

Immunoglobulin G4-related disease preceded by lung involvement

A case report

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Abstract

Rationale: Immunoglobulin G4-related disease (IgG4-RD) is a systemic condition involving various organs and vessels including the pancreas, bile duct, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, and aorta. Recently, some cases of IgG4-RD have been reported, in which only pulmonary lesions were present. It is not known whether IgG4-RD can be diagnosed on the basis of pulmonary lesions only, because increases in serum IgG4 levels and infiltration of IgG4-positive plasma cells into the lung tissue also occur in other inflammatory conditions. A case of IgG4-RD that was followed-up for 7 years after onset is described.

Patient concerns: Initially, only pulmonary lesions were present; however, other lesions in the submandibular glands, pancreas, periarterial region, and other areas occurred over time, with a gradual increase in serum IgG4 levels.

Diagnoses, interventions, and outcomes: Histopathology results from the patient's submandibular gland confirmed the diagnosis of IgG4-RD. Following diagnosis, the patient was treated with corticosteroids immediately, and his symptoms disappeared rapidly.

Lessons: Because other diseases, including malignancies, mimic IgG4-RD in clinical and histopathological features, an absolute diagnosis is necessary to avoid missing the presence of underlying diseases. This case more provides insight into the clinical pathology of IgG4-RD.

Abbreviations: CT = computed tomography, FDG = ¹⁸F-fluorodeoxyglucose, IgG4-RD = immunoglobulin G4-related disease, VATS = video-assisted thoracoscopic surgery.

Keywords: IgG4-related disease, pulmonary lesion, sclerosing sialadenitis

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic sclerosing disease, characterized by IgG4-positive plasma cell and T-lymphocyte infiltration of various organs, and elevated serum IgG4 levels. Initially, IgG4-RD was described as elevated serum IgG4 concentrations in patients with sclerosing pancreatitis.^[1] Thereafter, many cases of IgG4-RD with various clinical patterns have been reported, some of which presented pulmonary lesions only.^[2–5] However, many other inflammatory diseases and carcinomas also exhibit IgG4-positive cell

infiltration into the tissue. Therefore, careful attention is needed to diagnose IgG4-RD based on IgG4-positive cell infiltration into only one organ. We followed an IgG4-RD case for 7 years, in which only pulmonary lesions were initially present at disease onset and thus, gained insight into the clinical course.

2. Case report

2.1. Patient

A 70-year-old man presented to the authors' hospital with a chronic dry cough; an initial chest X-ray revealed no abnormalities. He was prescribed inhaled corticosteroids and his cough subsided. Two years later, his chest X-ray revealed an abnormal shadow (Fig. 1A). Chest computed tomography (CT) revealed subpleural ground-glass opacities or linear shadows (Fig. 1B). His serum IgG (1990 mg/dL) and IgG4 (590 mg/dL) levels were significantly elevated.

Bronchoalveolar lavage and transbronchial biopsy were performed twice over a 3-year period, with nonspecific results. After obtaining informed written consent, a surgical lung biopsy was obtained from a subpleural shadow using video-assisted thoracoscopic surgery (VATS) at 4 years. It revealed thickened alveolar septa and marked infiltration of lymphocytes, plasma cells, and some eosinophils, but no fibrosis or obliterative phlebitis. Immunohistochemically, most infiltrating plasma cells were IgG positive, approximately 50% of which were IgG4-

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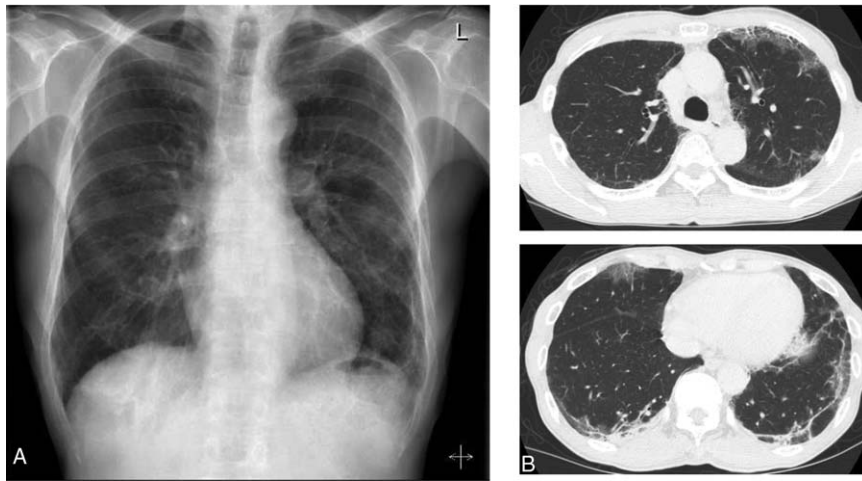


Figure 1. (A) Chest radiograph revealing partial ground-glass opacity and linear shadows in the bilateral outer layer of the lungs. (B) Chest computed tomography revealing subpleural linear and ground-glass shadows bilaterally from the upper to the lower regions.

positive (Fig. 2). κ or λ chain staining revealed no monoclonality. IgG4-RD was strongly suspected; however, only lung lesions were present and the patient was asymptomatic; therefore, simple observation was continued

2.2. Diagnostic history

Two years after VATS biopsy, the patient complained of shortness of breath and general fatigue. His body weight had decreased by 2.5 kg/y. In addition, his bilateral submandibular glands were clearly swollen. ^{18}F -fluorodeoxyglucose (FDG) positron-emission tomography–CT demonstrated increased

FDG uptake in the bilateral submandibular glands, pancreas, and peripheral tissues of the common iliac arteries. Abdominal CT and magnetic resonance imaging confirmed pancreatitis and periarteritis (Fig. 3). Serum IgG and IgG4 levels were increased (3551 and 1390 mg/dL, respectively), and the levels of complement components C3c and C4 were decreased (59 and 8 mg/dL, respectively). Serum anti-SS-A and anti-SS-B levels were normal.

With the patient's consent, his left submandibular gland was excised and revealed sclerosing sialadenitis with lymphocyte infiltration without monoclonality, and plasma cells, numerous IgG4-positive cells, storiform fibrosis, and obliterative phlebitis (Fig. 4).

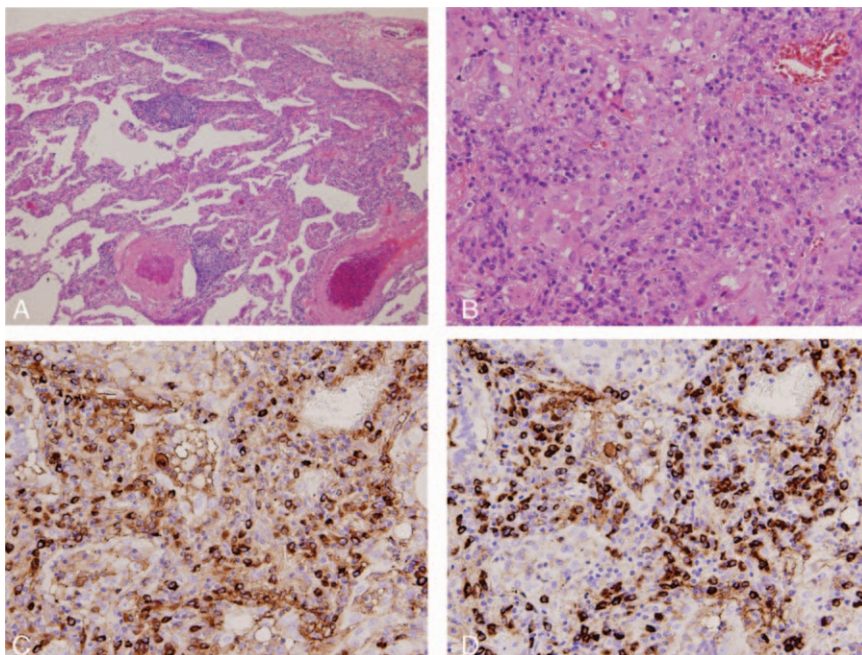


Figure 2. Hematoxylin and eosin staining (A: $\times 40$; B: $\times 200$) of a histopathological specimen and an immunohistochemically stained specimen (C: immunoglobulin G [IgG], $\times 200$; D: IgG4, $\times 200$) of a video-assisted thoracoscopic surgery lung biopsy. Thickening of the alveolar septa (A), and infiltrating plasma cells and lymphocytes in the alveolar septa (B) are apparent. Approximately 50% of the IgG-positive plasma cells are positive for IgG4 (C, D).

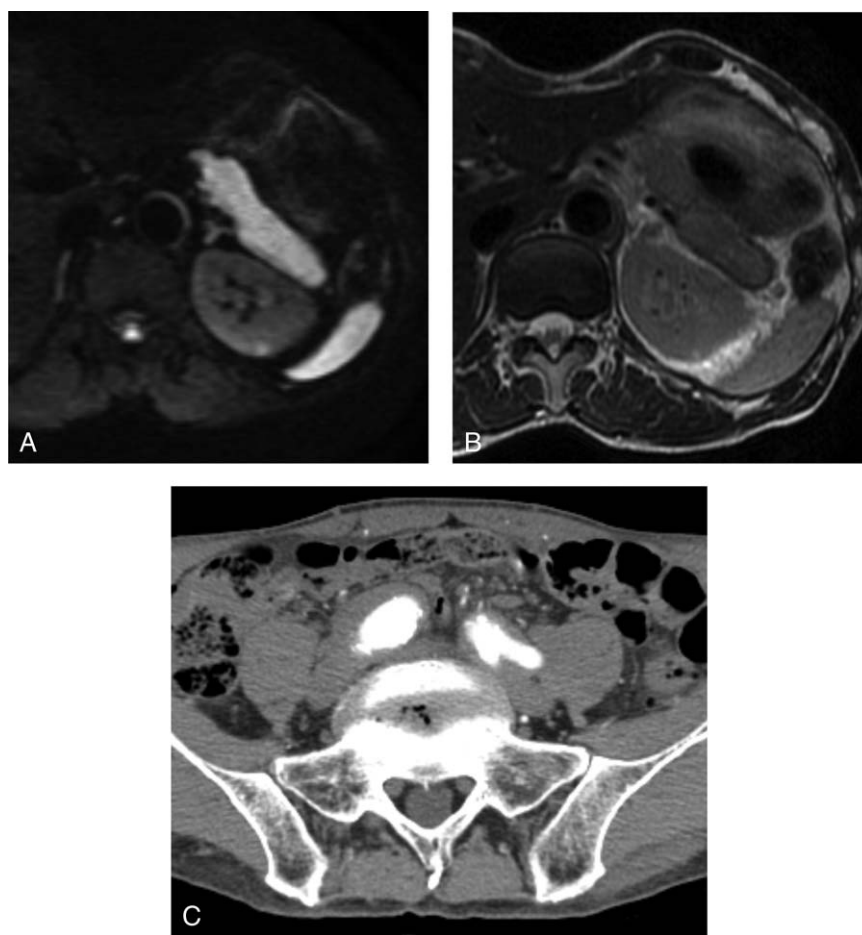


Figure 3. Abdominal magnetic resonance image revealing that the pancreatic body was enlarged and hyperenhanced in diffusion-weighted images (A). A capsule-like rim is apparent in the T2-weighted image (B). Abdominal enhanced computed tomography revealing an enlarged periaortic soft tissue shadow apparent around the bilateral common iliac arteries (C).

2.3. Treatment

The patient was diagnosed with IgG4-RD and immediately treated with corticosteroids (prednisolone 40 mg/d, 0.6 mg/kg body weight). His symptoms disappeared rapidly and swelling in the right submandibular gland decreased over a period of several days. Serum IgG and IgG4 levels decreased to 1247 and 241 mg/dL, respectively.

The oral prednisolone dose was tapered, without evidence of relapse over a period of 1 year.

3. Discussion

In this particular case of IgG4-RD, only pulmonary lesions were initially present, followed by the appearance of systemic organ lesions over a 7-year period. Despite high IgG4 levels and biopsy-proven IgG4-positive plasma cell infiltration, IgG4-RD diagnosis could not be initially confirmed, owing to the absence of multiple organ and sclerosing lesions.

IgG4-RD is usually associated with increased serum IgG4 levels, similar to many other diseases.^[6] Similarly, infiltration of IgG4-positive plasma cells occurs in numerous inflammatory conditions and is, therefore, not diagnostic for IgG4-RD.^[7] Diagnosis of IgG4-RD requires certain pathological findings, such as a dense lymphoplasmacytic infiltrate, storiform pattern

fibrosis, obliterative phlebitis, and a mild-to-moderate eosinophil infiltrate.^[8]

Our patient exhibited IgG4-positive plasma cell infiltration into the lung tissue, while the ratio of IgG4-positive to IgG-positive plasma cells was high; nevertheless, fibrosis and obliterative phlebitis were absent on the first VATS biopsy. As the disease progressed, both conditions became apparent in submandibular gland tissues, confirming IgG4-RD.

It is risky to assume IgG4-RD without strong evidence, because other diseases including malignancies (e.g., lymphoma and sarcoidosis), share clinical and histopathological features with IgG4-RD.^[7,9] Some malignant tumors are identified after IgG4-RD is diagnosed.^[10] Therefore, IgG4-RD should be followed up carefully, even after diagnosis is confirmed.

Our patient was followed-up without any medication after the first VATS biopsy because he was asymptomatic and did not experience organ failure. IgG4-RD often causes major, irreversible tissue damage. IgG4-related aortitis can cause aneurysms and aortic dissections,^[11] and IgG4-related tubulointerstitial nephritis causes renal dysfunction and even renal failure.^[12,13] Thus, detection and treatment of IgG4-RD should not be delayed, and a thorough pathological, radiological, and clinical diagnosis is necessary to avoid missing the presence of underlying diseases.

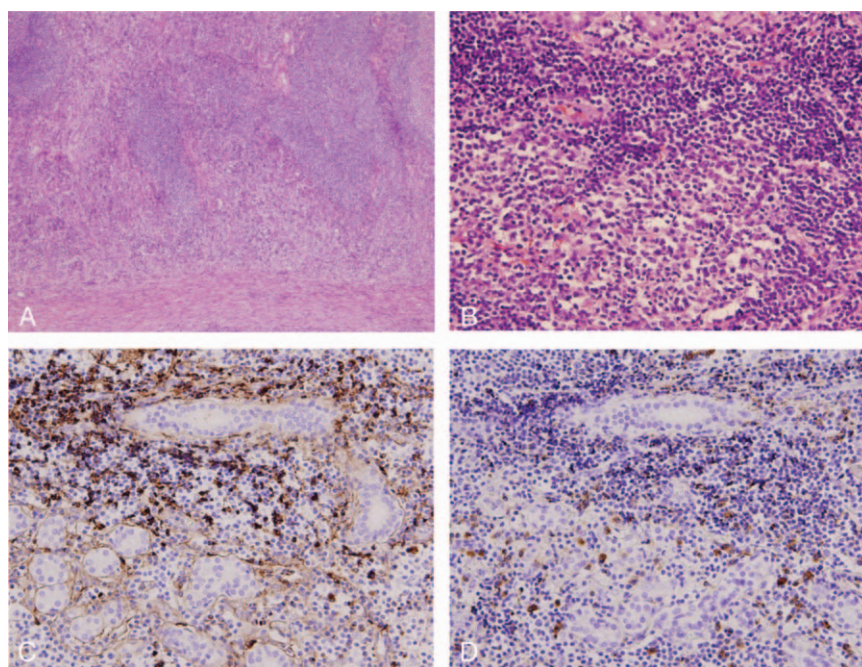


Figure 4. Hematoxylin and eosin staining (A: $\times 40$; B: $\times 200$) and immunohistochemical staining (C: immunoglobulin G [IgG], $\times 200$; D: IgG4, $\times 200$) of the left submandibular gland. Dense infiltration of lymphocytes and plasma cells with marked fibrosis and obliterative phlebitis are visible (A, B). IgG4 positive plasma cells have infiltrated into the submandibular gland (C, D).

4. Conclusion

We reported a case of IgG4-RD, in which only pulmonary lesions were initially present, but spread to other organs over time. The described clinical course provides insight into the pathology of IgG4-RD. Careful observation is necessary for monitoring suspected cases of IgG4-RD.

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