

IgG4-Related Systemic Disease Accounts for a Significant Proportion of Thoracic Lymphoplasmacytic Aortitis Cases

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Objective. IgG4-related systemic disease, a disorder recognized only recently, can cause lymphoplasmacytic inflammation in the thoracic aorta. The percentage of cases caused by IgG4-related systemic disease is not known. We aimed to determine the percentage of noninfectious thoracic aortitis cases that are associated with IgG4-related systemic disease and to establish pathologic criteria for identifying involvement of the thoracic aorta by this disorder.

Methods. We searched our Pathology Service database to identify patients with noninfectious thoracic aortitis who underwent resection over a 5-year time span. The histologic features of these cases were reviewed. All cases of lymphoplasmacytic aortitis and representative cases of giant cell aortitis and atherosclerosis were stained by immunohistochemistry for IgG4 and for the plasma cell marker CD138. We determined the fraction of plasma cells that stained for IgG4.

Results. Of 638 resected thoracic aortas, 33 (5.2%) contained noninfectious aortitis. Four of these cases (12% of all patients with noninfectious aortitis) had histologic features of lymphoplasmacytic aortitis. Three of those 4 cases (9% of the noninfectious aortitis cases) demonstrated pathologic involvement by IgG4-related systemic disease, with an elevated proportion of plasma cells staining for IgG4 (mean $\pm$ SD 0.82 ± 0.08) compared with cases of giant cell aortitis (0.18 ± 0.13) and atherosclerosis (0.19 ± 0.08 ; $P < 0.00001$).

Conclusion. IgG4-related systemic disease accounted for 75% of lymphoplasmacytic aortitis cases and 9% of all cases of noninfectious thoracic aortitis in our institution during a 5-year period. Immunohistochemical assessment of the percentage of plasma cells that stained for IgG4 in resected aortas was helpful in identifying patients with IgG4-related systemic disease.

INTRODUCTION

Noninfectious aortitis refers to a variety of clinically distinct conditions that lead to chronic inflammation within the aortic wall (1). The term isolated aortitis is sometimes employed when the vascular inflammation appears to be limited to the aorta, and is not associated with an underlying systemic disorder. The inflammation in noninfectious aortitis is most frequently localized to the thoracic aorta, regardless of whether the aortitis is caused by a systemic vasculitis (e.g., giant cell arteritis [GCA]), another

rheumatic condition (e.g., rheumatoid arthritis), or so-called isolated aortitis (2,3).

In contrast, a second major category of aortic inflammatory disease, chronic periaortitis, has a predilection for the abdominal aorta (4,5). The causes of chronic periaortitis have generally been viewed as distinct from the entities that cause thoracic aortitis. Chronic periaortitis encompasses idiopathic retroperitoneal fibrosis and inflammatory abdominal aortic aneurysms, sometimes referred to together as perianeurysmal retroperitoneal fibrosis (4,6,7). In the medical literature, chronic periaortitis and perianeurysmal retroperitoneal fibrosis are often not delineated sufficiently from atherosclerosis of the abdominal aorta.

Isolated thoracic aortitis is detected in a small but significant subset of patients who undergo surgery on the ascending aorta (3,8). The histopathology of such cases is characterized most often by granulomatous inflammation with or without giant cells. Such cases are indistinguishable from the aortitis detected in some patients with systemic GCA. Consequently, both entities are referred to by pathologists as giant cell aortitis. However, in other pa-

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tients with apparent isolated thoracic aortitis, the histopathologic findings include neither giant cells nor granulomatous inflammation, and their histopathology is characterized solely by a lymphoplasmacytic infiltrate. Because lymphoplasmacytic infiltrates can characterize a variety of primary systemic vasculitides or other rheumatologic conditions that can lead to aortitis, the detection of a lymphoplasmacytic infiltrate within the aorta has often been viewed as a nonspecific finding (9–21). It has remained unclear whether or not cases of lymphoplasmacytic aortitis that occur in the absence of an identified systemic disease represent a distinct entity.

Since 2008, a small number of cases of chronic peri-aortitis that involve the abdominal aorta have been reported in association with IgG4-related systemic disease (22–26). In addition, we have recently reported 2 patients with ascending aortitis whose aortic histopathology was characterized by a lymphoplasmacytic aortitis in which the plasma cells stained intensely for IgG4 (27,28). We hypothesized, therefore, that IgG4-related systemic disease accounts for a subset of cases of thoracic aortitis and for a significant fraction of lymphoplasmacytic thoracic aortitis cases. To test this hypothesis, we reviewed the experience at our institution with thoracic aortitis over a 5-year period and evaluated the existing literature in light of this experience. This analysis revealed that IgG4-related systemic disease accounted for a majority of the thoracic lymphoplasmacytic aortitis cases in our institution, and allowed us to define criteria for identifying this condition in resected aortas.

PATIENTS AND METHODS

Identification of cases. To identify cases of noninfectious thoracic aortitis, we searched the Pathology Service database at the Massachusetts General Hospital for cases of resected thoracic aortic segments that contained inflammation. We examined the 5-year interval between January 2004 and December 2008, and reviewed the slides from all cases identified. For the aortitis cases, the segments of resected aorta had a luminal surface area ranging from 21 cm² to 140 cm² (mean 65 cm², median 63 cm²). For initial screening, tissue had been sampled for histologic analysis in 1–2 tissue blocks, with each block containing 2–5 strips of aorta, with each strip being ~2 cm in length. Subsequently, up to 15 additional tissue blocks had been submitted in some cases. For the 33 aortitis cases identified here, there was 1 tissue block in 1 case, 2 tissue blocks in 19 cases, and for the remaining 13 cases, the number of tissue blocks ranged from 5 to 17 (mean 10, median 9).

Histopathologic criteria. The essential inclusion criterion for the designation of noninfectious aortitis was the presence of chronic inflammation that was not characteristic of either atherosclerosis or aortic dissection. The exclusion criteria were a history of previous aortic surgery or evidence of infectious/mycotic aortitis, defined by the presence of abscesses with necrosis and neutrophils. The noninfectious aortitis cases were subclassified into 2 categories based on the nature of the inflammatory compo-

nent. Those cases with granulomatous inflammation with or without a significant plasma cell component were classified broadly as granulomatous. Granulomatous inflammation was defined as an inflammatory infiltrate that was rich in activated (epithelioid) macrophages (>20/× 400 high-power field), with or without giant cells. In contrast, cases with lymphoplasmacytic infiltrates without granulomatous inflammation were classified as lymphoplasmacytic aortitis.

IgG4 plasma cell quantitation. Immunohistochemical studies using antibodies to IgG4 (Zymed, South San Francisco, CA; 1:200 dilution) and the plasma cell marker CD138 (Serotec, Raleigh, NC; 1:20 dilution) were performed on formalin-fixed, paraffin-embedded tissue sections. For each case, the number of plasma cells staining for IgG4 was assessed in 3 nonoverlapping high-power (× 400) fields. For each case, the 3 high-power fields with the highest degree of IgG4 reactivity were selected for quantitation. The number of IgG4+ plasma cells was then divided by the total number of plasma cells in these fields.

Statistical analyses. Groups were compared by one-way analysis of variance (ANOVA), followed by post hoc analysis using the Bonferroni correction to adjust for multiple comparisons. *P* values less than 0.05 were considered significant. All values are expressed as the mean ± SD.

RESULTS

Thoracic lymphoplasmacytic aortitis cases. During the 5-year time span from 2004–2008, 638 resections of thoracic aortas were performed. Of these, 33 (5.2%) met our criteria for noninfectious aortitis. Four cases contained lymphoplasmacytic infiltrates but lacked granulomatous inflammation, thereby meeting our criteria for lymphoplasmacytic aortitis (Table 1). Patients 1 and 2 have been reported previously (27,28). All 4 patients with lymphoplasmacytic aortitis were men whose ages at the time of surgery were 69, 65, 71, and 61 years. Concise summaries of the clinical features of these cases are provided below. The other 29 cases of noninfectious aortitis were characterized by granulomatous inflammation, and included patients with Takayasu aortitis, rheumatoid aortitis, and giant cell aortitis including both systemic GCA and isolated giant cell aortitis.

The histologic features of the 4 cases of lymphoplasmacytic aortitis are summarized in Table 2. Although the lymphoplasmacytic infiltrates involved all 3 layers of the aorta, the most severe involvement was found in the adventitia or media. Extensive medial laminar necrosis was present in 2 of the 4 cases. Involvement of adventitial veins by the inflammation (phlebitis) was seen in all 4 cases. Only 1 case showed inflammation and stenosis of small adventitial arteries (endarteritis obliterans). All 4 cases showed fibrosis particularly of the adventitia, but a storiform pattern of inflammatory fibrosis was only present in 2 cases.

Table 1. Characteristics of the lymphoplasmacytic aortitis patients

Patient	Age, years	Sex	Thoracic aortic segment	Aneurysm (size) or dissection	Extracavitary disease
1	69	Male	Ascending	Aneurysm (4.3 cm)	Liver, pancreas, submandibular glands, lymph nodes
2	65	Male	Ascending and proximal arch	Remote dissection	Lymph nodes
3	71	Male	Distal arch and descending	Aneurysm (6.5 cm)	
4	61	Male	Ascending and total arch	Aneurysm (6.4 cm)	

IgG4 immunohistochemical staining. We assessed the extent of plasma cell IgG4 expression in the 4 lymphoplasmacytic aortitis cases by immunohistochemistry for both IgG4 and the plasma cell marker CD138. In addition, in order to ascertain the fraction of plasma cells staining for IgG4 in other pathologic conditions, 6 randomly selected thoracic aortic specimens with atherosclerosis and 6 cases of giant cell aortitis were also stained (Figure 1). The 6 atherosclerosis cases included 3 men and 3 women who ranged in age from 58 to 83 years (mean $\pm$ SD 74 ± 11 years). The 6 giant cell aortitis cases included 4 men and 2 women who ranged in age from 53 to 87 years (mean $\pm$ SD 75 ± 13 years), and included 1 case of systemic GCA and 5 cases of likely isolated giant cell aortitis.

In the aortas with atherosclerosis, the mean $\pm$ SD fraction of plasma cells staining for IgG4 was 0.19 ± 0.08 (range 0.04–0.26). Similarly, in the aortas with giant cell aortitis, the mean $\pm$ SD fraction of plasma cells staining for IgG4 was 0.18 ± 0.13 (range 0.02–0.31).

In contrast, the intensity of IgG4 staining was increased greatly in 3 of the 4 cases of lymphoplasmacytic aortitis, compared with staining in the control groups (Table 2). For those 3 cases, the mean $\pm$ SD fraction of plasma cells staining for IgG4 was 0.82 ± 0.08 (range 0.74–0.89). In the fourth lymphoplasmacytic aortitis case, the fraction of plasma cells staining for IgG4 was at the high end of the normal range detected in the controls, 0.29. Comparison of the 3 cases of lymphoplasmacytic aortitis with elevated IgG4 plasma cell infiltrates (IgG4+ lymphoplasmacytic aortitis) with the 2 control groups by ANOVA demonstrated the enhanced IgG4+ plasma cell infiltration to be statistically significant, $P < 0.00001$ (Figure 2).

Clinical summaries of lymphoplasmacytic aortitis patients. *Patient 1.* A 68-year-old man underwent replacement of his bicuspid aortic valve and dilated ascending aorta (27). Preoperative assessment showed extensive me-

diastinal and hilar lymphadenopathy. A lymph node obtained at the time of his surgery showed follicular hyperplasia. Pathology of the aorta was reported as chronic sclerosing aortitis. One year later, he developed painless swellings in both submandibular regions consistent with sialadenitis.

Two years after his aortic surgery, he presented with painless jaundice. Computed tomography (CT) of his abdomen showed a hypodense lesion in the liver and intrahepatic ductal dilatation, suggestive of malignant disease. There was also evidence of abdominal aortic wall thickening in the CT scan. Endoscopic retrograde cholangiopancreatography and the results of the biopsy of his papilla and pancreas did not reveal malignancy. However, liver biopsy results showed a lymphoplasmacytic infiltrate, with positive staining for IgG4. The serum IgG level was 4,160 mg/dl (normal being 614–1,295 mg/dl), 86% of which was IgG4 (total IgG4 3,580 mg/dl; normal being <135 mg/dl). The patient's diagnosis was IgG4-related systemic disease with involvement of the liver, pancreas, and submandibular glands. His serum IgG4 level improved substantially but did not normalize following the institution of glucocorticoid therapy.

Patient 2. A 65-year-old man with a history of mediastinal lymphadenopathy and a lymph node biopsy result that showed "reactive follicular hyperplasia" was found to have a focal aortic dissection in the ascending aorta. He underwent repair of the ascending aorta and hemiarch as well as the aortic valve. The aortic pathologic evaluation showed active lymphoplasmacytic aortitis. Immunohistochemical studies revealed that >50% of the plasma cells present stained for IgG4. The serum IgG level was elevated at 1,863 mg/dl (normal 614–1,295 mg/dl). The serum IgG4 level was 1,340 mg/dl (normal being 8–140 mg/dl). Reexamination of the lymph node removed 4 years earlier revealed extensive infiltration by IgG4+ plasma cells (28). The results of a rapid plasma reagin (RPR) test and a

Table 2. Pathologic features of the lymphoplasmacytic aortitis cases

Patient	Site of inflammation	Medial laminar necrosis	Adventitial phlebitis	Endarteritis obliterans	Storiform fibrosis	IgG4+ plasma cells, fraction
1	Adventitia >> media > intima	Absent	Present	Absent	Present	0.82
2	Media > adventitia > intima	Present	Present	Absent	Absent	0.74
3	Adventitia > media > intima	Absent	Present	Absent	Absent	0.89
4	Adventitia, media > intima	Present	Present	Present	Present	0.29

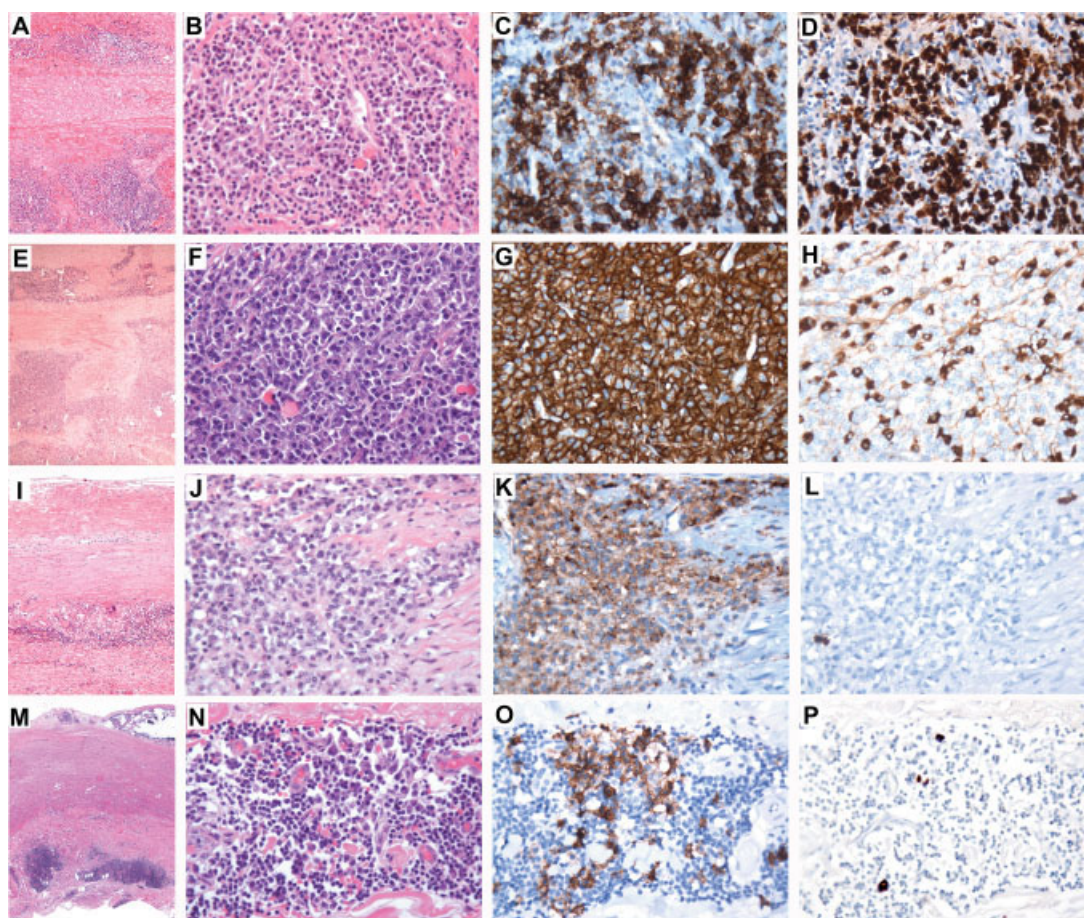


Figure 1. Histology and immunohistochemical staining. Shown are histologic images of resected aortas for patient 3 (A–D), patient 4 (E–H), a case of giant cell aortitis (I–L), and a case of atherosclerosis (M–P). The panels depict hematoxylin and eosin–stained sections (original magnification $\times 40$ in E and M, $\times 100$ in A and I, and $\times 400$ in B, F, J, and N) and immunohistochemical stains (original magnification $\times 400$) for CD138 (C, G, K, and O) and IgG4 (D, H, L, and P). All 4 cases shown contain CD138+ plasma cells. However, in the aorta from patient 3 (A–D), a much higher proportion of the plasma cells stain for IgG4 compared with the other 3 cases shown.

fluorescent treponemal antibody absorption (FTA-ABS) assay were both negative. His serum IgG4 level improved substantially but did not normalize following the institution of glucocorticoid therapy.

Patient 3. A 71-year-old man with a history of hypertension and a 5-year history of a small thoracic aortic aneurysm underwent a followup CT scan. He was found to have an enlarged distal aortic arch that measured 6.5 cm, a marked increase over his baseline. The patient underwent a thoracic aortic aneurysm repair with a graft extending from the distal arch to the T8 level. His postoperative course was uneventful, and he was lost to followup after surgery.

Patient 4. A 61-year-old man with a history of atypical chest pain and a widened mediastinum presented with acute chest pain radiating to his left arm. A CT angiogram of the chest showed an aneurysm of both the ascending and descending aorta. The aneurysm measured 6.4 cm at its maximal width. A second aneurysm (3.5 cm in diameter) was present in the abdominal aorta above the kidneys. A transthoracic echocardiogram revealed mild aortic valve insufficiency. The patient underwent replacement of his

ascending aorta and aortic arch. No serum sample was available for IgG4 testing.

The possibility of syphilitic aortitis was considered, but the patient's RPR test and FTA-ABS assay were both negative. Review of his record from 27 years earlier revealed that at age 34 years he had been admitted to our hospital with a lymphocytic meningitis. At that time, he had a positive VDRL in a 1:1 dilution, but a negative FTA-ABS and a negative VDRL on the cerebrospinal fluid screening. The patient had a scrotal mass and prostate nodule during that same hospitalization and underwent a right radical orchiectomy and a biopsy of the prostate. Pathologic evaluation from those procedures revealed granulomatous epididymitis with caseous necrosis, as well as granulomatous prostatitis. Multiple acid-fast bacillus stains and mycobacterial and fungal cultures of his cerebrospinal fluid and genitourinary pathologic evaluation were negative. He was treated for presumptive tuberculous involvement of the meninges, testicle, and prostate. Of note, the patient's chest radiograph during that admission 27 years ago was observed to show an ectatic proximal descending aorta suggestive of aneurysmal dilatation.

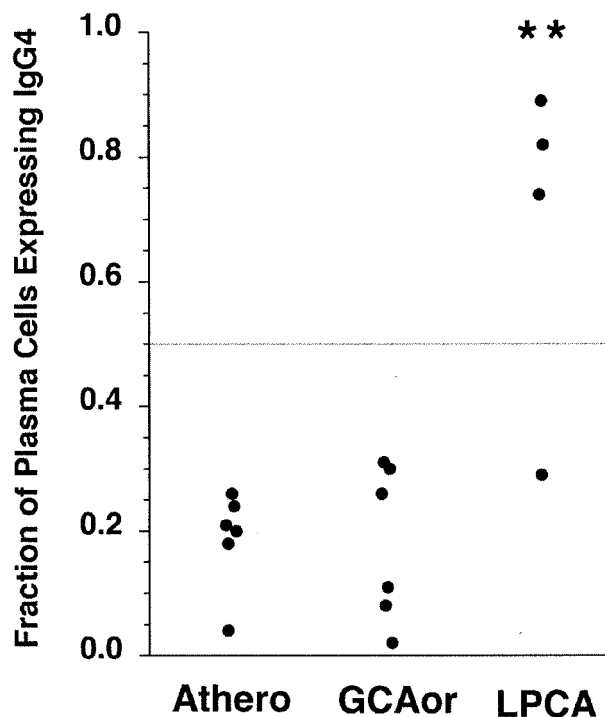


Figure 2. Statistical analysis of IgG4 plasma cell ratios. The atherosclerosis (Athero), giant cell aortitis (GCAor), and lymphoplasmacytic aortitis (LPCA) groups were compared for the fraction of plasma cells expressing IgG4 by analysis of variance. ** = $P < 0.001$ for all 4 LPCA cases versus the other 2 groups, and $P < 0.00001$ for the 3 IgG4+ LPCA cases versus the other 2 groups.

DISCUSSION

Over a 5-year period, 5.2% of resected thoracic aortas demonstrated noninfectious aortitis in our institution. This observation is consistent with previous reports in which the frequency of noninfectious aortitis in resected thoracic aortas has ranged from 2.1% to 12% (2,3,8,29). We identified nongranulomatous lymphoplasmacytic aortitis in 12% of the thoracic noninfectious aortitis cases. Three of the 4 lymphoplasmacytic cases we identified (9% of all noninfectious aortitis cases) had pathologic evidence of involvement by IgG4-related systemic disease, indicated by an abnormally high proportion of IgG4+ plasma cells. In the other patient, patient 4, the resected aorta showed features suggestive of involvement by IgG4-related systemic disease, i.e., storiform fibrosis and adventitial phlebitis. Therefore, the presence of IgG4-related systemic disease cannot be excluded in this patient even though the fraction of plasma cells staining for IgG4 was in the range seen in other conditions. The resected aorta also showed evidence of adventitial endarteritis obliterans, a feature classically associated with syphilitic aortitis (30). This patient had a history of granulomatous epididymitis and prostatitis 27 years earlier, but current serologies for syphilis were negative, and spirochetes were not identified in the aortic tissue with special stains. Therefore, for patient 4, the precise etiology of the aortitis is uncertain.

In previous series of thoracic noninfectious aortitis that were not limited to granulomatous disease, the frequency of cases with histology similar to that of our lymphoplas-

matic aortitis cases has ranged from 13–16% (compared with 12% in our series) (2,3). These cases were classified with various designations, including isolated aortitis, unclassified aortitis, aspecific lymphoplasmacytic aortitis, and inflammatory aneurysm. Our data would suggest that a significant number of these patients had IgG4-related systemic disease. The Cleveland Clinic series did not distinguish in detail between cases of aortitis characterized by granulomatous inflammation as opposed to lymphoplasmacytic aortitis (8). However, we note that 2 of their patients, both men whose aortic pathologic evaluation showed “nonspecific inflammation and fibrosis,” had clinical courses marked by retroperitoneal fibrosis, a clinical syndrome that has been linked in case reports to IgG4-related systemic disease (31). In addition, 1 of those patients also had an orbital pseudotumor, another complication linked to IgG4-related systemic disease (32). No series to date except ours has investigated the possibility of a link between IgG4-related systemic disease and thoracic aortitis.

The finding of IgG4-related systemic disease in the ascending aorta has important implications for both the classification and treatment of noninfectious aortitis. The ability of IgG4-related systemic disease to involve either the ascending or the abdominal portions of the aorta suggests that IgG4-related systemic disease should be considered in any patient with aortitis of unknown cause. Moreover, IgG4-related systemic disease is often highly responsive to glucocorticoid therapy. As an example, the majority of patients with autoimmune pancreatitis in one study achieved sustained disease responses when treated with high doses of prednisone tapered over months (33). The limited data currently available indicate that some patients require no further therapy beyond a single glucocorticoid course. However, the length of followup in most series reported has been short (34).

A larger clinical experience is required before any conclusions can be drawn about the intensity of therapy that is appropriate for patients with IgG4-related aortitis. Adverse outcomes have been described in these patients. One of our patients developed dissection of the thoracic aorta, which led to the detection of his IgG4-related systemic disease (28). Another progressed to abdominal involvement with autoimmune pancreatitis (27). Among the 7 patients with apparent thoracic lymphoplasmacytic aortitis in the Mayo Clinic experience, 1 died of a ruptured abdominal aortic aneurysm 1 year after surgery on the thoracic aorta (3). Fatal acute thoracic aortic dissection due to lymphoplasmacytic aortitis has also been reported (35).

The cutoff for “normal” levels of IgG4-staining plasma cells within the aorta has not been defined precisely. Data from our 2 control groups indicate that the fraction of plasma cells within the thoracic aorta that stain for IgG4 may be as high as 0.30, even in patients who do not have IgG4-related systemic disease. In contrast, the fraction of plasma cells that stained for IgG4 among our 3 patients whose cases were consistent with IgG4-related systemic disease ranged from 0.74 to 0.89. These higher values are consistent with the percentages seen in patients with IgG4-related systemic disease whose disease involves other organs, e.g., the pancreas (36). Therefore, using the quanti-

tative approach described here, a value of ~ 0.50 for the fraction of plasma cells staining for IgG4 appears to be a conservative cutoff for the determination of cases that are truly associated with IgG4-related systemic disease. Additional investigations that involve larger numbers of patients are required to determine the test characteristics of 0.50 as the cutoff value for this measurement. The cutoff value may be influenced by the method used to quantify the number of IgG4-positive plasma cells, which does employ a degree of subjectivity.

The presence of medial laminar necrosis has been suggested to be useful as a histologic feature for predicting in which patients the aortitis is likely to be isolated (37). However, the aortic specimens from patients 2 and 4 contained substantial medial laminar necrosis (Tables 1 and 2). Patient 2 had clear evidence of extraaortic involvement by IgG4-related systemic disease (28). Therefore, further studies are required to assess the utility of medial laminar necrosis as a predictor of "isolated aortitis." On the other hand, our data do indicate that a primary pathologic subclassification of thoracic aortitis as either granulomatous or lymphoplasmacytic combined with immunohistochemical assessment of the fraction of IgG4+ plasma cells is helpful in identifying patients with IgG4-related systemic disease. Because the granulomatous component may not be present on every slide, it is often necessary to submit additional tissue blocks beyond the standard 1–2 blocks used for screening such specimens, particularly in cases of apparent IgG4-negative lymphoplasmacytic aortitis. In the one such case in our series, 10 blocks of tissue were examined.

IgG4-related systemic disease is recognized increasingly as a condition that is capable of involving multiple organs in an insidious but potentially destructive fashion (38,39). The different organs affected by IgG4-related systemic disease can be involved simultaneously, but involvement is often observed to be metachronous, thereby making the full recognition of this disorder challenging (27,28). Serum assays for IgG4 levels are elevated in the majority of patients with this condition, but not all. Whenever histopathologic samples from the aorta are available, immunohistochemical staining for IgG4-bearing plasma cells is essential.

Rheumatologists might encounter IgG4-related systemic disease in settings that range from consults to exclude Sjögren's syndrome (in patients with submandibular or parotid gland enlargement) to questions about how to manage noninfectious aortitis after inflammatory findings have been detected on surgical pathologic specimens (27). Because IgG4-related systemic disease has a predilection for older men, the same type of patients who commonly undergo aortic surgery, the disorder can mimic a number of other causes of aortitis, particularly GCA and isolated giant cell aortitis. The growing recognition of IgG4-related systemic disease as a clinical entity underscores the importance of considering this diagnosis in patients with any type of idiopathic aortitis, not only those whose presentations are consistent with "chronic periaortitis," which has been reported previously to affect the abdominal aorta (22–26).

The pathophysiology of IgG4-related systemic disease

remains poorly understood. IgG4, normally the least abundant of all serum IgG isotypes, has been proposed to be a component of processes leading to the down-regulation of immune responses. Therefore, one way to view the IgG4-staining plasma cells in tissue is that they are part of a counter-regulatory response to an inciting event. The nature of this inciting event or events remains unknown.

In conclusion, our data suggest that IgG4-related systemic disease accounts for the majority of thoracic lymphoplasmacytic aortitis cases in our institution and $\sim 9\%$ of all cases of noninfectious thoracic aortitis. Because some patients with IgG4-related systemic disease respond well to a prolonged course of glucocorticoid treatment and do not require additional therapy, these findings have potential implications for the treatment and long-term management of patients with noninfectious aortitis. Furthermore, treatment of the patients' aortitis may prevent the involvement of other organs by IgG4-related systemic disease, as well as the progression of destructive disease within the aorta.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. James R. Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. John H. Stone, Khosroshahi, Deshpande, James R. Stone.

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