28,35,40,41]. In patients with clinically defined IAA, inflammatory markers elevated preoperatively have been reported to normalize after repair of the aneurysm, despite the aneurysm tissue not being resected. Likewise, by imaging, the periadventitial inflammation and fibrosis have often been reported to decrease following either endovascular or open repair of the abdominal aortic aneurysm [42,43]. These observations suggest that many patients clinically diagnosed with IAA likely have a localized inflammatory response to an atherosclerotic aneurysm.

For cases on the other end of the spectrum, IAA has often been difficult to distinguish from chronic periaortitis due to outright systemic rheumatologic diseases including GCA, rheumatoid arthritis, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), GPA, and IgG4-RD [44–46]. Such cases of chronic periaortitis may also involve other arteries, present with clinical features of autoimmune diseases, and/or be accompanied by retroperitoneal fibrosis or sclerosing mediastinitis.

4.3. Noninfectious aortitis/periaortitis

Noninfectious aortitis is defined as an inflammatory process involving one or more layers of the aortic wall in which the inflammation cannot be accounted for by some other process such as atherosclerosis or infection. If the inflammation is limited to the adventitia, then the term *periaortitis* is often employed. In studies involving primarily the thoracic aorta, noninfectious aortitis has been reported to involve from 2% to 16% of aortic resections [26,29,30,47–55]. Aortitis is often an unexpected diagnosis at histological examination of surgically resected thoracic aneurysms and dissections, and may be the presenting feature of a systemic vasculitis or may occur in the absence of other clinical signs or symptoms of systemic vasculitis.

In noninfectious aortitis, the aorta often shows thickening of the wall and irregular bulging of the intima giving a gross intimal cobblestone appearance. The normal aorta contains no inflammatory cells in its intima or media. However, in noninfectious aortitis, there are often lymphocytes and plasma cells in the adventitia singly, in aggregates, or in germinal centers. In noninfectious aortitis, there is inflammation in the media as well. In chronic periaortitis, the inflammation will be confined to the adventitia. The characteristics of the inflammatory infiltrate are to some extent dependent on the specific type of aortitis or periaortitis present. Inflammatory cells may be seen in and around the aorta in a variety of situations that are not vasculitis. In degenerative aortic disease, patchy mild chronic inflammation may be seen, often around vasa vasorum, presumably as a consequence rather than a cause of the degenerative change. As noted above, chronic inflammation frequently accompanies atherosclerosis. In aortic dissection, there may be an acute inflammatory reaction around the dissection plane. In the late phase, scarring can be seen in the media with disruption and disorganization of the remaining elastic fibers and replacement by dense fibrous tissue. In end-stage aortitis, there may be little inflammation but prominent fibrosis throughout the wall.

Specific rheumatologic diseases most commonly associated with noninfectious aortitis are discussed below. Many additional conditions have also been associated with aortitis including reactive arthritis, rheumatic heart disease, Kawasaki disease, Crohn's disease, and microscopic polyangiitis.

4.3.1. Giant cell arteritis

GCA (Horton's disease) is the most common systemic vasculitis that involves the aorta [47,49,56–61]. GCA primarily, if not exclusively, affects persons older than 50 years of age. Disease susceptibility has been associated with northern European descent, and two thirds of those affected are women. GCA typically causes vasculitis of the extracranial branches of the carotid arteries and the aorta, and often spares intracranial vessels. Clinical symptoms reflect end-organ ischemia. Presenting features are typically a unilateral headache, jaw claudication, or visual impairment. GCA is associated with polymyalgia rheumatica, a disorder characterized by severe myalgias and stiffness of the muscles of the neck, shoulder girdle, and pelvic girdle. Additional clinical features may include malaise, anorexia, weight loss, fever, night sweats, depression, and elevated inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein, and IL-6.

GCA confers an increased risk of both thoracic and abdominal aneurysms and of aortic dissection and/or rupture. Aortic involvement can precede cranial symptoms, be in association with cranial symptoms, or occur after the diagnosis of cranial GCA. Pathologically, the diagnosis of GCA is most often established by a superficial temporal artery biopsy. Occasionally, aortitis is the presenting feature of a patient with subsequent clinically recognized systemic GCA. Histologically, aortitis due to GCA is characterized by granulomatous inflammation in the media comprised of epithelioid macrophages and occasional giant cells. There is usually an accompanying lymphoplasmacytic infiltrate, which may predominate in the adventitia. This inflammation is often associated with so-called "laminar medial necrosis," areas of smooth muscle cell loss with collapsed elastic fibers. The vasa vasorum may also be abnormally prominent in the middle and inner thirds of the medial layer. Compact granulomas are usually absent. The inner half of the aorta often shows more involvement than the outer half and adventitia. Intimal hyperplasia is frequently present. In the later phases of the disease, there may be extensive scarring, but the adventitia is relatively spared compared with some other forms of aortitis, such as Takayasu arteritis.

Patients with histologic features strongly suggestive of aortic involvement by GCA often manifest no other clinical signs or symptoms for systemic GCA. Thus, the term *giant cell aortitis* is often used to help distinguish these patients from those with clinical and/or pathologic evidence of GCA with cranial involvement. Autopsy studies have shown that pathologic systemic GCA, even with cranial involvement, is most often an indolent condition, with the majority of cases remaining subclinical during life [62]. Likewise, patients who have been previously treated for systemic/cranial GCA and who do not have clinically apparent active vasculitis can be found to have active systemic GCA pathologically at autopsy [63,64].

4.3.2. Takayasu arteritis

In patients below the age of 50, Takayasu arteritis is the most common systemic vasculitis that afflicts the aorta [32,47,49,55,65–70]. Takayasu arteritis primarily involves large elastic arteries, particularly the aorta and arch vessels. The coronary ostia, renal arteries, and pulmonary arteries may also be involved. Clinical manifestations range from asymptomatic disease with impalpable pulses to subclavian steal syndrome to catastrophic neurologic strokes. Adolescent girls and women in their second and third decades of life are most affected. This arteritis

is most commonly seen in Japan, Southeast Asia, India, and Mexico. Panarteritic inflammatory infiltrates cause marked thickening of the involved artery with intimal hyperplasia and subsequent luminal narrowing and occlusion. Diffuse dilatation, formation of aneurysms, and thrombosis can occur. The inflammatory and stenotic phases of the disease frequently coexist. The acute phase is characterized by edema and diffuse inflammatory infiltrates involving the media, the media–intimal junction, and the adventitia, often affecting the vasa vasorum. The inflammatory infiltrate is overall granulomatous and is composed of macrophages with variable amounts of T- and B-lymphocytes, plasma cells, and eosinophils. A common feature is the presence of giant cells. Compact granulomas and medial necrosis may be present. In the late phase of the disease, scarring can be seen in the tunica media with disruption and disorganization of the remaining elastic fibers. Dense adventitial fibrosis is often present. The intima can show a great degree of fibrous thickening, often with an overlap of fibroatheromatous plaques. These two combined features give a gross "tree bark" appearance to the intimal surface, as in other forms of aortitis.

The histologic pattern of Takayasu arteritis may overlap with that of both GCA and sarcoidosis, and thus clinical–pathologic correlation is often required. However, there are pathologic features that may help to distinguish between GCA and Takayasu arteritis. Aortic wall thickness is generally greater in Takayasu arteritis than in GCA. In addition, GCA is more commonly associated with inflammation that is most severe in the inner media, and GCA is not as often associated with the severe adventitial scarring seen in Takayasu arteritis. Compact granulomas are more commonly seen in Takayasu arteritis than in GCA.

4.3.3. Rheumatoid arthritis

Aortitis is an uncommon extra-articular manifestation of rheumatoid arthritis. Rheumatoid aortitis may be associated with a more generalized rheumatoid vasculitis, which can occur in the early stage of the disease, but more commonly occurs in patients who have had seropositive rheumatoid arthritis for 10 years or longer. Rheumatoid vasculitis may affect blood vessels of all sizes, from small vessels of the vasa vasorum to the aortic wall itself [71,72]. An autopsy study identified 10 cases of rheumatoid aortitis from among 188 consecutive autopsy cases of rheumatoid arthritis [73]. A small number of rheumatoid aortitis cases have also been identified in surgically resected aortic segments [49,54,74]. Either the thoracic or abdominal aorta may be involved, and the inflammation may be present in all layers of the aorta or be limited to the media. The infiltrate is most often predominately composed of lymphocytes and plasma cells. A granulomatous component to the inflammation can be found in many of the cases, which may include giant cells and, in about half of the cases, actual rheumatoid nodules, which are associated with necrosis and palisading histiocytes/macrophages. When present, rheumatoid nodules can help to distinguish this disease from other forms of aortitis with a granulomatous/giant cell pattern, such as GCA, Takayasu arteritis, and sarcoidosis.

4.3.4. Systemic lupus erythematosus

Aortitis is an uncommon complication of SLE, and most aortic aneurysms in SLE are degenerative and not inflammatory. Most cases of lupus-associated aortitis have been described in conjunction with aortic aneurysms or aortic dissection. Histologic features have only been reported in a few cases [47,50,54,75–79]. In lupus aortitis, the inflammatory infiltrate is typically either lymphocytic or lymphoplasmacytic, and not usually granulomatous. Both the adventitia and media may be involved. There is often involvement of adventitial vessels, with fibrinoid necrosis of these vessels in some cases.

4.3.5. Ankylosing spondylitis

AS is a chronic inflammatory rheumatic disease of the spine (spondylitis) and sacroiliac joints (sacroiliitis) associated in many cases with inflammation of the peripheral joints (arthritis), eyes (uveitis), intestine (enteritis), and aortic root (aortitis). Predisposition to AS (90%) is associated with genetic factors, the key gene of which is HLA-B27. Patients may develop aortitis, which frequently involves the aortic root and the ascending aorta. Aortitis can occur in both late and early phases of the disease. The histologic features of the aortitis in AS have only been described in a few cases [26,80,81]. The aortic root is most affected, and the aortic valve may be involved. There is usually fibrosis, which is often more pronounced in the adventitia than in the media. The inflammation is lymphoplasmacytic and may be restricted to the adventitia.

4.3.6. Relapsing polychondritis

This disease causes destruction of the ear and nasal cartilage as well as scleritis. The aorta can rarely be involved, particularly the ascending aorta. Pathologic features have only been described in a few cases [82]. The medial elastic tissue is destroyed and replaced by vascular granulation tissue and focal necrosis. Neutrophil leukocyte aggregates forming microabscesses may be present in the media and intima. The adventitia shows lymphocytic infiltration and fibrosis. Giant cells, granulomas. and eosinophils are usually not present.

4.3.7. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

GPA is a rare multisystem disease that has been reported to affect almost every organ in the body. It is characterized by a small vessel neutrophilic vasculitis as well as a necrotizing granulomatous process, which may involve medium-sized and large vessels. It is often associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA) to either myeloperoxidase or proteinase-3. Most patients present with some evidence of respiratory tract involvement. Large-vessel involvement with aortic aneurysm or dissection has been occasionally reported [83–86]. Both the thoracic and abdominal aorta may be involved, and some cases present on imaging as primarily periaortitis. Histologically, there is granulomatous inflammation of the media and adventitia with geographic necrosis surrounded by palisading histiocytes and scattered giant cells admixed with neutrophils. The giant cells are not specifically restricted to the elastic lamellae, which is more typical of GCA. Also the degree of necrosis and neutrophil infiltration is more extensive than typically seen in GCA. Special stains to rule out infection are often helpful.

4.3.8. Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg Strauss syndrome)

The histological hallmark of EGPA is a necrotizing vasculitis similar to GPA but with a predominance of eosinophils. There may or may not be a previous history of asthma, peripheral eosinophilia, or systemic organ involvement. Aortic involvement is rare [87]. Histologically, there is granulomatous inflammation admixed with eosinophils. The inflammation may be largely restricted to the adventitia.

4.3.9. Cogan syndrome

Cogan syndrome is an unusual disorder characterized by episodes of interstitial keratitis and vestibuloauditory dysfunction (i.e., eye and ear symptoms). Aortitis occurs in up to 10% of cases of Cogan syndrome. Hearing loss, tinnitus, vertigo, as well as interstitial keratitis are common, but episcleritis, scleritis, or iritis has also been described. The aortitis usually affects the ascending aorta and the arch, and is usually due to inflammation with a mixed inflammatory pattern [88–90]. There is infiltration of the intima and media by neutrophils surrounding areas of medial necrosis with focal transmural destruction of the wall. Macrophages are also prominent, with very occasional giant cells noted in the necrotic areas of the media. An overtly granulomatous pattern of inflammation is not usually present.

4.3.10. Behçet's disease

Behçet's disease is characterized clinically by genital ulceration, oral ulcers (aphthous stomatitis), and uveitis. Vascular involvement can

result in venous thrombosis, arterial thrombosis, and aneurysm formation. Aortitis may be present, in some cases associated with aortic valve regurgitation [91,92]. Histologically, the inflammation in Behçet's disease typically shows a mixed pattern, being composed of most, if not all, cell types, without being overtly granulomatous. Histologic features of the aortitis in Behçet's disease have been reported in only a few cases [93].

4.3.11. Sarcoidosis

Sarcoidosis is a systemic disorder characterized by granulomatous inflammation usually containing non-necrotizing granulomas, which primarily involves the lungs, lymph nodes, and skin. The pathology of aortic involvement by sarcoidosis has only been reported in a small number of cases [94–98]. The features of the inflammatory infiltrate are consistent with those of sarcoidosis in other parts of the body. There is granulomatous inflammation including compact noncaseating granulomas and giant cells. There is usually an accompanying lymphocytic or lymphoplasmacytic infiltrate. In some cases, only a lymphocytic infiltrate is identified. The inflammation may involve the intima, media, and/or adventitia. The inflammation may be limited to the adventitia as a periaortitis. Sarcoidosis may involve either the thoracic or abdominal aorta, and may be seen in both younger and older patients.

4.3.12. IgG4-related disease

IgG4-RD is a recently recognized disease that may be associated with aortitis or periaortitis [31,32,41,52,53,99]. IgG4-RD is characterized by elevated serum levels of IgG4 and histopathological findings including fibrosis and prominent tissue infiltration by lymphocytes and IgG4-positive plasma cells. The disorder was first recognized in the pancreas as a form of autoimmune pancreatitis. Subsequently, numerous extrapancreatic lesions have been described in this disorder including sialadenitis, lacrimal gland inflammation, lymphadenopathy, aortitis/periaortitis, sclerosing cholangitis, tubulointerstitial nephritis, retroperitoneal fibrosis, and inflammatory pseudotumors. Multiorgan lesions can occur synchronously or metachronously in the same patient. The disease usually afflicts older individuals after 50 years of age. IgG4-RD may result in acute events due to aortic dissection or aneurysm rupture [99–101]. The vasculitis of IgG4-RD may also involve large and medium-sized arterial branches of the aorta [101–103].

IgG4-RD can either result in lymphoplasmacytic aortitis or be restricted to the adventitia as a periaortitis. The principal histopathologic findings are lymphoplasmacytic infiltration, lymphoid follicle formation, obliterative adventitial phlebitis, and fibrosis, which may have a storiform pattern. A modest tissue eosinophilia is reported in some but not all cases, most commonly in the abdominal aorta. International consensus guidelines for the pathologic diagnosis of IgG4-related aortitis/periaortitis require the presence of a lymphoplasmacytic aortitis/periaortitis with more than 50 IgG4+ plasma cells per 400× HPF and an IgG4/IgG ratio greater than 50%, when counting the three HPFs with the highest degree of IgG4 positivity [104]. Other conditions such as infection must also be excluded [105]. Granulomatous inflammation and suppurative inflammation are not components of this disease, although neutrophils may be present if there is a coexisting recent aortic rupture or dissection. When these guidelines are applied, IgG4-RD has been found to account for 9%–22% of thoracic aortitis cases [32,52,53]. IgG4-related periaortitis has been reported to be present pathologically in around half of patients with inflammatory abdominal aortic aneurysm [31,41], although uncertainty exists in differentiating systemic IgG4-RD from a localized reaction to atherosclerosis in this setting [46].

4.3.13. Clinically isolated aortitis

In some patients with pathologic aortitis in resected aortic segments, there is no clear clinical evidence of a systemic rheumatologic disease to account for the vasculitis, and the aortitis is referred to as "isolated" or "idiopathic." The frequency of this phenomenon ranges from 0% to 100% of thoracic aortitis cases in different series, with some of the variability likely being due to variations in patient demographics and the thoroughness of the clinical workup [26,41,47–49,51,54,90,106–108]. Such clinically isolated aortitis is encountered most commonly in the ascending aorta. Since this grouping of patients is through clinical features, there is no specific pattern of inflammation to define this proposed subgroup of aortitis. The inflammation is most often granulomatous and indistinguishable from that of GCA, but the inflammation may be purely lymphoplasmacytic and, by routine slides, indistinguishable from that of IgG4-RD. This group of patients includes both younger adults and older adults, although like noninfectious aortitis in general, the patients tend to be older.

Studies specifically focusing on the long-term follow-up of ascending aortitis in the absence of clinical evidence of systemic vasculitis are limited. One report has suggested that patients with clinically isolated aortitis are not at an increased risk for subsequent adverse events such as distal aortic aneurysms and dissections [49]. However, a subsequent report suggested that, on imaging, these patients frequently have concurrent aneurysms at additional sites throughout the body at the time of initial aortic surgery [51]. In a recent case–control study with long-term follow-up, including in most cases aortic imaging, patients with a giant cell aortitis pattern of inflammation in the ascending aorta but lacking clinical evidence of systemic vasculitis had a statistically significant higher rate of subsequent distal aortic aneurysms and dissections as compared with a matched control group [109].

Currently, it is unclear if clinically isolated aortitis is a distinct pathologic entity or a heterogeneous group of aortitis subtypes being lumped together based on clinical presentation. It is also not clear if the majority of these cases truly have a vasculitis that is pathologically completely isolated to a discrete aortic segment or if the vasculitis is systemic but largely subclinical. In a large autopsy study, 13 cases of noninfectious ascending aortitis were identified in older patients (mean age 81 years, range 62–96 years) [62]. Of these 13 cases, 12 (92%) had pathologic involvement of the temporal arteries by vasculitis, despite the fact that at least 10 (77%) of the patients lacked clinical evidence of systemic vasculitis before death. Furthermore, as our understanding of the specific types of aortitis continues to grow, it is also becoming clear that vasculitis in newly recognized systemic diseases, such as IgG4-RD, have in some cases previously been assumed to be isolated to the aorta based on clinical grounds [46]. More studies will be required to clarify our understanding on this issue.

While periaortitis may be due to some of the systemic disorders listed above, chronic periaortitis can be present without clinical evidence of systemic vasculitis, particularly in the abdominal aorta [44–46]. This, again, likely represents a heterogeneous group of conditions and may be associated with a more generalized retroperitoneal fibrosis in some patients. Chronic abdominal periaortitis usually occurs in the setting of severe aortic atherosclerosis, and in many cases, it may represent a localized reaction to atherosclerosis. Some authors have used the term *chronic periaortitis* almost synonymously with the term *inflammatory aortic aneurysm*.

4.4. Infectious aortitis

Atherosclerotic and systemic arterial hypertensive diseases are the most common (and important) etiologies of aortic aneurysmal disease. Elsewhere in these recommendations, the less frequent noninfectious aortitides are also discussed. Occurring with a substantially lesser frequency (at least in industrialized nations) are the infectious causes of aortic aneurysmal disease, including luetic and tuberculous forms.

4.4.1. Suppurative/mycotic infectious aortitis

Infectious aortitis can develop secondary to embolization of a septic embolus, typically as a complication of infective endocarditis. Osler used the term *mycotic aneurysm* to describe aneurysms associated with infective endocarditis, referring to the "mushrooming" appearance of the

aneurysm rather than the etiologic microbial agent. The vast majority of these are bacterial in nature, mostly arising from endocarditic vegetations initially embolizing to vessels of the vasa vasorum. Infectious aortitis may also develop by direct extension of an adjacent infectious process (e.g., from the esophagus, lung, or pericardium) or through direct vascular infection by circulating organisms, usually initiating as a nidus in the vasa vasorum or on the luminal surface of an ulcerated atherosclerotic plaque.

Lesions typically arise in areas of preexisting vascular dilation (e.g., due to systemic arterial hypertension) or injury (e.g., surgical or invasive monitoring), or in a preexisting atheromatous plaque. Immune compromise (e.g., due to diabetes mellitus, glucocorticoids, chemotherapy, and/or malignancy) is also an important risk factor. Antecedent infection (e.g., pneumonia, cholecystitis, urinary tract infection) can be identified in roughly half of cases, and half of these (25% overall) are attributable to infective endocarditis. Infectious aneurysms of the thoracic aorta are relatively rare and most commonly result from direct extension of a mediastinal infection or involvement of the aortic root by an aggressive infective endocarditis.

Patients typically present with fever and a rapidly enlarging, painful (back or abdominal pain) pulsatile mass. There is generally leukocytosis, and the ESR may be elevated. Imaging will typically demonstrate aneurysm formation, which may be multifocal, particularly in the setting of embolization of infective endocarditis lesions. Soft tissue inflammation adjacent to the lesion or perivascular fluid collections raises the suspicion of an infectious aneurysm. Blood cultures are positive in 50%–85% of cases, with *Staphylococcus* and *Salmonella* species being most common. *Streptococcus pneumoniae* and other non-*Salmonella* Gram-negative bacilli are also etiologic agents. Fungi are considerably less common, except in specific situations such as immune compromise or associated with broad-spectrum antibacterial treatment.

Histology will reveal transmural inflammation, which is primarily acute rather than chronic, with abscesses containing numerous neutrophils and variable degrees of necrosis and thrombosis [104,110]. Evidence of incipient or frank vascular rupture is also often present. Microbial stains (Gram or silver) are usually manifestly positive. Although prior antimicrobial therapy may reduce bacterial wall staining by Gram stain, silver stains will still typically reveal bacteria, albeit with some expansion and central clearing due to antibiotic effects.

Distinguishing infected aneurysms versus noninfectious inflammatory aneurysms is not usually difficult. In addition to the presence or absence of microbes (as demonstrated by cultures and/or staining), infected aneurysms will have a more dense transmural acute inflammatory response, while noninfectious inflammatory aneurysms are marked by more severe chronic inflammation and adventitial fibrosis. Perioperative mortality for infectious aortic aneurysms is 15%–20%, with worse outcomes in the setting of Gram-negative infections and/or ruptures.

4.4.2. Syphilitic aortitis

Syphilitic aneurysms develop as a manifestation of tertiary syphilis [111,112] and currently represent an exceedingly rare cause of aortic aneurysms. As opposed to the other more common infectious aneurysms described above, luetic aortitis more commonly affects the ascending and thoracic aorta. The obliterative endarteritis characteristic of tertiary syphilis shows a predilection for the vessels of the vasa vasorum, leading to ischemic injury of the aortic media and aneurysmal dilation that can include the aortic valve annulus with presentation as aortic valvular insufficiency. Indeed, the dilated valvular annulus and accompanying chronic valvular insufficiency can lead to massive cardiac enlargement and the classic "cor bovinum" (cow's heart) with heart weights in excess of a kilogram. Congestive cardiac failure in the setting of such chronic overload failure is the most common cause of death in these patients. The coronary ostia may also be involved, leading to cardiac ischemia. Imaging studies will classically demonstrate prominent ascending aorta aneurysm formation.

The predilection of the causal spirochetes for the small vessels of the vasa vasorum leads to adventitial chronic inflammation, particularly involving the small arteries and arterioles that perfuse the media. The ensuing immune response to the microbe causes direct vascular damage; there are luminal narrowing and obliteration (obliterative endarteritis), a dense surrounding rim of lymphocytes, and especially plasma cells that may extend into the media, with associated adventitial fibrosis. Focal areas of necrosis surrounded by palisading macrophages, often referred to as "microgummas," may also be present. The spirochetes are difficult if not impossible to demonstrate in these aneurysms.

In patients without prior known history of syphilis, the histologic findings may merit additional confirmation with serologic studies. Although rapid plasma reagin and Venereal Disease Research Laboratory tests have good sensitivity for tertiary syphilis (~95%), fluorescent treponemal antibody studies have almost 100% sensitivity.

The obliteration of the vasa vasorum results in aortic medial ischemic injury, with variable loss of smooth muscle cells and associated matrix. With medial destruction, elastic recoil is lost, and the aorta becomes dilated to produce an aneurysm. Subsequent medial scar contraction can "wrinkle" the intervening segments of aorta. With superimposed atherosclerotic plaque, such intimal lesions grossly resemble "tree bark."

4.4.3. Mycobacterial aortitis

Tuberculous aneurysms are exceedingly rare causes of infected aneurysms in developed countries; one study describes only 41 cases between 1945 and 1999 [113]. However, the condition may be more frequently encountered in less developed countries. These are most often attributable (75% of cases) to erosion of infected periaortic lymph nodes or other infected foci into the adjacent aortic wall. The thoracic and abdominal aortic regions are equally affected. Roughly half of patients have disseminated tuberculosis. Aortic involvement typically ranges from miliary tuberculosis of the intima to transmural tuberculosis and to aneurysm formation. Complications can also include fistula formation and, rarely, coronary artery ostial obstruction [114]. Although most lesions show characteristic granulomatous lesions (with or without central caseation and organisms identifiable by acid-fast bacillus staining), there are reports of fibrotic lesions attributable to hypersensitivity responses. Untreated, the tuberculous aortitis is almost uniformly fatal with death often due to aneurysm rupture. However, combined antibiotic and surgical therapy substantially improves survival. Abdominal mycobacterial aortitis may in rare cases also result from *Mycobacterium bovis* in the setting of intravesical bacillus Calmette–Guérin therapy for bladder cancer [115].

5. Discussion

These consensus criteria offer a first global approach to the general subclassification of inflammatory aortic diseases based on histologic features. It is acknowledged that there are some areas that remain difficult and controversial, such as the distinction between IAA and periaortitis. It is also acknowledged that, for some pathologists, these criteria will require a change in the manner in which certain diagnostic terms are employed.

One example is the use of the word *granulomatous*. The committee agreed to adopt the more general definition of this term, applying it to lesions that contain clusters of epithelioid macrophages in general and not restricting the use of the word to only lesions that contain compact/well-formed granulomas and/or giant cells. This is consistent with the current use of the term in general surgical pathology practice in many centers.

While the criteria provided here offer a mechanism for the initial classification of an aortitis based on the pattern of inflammation, definitive subclassification of the specific disease processes is often not achievable based solely on histologic features. A major limitation is that, for many of the diseases discussed, the published literature

concerning the histologic features is limited to a handful of case reports. Another limitation is the variable and sometimes nonspecific fashion in which clinical subclassifications are rendered in patients with aortitis, with, for example, the designation of Takayasu arteritis being applied to essentially all patients with aortitis under the age of 50 in some centers. It is also recognized that with the exception of IgG4, there are few tissue markers that have been demonstrated to subclassify the inflammatory infiltrates in a clinically useful manner. It is clear that for progress to be made in identifying the distinctive pathology of these conditions, more studies with larger numbers of patients utilizing novel tissue markers will need to be completed.

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