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【 CASE REPORT 】

Left Ventricular Dysfunction Caused by IgG4-related Small Intramural Coronary Periarteritis

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Abstract:
IgG4-related disease (IgG4-RD) is a systemic autoimmune disorder known to affect multiple organs. However, IgG4-RD rarely affects the myocardium. We herein report a case of left ventricular dysfunction due to cardiac involvement of IgG4-RD.

Key words: Ig-G4 related disease, heart failure, left ventricular dysfunction, periarteritis

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibroinflammatory systemic disease characterized by elevated serum IgG4 levels and infiltration and fibrosis of IgG4-positive plasma cells into multiple organs (1, 2). IgG4-RD involves various organs, including the pancreas, bile ducts, lacrimal and salivary glands, and retroperitoneum (1, 3). Periarteritis is common in cardiovascular lesions, although histological findings can be difficult to obtain outside of at an autopsy (3, 4). Furthermore, most reports are limited to lesions in large- and medium-sized vessels, such as the aorta, coronary arteries, and cerebral vessels (3, 5).

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a useful diagnostic tool for IgG4-related aortitis, although it is difficult to diagnose smaller than medium-sized vasculitis, including cases of the coronary arteries or cerebral vessels, due to the physiological accumulation and limited resolution (3, 6).

We herein report a case of IgG4-related small intramural coronary periarteritis diagnosed with endomyocardial biopsy (EMB) specimens and immunostaining.

Case Report

A 79-year-old man with type 2 diabetes mellitus and dyslipidemia was referred to our hospital because of exertional dyspnea. On admission, his height was 160.9 cm, and his weight was 59.9 kg. His blood pressure was 117/76 mmHg, heart rate was 57 beats/min, respiratory rate was 19 breaths/min, and transcutaneous oxygen saturation was 98% on ambient air. The third heart sound and pansystolic murmur at the apex were audible without jugular vein distension or edema of the lower extremities.

Chest X-ray showed no congestion or pleural effusion. An electrocardiogram showed sinus rhythm and no ST segment elevation. Laboratory tests revealed elevated levels of B-type natriuretic peptide and troponin T (664.7 pg/mL and 0.132 ng/mL, respectively). C-reactive protein (0.08 mg/dL), angiotensin-converting enzyme (22.7 U/L), and soluble interleukin-2 receptor (578 U/mL) levels were within the normal limits.

Transthoracic echocardiography showed diffuse hypokinesis of the left ventricle (LV) with a 37% LV ejection fraction (EF) (Fig. 1A, B). Coronary angiography showed no significant stenosis, although the left anterior descending coronary artery showed a beaded appearance (Fig. 1C).

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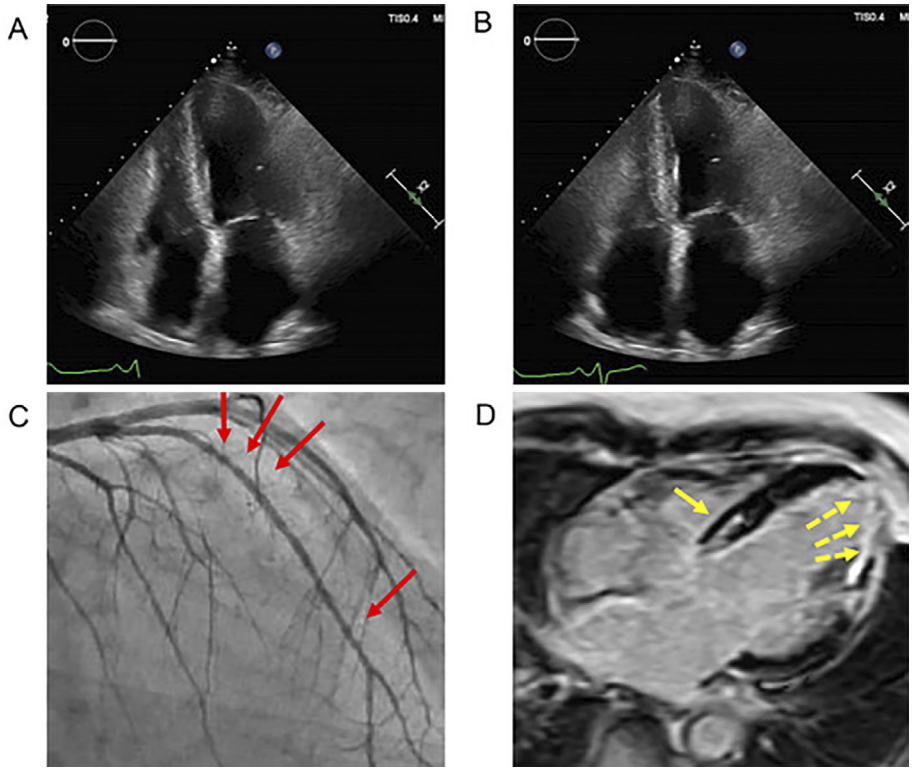

Figure 1. **Echocardiography, coronary angiography, and cardiac magnetic resonance imaging. (A, B) Apical four-chamber echocardiographic view showing diffuse hypokinesis of the left ventricle. (A) Diastolic phase. (B) Systolic phase. (C) Coronary angiography showing a beaded appearance in the left anterior descending coronary artery (red arrows). (D) Cardiac magnetic resonance imaging showing late gadolinium enhancement in the basal septum (yellow arrow) and the mid-to-apex area of the anterior, lateral, and inferior walls (yellow dotted arrows).**

Computed tomography angiography showed no significant coronary artery dilation or circumferential periarterial thickening around the coronary arteries.

Cardiac magnetic resonance imaging revealed late gadolinium enhancement (LGE) at the basal septum and mid-to-apex of the anterior to inferior region (Fig. 1D). ^{18}F-FDG-PET with a blood glucose level of 95 mg/dL revealed a focal on diffuse pattern with an ^{18}F-FDG uptake in the LV myocardium at the basal septum and the apex, which was consistent with the cardiac magnetic resonance imaging findings of LGE. The ^{18}F-FDG uptake was also detected in the ascending aorta; left common carotid, bilateral subclavian, brachial, external iliac, and femoral arteries; bilateral hilar region; bilateral cervical lymph nodes; and submandibular glands (Fig. 2A). Furthermore, ^{99m}Tc-single photon emission computed tomography (SPECT) showed a defect at the apex despite a positive uptake on ^{18}F-FDG-PET (Fig. 2B).

A systemic inflammatory disorder that included the myocardium was considered unlikely. Additional laboratory tests showed an elevated level of IgG4 (798 mg/dL), although perinuclear anti-neutrophil cytoplasmic antibody (ANCA) and cytoplasmic ANCA findings were negative. Biopsies from the cervical lymph nodes and submandibular glands revealed substantial plasma cell infiltration, and IgG4-positive plasma cells accounted for >40% of IgG-positive plasma cells without epithelioid granuloma (Fig. 3). The EMB specimens from the right side of the interventricular septum revealed no evidence of noncaseous epithelioid cell granuloma, although perivascular lymphocyte infiltration and fibrosis was observed around the small artery (Fig. 4A). These findings were consistent with small intramural coronary periarteritis in the myocardium. Indeed, additional immunohistochemical staining of the myocardial specimens with IgG and IgG4 showed diffuse IgG4-staining for perivascular lesions of adventitia without IgG4-positive plasma cells (Fig. 4B). Because the criteria for the clinical diagnosis of cardiac sarcoidosis were also met, EMB specimens of previous cardiac sarcoidosis cases were immunostained as a control group to search for similar pathological findings in cardiac sarcoidosis. However, IgG and IgG4 immunostaining were negative in the 15 sarcoidosis cases (Fig. 4C, D).

We ultimately diagnosed the patient with small intramural coronary periarteritis associated with IgG4-RD. We started prednisolone therapy (30 mg/day) with reduced dosing by 2.5-5 mg monthly to 12.5 mg/day. Follow-up blood tests showed an improved IgG4 level (25 mg/dL), although follow-up transthoracic echocardiography showed no change in the LVEF, with a value of 36% at 6 months after starting prednisolone therapy. Follow-up ^{18}F-FDG-PET with a blood glucose level of 105 mg/dL also revealed an improved uptake at the apex of the LV, hilar lymph nodes, bilateral cervical lymph nodes, submandibular glands, and aorta, while

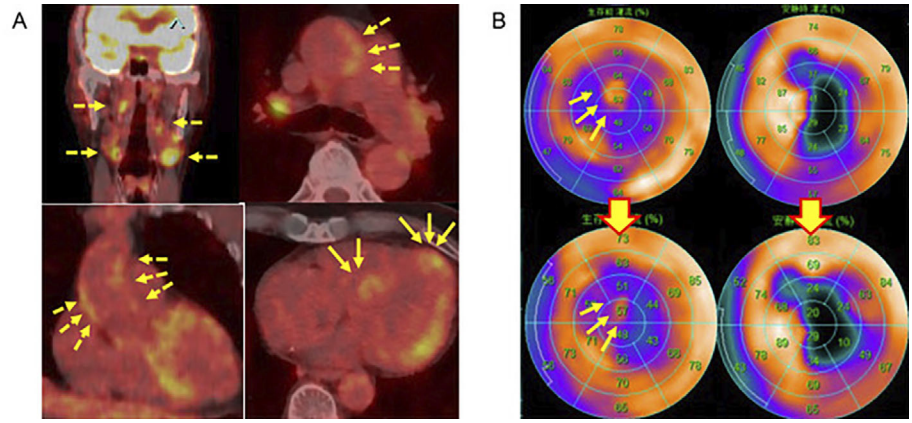

Figure 2. **^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and ^{99m}Tc-single photon emission computed tomography (SPECT). (A) ^{18}F-FDG-PET showing a focal on diffuse pattern of the ^{18}F-FDG uptake in the left ventricular myocardium at the basal septum and apex (yellow arrow), ascending aorta, bilateral cervical lymph nodes, and submandibular glands (yellow dotted arrow). (B) A combination of ^{18}F-FDG-PET (left side) and ^{99m}Tc-SPECT (right side) showing a mismatch between metabolism and perfusion at the apex (yellow allow). Pre- (upper part) and post- (lower part) immunosuppressive therapy.**

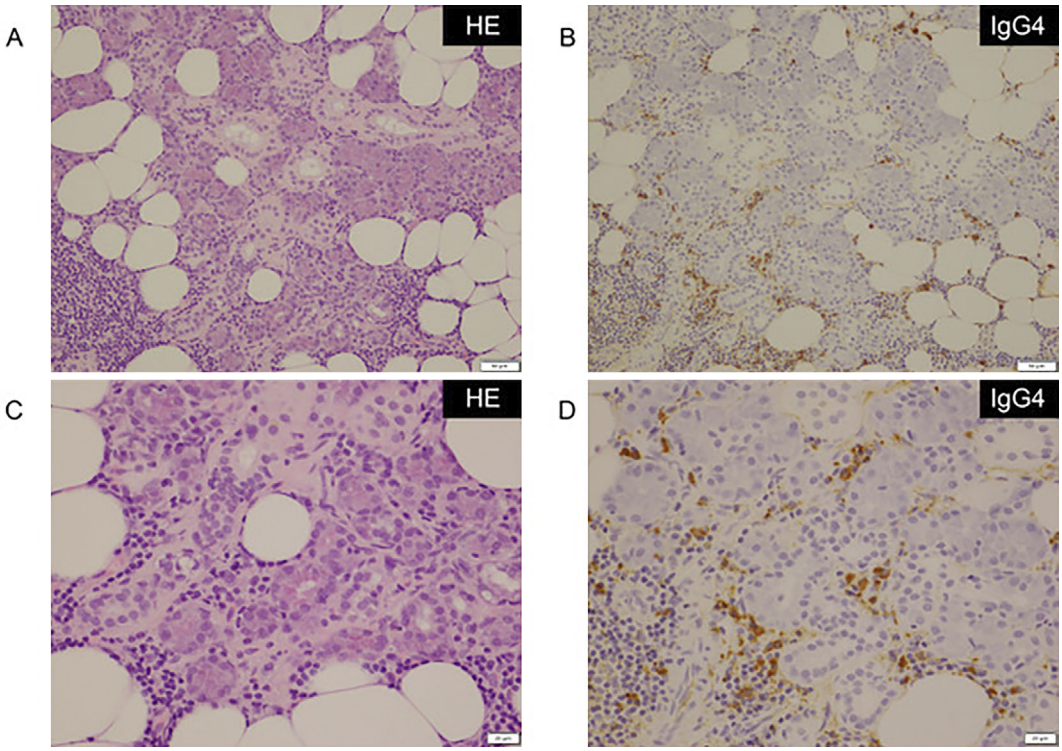

Figure 3. **Histopathological findings in the submandibular glands showing substantial plasma cell infiltration. IgG4-positive plasma cells accounted for >40% of all IgG-positive plasma cells. (A) Hematoxylin and Eosin (H&E) staining (×200 magnification, error bar =50 μm). (B) Immunohistochemical IgG4 stain (×200 magnification, error bar =50 μm). (C) H&E staining (×400 magnification, error bar =20 μm). (B) Immunohistochemical IgG4 stain (×400 magnification, error bar =20 μm).**

perfusion ^{99m}Tc-SPECT showed no marked changes at the apex (Fig. 2B). Steroid therapy for IgG4-RD including the myocardial lesion was effective.

Discussion

We herein report a rare case of IgG4-related myocarditis caused by small intramural coronary periarteritis diagnosed by EMB. IgG4-RD is a recognized cause of periaortitis/peri-

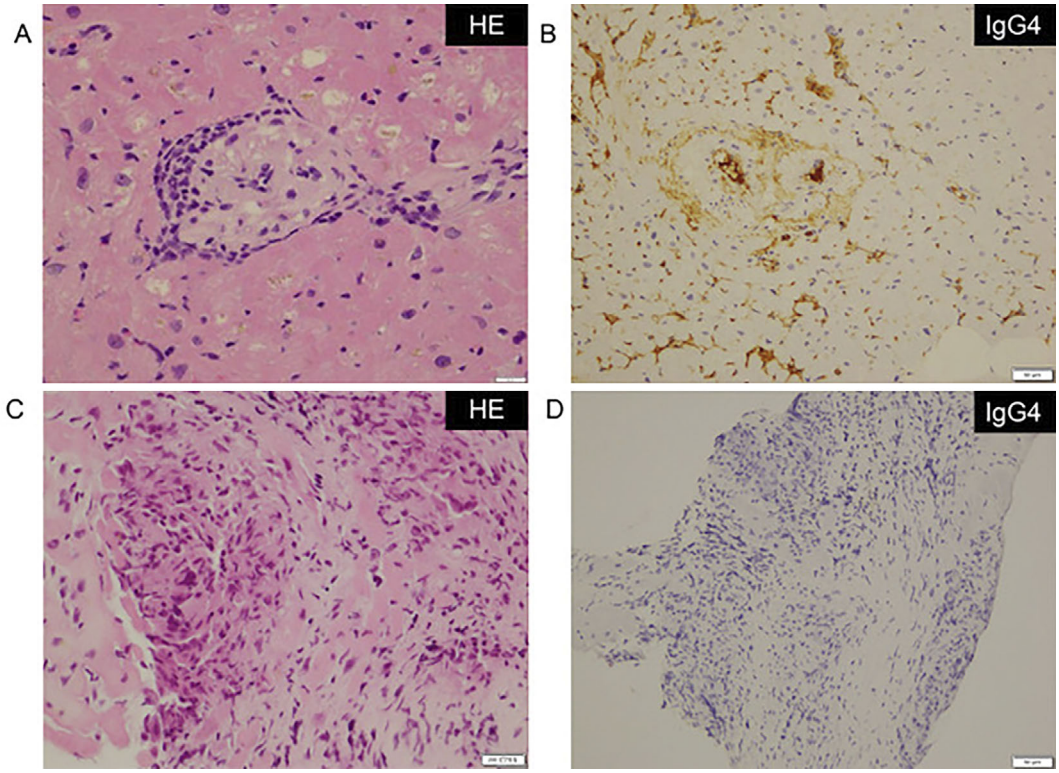

Figure 4. **Histopathological findings of the myocardium in this case and control. (A) Histopathological findings of the myocardium showing no evidence of noncaseous epithelioid cell granuloma, but evidence of perivascular lymphocyte infiltration and fibrosis around the small artery [Hematoxylin and Eosin (H&E) staining: ×400 magnification, error bar =20 μm]. (B) Histopathological findings of the myocardium showing diffuse IgG4-staining for perivascular lesions of adventitia without IgG4-positive plasma cells (immunohistochemical IgG4 stain: ×200 magnification, error bar =50 μm). (C) Control histopathological findings of the myocardium from cardiac sarcoidosis showing noncaseous epithelioid cell granuloma (H&E staining: ×400 magnification, error bar =20 μm). (D) Control histopathological findings of the myocardium from cardiac sarcoidosis showing no IgG4 staining (immunohistochemical IgG4 stain: ×200 magnification, error bar =50 μm).**

arteritis and is mainly characterized by inflammation of the outer membrane of blood vessels (7, 8). The target arteries of IgG4-RD are considered to be large- or medium-sized vessels, including the coronary, carotid, pulmonary, splenic, mesenteric, and iliac arteries (7, 8), with few reports of IgG 4-related vasculitis in small vessels. Furthermore, there have been no reports of LV dysfunction caused by small periarteritis associated with IgG4-RD, although LV dysfunction is known to occur in ANCA-related vasculitis, such as eosinophilic granulomatosis with polyangiitis or microscopic polyangiitis (9).

The main myocardial pathological findings in the present case were perivascular lymphocytic infiltration and positive IgG4 immunostaining of perivascular lesions of adventitia, while inflammatory cell infiltration of intercardiomyocytes was unclear. Although there was no obvious infiltration of IgG4-positive plasma cells, which is required in the current IgG4-RD diagnostic criteria, IgG4 antibody immunostaining was diffusely positive in the perivascular lesions (10). Considering the negative results from control IgG and IgG4 staining in the 15 sarcoidosis cases, we diagnosed our case as IgG4-related small intramural coronary periarteritis of the myocardium.

In the clinical setting, it is difficult to obtain sufficient EMB specimens of cardiovascular lesions. Thus, ^{18}F-FDG-PET is often used to help identify myocarditis or periarteritis (6). Carbajal et al. reported diagnosis of an IgG4-related cardiac pseudotumor based on positive ^{18}F-FDG-PET findings in the myocardium concomitant with biopsy data in an orbital IgG4-related pseudotumor, which improved with steroid therapy (11). In the present case, differentiation between sarcoidosis and vasculitis, including IgG4-RD, was a key point. Sarcoidosis is reportedly complicated by systemic vasculitis that can affect small- to large-sized vessels (12). However, a concomitant ^{18}F-FDG-PET uptake in the submandibular glands is characteristic for IgG4-RD (13). Therefore, the positive ^{18}F-FDG-PET findings in the ascending aorta and myocardium of this case led to a diagnosis of IgG 4-related aortitis and small intramural coronary periarteritis. This was supported by the elevated serum IgG4 levels and histological findings of infiltration of IgG4-positive plasma cells into the cervical lymph nodes and salivary glands. ^{18}F-FDG-PET is useful for diagnosing inflammatory diseases in cardiovascular lesions, and a multimodal diagnosis provides

important clues for the diagnosis of IgG4-related periaortitis/periarteritis.

Despite the utility of ^{18}F-FDG-PET in diagnosing IgG4-RD, the physiological uptake of ^{18}F-FDG-PET in the myocardium remains a major issue. Evaluating perfusion ^{99m}Tc-SPECT and identifying a metabolic and perfusion mismatch can help distinguish true inflammation in the myocardium from the physiological uptake (14, 15). In the present case, perfusion ^{99m}Tc-SPECT showed a defect at the apex, despite a positive ^{18}F-FDG-PET uptake, and a metabolic and perfusion mismatch was identified in the myocardium. Follow-up ^{18}F-FDG-PET and perfusion ^{99m}Tc-SPECT after steroid treatment also showed an improved ^{18}F-FDG-PET uptake, while perfusion ^{99m}Tc-SPECT showed no marked changes. Therefore, the concomitant evaluation of ^{18}F-FDG-PET and perfusion ^{99m}Tc-SPECT is important for identifying inflammation in the myocardium without histological findings.

Differentiation between IgG4-related small intramural coronary periarteritis and cardiac sarcoidosis is also difficult. Vasculitis associated with sarcoidosis has been reported (16, 17). Terasaki et al. also reported that serum IgG 4 values are sometimes slightly increased in cardiac sarcoidosis patients, despite no histological evidence of IgG4-RD (18). As such, the authors concluded that IgG4-RD does not overlap with sarcoidosis. However, in the present case, inflammatory cell infiltration in the myocardium was limited to the perivascular area, which is not typical for cardiac sarcoidosis, and IgG4 antibody staining around the small artery was also noted in the myocardium. Therefore, we diagnosed our case as IgG4-related small intramural coronary periarteritis.

In conclusion, we encountered a rare case of IgG4-related small intramural coronary periarteritis. IgG4-RD should therefore be considered as a differential diagnosis for left ventricular dysfunction.

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

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