

IgG4-related inflammatory abdominal aortic aneurysm

Satomi Kasashima^{a,b} and Yoh Zen^c

^aDepartment of Pathology, ^bDepartment of Clinical Laboratory, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Japan and ^cInstitute of Liver Studies, King's College Hospital, London, UK

Correspondence to Satomi Kasashima, MD, PhD, Department of Pathology and Department of Clinical Laboratory, National Hospital Organization, Kanazawa Medical Center, 1-1 Shimoisibikimachi, Kanazawa 920-8650, Japan
Tel: +81 76 262 4161; fax: +81 76 222 2758;
e-mail: sato-kasa@kinbyou.hosp.go.jp

Current Opinion in Rheumatology 2011, 23:18–23

Purpose of review

IgG4-related systemic disease is a recently proposed entity characterized by high serum IgG4 concentrations, sclerosing inflammation containing numerous IgG4-positive plasmacytes, dramatic responsiveness to steroid therapy, and occurrence of multiple organs. This review described that some cases of inflammatory abdominal aortic aneurysm (IAAA) have similar clinicopathological features that are now considered to represent aortic lesions of IgG4-related systemic disease under the concept of IgG4-related IAAA.

Recent findings

IgG4-related IAAA is characterized by high serum IgG4 and immunoglobulin E levels, high titers of antinuclear antibodies, and high prevalence of allergic disorders such as bronchial asthma. The patients show a risk of developing IgG4-related systemic diseases in other organs during their life. Histologically, sclerosing inflammation containing numerous IgG4-positive plasmacytes is observed predominantly in the adventitia. Similar lesions have also been reported in the thoracic aorta and large arteries.

Summary

Recognition of the fact that IgG4-related systemic disease could involve the vascular lesions offers potential new management of those. However, only 3 years have passed since the first report of IgG4-related IAAA. Further studies are necessary to elucidate other vascular lesions associated with IgG4-related systemic disease, the usefulness of steroid therapy for the management of IgG4-IAAA, and underlying pathological and immunological characteristics.

Keywords

aortitis, chronic periaortitis, IgG4, inflammatory aneurysm

Curr Opin Rheumatol 23:18–23
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8711

Introduction

Abdominal aortic aneurysm (AAA) is the most common type of aneurysm, usually developing in adults older than 60 years. On rare occasions, AAA shows diffuse thickening of the aneurismal wall with extensive fibrous adhesion to adjacent tissue. Since Walker *et al.* [1] first used the term inflammatory AAA (IAAA) in 1972, detailed clinicopathological features have been reported [2–8]. Several theories have been proposed for the pathogenesis of IAAA, but have yet to be completely confirmed [3–5,7]. Sclerosing inflammation in the aortic wall sometimes extends into the retroperitoneal soft tissue, representing IAAA with retroperitoneal fibrosis [5–7].

In 2001, Hamano *et al.* [9] reported that patients with autoimmune pancreatitis display high serum concentrations of IgG4. Autoimmune pancreatitis is pathologically characterized by diffuse lymphoplasmacytic infiltration and fibrosis with parenchymal atrophy [9]. Immunostaining for IgG4 reveals numerous IgG4-

positive plasma cells in the autoimmune pancreatitis. Similar sclerosing diseases characterized by IgG4-positive cell infiltration have since been identified in extrapancreatic organs such as the bile duct, salivary gland, lung, and retroperitoneum [10–14,15*,16–18]. Given the close relationship between IgG4 and idiopathic sclerosing disease, a disease entity named IgG4-related systemic disease (IgG4-SD) was proposed.

We recently published the first report to link IgG4-SD with IAAA [19], followed by some reports on IgG4-SD involvement in the cardiovascular system [20**,21–26,27*,28,29]. Herein, we review the clinicopathological features of IAAA in comparison with atherosclerotic AAA (aAAA) and IgG4-SD.

Inflammatory abdominal aortic aneurysm

IAAA accounts for approximately 2–10% of all AAAs [2,6,8]. Patients with IAAA are younger than patients with aAAA [8]. Clinical symptoms are usually nonspecific,

including dull abdominal or back pain, low-grade fever, weight loss, and general fatigue [2,8]. Systemic inflammatory markers, such as erythrocyte sedimentation rate, C-reactive protein levels and white blood counts are commonly elevated in IAAA [1,6]. Those features do not facilitate differentiation between IAAA and infectious aneurysms (from pathogens such as bacteria, fungi, syphilis and tuberculosis) [2,3]. Blood cultures and serum procalcitonin levels are helpful for making the differential diagnosis [30]. Other autoimmune diseases are occasionally seen in patients with IAAA [20^{••},21]. Elevated serum IgG levels and the presence of autoantibodies such as anti-nuclear antibody (ANA) are also frequent in IAAA patients [31,32], suggesting the involvement of autoimmune mechanisms in the pathogenesis [33]. Radiologically, IAAA is characterized by aortic dilatation, periaortic mantle zone, and adhesions to adjacent organs (Fig. 1) [6]. Positron emission tomography and computed tomography (PET/CT) is useful to detect inflammatory activity in the aneurysmal wall [34].

A macroscopic appearance of white, glistening, perianeurysmal fibrosis is characteristic of IAAA [1–3]. Histopathologically, extensive fibrosis with marked thickening of the aortic wall and severe lymphoplasmacytic infiltration are noted (Fig. 2). The sclerosing inflammation predominantly involves the adventitia with extension into adjacent soft tissues [5,7]. Inflammatory cells and relevant neovessels produce matrix metalloproteinases, which may play an important role in aortic wall vulnerability [35]. Lymph follicles are present in places associated with interfollicular plasmacytosis, but monoclonality is never shown on immunostaining or in-situ hybridization. Atherosclerotic changes are also noted in the intima and media in IAAA, as with aAAA.

Figure 1 Radiological features of inflammatory abdominal aortic aneurysm. Computed tomography showing periaortic soft tissue mantle in the abdominal aorta (arrow) of a patient with IgG4-related inflammatory abdominal aortic aneurysm

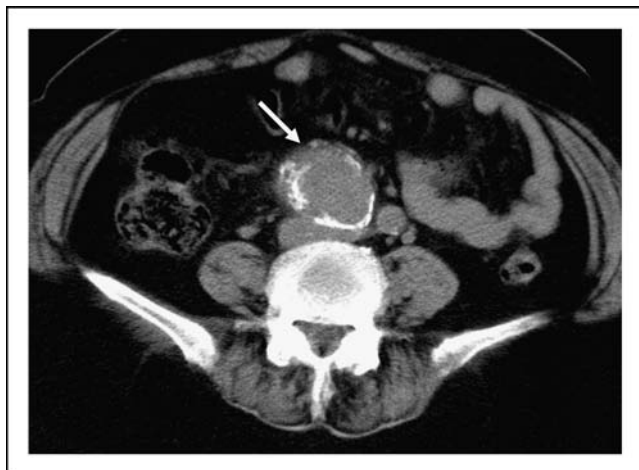
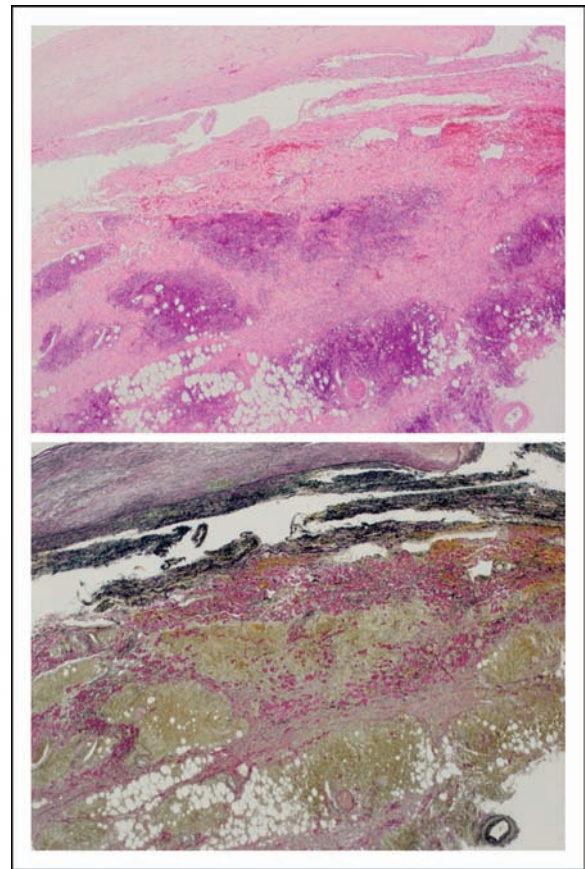


Figure 2 Histological features of IgG4-related inflammatory abdominal aortic aneurysm



Fibrous thickening and severe inflammation with lymphoid follicles are seen in the adventitia, extending into the periaortic adipose tissue. Upper, hematoxylin and eosin, $\times 20$; lower, elastica van Gieson, $\times 20$.

Some authors have suggested that IAAA is simply a variant of aAAA [3–5], whereas others have hypothesized different etiopathogenic factors such as autoimmunity with ceroid or lipid in atheromatous plaque as a potential autoantigen, and infection with *Chlamydia pneumoniae* or *Helicobacter pylori* [36–40].

IgG4-related systemic disease

IgG4 is the rarest subclass of IgG, accounting for only 3–6% of total IgG in normal populations [41]. IgG4 can induce the migration of leukocytes, and does not bind to complement [41]. High serum levels of IgG4 have been reported in a limited number of diseases, including atopic dermatitis, bronchial asthma, pemphigus vulgaris and pemphigus foliaceus [42,43].

Patients with IgG4-SD share clinical characteristics irrespective of the organ of origin [9–14,15[•],16–18]. These individuals are usually senior adult with a male predominance. IgG4 is no doubt the most useful serological

marker for the diagnosis. IgG4-SD exhibits tumorous swelling of the affected organ, which usually shows dramatic response to steroid therapy. Multiple synchronous or metachronous lesions can be seen in different organs. Histologically, the condition is characterized by infiltration of diffuse inflammatory cells containing numerous IgG4-positive plasmacytes, storiform fibrosis, frequent eosinophilic infiltration, and obliterative phlebitis [10–14,15*,16–18]. IgG4-SD commonly develops in organs with ductal or glandular complexes [8,9,13,14,18], but this is not a consistent feature [12,15*,17].

Subclassification of inflammatory abdominal aortic aneurysm: IgG4-related and IgG4-nonrelated

Our previous study revealed that a proportion of IAAA could be estimated as aortic lesions of IgG4-SD based on histological and serological characteristics (Fig. 3a) [19]. The key issues are that not all IAAAs are related to IgG4 and that IgG4-related cases are observed only in IAAA, not in aAAA. On the basis of these findings, IAAA can be classified into, at least, two groups: IgG4-related IAAA (IgG4-IAAA) and IgG4-nonrelated IAAA (non-IgG4-IAAA). This classification offers a first step in recognizing the heterogeneity of IAAA, but whether non-IgG4-IAAA is a single disease entity remains unclear.

Pathological differences between IgG4-related and IgG4-nonrelated inflammatory abdominal aortic aneurysm

The degrees of inflammatory activity and fibrosis are more severe in IgG4-IAAA, particularly with extensive thickening of the adventitia in IgG4-IAAA [19,20**,21]. The more important issue is that inflammatory activity and fibrosis differ from case to case in IgG4-IAAA, with some cases showing massive infiltration of lymphoplasmacytes with numerous lymph follicles, and others exhibiting a predominantly fibrotic appearance with reduced infiltration of inflammatory cells [19,20**,21–24]. IgG4-IAAA is much more common in inflammatory cases. Compared with non-IgG4-IAAA, IgG4-IAAA is characterized by frequent infiltration of eosinophils, lymphoid follicle formation, obliterative phlebitis, and extension of inflammation to perineural areas (Fig. 3b-d) [19,20**,21]. Neutrophilic infiltration and thicker atherosclerotic intima are more common in non-IgG4-IAAA [20**], which may indicate that non-IgG4-IAAA represents an inflammatory variant of aAAA. Numerous diffuse IgG4-positive plasma cells are seen in IgG4-IAAA (Fig. 3a), but are scarce or only focally accumulated in non-IgG4-IAAA.

Clinical differences between IgG4-related and IgG4-nonrelated inflammatory abdominal aortic aneurysm

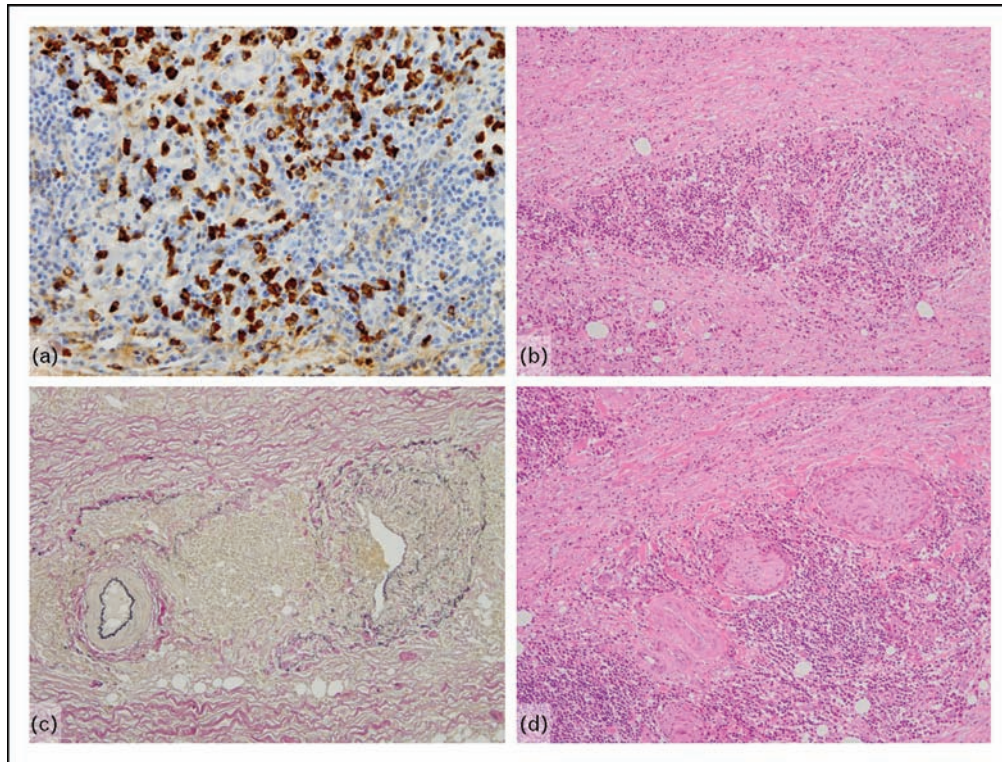
In our cohort, IgG4-IAAA made up about 50% of total IAAAs and about 5% of total surgical AAAs [20**]. Age,

gender, aneurysmal diameter and location did not differ between IgG4-IAAA and non-IgG4-IAAA [20**]. Whether these two forms can be differentiated radiologically is an important issue, but no published data are available to the best of our knowledge. The incidence of rupture is less frequent in patients with IgG4-IAAA compared with non-related cases [20**]. We have yet to see any patients with IgG4-IAAA presenting with aneurysmal rupture, but one such case was recently reported by Qian *et al.* [23].

Regarding risk factors and associated conditions, smoking habit, hypertension, ischemic heart disease, diabetes and hyperlipidemia are slightly less common in patients with IgG4-IAAA compared with those with non-IgG4-IAAA [20**]. Allergic predisposition and history of autoimmune diseases are more frequent in patients with IgG4-IAAA, and more than 30% of patients have bronchial asthma [20**]. Some patients with IgG4-IAAA have a history of other IgG4-SD, such as autoimmune pancreatitis [22,24] and lymphadenitis [26].

Serum IgG4 elevation is obviously the most useful pre-operative examination for diagnosing IgG4-IAAA. In our experience, serum IgG4 levels normalize with a few months postoperatively. White blood cell count and C-reactive protein levels do not remain consistently elevated in patients with IgG4-SD, but, interestingly, are sometimes noted in IgG4-IAAA as in non-IgG4-IAAA [19,20**]. Other features more commonly seen in IgG4-IAAA include elevated IgE levels and high titers (>320) of ANA [20**]. We now speculate that increased levels of IgE, high titers of ANA, and a history of allergic disorders may be clues to the diagnosis of IgG4-IAAA, which should be finally established by IgG4 serology and histological examination in surgical cases.

Another important issue is how clinical management will be changed by the discovery of IgG4-IAAA. IAAA usually shows tight fibrous adhesions to adjacent soft tissues, complicating surgical procedures [2,3,6,8]. Indeed, post-operative outcomes following IAAA are often poor, with some cases showing fatal complications. Given the dramatic response of IgG4-SD to steroid treatment [18], we would expect steroid therapy to be effective for sclerosing inflammation around the aorta. However, such therapy may increase the risk of aneurysmal rupture by making the wall thinner and more fragile. In addition, care must be taken to start steroid therapy if patients display IgG4-SD in multiple organs including the aorta. Further clinical studies are necessary to clarify this important issue. We have experience with treating a patient presenting with IgG4-IAAA and autoimmune pancreatitis using low-dose steroids. That therapy reduced aneurysmal wall thickness and pancreatic swelling, and improved obstructive jaundice. The diameter of the aortic aneurysm remained unchanged after steroid therapy.

Figure 3 Radiological features of inflammatory abdominal aortic aneurysm

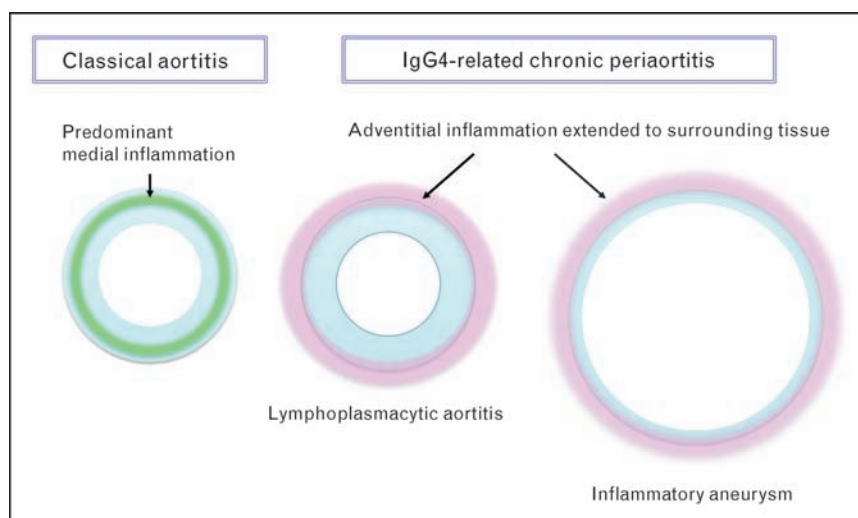
(a) Immunostaining for IgG4 reveals numerous IgG4-positive plasma cells in the aneurysmal wall of IgG4-related inflammatory abdominal aortic aneurysm ($\times 200$). IgG4-related inflammatory abdominal aortic aneurysm shows lymphoid follicle formation (b), obliterative phlebitis (c) and perineural inflammatory extension (d) (all $\times 50$).

Other vascular lesions related to IgG4-related systemic disease

Although inflammatory aneurysm is most common in the abdominal aorta, the same pathology can rarely develop in the thoracic aorta and large arteries. Indeed, IgG4-related thoracic aortic inflammatory aneurysm was reported just after the abdominal lesion was first reported [25]. However, different from the abdominal aorta, IgG4-related inflammatory thoracic aneurysms should differentiate from other particular types of thoracic vascular lesions, and yield vague entity [44,45]. For example, Takayasu aortitis is the prototype aortic aneurysm with thick aortic walls and diffuse lymphoplasmacytic infiltration [45]. Epithelioid granuloma, giant cells, and fibrinoid necrosis, which are extremely rare in IgG4-SD, are useful for differentiation from Takayasu aortitis [28]. Whether Takayasu aortitis shows elevated serum IgG4 concentrations is still not completely elucidated. Aortic syphilis is another differential diagnosis, because it is characterized by lymphoplasmacytic inflammation. Serological examination for *Treponema pallidum* latex agglutination would be useful. Aortic dissection also sometimes shows adventitial thickening and periaortic fibrosis as a process of wound healing.

The suggestion has been made that IgG4-SD in the thoracic aorta have been diagnosed as inflammatory aortic aneurysm or lymphoplasmacytic aortitis [26,27*,28]. Aortic dissection has also been reported as one manifestation of IgG4-SD in the thoracic aorta [27*]. Our previous study revealed that IgG4-related lesions comprised 4% of all surgical cases for thoracic aortic lesions, with an almost equal frequency among surgical cases of abdominal aneurysm [28]. Stone *et al.* [27*] also reported that IgG4-SD accounted for 75% of cases of lymphoplasmacytic aortitis and 9% of all cases of noninfectious thoracic aortitis. Frequent involvement of the aortic arch and a saccular morphology were characteristic features [28]. IgG4-related lesions in the thoracic aorta can show characteristic morphological manifestations as the abdominal ones. Aneurysmal dilatation is the predominant feature in some cases, whereas wall thickening with severe inflammatory cell infiltration is more conspicuous in others. These different morphological changes may reflect different manifestations of similar pathological processes. If the lamellar elastic fibers in the media are disrupted by sclerosing inflammation, high blood pressure may induce aneurysmal dilatation. More importantly, stricture or occlusive changes have not been reported in IgG4-related aortic lesions [28].

Figure 4 Comparison between classical aortitis (e.g. Takayasu aortitis, giant aortitis) and IgG4-related chronic periaortitis (lymphoplasmacytic aortitis and inflammatory aneurysm) from the perspective of the predominant location of inflammation



IgG4-SD can also involve arteries other than the aorta. We have identified some cases of IgG4-related lesions involving the superior mesenteric artery or right coronary artery [29]. These lesions shared similar clinicopathological characteristics to IgG4-SD, including IgG4-IAAA. Interestingly, these cases showed the predominant feature of periarterial masses without significant dilatation. Further studies are needed to elucidate the complete picture of IgG4-related aortic/arterial lesions.

Chronic periaortitis

The disease entity 'chronic periaortitis' has been proposed specifically for abdominal lesions [46]. This encompasses retroperitoneal fibrosis, IAAA, and perianeurysmal retroperitoneal fibrosis, as a spectrum of a single pathological process [46,47]. As mentioned above, IgG4-related aortic lesions can manifest with different morphological changes, with some displaying predominant aneurysmal dilatation and others showing severe wall thickening with or without periaortic inflammatory extension. 'IgG4-related chronic periaortitis' seems to represent a good term to understand the morphological variation of IgG4-related arterial lesions as well as peri-aortic retroperitoneal/mediastinal fibrosis (Fig. 4) [19].

Pathogenesis of IgG4-related inflammatory abdominal aortic aneurysm

The pathologic significance of elevated serum IgG4 levels and infiltration of numerous IgG4-positive plasma cells into the aorta remains unclear. Given the histological similarities between IgG4-IAAA and IgG4-SD, a common immunological process may be involved in the pathogenesis. IAAA has been immunologically

characterized [48,49], but simple application of these characteristics to IgG4-IAAA is difficult, as most previous studies have examined IAAA as a single disease group. Detailed pathological and immunological studies restricted to IgG4-IAAA seem warranted. Examination of whether the data on IgG4-SD in other organs would be applicable to IgG4-IAAA is also important. T helper-2cell-dominant immune reactions and possible involvement of regulatory T cells have been suggested to be involved in the pathogenesis of IgG4-related pancreato-cholangitis and sialadenitis [50,51].

Conclusion

IgG4-IAAA is a subtype of IAAA, and can be estimated as one of the manifestations of IgG4-SD. IgG4-IAAA shares clinicopathological characteristics with IgG4-SD in other organs. Further studies are needed to elucidate the complete clinical picture of IgG4-related vascular lesions, clarify the utility of steroid therapy for the management of IgG4-IAAA, and determine the underlying pathological and immunological characteristics.

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. 126).

- 1 Walker DI, Bloor K, Williams G, Gillie I. Inflammatory aneurysms of the abdominal aorta. *Br J Surg* 1972; 59:609–614.
- 2 Goldstone J, Malone JM, Moore WS. Inflammatory aneurysm of the abdominal aorta. *Surgery* 1978; 83:425–430.
- 3 Crawford JL, Stowe CL, Safi HJ, *et al*. Inflammatory aneurysms of the aorta. *J Vasc Surg* 1985; 2:113–124.

- 4 Rose AG, Dent DM. Inflammatory variant of abdominal atherosclerotic aneurysm. *Arch Pathol Lab Med* 1981; 105:409–413.
 - 5 Leu HJ. Inflammatory abdominal aortic aneurysms: a disease entity? Histological analysis of 60 cases of inflammatory aortic aneurysms of unknown aetiology. *Virchows Arch A Pathol Anat Histopathol* 1990; 417:427–433.
 - 6 Nitecki SS, Hallett JW Jr, Stahson AW, *et al*. Inflammatory abdominal aneurysms: a case-control study. *J Vasc Surg* 1996; 23:860–868.
 - 7 Hellmann DB, Grand DJ, Freischlag JA. Inflammatory abdominal aortic aneurysm. *JAMA* 2007; 297:395–400.
 - 8 Paravastu SC, Murray D, Ghosh J, *et al*. Inflammatory abdominal aortic aneurysms (IAAA): past and present. *Vasc Endovascular Surg* 2009; 43:360–363.
 - 9 Hamano H, Kawa S, Horiuchi A, *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344:732–738.
 - 10 Zen Y, Harada K, Sasaki M, *et al*. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004; 28:1193–1203.
 - 11 Kitagawa S, Zen Y, Harada K, *et al*. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* 2005; 29:783–791.
 - 12 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.
 - 13 Deshpande V, Chicano S, Finkelberg D, *et al*. Autoimmune pancreatitis: a systemic immune complex mediated disease. *Am J Surg Pathol* 2006; 30:1537–1545.
 - 14 Kojima M, Sipos B, Klapper W, *et al*. Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. *Am J Surg Pathol* 2007; 31:521–528.
 - 15 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.
- This report described the clinicopathological characteristics of 10 cases of IgG4-related retroperitoneal fibrosis relating to IgG4, in comparison with seven cases of unrelated cases.
- 16 Zen Y, Inoue D, Kitao A, *et al*. IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009; 33:1886–1893.
 - 17 Gill J, Taylor G, Carpenter L, *et al*. A case of hyper IgG4 disease or IgG4-related sclerosing disease presenting as retroperitoneal fibrosis, chronic sclerosing sialadenitis and mediastinal lymphadenopathy. *Pathology* 2009; 41:297–300.
 - 18 Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008; 14:3948–3955; Review.
 - 19 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.
 - 20 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.
- This report described the clinicopathological characteristics of 13 cases of IgG4-IAAA, in comparison with 10 cases of non-IgG4-IAAA and 40 cases of atherosclerotic abdominal aortic aneurysm.
- 21 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.
 - 22 Ito H, Kaizaki Y, Noda Y, *et al*. IgG4-related inflammatory abdominal aortic aneurysm associated with autoimmune pancreatitis. *Pathol Int* 2008; 58:421–426.
 - 23 Qian Q, Kashani KB, Miller DV. Ruptured abdominal aortic aneurysm related to IgG4 periaortitis. *N Engl J Med* 2009; 361:1121–1123.
 - 24 Matsuki Y, Sato K, Fujikawa A, *et al*. A case of incidentally detected IgG4-related sclerosing disease involving inflammatory abdominal aortic aneurysm and autoimmune pancreatitis. *Mod Rheumatol* 2010; 20:306–310.
 - 25 Ishida M, Hotta M, Kushima R, *et al*. IgG4-related inflammatory aneurysm of the aortic arch. *Pathol Int* 2009; 59:269–273.
 - 26 Stone JH, Khosroshahi A, Hilgenberg A, *et al*. IgG4-related systemic disease and lymphoplasmacytic aortitis. *Arthritis Rheum* 2009; 60:3139–3145.
 - 27 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 (Hoboken)* 2010; 62:316–322.
- This report focuses on the IgG4-related thoracic aortic lesions and describes that IgG4-SD accounted for 75% of lymphoplasmacytic aortitis cases and 9% of all 35 cases of noninfectious thoracic aortitis.
- 28 Kasashima S, Zen Y, Kawashima A, *et al*. A clinicopathological study of IgG4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* (in press).
 - 29 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.
 - 30 Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin: a new indicator of the systemic response to severe infections. *Infection* 1997; 25:329–334.
 - 31 Vaglio A, Corradi D, Manenti L, *et al*. Evidence of autoimmunity in chronic periaortitis: a prospective study. *Am J Med* 2003; 114:454–462.
 - 32 Kaipainen-Seppänen O, Jantunen E, Kuusisto J, Marin S. Retroperitoneal fibrosis with antineutrophil cytoplasmic antibodies. *J Rheumatol* 1996; 23:779–781.
 - 33 Jagadeesham VP, Scott DJ, Carding SR. Abdominal aortic aneurysms: an autoimmune disease? *Trends Mol Med* 2008; 14:522–529.
 - 34 Kotze CW, Menezes LJ, Endozo R, *et al*. Increased metabolic activity in abdominal aortic aneurysm detected by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT). *Eur J Vasc Endovasc Surg* 2009; 38:93–99.
 - 35 Reeps C, Pelisek J, Seidl S, *et al*. Inflammatory infiltrates and neovessels are relevant sources of MMPs in abdominal aortic aneurysm wall. *Pathobiology* 2009; 76:243–252.
 - 36 Nyberg A, Skagius E, Nilsson I, *et al*. Abdominal aortic aneurysm and infection with CagA positive strains of *Helicobacter pylori*. *Scand J Infect Dis* 2008; 40:204–207.
 - 37 Mazur E, Niedwiadek J, Wolski A, *et al*. *Chlamydia pneumoniae* infection in abdominal aortic aneurysm (AAA) patients and its clinical impact. *Pol J Pathol* 2004; 55:155–164.
 - 38 Sodeck G, Domanovits H, Khanakah G, *et al*. The role of *Chlamydia pneumoniae* in human aortic disease: a hypothesis revisited. *Eur J Vasc Endovasc Surg* 2004; 28:547–552.
 - 39 Vikatmaa P, Lajunen T, Ikonen TS, *et al*. Chlamydial lipopolysaccharide (cLPS) is present in atherosclerotic and aneurysmal arterial wall: cLPS levels depend on disease manifestation. *J Med Virol* 2008; 80:667–669.
 - 40 Parums DV, Brown DL, Mitchinson MJ. Serum antibodies to oxidized low-density lipoprotein and ceroid in chronic periaortitis. *Arch Pathol Lab Med* 1990; 114:383–387.
 - 41 Oxelius VA. Immunoglobulin constant heavy G subclass chain genes in asthma and allergy. *Immunol Res* 2008; 40:179–191.
 - 42 Jarvis D, Zock JP, Heinrich J, *et al*. Cat and dust mite allergen levels, specific IgG and IgG4, and respiratory symptoms in adults. *J Allergy Clin Immunol* 2007; 119:697–704.
 - 43 Mihai S, Chiriac MT, Herrero-González JE, *et al*. IgG4 autoantibodies induce dermal-epidermal separation. *J Cell Mol Med* 2007; 11:1117–1128.
 - 44 Homme JL, Aubry MC, Edwards WD, *et al*. Surgical pathology of the ascending aorta: a clinicopathologic study of 513 cases. *Am J Surg Pathol* 2006; 30:1159–1168.
 - 45 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.
 - 46 Vaglio A, Salvarani C, Buzio C. Retroperitoneal fibrosis. *Lancet* 2006; 367:241–251.
 - 47 Mitchinson MJ. Aortic disease in idiopathic retroperitoneal and mediastinal fibrosis. *J Clin Pathol* 1972; 25:287–293.
 - 48 Wallinder J, Bergqvist D, Henriksson AE. Proinflammatory and anti-inflammatory cytokine balance in patients with abdominal aortic aneurysm and the impact of aneurysm size. *Vasc Endovascular Surg* 2009; 43:258–261.
- This report analyzed serum cytokines of 78 patients with abdominal aortic aneurysm and 41 controls and revealed a significantly higher level of interleukin-6 in patients with AAA compared with controls.
- 49 Wang Y, Ait-Oufella H, Herbin O, *et al*. TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice. *J Clin Invest* 2010; 120:422–432.
 - 50 Zen Y, Fujii T, Harada K, *et al*. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007; 45:1538–1546.
 - 51 Miyoshi H, Uchida K, Taniguchi T, *et al*. Circulating naïve and CD4+CD25high regulatory T cells in patients with autoimmune pancreatitis. *Pancreas* 2008; 36:133–140.