Immunoglobulin G4-related Aortitis

A Clinical Pathology Conference Held by the Division of Rheumatology at the Hospital for Special Surgery

Ozan Unlu, MD · Elizabeth Schulman, MD · Steven D. Wolff, MD, PhD · Navneet Narula, MD · John H. Stone, MD, PhD · Anne Bass, MD · Doruk Erkan, MD, MPH

Received: 12 October 2016/Accepted: 16 May 2017/Published online: 23 June 2017
© Hospital for Special Surgery 2017

Keywords Immunoglobulin G4-related disease · IgG4 · Aortitis · Aortic aneurysm

Electronic supplementary material The online version of this article (doi:10.1007/s11420-017-9565-5) contains supplementary material, which is available to authorized users.

O. Unlu, MD (✉) · E. Schulman, MD · A. Bass, MD ·
D. Erkan, MD, MPH
Division of Rheumatology, Hospital for Special Surgery,
535 East 70th Street,
New York, NY 10021, USA
e-mail: ozanunlumd@gmail.com

O. Unlu, MD · E. Schulman, MD · A. Bass, MD ·
D. Erkan, MD, MPH
Division of Rheumatology, Weill Cornell Medicine,
New York, NY, USA

S. D. Wolff, MD, PhD
Carnegie Hill Radiology,
New York, NY, USA

N. Narula, MD
Clinical Pathology and Laboratory Medicine
New York Presbyterian Hospital,
New York, NY, USA

N. Narula, MD
Clinical Pathology and Laboratory Medicine
Weill Cornell Medicine,
New York, NY, USA

J. H. Stone, MD, PhD
Division of Rheumatology, Allergy & Immunology,
Massachusetts General Hospital, Harvard Medical School,
Boston, MA, USA

Clinical Presentation

A 62-year-old woman presented with progressive exertional substernal chest pain for 1 year. A cardiac computerized tomography angiography (CTA) was performed, demonstrating focal high-grade stenosis and possible occlusion of the middle portion of the left anterior descending (LAD) artery, as well as a stenosis with multifocal calcification/plaque in the proximal and middle right coronary artery (RCA). An ascending aortic aneurysm with intramural hematoma measuring 4.1×3.7 cm was also detected. The patient had a coronary artery calcium score (CAC) of 429. The CAC score predicts cardiovascular outcomes independent of traditional cardiovascular risk profile [3, 20] and the patient's calcium score corresponded to 97th percentile showing a high risk of coronary atherosclerotic plaque presence [3]. She subsequently underwent a cardiac catheterization, which confirmed three-vessel coronary disease (LAD, RCA, and diagonal 2). One week later, she underwent a three-vessel coronary bypass graft with repair of the ascending aortic aneurysm. After the operation, the rheumatology service was consulted about the appearance of the patient's aorta, which was thickened and covered with a whitish, fibrinous, and friable material. No hematoma was demonstrated on gross pathology, and the overall scenario raised a concern for aortitis (Fig. 1, arrow).

The patient's past medical history included diet-controlled hyperlipidemia, hypothyroidism, and Lyme disease, which had been treated 24 years earlier without any visceral or articular complications. She was married, had two healthy grown children, and was physically active. She did not have a history of tobacco use, illicit drug use, or sexually transmitted diseases. Her family history was significant for coronary artery disease in her father—diagnosed in his 70s—but no other autoimmune or connective tissue diseases. She had a penicillin allergy. Her medications at presentation included levothyroxine 75 mcg once daily and a multivitamin.

Fig. 1. Intraoperative image of the aorta. Arrow marks the thickened aortic wall which is covered with a whitish, fibrinous, and friable material.

Review of systems showed no abnormalities with the exception of the chest pain. She denied fever, chills, fatigue, night sweats, weight loss, change in appetite, headache, temporal or scalp tenderness, visual symptoms, jaw claudication, joint pain or swelling, muscle pain, abdominal pain, urinary complaints, rash, weakness, and numbness or tingling in her extremities.

On physical examination, she was in no acute distress following her thoracotomy and was afebrile and normotensive. Her heart rate, respiratory rate, and oxygen saturation were within normal limits. She had no temporal artery tenderness and no palpable cervical or supraclavicular lymphadenopathy. Her sternotomy scar was clean, dry, and intact. Her heart rhythm was regular with no murmurs, and she had no bruits. Her lungs were clear. Her abdomen was soft and nontender. She had no lower extremity edema. She had an unremarkable musculoskeletal examination and no rashes.

Extensive laboratory work-up was performed (Table 1). Her complete blood count, comprehensive metabolic panel, and coagulation panel were all within normal limits. An infectious and inflammatory work-up showed no evidence of hepatitis, human immunodeficiency virus infection, syphilis, Lyme disease, or latent tuberculosis. Urinalysis was normal. The inflammatory markers, serologies, and IgG 4 level were normal.

Radiological Discussion

For CTA, a test bolus of 15 ml of omnipaque was used to determine the timing of contrast in the ascending aorta. The scan parameters were 80×0.5 mm collimation, rotation time of 0.35 s, and a tube current of 150 mA. The total radiation dose during the procedure was 3.6 mSv. In the pre-contrast CTA image, the axial scan of the heart showed a hyperdense area in the wall of the aorta (Fig. 2a). Contrast images showed calcified plaques with severe narrowing of mLAD (mid left anterior descending) artery, proximal D2 (diagonal 2) (Fig. 2c) but widely patent left circumflex and obtuse marginal arteries (Fig. 2d). In addition, mRCA (mid right coronary artery) also showed calcified plaques and some areas of severe stenosis

Table 1 Laboratory values at presentation

	Result	Normal values
WBC	6.4	3.8–10.8 Thous/mcl
Hemoglobin	13.6	13.2–17.1 g/dl
Platelets	228	140–400 Thous/mcl
Hematocrit	40.5	38.5–50.0%
Calcium	9.8	8.6–10.3 mg/dl
Magnesium	1.8	1.5–2.5 mg/dl
Phosphorus	4	2.5–5.0 mg/dl
Sodium	141	135–145 mmol/l
Potassium	4.1	3.5–5.0 mmol/l
Chloride	112	97–107 mmol/l
CO ₂	25	20–30 mmol/l
BUN	8	5–25 mg/dl
Creatinine	0.6	0.4–1.2 mg/dl
Glucose	114	70–105 mg/dl
INR	1	0.94–1.09
PT	10.6	9.7–11.2 s
PTT	31.5	22.3–33.0 s
ESR	10	<20 mm/h
CRP	1.05	<5.0 mg/l
ANA	Neg	Neg
Anti dsDNA	Neg	Neg
RF	Neg	Neg
ANCA	Neg	Neg
Serum IgG4	35	<86 mm/dl

Abbreviations: ANA antinuclear antibody, ANCA antineutrophil cytoplasmic antibody, Anti dsDNA anti double-stranded DNA antibody, BUN blood urea nitrogen, CO₂ carbon dioxide, CRP C-reactive protein, dL deciliter, ESR erythrocyte sedimentation rate, g gram, h hour, Ig immunoglobulin, INR international normalized ratio, l liter, mcl microliter, mg milligram, mm millimeter, mmol milimol, Neg negative, PT prothrombin time, PTT partial thromboplastin time, RF rheumatoid factor, Thous thousand, sec seconds, WBC white blood cell

(Fig. 2e). There was also a prominent thickening of the aortic wall (Fig. 2b). The high signal in the aortic wall was also present in the pre-contrast image and was therefore unlikely due to contrast enhancement artifact.

The differential diagnosis of the thickened thoracic aorta found on imaging included the following: (a) intramural hematoma, (b) aortic dissection with a thrombosed false lumen, (c) aortitis, and (d) periaortic lymphoma. The circumferential thickening of the aortic wall argued against aortic dissection, because dissection typically leads to medial displacement of the intima.

Pathological Discussion

The operative specimen from the ascending aortic aneurysm had a thickness varying between 0.2 and 0.8 cm. Under microscopy, there was an inflammatory infiltrate, which was mainly in the outer portion of the media and adventitia. Nodules of inflammatory cells with pale-looking areas, i.e., germinal centers, were also seen (Fig. 2a). At higher magnification, besides lymphoid aggregates, there were sheets of plasma cells with eccentric nuclei and perinuclear halos (Fig. 2b). Obliterative phlebitis in the adventitia of the aorta was seen with marked luminal narrowing of veins (Fig. 3c). Storiform fibrosis, consisting of elongated spindle cells arranged in a cartwheel pattern, was also observed (Fig. 2d).

Fig. 2. Imaging studies. **a** Arrow marks the hyperdense area in the wall of the aorta. **b** Arrows point to prominent thickening of the aortic wall. **c** Arrows mark narrowed mLAD and proximal D2. **d** Left circumflex and obtuse marginal arteries were found to be patent. **e** mRCA is severely narrowed (arrow).

Immunostains for IgG (Fig. 2f) and IgG4 showed that 20–50% of IgG + plasma cells were IgG4 positive (Fig. 2f). Several high-power fields contained greater than 50 IgG4 cells (Fig. 2g). The majority of the lymphocytes were CD3-positive T cells (Fig. 2h) and there were aggregates of CD20-positive B cells (Fig. 2i). There were no giant cells, necrosis, or neutrophils. Acid fast and Warthin-Starry stains were negative for organisms. Taken together, the histopathology and immunostaining findings strongly suggested IgG4-related aortitis.

Clinical Discussion

The diagnosis of IgG4-related aortitis is challenging and often requires the combination of clinical, radiological, and

histopathologic evidence. In our patient, the pathologic findings allowed for an accurate and definitive diagnosis and were especially important because the serum IgG4 level was normal.

The differential diagnosis of aortic aneurysms includes infectious, inflammatory, and traditional etiologies. Inflammatory aortitis can be divided into three categories: primary vasculitides (giant cell arthritis, Takayasu's), connective tissue diseases (rheumatoid arthritis, systemic lupus erythematosus), and isolated aortitis, which can be subclassified as granulomatous or lymphoplasmacytic. IgG4-related disease is an example of lymphoplasmacytic isolated aortitis that appears to account for approximately 10% of all aortic aneurysm cases [17].

Rojo-Leyva et al. [16] found that among 383 thoracic aortic aneurysm (TAA) cases, approximately 12% had

Fig. 3. Microscopy from the ascending aorta. **a** Nodules of inflammatory cells are present with pale-looking areas (arrows). **b** Sheets of plasma cells are seen with eccentric nuclei and perinuclear halos. **c** Arrow points to obliterative phlebitis. **d** Storiform fibrosis which is a prominent feature of IgG4-related disease is seen. **e** Tissue was stained for IgG-positive cells (arrows). **f** Tissue was stained for IgG4-positive cells (arrows). 20–50% of IgG + plasma cells are IgG4 positive. **g** Several high-power fields contained greater than 50 IgG4 cells. **h** The majority of the lymphocytes are CD3-positive T cells (arrows). **i** Aggregates of CD20-positive B cells are present (arrow).

idiopathic inflammation. Of these, there were no patients with symptomatic systemic disease; however, two had retroperitoneal fibrosis and one had an orbital pseudotumor, both of which can be manifestations of IgG4-related disease (IgG4-RD). Rojo-Levy et al. also reported that many of the aortic specimens in their series had lymphoplasmacytic as opposed to granulomatous infiltrates, but these were not characterized further with immunostaining for IgG and IgG4.

A study from Japan in 2008 [4] found that 40% of the patients with abdominal aortic aneurysms (AAA) had IgG4-related disease. In another study [17], 12% of the patients with inflammatory aortitis had IgG4-related disease. A broader study of large vessel vasculitis from that same institution demonstrated that, out of 130 patients with biopsy-proven IgG4-related disease, 33 patients had large vessel disease [14]. The large vessel involvement included the thoracic aorta, abdominal aorta, left pulmonary artery, carotid and other primary aortic branches, coronary arteries, and superior vena cava.

Syphilitic aortitis is typically high on the differential diagnoses of thoracic aortitis lesions and, similar to IgG4-

RD, the histopathology of syphilitic lesions generally consists of lymphoplasmacytic findings. A clinicopathologic conference presented in the New England Journal of Medicine from 1962 [1], in fact reported a case of a 73-year-old woman who was admitted to the hospital with shortness of breath and died within 24 h of a ruptured aortic aneurysm. Despite negative serologies for syphilis and the absence of other confirmatory proof of this suspicion, the patient was diagnosed as having syphilitic aortitis. In fact, this case may represent the first case of IgG4-related aortitis.

IgG4-RD is an immune-mediated condition comprised of a collection of disorders involving several organ systems, which were previously thought to be unrelated [18]. IgG4-RD is characterized by histologic findings of dense lymphoplasmacytic inflammation, storiform fibrosis, obliterative phlebitis, and eosinophilia. The microscopic appearance of this disease is strikingly similar across all affected organs [18]. Inflammatory pseudotumor is another complication of IgG4-RD [18]. Diagnosis is based upon tissue biopsy demonstrating these characteristic findings and careful clinicopathologic correlation. A diffuse plasma-cell infiltrate with more than 30 IgG4-positive cells per high-power

field and a ratio of IgG4 to IgG that is higher than 50% provides further evidence of IgG4-RD in the presence of other characteristic findings. However, the diagnosis cannot be made or ruled out entirely upon the number of IgG4-positive plasma cells [18].

Although many of the initial observations regarding this condition were made in patients with autoimmune pancreatitis (AIP) and patients with lacrimal and salivary gland involvement, IgG4-related disease has been reported in almost every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, testes, and skin [11, 18]. IgG4-RD should be suspected especially in patients with pancreatitis of unknown origin, sclerosing cholangitis, bilateral salivary and/or lacrimal gland enlargement, retroperitoneal fibrosis, and orbital pseudotumor or proptosis [18].

The epidemiology of IgG4-RD remains poorly understood. However, previous studies commonly reported that unlike other autoimmune diseases that mimic IgG4-related disease and show female predominance, IgG4-RD is most commonly seen in middle-aged and older men [2, 15]. A study on Japanese patients with autoimmune pancreatitis reported a male to female ratio of approximately 2.8:1 [12]. Among patients with IgG4-related sialadenitis and IgG4-related ophthalmic disease, however, males and females appear to be affected equally [9, 21].

There is an overall male predominance in the prevalence of aortic aneurysms. About 40% of inflammatory AAA [4] are IgG4 related and inflammatory AAA represents up to 15% of AAA. Therefore, it might be speculated that up to 6% of all AAA represents IgG4-related disease. Considering that AAA is present in 4% of men aged 65–74, IgG4-related aortic disease may be present in 1/1000 older men.

No optimal treatment regimen for IgG4-RD has been established. However, a 2015 consensus statement by international experts drew the following conclusions [8]: (a) All patients with symptomatic, active IgG4-RD require treatment, some urgently; (b) A subset of patients with asymptomatic IgG4-RD also requires treatment; (c) Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD, unless contraindications to such treatment are present; (d) Following a successful course of induction therapy, certain patients benefit from maintenance therapy; and (e) Retreatment with glucocorticoids is indicated in patients who relapse off of treatment following successful remission induction and following relapse. The introduction of a steroid-sparing agent for continuation in the remission maintenance period should be considered. Although there are no randomized control trials, B cell depletion with rituximab was reported to be efficient in some case series [5–7].

Surgery still plays an important role in the management of inflammatory large vessel aneurysms since medical treatment is not expected to reduce vessel dilation [10]. A few studies showed endovascular repairs to be more effective than open repair in inflammatory AAA [13, 19]. Surgical repair of inflammatory thoracic aortic aneurysm, on the other hand, has been poorly studied [13]. An unresolved question is whether, in cases of localized inflammatory

aortitis with no active inflammation at the surgical anastomosis site, surgery might be considered the definitive treatment without need for steroid therapy. Further studies to address this question are clearly needed.

Hospital Course

The patient was immediately started on methylprednisolone 16 mg intravenously (IV) every 8 h postoperatively due to a concern regarding remaining active inflammatory tissue at the surgical anastomosis site. She was discharged on methylprednisolone 24 mg by mouth every 12 h. A PET/CT done 1 week later showed mildly increased activity in the ascending aorta which was likely related to recent surgery, but no other areas of uptake.

The patient's glucocorticoids were tapered over the next several months. Two months after she was discharged, while she was on methylprednisolone 12 mg orally daily, the patient developed a severe right pre-mandibular abscess that improved on intravenous broad-spectrum antibiotics. A repeat PET/CT 1 month after this showed no further active vasculitis. Methylprednisolone dosage was ultimately tapered to 4 mg orally daily.

Compliance with Ethical Standards

Conflict of Interest: Ozan Unlu, MD; Elizabeth Schulman, MD; Steven D. Wolff, MD, PhD; Navneet Narula, MD; John H. Stone, MD, PhD; Anne Bass, MD; and Doruk Erkan, MD, MPH have declared that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed Consent: Informed consent was waived from all patients for being included in the study.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

References

1. Dalton JC, Case 22-1962. *New England Journal of Medicine*, 1962. 266(14): p. 719–725.
2. Frulloni L, et al., Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med*, 2009. 361(22): p. 2135–42.
3. Hoff JA, et al., Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. *Am J Cardiol*, 2001. 87(12): p. 1335–9.
4. Kasashima S, et al., Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis. *Am J Surg Pathol*, 2008. 32(2): p. 197–204.
5. Khosroshahi A, et al., Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. *Arthritis Rheum*, 2010. 62(6): p. 1755–62.

6. Khosroshahi A, et al., Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)*, 2012. 91(1): p. 57–66.
7. Khosroshahi A and JH Stone, Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol*, 2011. 23(1): p. 67–71.
8. Khosroshahi A, et al., International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol*, 2015. 67(7): p. 1688–99.
9. Masaki Y, 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(8): p. 1310–5.
10. Monach PA, IgG4-related disease: 2013 update. *Curr Treat Options Cardiovasc Med*, 2013. 15(2): p. 214–23.
11. Najari BB, et al., Clinical, radiographic, and pathologic description of IgG4-related perivascular fibrosis: a previously undescribed etiology of chronic orchialgia. *Urology*, 2014. 84(4): p. 748–50.
12. Nishimori I, A Tamakoshi, M Otsuki, Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol*, 2007. 42 Suppl 18: p. 6–8.
13. Paravastu SC, et al., A systematic review of open versus endovascular repair of inflammatory abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*, 2009. 38(3): p. 291–7.
14. Perugino CA, et al., Large vessel involvement by IgG4-related disease. *Medicine (Baltimore)*, 2016. 95(28): p. e3344.
15. Raina A, et al., Evaluation and management of autoimmune pancreatitis: experience at a large US center. *Am J Gastroenterol*, 2009. 104(9): p. 2295–306.
16. Rojo-Leyva F, et al., Study of 52 patients with idiopathic aortitis from a cohort of 1,204 surgical cases. *Arthritis Rheum*, 2000. 43(4): p. 901–7.
17. Stone JH, et al., IgG4-related systemic disease accounts for a significant proportion of thoracic lymphoplasmacytic aortitis cases. *Arthritis Care Res (Hoboken)*, 2010. 62(3): p. 316–22.
18. Stone JH, Y Zen, V Deshpande, IgG4-related disease. *N Engl J Med*, 2012. 366(6): p. 539–51.
19. Stone WM, et al., Comparison of open and endovascular repair of inflammatory aortic aneurysms. *J Vasc Surg*, 2012. 56(4): p. 951–5; discussion 955–6.
20. Waheed S, et al., Collective impact of conventional cardiovascular risk factors and coronary calcium score on clinical outcomes with or without statin therapy: the St Francis Heart Study. *Atherosclerosis*, 2016. 255: p. 193–199.
21. Zen Y Y Nakanuma, IgG4-related disease: a cross-sectional study of 114 cases. *Am J Surg Pathol*, 2010. 34(12): p. 1812–9.