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【 CASE REPORT 】

Immunoglobulin G4-related Coronary Periarteritis and Luminal Stenosis in a Patient with a History of Autoimmune Pancreatitis

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Abstract:
Immunoglobulin G4 (IgG4)-related disease is a systemic inflammatory disorder that was first described in patients with autoimmune pancreatitis. Although IgG4-related disease is thought to involve the cardiovascular system, case reports describing coronary artery involvement are relatively rare. We describe a patient who was previously diagnosed with autoimmune pancreatitis and found to have coronary periarteritis and luminal narrowing. After the initiation of steroid treatment, the patient's coronary periarteritis and luminal stenosis were both ameliorated with an improvement in the serum IgG4 concentration. The present findings collectively suggest that IgG4-related immuno-inflammation may have a role in the development of coronary periarteritis and luminal atherosclerosis.

Key words: IgG4, coronary periarteritis, coronary artery stenosis, atherosclerosis

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Introduction

Immunoglobulin G4 (IgG4)-related disease is a newly proposed systemic inflammatory disorder that is characterized by the infiltration of IgG4-positive plasma cells, diffuse fibrosis, and often, but not always, an increased serum IgG4 concentration (1, 2). Since IgG4-related disease was first reported in patients with autoimmune pancreatitis (3), similar clinicopathological conditions have been identified in various organs, including the lung, kidney, and thyroid (4-6). In addition, it has been recently suggested that IgG4-related disease may involve the cardiovascular system (7, 8). Although IgG4-related perivascular immuno-inflammation has been observed not only in large vessels but also in smaller vessels, including the coronary arteries (9, 10), the association of IgG4-related disease with coronary periarteritis and coronary luminal narrowing has not been fully demonstrated. We herein describe a case of coronary periarteritis at the site of coronary artery stenosis in a patient who was previously diagnosed with autoimmune pancreatitis. The initiation of steroid treatment resulted in the improvement of the patient's coronary artery lesions.

Case Report

A 67-year-old Japanese man was referred to the Department of Cardiovascular Medicine to undergo assessment for an abnormal electrocardiogram (ECG) prior to orthopedic surgery. He had been diagnosed with autoimmune pancreatitis at 58 years of age based on abdominal computed tomography (CT) images showing a diffusely enlarged pancreas, endoscopic retrograde cholangiopancreatography (ERCP) images showing the irregular narrowing of the main pancreatic duct in the body and tail of the pancreas, and an elevated serum IgG4 concentration (481 mg/dL). Extrapancreatic lesions, which may be associated with IgG4-related disease, were not detected. Oral steroid therapy (prednisolone, 30 mg/day) was initiated, and then tapered off when the patient was 65 years of age as he showed clinical im-

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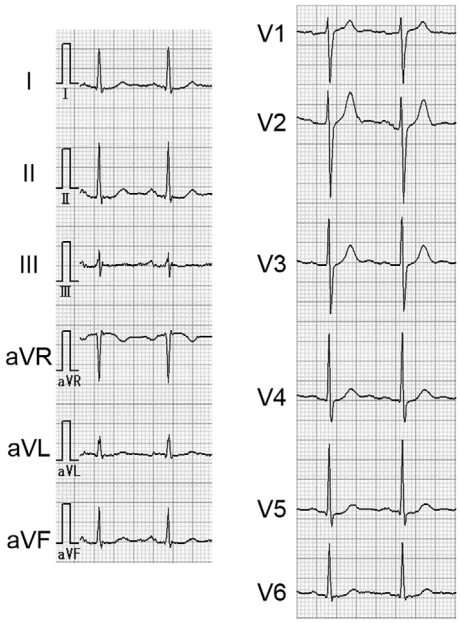

Figure 1. An electrocardiogram at the time of consultation. A slight ST segment depression was observed in leads II, aVF, and V5-6.

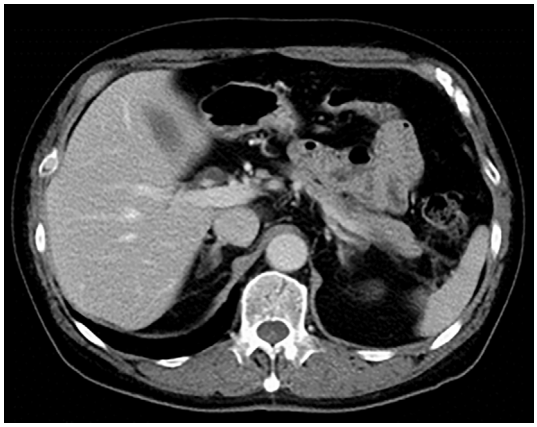

Figure 2. Abdominal contrast-enhanced computed tomography image showing no evidence of an enlarged pancreatitis, periaortic soft tissue, or aortic dilation.

provement (11). At the time of the cessation of steroid treatment, the patient's serum IgG4 concentration slightly exceeded the upper normal limit (139 mg/dL).

Although he had no apparent chest symptoms, the ECG revealed a slight ST depression in II, aVF, and V5-6 (Fig. 1). He was a former smoker and had borderline dyslipidemia, but did not have hypertension, diabetes, or a family history of cardiovascular disease at the time of the initial consultation. A laboratory evaluation revealed a normal leukocyte count (6,800/μL), and elevated serum concentrations of C-reactive protein (2.07 mg/dL), IgG (1,836 mg/dL) and IgG4 (231 mg/dL). Abdominal CT showed no signs indicating an exacerbation of autoimmune pancreatitis. In addition, we did not detect aneurysmal dilation of the abdominal aorta or periaortic soft tissue (Fig. 2). Coronary CT angiography demonstrated soft tissue with a thickness of 3 to 5 mm, suggesting coronary periarteritis, at the site of the luminal narrowing of the left anterior descending artery (LAD) (Fig. 3A-D). Coronary periarteritis could not be found in the right coronary artery (RCA) or the left circumflex artery (LCX). In addition, only a focal significant stenotic lesion of distal RCA was detected, and there was a moderate, but not significant, stenotic lesion without calcification of the LCX. As the relapse of IgG4-related disease was suspected, steroid treatment (prednisolone, 25 mg/day) was resumed for management of IgG4-related disease, including the recurrence prevention of autoimmune pancreatitis and the treatment of coronary periarteritis. The patient continued to receive drug therapy without coronary intervention, because invasive coronary angiography, which was performed 1 week after the reinstitution of steroid treatment, showed moderate, but not severe, stenosis of the LAD (Fig. 3E, F).

The steroid treatment was effective and the patient's laboratory data gradually improved (C-reactive protein, 0.19 mg/dL; IgG, 1,132 mg/dL; IgG4, 88.3 mg/dL). Furthermore, at 4 months after the initiation of steroid therapy, coronary CT angiography showed both a resolution of the coronary stenosis of the LAD and a reduction in the volume of soft tissue with a thickness of 2 to 3 mm (Fig. 4A, D, G). When the steroid dose was tapered to 5 mg/day, however, the patient's serum IgG4 concentration became elevated again (116 mg/dL) and coronary periarteritis of the LAD (thickness, 3 - 4 mm) was found to have worsened by coronary CT angiography. The luminal narrowing was also found to have slightly progressed (Fig. 4B, E, H). After the dose of steroid was increased to 7.5 mg/day, an improvement in both the serum IgG4 concentration (73.9 mg/dL) and the coronary CT angiography findings (Fig. 4C, F, I) was observed. The thickness of soft tissue around the LAD was 1 to 2 mm. The patient has remained under observation at a steroid dose of 7.5 mg/day without apparent changes in his coronary artery lesions or the development of new lesions in other organs.

Discussion

We described the case of a patient with a history of autoimmune pancreatitis who presented with coronary periarteritis around a coronary luminal stenotic lesion, and showed that both of these coronary artery findings improved after the initiation of steroid treatment.

IgG4, which is the least common of the four subclasses of IgG, may contribute to certain immune-mediated conditions (1). In 2009 in Japan, the total number of patients with IgG4-related disease, such as autoimmune pancreatitis and Mikulicz's disease, was reported to be approximately 8,000, indicating that IgG4-related disease is not such a rare disease (12). Furthermore, several recent reports have shown that IgG4-related disease can involve the cardiovascular system; however, IgG4-related cardiovascular disorders remain relatively uncommon among patients with IgG4-related disease. For example, a case of inflammatory abdominal aortic

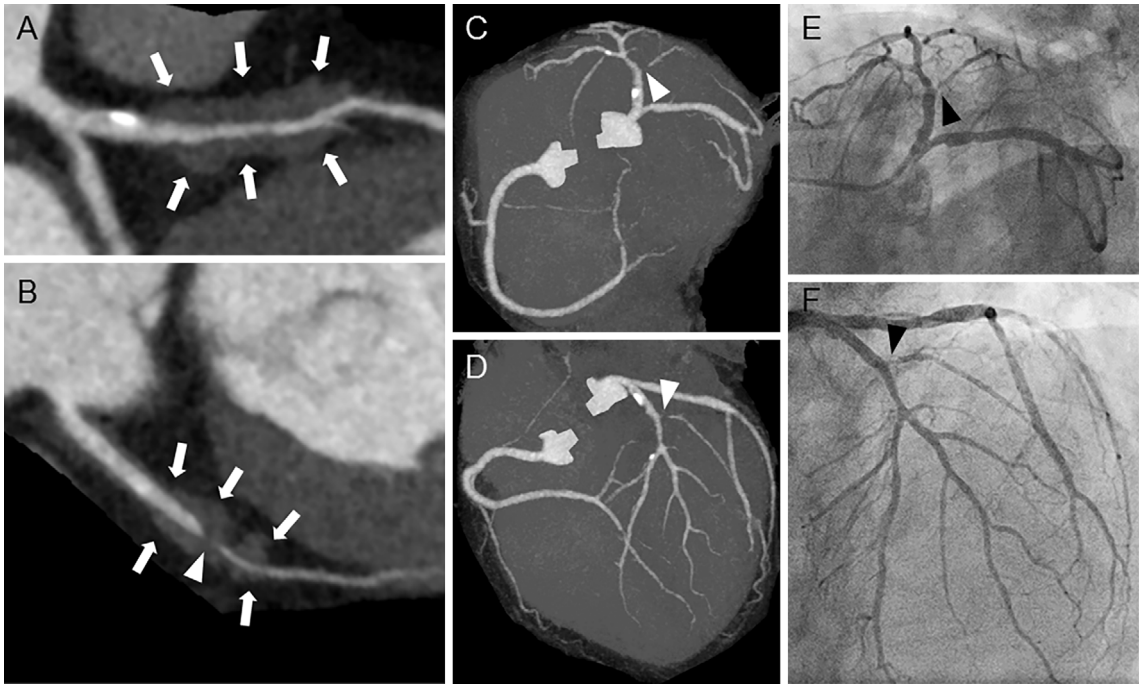

Figure 3. **Curved multiplanar reformatted images (A, B) and maximum intensity projection (MIP) images (C, D) obtained by coronary computed tomography angiography before steroid treatment, and left coronary artery images (E, F) obtained by invasive coronary angiography 1 week after the initiation of steroid treatment. A: Soft tissue (arrows) was observed around the left anterior descending artery (LAD), suggesting coronary periarteritis. B-F: Soft tissue (arrows) and coronary luminal narrowing (arrowheads) of the diagonal branch of the LAD were detected.**

aneurysm and retroperitoneal fibrosis (a disorder that is sometimes recognized as being IgG4-related) with autoimmune pancreatitis has been reported (13). In this case, numerous IgG4-positive plasma cells were detected in the thickened adventitia of the aortic wall. Another case of retroperitoneal fibrosis, where the marked infiltration of IgG4-positive plasma cells was observed, was associated with subclinical pancreatitis that was probably autoimmune pancreatitis (14).

Recently, several cases have been reported that involved IgG4-related perivascular immuno-inflammation in the coronary arteries, including a patient with multiple aneurysms of the coronary arteries who was diagnosed as having IgG4-related disease based on the examination of a kidney biopsy specimen (15) and a patient with mass lesions surrounding the coronary arteries and the abdominal aorta who was diagnosed with IgG4-related disease by a needle biopsy of a coronary artery (16). In the latter case, steroid therapy was effective and led to a marked reduction in the mass lesions around the patient's coronary and abdominal arteries. Furthermore, coronary artery stenosis as well as coronary periarteritis and/or aneurysms has been identified in patients diagnosed with IgG4-related disease (17, 18). In a case of acute coronary syndrome, coronary periarteritis, in the lesion of which IgG4-positive plasma cells were observed, was found to be located outside the luminal narrowing (19). Cases of sudden cardiac death in patients with coronary artery lesions caused by IgG4-related disease have been recently reported (20, 21), suggesting that IgG4-related cardiovascular disorders may have a fatal outcome.

As IgG4-positive inflammatory cells infiltrate the adventitia (22), previous reports regarding IgG4-related cardiovascular disorders have mostly involved dilated lesions or perivasculitis. However, it has been suggested that atherosclerotic plaques may contribute to the pathogenesis of chronic periaortitis (23, 24). Castelein et al. recently raised the possibility that the reaction of IgG4 autoantibodies against antigens in intimal atherosclerotic plaques might cause IgG4-related periaortitis (25). In our previous analyses, we found that, among patients who underwent invasive coronary angiography, the serum IgG4 concentrations of patients with CAD were significantly higher than those without CAD (26). Additionally, by analyzing the data from patients who underwent coronary CT angiography, the serum IgG4 concentrations of patients with low-density coronary plaques were found to be significantly elevated in comparison to those without low-density coronary plaques (27). In both analyses, increased serum IgG4 concentrations had a significant association with CAD or low-density coronary plaques, independent of traditional cardiovascular risk factors, even though the serum IgG4 concentrations did not exceed the upper normal limit. These findings may partly explain why the coronary artery lesions of the patient in the present case worsened again without a marked elevation in the patient's serum IgG4 concentration. Careful follow-up may be required in patients with IgG4-related cardiovascular lesions,

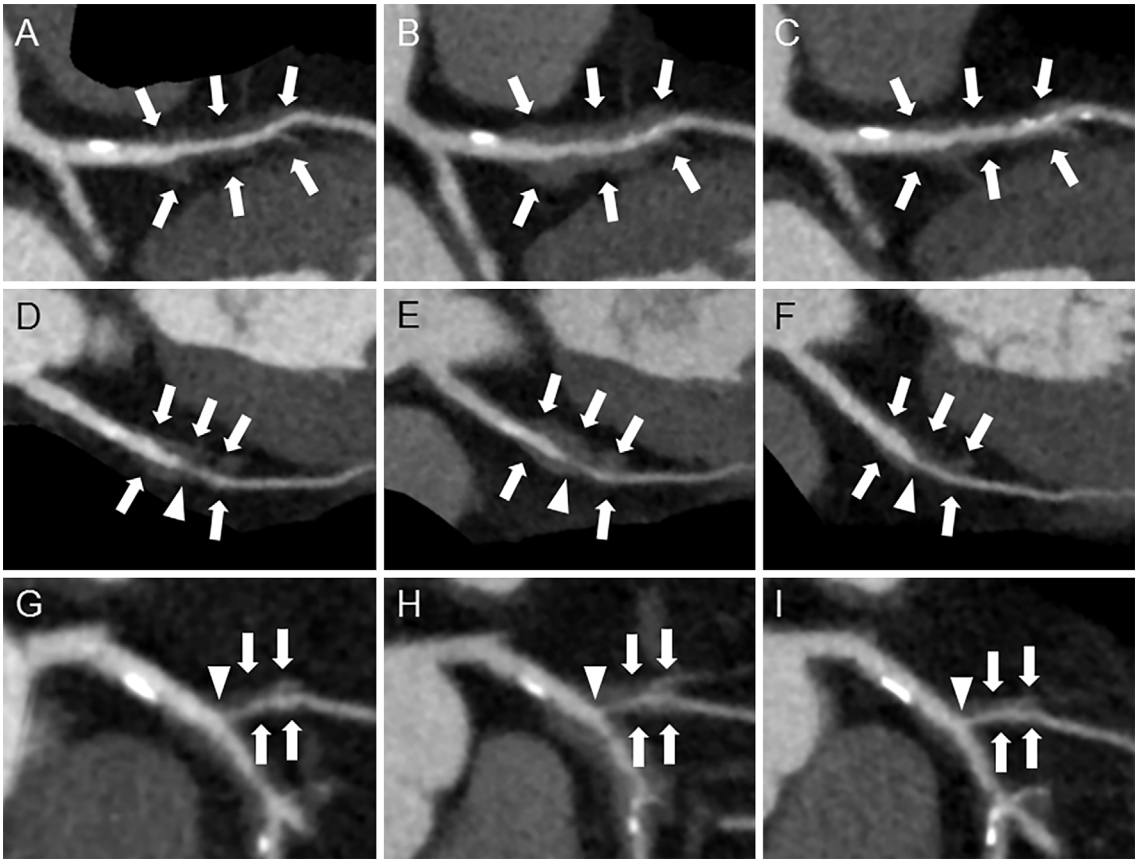

Figure 4. **Curved multiplanar reformatted images of the left anterior descending artery (LAD) (A-C) and the diagonal branch of the LAD (D-I) obtained by coronary computed tomography (CT) angiography. Coronary CT angiography was performed 4 months after the initiation of steroid treatment (A, D, G), when the dose was tapered to 5 mg/day (B, E, H), and after it was increased to 7.5 mg/day (C, F, I). The arrows represent the soft tissue around the coronary artery. The arrowheads represent the site of coronary luminal narrowing shown in Fig. 3.**

even when their serum IgG4 concentrations are maintained to within almost normal limits.

The mechanisms underlying luminal narrowing at the site of IgG4-related coronary periarteritis have not been fully elucidated. On the one hand, intimal inflammation is increasingly recognized to be cross-linked to a distinct inflammatory reaction in the adjacent adventitia (28). Epicardial adipose tissue, which is a source of various inflammatory mediators surrounding the coronary arteries, may have paracrine effects on coronary atherogenesis (29, 30). We previously demonstrated that elevated serum IgG4 concentrations were significantly associated with an increased epicardial fat volume in patients who underwent coronary CT angiography (31). Taken together, we hypothesize that IgG4-related immuno-inflammation may, at least in part, play a certain role in the development of luminal stenosis as well as coronary periarteritis. On the other hand, among patients with IgG4-related vascular disorders, it was reported that luminal stenosis was only detected in the splenic artery (which is a medium vessel) and not the aorta (32). This finding suggests another possibility: that physical compression by adventitial thickening due to coronary periarteritis may affect the development of coronary luminal narrowing in patients with IgG4-related cardiovascular disease. The accumulation of experience in cases of IgG4-related disease involving the vascular system will be necessary to further investigate the association of IgG4-related vascular disorders with luminal stenotic lesions.

In the present case, ECG revealed a slight ST depression in II, aVF, and V5-6. However, coronary periarteritis and luminal stenosis of the LAD may not have had a close association with the ECG findings, which were recognized as almost nonspecific ST changes. It can be considered fortuitous that coronary periarteritis was found during the assessment of the ECG findings. Patients with coronary periarteritis and/or aneurysms are frequently asymptomatic, and recent developments and the spread of various imaging techniques have increased the number of IgG4-related cardiovascular lesions that are detected by chance (18, 33). As multiple organ involvement is often identified in patients with IgG4-related disease (32, 34), other organ lesions, including lesions of the coronary arteries, should not be overlooked.

Coronary periarteritis at the site of luminal narrowing in the present case was recognized as IgG4-related based on the coronary CT angiography images, the elevated serum IgG4 concentration, the effects of steroid treatment, and the

patient's history of autoimmune pancreatitis. However, pathological and immunohistochemical analyses were not performed, because the coronary artery findings were managed by drug therapy and surgery was not performed. Thus, we could not demonstrate the infiltration of IgG4-positive plasma cells in the coronary artery lesions, which may be a limitation of this report. In comparison to other organs, it is often difficult to obtain samples of vascular tissues, such as coronary artery tissue, for histological examination (18, 25); therefore, clinical features that are useful for the diagnosis of IgG4-related periarteritis, such as serum biomarkers and imaging findings, should be established. On the other hand, as the clinical characteristics of patients with chronic periaortitis, including inflammatory abdominal aortic aneurysm and retroperitoneal fibrosis, are frequently similar in patients with IgG4-related and non-IgG4-related disease (2, 7, 8), the histological analysis of other organs may be necessary to make an accurate diagnosis of IgG4-related cardiovascular disorder.

In summary, we have described a case of coronary periarteritis and luminal stenosis in a patient who was previously diagnosed with autoimmune pancreatitis, suggesting the cardiovascular involvement of IgG4-related disease. To our knowledge, this is the first detailed case report to demonstrate an improvement in coronary artery lesions, including both periarteritis and luminal narrowing, after the initiation of steroid treatment. Further studies will be needed to determine the appropriate management of IgG4-related cardiovascular disease.

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

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