

Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease

James R. Stone

Center for Systems Biology, Massachusetts General Hospital, and Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Correspondence to James R. Stone, MD, PhD, Massachusetts General Hospital, Simches Research Building Room 8236, 185 Cambridge Street CPZN, Boston, MA 02114, USA
Tel: +1 617 726 8303; fax: +1 617 643 3566; e-mail: jrstone@partners.org

Current Opinion in Rheumatology 2011, 23:88–94

Purpose of review

In last few years, there have been significant advances in our understanding of a newly recognized condition known as IgG4-related systemic disease. This review will focus on IgG4-related systemic disease as a cause of thoracic aortitis, inflammatory abdominal aortic aneurysm or periaortitis, and retroperitoneal fibrosis.

Recent findings

A significant fraction of thoracic lymphoplasmacytic aortitis cases, about 40% of inflammatory abdominal aortic aneurysms/abdominal periaortitis cases, and a portion of retroperitoneal fibrosis cases are all caused by IgG4-related systemic disease. Assessing pathologic specimens for the fraction of plasma cells that express IgG4 is useful in identifying patients with this disorder. Recently reported data may indicate IgG4-related aortic disease to be more common than widely realized.

Summary

IgG4-related systemic disease is a newly recognized disorder that may manifest as thoracic aortitis, inflammatory abdominal aortic aneurysm or retroperitoneal fibrosis. IgG4-related systemic disease should be considered in any patient found to have aortitis or periaortitis. Further studies into diagnostic criteria, disease prevalence, prognosis, therapeutic interventions, and differentiating possible localized hypersensitivity reactions from systemic disease are areas of active investigation. Criteria are presented for the pathologic diagnosis of IgG4-related aortitis.

Keywords

arteritis, inflammatory aneurysm, inflammatory aortopathy, pancreatitis, periaortitis, plasma cells, vasculitis

Curr Opin Rheumatol 23:88–94
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8711

Introduction

Noninfectious thoracic aortitis, inflammatory abdominal aortic aneurysms/abdominal periaortitis, and idiopathic retroperitoneal fibrosis are all chronic inflammatory conditions of diverse and often unclear cause. Recent work in the last few years has revealed that for each of these conditions, a fraction of the cases are in fact due to a recently recognized systemic inflammatory condition known as IgG4-related systemic disease (IgG4-RSD). IgG4-RSD is characterized by elevated circulating levels of IgG4 in the serum, and by the infiltration of organs throughout the body by IgG4-expressing plasma cells accompanied by fibrosis [1–3]. This disorder was first recognized to involve the pancreas as auto-immune pancreatitis and is now known to involve diverse organs including salivary glands, kidneys, lungs, thyroid, heart, mediastinum, retroperitoneum, and aorta. This review will focus on recent progress in identifying IgG4-RSD as

a cause of aortitis, inflammatory abdominal aortic aneurysm, and retroperitoneal fibrosis.

Noninfectious aortitis

Noninfectious aortitis refers to a group of inflammatory disorders characterized by chronic inflammation within the aortic wall, in which the inflammation is not thought to be a result of infection [4,5]. Noninfectious aortitis is most commonly observed in the thoracic aorta, particularly the ascending aorta, and may result from well known systemic rheumatologic disorders such as giant cell arteritis, Takayasu arteritis, rheumatoid arthritis, Cogan disease, ankylosing spondylitis, and Behcet's disease [6–13]. However, in a large percentage of cases, the aortitis is found unexpectedly upon pathologic examination of aortic segments resected from patients undergoing repair of thoracic aortic aneurysms or dissections. In many of these cases, no obvious systemic rheumatologic condition

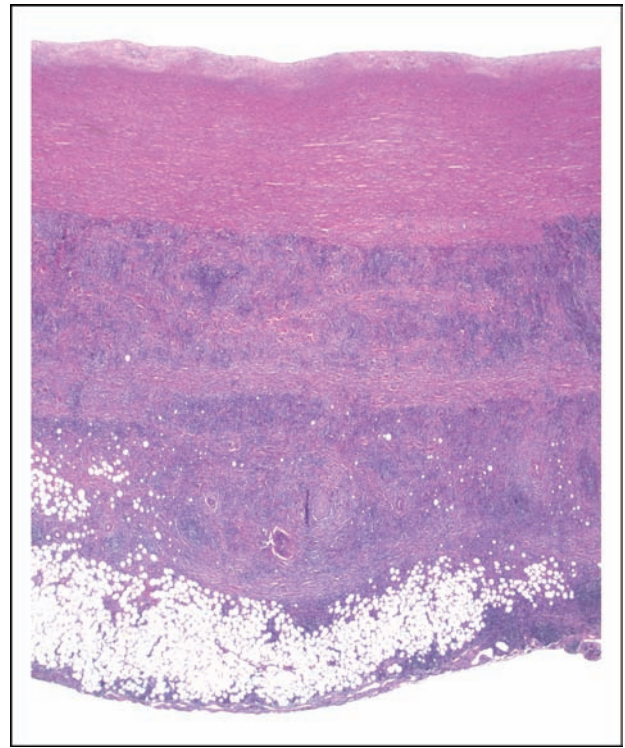
is thought to be present. In such cases, the aortitis is sometime referred to as 'isolated', indicating that the clinically apparent manifestations of the vasculitis are isolated to the segment of aorta that has been resected [14–16]. However, the term 'isolated aortitis' is not a precise pathologic entity, but rather a clinical subcategorization of the level of systemic activity of a patient's vasculitis. Certainly, much effort is now being focused on determining how to discern which patients with thoracic aortitis will in fact show systemic manifestations. It is becoming clear that some cases of aortitis that may have been viewed previously as 'isolated aortitis' are in fact the result of IgG4-RSD.

Thoracic aortitis and IgG4-related systemic disease

Table 1 summarizes the six cases of thoracic aortitis due to IgG4-related systemic disease reported thus far [17,18,19,20,21]. These cases all derived from surgical resections, and all six were published in 2009–2010. Interestingly, all six patients were men in a relatively narrow age range (65–74 years). The arch was the most commonly involved site, being involved in five of the six cases, with two of the six cases having involvement of the ascending aorta, and only one case having involvement of the descending aorta. Five of the six patients presented with an aneurysm, whereas one presented with a chronic dissection.

By histologic assessment, all six cases displayed a prominent lymphoplasmacytic infiltrate, with a high percentage of the plasma cells staining for IgG4 (74–89%). In addition, at least five of the six patients showed an obstructive phlebitis within the adventitia. However, there was some variability in the location of the inflammation within the aortic wall. In three cases (case 1, case 3, and case 5), there was a marked predominance for the adventitia compared with the media and intima (Fig. 1). However, in at least two of these three cases, the inflammation did extend into the media of the aorta, indicating the disorder to be a true aortitis and not just a periaortitis.

Figure 1 IgG4-related thoracic aortitis, adventitia-predominant pattern



Displayed is a low-power histologic image of a hematoxylin and eosin stained section of the thoracic aorta from case 1 in Table 1. There is a marked lymphoplasmacytic infiltrate with fibrosis, predominantly in the adventitia. There is only mild atherosclerosis.

In at least two of these adventitia-predominant cases, there was storiform fibrosis similar to that reported in abdominal IgG4-related periaortitis and in the pancreas in auto-immune pancreatitis. Interestingly, one of these two patients, case 1, in fact, later developed abdominal aortic and pancreatic involvement. In the other three cases, the media was involved by the lymphoplasmacytic infiltrate as much as or even more than the adventitia. In at least two of these media-predominant cases, there was no evidence of storiform fibrosis. All six cases lacked the

Table 1 Published cases of IgG4-related thoracic aortitis

No.	Age	Aortic segment	Aneurysm (size) or dissection	Site of inflammation	IgG4 ⁺ plasma cells (fraction)	Serum IgG4 (mg/dl)	Extra-aortic disease	Reference
1	69 years	Ascending	Aneurysm (4.3 cm)	Ad >> Med	0.82	4160	Liver, pancreas, retroperitoneum, salivary glands, lymph nodes	[17 [•]]
2	65 years	Ascending and arch	Remote Dissection	Med > Ad	0.74	1863	Lymph nodes	[18 [•]]
3	71 years	Arch	Aneurysm (5.5 cm)	Ad	0.84			[19]
4	71 years	Arch and descending	Aneurysm (6.5 cm)	Ad, Med	0.89			[20 ^{••}]
5	67 years	Arch	Aneurysm (4.2 cm)	Ad >> Med	0.76			[21 [•]]
6	74 years	Arch	Aneurysm (7.0 cm)	Ad, Med	0.86			[21 [•]]

All six cases were men. Ad, adventitia; Med, media.

granulomatous inflammation seen in the giant cell aortitis, Takayasu arteritis, and rheumatoid aortitis.

Follow-up was reported for two of the six cases (cases 1 and 2). Case 3 died shortly after surgery, and case 4 was discharged and lost to follow-up. Serum IgG4 levels were not reported in either of these latter two patients or for cases 5 and 6. However, serum IgG4 levels were found to be markedly elevated in cases 1 and 2. In addition, both of these patients had documented extra-aortic involvement. Case 1 showed progression to abdominal involvement affecting the abdominal aorta, pancreas, and liver, as well as salivary gland involvement. Case 2 had pathologically documented involvement of thoracic lymph nodes. Both patients showed partial response to prednisone, with subsequently more complete response to rituximab [20^{••},22].

Assessment of all thoracic aortitis cases in a 5-year time span at one institution in Boston revealed that IgG4-related systemic disease was responsible for three of four cases of lymphoplasmacytic aortitis and 9% of all cases of thoracic aortitis [20^{••}], indicating IgG4-RSD to be roughly as frequent a cause of thoracic aortitis as more traditional disorders such as systemic giant cell arteritis, Takayasu arteritis, and rheumatoid arthritis [14,16]. In that study, IgG4-related aortitis was present in 0.5% of all thoracic aorta resections [20^{••}]. In a subsequent study [21[•]] from Japan, assessment of 125 thoracic aorta resections revealed two cases of IgG4 aortitis/periaortitis, indicating 1.6% of all resected thoracic aortas contained IgG4-related aortitis, similar to the rate of 0.5% from the earlier Boston study.

In the study [21[•]] from Japan, a similar degree of IgG4 plasma cell staining was also observed in three cases of atherosclerotic thoracic aortic aneurysms. These three patients were asymptomatic, and had no evidence of extra-aortic involvement by IgG4-RSD, but one had a mildly elevated serum IgG4 level of 185 mg/dl. The authors in that study suggested labeling all five of these patients as 'IgG4-related thoracic aortic aneurysm' regardless of whether the overall pathology was indicative of an aortitis or atherosclerosis. At present it is not clear if focal high IgG4 staining in an atherosclerotic aneurysm is entirely diagnostic of IgG4-RSD, or if in some cases such staining could represent a localized hypersensitivity reaction. Additional studies with close patient follow-up will be required to address this issue.

Inflammatory aortic aneurysm and periaortitis

The term inflammatory aortic aneurysm or periaortitis has traditionally been applied to abdominal aortic aneurysms with severe atherosclerosis, which contained more chronic inflammation and scarring in the adventitia than typical atherosclerotic aneurysms [23–25]. Approxi-

mately 2–15% of all abdominal aortic aneurysms are thought to be inflammatory aneurysms. In some cases, this disorder has been reported in the setting of well recognized rheumatologic conditions such as rheumatoid arthritis and ankylosing spondylitis [26]. However, in most cases, the significance of the pathology has not been so certain. As atherosclerosis itself can result in substantial adventitial scarring and inflammation, it has been unclear whether most inflammatory abdominal aortic aneurysms were a manifestation of a systemic rheumatologic disease or were simply a subtype of atherosclerosis with more than the average amount of inflammation, perhaps resulting in part from a localized hypersensitivity reaction to atherosclerotic plaque components.

In a comprehensive study [16] from the Cleveland Clinic, true aortitis was felt to be present in only two of approximately 700 (0.3%) abdominal aortic aneurysms, far lower than the 2–15% of cases being labeled as inflammatory aneurysms, suggesting that the majority of the inflammatory abdominal aortic aneurysms may not represent true aortitis. Progress in understanding the disorder of inflammatory abdominal aortic aneurysms has been hampered in some institutions by surgical procedures in which none of the aorta is removed for pathologic analysis. Likewise, the more recently adopted endovascular procedures, while having the benefit of allowing for a less invasive procedure, have a downside in limiting diagnosis of the underlying disease process, which lead to the formation of the aneurysm. Despite these difficulties and controversies, recent reports have indicated that a subset of inflammatory abdominal aortic aneurysm cases is in fact a result of IgG4-RSD.

Inflammatory abdominal aortic aneurysm and IgG4-related systemic disease

In the last few years, it has become clear that some cases being labeled as inflammatory abdominal aortic aneurysm are in fact a manifestation of IgG4-RSD. Sakata *et al.* [27] compared 11 cases of inflammatory abdominal aortic aneurysm to 12 cases of atherosclerotic abdominal aortic aneurysm and demonstrated that the aneurysms defined as inflammatory contained more IgG4⁺ plasma cells than those defined as atherosclerotic. However, in that study there was no clear delineation as to which inflammatory aneurysms actually represented involvement by IgG4-RSD. In addition, the fraction of plasma cells expressing IgG4 was not reported for either aneurysm group, making it unclear if the enhanced number of IgG4⁺ plasma cells was simply a manifestation of more plasma cells in general being present in the aneurysms labeled as inflammatory.

There have been several cases reported of inflammatory abdominal aortic aneurysm/abdominal periaortitis, which

Table 2 Published cases of IgG4-related inflammatory abdominal aortic aneurysm

No.	Age	M/F	Abdominal aortic segment	Aneurysm (size) or ruptured aneurysm	Site of inflammation	IgG4 ⁺ plasma cells (fraction)	Serum IgG4 (mg/dl)	Extra-aortic disease	Reference
1–4	58–72 years	3 M 1 F	Not Specified	Aneurysms	Ad	0.67 ± 0.11 ^a	109,112, 559		[28]
5	77 years	M	Infrarenal	Aneurysm	Ad > Med	0.88	571	Pancreas RF	[29]
6	63 years	F	Infrarenal	Aneurysm (5.5 cm)	Ad > Med	0.50	456	Coronary Artery	[30]
7	63 years	F	Infrarenal	Ruptured Aneurysm	Ad	0.64	61		[31]

Ad, adventitia; Med, media; RF, retroperitoneal fibrosis.

^aMean and presumed standard deviation, estimated from reported bar graph.

were attributed to IgG4-RSD, and which included pathologic evaluation of the aorta [28–31]. Comparison of these cases in Table 2 with the six thoracic IgG4-related aortitis cases in Table 1 demonstrates some potential differences in these two groups of patients. The thoracic cases in general appear to have more severe disease with trends toward higher fractions of infiltrating plasma cells staining for IgG4⁺, higher serum IgG4 levels, and increased frequency of involvement of the aortic media. In fact, three of the six patients with abdominal IgG4-related periaortitis for whom serum IgG4 values were reported actually had serum IgG4 levels below 120 mg/dl, essentially normal levels. Additional cases will be needed to establish the significance of these trends and if in fact patients with thoracic IgG4-related aortitis have more severe disease than those with involvement of the abdominal aorta.

Pathologically, all seven cases of abdominal aortic involvement by IgG4-related systemic disease are comparable to the adventitia-predominant form of thoracic IgG4-related aortitis, with medial involvement only clearly stated for two of the seven cases. A media-predominant form of IgG4-related aortitis has not yet been reported in the abdominal aorta. Focal granulomatous inflammation was reported in two of the seven abdominal aorta cases, compared with none of the six thoracic aortitis cases. Similarly, a relatively prominent eosinophilic infiltration was reported with three of the seven abdominal aorta cases, whereas at least four of the six thoracic aortitis cases lacked a prominent eosinophil component. These latter two histologic findings may suggest that the IgG4⁺ plasma cells in some abdominal aortic aneurysm cases may be occurring in the setting of a localized allergic/hypersensitivity reaction.

The relationship of IgG4-related systemic disease to inflammatory abdominal aortic aneurysms may allow some insight into the prevalence of this disorder. Kasashima *et al.* [28] reported that four of 10 cases (40%) of inflammatory abdominal aortic aneurysm were due to IgG4-RSD. As indicated above, inflammatory aneurysms may represent 2–15% of all abdominal aortic aneurysms. This would suggest 1–6% of all abdominal aortic aneurysms

could be due to IgG4-related systemic disease. Because moderate to large abdominal aortic aneurysms (>39 mm) are known to be present in about 4% of men age 65–74 [32], IgG4-related aortic disease could potentially be present in roughly one out of every 1000 older men. Additional studies will be required to confirm these numbers. Specifically, it will be important to ascertain if all of the cases of IgG4-related inflammatory abdominal aortic aneurysms are truly systemic disorders, or if a portion of these cases are actually localized hypersensitivity reactions.

Retroperitoneal fibrosis

Retroperitoneal fibrosis is a chronic inflammatory fibrosing condition that may result from multiple distinct etiologies including infection (particularly mycobacterial), radiation therapy, drugs (such as ergot alkaloids), malignant neoplasms, and trauma [33,34]. True, idiopathic retroperitoneal fibrosis is a relatively rare condition that is believed to afflict approximately one in every 100 000 people. In recent years, it has become clear that in a subset of patients with idiopathic retroperitoneal fibrosis, the disorder is in fact occurring in the setting of IgG4-RSD.

IgG4-related systemic disease as a cause of retroperitoneal fibrosis

As early as 2002, it was clear that auto-immune pancreatitis could be associated with inflammatory masses within the retroperitoneum, and it was later recognized that both conditions were a manifestation of IgG4-RSD. Table 3 summarizes the characteristics of 14 published cases of retroperitoneal fibrosis due to IgG4-RSD in the absence of aortic aneurysm [35–45]. By imaging, the retroperitoneal involvement is typically not entirely diffuse, but present primarily as inflammatory masses that often primarily involve the abdominal aorta, the kidneys or the ureters. In fact, ureteral obstruction with hydronephrosis is a common associated finding. The inflammatory masses are composed of lymphoplasmacytic inflammation and fibrosis with a substantial number of the plasma cells expressing IgG4.

Table 3 Published cases of IgG4-related retroperitoneal fibrosis without aortic aneurysm formation

No.	Age	Sex	Predominant location	Serum IgG4 (mg/dl)	Other sites of disease involvement	Reference
1	60 years	Male	Periureteral	265	Pancreas	[35]
2	74 years	Male	Periureteral	965	Pancreas	[35]
3	63 years	Male	Periureteral	265	Pancreas	[35]
4	56 years	Male	Periaortic	ND	Pancreas	[36]
5	68 years	Male	Perirenal	ND	Pancreas	[37]
6	71 years	Male	Periaortic	ND	Pancreas	[38]
7	62 years	Male	Not specified	ND	Pancreas	[38]
8	68 years	Male	Not specified	540	Pancreas, salivary glands	[39]
9	52 years	Male	Periaortic	392	Mediastinum, perithoracic aorta	[40]
10	70 years	Male	Perirenal	619	Pancreas	[41]
11	71 years	Male	Periaortic	405	Salivary glands, lymph nodes, pituitary	[42]
12	75 years	Male	Periaortic	240	Pancreas	[43]
13	77 years	Male	Periaortic	348	Pancreas	[44]
14	70 years	Male	Perirenal	>2000	Salivary glands, lymph nodes	[45]

ND, no data.

Table 4 Comparison of patients with IgG4-related thoracic aortitis, IgG4-related inflammatory abdominal aortic aneurysm, and IgG4-related retroperitoneal fibrosis

Patient group	Number sex (M/F)	Age mean	Mean IgG4 ⁺ plasma cell fraction	Mean serum IgG4 (mg/dl)	Aortic medial involvement (%)	Additional sites of involvement (%)
Thoracic aortitis	6/0	70	0.82	3012	83	33
Abdominal aneurysms	4/3	67	0.67	311	29	29
Retroperitoneal fibrosis	14/0	67	NR	604	NA	100

Includes the patients in Tables 1–3. NA, not applicable; NR, not reported.

Just like the six IgG4-related thoracic aortitis cases, all 14 cases of IgG4-related retroperitoneal fibrosis were men. In fact, comparison of these 14 cases with the seven cases of IgG4-related abdominal periaortitis (Table 4) reveals a statistically significant difference in the sex distribution between these two groups ($P = 0.026$, Fisher's exact test), suggesting the relatively low male predominance of the IgG4-related abdominal aortic aneurysm cases to not have resulted from chance alone. All 14 of the IgG4-related retroperitoneal fibrosis cases demonstrated systemic/multifocal involvement, which included pancreatic involvement in 11 cases, salivary gland involvement in three cases, lymph node involvement in two cases, and pituitary and mediastinal periaortic involvement in one case each. A positive response to corticosteroid treatment was reported in 11 of 11 cases; however, in at least one of these cases, the size of the retroperitoneal mass did not decrease. These cases clearly demonstrate that aortic adventitial involvement is a feature of IgG4-RSD, even in the absence of aortic aneurysm formation.

In a recent study [46^{••}] of retroperitoneal biopsies of patients with idiopathic retroperitoneal fibrosis, 10 of 17 cases were felt to be due to IgG-RSD. In these 10 patients, the fraction of plasma cells staining for IgG4 ranged from 35 to 76% compared with 0 to 10% for the other seven patients. Likewise, for the IgG4-RSD patients, the mean serum IgG4 concentration was 695 mg/dl (range 154–2330 mg/dl) compared with 30 mg/dl (range 10–53 mg/dl) for the other seven

patients. Interestingly, all 10 patients with IgG4-related retroperitoneal fibrosis were men, while six of the seven patients with non-IgG4-related retroperitoneal fibrosis were women. Five of the 10 patients with IgG4-related retroperitoneal fibrosis had extraretroperitoneal involvement compared with none of the other seven patients.

Conclusion

Moving forward, it will be important to establish criteria for a pathologic diagnosis of aortic involvement by IgG4-RSD, particularly because the condition is being reported in patients with normal serum IgG4 levels and without clinical evidence of systemic involvement [47]. It is important to bear in mind that simply identifying IgG4⁺ plasma cells does not necessarily indicate involvement by IgG4-RSD [20^{••}]. In general, the cases reported in Tables 1 and 2 showed a high percentage of plasma cells staining for IgG4, typically 50% or greater. In addition, there should also be a reasonably high absolute number of IgG4⁺ plasma cells. The three IgG4-related thoracic aortitis cases reported by us [20^{••}] in fact had greater than 150 IgG4⁺ plasma cells per 400× high-power field (40× objective and 10× ocular). In addition, to diagnose IgG4-related aortitis, it is important for the histologic changes to overall be consistent with an aortitis or periaortitis, and to not be readily explainable by another process such as atherosclerosis. The following three criteria compose the 50/50 rule for the pathologic diagnosis of IgG4-related aortitis/periaortitis:

- (1) An overall histology that is consistent with an aortitis or periaortitis and that is not readily explained by another process such as atherosclerosis.
- (2) At least 50% of the plasma cells stain for IgG4.
- (3) At least 50 IgG4⁺ plasma cells per 400× high-power field, counting at least three fields.

Additional cases will need to be assessed to determine the sensitivity and specificity of these criteria. It will also be important to establish the significance of focal high IgG4⁺ plasma cell counts in aortas having an overall histology more consistent with routine atherosclerosis.

Acknowledgement

This work was supported by Massachusetts General Hospital.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 128).

- 1 Deshpande V, Chicano S, Finkelberg D, *et al.* Autoimmune pancreatitis: a systemic immune complex mediated disease. *Am J Surg Pathol* 2006; 30:1537–1545.
- 2 Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008; 14:3948–3955.
- 3 Masaki Y, Dong L, Kurose N, *et al.* Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009; 68:1310–1315.
- 4 Gornik HL, Creager MA. Aortitis. *Circulation* 2008; 117:3039–3051.
- 5 Pacini D, Leone O, Turci S, *et al.* Incidence, etiology, histologic findings, and course of thoracic inflammatory aortopathies. *Ann Thorac Surg* 2008; 86:1518–1523.
- 6 Walker M, Gallagher PJ. The surgical pathology of large vessel disease. *Diagn Histopathol* 2009; 16:10–16.
- 7 Haynes BF, Kaiser-Kupfer MI, Mason P, Fauci AS. Cogan syndrome: studies in 13 patients, long-term follow-up, and a review of the literature. *Medicine (Baltimore)* 1980; 59:426–441.
- 8 Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. *Semin Arthritis Rheum* 1995; 24:422–431.
- 9 Hotchi M. Pathological studies on Takayasu arteritis. *Heart Vessels* 1992; 7 (Suppl):11–17.
- 10 Chikamori T, Doi YL, Yonezawa Y, *et al.* Aortic regurgitation secondary to Behcet's disease: a case report and review of the literature. *Eur Heart J* 1990; 11:572–576.
- 11 Lautermann D, Braun J. Ankylosing spondylitis: cardiac manifestations. *Clin Exp Rheumatol* 2002; 20 (Suppl 28):S11–S15.
- 12 Slobodin G, Naschitz JE, Zuckerman E, *et al.* Aortic involvement in rheumatic diseases. *Clin Exp Rheumatol* 2006; 24:S41–S47.
- 13 Gravalles EM, Corson JM, Coblyn JS, *et al.* Rheumatoid aortitis: a rarely recognized but clinically significant entity. *Medicine (Baltimore)* 1989; 68:95–106.
- 14 Miller DV, Isotalo PA, Weyand CM, *et al.* Surgical pathology of noninfectious ascending aortitis: a study of 45 cases with emphasis on an isolated variant. *Am J Surg Pathol* 2006; 30:1150–1158.
- 15 Burke AP, Tavora F, Narula N, *et al.* Aortitis and ascending aortic aneurysm: description of 52 cases and proposal of a histologic classification. *Hum Pathol* 2008; 39:514–526.
- 16 Rojo-Leyva F, Ratliff NB, Cosgrove DM 3rd, Hoffman GS. Study of 52 patients with idiopathic aortitis from a cohort of 1,204 surgical cases. *Arthritis Rheum* 2000; 43:901–907.
- 17 Khosroshahi A, Stone JR, Pratt DS, *et al.* Painless jaundice with serial • multiorgan dysfunction. *Lancet* 2009; 373:1494.
This report describes the first case of thoracic aortitis due to IgG4-RSD with marked elevation of serum IgG4 levels and with progression to auto-immune pancreatitis.
- 18 Stone JH, Khosroshahi A, Hilgenberg A, *et al.* IgG4-related systemic • disease and lymphoplasmacytic aortitis. *Arthritis Rheum* 2009; 60:3139–3145.
This report describes the first case of IgG4-related thoracic aortitis with a media-predominant pattern of aortic wall infiltration with marked elevation in serum levels of IgG4. This report unequivocally links IgG4-RSD with thoracic lymphoplasmacytic aortitis.
- 19 Ishida M, Hotta M, Kushima R, *et al.* IgG4-related inflammatory aneurysm of the aortic arch. *Pathol Internat* 2009; 59:269–273.
- 20 Stone JH, Khosroshahi A, Deshpande V, Stone JR. IgG4-related systemic • disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res* 2010; 62:316–322.
This was the first study published to assess the frequency of IgG4-related thoracic aortitis. The study revealed that in a 5-year time span, IgG4-RSD accounted for 0.5% of all resected thoracic aortas, 9% of all thoracic aortitis, and three of four cases (75%) of lymphoplasmacytic aortitis. The study delineated the distinction between granulomatous aortitis, which is typically not due to IgG4-RSD, and lymphoplasmacytic aortitis, which is frequently due to IgG4-RSD.
- 21 Kasashima S, Zen Y, Kawashima A, *et al.* A clinicopathologic study of • immunoglobulin G4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* (in press).
This study showed that IgG4-RSD accounted for 1.6% of all resected thoracic aortas in one institution, in general agreement with the frequency of 0.5% reported above. The study also indicated that a small number of cases of aortic atherosclerosis have, at least focally, similar amounts of IgG4-positive plasma cells as present in IgG4-related aortitis.
- 22 Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum* 2010; 62:1755–1762.
- 23 Walker DI, Bloor K, Williams G, Gillie I. Inflammatory aneurysms of the abdominal aorta. *Brit J Surg* 1972; 59:609–614.
- 24 Feiner HD, Raghavendra N, Phelps R, Rooney L. Inflammatory abdominal aortic aneurysm: report of six cases. *Hum Pathol* 1984; 15:454–459.
- 25 Boontje AH, van den Dungen JJAM, Blanksma C. Inflammatory abdominal aortic aneurysms. *J Cardiovasc Surg* 1990; 31:611–616.
- 26 Vaglio A, Buzio C. Chronic periaortitis: a spectrum of diseases. *Cur Opin Rheumatol* 2005; 17:34–40.
- 27 Sakata N, Tashiro T, Uesugi N, *et al.* IgG4-positive plasma cells in inflammatory abdominal aortic aneurysm: the possibility of an aortic manifestation of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008; 32:553–559.
- 28 Kasashima S, Zen Y, Kawashima A, *et al.* Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. *Am J Surg Pathol* 2008; 32:197–204.
- 29 Ito H, Kaizaki Y, Noda Y, *et al.* IgG4-related inflammatory abdominal aortic aneurysm associated with autoimmune pancreatitis. *Pathol Internat* 2008; 58:421–426.
- 30 Matsumoto Y, Kasashima S, Kawashima A, *et al.* A case of multiple immunoglobulin G4-related periarteritis: a tumorous lesion of the coronary artery and abdominal aortic aneurysm. *Hum Pathol* 2008; 39:975–980.
- 31 Qian Q, Kashani KB, Miller DV. Ruptured abdominal aortic aneurysm related to IgG4 periaortitis. *N Eng J Med* 2009; 361:1121–1123.
- 32 Singh K, Bonaa KH, Jacobsen BK, *et al.* Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: The Tromsø Study. *Am J Epidemiol* 2001; 154:236–244.
- 33 Gilkeson GS, Allen NB. Retroperitoneal fibrosis: a true connective tissue disease. *Rheum Dis Clin North Am* 1996; 22:23–38.
- 34 Uibu T, Oksa P, Auvinen A, *et al.* Asbestos exposure as a risk factor for retroperitoneal fibrosis. *Lancet* 2004; 363:1422–1426.
- 35 Hamano H, Kawa S, Ochi Y, *et al.* Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002; 359:1403–1404.
- 36 Uchida K, Okazaki K, Asada M, *et al.* Case of chronic pancreatitis involving an autoimmune mechanism that extended to retroperitoneal fibrosis. *Pancreas* 2003; 26:92–94.
- 37 Fukukura Y, Fujiyoshi F, Nakamura F, *et al.* Autoimmune pancreatitis associated with idiopathic retroperitoneal fibrosis. *AJR Am J Roentgenol* 2003; 181:993–995.
- 38 Kamisawa T, Matsukawa M, Ohkawa M. Autoimmune pancreatitis associated with retroperitoneal fibrosis. *JOP J Pancreas* 2005; 6:260–263.

- 39 Fukui T, Okazaki K, Yoshizawa H, *et al.* A case of autoimmune pancreatitis associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjögren's syndrome. *Pancreatology* 2005; 5:86–91.
 - 40 Zen Y, Sawazaki A, Miyayama S, *et al.* A case of retroperitoneal and mediastinal fibrosis exhibiting elevated levels of IgG4 in the absence of sclerosing pancreatitis (autoimmune pancreatitis). *Hum Pathol* 2006; 37:239–243.
 - 41 Miyajima N, Koike H, Kawaguchi M, *et al.* Idiopathic retroperitoneal fibrosis associated with IgG4-positive plasmacyte infiltrations and idiopathic chronic pancreatitis. *Int J Urol* 2006; 13:1442–1444.
 - 42 Tanabe T, Tsushima K, Yasuo M, *et al.* IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. *Intern Med* 2006; 45:1243–1247.
 - 43 Kamisawa T, Chen PY, Tu Y, *et al.* Autoimmune pancreatitis metachronously associated with retroperitoneal fibrosis with IgG4-positive plasma cell infiltration. *World J Gastroenterol* 2006; 12:2955–2957.
 - 44 Ohtsubo K, Watanabe H, Tsuchiyama T, *et al.* A case of autoimmune pancreatitis associated with retroperitoneal fibrosis. *JOP* 2007; 8:320–325.
 - 45 Gill J, Taylor G, Carpenter L, *et al.* A case of hyperIgG4 disease or IgG4-related sclerosing disease presenting as retroperitoneal fibrosis, chronic sclerosing sialadenitis, and mediastinal lymphadenopathy. *Pathology* 2009; 41:297–300.
 - 46 Zen Y, Onodera M, Inoue D, *et al.* Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; 33:1833–1839.
- In this report, IgG4-RSD was found to account for 59% of patients with biopsies of retroperitoneal fibrosis. There was a striking sex disparity with 100% of the IgG4-related patients being men and 86% of the non-IgG4-related retroperitoneal fibrosis patients being women.
- 47 Kasashima S, Zen Y, Kawashima A, *et al.* A new clinicopathological entity of IgG4-related inflammatory abdominal aortic aneurysm. *J Vasc Surg* 2009; 49:1264–1271.