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CASE REPORT

A case of IgG4-related lymphadenopathy, pericarditis, coronary artery periarteritis and luminal stenosis

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Abstract Immunoglobulin G4 (IgG4)-related disease is an emerging new clinicopathological disorder that is characterized by elevation of serum IgG4 levels and histological findings of IgG4-positive plasmacytic infiltration. IgG4-related disease may appear synchronously or metachronously in a wide variety of organs. The current patient was found to have pericardial effusion and retroperitoneal fibrosis. He was subsequently diagnosed with coronary artery stenosis. ^{18}F-FDG positron emission tomography showed enhanced FDG uptake in lymph nodes as well as pericardial and peri-aortic tissue. Histopathology of the mediastinal lymph node showed the infiltration of numerous IgG4-positive cells, leading to the diagnosis of IgG4-related lymphadenopathy with pericardial and periarterial involvement.

Keywords IgG4-related disease · Lymphadenopathy · Cardiovascular system

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Introduction

Since Hamano et al. discovered that serum immunoglobulin G4 (IgG4) concentrations are specifically increased in autoimmune pancreatitis (AIP) [1], clinicopathological features bearing similarities to AIP (e.g., dense IgG4-positive lymphoplasmacytic infiltrate, storiform fibrosis, and elevated serum IgG4 concentration) have been reported in almost every organ system, leading to the proposal of a novel clinical entity termed "IgG4-related disease" [2]. The heart and central/peripheral arteries are also a possible target of IgG4-related disease [3, 4]; however, there is a difficulty in diagnosing IgG4-related disease in the cardiovascular system, mainly due to the risks inherent in the tissue sampling. We herein report a patient with IgG4-related lymphadenopathy, pericarditis (pericardial effusion), retroperitoneal fibrosis, and coronary artery stenosis. Prior approval and informed consent was obtained both from the institutional research ethics committee and the patient, and this study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Case report

A 75-year-old man was found to have elevated levels of hepatic enzymes. He was screened by computed tomography (CT) which revealed pericardial effusion and thickening of the perivascular regions of the abdominal aorta. The patient was then referred to our department for further evaluation. The patient had an occupational history of mason and clinical history of myocardial infarction at 60 years of age, and underwent percutaneous coronary intervention

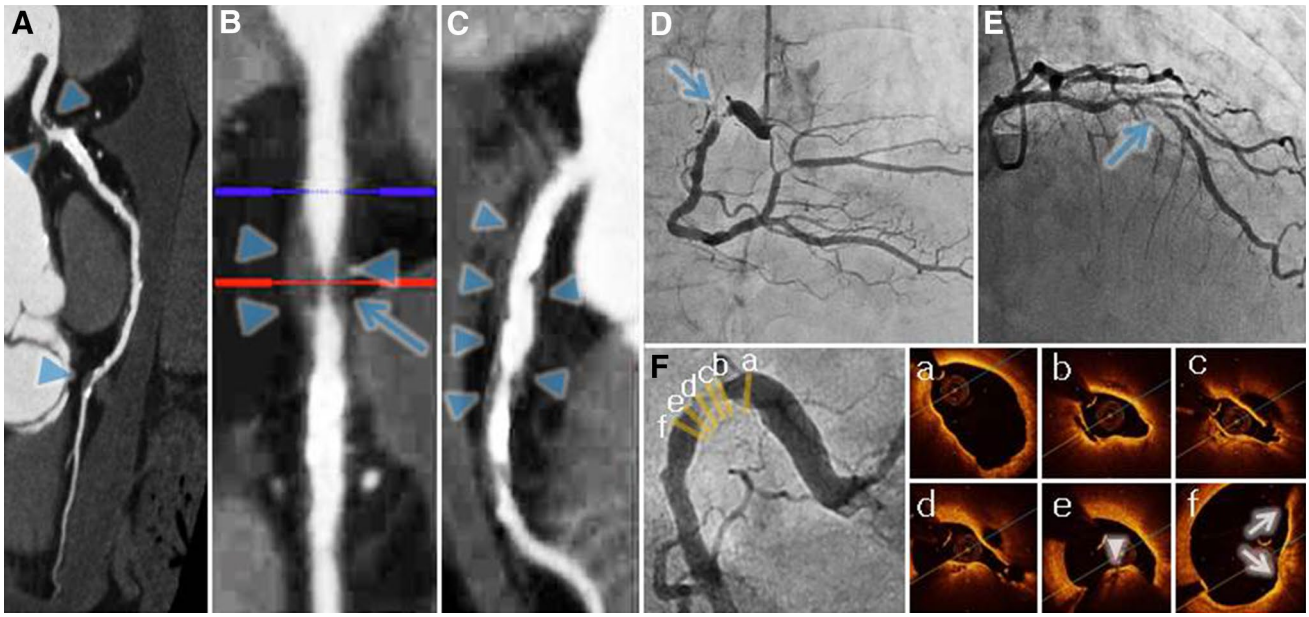

Fig. 1 Coronary artery lesions and findings. **A–C** Curved planar reconstruction view of the right coronary artery (RCA; **A**, **B**) and left anterior descending artery (LAD; **C**). Perivascular thickening of the coronary arteries (*arrowheads*) was noted, and severe luminal stenosis was observed in the middle of the surrounded periarterial soft mass (*arrow*). **D**, **E** Invasive coronary artery angiography of the RCA (**D**) and LAD (**E**). Severe and moderate luminal stenosis (*arrows*) in the RCA and LAD, respectively, was observed. **F** Optical coherence tomography examination of the stenosed RCA lesion. Discontinuation of the plaque, suggestive of plaque rupture, thrombus (*arrowhead*) and wall calcification (*arrows*) were suspected

(PCI) of the right coronary artery (RCA) and the left anterior descending artery (LAD); for PCI of the RCA, directional coronary atherectomy was performed.

On admission, his vital signs included a body temperature of 36.6 degrees, blood pressure of 124/76 mmHg, and heart rate of 78 beats/min. Chest X-ray revealed a cardiothoracic ratio of 54 %. Laboratory studies showed a white blood cell count of 2600/μL, hemoglobin level of 12.0 g/dL, platelet count of 22.6 × 10^4/μL, and erythrocyte sedimentation rate of 51 mm/h. Fasting blood sugar was 107 mg/dL and plasma insulin was 15.7 μU/mL. Serum C-reactive protein was 1.05 mg/dL, soluble interleukin-2 receptor was 1100 U/mL, and B-type natriuretic peptide was 38.2 pg/mL. Serum levels of IgG (3513 mg/dL), IgG4 (625 mg/dL; IgG4/IgG ratio of 18 %) and IgE (359 IU/mL) were elevated, but IgA (325 mg/dL) and IgM (38 mg/dL) remained within normal range. The test result for antinuclear antibody was <20×, and anti-double-stranded DNA, anti-SSA, and anti-SSB, myeloperoxidase antineutrophil cytoplasmic antibody (ANCA), proteinase-3 ANCA, and rheumatoid factor were all negative. Total complement activity (CH50) was 21.4 U/mL, and C4 and C3 were 4.1 and 67 mg/dL, respectively. Serum antibody titers against coxsackie virus, adenovirus, and echovirus were all below the detectable range, and the rapid test for influenza A/B antigen was negative. Urinary protein, glucose, and occult blood were all negative. The serum interleukin-6 (IL-6) level was 8.4 pg/mL (normal range <4.0 pg/mL).

Electrocardiogram-synchronized computed tomography (CT) demonstrated focal periarterial thickening in both the RCA and LAD (Fig. 1A–C, arrowheads), and luminal stenosis in the RCA (Fig. 1B, arrow) in addition to pericardial effusion and thickened pericardium. Luminal stenosis, especially at one site in the RCA located distal to a previously inserted coronary stent, was presumed to be surrounded by tumefactive periarterial tissue. Subsequent coronary artery angiography showed severe stenosis in the RCA and moderate stenosis in the LAD (Figs. 1D, E, arrows). Intracoronary optical coherence tomography (OCT) of the RCA illustrated ruptured plaque and wall calcification at the stenosed site (Fig. 1F, sections a–f). A bare-metal stent was inserted in the RCA lesion.

^{18}F-FDG positron emission CT (Figures G–I) showed enhanced uptake of FDG in mediastinal lymph nodes, pericardium (arrowheads), and perivascular regions of the abdominal aorta and aortic wall (arrows) (Fig. 2). Histology of a mediastinal lymph node biopsy sampled via video assisted thoracoscopic surgery showed distorted lymph node architecture with usual reactive follicles, intact sinuses, eosinophils and abundant plasma cells. Fibrosis, anthracosis and dust-laden macrophages, were also observed, which may be related to the patient's occupational history. On immunohistochemistry, staining by IgG4 antibody (Invitrogen, Paisley,

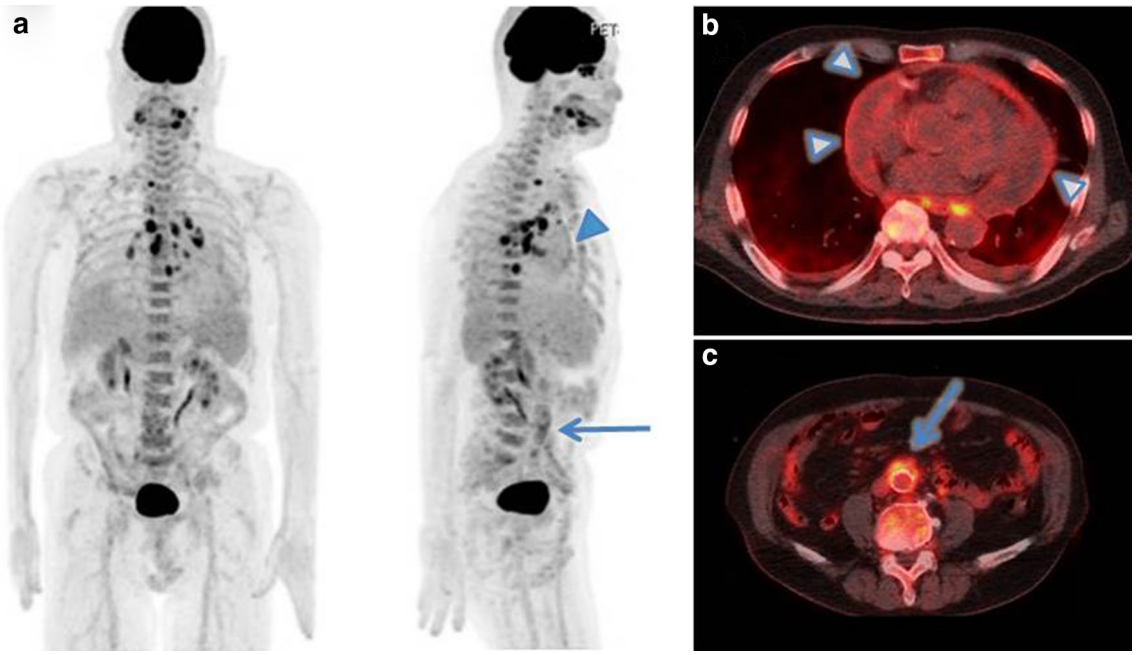

Fig. 2 ^{18}F-FDG-PET/CT. ^{18}F-FDG-PET. Increased uptake was observed in the mediastinal lymph node, pericardium (*arrowheads*), and abdominal aorta (*arrows*)

UK) showed a large majority of the infiltrated plasma cells were IgG4-positive (>200/high power field) and the IgG4 +/IgG + ratio was >70 % (Fig. 3). There was no light-chain restriction. On the basis of the consensus statement on pathological criteria for IgG4-related disease [5], IgG4-related disease was diagnosed. Taken together, IgG4-related lymphadenopathy (Type II) with cardiac and vascular lesions was diagnosed. About 8 months after the nodal biopsy, chest X-ray showed that the amount of pleural effusion was markedly increased. After draining the fluid from the chest cavity, corticosteroid therapy (20 mg/day) was initiated that effectively suppressed the reaccumulation of pleural fluid.

Discussion

We herein have described a patient who showed pericardial effusion, coronary artery stenosis, perivascular thickening of coronary arteries, and retroperitoneal fibrosis. IgG4-related lymphadenopathy was diagnosed on the basis of immunohistochemical examination of a mediastinal lymph node. About 8 months after the nodal biopsy, the pericardial effusion showed a rapid increase and corticosteroid therapy (20 mg/day) was initiated after the pleural fluid drainage, and this treatment effectively suppressed the reaccumulation of the pleural fluid.

In the current comprehensive diagnostic criteria for IgG4-related disease in Japan, histological findings (ratio of IgG4/IgG-positive cells, >40 %; and IgG4-positive plasma cells, >10 per HPF) are required in addition to the presence of characteristic diffuse/localized swelling or masses in single or multiple organs and elevated serum IgG4 concentrations (>135 mg/dL) for a definitive diagnosis [6]. IgG4-related disease can also be diagnosed with organ-specific diagnostic criteria formulated for lacrimal/salivary glands [7], pancreas [8], and kidney [9]. IgG4-related lymphadenopathy may precede IgG4-related extranodal lesions [10]. In their study of 31 cases of IgG4-related lymphadenopathy, Takeuchi et al. reported that 19 (61 %) patients had extranodal involvement, including lacrimal/salivary glands, lung, and kidney [11]. IgG4-related lymphadenopathy may show various histopathological patterns [11], and a pattern similar to that observed in the current case has also reported [12].

Lymphadenopathy with abundant IgG4-positive plasma cell infiltration, however, may also be seen in hyper-IL-6 syndromes such as multicentric Castleman's disease, rheumatoid arthritis, and other immune-mediated conditions [12]. Serum IL-6 was slightly elevated (8.4 pg/mL) in the current case. On the other hand, Sato et al. reported that the mean IL-6 levels in patients with IgG4-related lymphadenopathy was 8.45 pg/mL, which was significantly lower than that observed in patients with multicentric Castleman's disease at 34.8 pg/mL [13]. In addition, other characteristic findings observed in hyper-IL-6 syndromes—namely, elevation of IgA and IgM [14] and high elevation of CRP [13]—were absent in the current case. Although the presence of compatible histology and immunohistochemistry

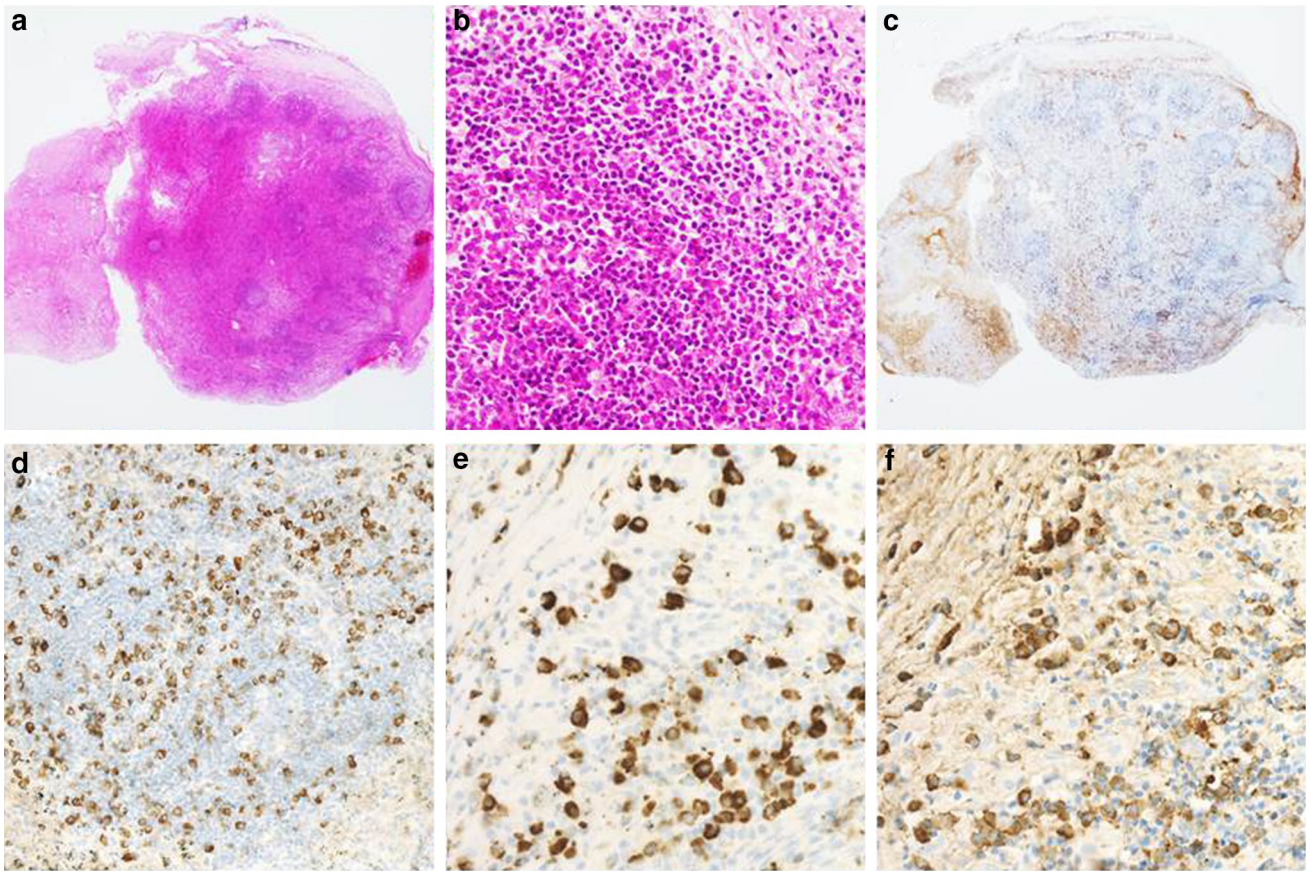

Fig. 3 Histopathological findings of biopsied lymph nodes. **a**, **b** HE staining. The lymph node showed usual reactive follicular hyperplasia with intact sinuses (**a**), and a large number of mature plasma cells and histiocytes are observed (**b**). **c**–**e** IgG4 staining. Numerous IgG4-positive cells are observed in the interfollicular zone. **f** IgG staining of the neighboring slide of **e**. The majority of the IgG-positive cells (>70 %) are found to be IgG4-positive. Original magnification, ×20 (**a**, **c**), ×100 (**b**, **d**), ×400 (**e**, **f**)

alone is not sufficient for the diagnosis of IgG4-related lymphadenopathy, the existence of features consistent with IgG4-related disease in additional organs/tissues is supportive of the diagnosis [15]. In the current case, retroperitoneal fibrosis, presumably IgG4-related, was also observed. These findings collectively indicate that the possibility of a hyper-IL-6 syndrome was rather remote. The IgG4-related lymphadenopathy in the current case may be categorized as type II according to the previous classification [12].

By analyzing the clinical course of 40 patients with IgG4-related aortitis/periaortitis, Mizushima et al. showed the possibility that corticosteroid therapy can prevent new appearance of luminal dilatation in patients without such lesions before therapy; however, two patients among their study population who had luminal dilatation before corticosteroid therapy showed exacerbation of luminal dilatation after the therapy [16]. Considering that several previous case reports also showed that initiation of steroid therapy may increase the risk of life-threatening aneurysmal formation or rupture of the peripheral arteries, including coronary artery, as well as aorta [17–19], we should periodically follow-up the diameter of abdominal aorta and coronary arteries after the initiation of steroid therapy.

Whether IgG4-related cardiovascular disease (pericardial/coronary arterial) can be diagnosed in the current case may be an issue for debate. Previous reports showed that patients with histologically-proven IgG4-related coronary artery disease may have concomitant involvement of IgG4-related disease in other organs and tissues including abdominal aorta, peripheral arteries, pancreas, and parotid gland [17, 19–21]. On the other hand, IgG4-related disease may appear in the coronary periarterial region alone [4]. In either case, histological assessment of the wall or the periarterial region of the coronary artery is necessary to definitively diagnose the IgG4-related coronary artery disease.

On the other hand, tissue sampling, either by biopsy or surgically, is frequently not feasible for cardiovascular tissues. Without histological finding, however, IgG4-related cardiovascular disease cannot be made according to the current comprehensive diagnostic criteria for IgG4-related disease. In several organs for which tissue sampling is not always feasible, such as pancreas, definitive diagnosis of

IgG4-related disease can be made by organ-specific diagnostic criteria even without the histopathological examination [6]. Considering that enhanced immune-inflammatory reaction may aggravate the arterial wall remodeling [22, 23], physicians should be aware of this newly emerging arterial disorder, IgG4-related cardiovascular disease. We need to deepen the knowledge of the characteristics of IgG4-related cardiovascular disease and its responsiveness to corticosteroid therapy; thus, necessity of "organ-specific" diagnostic criteria for IgG4-related cardiovascular disorder needs further discussion.

Complaince with ethical standards

Conflict of interest Authors do not have a financial relationship with the organization that sponsored the research.

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