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Original Article

A case report of recurrent acute myocardial infarction and cardiac arrest due to aortic dissection secondary to IgG4-related aortitis

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ABSTRACT

Occlusion of the right coronary artery is a relatively rare complication of type A aortic dissection and an example of type 2 myocardial infarction (MI) as well but when it occurs, it may have a fatal result for the patient. Aortic pseudoaneurysms are local type A dissections with a restricted extent in which the majority of the aortic wall has been breached and luminal blood is held in only by a thin rim of the remaining wall, mainly purely the adventitia. They typically occur from iatrogenic trauma by interventional procedures or previous cardiac surgery. We present a case of a 56 years old patient who suffered an acute functional MI due to such pseudoaneurysm formed in the context of an undiagnosed aortitis. The etiology remained unclear until the surgical aortic prosthesis was deemed necessary, finding chronic IgG4 infiltrates in the aortic tissue. To our knowledge, this is the first case of IgG4-related aortitis causing functional MI and cardiogenic shock.

1. Introduction

Acute chest pain is one of the most common reasons for seeking care in the emergency department and can have multiple causes: myocardial ischemia or infarction, pericardial disease, vascular disease, pulmonary conditions, gastrointestinal conditions, musculoskeletal and other conditions [1]. Myocardial infarction (MI) alone can be subdivided into Type 1 MI, which is a primary coronary arterial event attributable to atherothrombotic plaque rupture or erosion, and type 2 MI, which occurs secondary to an acute imbalance in myocardial oxygen supply and demand without atherothrombosis. The reported prevalence of type 2 MI ranges from 2% to 58% of patients with MI [2,3].

Occlusion of the right coronary artery (RCA) is a relatively rare complication of type A aortic dissection and an example of type 2 MI as well but when it occurs, it may be fatal. Aortic pseudoaneurysms are local type A dissections with a restricted extent in which the majority of the aortic wall has been breached and luminal blood is held in only by a thin rim of the remaining wall, mainly the adventitia. Chronic inflammation of the aortic wall (aortitis) can also lead to such localized dilatations [1]. They typically occur from iatrogenic trauma by interventional procedures or previous cardiac surgery. In our case, the etiology remains unclear although the patient's background might be related to his later, life-threatening complication. We report herein a case of IgG4 periaortitis-related pseudoaneurysm causing type 2 functional MI, cardiogenic shock and cardiac arrest.

2. Case presentation

A 56-year-old Caucasian male patient presented to our emergency catheterization laboratory following a sudden onset of chest pain and electrocardiographic findings of inferior ST-segment elevation myocardial infarction (STEMI). Upon arrival, he displayed progressive impairment of hemodynamic status equaling to cardiogenic shock (heart rate of 90 bpm and blood pressure of 85/50 mmHg, confirmed by noninvasive and invasive measurements, as well). He had no previous medical history other than a recently diagnosed Hairy-Cell Leukemia (HCL) and took no regular medication. Orienting echocardiography showed a slightly enlarged left ventricle, ejection fraction of 45%, moderate-to-severe aortic regur-

Abbreviations: CPR, Cardio-pulmonary resuscitation; STEMI, ST-Elevation Myocardial Infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; GCS, Glasgow Coma Score; BP, blood pressure; TIMI, Thrombolysis In Myocardial Infarction; ED, emergency department; EF, ejection fraction; ICU, intensive care unit; HCL, hairy-cell leukemia; BNP, brain natriuretic peptide; CT, computer tomography; IgG4-RD, IgG4-related-disease.

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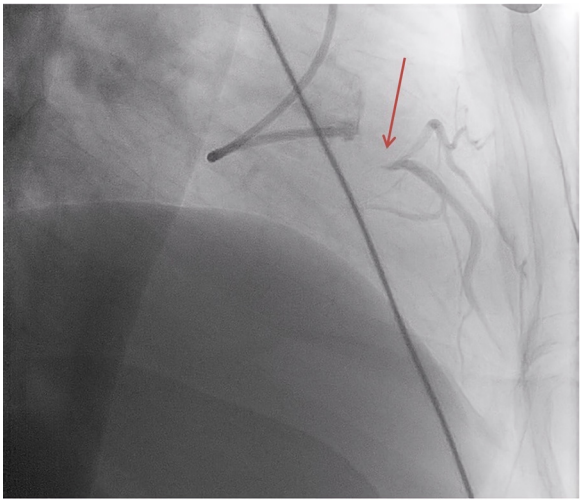

Fig. 1. Nonselective injection of the RCA. Ostial stenosis (arrow).

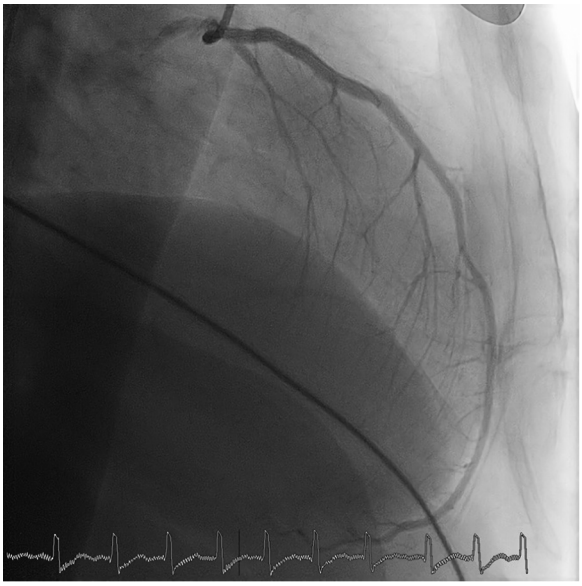

Fig. 2. First RCA stenting, with good final angiographic result.

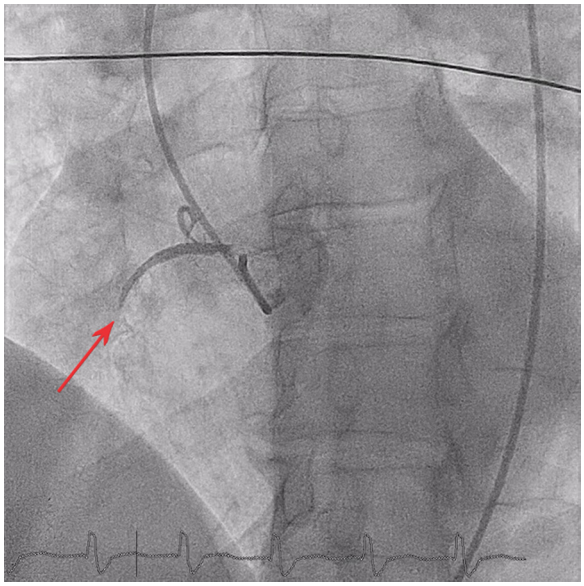

Fig. 3. RCA re-occlusion shortly after the first PCI (arrow).

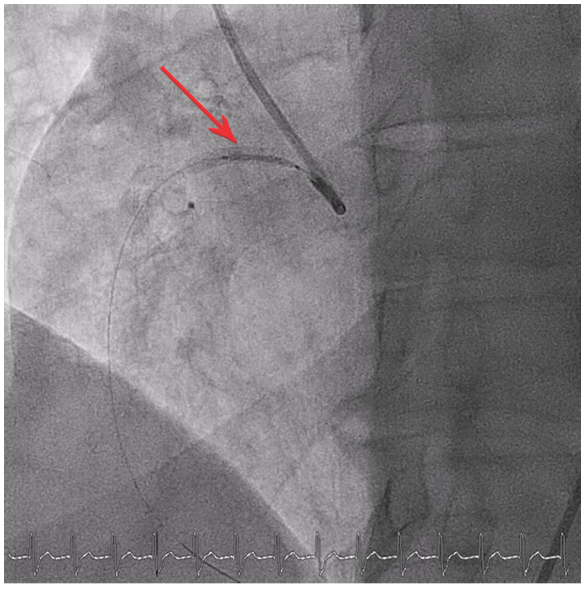

Fig. 4. Second RCA stenting, with significant stent protrusion into aorta (arrow).

gitation. Emergency diagnostic coronary angiography was immediately performed, showing a patent left coronary system but the RCA could not be found. Aortic angiography was then carried out, showing an aberrant orifice of the RCA and an atypical contour of the right sinus (Video 1). However, being focused on the RCA occlusion, the latter was not carefully evaluated at this moment. No intimal flap or double-lumen was detected. With the support of non-selective visualization, RCA was finally found, showing sharp-contoured obstruction in the proximal segment (Fig. 1). Percutaneous coronary intervention (PCI) was performed, ST segment elevation resolved and Thrombolysis In Myocardial Infarction (TIMI) 3 flow achieved (Fig. 2), with rapid relief of symptoms. Operators considered the angiographic appearance a 'typical occlusion of an RCA with atypical orifice' with no clinical or angiographic hint for embolic background. The operator failed to consider the unique expansion of the right sinus of Valsalva, visible in the cine loops. This decision may have been influenced by the operator's personal experience and the effect of confirmation bias with regards to culprit stenoses.

Shortly after, the patient presents with cardiac arrest (ventricular fibrillation), cardiopulmonary resuscitation (CPR) and intubation were conducted. Second-look coronary angiogram revealed a reocclusion of the RCA. Two more stents were implanted in the proximal part, with difficulty in maintaining the vessel open, with significant stent-protrusion in the aorta (Figs .3 and 4). The patient was then stabilized and transferred to the intensive care unit (ICU) where the echocardiogram confirmed a slightly enlarged left ventricle, with a mild systolic dysfunction, severe aortic regurgitation but a normal-sized ascending aorta with no signs of dissection. The careful review of the coronary angiogram and especially the aortogram raised the suspicion for actual aortic root pathology. Computer tomography (CT) was performed which revealed the formation of pseudoaneurysms in the right and non-coronary sinuses, measuring 1.5 cm each (Fig. 5). The interdisciplinary heart team decided on semi-elective surgical sanitation of the pseudoaneurysm. Full replacement of the ascending aorta, aortic valve, relocation of the left coronary system and graft over the RCA, distal of the stents, with ostial ligature of the native vessel were performed (the Bentall procedure). Intraoperative findings revealed

Table 1
Case timeline and synthesis

Date	Events
First admission to hematologist	Hairy-Cell Leukemia diagnosis (bone marrow aspiration)
Day 1, first admission	1. Ambulance Diagnosis of Inferior STEMI. Direct presentation at the Catheterization Laboratory. Complains: constrictive chest pain, mid-thorax located, mild dyspnea. Hemodynamics: BP 85/50 mmHg, HR 90 bpm, neurological status – GCS 13 points. 2. ED Echocardiography (on the table) – slightly enlarged left ventricle, EF 45%, moderate aortic regurgitation. 3. Coronary angiogram – RCA stenting. Rapid relief of symptoms. 4. Chest pain and ventricular fibrillation. Successful CPR. Intubation. Second angio: stent occlusion. Second PCI. Patient stabilization. 5. Transfer to ICU. Chest CT scan – sinus Valsalva aneurysm rupture diagnosis through CT. Labs: anemia, lymphopenia, thrombocytopenia, hyperglycemia, increased serum creatinine, BNP, D-Dimer and Troponin-I. Echocardiography – severe aortic regurgitation.
Day 2	6. Heart-Team – call for planned surgery. Patient extubated, stable, GCS 15 pcts. No complains.
Day 8	7. Heart surgery performed: aortic prosthesis and 1 RCA bypass.
Day 9	8. ECG – Paroxysmal Atrial Fibrillation 11. Treatment: amiodarone cardioversion, crystalloids, norepinephrine, midazolam adjusted and ventilation parameters, extubation.
Day 10	12. Second look angiography - no complications 13. Histology interpretation: chronic aortitis with microscopic infiltrates of lymphocytes and plasma cells.
Day 20	14. Patient discharge

STEMI, ST-elevation myocardial infarction; BP, blood pressure; HR, heart rate; GCS, Glasgow Coma Score; ED, emergency department; RCA, right coronary artery; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; ICU, intensive care unit; CT, computer tomography; BNP, brain natriuretic peptide.

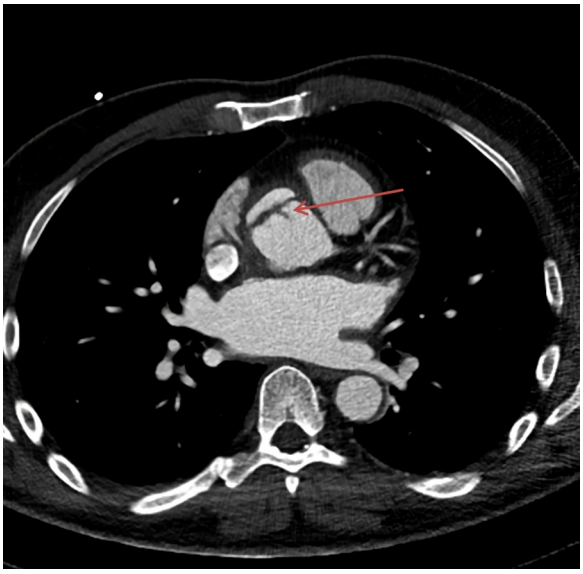

Fig. 5. Chest CT scan, the intimal flap (arrow), marking the pseudoaneurysm.

the protruding stent covered with dissected intima and the tear in the aortic wall, forming "pouches" in the noncoronary sinus, due to layer destruction and intima loss (Fig. 6).

The patient made a good recovery and was extubated the next day. A control angiogram was performed: the left native coronary and the right vein-bypass were found normal, with TIMI 3 flow, and the aortic bioprosthesis in physiological position. He was discharged after 20 days, without complications. The histopathological report described a chronic IgG4 periaortitis with findings of lymphocytic and plasmacytic infiltrates in the aortic adventitia (Figs. 7, 8). Profound atherosclerotic changes in both intima and media were also found, with coarse heterogeneous calcifications, cholesterol crystals and foamy histiocytes. The Verhoeff-Van Gieson elastic staining showed diffuse loss of elastic fibers; in the adventitia, numerous band-shaped or nodularly-arranged, lymphocytic and plasmacellular infiltrates surrounded by fibrosis were noted. (Table 1)

3. Discussion

3.1. Acute aortic dissection mimicking STEMI

Risk factors for aortic dissection are hypertension, heritable or genetic thoracic aortic disease, congenital diseases/syndromes, atherosclerosis, trauma, blunt or iatrogenic and inflammatory/infectious diseases. Patients with acute aortic dissection have very high early mortality, with up to 1% per hour reported in the first 24 hours before surgery for type A dissection [4].

The thoracic aortic disease guidelines suggest a management pathway for patients with acute aortic dissection. Initial medical management includes stabilizing the patient, controlling the pain, and lowering the blood pressure (BP) with beta blockers to reduce the force of left ventricular contraction. These measures should commence immediately while the patient is undergoing diagnostic evaluation. Lowering BP may help prevent further propagation of the dissection and lessen the risk for aortic rupture. Emergency surgery leads to improved survival in patients with acute type A dissection, with an 18% in-hospital mortality for surgically treated type A dissection and 50% mortality in the first 48 hours, if not treated [4,5].

Acute MI related to the false lumen compressing the coronary ostium or the dissection flap involving the coronary artery complicates 10-15% of patients with acute type A aortic dissection [5]. It most frequently involves the right coronary artery and leads to acute inferior MI [6]. Troponin elevations and electrocardiographic changes may occur in acute dissection.

Aortic dissection may not be suspected as a cause of coronary ischemia, and misdiagnosis may lead to inappropriate therapy and delays in treatment. Our case made no exception. Emergency echocardiogram showed a normal sized aorta with no signs of dissection. Encountering difficulty in cannulating RCA and the subsequent aortography aspect were indirect signs of aortic dissection but the patient's hemodynamic instability and malignant arrhythmia forced us to focus on the myocardial infarction and pro-

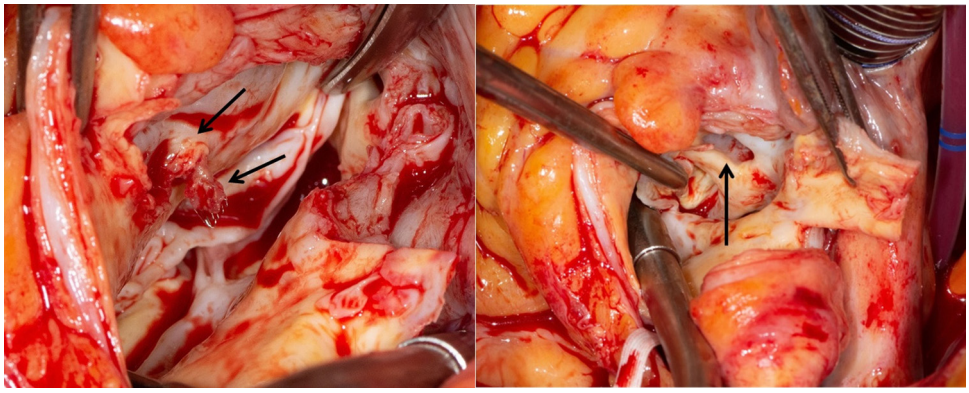

Fig. 6. Intraoperative pictures of the aortic sinus, showing the exaggerated stent protrusion with the intimal flap covering the stent (left, arrows). Pouch orifice is marked by the arrow from the second picture.

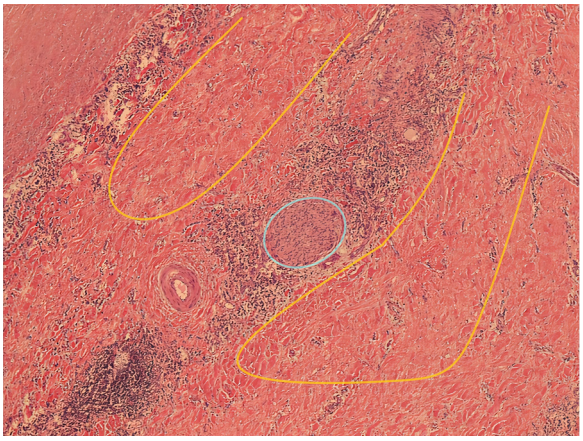

Fig. 7. The hematoxylin & eosin stain shows a dense lympho/plasmacytic infiltrate in association with neural hypertrophy (blue line) and storiform fibrosis (yellow line) (x100).

ceed with PCI. Planned surgery resolved both the dissection and the valvulopathy. While surgical repair of aortic dissection is normally a highly acute intervention, in the present case, several aspects were considered when defining the best timing for the procedure. Firstly, the recent transmural myocardial infarction with a massive rise of necroenzymes made the patient's conditions unfavorable for an acute cardiac surgery with extracorporeal circulation. The dissection did not show the typical radiologic signs of an acute dissection on the CT images, suggesting that rapid progression as natural history is not to be expected. However, the newly introduced double-antiplatelet therapy might have destabilized the dissection, if waiting too long. The acute event occurred from one of its complications, which was resolved and the patient was stabilized, therefore affording to schedule the surgical intervention in a semi-elective fashion.

3.2. From IgG4-related disease to aortic dissection

IgG4 aortitis/periaortitis is one of the entities seen in the spectrum of IgG4-related disease (IgG4-RD). IgG4-RD is a cluster of seemingly unrelated conditions that share common clinical, serologic and histopathologic characteristics. After the first description of IgG4-RD in 2001, in patients with autoimmune pancreatitis [7], many studies have been published regarding the myriad manifestations of this entity. Involvement of the aortic wall, particularly of the media and the adventitia is named *"IgG4-aortitis"*. When there is inflammation in the tissue surrounding the aorta, the terms *"IgG4-periaortitis"* or *"IgG4-chronic periaortitis"* are used. The hallmarks of IgG4 aortitis are dense lymphoplasmacytic infiltrations rich in $IgG4^{+}$ plasma cells along with fibrosis. Diagnosing IgG4 aortitis is complicated by variability in published criteria and how rigidly they are applied. Elevated serum IgG4 levels are not specific. Furthermore, the diagnosis cannot be predicated entirely upon the number of IgG4-positive plasma cells seen in biopsies because a large number of other entities can have such cells. For example, in Japan, the diagnosis is generally made either by comprehensive- or by organ-specific diagnostic criteria, and histology is not indispensable because peri-vascular tissue cannot be al-

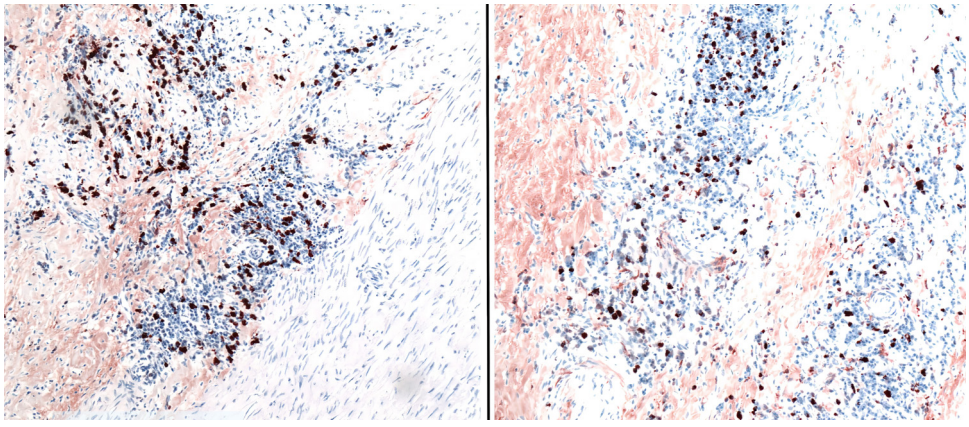

Fig. 8. Immunhistochemical analysis (IgG-4) reveals a substantial increase of plasma cells (in two different areas, x400).

ways obtained, which may lead to underdiagnosis [8]. The number of IgG4-positive plasma cells per high-power field (HPF) varies even more over the reports, but generally, when making the diagnosis, the minimum for most tissues is 30-50 IgG4-cells/HPF. In the absence of a more specific biomarker, in the appropriate clinical context, morphological features form the fundamental basis for the diagnosis. The three major histopathological features associated with IgG4-related disease are dense lymphoplasmacytic infiltrate, fibrosis, arranged at least focally in a storiform pattern, and obliterative phlebitis. In most cases, the presence of two histological characteristics is sufficient for a confident pathological diagnosis of IgG4-RD [9]. In most instances, these include a dense lymphoplasmacytic infiltrate and storiform-type fibrosis because obliterative phlebitis, although considered nearly pathognomonic, may be absent in certain organs (as in our case).

It is worth noting that our patient meets all the criteria discussed in the last International Consensus: (1) aortitis (organ involvement); (2) serum IgG4 of 181 mg/dL (min. 135 mg/dl); (3) IgG4/IgG ratio of 0.6 (min. 0.4); and (4) 55 IgG4 positive plasma cells per HPF (min. 10 cells) [10]. Moreover, lymphocytes, plasma cells, and fibrosis were manifest in the aortic tissue.

IgG4-related aortitis can lead to aneurysms or dissections of the thoracic aorta, with this segment being involved twice as often compared to the abdominal aorta. A good initial therapeutic response to glucocorticoids is characteristic (particularly if excessive tissue fibrosis has not supervened). It is associated with back pain as the most prevalent symptom observed, and it can simulate an acute aortic syndrome due to aneurysmal luminal dilation [11]. Diffuse periaortic soft tissue thickening is seen radiologically. The degree of ascending aortic wall inflammation may determine the risk of further intima dissection and the outcome after surgery. In cases of rapid enlargement of an aneurysm or dissection, emergency surgery is required [11]. To our knowledge, this is the first case of IgG4-related aortitis causing functional MI and cardiogenic shock. On the other hand, there are also a few similar cases of vasculitis reported in patients with HCL. This theory is also attractive because multiple focal lesions, with subacute evolution are associated with lymphoproliferative disorders [12]. Although rarely occurring, it is important to recognize this condition in patients with HCL. Forty-two cases of vasculitis coincident with HCL have been reported, of which 17 had polyarteritis nodosa, 21 had cutaneous leukocytoclastic vasculitis, and 4 had vessel wall infiltration by hairy cells [13]. Therapy is controlling the underlying leukemia. The authors acknowledge the speculative nature of this association because IgG4 infiltrates are not associated with HKL and no specific stains were used to further investigate this hypothesis, nevertheless, it is worth mentioning the rare aortic involvement with lymphoproliferative disorders [12].

4. Conclusion

To conclude, the MI has resulted from external coronary artery occlusion due to aortic dissection, where the dissection flap temporarily occluded the ostium of the right coronary artery and affected the blood flow to the vessel. The significant aortic regurgitation in a young patient with acute chest pain should make every physician suspicious of aortic dissection. Prompt diagnosis and treatment can be lifesaving. Later understanding through a multidisciplinary approach can offer the bigger picture. When aortitis is suspected, IgG4-RD should be sought as an etiology because the response to steroid therapy is fast and effective.

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Patient informed consent statement

Informed consent for patient information and images to be published was provided by the patient.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.carpath.2022.107415.

References

[1] Mann Douglas L, Douglas Zipes P, Libby P, Robert Bonow O, Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Philadelphia, PA: Elsevier/Saunders; 2015. Tenth edition.
[2] DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK, et al. Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. Circulation 2019;140:1661–78.
[3] Kanoun Schnur SS, Achim A, Toth GG. Clinical application of results of the ISCHEMIA trial. Trends Cardiovasc Med 2021(21):S1050–738 Nov 200126-2. doi: 10.1016/j.tcm.2021.10.011.
[4] Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873–926.
[5] Hiratzca LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for diagnosis and management of patients with Thoracic Aortic disease. Circulation 2010;121:266–369.
[6] Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, et al. Presentation, diagnosis, and outcomes of acute aortic dissection: 17-year trends from the International Registry of Acute Aortic Dissection. J Am Coll Cardiol 2015;66:350–8.
[7] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732–8.
[8] Mizushima I, Kasashima S, Notohara K, Fujinaga Y, Saeki T, Zen Y, et al. Clinical and pathological characteristics of IgG4-related periaortitis/periarteritis and retroperitoneal fibrosis diagnosed based on experts' diagnosis. J Jpn Coll Angiol 2018;58:117–29.
[9] Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25:1181–92.
[10] Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International consensus guidance statement on the management and treatment of IgG4-related disease. Arthritis Rheumatol 2015;67:1688–99.
[11] Peng L, Zhang P, Li J, Liu Z, Lu H, Zhu L, et al. IgG4-related aortitis/periaortitis and periarteritis: a distinct spectrum of IgG4-related disease. Arthritis Res Ther 2020;22:103.
[12] Inra ML, McCormick MG, Bagameri G, Lin PT. Thoracic aortic dissection associated with involvement by small lymphocytic lymphoma/chronic lymphocytic leukemia: a possible underappreciated risk factor? Cardiovasc Pathol 2020;45:107179.
[13] Hasler P, Kistler H, Gerber H. Vasculitides in hairy cell leukemia. Semin Arthritis Rheum 1995;25:134–42.