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Case report

Multifocal IgG4-related aortitis and periaortitis simulating aortic dissection ☆☆☆

Amrita Valluri, BS^a, Juliana Sitta, MD^{b,*}, Candace M. Howard, MD, PhD^b^a Joan C. Edwards School of Medicine, Marshall University, 1 John Marshall Dr, Huntington, WV, 25755, USA^b Department of Radiology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS, 39216 USA

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ABSTRACT

Immunoglobulin G4-related aortitis (IgG4-RA) is histologically characterized by the infiltration of IgG4 positive plasma cells and fibrosis in systemic organs and the elevation of serum IgG4 levels. The cardiovascular system is commonly involved with various possible presentations such as aortitis, arteritis, periaortitis, periarteritis, and inflammatory aneurysm. We present a case of a 48-year-old male without known previous medical history, admitted for further workup of long-standing chest pain and shortness of breath with suspected aortic dissection on initial assessment. Investigation with computed tomography angiography (CTA) and magnetic resonance angiography (MRA) indicated severe thoracic and abdominal aortoarteritis associated with an ascending thoracic aortic aneurysm, which was confirmed to be IgG4-RA on histopathologic analysis. Thoracic and abdominal IgG4-RA clinical and radiological presentation may simulate other causes of acute aortic syndrome such as aortic dissection, atherosclerotic aneurysm and inflammatory conditions. Accurate recognition of IgG4-RA diagnostic imaging features are essential for early diagnosis and treatment surveillance.

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Introduction

IgG4-related disease (IgG4-RD) is an immune-mediated condition characterized by a relapsing-remitting course, multiorgan involvement, and fibroinflammatory changes [1]. The clin-

ical progression of IgG4-RD is typically slow with the median age of onset at 58.3 ± 11.1 years [2]. Common risk factors for the development of IgG4-RD are male gender, tobacco exposure, allergic diseases, and a history of malignancy [1,3,4,5]. Patients usually present with subacute symptoms related to diffuse enlargement or development of a mass in the affected

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* Corresponding author. J.Sitta

E-mail addresses: valluri3@marshall.edu (A. Valluri), jsitta@umc.edu (J. Sitta), chowardclaudio@umc.edu (C.M. Howard).

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organ. Signs of inflammation and infection are not typically associated with the disease course even as it progresses [1]. Rather, symptoms may manifest due to compression from fibrotic masses [1].

There is anatomically widespread documentation of IgG4-RD in the human body, including the pancreas, salivary glands, orbits, retroperitoneum, and the vasculature. The most commonly affected vessels are the abdominal aorta, iliac artery, and thoracic aorta [5]. With regards to IgG4-related aortitis, involvement of the thoracic aorta is far less common than with the abdominal aorta [1,2]. Histopathology, laboratory tests, and radiological imaging are valuable in identifying features that can differentiate IgG4-RA from other etiologies [6]. We describe the case of a 48-year-old male admitted for initial suspicion of aortic dissection and later diagnosed by radiology findings and histopathologic analysis to be IgG4-related aortitis complicated by an ascending aortic aneurysm.

Case report

A 47-year-old male was admitted with left-sided chest pain and shortness of breath. The patient described a focal, sharp, intermittent pain localized under the left nipple, which worsened with movement and deep inspiration. The chest pain was first noted 1 month prior to admission, while shortness of breath started two months before. The patient denied any prior known medical history and noted that his functional capacity was optimal before the symptoms. His family history included a massive fatal heart attack in his father at the age of 57 and cancer in his mother.

Initial laboratory workup indicated negative troponin, positive D-dimer, and positive inflammatory markers. The patient underwent a chest CT with pulmonary embolism protocol, which revealed diffuse soft tissue thickening adjacent to the ascending thoracic aorta, aortic arch, and proximal descending aorta, as well as involvement of the great vessels with significant narrowing of the left common carotid artery. These findings were first thought to be related to aortic dissection with intramural hematoma. Additionally, CT indicated an aneurysm of the ascending aorta, measuring up to 6.1 cm in the greatest dimension (Fig. 1).

Given the atypical presentation, the patient underwent MRA for further evaluation, which excluded intramural hematoma and indicated severe aortoarteritis and periarteritis associated with an ascending thoracic aortic aneurysm (Fig. 2). Given the main large vessel involvement identified by both MRA and CTA, Takayasu's arteritis was suggested as a primary diagnosis at this time.

The cardiothoracic team recommended replacement of the aortic arch and hemi-arch. Intraoperative findings included a chronic appearing thickened and dilated ascending aorta and proximal transverse arch, absent right coronary artery, and a normal aortic valve. Histopathologic analysis of the aortic surgical specimen revealed marked aortitis with lymphoplasmacytic infiltrate. Sections of the aortic wall showed fibrous artery with dense lymphoplasmacytic infiltrate arranged in a

patchy fashion, many associated with the vasa vasorum and other areas with a perineural pattern (Fig. 3).

Unfortunately, the surgical specimen was not tested specifically for IgG4 disease at the time of analysis; however, the histopathologic findings were sufficient to indicate IgG4-RA diagnosis. Once the diagnosis was made, treatment with high dose glucocorticoids was recommended by rheumatology. The postoperative course was uneventful, and the patient was successfully discharged home four days after the procedure.

Although there were clear concerns for IgG4-related disease, the patient was lost to follow up for the following two years. He later came back to the emergency department complaining of a new stabbing chest pain. Repeated CTA of the chest and abdomen showed the thoracic aortic findings remained essentially unchanged, but new findings were described in the abdomen. CTA of the abdomen revealed mild periaortic soft tissue thickening of the infrarenal abdominal aorta, below the level of the inferior mesenteric artery origin, with extension to the common iliac arteries bilaterally, reflecting additional areas of inflammatory involvement (Fig. 4). The patient was successfully managed with prednisone and maintained regular follow up with rheumatology.

Discussion

Criteria for the diagnosis of IgG4-related disease include fibrotic masses in multiple organ systems, increased serum IgG4 concentrations, and lymphoplasmacytic infiltration consisting predominantly of IgG4-positive plasma cells.⁷ The role of IgG4 itself in its disease processes is not clear [8]. The antibody typically plays a minimal part in inflammation due to its low affinity to Fc receptors and complement molecules [8,9]. Despite this, IgG4 levels directly correlate with disease severity in the majority of affected patients [8,9]. Th2 mediated immunity and the production of IgG4 in response to stimulation from IL-4, IL-10, and Treg cells is thought to be the driving force behind IgG4-RD [8,10,11]. High serum levels of IgG4 have been indicated in hypersensitivity conditions such as atopic dermatitis and asthma [12]. Increased IgG4 serum levels and auto-antibodies have also been indicated in certain autoimmune disorders, such as pemphigus vulgaris and membranous nephropathy [12]. Our case draws attention to IgG4 related aortitis in the absence of any other health conditions commonly associated with IgG4-RD. Analysis of the aortic surgical specimen obtained in our patient revealed aortitis with lymphoplasmacytic infiltrate. Typical findings in IgG4-RA are 50% of the infiltrate consisting of IgG4 producing plasma cells and a minimum of 50 of these cells visualized at high power magnification exam of three fields [13]. Although histopathologic findings led to the final diagnosis, the samples obtained from our patient were unfortunately not tested specifically for IgG4 plasma cell concentrations at the time of his initial presentation. Another defining feature unique to IgG4-RD is storiform fibrosis [11,14]. Storiform fibrosis consists of collagen fibers in a spiral pattern interspersed among lymphoplasmacytic infiltrate [7]. It commonly involves the adventitia, media, and medial elastic fibers of the aorta in IgG4-RA [15]. This characteristic pattern of fibrosis was present in the aortic wall

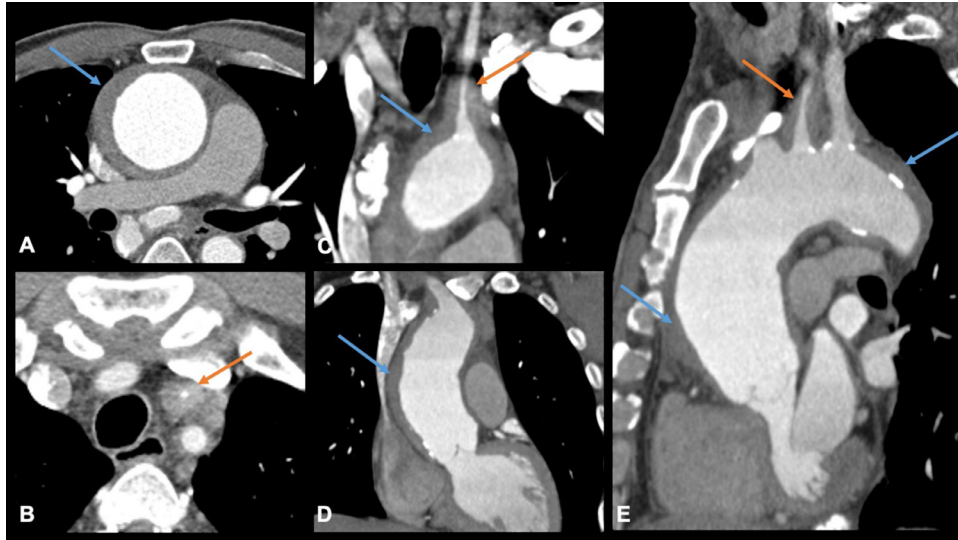


Fig. 1 – Aortitis and aortic aneurysm on initial chest CT. CT angiography of the chest axials (A,B) coronals (C,D), and sagittal (E). There is diffuse wall thickening (blue arrows) of the ascending thoracic aorta, aortic arch, and proximal descending aorta, as well as involvement of the great vessels with significant narrowing of the left common carotid artery (orange arrows). There is an aneurysm of the ascending thoracic aorta measuring up to 6.1 cm that does not spare the sinotubular junction

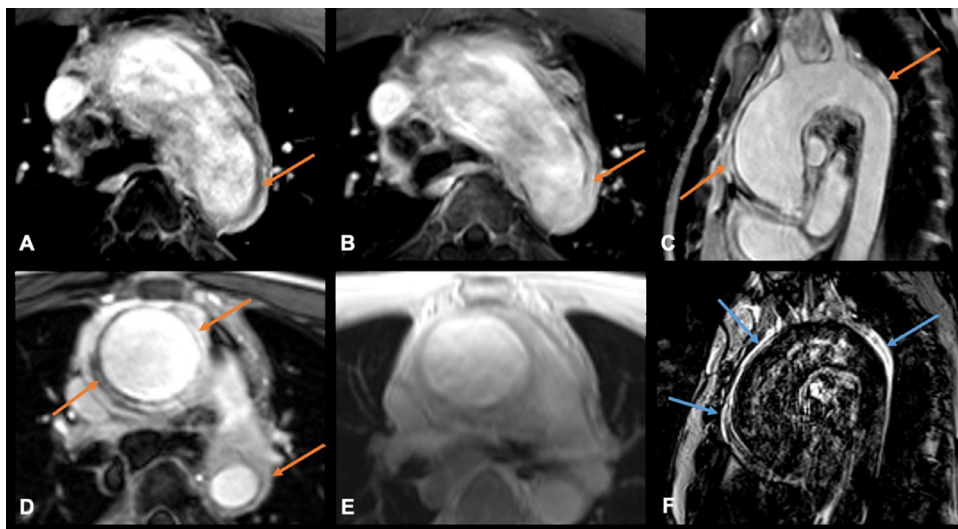


Fig. 2 – Aortitis Periaortitis and aortic aneurysm on MRA of the chest. MR angiography T1 axials pre-contrast (A) and post-contrast arterial (B) show faint rim enhancement of the adventitia of the aorta in the arterial phase that was T1 hypo-intense pre-contrast (orange arrows). Delayed postcontrast sagittal (C) and axial (D) images demonstrate enhancement involving the circumferential ascending aorta, arch, and proximal descending aorta with extension into the aortopulmonary window and adjacent mediastinum. T2* axial (E) shows no evidence of intramural blood products. Sagittal STIR (F) demonstrates a significant amount of edema (blue arrows) within the ascending arch and proximal descending aorta along the inner and outer margins of the thickened aortic wall.

specimen obtained from our patient. Additionally, our patient also had extensive fibrotic involvement of the vasa vasorum within the adventitia.

As the clinical symptoms of IgG4-related aortitis are typically nonspecific, a tissue biopsy may not be obtained early in a patient's presentation. Imaging plays a crucial role in diagnosis due to its non-invasiveness and routine use in dis-

ease workup. Typical features of IgG4-related aortitis/arteritis include vessel wall thickening greater than 2 mm [16,17]. Homogenous enhancement of the aortic/arterial wall during the delayed phase of contrast-enhanced CT is characteristic [6]. The arterial and delayed phases of dynamic contrast-enhanced CTA or MRA show soft tissue density and thickening of affected vasculature [2]. This characteristic IgG4-RA finding

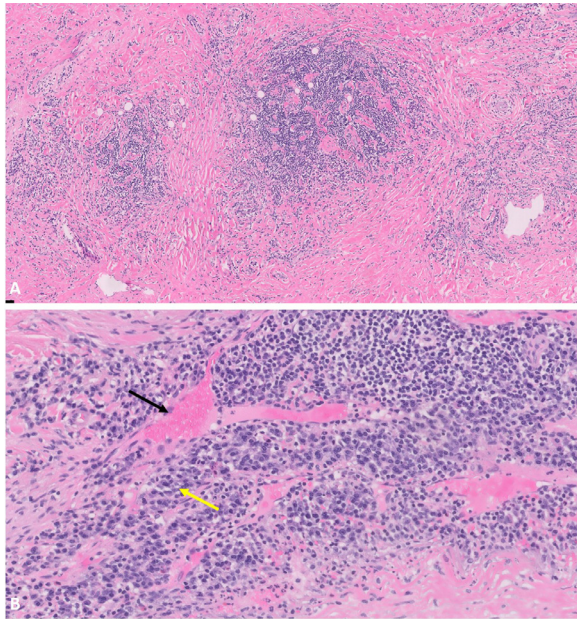


Fig. 3 – Lymphoplasmocytic infiltrate. Hematoxylin-eosin stain, original magnification, 10x (A) and 20x (B) of the ascending aortic wall. Photomicrograph of the ascending aorta showing lymphoplasmocytic infiltrate (yellow arrow) around the vessels (black arrow).

is associated with sclerosing inflammation caused by lymphoplasmacytic infiltration mainly involving the adventitia [18]. The soft-tissue masses can be associated with severe luminal stenosis of affected small to middle-sized vessels such as the iliac arteries, carotid arteries, or coronary arteries [19]. Stenosis of the aorta itself, however, is not seen in IgG4-RA [19–22]. Rather, aneurysmal luminal dilation and dissection are potential findings in addition to diffuse periaortic soft tissue thickening [20–22]. Radiologists must be aware of these findings typical of IgG4-RA as aortitis and inflammatory aortic aneurysms have the potential to escalate to aortic dissection [19,2]. Furthermore, the involvement of the pericardium and surrounding cardio-vasculature significantly affects disease prognosis [18]. Thus, careful consideration of IgG4-RD must be taken in the fitting scenarios.

Distinguishing IgG4-RA as the etiology behind the cardio-vascular changes was initially a challenge in our patient's case. Initial findings were thought to be an aortic dissection accompanied by intramural hematoma, as only single phase imaging was obtained and aligned with the clinical suspicion. MRA played a critical role for identifying aortoarteritis with the presence of an ascending aortic aneurysm in this patient. With regards to complications such as aneurysm formation, it has been recommended that multimodality imaging be utilized such as in our patient to differentiate IgG4 related disease from other potential causes of large vessel vasculitis [18–20]. These causes could include Takayasu

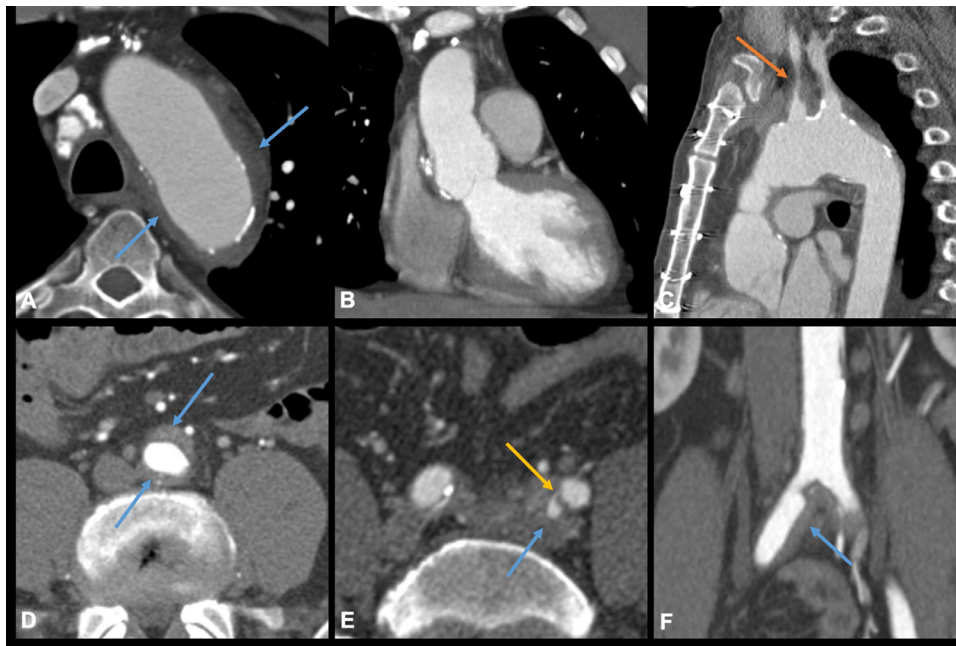


Fig. 4 – Thoracic aorta follow-up and abdominal involvement. CTA of the chest, axial (A), coronal (B), and sagittal (C) views show postsurgical changes of ascending aorta replacement with mild perigraft soft tissue changes. The aortic arch is ecstatic, and there is periaortic soft tissue thickening along the aortic arch measuring up to 8 to 9 mm in thickness. The proximal left common carotid artery demonstrates increased periaortic soft tissue thickening with a similar degree of severe proximal stenosis. CTA of the abdomen axials (D,E) and coronal (F) show increased periaortic soft tissue thickening of the distal abdominal aorta, measuring up to 6 mm, extending along the common iliac arteries. Periaortic soft tissue thickening extends along the bilateral common iliac arteries causing mild luminal irregularities with no significant stenosis. Soft tissue thickening extends along the proximal left internal iliac artery causing focal proximal severe stenosis.

arteritis, giant cell disease, or antineutrophil cytoplasmic antibody-associated vasculitis among others [18,22]. Due to the large vessel involvement, Takayasu's arteritis was the primary working diagnosis for our patient. The aforementioned intraoperative findings and histopathology helped rule out Takayasu's arteritis in favor of IgG4-RA in our case, but other defining differences can be used to distinguish the two etiologies. Takayasu arteritis typically affects the thoracic aorta along with the primary aortic branches [13,23]. Young females consist of the majority of affected individuals [13,23]. While our patient did have thoracic aorta involvement, repeat imaging two years later indicated the involvement of the abdominal aorta as well. Furthermore, adult males such as our patient are far more at risk for developing IgG4-RA than Takayasu arteritis [18,24]. When the patient returned two years later after recurrent onset of symptoms, additional findings on imaging included stenosis of the proximal left common carotid artery and the proximal left internal iliac artery. The aorta itself was consistently visualized as widely patent on imaging from the first patient presentation. This is in contrast to Takayasu arteritis where luminal stenosis of the aorta is present in the majority of cases [19,24].

IgG4-related diseases are known to have a positive prognosis in response to appropriate treatment. Glucocorticoid therapy has been established as the first-line therapy for IgG4-related disease, and by extension, IgG4-related aortitis [2,19]. Research has found perivascular masses shrink by over 30% in patients receiving glucocorticoid therapy [2]. According to current guidelines, inflammatory aortic aneurysms should be treated with glucocorticoid therapy immediately due to the risk of enlargement and dissection [2]. However, it should be noted that luminal dilation may progress or occur even while the patient is receiving medical treatment due to steroid-induced aortic wall remodeling [2,20–22]. Therefore, appropriate follow up should ideally be maintained even while the patient is receiving therapy. Surgery, immunomodulators, and immunosuppressants are other potential options that could be utilized in treatment [19]. As a relapse-remitting course is quite common in IgG4-RD, it is not uncommon for progression of disease despite corticosteroid treatment as in our patient [18]. When our patient returned two years later with the onset of chest pain, repeated CTA once again suggested IgG4-RA. The patient was successfully managed with prednisone treatment and rheumatology follow up.

Conclusions

IgG4-RD is a recently recognized immune condition that may distinctly affect multiple organs. Typical findings of IgG4-related arteritis include vessel wall thickening, peri-arterial involvement and aneurysmal formation. This immune-mediated entity is known to simulate other acute aortic syndromes on clinical and radiologic presentation, including aortic dissection, atherosclerotic aneurysm and other inflammatory conditions. Thoracic and abdominal vessel involvement in IgG4-RA have been scarcely described in the literature; however, its recognition is of utmost importance to guide appropriate treatment and to avoid potentially life-threatening

complications such as aortic dissection and aneurysm formation.

Patient Consent

Written informed consent for the case to be published was obtained from the patient.

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