## The pathology of large-vessel vasculitides

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### ABSTRACT

Vasculitis affecting large elastic arteries, including the aorta and major proximal branches, encompasses various diseases including Takayasu arteritis, giant cell (or temporal) arteritis, and tertiary syphilis, but also may occur as a rare complication of Behçet's disease, rheumatoid arthritis, sarcoidosis, Cogan syndrome, Kawasaki disease, ankylosing spondylitis, systemic lupus erythematosus and Wegener's granulomatosis. Recent reports have also established a link between inflammatory abdominal aortic aneurysm as well as lymphoplasmacytic thoracic aortitis with an overabundance of IgG4-producing plasma cells and the burgeoning constellation of "Hyper-IgG4" syndromes. This review focuses on morphologic aspects of large-vessel vasculitis pathology associated with giant cell arteritis, Takayasu arteritis, idiopathic or isolated aortitis, lymphoplasmacytic thoracic and ascending aortitis, and the inflammatory aneurysm/retroperitoneal fibrosis syndrome.

### Introduction

Vasculitis affecting elastic arteries, including the aorta and major proximal branches, is most commonly associated with Takayasu arteritis, giant cell (or temporal) arteritis, and tertiary syphilis, but is also recognised as a rare complication of Behçet's disease (1), rheumatoid arthritis (2), sarcoidosis (3), Cogan syndrome (4), Kawasaki disease (5), ankylosing spondylitis (6), systemic lupus erythematosus (7) and Wegener's granulomatosis (8). While the pathogenetic mechanisms differ, the tissue level and histopathologic changes occurring in these various conditions are often quite similar. Complications ensuing from damage to these large elastic arteries include rupture, dissection, aneurysmal dilatation, thrombosis with or without distal embolisation, and progressive stenosis due to wall thickening. This review focuses on morphologic aspects of large-vessel vasculitis pathology associated with giant cell arteritis, Takayasu arteritis, idiopathic or isolated aortitis, and the inflammatory aneurysm/retro-peritoneal fibrosis syndrome and lymphoplasmacytic thoracic and ascending aortitis.

# Giant cell arteritis with large-vessel involvement

Structure-function relationships and molecular pathogenesis

In the Chapel Hill schema, giant cell (or temporal) arteritis is considered one of the large-vessel vasculitis syndromes, despite its enigmatic predilection for involving tiny muscular branches of the external carotid artery (9). Involvement limited to these small muscular arteries is common in patients with this syndrome, but it is still considered a form of large-vessel vasculitis because of 1) its chronic inflammatory pattern, as opposed to the acute necrotising pattern characterising the medium vessel vasculitides and 2) its occasional involvement of the ascending aorta and larger elastic arteries. Such involvement of the ascending aorta has been reported in 8-13% of giant cell arteritis by tissue histology (10-12), and up to 33% of patients in a study using positron emission tomography imaging (13). This review will focus on the pathology of giant cell arteritis affecting the ascending aorta and major aortic branches; or giant cell arteritis with large-vessel involvement (GCA-LVI).

An appreciation of the comparative microanatomy of elastic arteries such as the aorta and its primary branches *versus* muscular arteries is critical to understanding the pathology of GCA-LVI. Whereas the walls of muscular arteries are comprised primarily of medial smooth muscles bounded by only two discrete prominent single-layered elastic laminae (Fig. 2A), the full thickness of an elastic artery wall consists

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Fig. 1. Gross appearance of aoritis. A) Normal thoracic aorta (for comparison). B) Aoritis, characterised by proximal aneurysmal dilatation, diffuse wall thickening, intimal cobbling, and "tree bark" vertical wrinkling of the intima (autopsy specimen). C) Surgical specimen showing similar, though less pronounced changes as the specimen in B.

of elastic lamellae (lamella being the diminutive form of lamina) with intervening single-layered smooth muscle cells (Fig. 2B). These structural differences reflect differences in function as well, with the more abundant elastic layers in elastic arteries accounting for the greater distensibility and elasticity of the aortic wall.

Damage to the elastic layer of any vessel is a hallmark of vasculitis. In muscular arteries this appears as a segmental disruption of the circumferential laminar ring when the vessel is viewed in cross section, which persists even after the inflammation subsides (Fig. 2C). In elastic arteries, the appearance is described as "laminar medial necrosis" and is characterised by the disappearance of intervening smooth muscle layers resulting in islands or bands of collapsed elastic lamellar scaffolding within the medial wall (Fig. 2D). It is this focal collapse along with irregular areas of intimal thickening that produce the longitudinal or "tree bark" ridges seen grossly in aortitis (Fig. 1).

These differences in the histology and histopathology of elastic and muscular arteries in the normal state and in GCA-LVI and other forms of vasculitis appear to be undergirded by disparate molecular phenotypes as well. It has long been recognised that the embryology of different vascular beds may account for inherent molecular differences; for example, that the ascending aortic smooth muscle cells (but not those in the more distal aorta) derive in part from neural crest cells (14). More recent studies

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have demonstrated unique patterns of toll-like receptor expression patterns and other resident dendritic cell phenotypes in various vascular beds (15, 16). There is also some evidence that inhibition of NOTCH signalling pathways attenuates vasculitis in this setting (17). These findings may help unravel the immunologic basis for the apparent "tissue tropism" observed with vasculitis syndromes in general, including the predilection of GCA-LVI for only the most proximal portion of the aorta.

### Histopathology of GCA-LVI

The inflammatory constituents in most large-vessel arteritis, including GCA-LVI, are primarily T-lymphocytes and macrophages or histiocytes (some of which fuse to form Langhans type multinucleated giant cells). So constituted, the pattern of inflammation has rightly been characterised as chronic and granulomatous (9), even though acute inflammatory cells may also be seen and the granulomas are not wellformed. The other hallmark feature of aortitis is laminar medial necrosis (18-20); essentially an intramural infarction causing loss of smooth muscle cells with resulting collapse of the elastic fibre strata. This pattern of laminar medial necrosis is distinct from the degenerative medial pathology seen in Marfan syndrome and other connective tissue disorders in which there is loss of both smooth muscle and elastic lamellae with accumulating pools of glyocasaminoglycans (so-called "cystic" medial degeneration). Inflammation in the aortic wall tends to concentrate around and assume the appearance of "cuffing" these acellular islands of elastic tissue in a foreign body-like response (21) (Fig. 3).

The lymphohistiocytic inflammatory infiltrate also appears to track along vasa vasorum penetrating into the aortic wall. In fact, the migration and ingrowth of vasa vasorum past the outermost muscular/elastic layers of the aorta is another abnormal finding that is relatively conserved in cases of GCA-LVI (Fig. 4). Penetration of these vessels into the centre of the media and beyond may reflect an angiogenic response to relative hypoxia.

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Clinical and pathologic conundra in GCA-LVI

- Aortitis without temporal or other systemic arteritis ("isolated aortitis") Patients with giant cell arteritis are more likely to develop ascending aortic aneurysms (22). Since screening for aneurysms is not always routine, the true incidence in this population is not known, but clearly giant cell arteritis without aortitis is common (11). The converse also appears to be true; in nearly every major series of giant cell aortitis a subset of patients is identified in whom no signs or symptoms referable to extra-aortic vasculitis can be found. These cases have been called "idiopathic aortitis" (23), "occult aortitis" (24) or "isolated aortitis" (25). The proportion of aortitis patients with disease apparently limited to the aorta is quite high, with estimates varying from 47%-84% (23, 25-28) (Table I). Whether the apparent absence of systemic vasculitis may actually represent early incipient or even old inactive disease elsewhere in the vascular tree (either of which could be clinically silent) is not known, but the phenomenon of aorta-limited disease is well established. Retrospective and anecdotal outcome and treatment data are limited, but suggest a relatively indolent course for isolated aortitis, with few recurrent aneurysms and deaths even in patients not receiving corticosteroids or other immuno-

### - Aortitis without giant cells

suppressive agents (23-27).

It is recognised that the inflammation in temporal arteries involved by giant cell arteritis may in fact be devoid of giant cells in up to 50% of cases (29). Whether the presence of giant cells is necessary for a diagnosis of giant cell aortitis has not been investigated as thoroughly. A pattern of inflammation including laminar medial necrosis and chronic inflammation without giant cells has certainly been noted. This phenomenon has been referred to as "lymphoplasmacytic aortitis" by some authors (25, 30) and was seen in 14% (31), 28% (26), and 55% (23) of aortitis cases. The absence of giant cells may simply be due to sampling issues, as in most cases the remaining



**Fig. 2.** Muscular artery and elastic artery comparison. Photomicrographs (elastic stain - elastic fibres stain black), showing: **A**) Normal muscular artery in cross section with distinct and intact external and internal laminae (x200). **B**) Normal aortic wall architecture with nearly full-thickness elastic lamellae, each layer separated by single layers of vascular smooth muscle (x20). **C**) Chronic healed arteritis affecting a small muscular artery (temporal artery biopsy) with intimal thickening, disruption of the internal elastic lamina (arrows delineate the breakpoints) and fibrosis instead of medial smooth muscle in the area of healed vasculitis (x200). **D**) Chronic (giant-cell) aortitis with laminar medial necrosis (dense black band of collapsed elastic fibres in the inner third of the media) (x20).



**Fig. 3.** Laminar medial necrosis cuffed by multinucleated giant cells. Photomicrographs showing laminar medial necrosis, characterised by: **A** and **B**) An eosinophilic and acellular island of infarcted media, devoid of smooth muscle cells, and surrounded by lymphohistiocytic inflammation with multinucleated giant cells (**A**: H&E, x20; **B**: H&E, x200). **C** and **D**) higher magnification views showing the infarcted media with collapsed elastic lamellae and cuffing by inflammation and giant cells (**C**: H&E x400; **D**: elastic stain x400).

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Table I.	Summary	of "is	olated",	"occult"	or '	'idiopat	thic"	aortitis	series.
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Liang (26)	Tavora (28)	Miller (25)	Rojo-Leyva (23)	Kerr (24)	Liu (27)
2009	2006	2006	2000	2000	1995
8%	-	9%	14%	_	-
64	52	45	52	17	24
69	73	66	72	65	74.5
11:32	32:32	8:27	17:35	6:11	5:19
81%	84%	47%	63%	100%*	38%
19%	16%	31%	37%	_*	62%
	Liang (26) 2009 8% 64 69 11:32 81% 19%	Liang (26) Tavora (28)   2009 2006   8% -   64 52   69 73   11:32 32:32   81% 84%   19% 16%	Liang (26) Tavora (28) Miller (25)   2009 2006 2006   8% - 9%   64 52 45   69 73 66   11:32 32:32 8:27   81% 84% 47%   19% 16% 31%	Liang (26) Tavora (28) Miller (25) Rojo-Leyva (23)   2009 2006 2006 2000   8% - 9% 14%   64 52 45 52   69 73 66 72   11:32 32:32 8:27 17:35   81% 84% 47% 63%   19% 16% 31% 37%	Liang (26) Tavora (28) Miller (25) Rojo-Leyva (23) Kerr (24)   2009 2006 2006 2000 2000   8% - 9% 14% -   64 52 45 52 17   69 73 66 72 65   11:32 32:32 8:27 17:35 6:11   81% 84% 47% 63% 100%*   19% 16% 31% 37% -*

\*Only "isolated" cases included

Table II. Summary of thoracic aorta IgG4 related aortitis.

First Author	Stone (40)	Laco (39)	Notohara & Miller (unpublished data)
Year	2010	2010	2009
n.	4	11	9
Aortitis subset evaluated	Lympho- plasmacytic	"isolated" thoracic aortitis	Lympho -plasmacytic
Age	61 – 71	59 - 72	38 - 84
Male:Female	4:0	2:9	7:2
% with ↑ IgG4 fraction	75%*	54%*	11%+

\*IgG4:total IgG >50% +IgG4:IgG1 >50%



**Fig. 4.** CD31 staining demonstrating vasa vasorum ingrowth in aortitis. Photomicrographs of normal aortic wall (A: x20) and aortitis (B: x20) stained by immunoperoxidase, using antibodies directed against the vascular endothelial antigen CD31. Note the paucity of stained vessels in the normal aorta, being confined to the outermost medial layers whereas vasa vasorum extend well into the inner third of the media in aortitis. There is also a proliferation of small capillary structures associated with the obvious inflammation in B.

inflammatory constituents and presence of laminar medial necrosis are indistinguishable from giant cell aortitis with giant cells. Still, the possibility exists that this pattern represents a distinct and unique entity, and there is some recent evidence that such cases may represent part of the spectrum of hyper-IgG4 syndrome diseases (discussed below).

### - Aortitis without laminar medial

*necrosis ("non-necrotising aortitis")* While the usual pattern of laminar medial necrosis with cuffs of lymphohistiocytic inflammation is the most common and widely recognised pattern of aortitis, there are also reports of transmural inflammation without appreciable laminar medial necrosis. This pattern (termed "non-necrotising aortitis") was seen in 9 of 52 patients in one series (18).

### - Laminar medial necrosis without vasculitis and the possible role of vasa vasora

Anecdotal and unpublished observations with aortic specimens in surgical pathology practice may offer potential insights into the mechanisms and pathogenesis of laminar medial necrosis in aortitis. Occasionally, nonaneurysmal aortic specimens from patients with prior aortotomy (such as for aortic valve replacement or bypass cannulation) can show features virtually indistinguishable from aortitis (Fig. 5). The surrounding aortic tissue is completely normal, and patients have no clinical evidence of vasculitis. These areas are associated with scarring in the adventitia and inevitable disruption of the vasa vasora. The effects of this controlled iatrogenic injury to the adventitia and vasa vasora helps substantiate a possible link between aortitis and aortic vasa vasorum. While giant cell arteritis of small muscular arteries is characterised by transmural destructive inflammation, involvement of the aorta manifests quite differently and with comparatively less inflammation. Furthermore, for laminar medial necrosis an analogy can be drawn between myocardial infarction due to coronary obstruction and aortic

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medial infarction due to vasa vasorum obstruction. Since the caliber of aortic adventitial aortic vasa vasora approximates that of other small muscular arteries affected by giant cell arteritis, some have proposed that involvement of these vasa vasorum by the kind of transmural destructive arteritis seen in temporal artery biopsies may be the primary lesion in aortitis, with the more obvious and prominent changes in the media being a secondary downstream consequence.

This hypothesis has proven difficult to prove. While perivascular lympho-plasmacytic inflammation is common in the adventitia, frank arteritis affecting the aortic vasa vasora is not and has yet to be reported in the literature. At least one author has noted intimal thickening in these small adventitial vessels in association with aortitis (18), but this type of thickening can be seen frequently in non inflamed aortic specimens (aneurysms from patients with hypertension or connective tissue disease), perhaps serving a sphincter-like role in regulating flow. No such control group was used for comparison in that series.

### Takayasu arteritis

Despite the wide clinical gap between Takayasu disease and GCA-LVI, the histopathologic features of these two conditions, and indeed nearly every other form of aortitis, overlap considerably. Reports directly comparing the pathologic changes in these two causes of aortitis are rare. Features unique to or more characteristic of Takayasu arteritis are reported to include 1) a more active (neutrophilic) and necrotising inflammatory pattern, 2) microabscess formation with "dirty" necrosis rich in karyorrhectic debris, 3) more prominent adventitial thickening due to fibrosis (Fig. 6), 4) greater numbers of multinucleated giant cells, and 5) conspicuous well-formed granulomas (19, 23, 25). Two-thirds of cases demonstrated laminar medial necrosis (25).

The temporal evolution of Takayasu arteritis is much better understood than other causes of aortitis, likely owing to the young age at presentation and greater potential for following the disease progression over many years. This progression is reported to include



**Fig. 5.** Non-aortitis related laminar medial necrosis. Photomicrographs of an ascending aortic specimen taken at the time of aortic valve and root replacement. The patient had coronary bypass grafting 5 years prior to this surgery, with insertion of a cardiopulmonary bypass cannula in the ascending aorta. Sections from the prior aortotomy site showed laminal medial necrosis and giant-cell inflammation, but the remaining aorta was completely normal (panel **A**: H&E x40; panel **B**: elastic stain x40; inset: H&E x200). "S" indicated the tract created by suture in the periadventitial tissue. This case represents laminar medial necrosis with giant cells due to an iatrogenic rather than primary vasculitic cause.



**Fig. 6.** Takayasu arteritis. Photomicrographs showing chronic ("pulseless" phase) changes of Takayasu disease in the ascending aorta. Note the marked adventitial fibrosis (nearly double the thickness of the media), dense leukocyte aggregates in the adventitia, and patchy medial elastic fibre loss with replacement type fibrosis (best appreciated in **B**). Laminar medial necrosis is not seen in this example. Singly distributed multinucleated giant cells were seen in the fibrotic adventitia (inset). (**A**: H&E x20; **B**: elastic stain x20; inset: H&E x200).

an acute florid inflammatory or "prepulseless" phase and a healed fibrotic phase (19). In the first phase, the active inflammatory component and necrotising character are more prominent (along with lymphocytes, histiocytes, and plasma cells). In the healed phase, the adventitial fibrosis and scarring along with laminar medial necrosis are more impressive, though lymphoplasmacytic

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Fig. 7. IgG4-related periaortitis in an ascending aortic aneurysm. Photomicrographs from an ascending aortic aneurysm with chronic periaortitis and increased IgG4 plasma cells showing: A) Dense collagenous adventitial and periadventitial fibrosis with chronic inflammation (H&E x40). B) The inflammatory infiltrate is rich in plasma cells (H&E, x200). C) A substantial proportion of the plasma cells produce IgG4 immunoglobulin (more than 50 IgG4 plasma cells per high power field and IgG4:IgG1 ratio of 65%) (x200).

inflammation and multinucleated giant cells also persist. While this progression seems to be orderly from a morphologic perspective, the correlation with clinical evidence of disease progression is poor. Active phase disease may be ongoing (histologically) for many years, even despite immuno-suppressive therapy (32). Much progress remains to be made elucidating the inciting mechanisms and the molecular pathogenesis of Takayasu arteritis.

### Inflammatory abdominal aortic aneurysm, chronic periaortitis, and idiopathic retroperitoneal fibrosis

Over the past decade, following recognition of the IgG4-restricted plasma cell's role in autoimmune pancreatitis, there has been explosive interest in a variety of primary idiopathic sclerosing diseases and the role that the so-called "Hyper-IgG4 syndrome" may play in their development. Among these is the spectrum of clinical conditions encompassing inflammatory abdominal aortic aneurysm, chronic (or inflammatory) periaortitis, and idiopathic retroperitoneal fibrosis. Each of these disorders is characterised by extensive adventitial scarring and lymphoplasmacytic inflammation, typically without other medial changes of aortitis. The fibrosis may extend into periadventitial adipose and connect tissue and well beyond. Several studies have demonstrated an increase in the fraction of IgG4 producing plasma cells among the inflammatory constituents in these conditions along with increased serum IgG4 levels, similar to what is observed in autoimmune sclerosing pancreatitis (33-37).

While this phenomenon appears specific to this set of disorders, and a diagnostic boon to pathologists, criteria for defining thresholds for what constitutes IgG4 plasma cell excess are important. Quantitation of these cells has been expressed as the number per high power field, per total plasma cells, per total IgG producing plasma cells, and as a ratio of IgG4 positive plasma cells to plasma cells producing another IgG subclass (such as IgG1). The normal reference range value for IgG4 plasma cells has not been firmly established in aortic adventitia and periaortic connective tissue, but is thought to be far less than 10% (37). In a recent review article, a threshold fraction of 50% IgG4 positive cells per total IgG producing plasma cells is proposed as point with high specificity and reasonable sensitivity (35).

There may be morphologic similarities between these forms of aortitis and autoimmune pancreatitis, the clinical risk factors, response to corticosteroid therapy, and prognostic profiles are distinctly different. These diseases remain difficult to treat and with unrelenting progression. There is at least one report of success with rituximab (38).

### IgG4-related thoracic aortitis

The fervour and interest in IgG4 plasma cells with inflammatory abdominal aortic disorders inevitably migrated proximally, and there have also been several recent investigations regarding the prevalence of IgG4 plasma cells in ascending and descending thoracic aortitis. As eluded above, the majority have focussed on the lymphoplasmacytic form of ascending and thoracic aortitis. This is logical given the semblance born to the pattern of inflammation in autoimmune pancreatitis and other IgG4-related disorders. At least two such studies have demonstrated that the majority, though not all, cases of lymphoplasmacytic thoracic and ascending aortitis de-monstrated a significant fraction (>50%) of IgG4 plasma cells in the inflammatory milieu (39, 40) (Table II). In our own experience, taking specimens from the Mayo Clinic Pathology Tissue Registry and in collaboration with Dr Kenji Notohara at Kurashiki Central Hospital in Japan, only one of nine lymphoplasmacytic aortitis cases (Fig. 7) showed >50% IgG4 plasma cells (using IgG1 positive plasma cells as the denominator, whereas the other studies used total IgG) (Unpublished observations). Whatever the true inci-

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dence, it does appear that at least some fraction of lymphoplasmacytic thoracic and ascending periaortitis is due to an IgG4 plasma cell related mechanism. Importantly, in our own study we also examined ten typical giant cell aortitis cases with staining for IgG4; none showed an increase in IgG4 plasma cells (unpublished observations).

The clinical significance of this discovery in lymphoplasmacytic periaortitis remains to be established.

### Conclusions

Vasculitis syndromes affecting large elastic arteries comprise a wide and diverse group of conditions with equally varied pathobiology reflected in their gross and microscopic pathology. While critical advances have been attained in the understanding of giant cell arteritis, inflammatory abdominal aneurysm/ chronic periaortitis, and lymphoplasmacytic thoracic periaortitis in particular, their translation to clinical relevance remains a challenge for the future.

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