CASE REPORT

IgG4-related Disease with a Cardiac Mass

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Abstract:
A 69-year-old man with palpitations and decreased blood pressure was referred. Echocardiography showed a mass in the right atrium and cardiac septum. The serum IgG4 level was 1450 mg/dl. A biopsy of the cardiac mass showed fibrosis with inflammatory cells and increased IgG4-positive plasma cells and lymphocytes. Flow cytometry and polymerase chain reaction of the immunoglobulin heavy chain did not demonstrate monoclonality. He was diagnosed with IgG4-related disease (IgG4-RD). IgG4-RD with a cardiac mass is rare and it is difficult to distinguish it from malignant lymphoma by a pathological examination alone. We therefore performed a biopsy and analyzed the clonality in order to make an accurate diagnosis of IgG4-RD.

Key words: IgG4-related disease, Non-Hodgkin Lymphoma, Cardiac mass

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Introduction

IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disease characterized by elevated serum IgG4 levels, increased IgG4-positive plasma cells and lymphocytes, and the tumor-like involvement of one or more exocrine glands or other extranodal sites with lymphoplasmacytic infiltrates and sclerosis (1). The major involved organs are the salivary glands, lacrimal glands, pancreas, and retroperitoneal space (1-5). IgG4-RD characteristically responds to glucocorticoid therapy (1).

Cardiac masses include hematoma, tumors, vegetations, calcific lesions, and other rare conditions. Cardiac tumors are rare and include a variety of benign and malignant entities. Reynen et al. reported that the frequency of primary cardiac tumors was 0.02% based on the data of 22 autopsy series (6). The most common tumors that involve the heart are metastatic neoplasms, the incidence of metastatic tumors of the heart was 1.23% in an autopsy series (7). Myxomas represent the most common benign tumor, whereas sarcomas account for most primary malignant neoplasms of the cardiac muscles (8). IgG4-RD of the heart, especially involving the cardiac muscles, is very rare. To our knowledge, there have been 13 reports of IgG4-RD affecting the heart (9-20), with 4 of those 13 reports on IgG4-RD of the atrium, ventricle, and ventricular septum (12, 13, 19, 20).

The diagnosis of IgG4-RD is based on the histopathologic features, disease site, and serum IgG4 levels. Malignant lymphoma is a histopathologic mimicker of IgG4-RD. Therefore, it is difficult to discriminate IgG4-RD involving a rare site from malignant lymphoma in daily practice. We herein report the case of a patient with IgG4-RD with a mass lesion in the right atrium that was difficult to discriminate from malignant lymphoma.

Case Report

A 69-year-old Japanese man was referred to our hospital because of vertigo, palpitations, and decreased blood pressure. Echocardiography showed a mass in the right atrium and cardiac septum. The serum IgG4 level was 1450 mg/dl. A biopsy of the cardiac mass showed fibrosis with inflammatory cells and increased IgG4-positive plasma cells and lymphocytes. Flow cytometry and polymerase chain reaction of the immunoglobulin heavy chain did not demonstrate monoclonality. He was diagnosed with IgG4-related disease (IgG4-RD). IgG4-RD with a cardiac mass is rare and it is difficult to distinguish it from malignant lymphoma by a pathological examination alone. We therefore performed a biopsy and analyzed the clonality in order to make an accurate diagnosis of IgG4-RD.

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sure. His medical history included appendicitis, cholecystitis, lumbar discitis, iliopsoas abscess, and spinal canal stenosis. A physical examination on admission showed swelling of the maxilla, bilateral lacrimal glands, and subcutaneous nodules of bilateral upper arms, but tachycardia and decreased blood pressure were not observed after the administration of verapamil hydrochloride.

Laboratory data are shown in Table 1. Blood cell counts and the liver and renal function were normal. Serum lactate dehydrogenase (LDH) was not elevated. The total protein level was 8.9 g/dL (normal range, 6.3-7.9), and the serum albumin level was 2.9 g/dL (normal range, 3.9-5.0). Serum IgG and IgG4 levels were 5294 mg/dL (normal range, 870-1700) and 1450 mg/dL (normal range, 4-108), respectively, whereas other immunoglobulin levels were in the normal ranges. However, serum IgG-κ type M-protein was detected by an immunofixation test. Soluble interleukin-2 receptor (sIL-2R) was 1672 U/mL (normal range, 246-742). The serum brain natriuretic peptide (BNP) level was 97.6 pg/mL (normal range, 0-18.4).

Echocardiography and computed tomography (CT) showed a right atrial tumor that infiltrated into the cardiac septum (Fig. 1A, B). 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG-PET/CT), which was performed after a cardiac mass biopsy, showed the accumulation of 18F-FDG in the cardiac muscle (maximum standardize uptake value [SUVmax], 5.2), mediastinal lymph nodes, lacrimal glands, salivary glands, and subcutaneous nodules in the bilateral upper arms (Fig. 1C). The electrocardiogram showed first-degree atrioventricular block (Fig. 1D).

Because of his symptoms of cardiac mass, tachycardia, and decreased blood pressure, cardiac mass reduction was urgently required. Therefore, the patient underwent a cardiac tumor biopsy. Flow cytometry showed a normal kappa/lambda ratio in the lymphocyte population (Fig. 2A). On low-magnification light microscopy, follicles of various sizes were found to be distributed irregularly in the tumor (Fig. 2B). Slightly atrophic germinal centers containing fibrosis and infiltrating small vessels were observed. At high magnification, a polymorphous population consisting of numerous mature plasma cells, plasmacytoid cells, and small-to medium-sized lymphocytes was found to have infiltrated diffusely (Fig. 2C). Staining with CD3 and CD20 showed a mixture of small and medium-sized lymphocytes and immunoblasts (Fig. 2D, E). Immunohistochemical studies of light chain determinants for interfollicular plasma cells, plasmacytoid cells, and B-immunoblasts demonstrated a polyclonal pattern (Fig. 2F, G). There were many IgG-positive cells in the lesion (Fig. 2H), with IgG4-positive cells accounting for over 50% of IgG-positive plasma cells (Fig. 2I).

IgG4-RD and malignant lymphoma are very rare in the cardiac muscle. The differential diagnosis between IgG4-RD and malignant lymphoma can be difficult when involving a rare disease site. Furthermore, IgG-κ M-protein was detected in this patient. We need to distinguish between IgG4-RD and malignant lymphoma carefully. Therefore, to examine the clonality of the cardiac biopsy specimen, polymerase chain reaction (PCR) of the immunoglobulin heavy chain (IgH) genes was performed using DNA extracted from fresh-frozen biopsy specimen as templates. A total of 100 ng of DNA was amplified by PCR (21). When the products were electrophoresed on a 4-20% gradient polyacrylamide gel (TEFCO, Tokyo, JAPAN), a single band representing the IgH gene, IgG4-RD was diagnosed.

The patient’s clinical course is shown in Fig. 4. With the daily administration of 30 mg prednisolone (0.6 mg/kg/day), the cardiac mass and subcutaneous nodule shrank, and the serum IgG4 level decreased. After 4 weeks’ administration of prednisolone, CT and echocardiography showed that the cardiac mass had shrunk even further but was still present (Fig. 5). The patient’s clinical course was uneventful for 12 months.

Table 1. Laboratory Findings on Admission.

| Blood Cell Count | Biochemical test |
|------------------|------------------|
| WBC 5300/μL     | TP 8.9 g/dL      | BNP 97.6 pg/mL |
| Neu 32.9 %      | Alb 2.9 g/dL     | IgG 5294 mg/dL |
| Eos 28.3 %      | T-Bil 0.3 mg/dL  | IgA 67 mg/dL   |
| Ba 2.8 %        | AST 34 U/L       | IgM 43 mg/dL   |
| Mo 7.0 %        | ALT 41 U/L       | IgG4 1450 mg/dL|
| Ly 29.0 %       | LDH 151 U/L      | sIL-2R 1672 U/mL|
| RBC 3.53 10^6/μL| Cr 0.78 mg/dL    | β2MG 4.2 mg/L  |
| MCV 86.7 fl     | Na 135 mEq/L     | Coagulation test |
| MCH 28.6 pg     | K 4.3 mEq/L      | PT 74 %       |
| MCHC 33.0 g/dL  | Cl 101 mEq/L     | APTT 32.3 sec |
| Hb 10.1 g/dL    | Ca 8.6 mg/dL     | Fib 312 mg/dL |
| Pt 264 10^3/μL  | CRP 0.27 mg/dL   | FDP 8.4 μg/dL |

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Discussion

IgG4-RD frequently involves the salivary glands, lacrimal glands, pancreas, lymph nodes, and retroperitoneal space (1-5). IgG4-RD involving the heart is very rare. Among the cases of IgG4-RD involving the heart (Table 2), the median age was 59.5 (range: 52-75) years, and the most
commonly affected regions were the coronary arteries and aortic and mitral valves. The most common first symptoms were syncope, dyspnea, and chest pain. However, sudden cardiac death occurred in some patients with coronary artery lesions. Regarding the treatment of IgG4-RD of the heart, nine cases have been reportedly treated via surgery, such as tumor resection and/or replacement of a cardiac valve (9, 10, 13, 15, 17-20). Two cases required pacemaker implantation (12, 13), and one case received rituximab treatment (18). The first-line, standard-of-care approach for most IgG4-RD patients is glucocorticoid administration. While previous reports showed that only three patients were treated

Figure 2. Histological findings of the cardiac mass. (A) Flow cytometry shows that the kappa/lambda ratio is in the normal range. (B) Hematoxylin and Eosin (H&E) staining (×40). Various sizes of follicles are distributed irregularly in the tumor. Slightly atrophic germinal centers containing fibrosis and infiltration of small vessels are observed. (C) H&E staining (×200). Proliferation of immunoblast-like cells and heavy infiltration of mature plasma cells and small lymphocytes are observed in the interfollicular area. (D, E) Staining with CD3 (D) and CD20 (E) shows a mixture of small and medium-sized lymphocytes and immunoblasts. (F, G) Immunohistochemical studies of light chain, kappa (F) and lambda (G), determinants for interfollicular plasma cells, plasma cytid cells, and B-immunoblasts demonstrate a polyclonal pattern (×100). (H) There are numerous IgG-positive cells in the lesion (×100). (I) Over 50% of the IgG-positive cells are IgG4-positive (×100).
with glucocorticoids, all three showed an uneventful course after the administration of glucocorticoids (10, 19, 20). In the present patient, only prednisolone was administered because of the multifocal lesions. The mass lesions shrank gradually, and the serum IgG4 level decreased (Fig. 4).

Cardiac IgG4-RD is very rare, so it is clinically important to discriminate between IgG4-RD and malignant lymphoma, which is a histopathologic mimicker of IgG4. There have been several reports of the development of non-Hodgkin’s lymphoma (NHL) superimposed on IgG4-RD (23-25). Among the cases of IgG4-RD with malignant lymphoma, especially that involving the ocular adnexa and salivary
glands, most showed MALT lymphoma (23, 26), and some IgG4-producing cells were identified as neoplastic (24). There have been several reports of IgG4-RD following malignant lymphoma (27-29). Therefore, it is difficult to discriminate IgG4-RD at a rare site from malignant lymphoma in daily practice.

To avoid inappropriate treatment in patients suspected of having malignant lymphoma, clarifying the clonality of the specimen is important. Several methods for examining the clonality have been reported, including flow cytometry, Southern blotting, and PCR of the IgH gene. For PCR of the IgH gene, DNA from not only fresh-frozen specimens but also formalin-fixed paraffin-embedded tissue samples can be used. In the present case, the clonality of the IgH gene was analyzed by PCR using fresh-frozen specimens, and no clonality was found. Based on the pathological findings and the PCR results, this patient was diagnosed with IgG4-RD. The patient was then treated with prednisolone, and inappropriate chemotherapy was avoided. However, we need to continue following this patient carefully for a long period because M-protein was detected.

In conclusion, this rare case of IgG4-RD with a cardiac mass was difficult to distinguish from malignant lymphoma by a pathological examination alone. We therefore performed a biopsy to analyze the clonality of the cardiac tumor and made an accurate diagnosis of IgG4-RD.

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

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**Table 2.** Cases of IgG4-related Disease with a Cardiac Mass.

| Case | Age (y) | Sex | Symptom | Site of disease | Treatment | Clinical course |
|------|---------|-----|---------|----------------|-----------|----------------|
| 1    | 63      | F   | Abdominal mass, SOB Pulitation | AAA | Operation | Uneventful for 5 mo |
| 2    | 75      | M   | Chest Pain | Pancreas, Parotid glands | Operation, Steroid | Angina-free for 4 mo |
| 3    | 61      | M   | Syncope, Dizziness | CA | Operation | Sudden death |
| 4    | 55      | F   | SOB, Leg edema | RA, AS | Pacemaker | Uneventful for 12 mo |
| 5    | 59      | F   | Syncope | LA | Operation, Pacemaker | Uneventful for 6 mo |
| 6    | 54      | M   | Syncope | Kidney, Pancreas, LN | Operation | Uneventful for 16 mo |
| 7    | 58      | F   | Syncope | PV | Operation | Sudden death |
| 8    | 53      | M   | Chest pain | CA | Operation | Sudden death |
| 9    | 64      | F   | SOB | MV, AV | Operation | Uneventful for 6 mo |
| 10   | 60      | F   | Chest oppression, SOB | General malaise | Operation | Valve function improved |
| 11   | 70      | M   | SOB, Dizziness | AV | Operation, Rituximab | Bioprosthesis function was well after 5 mo |
| 12   | 52      | M   | Chest pain | RV | Operation, Steroid | No recurrence |
| 13   | 64      | M   | PV, RV | LA | Operation, Steroid | No recurrence for 48 mo |
| 14   | 69      | M   | Tachycardia, Hypotension | RA, AS | Operation, Steroid | Tumor shrank after 12 mo |

F: female, M: male, SOB: shortness of breath, CA: coronary artery, RA: right atrium, AS: atrial septum, LA: left atrium, PV: pulmonary valve, MV: mitral valve, AV: aortic valve, RV: right ventricle, AAA: abdominal aortic aneurysm, LN: lymph node, TAA: thoracic aortic aneurysm, mo: months
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