Successful Transcatheter Diagnosis and Medical Treatment of Right Atrial Involvement in IgG4-related Disease
A Case Report and Review of the Literature

Toshiyuki Yano,1 MD, Motohisa Yamamoto,2 MD, Atsushi Mochizuki,1 MD, Toshifumi Ogawa,1 MD, Nobutaka Nagano,1 MD, Takefumi Fujito,1 MD, Junichi Nishida,1 MD, Daigo Nagahara,1,3 MD, Koki Abe,1 MD, Takayuki Miki,1 MD, Chisako Suzuki,2 MD, Hiroki Takahashi,2 MD, Hatsue Ishibashi-Ueda,4 MD and Tetsuji Miura,1 MD

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 (Table I),5-12) 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.

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

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). 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography showed 18F-FDG uptake in the eyes and hilar/mediastinal lymph nodes (Figure 1B), typical findings in IgG4-RD. In addition, strong 18F-FDG uptake was observed in the right atrium (Figure 1B-E). No 18F-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...
plasma cells in one high-power field with an IgG4/IgG ratio of more than 0.5) as shown in Figure 3D-F. 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 methotheial/monocytic incidental cardiac exsiccences. In 2013, Song, et al. and we reported cases of a cardiac pseudotumor that met with the pathological diagnostic criteria of IgG4-RD. Yamachi, et al. reported aortic valve (AV) involvement in IgG4-RD. Thereafter, several cases of myocardial involvement in IgG4-RD with histological confirmation were reported, but surgical resection or open biopsy of affected tissues was needed for diagnosis in all IgG4-RD cases with myocardial involvement. 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, which mimics large-vessel vasculitis. In contrast, valvular dysfunction in IgG4-RD is often an unexpected finding in pathological analysis of surgically excised valves, predominantly the AV (Table 1). Importantly, relapse after surgical resection was observed in three of five IgG4-RD cases with AV dysfunction. 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. 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.

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: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) showing strong ¹⁸F-FDG uptake in the eyes, mediastinal lymph nodes, and right atrium. No ¹⁸F-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.

Requirement in comprehensive diagnostic criteria for IgG4-RD (i.e., ratio of IgG4+/IgG+ cells > 40% and > 10 IgG4 + plasma cells/HPF together with fibrosis). 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. 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. 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. Infiltration of IgG4-positive cells was detected in 5 of 24 cases with aortic stenosis, one of which fulfilled histological criteria of IgG4-RD. However, other systemic manifestations of IgG4-RD or fibrosis in a storiform pattern and phlebitis with...
obliteration of the lumen, other typical histological features of IgG4-RD, were not observed in these cases. 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. Nevertheless, prevalence of storiform fibrosis and obstructive phle-
bits 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. 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. DAMPs 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. In 10 IgG4-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. 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.

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

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

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.

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. Although trans-esophageal 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. Although several case reports and the present case showed the usefulness and safety of ICE in differential diagnosis of cardiac masses including malignant tumors, 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