Case Report

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Immunoglobulin G4-Related Myocarditis with Eosinophilic Infiltration: A Case Report

면역글로불린 G4연관 호산구 침윤성 심근염: 증례 보고

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Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a fibroinflammatory disorder that can involve any organ system; however, myocarditis is extremely rare. A 52-year-old male with dyspnea and chest discomfort underwent cardiac MRI that revealed edema and nodular, patchy, mesocardial and subendoardial delayed enhancement of left ventricle, suggesting myocarditis. Laboratory findings revealed elevated serum IgG4 and eosinophilia. Cardiac biopsy confirmed eosinophilic myocarditis with IgG4-positive cells. Here, we present an unusual case of IgG4-RD manifesting as eosinophilic myocarditis.

Index terms Immunoglobulin G4-Related Disease; Inifltration, Eosinophil; Myocarditis; Computed Tomography; Magnetic Resonance

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a fibro-inflammatory disorder with systemic involvement (1). IgG4-RD can progress to organ failure. Patients with IgG4-RD usually respond well to corticosteroid therapy. IgG4-RD affects nearly all organs. It commonly affects the salivary glands, kidneys, and pancreas. The cardiovascular system can also be involved, especially in large-to medium-sized vessels and the pericardium. Typical cardiovascular

manifestations of IgG4-RD include aortitis, periaortitis, periarteritis, and inflammatory aneurysms (2). However, IgG4-RD involving the myocardium is rare. Radiological findings of IgG4-RD involving the myocardium are not well known (3). In this report, we present an unusual case of IgG4-RD manifesting as eosinophilic myocarditis.

CASE REPORT

A 52-year-old male with a history of asthma presented with aggravated dyspnea, generalized edema, and wheezing sounds for a few days prior to hospitalization. Laboratory findings revealed elevated C-reactive protein level of 3.0 mg/dL (normal: 0–0.6 mg/dL), creatine kinase level of 991 U/L (normal: 45–44 U/L), creatine kinase MB isoenzyme of 159.7 ng/mL (normal: 0.6–6.3 ng/mL), N-terminal–pro B-type natriuretic peptide level of 20813 pg/mL (normal: 2.3–7.5 pg/mL), liver enzymes, including alanine transaminase of 157 U/L (normal: 13–33 U/L) and alkaline phosphatase of 51 U/L (normal: 8–42 U/L), and white blood cell count of 31000/μL (normal: 3800–10000/μL) with eosinophilia (eosinophil percentage: 39.1%; normal: 0%–10%). An electrocardiogram revealed ST depression. A transthoracic echocardiogram (TTE) revealed akinesia of the apex, apical septum, and inferior, anterior, and anteroseptal walls with mild left ventricular (LV) dysfunction (ejection fraction = 50%). Ischemic insult to the left anterior descending artery was suspected. However, the patient's coronary angiography was unremarkable, except for diffuse mild stenosis of the distal left anterior descending artery.

The following day, chest CT was performed, and pulmonary thromboembolism was excluded. However, consolidation with bronchial wall thickening was observed at the posterior basal segments of both lower lobes, suggestive of pneumonia. With conservative management of pneumonia and asthma, the patient's condition stabilized. The total hospitalization period was one week. The patient was discharged with cardiac MRI scheduled during the outpatient follow-up visit one week after discharge to rule out myocarditis. Short-axis balanced steady-state free precession images from cardiac MRI revealed hypokinetic systolic wall motion from the middle to the apical anterior wall of the LV, with preserved LV wall thickness on cine images (ejection fraction assessed with cardiac MR = 34%). Short tau inversion recovery T2 weighted images demonstrated high circumferential subendocardial and mesocardial signal intensity in the middle to apical area of the LV, suggesting inflammation and edema (Fig. 1A). Two-dimensional phase-sensitive inversion recovery late enhancement images revealed diffuse circumferential delayed subendocardial enhancement at the basal anterior wall and nearly the entire middle to apical wall of the LV (Fig. 1B, C). Additionally, mesocardial patchy and nodular delayed enhancement foci were noted in the mid-septal, lateral, and apical septal walls of the LV (Fig. 1D). Taken together, the laboratory and MRI findings suggested myocarditis with endomyocardial fibrosis or eosinophilic myocarditis.

Approximately three weeks after discharge, the patient visited the emergency center again for chest pain. Repeated TTE revealed aggravation of diastolic dysfunction compared to previous TTE findings. However, akinesia of the LV wall with mild LV dysfunction (ejection fraction = 50%) was similar to that observed in the previous TTE. Laboratory findings revealed eosinophilia (eosinophil percentage: 18%, white blood cell count: 11100/μL) and elevated IgG4 level of 5590 mg/L (normal 30–2010 mg/L). Serological tests for parasitic infections, in-

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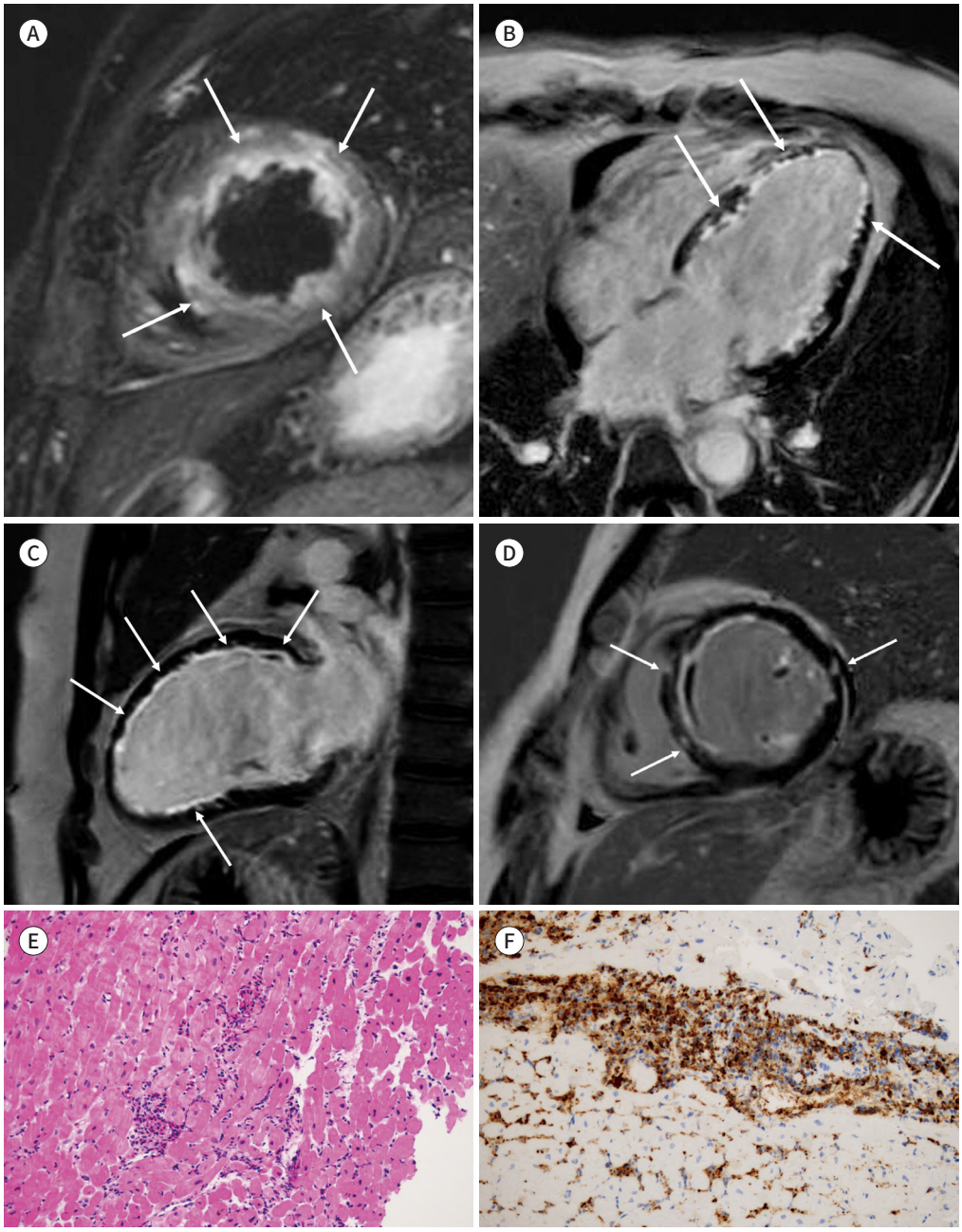
Fig. 1. A 52-year-old male with eosinophilic myocarditis associated with IgG4-related disease.
A. Circumferential subendocardial and patchy mesocardial, subepicardial high signal intensity areas (arrows) at middle LV on the short tau inversion recovery T2 weighted SA image, suggest inflammation and edema.
B, C. Diffuse circumferential delayed subendocardial enhancement foci (arrows) at the basal anterior and nearly the whole middle to apical wall of the LV with spring apex are observed on 2D PSIR late enhancement of four- and two-chamber images.
D. Patchy, nodular, and curvilinear delayed enhancement foci (arrows) at the mesocardial and subendocardial mid-septal, anterior, and lateral walls of the LV on the 2D PSIR late-enhancement SA image.
E. Photomicrographs showing the infiltration of lymphocytes, histiocytes, and eosinophils (hematoxylin and eosin stain, × 200).
F. Immunohistochemical staining of IgG4 shows more than 80 IgG4-positive cells/high-power field (× 400).
Ig = immunoglobulin, LV = left ventricular, PSIR = phase sensitive inversion recovery, SA = short axis



cluding *Clonorchis*, *Cysticercus*, *Sparganum*, *Paragonimus*, and *Toxocara canis* IgG, and vasculitis, including myeloperoxidase and proteinase 3 antibodies, were all negative. Fluoroscopy-guided myocardial biopsy was performed via the right jugular vein, and the right ventricle apex tissue was obtained. Pathologically, infiltration of lymphocytes, histiocytes, and eosinophils in the myocardium was observed, suggestive of eosinophilic myocarditis (Fig. 1E, F). Immunohistochemical analysis revealed IgG4-positive cells (up to 80 cells per high-power field) and an IgG4/IgG ratio > 40%. The patient met the diagnostic criteria for IgG4-RD, including organ dysfunction, elevated serum IgG4 concentration, and IgG4-positive plasma cell organ infiltration. The final diagnosis was definite IgG4-RD. Three days after the cardiac biopsy, the patient was discharged.

However, the patient was transferred to the emergency center for cardiac arrest the following day. After successful resuscitation with extracorporeal membrane oxygenation and targeted temperature management, the patient regained consciousness within four days. The patient was treated with a high dose of methylprednisolone (1000 mg/d) for three days followed by gradual tapering to oral methylprednisolone (30 mg/d). Approximately three weeks after the cardiac arrest event, the patient's serum IgG4 level (1960 ml/L) and the percentage of eosinophil (eosinophil percentage: 0.8%, white blood cell count: 18830/μL) were normalized. After discharge, the rheumatologist gradually tapered the oral methylprednisolone dose to 5 mg/d. Oral methylprednisolone treatment was continued for IgG4-RD.

Written informed consent was obtained from the patient.

DISCUSSION

In this report, we present a unique case of IgG4-RD involving the myocardium with eosinophilic infiltration manifesting as eosinophilic myocarditis in the cardiovascular system that showed compatible cardiac MRI findings in a patient who recovered from cardiac arrest.

Eosinophilic myocarditis is a rare type of myocarditis that is caused by eosinophilic infiltration. This condition is often associated with peripheral eosinophilia. Eosinophilic myocarditis can progress rapidly, leading to fatalities. Cardiac MRI is a useful noninvasive imaging modality for evaluating eosinophilic myocarditis (4). Typically, cardiac injuries due to eosinophilia occur in three successive phases. In the early phase, eosinophils infiltrate the endocardium and subendocardial interstitium. These inflammatory changes can be detected on cardiac MRI as intensely delayed subendocardial enhancement. As eosinophilic activation continues, the endomyocardial surface is damaged and apical thrombi are formed (5). Normal myocardium, thickened enhanced endomyocardium, and overlying thrombus make a "double V" sign at the ventricular apex, which can help us diagnose eosinophilic myocarditis more easily (6). During the fibrotic stage, irreversible damage to the endomyocardium develops into restrictive cardiomyopathy. It also involves the atrioventricular valves (7).

In our patient, cardiac MRI revealed hypokinetic systolic motion of the LV wall without wall thickening, old ischemic changes, or infarction. Other significant findings were diffuse delayed subendocardial enhancement and delayed mid-myocardial patchy, nodular enhancement in the LV. The initial differential diagnoses were myocarditis with fibrosis, Churg-Strauss syndrome, and eosinophilic myocarditis. No evidence of typical apical thrombus was ob-

served. A diagnosis of Churg-Strauss syndrome requires at least four of the following six criteria: asthma, eosinophilia, mono- or polyneuropathy, migratory or transitional pulmonary infiltration, paranasal sinusitis, and biopsy-proven extravascular eosinophils (8). Our patient had a history of asthma, eosinophilia, and a biopsy-proven infiltration of eosinophils into the endocardium. However, our patient did not meet any of the other criteria. Based on laboratory findings, peripheral eosinophilia led us to prioritize eosinophilic myocarditis. Additional evaluation was performed to determine the cause of the eosinophilia, and elevated IgG4 levels were observed. Pathological examination confirmed eosinophilic myocarditis, IgG4-positive plasma cells, and an elevated IgG4/IgG ratio. Therefore, IgG4-RD-associated eosinophilic infiltration with radiological findings of eosinophilic myocarditis was considered.

IgG4-RD is a chronic fibroinflammatory disorder with systemic involvement. It is characterized by IgG4-positive plasma cell infiltration and elevated serum IgG4 levels (9). IgG4-RD can involve nearly all organs, including the salivary and lacrimal glands, pancreas, retroperitoneum, kidneys, lymph nodes, and lungs. IgG4-RD can also affect the cardiovascular system, including the coronary arteries, pericardium, and walls of large- and medium-sized vessels (2). However, IgG4-RD involving the myocardium and manifesting as myocarditis is extremely rare (3). Based on previous studies, approximately 11%–38% of IgG4-RD cases are associated with eosinophilia. Patients with IgG4-RD with eosinophilia have a higher disease burden than those without eosinophilia (1).

Glucocorticoid therapy is the first-line treatment for IgG4-RD. Patients with IgG4-RD usually respond well to corticosteroid therapy, particularly during the early stages. The treatment may be maintained for 2–4 weeks. Subsequently, the steroid dose should be tapered within two months. Rituximab can also be administered to patients with life-threatening conditions. The prognosis of IgG4-RD varies depending on the organ involved and combined complications. IgG4-related aortic aneurysm and IgG4-RD involving the coronary arteries significantly affect morbidity and mortality (2).

In summary, we present an unusual case of IgG4-RD with eosinophilic infiltration manifesting as eosinophilic myocarditis.

Author Contributions

Writing—original draft, W.H.; and writing—review & editing, K.S.S., A.K.T., J.S.A., K.H.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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면역글로불린 G4연관 호산구 침윤성 심근염: 증례 보고

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면역글로불린(immunoglobulin; 이하 Ig) G4 연관 질환은 어떤 장기도 침범할 수 있는 섬유염증성 질환이며, 심근염의 형태로 발현되는 경우는 매우 드물다. 호흡곤란과 흉통이 있는 52세 남성이 심장자기공명영상에서 좌심실벽에 부종 및 심장간막과 심내막에 반점형과 결절형 지연 조영증강을 보이는 심근염 소견을 보였다. 혈액검사상 혈청 IgG4 상승과 호산구 증가증이 동반되었으며 심장 생검으로 호산구성 심근염과 IgG4 양성 세포가 확인되었다. 이에 저자들은 IgG4 연관 질환이 호산구성 심근염으로 발현된 드문 증례를 보고하고자 한다.

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