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A Case of IgG4-Related Aortitis and Pericarditis: Diagnostic Challenges and Natural History

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 83
Final Diagnosis: IgG4-related aortitis and pericarditis
Symptoms: L hip pain
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual clinical course

Background: IgG4-related disease (IgG4-RD) is a systemic inflammatory condition with a myriad of presentations related to the pattern of organ involvement. Diagnostic workup for IgG4-RD requires a high index of suspicion, and further workup often includes the results of serological testing for elevated levels of IgG4. Correlation of presentation, past medical history, and histopathologic analysis are required to make a diagnosis.

Case Report: In this case, incidental discovery of non-infectious aortitis and pulmonary mass lesions were the specific signs that led to the consideration of IgG4-RD. It was only after careful consideration of the patient's past medical history and examination of previously stored surgical specimens (pericardial tissue) that a conclusive, retrospective diagnosis of IgG4-related disease was reached.

Conclusions: This case demonstrates that the natural history of IgG4-related disease can be indolent and variable in presentation. Appropriate diagnosis requires consideration of all manifestations of the disease, sometimes with surveillance over several years.

MeSH Keywords: Aortitis • Immunoglobulin G • Pericarditis

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Background

IgG4-related disease (IgG4-RD) is a systemic inflammatory condition with a myriad of presentations related to the pattern of organ involvement. Diagnosis requires correlation of clinical presentation with histologic features described in a 2012 consensus statement by the United States and Canadian Academy of Pathology [1,2]. Confirmation typically requires the presence of 2 major histologic features, such as storiform fibrosis, dense lymphoplasmacytic infiltrate enriched with IgG4+ plasma cells, and obliterative phlebitis [1]. In practice, histopathologic analysis is often preceded by laboratory testing for elevated serum IgG4 in the setting of a classic presentation for IgG4-related disease. There is limited information regarding the natural history of disease, including factors influencing location of primary lesions, patterns of organ involvement, and progression to systemic disease. Limitations of serum IgG4 levels and a lack of specific physical exam findings complicate diagnosis, leading to delays of diagnosis and treatment. These issues underlie the challenges that clinicians face with regard to diagnosis and management of IgG4-RD.

Here, we present a case of asymptomatic IgG4-RD discovered incidentally. We discuss the unique disease course in this patient, the diagnostic challenges, and the implications for our understanding of the natural history and management of IgG4-RD.

Case Report

The patient was an 83-year-old white man with a past medical history of prostate cancer, constrictive pericarditis (2011), pericardial effusion, and coronary artery disease. In August 2016, he presented to the emergency department of an outside hospital with acute left-hip pain. X-rays revealed a new left pulmonary opacity, enlarged aorta, and no evidence of acute fracture. The enlarged aorta raised concern for aorto-iliac dissection, so a CT angiogram was done. This revealed a 2.7-cm ectatic infrarenal aorta with heterogeneous soft-tissue thickening around the aorta (Figure 1). The patient was transferred to our hospital for further evaluation.

Vital signs were completely normal. Physical exam findings included clear lung fields, normal heart tones, symmetrical peripheral pulses, and no abdominal bruits. There were no palpable masses. Range of motion of hips and knees was full with no pain. Neurologic examination was intact. A chest x-ray revealed a wedge-shaped peripheral opacity in the left lower lobe. A complete blood count, blood cultures, procalcitonin, and lactate dehydrogenase were normal. The erythrocyte sedimentation rate, C-reactive protein, Myeloperoxidase antibody, and Proteinase 3 antibody were also unremarkable. His prostate-specific antigen was 0. Initial laboratory markers of acute infectious and

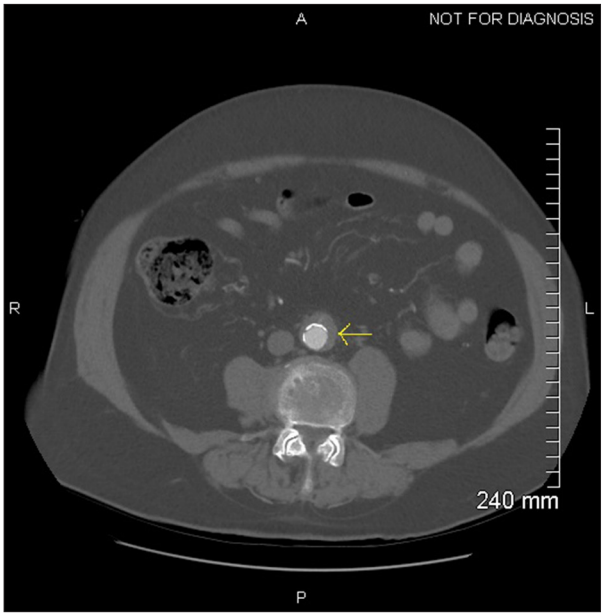

Figure 1. Contrast-enhanced CT demonstrating "heterogeneous, lobulated, indistinctly-defined soft tissue with periaortic stranding" suggestive of aortitis.

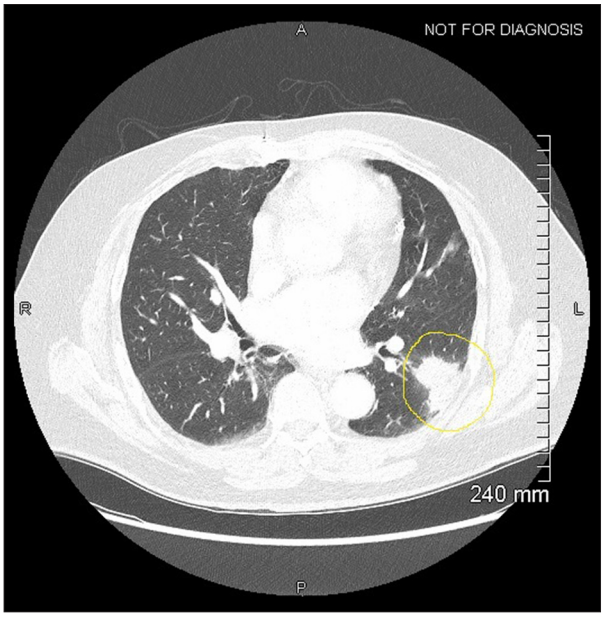

Figure 2. Chest CT demonstrating 4-cm mass-like consolidation in the left lower lobe of the lung.

inflammatory processes were unremarkable, and the patient was scheduled for a chest CT to further characterize the left lower-lobe opacity. The radiologist recommended a magnetic resonance angiogram (MRA) of the abdomen to further evaluate aortic abnormalities.

Chest CT with contrast revealed a peripheral 4-cm mass-like consolidation in the left lower lobe (Figure 2). The MRA revealed

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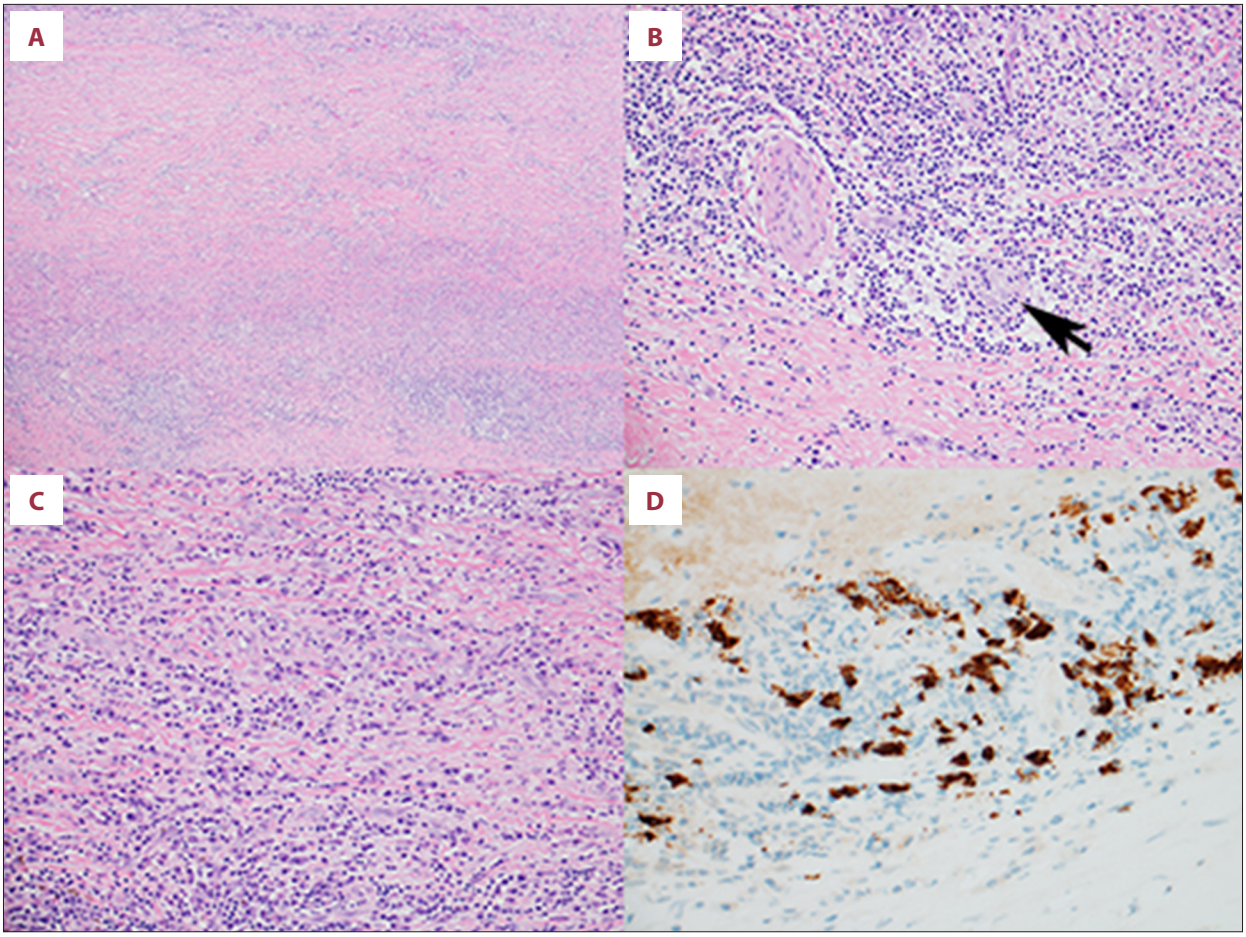

Figure 3. (**A**) The aortic wall was markedly thickened by fibrosis, which focally was storiform. Even at this low-power magnification, a dense inflammatory infiltrate is appreciated (H&E, 40×). (**B**) A small vein (arrow) is infiltrated by lymphocytes and plasma cells, resulting in obliteration of the lumen, characteristic of obliterative phlebitis (H&E, 200×). (**C**) The dense inflammatory infiltrate consists of many plasma cells admixed with small lymphocytes (H&E, 200×). (**D**) An average of 65 IgG4-positive plasma cells/hpf was counted (IgG4 immunostain, 400×). The ratio of IgG4+/IgG+ plasma cells was counted at 45% (not illustrated).

a 2.7-cm ectasia of the infrarenal aorta with nearly circumferential periaortitis and potential periaortic fibrosis. Additional findings included ascending periaortic soft-tissue changes resembling those of the abdominal aorta. Quantitative serum IgG4 was normal. In the absence of aortic symptoms, serum inflammatory markers, or elevated IgG4, biopsy of aortic lesions was not indicated. The patient was scheduled for CT-guided left lung biopsy to evaluate for IgG4 histopathology and exclude malignancy.

Three 20-gauge core samples of the left lower lobe mass were collected. Initial pathology revealed an airway-predominant process characterized by fibrosis and a dense lymphoplasmacytic infiltrate suspicious for IgG4-RD. The slides were sent in consultation to the Mayo Clinic for further opinion.

The patient was managed conservatively and had an uncomplicated clinical course. Hip pain resolved with symptomatic treatment, and he remained clinically stable. He was discharged with a preliminary diagnosis of unruptured abdominal aortic aneurysm. Cardiology and Rheumatology were consulted for follow-up and a repeat abdominal MRA was scheduled to monitor for changes of the abdominal aorta. Results of the Mayo Clinic pathology report were received shortly after discharge. The report described a pattern of organizing pneumonia with a lymphoplasmacytic infiltrate comprised predominantly of CD3-positive T cells and small foci of CD20-positive B cells. An immunohistochemical battery was performed, demonstrating few IgG-positive plasma cells and no increase in the IgG4 subtype. The final diagnosis was organizing pneumonia.

The patient remained asymptomatic after discharge. The follow-up MRA was performed after 6 weeks, and aortic findings

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were unchanged from the prior study. The etiology of the patient's aortic changes remained elusive. The changes affecting the ascending aorta described on prior chest CT extended proximally to the level of the sinuses of Valsalva. This led to the re-examination of slides originating from the patient's 2011 pericardiectomy for constrictive pericarditis. Initial pathology had described chronic inflammation and fibrosis, but an immunohistochemical study was not performed at that time. The specimen material was sent to the Mayo Clinic for further analysis. Histologically, the pericardium was severely thickened by fibrosis associated with a dense lymphoplasmacytic infiltrate. Some vessels also showed features of endothelitis. The immunohistochemical study revealed an increased number of IgG4-positive plasma cells, greater than 50 per high-power fields in several fields (Figure 3). Using the consensus statement diagnostic scheme [1,2], a diagnosis probable for IgG4-RD was rendered.

Discussion

In the case described, the suspicion for a diagnosis of IgG4-RD was based on incidental findings of periaortic soft-tissue abnormality suggestive radiographically of aortitis, a pulmonary density, and a known history of constrictive pericarditis. Similar peri-aortic findings have been reported by Horger and colleagues in a patient with IgG4-RD [3]. Biopsy of the periaortic area was not felt to be indicated because his presenting symptoms resolved and it was a high-risk procedure. The biopsy of the pulmonary lesion was non-diagnostic. While it showed dense lymphocytoplasmic infiltrate and endothelitis, the stain for IgG4-positive cells was negative. Therefore, the best diagnosis was "organizing pneumonia." Because of continued suspicion that these findings might be driven by an IgG4-related disease process, we retrieved pericardial tissue from his pericardiectomy done 5 years previously (only H&E stains had been performed, and the pathologic diagnosis in 2011 was only "Chronic inflammation and fibrosis"). The tissue was sent to the lab of one of us (MC Aubry) and reprocessed for immunohistochemical staining. The result was most consistent with IgG4 RD, as noted above. The unique time-course and atypical presentation described are examples of the challenges faced when diagnosing IgG4-related disease. We believe these challenges are related to limitations of current testing modalities and an incomplete understanding of the natural history of IgG4 disease.

The individual presented in this case report had a history of IgG4-related pericarditis. If not for the ability to retrospectively diagnose IgG4-RD from stored pericardial tissue, the diagnosis may have remained elusive. According to an article by Stone, about 40% of thoracic and abdominal inflammatory aortic aneurysms are caused by IgG4 systemic disease [4]. We believe the radiographic evidence of aortic wall thickening might be a manifestation of IgG4-related disease responsible for this patient's inflammatory pericarditis. It is unclear if this is an example of insidious progression of preexisting lesions or acute relapse of new aortic disease. Biopsy of these lesions was deemed too high-risk to perform in an asymptomatic elderly patient, so we were unable to correlate the histopathology with stored samples of pericardial tissue. This demonstrates the challenge associated with reliance on biopsy for confirmational diagnosis of disease. This is further limited by lack of sensitivity of diagnostic and imaging modalities to detect early or subclinical foci of disease. Typically, the decision to pursue more advanced diagnostic testing, such as imaging or biopsy for histopathology, is based on an elevated serum IgG4. However, the sensitivity of serological testing is limited, and a negative test result further precludes reaching a timely diagnosis. These types of problems may lead to delayed diagnosis, underestimation of disease severity, and even inadequate treatment.

This case demonstrates the challenges clinicians face with the diagnosis and management of IgG4-related disease. Failure to diagnose IgG4-related disease can have serious implications for patient outcomes. The 3-year relapse rates for some forms of IgG4-RD are reported to be as high as 92% [5]. Autoimmune pancreatitis has been shown to extend to the liver, resulting in hepatic cirrhosis and portal hypertension. Cardiovascular lesions such as aortitis and abdominal aortic aneurysms have been reported to grow and even progress to aortic dissection [6–9]. Unfortunately, there is a paucity of high-quality evidence-based recommendations for the treatment and surveillance of IgG4-related aortitis/periaortitis (Ao/PaO). One Japanese retrospective study investigated the utility of systemic corticosteroids for induction and maintenance therapy of Ao/PaO [7]; the authors demonstrated improvement or resolution of lesions with glucocorticoid treatment, as well as prevention of lesion progression and aneurysm formation.

The patient in our report was followed by a rheumatologist, and the decision was made to observe without steroids or other treatment because he was asymptomatic at that point and the risk/benefit ratio was felt to be unfavorable. He has done well clinically for 18 months and follow-up MRI of the abdominal aorta show he remained stable as of 8 months after presentation.

Conclusions

Diagnostic workup for IgG4-RD requires a high index of suspicion. Correlation of presentation, past medical history, and laboratory and histopathologic analysis are often required to make a diagnosis. This case illustrates these challenges and

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provides insight into the variable natural history of this condition. The patient's initial episode of constrictive pericarditis did not yield a diagnosis by routine pathologic testing. Five years later, when asymptomatic but unusual findings were incidentally noted, re-examination of the pericardial tissue resulted in a diagnosis of IgG4-RD. Our patient's benign clinical course after the initial episode suggests that treatment decisions must be made on an individual basis.

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Statement

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Conflicts of interest

None.

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