Elevated Serum IgG4 Complicated by Pericardial Involvement with a Patchy ¹⁸F-FDG Uptake in PET/CT: Atypical Presentation of IgG4-related Disease

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Abstract

IgG4-related pericardial involvement has rarely been reported and its clinical features remain unknown. We herein report a case of a 50-year-old woman with pericarditis who presented with a fever, elevated C-reactive protein levels, elevated serum IgG4 concentrations, and thickened pericardium with a patchy ¹⁸F-fluorodeoxyglucose (FDG) uptake. A biopsy specimen of ¹⁸F-FDG accumulated in the mediastinal lymph nodes revealed an abundant infiltration of IgG4-bearing plasma cells without fibrosis. Moderate-dose glucocorticoids promptly resolved the physical, serological, and imaging abnormalities, thus indicating a relatively acute and reversible nature of IgG4-related pericardial involvement.

Key words: IgG4, IgG4-related disease, pericarditis, positron emission tomography, glucocorticoid

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized syndrome with a presumed autoimmune pathogenesis comprising a collection of disorders that share similar clinical features, including tumor-like swelling of involved organs, a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, variable degrees of fibrosis with a characteristic storiform pattern, and elevated levels of serum IgG4. IgG4-RD affects multiple organs, such as the pancreas, lacrimal and salivary glands, kidney, lung, retroperitoneum, aorta, and lymph nodes; however, pericardial involvement is relatively rare (1-3). The relationship between the elevated IgG4 levels and the plasma cell infiltration, resulting in fibrosis, remains unknown. Of note, a certain tissue, i.e., lymph nodes, does not always show fibrotic

pathology even in the cases with typical fibrotic pathology in the other tissues (1-3). This indicates that not only the pathological but also the clinical presentation of IgG4-RD may be distinct among the tissues involved. Accordingly, IgG4-related pericardial disease is mostly characterized by fibrosis of the thickened pericardium and clinical presentation of constrictive pericarditis; however, one report has described acute inflammatory pathology in the pericardium (4-13).

Recently, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been used to examine a variety of diseases, including cancers and IgG4-RD; this modality is considered to be able to detect metabolically active lesions with increased glucose uptakes (14, 15). In IgG4-RD, FDG-PET/CT may help to determine the biopsy site and to evaluate the therapeutic response (15, 16). Together with a favorable response to glu-

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Figure 1. A CT scan of the chest before glucocorticoid therapy shows the mediastinal lymph node swelling (a) and diffuse pericardial thickening without calcification (b).

cocorticoids, therefore, IgG4-RD is suggested to contain both active and chronic lesions, the former which may be detected by FDG-PET/CT and responsive to glucocorticoids (15-18).

We herein report a rare case of IgG4-related pericarditis with acute inflammatory characteristics, a patchy ^{18}F -FDG uptake pattern in the pericardium, and good response to glucocorticoid therapy, and discuss the variation in the clinical presentations of IgG4-RD and the diagnostic role of FDG-PET/CT in IgG4-related pericarditis.

Case Report

A 50-year-old Japanese woman had been well until one month before admission, when a fever, chill, general malaise, and anterior chest pain developed. Because several antibiotics and non-steroidal anti-inflammatory drugs did not relieve her symptoms, the patient was admitted to our hospital. Her medical history included smoking (8 cigarettes/day) and an active consumption of alcohol (20 g ethanol/day), a previous diagnosis of infantile asthma, and a history of drug allergy.

On the physical examination, her blood pressure was 90/48 mmHg and equal in both arms, pulse rate 88 per minute, the temperature 38.1°C, and the cervical, supraclavicular and axillary lymph nodes were palpable with good mobility. Jugular vein distention, friction rub, diminished breath sounds over the lung, and lower leg edema were not revealed. The laboratory tests showed white blood cells of 11,840/ μL , eosinophil 200/ μL , an erythrocyte sedimentation rate 138 mm/h, C-reactive protein (CRP) concentration 10.02 mg/dL, serum amyloid A protein level 833 $\mu\text{g/mL}$, and soluble interleukin (IL)-2 receptor level 745 U/mL. IgG, IgA, and IgM levels were within the normal ranges (1,631, 199, and 93 mg/dL, respectively), however, the IgG4 and IgE levels were elevated (428 mg/dL and 1,765 IU/mL, respectively). The serum IL-6 concentration was 2.0 pg/mL (normal range: <4.0 pg/mL). All the following laboratory investigations were negative or normal: chest radiography, electrocardiogram, a blood culture, procalcitonin level, the interferon gamma release assay, β -D-glucan level,

angiotensin-converting enzyme concentration, rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies and a serological test for hepatitis A, B and C viruses. Echocardiography revealed pericardial thickening. The CT scan images showed a small amount of left pleural effusion, mediastinal lymphadenopathy (Fig. 1a), and diffuse pericardial thickening (Fig. 1b). PET/CT imaging showed a patchy ^{18}F -FDG uptake in the pericardium and a dense ^{18}F -FDG uptake in the mediastinal lymph nodes (Fig. 2a-d). A video-assisted thoracoscopic biopsy of ^{18}F -FDG uptake-positive mediastinal lymph nodes was preferred to open thoracotomy for an extensive biopsy of the pericardium and lymph nodes. A histological and immunohistochemical examination of the biopsy specimen revealed an increase in the number of IgG4-positive plasma cells (>100 per high-power field), an IgG4⁺/IgG⁺ plasma cells ratio >50%, similar to IgG4-related lymphadenopathy type II (follicular hyperplasia) (Fig. 3) (19, 20). However, storiform fibrosis, obliterative phlebitis, eosinophilic infiltration and immunoglobulin light-chain restriction were not observed. According to these findings, we tentatively diagnosed the patient with IgG4-RD using a diagnostic algorithm of comprehensive diagnostic criteria for IgG4-RD (21). We then treated the patient with 30 mg (0.6 mg/kg) per day of oral prednisolone (21). Her symptoms immediately improved and the serum IgG4 levels decreased to 134 mg/dL after one month of treatment. Furthermore, the ^{18}F -FDG uptakes in the pericardium and mediastinal lymph nodes were dramatically diminished (Fig. 2e-h) as diffuse pericardial thickening on the CT scan images. Recurrence of the disease was not observed during the 28-month follow-up.

Discussion

The present patient represented unusual characteristics of IgG4-RD; an acute febrile episode and anterior chest pain with elevated levels of CRP, resembling acute pericarditis. Moreover, elevated serum levels of IgG4 and multiple lymphadenopathies do not always support the diagnosis of IgG4-RD. As described above, the pathological finding of the mediastinum lymph node specimen was lymphadenopa-

Figure 2. PET/CT images of the heart before and after glucocorticoid therapy for IgG4-RD with pericardial involvement. Volume-rendering fusion images of PET and CT of the heart and surrounding tissues are shown (a-d). Abnormal ^{18}F -FDG uptakes within the thickened pericardium and mediastinal lymph nodes are shown. Coronal whole-body maximum-intensity-projection images (e, g) and transaxial fusion images (f, h) were obtained before (e, f) and after (g, h) glucocorticoid therapy. Abnormal ^{18}F -FDG uptakes in the thickened pericardium and mediastinal lymph nodes were diminished after 5 weeks of glucocorticoid therapy.

Figure 3. Marked infiltration of the IgG4-positive plasma cells in the mediastinal lymph node. The lymph node showed reactive follicular hyperplasia with intact sinuses. A moderate number of mature plasma cells with small lymphocytes are present (a, d). Immunohistochemical staining for IgG (b, e) and IgG4 (c, f) was examined. Immunostaining showed numerous IgG4-positive plasma cells in the interfollicular zone (>100 per high-power field with an IgG4⁺/IgG⁺ plasma cell ratio >50%). The boxed area in a, b, and c is shown at a higher magnification in d, e, and f, respectively. HE: Hematoxylin and Eosin staining

Table. Clinicopathological Features of Patients with IgG4-related Pericarditis.

Case No.	Age (years) /Gender	Fever	RHF	PC / PL effusion	Pericardial thickening	MLN swelling	IgG4-RD involvement	CRP	serum IgG4 (mg/dL)	Pathology ^a		Treatment		Prognosis	Reference
										IgG4 ^b	Fibrosis	Ope	GC		
1	68 / M	(+)	(+)	(-)/(+)	(+)	(-)	(-)	Elevated	206	(+)	(+)	(+)	(-)	NA	4
2	63 / F	(-)	(+)	(+)/(+)	(+)	(+)	AP, HT	NA	420	NA	NA	(-)	(+)	Effective	5
3	69 / M	(-)	(+)	(+)/(+)	(-)	(-)	RP	Normal	408	(+)	NA	(-)	(+)	Effective	6
4	76 / M	(-)	(+)	(-)/(+)	(+)	(-)	(-)	Normal	NA	(+)	(+)	(+)	(-)	Effective	7
5	29 / F	(-)	(+)	(+)/(+)	(+)	(-)	(-)	Normal	136	(+)	(+)	(-)	(+)	Effective	8
6	69 / M	NA	(+)	(+)/(+)	(+)	NA	RP	Elevated	25	(+)	(+)	(-)	(-)	Fatal	9
7	83 / M	NA	(+)	(+)/(+)	(+)	NA	RP, AP	Normal	812	(+)	(+)	(-)	(-)	Fatal	9
8	81 / M	(-)	(+)	(+)/(+)	(+)	(-)	(-)	NA	196	(+)	(-)	(+)	(+)	Effective	10
9	71 / F	(-)	(-)	(+)/(+)	(+)	(+)	Periaorta	NA	684	(+)	(+)	(-)	(+)	Effective	11
10	75 / M	(-)	(+)	(+)/NA	(+)	NA	Liver	NA	normal	(+)	(+)	(+)	(-)	Effective	12
11	60 / F	(-)	(-)	(+)/(+)	(+)	(-)	MD	NA	1,800	(+)	(-)	(-)	(+)	Effective	13
Present															
Case	50 / F	(+)	(-)	(+)/(+)	(+)	(+)	(-)	Elevated	427	(+)	(-)	(-)	(+)	Effective	

RHF: right ventricular heart failure, PC: pericardial, PL: pleural, MLN: mediastinal lymph node, CRP: C-reactive protein, Ope: operation, GC: glucocorticoid, M: male, F: female, AP: autoimmune pancreatitis, HT: Hashimoto thyroiditis, RP: retroperitoneal fibrosis, MD: Mikulicz's disease, NA: not available

^a The examined specimen was the pericardium in cases #1, 4, 6, 7, 8, 10 and 11, and the pleural specimen in cases #5 and 9. The fine needle aspiration cytology of pericardial effusion and the mediastinal lymph node biopsy were performed in case #3, 11 and the present case, respectively.

^b Infiltration of IgG4-positive plasma cell.

thy with an increase in the IgG4⁺ plasma cells similar to IgG4-related lymphadenopathy type II (follicular hyperplasia) (19, 20) without fibrosis. Conversely, we were unable to obtain evidence to support the diagnosis of either Castleman disease or malignancies such as mesothelioma. Thus, according to the assumption that the coexistence of the dense ¹⁸F-FDG uptake in the mediastinum lymph nodes and the characteristic patchy pattern of ¹⁸F-FDG uptake suggestive of a complicated mechanism of the disease, we tentatively diagnosed the patient with IgG4-RD and administered a synthetic glucocorticoid. The patient responded well and has remained in good condition without recurrence of the disease.

The present case raised several important questions in the diagnosis and management of IgG4-RD. One is the requirement of typical fibrotic pathology for the diagnosis of this disease. It is apparent that the diagnostic algorithm for recent diagnostic criteria for IgG4-RD (21, 22) did not exclusively support the diagnosis of IgG4-RD in the present case. Although the lymph node pathology in IgG4-RD often lacks typical fibrosis or obliterative phlebitis and demonstrates compacted inflammatory cell infiltration, other diseases should be considered, including Castleman disease (19). We, therefore, reasoned to obtain a biopsy specimen from the mediastinum lymph node to exclude Castleman disease. Unquestionably, an expanded open biopsy would be reliable to make a diagnosis, however, the patient's condition does not always allow for such an invasive procedure.

The second question is the relevance of the application of the diagnostic algorithm of IgG4-RD in patients with pericardial involvement. Our literature review found two patients from seven reported cases with IgG4-related pericarditis who did not demonstrate fibrosis in the pericardium (Table) (4, 7, 9, 10, 12, 13). In addition, four reported patients with IgG4-related pericarditis were not pathologically diagnosed with a pericardial specimen, such as in the present case (Table). Previous reports have also described that the clinical presentation and pathology may be distinct according to the

damaged tissues (3, 22, 23). As evidenced in other inflammatory disorders, inflammatory cell infiltration may be observed in the early stage of IgG4-RD and inflammation is replaced with severe fibrosis in the advance stage (2, 24).

Finally, what is the diagnostic role of ¹⁸F-FDG-PET/CT in IgG4-RD? Although this procedure is expensive and not generally applicable, it may be considered for the evaluation of such diseases with multi-organ involvement, including IgG4-RD. Because IgG4-RD contains a variety of pathological changes which is dependent on the tissues involved, this modality would be helpful for the determination of biopsy sites. In the present case, the uptake pattern of the pericardial thickening and mediastinum lymphadenopathy appeared to be characteristic, showing a patchy and intense pattern, respectively (Fig. 2). Recently, Nakao et al. (25) reported a patient with transient constrictive pericarditis who showed the diffuse uptake of ¹⁸F-FDG in the pericardium which diminished after glucocorticoid therapy, suggesting the presence of acute and reversible lesions in the pericardium. Moreover, Zhang et al. (16) described the imaging characteristics of ¹⁸F-FDG-PET/CT in IgG4-RD patients, including a patchy pericardial lesion. Therefore, it may be possible that the patchy appearance of the pericardium in our case indicates the coexistence of acute and chronic lesions, in particular the dense uptake in the lymph node indicates acute lesions. Although further studies are needed to confirm its usefulness, the utilization of ¹⁸F-FDG-PET/CT may contribute to unveiling the yet unknown clinical course of IgG4-RD. Moreover, this modality may complement insufficient pathological findings and refine the diagnostic criteria of the disease.

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

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