CASE REPORT

Successful Transcatheter Diagnosis and Medical Treatment of Right Atrial Involvement in IgG4-related Disease

A Case Report and Review of the Literature

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Summary

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder characterized by lymphoplasmacytic infiltration of numerous IgG4-positive plasma cells, leading to fibrous thickening in the affected tissue. Typical cardiovascular manifestations of IgG4-RD are periaortitis, coronary arteritis, and pericarditis. Rare cases of myocardial involvement in IgG4-RD have been reported, but surgical resection or open biopsy was required for the diagnosis in those cases. Here, we report a case in which percutaneous transcatheter biopsy under the guidance of intracardiac echocardiography was useful for diagnosis of IgG4-RD manifested as an intracavitary right atrial mass, extending into the superior vena cava. Successful transcatheter diagnosis of myocardial involvement of IgG4-RD led to immediate favorable response to steroid therapy. Including the present case, previous IgG4-RD cases with myocardial involvement are reviewed to delineate its clinical characteristics.

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Key words: Cardiac tumor, Heart, Biopsy, Intracardiac echocardiography

IgG4-related disease (IgG4-RD) is a fibro-inflammatory disorder characterized by lymphoplasmacytic infiltration of numerous IgG4-positive plasma cells, leading to fibrous thickening in the affected tissue.[1,2] Typical cardiovascular manifestations of IgG4-RD are periaortitis, coronary arteritis, and pericarditis.[3,4] Rare cases of myocardial involvement in IgG4-RD have been reported (Table I),[5-12] but surgical resection or open biopsy were required for the diagnosis in those cases. Here we report a case in which percutaneous transcatheter biopsy under the guidance of intracardiac echocardiography (ICE) was useful for diagnosis of IgG4-RD manifested as a cardiac mass.

Case Report

A 69-year-old woman with bilateral proptosis with orbital pain and chest discomfort was referred to our institute for etiological diagnosis of bilateral exophthalmos. Her previous medical history included bronchial asthma and submandibular gland resection. Resected tissue of submandibular glands was not available. Laboratory studies revealed white blood cells of $6.7 \times 10^3/\mu L$, C-reactive protein of 0.14 mg/dL, and low serum angiotensin-converting enzyme activity. Serum antinuclear antibodies and anti-Ro/SSA and La/SSB antibodies were negative, but IgG4 level was markedly elevated (816.0 mg/dL, normal range: 4.8-105.0). Electrocardiography revealed ectopic atrial rhythm (EAR) at a rate of 86 per minute (Figure 1A). ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography showed ^{18}F-FDG uptake in the eyes and hilar/mediastinal lymph nodes (Figure 1B), typical findings in IgG4-RD. In addition, strong ^{18}F-FDG uptake was observed in the right atrium (Figure 1B-E). No ^{18}F-FDG uptake was found in the thoracic aorta or coronary artery (Figure 1C-E). Cardiac magnetic resonance imaging (CMR) showed a well-demarcated intracavitary right atrial mass, extending into the superior vena cava (Figure 2A-C). Elevation in serum IgG4 levels with typical extra-cardiac findings prompted us to histological diagnosis of right atrial involvement in IgG4-RD. Percutaneous transcatheter biopsy under the guidance of ICE (8Fr AcuNav, Biosense Webster Inc., CA, USA) was successfully performed. In histology, there was modest infiltration of lymphocytes and plasma cells around cardiomyocytes together with an area of massive replacement fibrosis, though fibrosis in a storiform pattern and phlebitis with obliteration of the lumen, other typical

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Table I. Laboratory Data on Admission

Variable	
Complete blood counts	
WBC, /μL	6.7×10^3
RBC, /μL	3.94×10^6
Hemoglobin, g/dL	12.2
Hematocrit, %	36.5
Platelet, /μL	219×10^3
Blood chemistry	
Total protein, g/dL	7.5
Albumin, g/dL	3.5
Total bilirubin, mg/dL	0.7
AST, U/L	25
ALT, U/L	14
LDH, U/L	189
ALP, U/L	91
BUN, mg/dL	10
Cr, mg/dL	0.7
Na, mEq/L	142
K, mEq/L	3.8
Cl, mEq/L	106
Ca, mg/dL	9.1
P, mg/dL	2.6
CRP, mg/dL	0.14
Serological test	
IgG, mg/dL	2296
IgG4, mg/dL	816
IgM, mg/dL	96
IgE, mg/dL	20
C3, mg/dL	80
C4, mg/dL	12
CH50, U/mL	46.1
sIL-2R, U/mL	826
ACE, U/L	8.1
anti-Ro/SSA antibodies, U/mL	< 1.0
anti-La/SSB antibodies, U/mL	< 1.0
Urinalysis	
Protein	(-)
Blood	(2+)
Glucose	(-)
RBC, /HPF	5-9
WBC, /HPF	< 1
Cast	(-)
NAG, U/L	4.6
β2MG, μg/L	87
α1MG, mg/L	0.5

WBC indicates white blood cell; RBC, red blood cell; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P, phosphorus; CRP, C-reactive protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; IgE, immunoglobulin E; C3, complement C3; C4, complement C4; CH50, hemolytic complement; sIL-2R, soluble interleukin-2 receptor; ACE, angiotensin-converting enzyme; NAG, N-acetyl-b-glucosaminidase; β2MG, β2microglobulin; and α1MG, α1microglobulin.

histological features of IgG4-RD, were not observed (Figure 3A-C). There was no granuloma or cell abnormalities suggestive of lymphoma. Immunostaining with anti-IgG4 antibody was positive in a large number of infiltrating IgG-positive plasma cells (more than 10 IgG4-positive plasma cells in one high-power field with an IgG4/IgG ratio of more than 0.5) as shown in Figure 3D-F.[13] Collectively, a final diagnosis of IgG4-RD was made. Treatment with 40 mg of prednisolone per day was commenced. Her orbital and chest symptoms were relieved, and electrocardiography showed normal sinus rhythm at a rate of 96 per minute 2 weeks later (Figure 4A). At 4 weeks after initiation of steroid therapy, the right atrial mass volume was reduced with a decreased serum IgG4 level (235 mg/dL) and decreased T2 signal intensity in CMR (Figure 4B and C). Eight months later, the prednisolone dosage was reduced to 10 mg/day without re-elevation of serum IgG4 level (150 mg/dL) or enlargement of the right atrial mass. Her bilateral proptosis was also relieved, suggesting IgG4-related ophthalmic disease.

Discussion

Cardiac masses are categorized as either neoplastic masses (benign and malignant tumors) or pseudotumors such as inflammatory myofibroblastic tumors and methothelial/monocytic incidental cardiac excrescences.[14] In 2013, Song, *et al*. and we reported cases of a cardiac pseudotumor that met with the pathological diagnostic criteria of IgG4-RD.[5,6] Yamauchi, *et al*. reported aortic valve (AV) involvement in IgG4-RD.[7] Thereafter, several cases of myocardial involvement in IgG4-RD with histological confirmation were reported,[8-12] but surgical resection or open biopsy of affected tissues was needed for diagnosis in all IgG4-RD cases with myocardial involvement.[5-12] In the present case, ICE-guided percutaneous transcatheter biopsy enabled tissue sampling from the cardiac mass, indicating that this technique is a safe and plausible approach for diagnosis of IgG4-RD, though its feasibility depends on localization of the mass.

Major presentations of IgG4-RD in the cardiovascular system are thoracic/abdominal periaortitis and coronary arteritis,[3,4] which mimics large-vessel vasculitis. In contrast, valvular dysfunction in IgG-RD is often an unexpected finding in pathological analysis of surgically excised valves, predominantly the AV (Table I).[5-12] Importantly, relapse after surgical resection was observed in three of five IgG4-RD cases with AV dysfunction.[6,8,9] Interestingly, no relapse was reported for two cases of IgG4-RD with AV dysfunction that received postoperative immunosuppressive therapy because of multiple systemic manifestations of IgG4-RD and very high levels of serum IgG4.[8,12] The findings in earlier cases and the present case support the notion that systemic immunosuppressive therapy is a cornerstone in IgG4-RD cases with myocardial involvement. Because complete resection of affected tissues seems to be difficult in this setting, postoperative immunosuppressive therapy is needed especially in cases with significant elevation of serum IgG4 level or other organ manifestations to prevent myocardium from inflammatory damage or fibrotic change. Furthermore, careful follow-up is required even in cases that did not receive surgical resection or immunosuppressive therapy because IgG4-RD can present with only a single organ lesion.[2]

In IgG4-RD cases with myocardial involvement, tissue diagnosis was made according to the histological re-

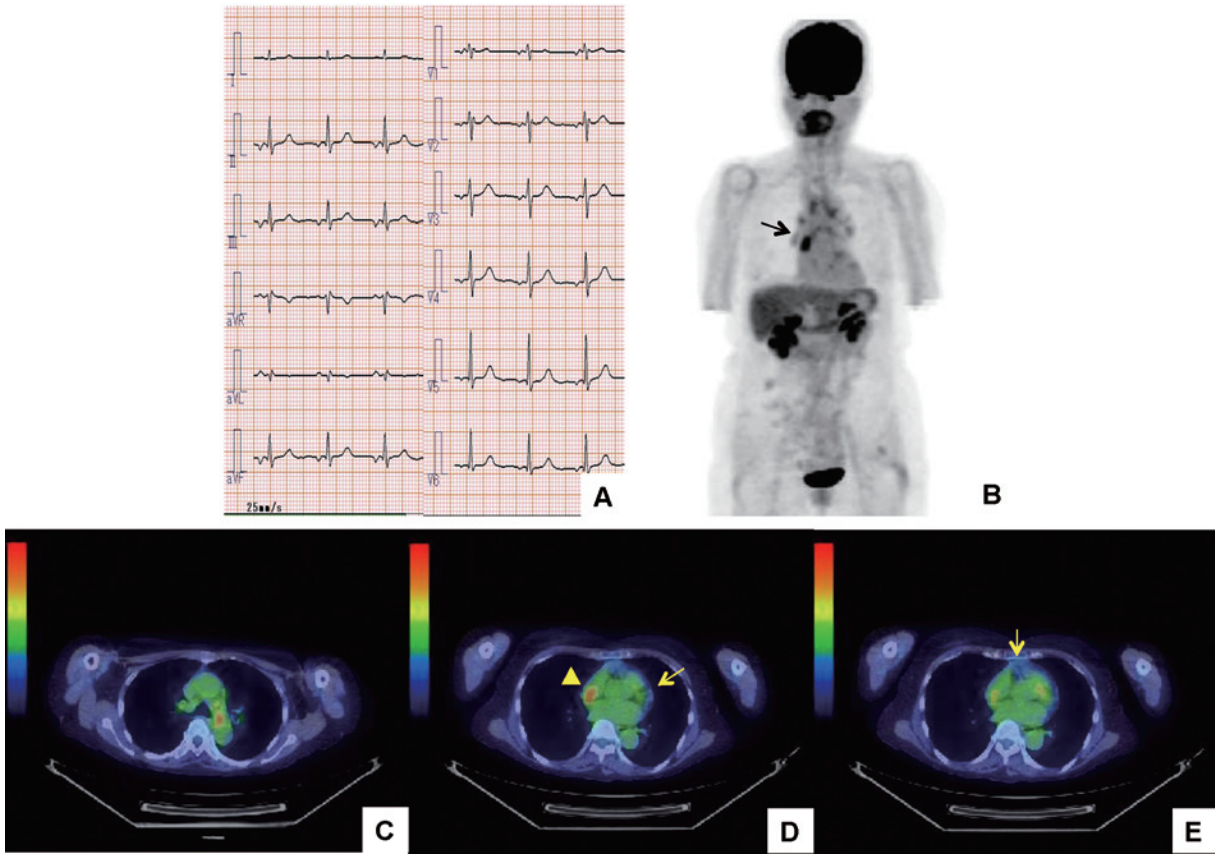

Figure 1. **A:** Twelve-lead electrocardiography showing ectopic atrial rhythm (p wave axis: -50°). **B-E:** ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) showing strong ^{18}F-FDG uptake in the eyes, mediastinal lymph nodes, and right atrium. No ^{18}F-FDG uptake was found in the thoracic aorta or coronary artery. Arrows: coronary artery. Arrow heads: right atrial mass.

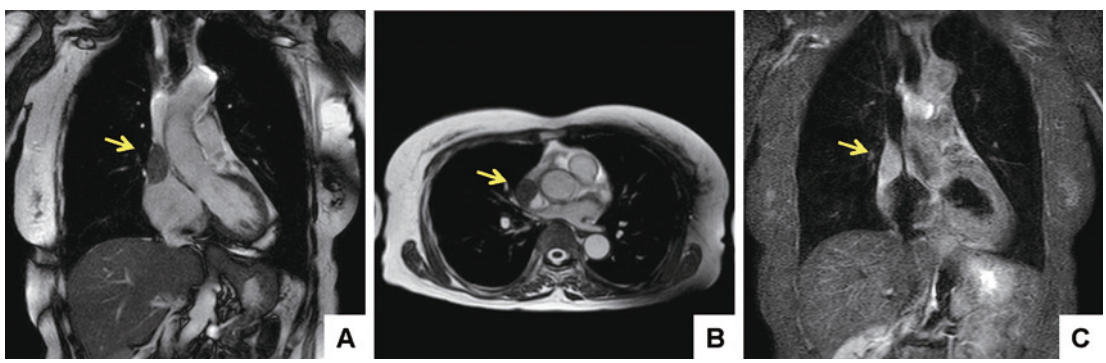

Figure 2. **A**, **B:** T1-weighted magnetic resonance imaging (MRI) showing a well-demarcated intracavitary right atrial mass, extending into the superior vena cava. **C:** T2-weighted MRI showing a hyperintense mass.

quirement in comprehensive diagnostic criteria for IgG4-RD (i.e., ratio of IgG4+/IgG+ cells > 40% and > 10 IgG4 + plasma cells/HPF together with fibrosis).[13] Thus, diagnosis of IgG4-RD with myocardial involvement relied on the extent of infiltrating IgG4-positive plasma cells. Steiner, *et al*. immunohistochemically examined the features of inflammatory infiltrates in calcified AVs.[15] Mild infiltration of IgG4-positive plasma cells was observed in 13 of 15 cases with a calcified AV, but there were no cases that fulfilled the histological criteria of IgG4-RD.[15] Hourai, *et al*. comprehensively analyzed the prevalence of IgG4-positive lymphoplasmacytic infiltration in 103 consecutive cardiovascular surgical samples from 98 patients with various cardiovascular diseases.[16] Infiltration of IgG 4-positive cells was detected in 5 of 24 cases with aortic stenosis, one of which fulfilled histological criteria of IgG 4-RD.[16] However, other systemic manifestations of IgG4-RD or fibrosis in a storiform pattern and phlebitis with

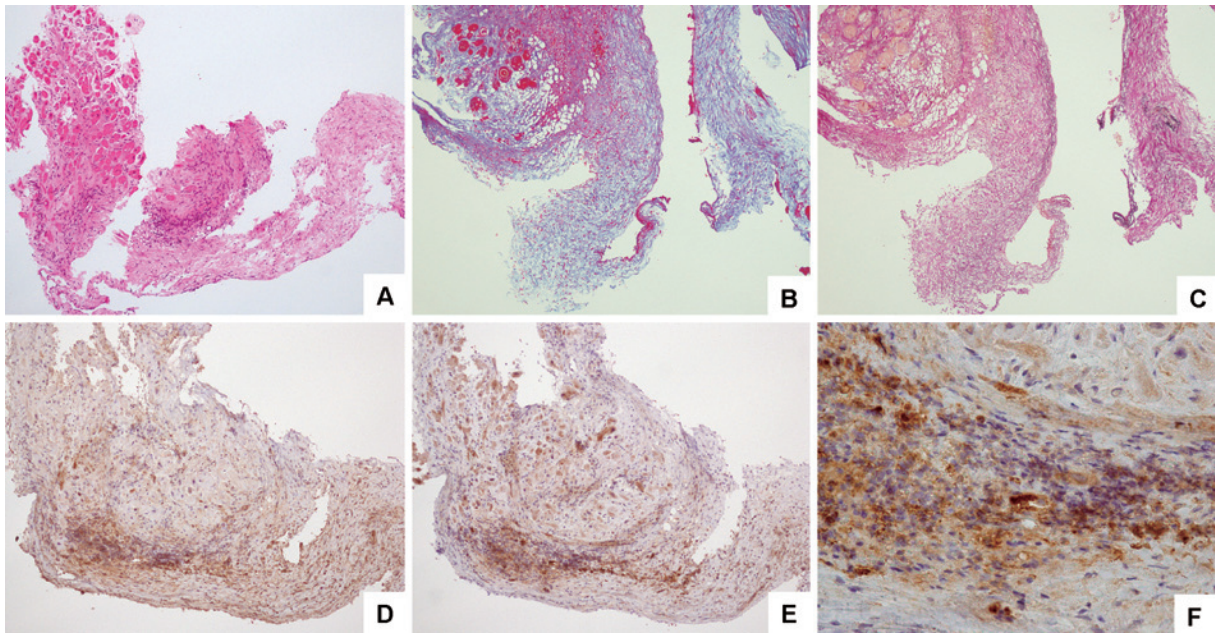

Figure 3. Histological sections of percutaneous transcatheter biopsy specimens from the right atrium. **A:** Lymphocytic and plasma cell infiltration of the right atrial myocardium together with an area of massive replacement fibrosis (arrow), hematoxylin and eosin staining (original magnification 100 ×). **B**, **C:** Azan staining (**B**) and Elastica van Gieson staining (**C**) showing an area of massive fibrosis (100 ×). **D:** Most of the inflammatory cells were positive for IgG-immunohistochemical staining (100 ×). **E:** More than 50% of the IgG-positive cells were reactive to IgG4-immunohistochemical staining (100 ×). **F:** High-power magnification of Figure 2C (400 ×). A large number of plasma cells expressed IgG4 (more than 10 per high-power fields).

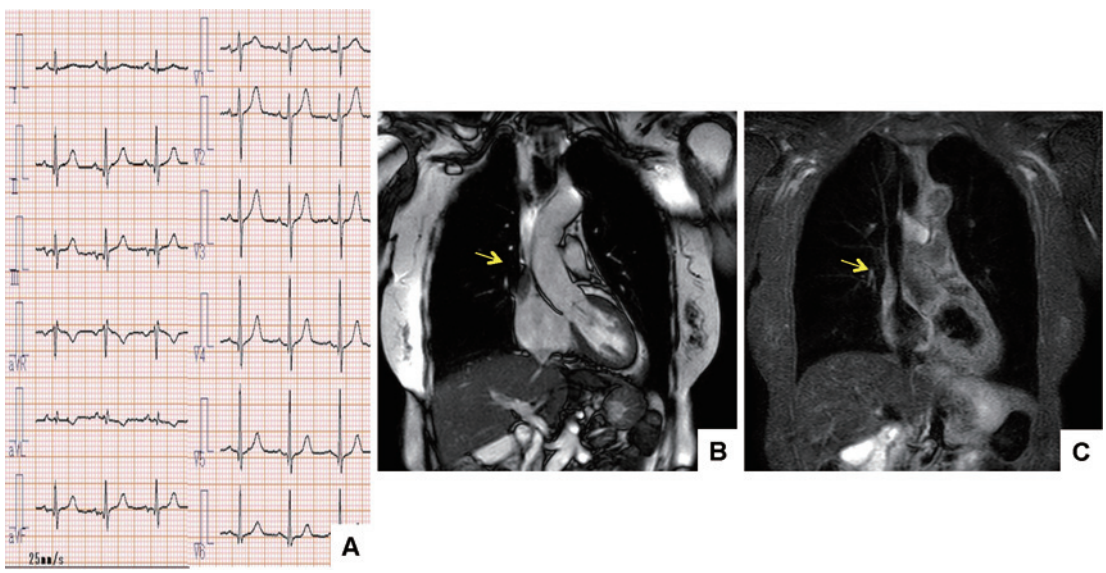

Figure 4. **A:** Twelve-lead electrocardiography showing normal sinus rhythm (p wave axi**s:** 5°) 2 weeks after commencement of steroid therapy. **B**, **C:** T1-weighted (**B**) and T2-weighted (**C**) MRI images 4 weeks after commencement of steroid therapy.

obliteration of the lumen, other typical histological features of IgG4-RD, were not observed in these cases.[16] Although there are no available data for an intracavity mass in the heart, infiltration of IgG4-positive plasma cells may be observed as a non-specific finding in cardiovascular disorders induced by atherosclerosis, inflammation, and infection. These findings indicate the importance of comprehensive analysis, including analysis of systemic complications and hematologic studies, for the diagnosis of IgG4-RD with myocardial involvement. The absence of storiform fibrosis and obstructive phlebitis in our case is not surprising because the prevalence of these findings in the needle biopsy specimens is relatively low.[13] Nevertheless, prevalence of storiform fibrosis and obstructive phle-

Table II. Myocardial Involvement in IgG4-Related Disease, Summary of Histologically Confirmed Cases

	Age/ Sex	Histological diagnosis	Localization	Clinical manifestation	Other systemic involvement	Serum IgG4 levels (mg/dL)	Treatment	Relapse after surgery	References
1	55/F	Open biopsy	RA, SVC	Heart block Sick sinus syndrome	none	N/A	Pacemaker	-	5
2	59/F	Surgically resected tissue	AV, MV, LA	Aortic regurgitation Heart block	Lacrimal gland	65.9 (post surgery)	Resection/ Valvuloplasty Pacemaker	+	7
3	58/F	Surgically resected tissue	RVOT, PV	RVOT obstruction with syncope	none	64.2 (post surgery)	Resection/ Valvuloplasty	-	6
4	60/F	Surgically resected tissue	AV	Aortic regurgitation	none	90 (post surgery)	Resection/ Valvuloplasty	+	8
5	70/F	Surgically resected tissue	AV (BAV)	Aortic stenosis	Submandibular gland, Pancreas	1363 (post surgery)	Resection/ Valvuloplasty Rituximab	-	8
6	64/F	Surgically resected tissue	AV, MV	Aortic regurgitation Mitral stenosis	Lacrimal gland	N/A	Resection/ Valvuloplasty	+	9
7	52/M	Surgically resected tissue	RV (apex)	Chest pain	Ascending aorta	227 (post surgery)	Resection	-	10
8	64/M	Surgically resected tissue	RVOT, PV	RVOT obstruction	none	259	Resection/ Valvuloplasty	+	11
9	82/M	Surgically resected tissue	AV	Aortic stenosis	Retroperitoneum, kidney	2280	Valvuloplasty Prednisolone	-	12
10	69/F	Transcatheter biopsy	RA, SVC	Ectopic atrial rhythm Chest discomfort	Lacrimal gland, Bronchial asthma, Submandibular gland	816	Prednisolone	N/A	Our case

AV indicates aortic valve; MV, mitral valve; LA, left atrium; RA, right atrium; SVC, superior vena cava; PV, pulmonary valve; BAV, bicuspid aortic valve; RV, right ventricle; RVOT, right ventricular outflow tract; and N/A, not available.

bitis in IgG4-RD with myocardial involvement needs to be analyzed in the near future.

The etiology of IgG4-RD with myocardial involvement remains unclear. IgG4-RD is associated with a predominantly type 2 T-helper-cell cytokine profile, and infiltration of regulatory T cells is thought to be involved in its pathogenesis.[2] Activation of these T cells has been shown to be triggered by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), though specific PAMPs or DAMPs responsible for the pathogenesis of IgG4-RD have not been determined.[2] PAMPs or DAMPs are recognized by Toll-like receptors and nucleotide-binding oligomerization domain-containing protein 2 in monocytes/macrophages and basophils, leading to abnormal immune responses.[2] In 10 IgG 4-RD cases with myocardial involvement, 8 cases were associated with valvular lesions, especially AVs (Table II). Although there are few macrophages in intact valves, infiltration of macrophages is known to be an early event in the development of atherosclerotic and degenerated valves.[17-19] The macrophages in valves can be stimulated by PAMPs or DAMPs in the blood, leading to an abnormal immune response in IgG4-RD. In the present case, it is possible that an embryologic remnant of the valves or crista terminalis within the right atrium served as a template of the inflammatory mass. Further investigation is needed to determine the pathogenesis of myocardial lesions in IgG4-RD.

In cases with cardiac masses, histological diagnosis of cardiac masses affords clinical guidance for the decision regarding treatment strategy. Endomyocardial biopsy for a suspected cardiac tumor has been shown to be a reasonable approach for its differential diagnosis if the diagnosis cannot be established by noninvasive modalities or less invasive (noncardiac) biopsy.[20] Although transesophageal echocardiography (TEE)-guided percutaneous transcatheter biopsy has been widely used in this setting, general anesthesia is required to perform it safely. ICE is known to give compatible or superior imaging quality to TEE in guiding transcatheter endomyocardial biopsy without the need for general anesthesia.[21] Although several case reports and the present case showed the usefulness and safety of ICE in differential diagnosis of cardiac masses including malignant tumors,[22-25] the diagnostic accuracy and complication rate of ICE-guided percutaneous transcatheter biopsy for cardiac masses need to be investigated.

EAR is known to be a relatively benign condition, but it possibly reflects perturbation of sinus node function or dominant pacemaker activity of the ectopic focus in the atrium. In the present case in which there was an inflammatory mass localized in the right atrium, steroid therapy led to recovery of sinus rhythm from EAR, followed by reduction of the mass volume and T2 signal intensity in MRI. Thus, it is likely that inflammation or mechanical compression of the sinus node by IgG4-RD was responsible for EAR in the present case. In other words, EAR may be a clue to suspect the presence of a right atrial mass, particularly in patients with systemic inflammatory diseases such as IgG4-RD or malignant tumors. Further experience is needed to demonstrate the prevalence and significance of EAR in this clinical setting.

Disclosures

Conflicts of interest: None declared.

References

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012; 366: 539-51.
2. Yamamoto M, Takahashi H, Shinomura Y. Mechanisms and assessment of IgG4-related disease: lessons for the rheumatologist. Nat Rev Rheumatol 2014; 10: 148-59.
3. Tajima M, Nagai R, Hiroi Y. IgG4-related cardiovascular disorders. Int Heart J 2014; 55: 287-95.
4. Sakamoto A, Nagai R, Saito K, *et al*. Idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pericarditis--retrospective analysis of 11 case histories. J Cardiol 2012; 59: 139-46.
5. Song C, Koh MJ, Yoon YN, Joung B, Kim SH. IgG4-related sclerosing disease involving the superior vena cava and the atrial septum of the heart. Yonsei Med J 2013; 54: 1285-8.
6. Kouzu H, Miki T, Mizuno M, *et al*. Inflammatory myofibroblastic tumor of the heart. Overlap with IgG4-related disease? Circ J 2014; 78: 1006-8.
7. Yamauchi H, Satoh H, Yamashita T, *et al*. Immunoglobulin G4-related disease of the heart causing aortic regurgitation and heart block. Ann Thorac Surg 2013; 95: e151-3.
8. Maleszewski JJ, Tazelaar HD, Horcher HM, *et al*. IgG4-related disease of the aortic valve: a report of two cases and review of the literature. Cardiovasc Pathol 2015; 24: 56-9.
9. Besik J, Pirk J, Netuka I, *et al*. Aortic and mitral valve replacement due to extensive inflammatory immunoglobulin G4-related pseudotumor. Ann Thorac Surg 2015; 100: 1439-41.
10. Li L, Wang Z, Xu P, Ruan Y, Jiang W, Wu Z. Cardiac mass, aortic intramural hematoma, and IgG4-related disease: A case report. Ann Vasc Surg 2016; 35: e5-8.
11. Ishida M, Sakaguchi T, Miyagawa S, *et al*. Right ventricular outflow tract obstruction due to immunoglobulin G4-related disease. Ann Thorac Surg 2017; 103: e235-7.
12. Bruls S, Courtois A, Delvenne P, *et al*. IgG4-related disease causing rapid evolution of a severe aortic valvular stenosis. Ann Thorac Surg 2017; 103: e239-40.
13. Umehara H, Okazaki K, Masaki Y, *et al*. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Pathol 2012; 22: 21-30.
14. Miller DV, Tazelaar HD. Cardiovascular pseudoneoplasms. Arch Pathol Lab Med 2010; 134: 362-8.
15. Steiner I, Krbal L, Rozkoš T, Harrer J, Laco J. Calcific aortic valve stenosis: Immunohistochemical analysis of inflammatory infiltrate. Pathol Res Pract 2012; 208: 231-4.
16. Hourai R, Kasashima S, Sohmiya K, *et al*. IgG4-positive cell infiltration in various cardiovascular disorders - results from histopathological analysis of surgical samples. BMC Cardiovasc Disord 2017; 17: 52.
17. Leopold JA. Cellular mechanisms of aortic valve calcification. Circ Cardiovasc Interv 2012; 5: 605-14.
18. Soeki T, Sata M. Inflammatory biomarkers and atherosclerosis. Int Heart J 2016; 57: 134-9.
19. Kono M, Aoyagi S, Okazaki T, Tayama KI. Aortic stenosis in a patient with Sjogren' disease. Int Heart J 2016; 57: 251-3.
20. Cooper LT, Baughman KL, Feldman AM, *et al*. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation 2007; 116: 2216-33.
21. Jongbloed MR, Schalij MJ, Zeppenfeld K, Oemrawsingh PV, van der Wall EE, Bax JJ. Clinical applications of intracardiac echocardiography in interventional procedures. Heart 2005; 91: 981-90.
22. Higo T, Takemoto M, Ogawa K, *et al*. Intracardiac echocardiography-guided cardiac tumor biopsy. Circ J 2009; 73: 381-3.
23. Kamiya K, Sakakibara M, Yamada S, *et al*. Diffuse large B-cell lymphoma diagnosed by intracardiac echocardiography-guided cardiac tumor biopsy. Intern Med 2012; 51: 1043-7.
24. Azzalini L, de Hemptinne Q, Asgar A, Ibrahim R. Right atrial mass in a patient with breast cancer: percutaneous transcatheter biopsy under intracardiac echocardiography guidance. BMJ Case Rep 2016; 10.1136/bcr-2016-215146.
25. Park KI, Kim MJ, Oh JK, *et al*. Intracardiac echocardiography to guide biopsy for two cases of intracardiac masses. Korean Circ J 2015; 45: 165-8.