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【 CASE REPORT 】

# IgG4-related Disease with a Cardiac Mass Causing Cerebral Infarction

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**Abstract:**
Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by infiltration of extensive IgG4-positive plasma cells and lymphocytes. Although IgG4-RD has been observed in almost all organs, it rarely affects the myocardium. Cardiovascular lesions of IgG4-RD appear as aortic (aortic aneurysm and aortitis) and pericardial (constrictive pericarditis) lesions as well as pseudotumors around the coronary arteries. We herein report a case of IgG4-RD with a cardiac mass in the right atrium involving a sinus node. This condition caused arrhythmia and repeated strokes. We successfully treated the patient through resection of the cardiac mass, catheter ablation and immunosuppressive therapy.

**Key words:** IgG4-related disease, cardiac mass, cerebral infarction

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## Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a clinical entity characterized by the infiltration of IgG4-positive plasma cells and lymphocytes (1). In 2001, Hamano et al. reported for the first time that serum IgG4 concentrations were elevated in patients with autoimmune pancreatitis (AIP) (2). The pancreatic research team of the Ministry of Health, Labor, and Welfare Japan showed that AIP is related to IgG4 (3). Subsequently, many reports have shown that IgG4-RD involves nearly all organs (4).

Cardiovascular disorders of IgG4-RD are typically characterized by aortitis, periaortitis, pericarditis, and pseudotumor around the coronary arteries (5). Several cases of IgG4-RD with a cardiac mass have been reported recently (6-17). However, there have been no cases of IgG4-RD with a cardiac mass that caused a cerebral infarction.

We herein report a case of IgG4-RD with a cardiac mass in the right atrium that involved a sinus node. This mass caused arrhythmia and repeated strokes. We successfully treated the patient through resection of the cardiac mass, catheter ablation and immunosuppressive therapy.

## Case Report

In September 2018, a 58-year-old man was admitted to a hospital with recurrent episodes of dysarthria and dysesthesia. He was diagnosed with paroxysmal atrial fibrillation and placed on apixaban for a week. His physical examination findings were nearly normal, although diffusion-weighted imaging of brain magnetic resonance imaging (MRI) revealed hyperintense lesions in the left parietal lobe (Fig. 1A). During Holter monitoring, atrial fibrillation and frequent episodes of sinus pause (maximum 11 seconds) were observed. The patient developed cerebral infarction despite taking anticoagulants. Consequently, he was treated with argatroban and clopidogrel for atherothrombotic cerebral infarction.

Laboratory tests revealed no risk factors for arteriosclerosis, such as diabetes mellitus or dyslipidemia. Antinuclear and anti-neutrophil cytoplasmic antibodies were negative. Serum levels of coagulation factors were normal. Tests for anti-cardiolipin antibodies and lupus anticoagulants were

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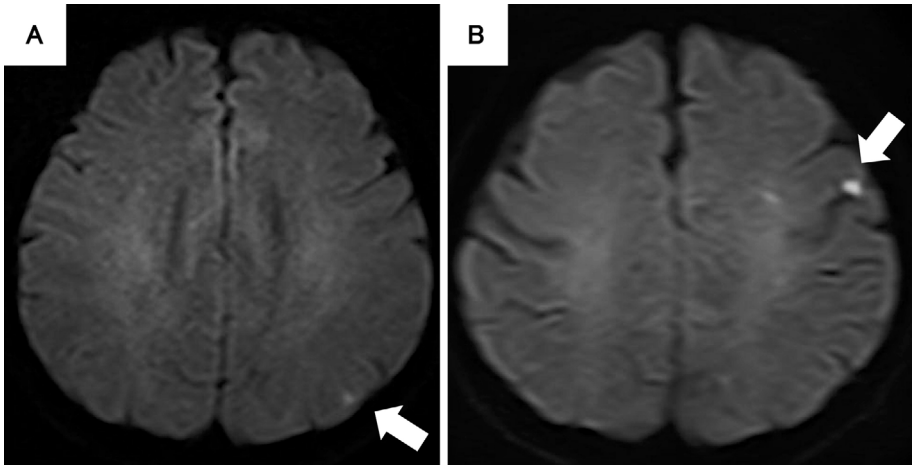


**Figure 1.** **Diffusion-weighted imaging of brain magnetic resonance imaging (MRI). (A) was taken on admission and (B) on day 7 of hospitalization. MRI revealed hyperintense lesions in the left parietal lobe (A, arrow). Despite the treatment, a new cerebral infarction in the left frontal lobe appeared (B, arrow).**

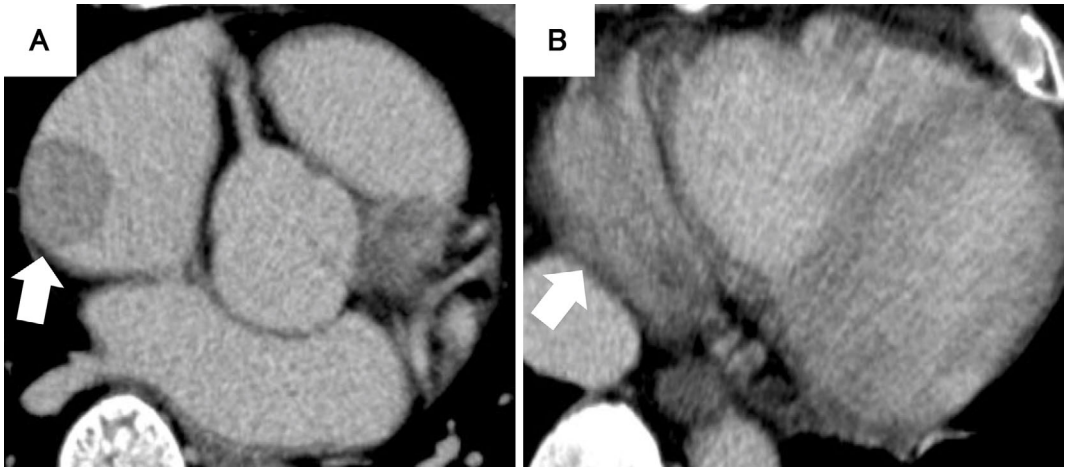


**Figure 2.** **Contrast-enhanced computed tomography (CT). Contrast-enhanced CT showing a well-demarcated mass in the right atrium (A, arrow) and right atrioventricular groove (B, arrow).**

also negative.

Carotid ultrasound showed no significant narrowing of the arteries. In contrast, an echocardiogram revealed a mass in the right atrium. Paradoxical embolism was suspected, but probe patency of the oval foramen was not observed. Contrast-enhanced computed tomography (CT) showed a well-demarcated mass in the right atrium and right atrioventricular groove (Fig. 2). No other mass was detected on enhanced whole-body CT.

Myxoma was suspected as the cause of the cerebral infarction rather than a metastatic tumor. Although his symptoms were relieved by the prescribed treatment, brain MRI revealed new cerebral infarctions in the left frontal lobe on day 7 of hospitalization (Fig. 1B). He was transferred to our hospital for open chest surgery.

The mass extended from the superior vena cava to the right atrial free wall. Another mass in the interatrial septum was also detected. Resection of the masses in the right atrium and interatrial septum, reconstruction of the right atrium and left atrial appendage excision were performed. Pericardial dissemination was suspected, so complete excision of the mass could not be performed. The masses were pale yellow in color with a smooth surface. Histologically, they were composed of the infiltration of lymphocytes and fibrotic tissues (Fig. 3A-C). Plasma cells were also observed around lymphoid follicles, and the infiltration of lymphocytes and plasma cells around specialized cardiac muscle cells was observed in the sinus node (Fig. 3D). Immunostaining for IgG4 showed a significant number of IgG 4-positive plasma cells (Fig. 3E). The proportion of IgG4-/IgG-positive cells was 72.3% (Fig. 3E, F). There were no cell abnormalities or monoclonality suggestive of malignancy. The serum IgG4 levels on admission to the previous hospital increased to 832 mg/dL (normal range: 5.0-117.0). The serum IgG level was 1,656 mg/dL (normal range: 820-1,740). The patient met the comprehensive diagnostic crite-

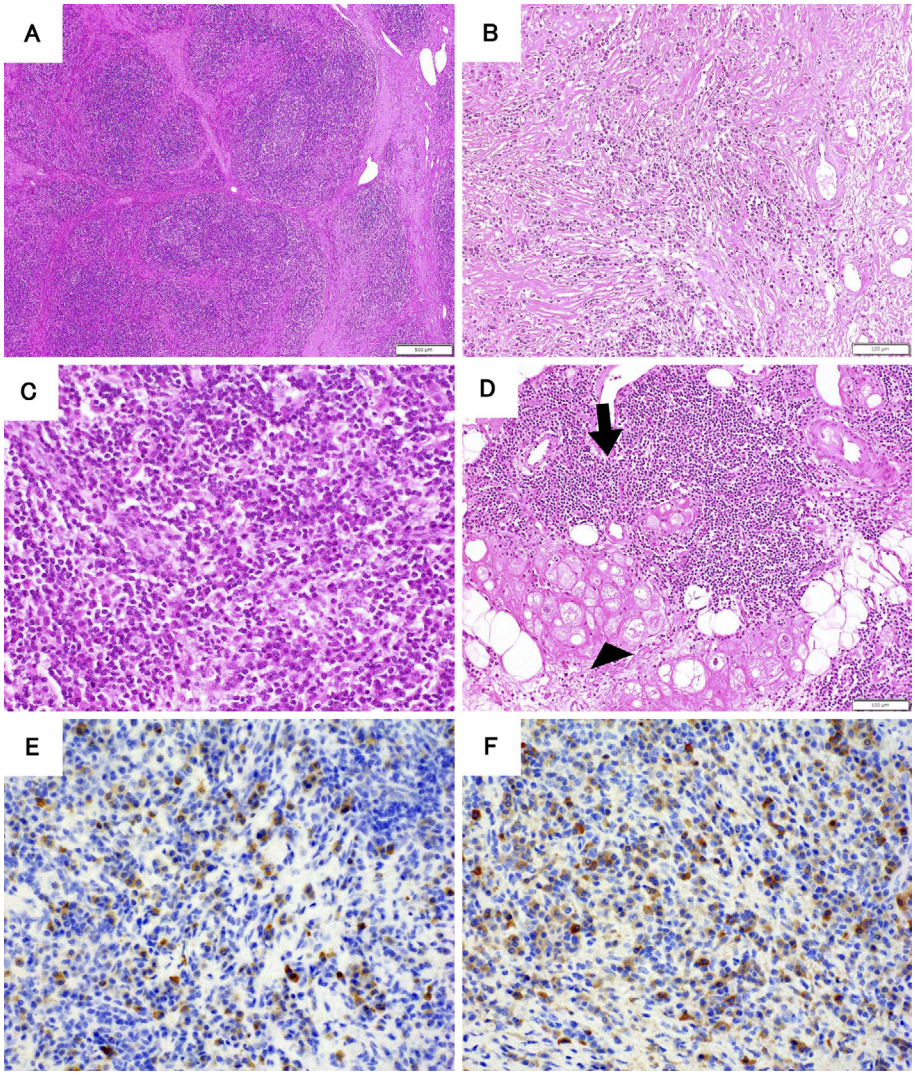


**Figure 3.** **Histopathological and immunohistochemical findings of the cardiac tumor. Resected tissues showed dense fibrosis and extensive infiltration of lymphocytes and plasma cells [A: Hematoxylin and Eosin (H&E) staining, 4×, B: H&E staining, 20×, C: H&E staining, 40×]. Infiltration of lymphocytes and plasma cells (arrow) around specialized cardiac muscle cells (arrow head) was also observed in the sinus node (D: H&E staining, 20×). Immunohistochemical analyses revealed significant infiltration of IgG4-positive plasma cells (E: Immunohistochemical staining for IgG4, 40×). The proportion of IgG4-/IgG-positive cells was 72.3% from serial sections (E and F, F: Immunohistochemical staining for IgG, 40×).**

ria for IgG4-RD: 1) serum IgG4 concentration >135 mg/dL, and 2) >40% of IgG+ plasma cells being IgG4+ and >10 cells/high-powered field in a biopsy sample (18). No typical storiform pattern or phlebitis with obliteration of the lumen were observed.

Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed an increased uptake only in the mass at the right atrioventricular groove and post-operation wound (Fig. 4). No other uptake was observed in the salivary glands or lymph nodes. The patient's postoperative course was uneventful. A pacemaker was implanted due to sick sinus syndrome and resection of the sinus node by surgery. Catheter ablation was performed to prevent atrial fibrillation. In November 2018, prednisolone was administered at 40 mg/day as the initial dose to prevent the recurrence of stroke due to the residual mass. In April 2019, azathioprine was added to taper the prednisolone as the patient's serum IgG4 level gradually increased. The prednisolone dosage was gradually tapered to 5 mg/day without re-elevation of the serum IgG4 levels.

The patient remained asymptomatic at two years post-surgery. The mass in the right atrioventricular groove decreased in size (Fig. 5).

## Discussion

IgG4-RD is a systemic inflammatory disease characterized by infiltration of IgG4-positive plasma cells and lymphocytes (1). Tissue infiltration by IgG4-positive plasma cells and extensive fibrosis leads to mass formation. Pseudotumor

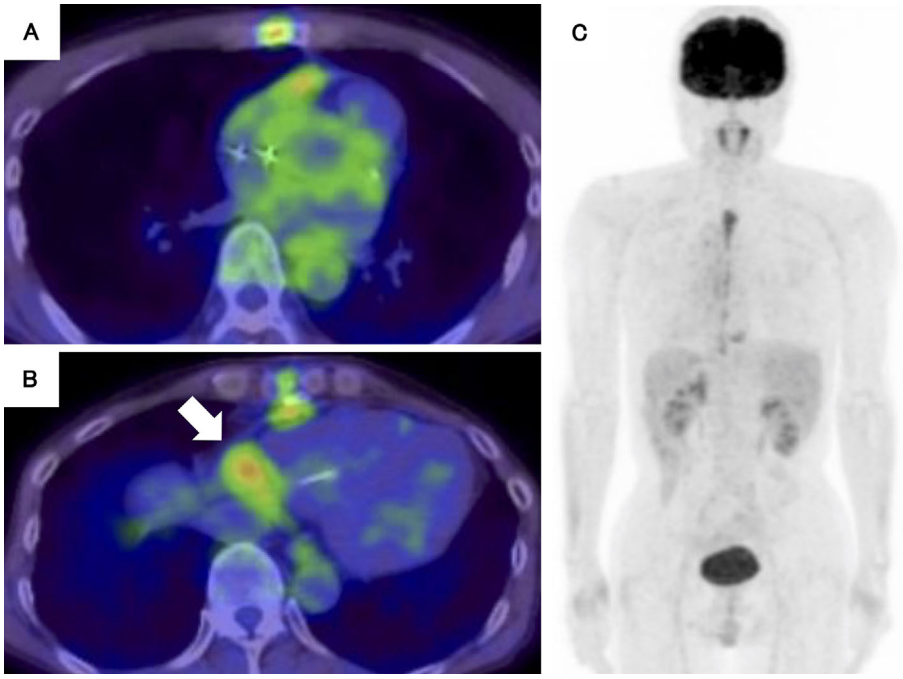


**Figure 4.** **Fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET showed an increased uptake only in the mass in the right atrioventricular groove (B, arrow) and postoperative wound (A) two months after the operation. No other uptake was observed in the salivary glands or lymph nodes (C).**

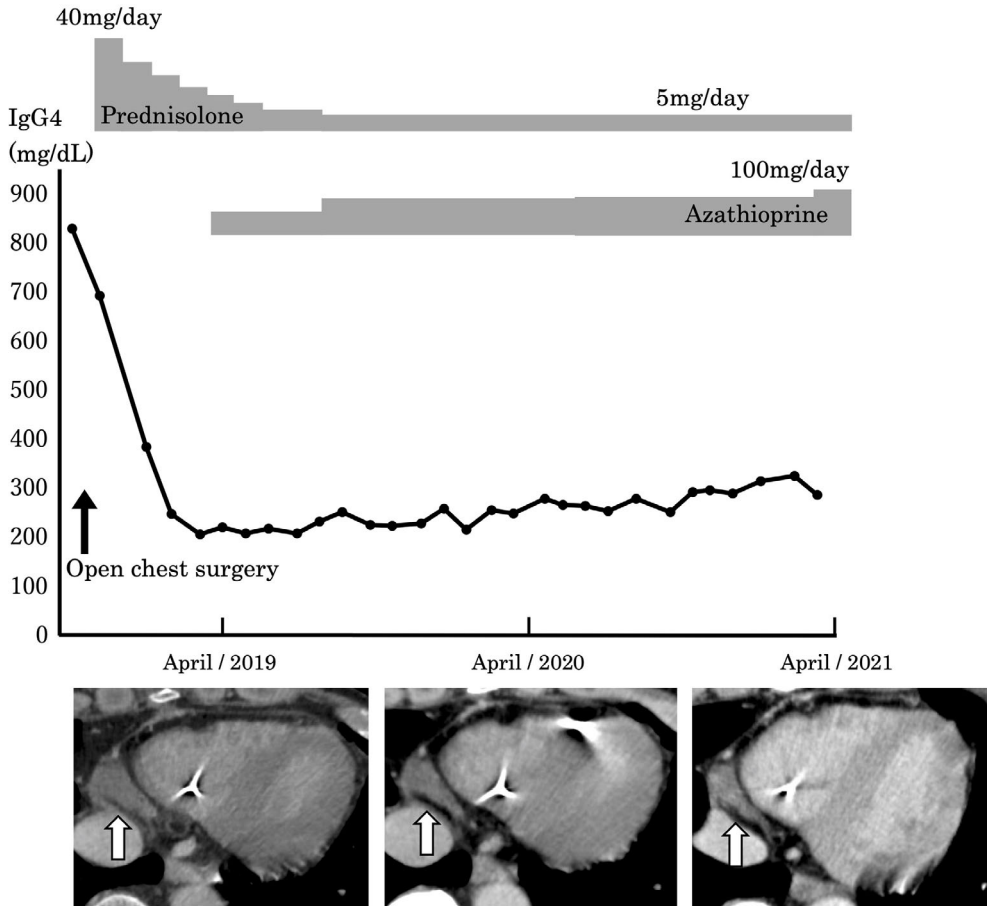


**Figure 5.** **Clinical course of this patient. Prednisolone was administered to prevent the recurrence of stroke. Azathioprine was added to taper the prednisolone as the patient's serum IgG4 level gradually increased. The patient remained asymptomatic two years post-surgery, and the mass in the right atrioventricular groove gradually decreased in size (arrow).**

**Table. The Clinical and Demographic Characteristics of IgG4-related Disease in the Myocardium.**

| Age/Sex | Symptoms | Serum IgG4 levels (mg/dL) | Cardiac mass localization | Other organ involvement | Treatment | | | References |
|---|---|---|---|---|---|---|---|---|
| | | | | | Tumor resection | Pacemaker implantation | Immuno-suppressant | |
| 55 / F | Syncope | N.D. | RA, SVC | - | - | + | - | 6 |
| 59 / F | Dyspnea, Ocular pain | 65.9 | AV, LA | Lachrymal gland s/o | + | + | PSL | 7 |
| 59 / F | Chest pain, Dyspnea | N.D. | LV | Oculomotor muscle, Lymph node | - | + | PSL, Cyclosporine | 8 |
| 58 / F | Syncope | 64.2 | RVOT, PV | - | + | - | - | 9 |
| 64 / F | Dyspnea | N.D. | AV, MV | - | + | - | - | 10 |
| 52 / M | Chest pain | 227 | RV | - | + | - | PSL | 11 |
| 64 / M | - | 259 | RVOT | - | + | - | PSL | 12 |
| 82 / M | - | 2280 | AV | Lymph node, Renal hilum | + | - | PSL | 13 |
| 69 / F | Orbital pain, Chest pain | 816 | RA | Lymph node, eyes | - | - | PSL | 14 |
| 61 / M | Jaundice, Fatigue | 1440 | RA, CS | Submandibular gland, Lymph node, Pancreas | - | - | PSL | 15 |
| 48 / M | Headache | 130 | LV | Lymph node | - | - | PSL, AZA | 16 |
| 69 / M | Vertigo, palpitation | 1450 | RA, CS | Lachrymal, Salivary, Submandibular glands | - | - | PSL | 17 |
| 58 / M | Dysarthria, Dysesthesia | 832 | RA, CS, RAG | - | + | + | PSL, AZA | Our case |

N.D: no data, RA: right atrium, SVC: superior vena cava, SOB: shortness of breath, AV: aortic valve, LA: left atrium, PSL: prednisolone, LV: left ventricle, RVOT: right ventricular outflow tract, PV: pulmonary valve, MV: mitral valve, RV: right ventricle, CS: cardiac septum, AZA: azathioprine, RAG: right atrioventricular groove

caused by IgG4-RD has been reported primarily in the lungs and liver (19). In 2004, cardiac plasma cell granulomas were successfully treated with immunosuppressive therapy without a histological examination by IgG4 immunostaining (20).

The diagnosis of IgG4-RD is based on histopathological findings, including fibrosis. It is marked by the infiltration of lymphocytes and IgG4-positive plasma cells (18). In 2013, Song et al. (6) and Yamauchi et al. (7) reported cardiac masses that were consistent with the pathological diagnostic criteria for IgG4-RD. Thereafter, several cases of IgG 4-RD with cardiac masses were reported (8-17) (Table). The initial symptoms were non-specific and included syncope (6, 9), dyspnea (7, 8, 10) and chest pain (8, 11, 14).

Only a few cases of cerebral infarction in IgG4-RD have been reported previously (21-23). The cause of cerebral infarction in these cases was an IgG4-related arterial lesion. In our case, magnetic resonance angiography showed neither stenosis nor an aneurysm of the cerebral arteries. The patient had no risk factors for arteriosclerosis. Probe patency of the oval foramen was not observed. Therefore, we believe that stroke in this case might have been caused by arrhythmia, which is evoked by lymphocyte and plasma cell infiltration of the sinus node. To our knowledge, this is the first reported case of IgG4-RD with a cardiac mass that involved a sinus node, causing arrhythmia and repeated strokes.

In patients suffering from IgG4-RD, elevated serum IgG4 concentrations are usually detected. Seven of the 13 patients with IgG4-RD with cardiac masses had high IgG4 levels (>135 mg/dL), although primary cardiac tumors are extremely rare, and secondary tumors are not common. Cardiac metastases are found in 9% of autopsy cases in which a primary tumor is detected (24). Cardiac myxoma is the most prevalent type of primary cardiac tumor in adults, accounting for up to 50-85% of all benign lesions (25). A retrospective study showed that cardiac myxoma causes embolism in 15.5% of patients (26). Initially, we believed that the stroke had been caused by a myxoma, as we were unable to detect the primary tumor. Primary cardiac myxoma most frequently (60-80%) affects the left atrium (27). In contrast, IgG4-RD with cardiac masses involves all regions of the heart.

Carbajal et al. reported a cardiac mass detected by FDG-PET in a patient with a medical history of IgG4-RD in the oculomotor muscle (8). FDG-PET is an effective method for conducting the clinical examination of IgG4-RD with cardiac masses. However, 6 of 13 patients with cardiac masses with IgG4-RD showed only myocardial involvement. Therefore, we believe that a histological diagnosis is critical for diagnosing cardiac masses with IgG4-RD, as malignant lymphoma mimics IgG4-RD.

A recent guideline recommends glucocorticoids as the first-line agents for remission induction therapy for IgG4-RD (28). Most patients respond well to this therapy. Postoperative immunosuppressive therapy is required. This is especially true in cases where complete resection of the mass is difficult because of the location. In our case, we administered glucocorticoids to treat the mass at the right atrioventricular groove and suspected pericardial involvement and

residual tiny masses.

In our case, the serum IgG4 level gradually increased during steroid tapering. Wallace et al. reported an elevation in serum IgG4 concentrations as a predictor of relapse (29). Brito-Zerón et al. reviewed 62 studies for therapy of IgG4-RD (30). They reported that relapse occurred in 33% of patients after initial treatment. Azathioprine was used most frequently, being used in 85% of cases as additional therapy. Therapeutic efficacy was reported in 81% of IgG4-RD patients treated with azathioprine. Therefore, we chose azathioprine as maintenance therapy. However, further investigations are required to identify which immunosuppressants are most effective against IgG4-RD with cardiac masses.

IgG4-RD has been reported in nearly all organs. If a cardiac mass is discovered in an atypical location without a primary tumor, IgG4-RD should be considered as a differential diagnosis. In addition, IgG4-RD with cardiac masses causing cerebral infarction should be treated with caution.

**The authors state that they have no Conflict of Interest (COI).**

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