

Chronic Sclerosing Sialadenitis of the Submandibular Gland as the Initial Symptom of IgG4-Related Disease: A Case Report

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Immunoglobulin G4-related disease (IgG4-RD) is a systemic condition accompanied by tumefactive lesions, dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis in various organs, and, frequently, elevated serum IgG4 levels. Chronic sclerosing sialadenitis (also termed Küttner's tumor) is thought to be a lesion of IgG4-RD; thus, IgG4-related sialadenitis may be the initial symptom of IgG4-RD. We herein report a 64-year-old Japanese female with IgG4-related chronic sclerosing sialadenitis of the right submandibular gland and retroperitoneal fibrosis, who subsequently developed tubulointerstitial nephritis and pancreatitis. She was referred to our Department for treatment of swelling of the right submandibular gland; preoperative imaging studies suggested a malignant tumor. We extirpated the submandibular glands bilaterally and diagnosed IgG4-related chronic sclerosing sialadenitis pathologically. Subsequently, the patient's serum IgG4 concentration increased, and lesions in the retroperitoneum, kidney, and pancreas were confirmed by imaging. Although the radiological characteristics of these lesions mimicked malignancy, steroid treatment was commenced based on the pathology of the submandibular gland and elevated serum IgG4 level. This caused the lesions to disappear, indicating that the patient had experienced IgG4-related retroperitoneal fibrosis, tubulointerstitial nephritis, and pancreatitis. No relapse was detected for 4 years 8 months after surgery. A pathological diagnosis is crucial to exclude the possibility of malignancy and to make treatment decisions when lesions are evident in other organs. In addition, periodic evaluation of the serum IgG4 concentration and imaging of the whole body are warranted in long-term follow-up.

Keywords: chronic sclerosing sialadenitis; immunoglobulin G4-related disease; pancreatitis; retroperitoneal fibrosis; tubulointerstitial nephritis

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Introduction

Since Hamano et al. (2001) first reported an association between sclerosing pancreatitis and high serum immunoglobulin (Ig) G4 concentrations, the concept of IgG4-related disease (IgG4-RD) has become accepted worldwide. IgG4-RD is a recently designated fibroinflammatory condition characterized by tumefactive lesions, dense IgG4-positive plasma cell-rich lymphoplasmacytic infiltrate, storiform fibrosis, and, frequently, elevated serum IgG4 levels (Stone et al. 2012). Affected parts of the body may include the pancreas, biliary duct, central nervous system, lungs, liver, digestive tract, kidneys, prostate, retroperitoneum, aorta, pericardium, lymph nodes, skin, and mammary glands (Masaki et al. 2011; Stone et al. 2012). The head and neck can also be affected in IgG4-RD, commonly

involving the salivary glands, lacrimal glands, orbits, thyroid gland, lymph nodes, sinonasal cavities, and pituitary stalk, as well as (though less commonly) the larynx, tongue, and palate (Fujita et al. 2012; Khurram et al. 2013; Andrew et al. 2014). Lesions tend to develop in multiple organs simultaneously or metachronously, but are sometimes confined to a single organ. The sites of such lesions vary, but the histopathological features are similar across organs and all lesions generally respond well to steroids.

Herein, we report the case of a patient with IgG4-related chronic sclerosing sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, and pancreatitis that developed metachronously.

Case Presentation

A 64-year-old Japanese female presented with a five-

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year history of swelling of the right submandibular region. Her medical history included hypertension, hyperlipidemia and prior leiomyomectomy. Physical examination revealed an elastic, somewhat hard mass measuring 3.8×2.5 cm in the right submandibular region, and a salivary stone in the left submandibular gland. No salivation from either of the bilateral sublingual caruncles was detected. The parotid and lacrimal glands were not swollen, and cervical lymphadenopathy was absent.

Computed tomography (CT) showed enlargement of the right submandibular gland and atrophy of the left submandibular gland with a salivary stone (Fig. 1). Ultrasonography revealed internal heterogeneity of the right submandibular gland without normal glandular tissue. Magnetic resonance imaging (MRI) demonstrated a sharply margined mass measuring $3.5 \times 2.3 \times 1.9$ cm, which showed relatively homogeneous contrast enhancement (Fig. 2). On dynamic MRI, the time-intensity curve indicated an early peak of enhancement and a low washout pattern—categorized as type C by Yabuuchi et al. (2003)—suggesting malignancy. ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT demonstrated increased FDG uptake in the right submandibular gland (maximum standardized uptake value [SUVmax], 12.1) and anterior aspect of the sacrum (SUVmax, 4.7) (Fig. 3). PET-CT also showed two small nodules in the right lung without FDG uptake but no other lesions. The laboratory findings were non-specific, but the patient's serum IgG4 level was not measured at the time of admission.

Based on a clinical diagnosis of a tumor in the right submandibular gland and sialolithiasis of the left submandibular gland, the patient underwent extirpation of the bilateral submandibular glands. Considering the possibility of malignancy in the right submandibular gland, we examined

intraoperative frozen sections and identified chronic sclerosing sialadenitis. Microscopically, the right submandibular gland exhibited dense infiltration of inflammatory cells into the parenchyma. Marked acinar atrophy and lymphoid follicles with a geographic germinal center were also observed. Thickened interlobular septa composed of fibroblasts and collagen fibers due to severe fibrosis were noted (Fig. 4A). The inflammatory cells were mainly composed of lymphocytes and plasma cells (Fig. 4B). Immunohistochemistry revealed that many IgG-positive plasma cells were present in the lobules and lobular septa (Fig. 4C). Additionally, the ratio of IgG4/IgG-positive cells exceeded 40% (Fig. 4D), suggesting IgG4-related chronic sclerosing sialadenitis. The left submandibular gland was diagnosed as atrophic sialadenitis (data not shown). A postoperative blood evaluation revealed a slightly elevated serum level of IgG4 (115 mg/dL; normal range, 4.8–105 mg/dL).

We referred the patient to the Departments of Orthopedic Surgery and Pulmonary Medicine for an evaluation of the lesion exhibiting FDG uptake in the anterior aspect of the sacrum (the retroperitoneum) and the small nodules in the right lung. However, no lesion was definitively diagnosed, and follow-up CT was scheduled.

CT performed 5 months after surgery revealed a soft tissue mass in the ureteropelvic junction of the left kidney and swelling of the pancreatic tail. The patient consulted the Department of Urology, and the mass was suspected to be malignant by MRI; however, class II urine cytology findings were reported. Magnetic resonance cholangiopancreatography performed at the Department of Hepatobiliary and Pancreatic Surgery suggested pancreatitis or pancreatic cancer. Based on these findings, the lesion exhibiting high-level FDG uptake in the anterior aspect of the sacrum (the retroperitoneum) was suspected to be a metastatic lesion or

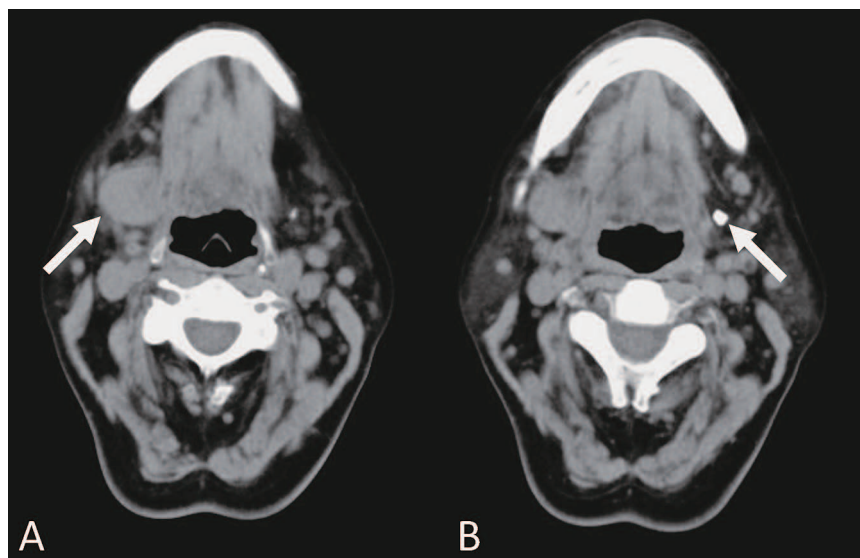


Fig. 1. Computed tomography (CT) imaging of the submandibular glands.

CT showing (A) enlargement of the right submandibular gland and (B) atrophy of the left submandibular gland with a salivary stone.

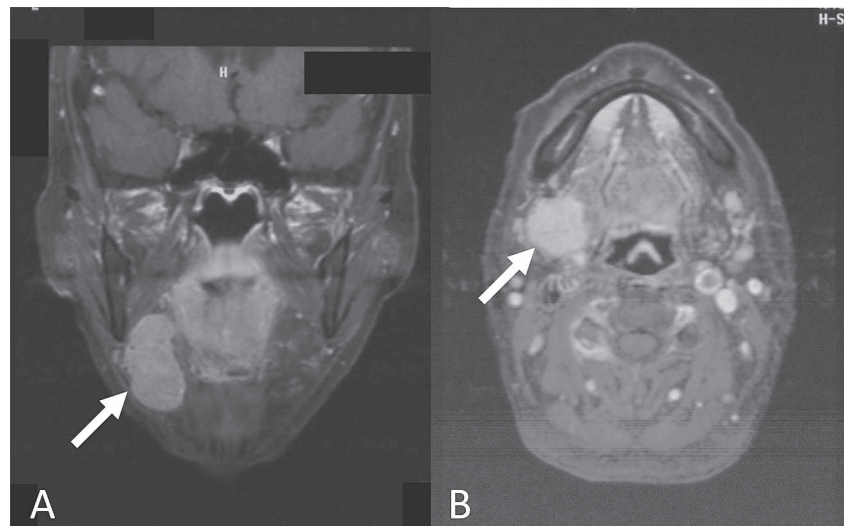


Fig. 2. Magnetic resonance imaging (MRI) of the submandibular glands.
MRI demonstrating a sharply margined mass with relatively homogeneous contrast enhancement. (A) Coronal section.
(B) Transverse section.

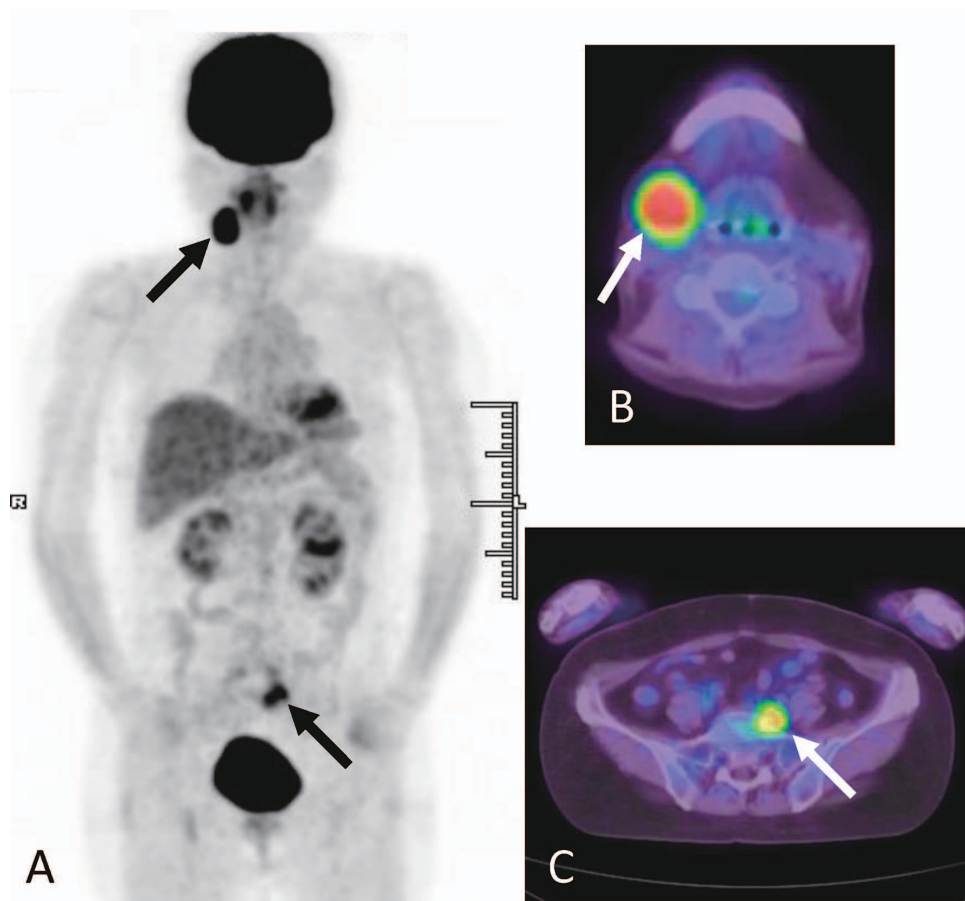


Fig. 3. Positron emission tomography (PET) and PET-CT.
PET and PET-CT demonstrating areas of high uptake in (A, B) the right submandibular gland and (A, C) anterior aspect of the sacrum.

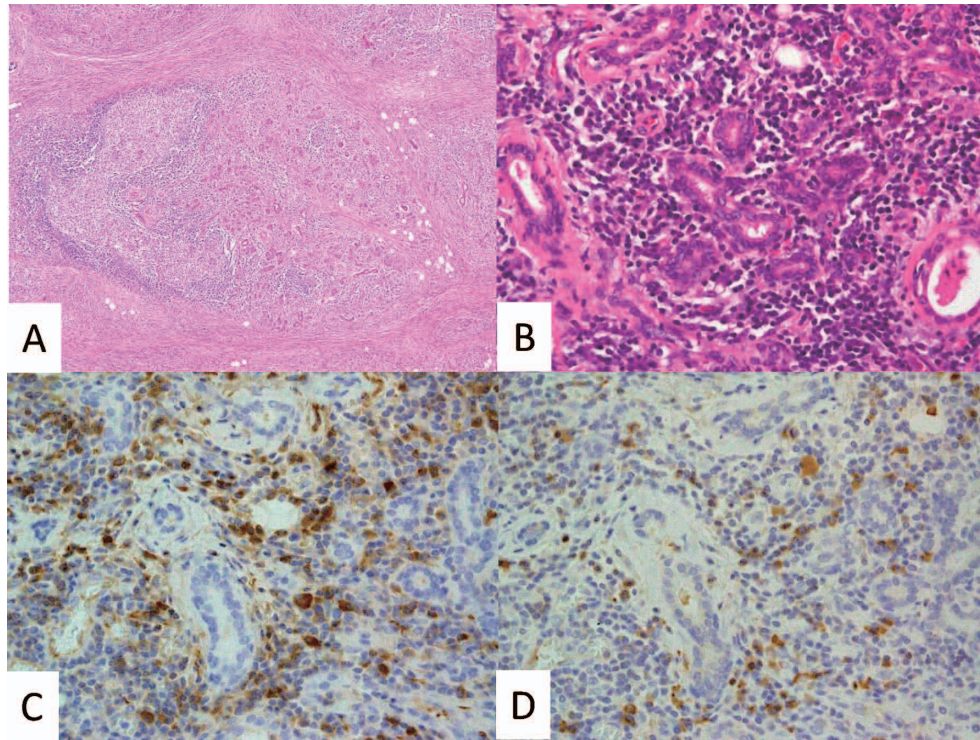


Fig. 4. Hematoxylin and eosin (HE) staining and immunohistochemical staining. HE staining (A: $\times 40$; B: $\times 400$) and immunohistochemical staining (C: IgG, $\times 400$; D: IgG4, $\times 400$) of the right submandibular gland. (A, B) Dense infiltration of lymphocytes and plasma cells with marked fibrosis. (C, D) The IgG4/IgG-positive cell ratio was $> 40\%$.

retroperitoneal fibrosis.

However, no lesion either grew or exhibited an invasion tendency on CT performed 7 months after surgery (Fig. 5A-C). Additionally, the serum IgG4 level became elevated (to 279 mg/dL). These radiological and laboratory findings, in addition to the pathological findings for the right submandibular gland, suggested that each lesion was caused by IgG4-RD. Thus, prednisolone therapy (30 mg/day) was commenced, even though the consulted Departments were considering the possibility of a malignancy. CT performed 2 weeks after the start of steroid treatment showed that each lesion had decreased in size, indicating that the lesions were not malignant. Therefore, we decided to continue prednisolone therapy. The serum IgG4 concentration decreased over time, and all lesions were completely absent upon CT performed 5 months after the initiation of treatment (Fig. 5D-F), indicating IgG4-related retroperitoneal fibrosis, tubulointerstitial nephritis, and pancreatitis. The dose of prednisolone was then tapered to a low level (5 mg/day). However, re-elevation of the serum IgG4 level (130 mg/dL) was confirmed 15 months after commencement of medication. This required intervention to prevent relapse, especially in vital organs, because the elevated IgG4 level was thought to be linked to the lesions development. The patient had already developed steroid diabetes and a compressed fracture of the thoracic vertebra, and additional azathioprine was thus prescribed (50-75 mg/day) rather than increasing the prednisolone dose. Currently (4 years 8

months after surgery), the patient's serum IgG4 level was under control, and recent CT revealed no evidence of relapse, although the small nodules in the lung remained unchanged.

Discussion

IgG4-RD is a lymphoproliferative disorder characterized by hyper-IgG4- γ -globulinemia and IgG4-producing plasma cell expansion in affected organs, with fibrotic or sclerotic changes (Masaki et al. 2011). In the head and neck region, Mikulicz's disease (affecting the salivary and lacrimal glands), Küttner's tumor (affecting mainly the submandibular glands), Riedel's thyroiditis, Hashimoto's thyroiditis, idiopathic orbital inflammatory syndrome, and pituitary hypophysitis may all be attributable to IgG4-RD (Fujita et al. 2012; Stone et al. 2012). When such conditions are apparent, it is important to investigate the entire body (not just the head and neck). The salivary glands are the organs most frequently involved in IgG4-RD of the head and neck (Fujita et al. 2012).

Most patients with IgG4-RD are male (62-83%) and aged over 50 years, in contrast to patients with other autoimmune diseases such as Sjögren's syndrome and primary biliary cirrhosis (Stone et al. 2012). Up to 40% of patients with IgG4-RD have a history of allergic disease such as bronchial asthma or chronic sinusitis (Stone et al. 2012). Our patient was female and had no history of allergic disease. Although the most common clinical findings in

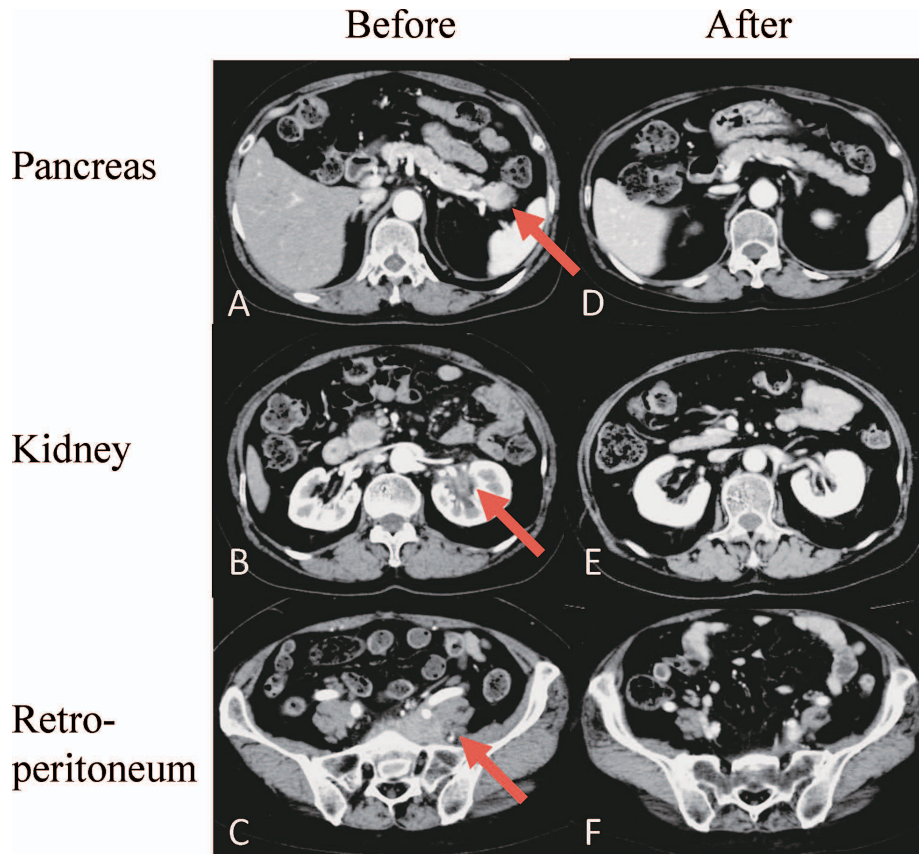


Fig. 5. CT of the abdomen.

CT showing complete disappearance of lesions in the (A, D) pancreas, (B, E) kidney, and (C, F) retroperitoneum. (A-C) Before steroid therapy. (D-F) Five months after the initiation of steroid therapy.

IgG4-RD patients are tumefactive in nature, the imaging features are generally nonspecific and do not permit IgG4-RD and cancer to be reliably distinguished (Stone et al. 2012). Preoperative imaging indicated the possibility of malignancy in our case. However, PET or ^{67}Ga scans should be performed to explore lesions in other organs (Masaki et al. 2011).

In healthy individuals, IgG4 accounts for less than 5% of the total IgG and is the least abundant IgG subclass. The serum IgG4 concentrations of healthy individuals vary, but are generally individually stable (Stone et al. 2012). Most patients with IgG4-RD have elevated serum IgG4 concentrations, but the levels vary widely. In Japan, 95% of patients exhibit elevated serum IgG4 concentrations (Hamano et al. 2001), while approximately 30% of patients in the United States have normal concentrations, despite exhibiting characteristic histopathological and immunohistochemical findings (Sah and Chari 2011). Our patient initially had a slightly elevated IgG4 concentration (115 mg/dL) postoperatively, but this increased gradually over time.

The diagnostic criteria for IgG4-RD are based on clinical, hematological, and histopathological findings: 1) characteristic diffuse or localized swelling or masses in single or multiple organs, 2) a serum IgG4 concentration ≥ 135 mg/dL, and 3) marked lymphocyte and plasma cell infiltra-

tion and fibrosis, along with a ratio of IgG4-positive cells to IgG-positive cells $> 40\%$ and more than 10 IgG4-positive cells per high-power field. A definite case is proposed to fulfill all three criteria, while a probable case fulfills criteria 1 and 3, and a possible case fulfills criteria 1 and 2 (Umehara et al. 2012). The present case was categorized as probable at the time of extirpation of the submandibular glands. Among such tests, histopathological examination is the most important to rule out carcinoma, malignant lymphoma, or similar diseases, including Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome (Umehara et al. 2012). Salivary gland tumors exhibit exceptionally diverse architectural and cellular features, and accurate diagnosis often requires evaluation of both the tumor and its interface with surrounding tissues. Therefore, we extirpated rather than biopsied the submandibular glands to allow for a definite diagnosis. The histopathological findings refuted malignancy and supported the planned treatment of lesions in other organs that can be biopsied only with difficulty.

Currently, glucocorticoids are the recommended first-line therapy (Kamisawa et al. 2010), but spontaneous regression without any treatment may occur in IgG4-RD (Masaki et al. 2011); thus, no conclusion has yet been

reached regarding the relative merits of aggressive treatment over watchful waiting. However, treatment with glucocorticoids should be applied in cases involving the pancreas, kidneys, lungs, or liver, because irreversible functional failure of these organs will affect quality of life (Masaki et al. 2011; Stone et al. 2012). In typical cases of IgG4-RD, the lesions respond to glucocorticoids within several days. Imaging studies are recommended 2 weeks after the start of glucocorticoid administration to evaluate the effects of pharmacotherapy. If the effects are unremarkable, other diseases, including cancer, should be suspected (Masaki et al. 2011). In the present case, each Department was ready to begin other treatments, considering the possibility of malignancy, should the response to prednisolone be inadequate. The efficacy of azathioprine has not been confirmed, but the drug is frequently used as a glucocorticoid-sparing agent or a remission-maintenance drug after glucocorticoid-induced remission (Stone et al. 2012). A multicenter study performed in Japan showed that IgG4 levels failed to normalize in 63% of patients treated with glucocorticoids, and that some patients continued to show an elevated serum IgG4 concentration despite disease remission (Kamisawa et al. 2009). That study also reported that 30% of patients with persistently elevated IgG4 concentrations experienced relapse, compared with 10% of patients with normalized IgG4 concentrations (Kamisawa et al. 2009). Moreover, an elevated serum IgG4 level was associated with disease activity in Japanese patients (Hamano et al. 2001; Kamisawa et al. 2009). Conversely, another cohort study of patients with IgG4-related pancreatitis in the United States reported that the proportion of patients showing normalization of IgG4 levels did not differ between those who did and did not experience relapse (Ghazale et al. 2008).

Our patient was diagnosed with probable IgG4-RD based on clinical and pathological criteria at the time of surgery. Her serum IgG4 concentration was subsequently elevated, and new lesions developed in other organs over time, suggesting that periodic evaluation of the serum IgG4 concentration and imaging of the whole body are warranted in the long term, even after surgery. In addition, the department that diagnoses the disease first should coordinate with other departments because IgG4-RD may involve multiple organs.

Conflict of Interest

The authors declare no conflict of interest.

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