

Never forget the aorta: a case report of IgG4-related disease causing aortitis

Chiara Tioni^{1,2*}, Marco Antonutti^{1,2}, Concetta Di Nora^{1,2}, and Alessandro Proclemer¹

¹Cardiology Division, Department of Cardiothoracic Science, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia, Piazzale S. Maria della Misericordia 15, 33100, Udine, Italy; and ²Cardiovascular Department, Ospedali Riuniti, Via Valdoni, 34149, Trieste, Italy

Received 19 December 2017; accepted 13 September 2018; online publish-ahead-of-print 16 October 2018

Background

Chest pain is a common reason for admission to the Emergency Department and aortic disease is a relatively frequent cause amongst the total number of admissions due to chest pain. IgG4-related disease (IgG4-RD) is a multi-organ immune-mediated condition that mimics several malignant, infectious, and inflammatory disorders.

Case summary

We report a rare case of IgG4-related aortitis complicated with severe aortic regurgitation and multivessel coronary artery disease in a 64-year-old man with a history of atypical chest pain. The diagnosis was made performing transthoracic echocardiography, transoesophageal echocardiography, and left heart catheterization; the aortitis was an incidental finding discovered by computed tomography angiography. Unusually, the positron emission tomography–computed tomography (PET-CT) scans did not reveal metabolic activity in the aortic wall. This last finding prompted us to exclude more aggressive arteritis (such as Horton's disease or Takayasu arteritis); syphilis infection and other infective or autoimmune diseases were excluded with laboratory tests. The patient underwent cardiac surgery with replacement of both the aortic valve and the ascending aorta, also performing a coronary aortic bypass graft (CABG). Despite the PET-CT scans were negative in the aortic wall, the histological specimens showed diffuse lymphoid infiltration, fibro-atheromatosis lesions, and medium-interstitial hyperplasia compatible with aortic atherosclerosis and IgG4-RD. The post-surgery course was free of complications and the patient was discharged in good clinical condition. He was referred to the Rheumatologic Department and a corticosteroid therapy has been started.

Discussion

The growing recognition of IgG4-related systemic disease as a clinical entity underscores the importance of considering this diagnosis in patients with any type of idiopathic aortitis and aortic valve disease. Noteworthy, the PET-CT scans could be negative in this disease, so histological exams are mandatory to make the diagnosis; in our case an unusual post-surgery histopathological finding prompted us to diagnose a rare, unrecognized disease and allowed us to treat the patient properly.

Keywords

Aortic disease • Aortic regurgitation • IgG4-related disease • Case report

Learning points

- The growing recognition of IgG4-related systemic disease as a clinical entity underscores the importance of considering this diagnosis in patients with any type of idiopathic aortitis and aortic valve disease.
- Positron emission tomography–computed tomography scans could be negative in the disease, so histological exams are mandatory to make the diagnosis.
- Although rare, the vascular involvement in IgG4-related disease could be wide and life threatening.

* Corresponding author. Tel: +39 0432 552459, Fax: +39 0432 554448, Email: chiara.tioni@gmail.com. This case report was reviewed by Savvas Loizos, Cemil Izgi, Anastasia Vamvakidou, Christian Fielder Camm, and Peregrine Green.

© The Author(s) 2018. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Introduction

Chest pain is a common reason for admission to the Emergency Department and aortic disease is a relatively frequent cause amongst the total number of admissions due to chest pain. Among all aortic pathologies, the most dramatic event is aortic dissection, with an incidence of 2.6–3.5 cases per 100 000 person-years.¹ Although the most frequent entities are mainly three (aortic dissection, intramural haematoma, and penetrating aortic ulcer), other uncommon pathologies might affect the aortic wall, such as inflammatory aortitis.

One of the uncommon and unrecognized causes of aortitis is IgG4-related disease (IgG4-RD). This disease is a multi-organ immune-mediated condition that mimics several malignant, infectious, and inflammatory disorders. The three main pathology features of IgG4-RD are lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis.² IgG4-related aortitis can lead to aneurysms or dissections of the thoracic aorta.³ Aortitis, usually an incidental radiological finding, is sometimes also an unexpected finding during surgery.

Timeline

Time	Events
Initial presentation (Day 1)	Onset of atypical chest pain and initial assessment revealing severe aortic regurgitation. Blood test showed minimal rising of troponin enzyme, moderate elevation of brain natriuretic peptide and mild elevation of C-reactive protein.
Day 2	Coronary angiography revealed severe aortic regurgitation and severe left main stem disease. Computed tomography aortogram revealed parietal thickening of the aorta.
Day 3	Positron emission tomography–computed tomography scans revealed abnormal spotty concentration of ¹⁸ F-FDG at mandibular nodes and prostate, without aortic involvement.
Day 7	The patient underwent to tissue aortic valve and ascending aorta replacement. The histopathological exam showed diffusely positive population for CD20, BCL2, and CD5, immunoreactive plasmacytic elements CD38+, with IgG4 count of 35/high-power field in hot spots, and IgG4/IgG ratio of 70%. The set of findings is consistent with the diagnosis of aortic localization of chronic lymphocytic leukaemia and consensual IgG4-related disease (IgG4-RD)
Day 15	The patient remained asymptomatic and haemodynamically stable and was discharged home a week later. He was referred for further rheumatology assessment. Furthermore, a corticosteroid therapy was suggested from the specialist and started.

Case summary

A 64-year-old man was admitted to the hospital with an atypical retrosternal chest pain for more than 3 days and exertional shortness of breath on a background of arterial hypertension. Other comorbidities were: MGUS IgG k, chronic lymphocytic leukaemia (CLL), benign prostatic hypertrophy, and moderate chronic kidney disease (GFR MDRD 40.6 mL/min/1.73 m²).

On examination the patient was comfortable at rest, with a heart rate of 85 b.p.m. and a blood pressure of 170/70 mmHg with widely and rapidly collapsing peripheral pulses. Normal S1 and S2 heart sounds were present, with a 3/6 decrescent diastolic murmur present in all cardiac areas, but louder on Erb's area. There were no signs of heart failure present.

An electrocardiogram was performed, which showed sinus rhythm, with high-amplitude QRS complexes and secondary ST changes (Supplementary material online, Figure S1).

A transthoracic echocardiogram was performed, which showed a mildly dilated left ventricle (LV) with normal LV systolic function and a severe aortic regurgitation in the tricuspid aortic valve, without evidence of infective endocarditis. Regular dimensions were found for both the aortic root and the ascending aorta (Figure 1).

Troponin [0.135 ng/mL, normal values (n.v.) <0.045 ng/mL] and C-reactive protein (CRP) (8.35 mg/L, n.v. 0–5 mg/L) were slightly above average, whereas brain natriuretic peptide (515 pg/mL, n.v. 2–100) was moderately increased.

A left heart catheterization was performed, which confirmed severe aortic regurgitation and revealed severe stenosis of left main coronary artery (Figure 2).

Considering these anomalies, an urgent computed tomography angiography (CTA) was requested, which showed widespread circumferential attenuation of the aortic wall with parietal thickening (maximum 8 mm) of the entire aorta up to the left common iliac artery. This parietal alteration caused sub-occlusive stenosis at the origin of both renal arteries, and sub-occlusive stenosis of the coeliac trunk. A computed tomography coronary angiogram was also performed, which revealed critical stenosis (75%) of the left main coronary artery and subcritical stenosis (60%) of the right coronary artery. Both arteries were involved in an inflammatory process which also

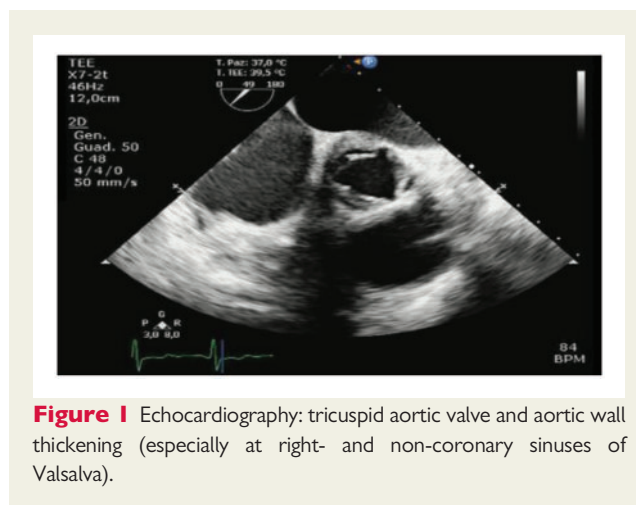


Figure 1 Echocardiography: tricuspid aortic valve and aortic wall thickening (especially at right- and non-coronary sinuses of Valsalva).

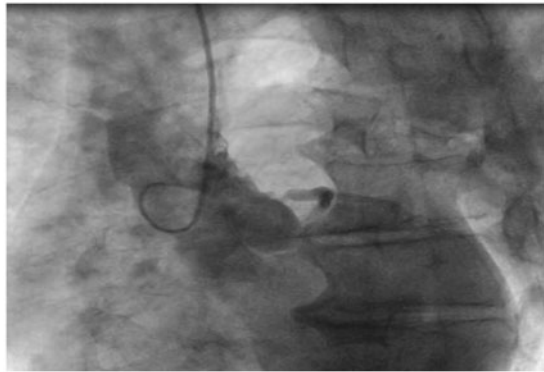


Figure 2 Aortic angiogram: left main stem subocclusion, aortic wall ulcerations, and normal aortic dimension.

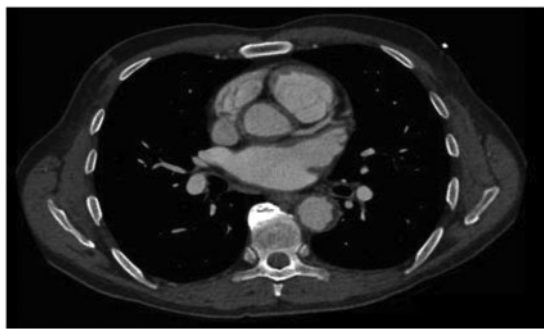


Figure 3 Computed tomography scan: diffuse aortic wall thickening in ascending and descending thoracic aorta.

determined medial-intimal hyperplasia. No signs of aortic dissection were found (Figure 3).

A transoesophageal echocardiogram was also performed, which revealed a severe aortic regurgitation with central jet caused by thickening and retraction of the aortic cusps (Supplementary material online, Figure S2).

The immunological studies were normal (including IgG and IgA serological levels, antinuclear antibodies, extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, and serology for treponema pallidum); only low levels of serum IgM were found (8 mg/dL, n.v. 65–210 mg/dL).

The positron emission tomography–computed tomography (PET-CT) scans revealed abnormal spotty concentrations of ^{18}F -FDG at mandibular nodes and prostate, without aortic involvement (Figure 4).

The patient showed symptoms of chest pain, which were not clearly attributable neither to arteritis nor to severe aortic regurgitation, but possibly to both of them. However, he also complained of shortness of breath on exertion, and this condition is more typical of severe aortic regurgitation. These symptoms provided us with a clear indication in order to proceed with cardiac surgery.

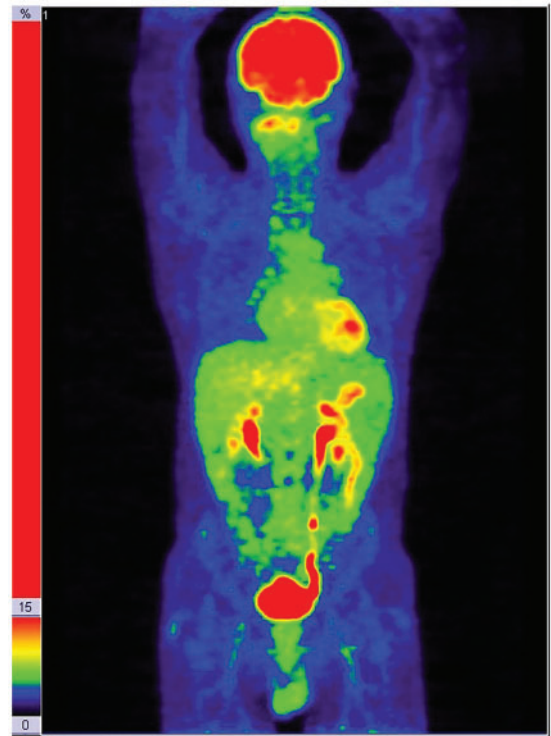


Figure 4 Positron emission tomography–computed tomography scans: absence of aortic inflammation.

The patient underwent tissue aortic valve replacement and ascending aorta replacement with a vascular graft. A CABG using both right and left internal mammary arteries was also performed, in order to get a complete coronary revascularization. Macroscopic examination of the tricuspid aortic valve revealed severe hypoplasia of the right cusp and wide clefts both between the right and the non-coronary cusps and between the left and the non-coronary cusps. Furthermore, the ostia were ulcerated. Tissue cultures of the aortic valve and ascending aorta were negative; conversely, the histopathological exam showed fibro-atheromatosis lesions on the aortic wall, together with medium-interstitial hyperplasia with diffuse lymphoid infiltration. The lymphoid infiltration showed a count of 35/high-power field (HPF) in hot spots, and IgG4/IgG positive plasma cell ratio of 70% (Figure 5). The set of findings was characterised by fibro-atheromatosis lesions and medium-interstitial hyperplasia compatible with aortic atherosclerosis. Conversely, the diffuse lymphoid infiltration could be related to both CLL and to IgG4-RD. Please note that the diagnosis of CLL was not excluded, in fact the histological specimen showed a lymphocytic infiltration diffusely positive for CD20, BCL2, and CD5 (compatible with CLL cells) and immunoreactive plasmocytic elements CD38+, with IgG4 positive plasma cell (compatible with IgG4-RD cells). The aortic wall infiltration could be related to both CLL and to IgG4-RD. In order to understand this case, CLL was quite silent (Stage 0–1 RA), so overall clinical and histopathological alterations could not be attributed only to CLL, rather to aortic wall invasion by IgG4 antibodies.

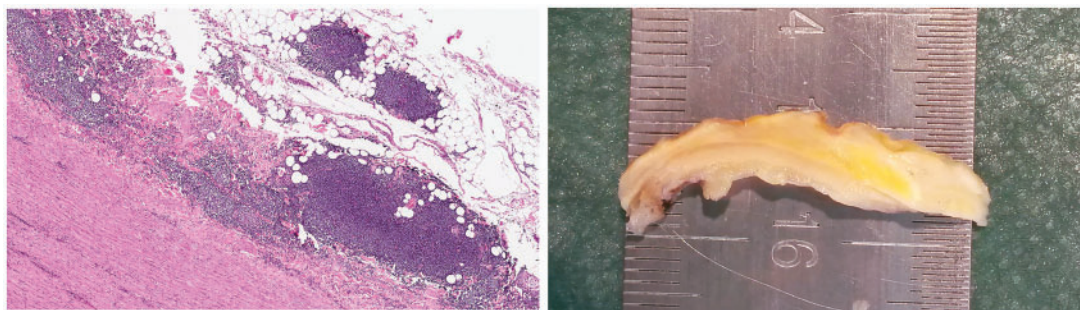


Figure 5 Anatomic (diffuse aortic wall thickening with initial ulceration) and histological correlates (diffuse and dense aortic wall lymphoplasmacytic infiltration with germinal centres).

The post-surgery course was free of complications and the patient was discharged after 1 week asymptomatic and in good clinical condition.

He was referred to the Rheumatologic Department for a more in-depth investigation regarding the disease assessment. It is worth noting that the serum IgG4 was 173 mg/dL (n.v. <110 mg/dL). Furthermore, a corticosteroid therapy was suggested by the specialist and started immediately after.

Subsequently, the patient had a transthoracic echocardiography 1 month after the surgery. It revealed normal aortic prosthesis, without aortic regurgitation. Furthermore a CTA was performed during the follow-up, showing no differences with the previous, despite steroid therapy; anyway the patient is now asymptomatic and in good clinical condition. Moreover, in the last blood test, performed during steroid therapy, serum IgG4 was normalized (27 mg/dL; n.v. <110 mg/dL), likely attributable to effectiveness of corticosteroids on IgG4 producing—plasmacells.

Discussion

This patient shows many characteristics of IgG4-RD, namely, male sex, age older than 50 years, and the presence of the disease in the aorta, with the typical histopathological features.^{4,5} Nevertheless, some reports suggested that at least 50 IgG4+ plasma cells per HPF are needed for a diagnosis, the latest diagnostic criteria state that it is necessary to have IgG4/IgG ratio >0.4 and >10 IgG4+ cells per HPF.⁶ These criteria also state that the diagnosis is definite if there are all of the following features: (i) organ involvement; (ii) serum IgG4 >135 mg/dL; (iii) IgG4/IgG ratio >0.4 in histopathological specimens; and (iv) more than 10 IgG4 positive cells per HPF. It is worth noting that our patient meets all the criteria mentioned above: (i) aortitis (organ involvement); (ii) serum IgG4 of 173 mg/dL; (iii) IgG4/IgG ratio of 0.7; and (iv) 35 IgG4 positive plasma cells per HPF.

IgG4-related disease usually affects various organ systems.⁷ Our patient showed extravascular involvement as revealed by PET-CT positivity in the prostatic gland and nodes. However, the PET-CT scans were negative in the aortic walls, so this could be a misleading point. Different studies have showed that ¹⁸F-FDG PET sensitivity is

60–92% with a specificity of 88–100% for the diagnosis of active inflammation in arteritis. Hybrid imaging with ¹⁸F-FDG PET and either CT or magnetic resonance allows more precise anatomic localization of disease activity.^{8,9}

The degree of ascending aortic wall inflammation may determine the outcome after surgery. The diagnosis of inflammation is fundamental because aortitis and ascending aortic dissection are associated with increased mortality.¹⁰ Nevertheless, our patient had normal ascending aortic diameters; the surgeons replaced both the aortic valve and the ascending aorta. Specifically, during surgery they noticed that the aortic wall presented ulcerated plaques, preventing to fix the coronary ostia. Inflammation is the main factor in the IgG4-RD pathophysiology, so in our case it was the driving factor of macroscopic alteration in the aortic walls with partial sparing of the distal ascending aorta and the aortic arch, seen as ulcerative plaques and thickness. Considering that macroscopic alterations could be responsible of adverse outcomes on follow-up, the surgeons decided to replace the entire ascending aorta and not only the aortic valve.

After surgery, however, immunosuppressive therapy must be set to stop the further evolution of the disease. Most clinical manifestations of IgG4-RD respond to glucocorticoids and these agents are the first-line, standard-of-care approach for most patients, despite no randomized treatment trials have been done yet. Usually, a starting prednisolone dose of 0.6–1.0 mg/kg daily is recommended, then tapered, after 2–4 weeks by 5 mg every 1–2 weeks, according to clinical responses. Some physicians decide to discontinue entirely prednisolone after 2 or 3 months, others decide to maintain it at a low dose.²

Clinical improvement after the start of glucocorticoid therapy is rapid, usually in some weeks, and a follow-up serological assessment should be done about 2 weeks after treatment initiation, dosing serum IgG4. Remember that the response to glucocorticoids varies according to the affected organs and the degree of fibrosis.²

Follow-up radiological assessment is appropriate for some types of organ involvement, such as the pancreas, biliary tree, lungs, kidneys, and vascular involvement; imaging type and its timing is up to the clinician. Furthermore, PET-CT is useful to assess treatment response, when indicated.²

Another interesting point about this uncommon disease is its possible link with malignancy. A history of invasive malignancy (mostly prostatic cancers and lymphomas) appears to be associated with the subsequent development of IgG4-RD.¹¹ Therefore, there is some evidence that IgG4 represents a pre-malignant state or paraneoplastic condition.^{12,13} Even our patient had a previous history of CLL and MGUS.

Conclusion

There are only a few other reports similar to this, where IgG4-RD shows aortitis and severe aortic regurgitation. In these cases, the grade of aortic defect becomes severe before the diagnosis, because symptoms frequently appear late. Unlike other arteritis, such as Takayasu's arteritis, that must be added to the known list of causes of severe aortic regurgitation,¹⁰ IgG4-related aortitis rarely shows isolated severe aortic regurgitation, more frequently both severe stenosis and regurgitation valve features.^{14,15}

The growing recognition of IgG4-related systemic disease as a clinical entity underscores the importance of considering this diagnosis in patients with any type of idiopathic aortitis and aortic valve disease, not only in those patients whose manifestations are consistent with the 'chronic periaortitis' or secondary aortic regurgitation.

Our patient signed informed consent form for the material presented to appear in the publication above and in related publications, prior to submission.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

Professor Livi with the Cardiosurgery team, and Professor De Vita with the Rheumatology Unit for their contribution to the management of this case.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References

1. Corvera JS. Acute aortic syndrome. *Ann Cardiothorac Surg* 2016;**5**:188–193.
2. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015;**385**:1460–1471.
3. Kasashima S, Zen Y, Kawashima A, Endo M, Matsumoto Y, Kasashima F, Ohtake H, Nakanuma Y. A clinicopathologic study of immunoglobulin G4-related sclerosing disease of the thoracic aorta. *J Vasc Surg* 2010;**52**:1587–1595.
4. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Löhr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol* 2015;**67**:1688–1699.
5. Brito-Zerón P, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014;**13**:1203–1210.
6. Pieringer H, Parzer I, Wohrer A, Reis P, Oppl B, Zwerina J. IgG4 related disease: an orphan disease with many faces. *Orphanet J Rare Dis* 2014;**9**:110.
7. Stone JH, Khosroshahi A, Hilgenberg A, Spooner A, Isselbacher EM, Stone JR. IgG4-related systemic disease and lymphoplasmacytic aortitis. *Arthritis Rheum* 2009;**60**:3139–3145.
8. Gornik HL, Creager MA. Aortitis. *Circulation* 2008;**117**:3039–3051.
9. Walter MA, Melzer RA, Schindler C, Muller-Brand J, Tyndall A, Nitzsche EU. The value of 18F FDG-PET in the diagnosis of large-vessels vasculitis and the assessment of activity and extent of disease. *Eur J Nucl Med Mol Imaging* 2005;**32**:674–681.
10. Kajander H, Paavonen T, Valo T, Tarkka M, Mennander AA. Immunoglobulin G4-positive ascending thoracic aortitis may be prone to dissection. *J Thorac Cardiovasc Surg* 2013;**146**:1449–1455.
11. Wallace ZS, Wallace CJ, Lu N, Choi HK, Stone JH. Association of IgG4 related disease with history of malignancy. *Arthritis Rheumatol* 2016;**68**:2283–2289.
12. Hirano K, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, Watanabe T, Saito T, Kawahata S, Uchino R, Hamada T, Miyabayashi K, Mohri D, Sasaki T, Kogure H, Yamamoto N, Nakai Y, Yoshida H, Ito Y, Akiyama D, Toda N, Arizumi T, Yagjoka H, Takahara N, Matsubara S, Yashima Y, Koike K. Incidence of malignancies in patients with IgG4 related disease. *Intern Med* 2014;**53**:171–176.
13. Schwartz JB, Shamsuddin AM. The effects of leukemic infiltrates in various organs in chronic lymphocytic leukemia. *Human Pathol* 1981;**12**:432–440.
14. Honig HS, Weintraub AM, Gomes MN, Hufnagel CA, Roberts WC. Severe aortic regurgitation secondary to idiopathic aortitis. *Am J Med* 1977;**63**:623–633.
15. Maleszewski JJ, Tazelaar HD, Horcher HM, Hinkamp TJ, Conte JV, Porterfield JK, Halushka MK. IgG4-related disease of the aortic valve: a report of two cases and review of the literature. *Cardiovasc Pathol* 2015;**24**:56–59.