

Immunoglobulin G4-Related Disease with Several Inflammatory Foci

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Abstract

We herein report the case of a 62-year-old Japanese man who presented with jaundice, dry eyes and abdominal discomfort. Imaging studies revealed swelling of the periorbital tissue, parotid and submandibular glands, pulmonary hilar lymph nodes, pancreas, bile ducts, gall bladder walls, bilateral kidneys, arterial walls and prostate. A significant increase in the serum level IgG4 was seen, and the patient was diagnosed with IgG4-related disease after undergoing a biopsy of the pancreas and prostate. We herein report a case of IgG4-related disease with multiple ten organ involvement at the onset of the disease that was successfully treated with prednisolone (PSL) therapy.

Key words: IgG4-related disease, autoimmune pancreatitis, corticosteroids, multiple organ, IgG4

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Introduction

Immunoglobulin (Ig) G4-related disease is a new disease entity that was first reported in 2001 (1) and officially named in 2011 (2-5). Inflammation may occur in various organs, thereby causing systemic symptoms. The serum IgG4 levels are related to disease activity and recurrence (2, 6-8). We herein report a case of IgG4-related disease with inflammation in the periorbital tissue, parotid and submandibular glands, pulmonary hilar lymph nodes, pancreas, bile ducts, gall bladder, bilateral kidneys, prostate and arterial walls from the ascending aorta to the left subclavian and bilateral iliac arteries, forming a retroperitoneal lesion. In addition, the patient's serum IgG4 level was significantly high (>1,900 mg/dL). As per our knowledge, this case of multiple organ involvement at the onset of disease is the first if its kind to be reported. Oral corticosteroid administration improved the inflammation and normalized the serum IgG4 level. A discussion of the case presented here is intended to

promote wider recognition and understanding of this disease.

Case Report

A 62-year-old Japanese man presented at our hospital with jaundice, dry eyes, abdominal discomfort and pretibial edema in July 2011. A physical examination revealed swelling of the bilateral submaxillary glands and mild tenderness in the epigastric area in addition to the jaundice and pretibial edema. Laboratory test results revealed increased levels of direct bilirubin and the hepatobiliary enzymes aspartate aminotransferase and alanine aminotransferase at 4.4 mg/dL, 121 IU/L and 145 IU/L, respectively. A serum protein analysis revealed an increased IgG level (3,877 mg/dL) that was caused by a significantly high level of an IgG4 subclass (1,920 mg/dL) known as a specific marker of IgG4-related disease. An increase in the serum creatinine level to 1.13 mg/dL, a decrease in creatinine clearance to 60 mL/min and a high level of urinary protein (2.06 g/day) were also de-

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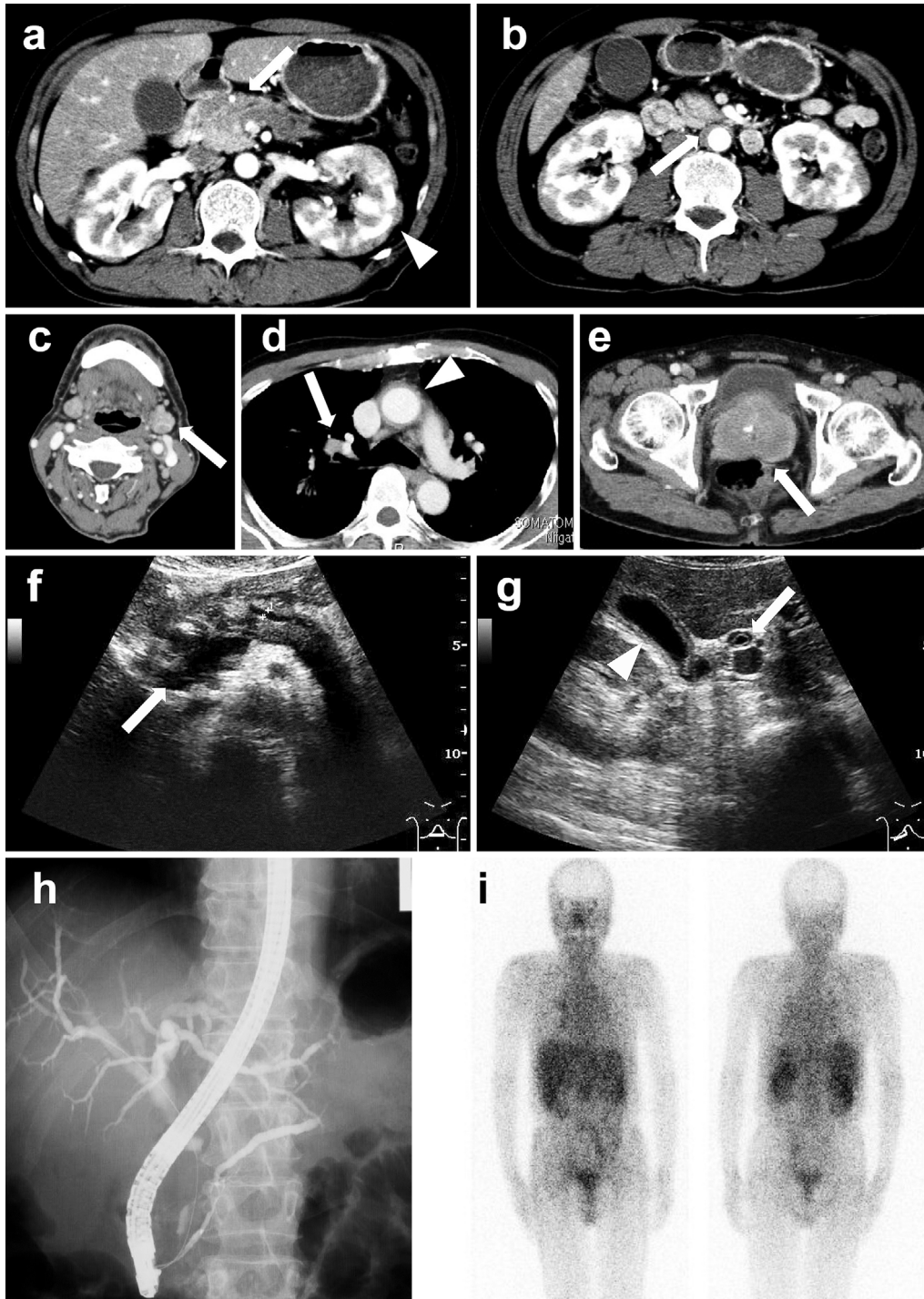


Figure 1. The multiple inflammatory lesions of IgG4-related disease found in our case. Contrast-enhanced computed tomography (CT) showed diffuse enlargement of the pancreas with tumorous changes in the head (a, white arrow), multiple, small, low-attenuation lesions with mild swelling in the bilateral kidneys (a, white arrowhead) and homogeneous thickness in the arterial walls of the abdominal aorta (b, white arrow). Swelling of the submandibular glands (c, white arrows), swelling of the pulmonary hilar lymph nodes (d, white arrow), wall thickness in the ascending aorta (d, white arrowhead) and swelling of the prostate (e, white arrow) were marked. Ultrasonography (US) revealed tumorous swelling in the pancreatic head (f, white arrow), mild dilatation of the pancreatic duct on the tail side and diffuse thickening of the bile duct (g, white arrow) and gall bladder walls (g, white arrowhead). Endoscopic retrograde cholangiopancreatography (ERCP) revealed an irregular surface pattern in the pancreatic and common bile duct walls. A stricture was observed on the pancreatic head side, and mild dilatation was observed in the pancreatic tail and peripheral bile duct (h). Gallium-scintigraphy revealed accumulation in the periorbital tissues, salivary glands, pulmonary hilar lymph nodes, kidneys, prostate and retroperitoneum (i).

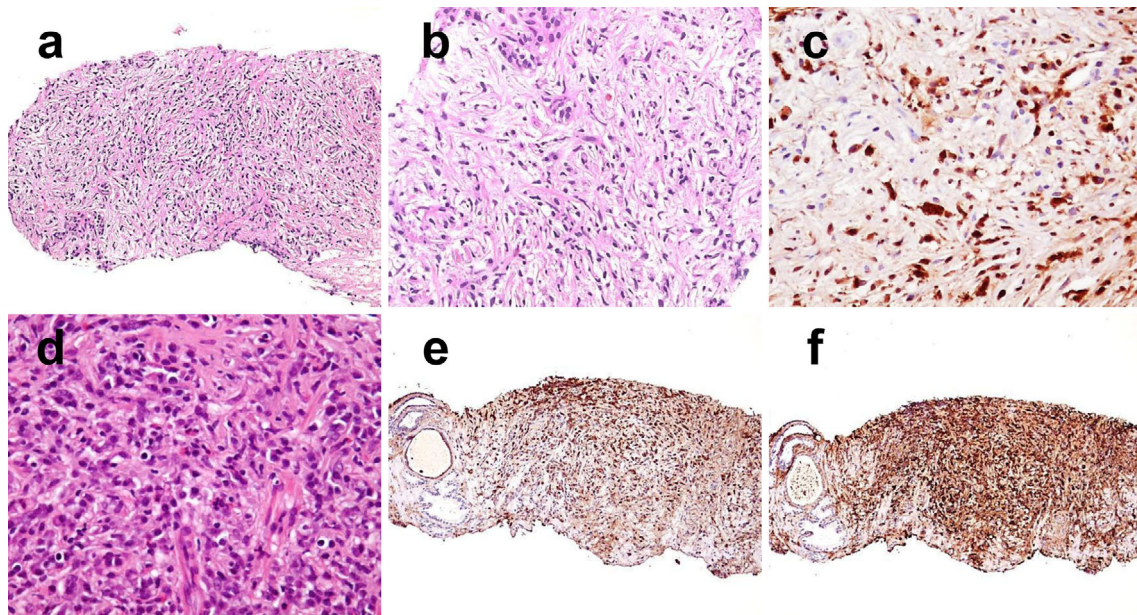


Figure 2. Histopathological findings. Endoscopic US-guided fine needle aspiration of the pancreatic lesion was performed (a-c), and a needle biopsy specimen was obtained from the prostate (d-f). Both tissues revealed storiform fibrosis, lymphoplasmacytic infiltration (a, b, d) and an increased number of IgG4-positive plasma cells (c, e). The ratio of IgG4-positive plasma cells (e) to IgG-positive plasma cells (f) exceeded 50% in the prostate. a, b, d. Hematoxylin and Eosin staining. c, e. IgG4 staining. f. IgG staining, a, e, f, $\times 40$; b, c, $\times 200$; d, $\times 400$.

tected. There were no increases in tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein and prostate-specific antigen. Furthermore, no SS-A or SS-B autoantibodies were detected.

Imaging studies

Contrast-enhanced computed tomography (CT) revealed diffuse enlargement of the pancreas with homogeneous density. At the pancreatic head, a 50-mm tumorous lesion with a weak and heterogeneous enhancement pattern was observed. The pancreatic duct was diffusely narrowed (Fig. 1a). The bilateral kidneys exhibited multiple, small, low-attenuation lesions with mild swelling (Fig. 1a, b). Homogeneous thickness was observed in the arterial walls from the ascending aorta to the left subclavian and bilateral iliac arteries, thus forming a retroperitoneal lesion (Fig. 1b). Swelling of the parotid glands, submandibular glands, pulmonary hilar lymph nodes and prostate was marked (Fig. 1c-e). Magnetic resonance imaging (MRI) revealed swelling of the periorbital tissue. Ultrasonography (US) revealed tumorous swelling at the pancreatic head and mild dilatation of the main pancreatic duct on the tail side caused by a stricture of the duct on the head side (Fig. 1f). Diffuse thickening of the bile duct and gall bladder walls was clearly observed (Fig. 1g). Structural changes in the common bile duct resulted in dilatation of the intrahepatic bile duct. Endoscopic retrograde cholangiopancreatography (ERCP) revealed an irregular surface pattern in the pancreatic and common bile duct walls. The stricture was observed especially on the pancreatic head side, most likely due to

the unevenness of the pancreatic swelling. In addition, mild dilatation was observed in the pancreatic tail and peripheral bile duct (Fig. 1h). Gallium scintigraphy revealed inflammatory foci in the following organs: pancreas, periorbital tissues, salivary glands, pulmonary hilar lymph nodes, kidneys, prostate and retroperitoneum (Fig. 1i).

Histopathology

A diagnosis of systemic IgG4-related disease was suspected on the basis of the information obtained from the laboratory data and imaging studies. To confirm the diagnosis, endoscopic US-guided fine needle aspiration of the pancreatic lesion was performed (Fig. 2a-c) and a needle biopsy specimen was obtained from the prostate to rule out prostate cancer (Fig. 2d-f). The analysis of the pancreatic tissue revealed lymphoplasmacytic infiltration and storiform fibrosis with disruption and atrophy of the acinar component (Fig. 2a, b). The analysis of the prostatic tissue showed fibrosis with lymphoplasmacytic infiltration, lymphoid follicles, scattered eosinophilic infiltration and a decrease in the number of glands (Fig. 2d). A high number of IgG4-positive plasma cells per high-power field was observed in both tissue specimens (Fig. 2c, e), and the ratio of IgG4-positive plasma cells to IgG-positive plasma cells (Fig. 2f) exceeded 50%. No malignant cells were evidenced in either tissue.

Clinical course

On the basis of the above mentioned findings, a diagnosis of IgG4-related disease with pancreatitis, sialadenitis, dacryoadenitis, pulmonary hilar lymphadenopathy, sclerosing

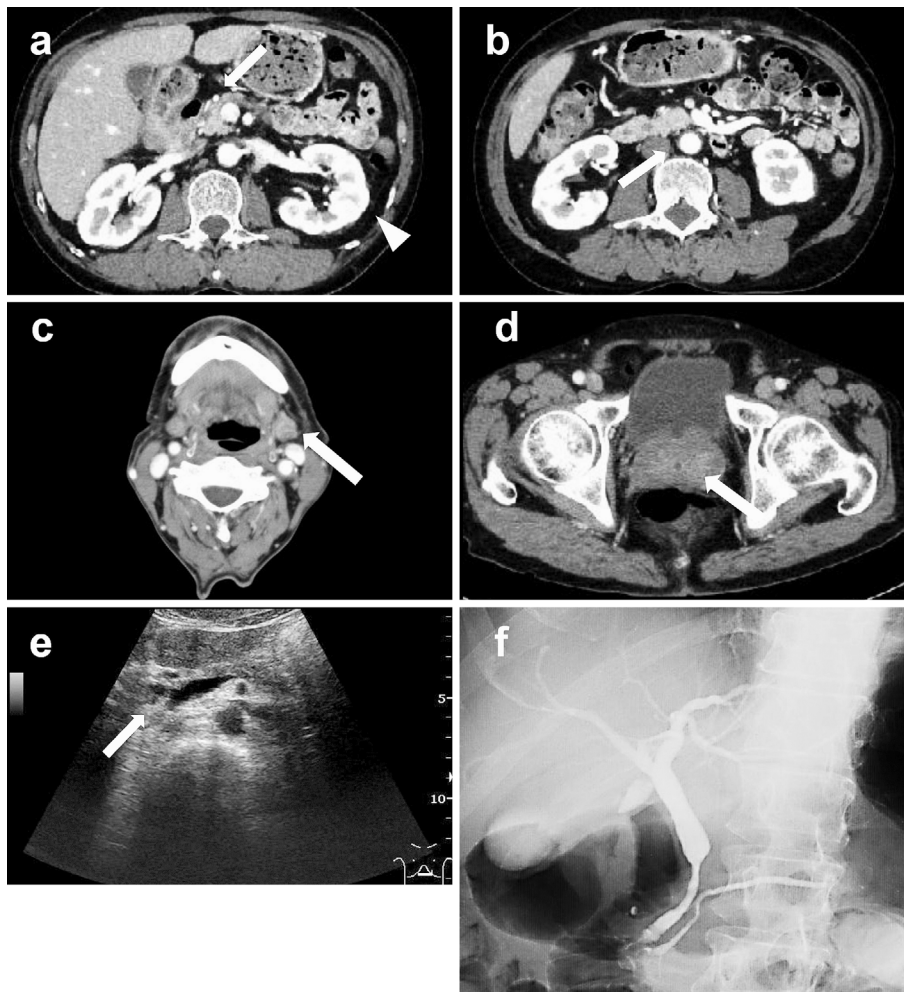


Figure 3. Imaging studies performed four weeks after the administration of prednisolone. CT showed marked decreases in pancreatic swelling (a, white arrow), the kidneys (a, white arrowhead), the retroperitoneal lesion (b, white arrow), the submandibular glands (c, white arrows) and the prostate (d, white arrow). The decrease in pancreatic swelling was marked on US (e, white arrow). ERCP revealed a marked decrease in the irregular surface pattern and narrowing of the pancreatic duct. The stricture of the common bile duct was not fully recovered four weeks after the administration of prednisolone (f).

cholecystitis and cholangitis, tubulointerstitial nephritis, prostatitis and retroperitoneal fibrosis was made. Since September 2011, corticosteroid therapy with 40 mg/day of oral prednisolone (PSL) was initiated. The dose per day was tapered to 35 mg after four weeks of 40 mg administration, then to 30 mg for the next four weeks and tapered by 2.5 mg every four weeks thereafter until July 2012. Since then, the patient has been consuming 10 mg/day for 12 weeks. The symptoms of jaundice, epigastric discomfort, dry eyes, edema and enlarged submandibular glands decreased within four weeks of treatment initiation. Imaging studies showed a marked decrease in pancreatic swelling (Fig. 3a) and the low-attenuation lesions in the kidneys (Fig. 3b). Swelling also diminished in the retroperitoneal lesion (Fig. 3b), submandibular glands (Fig. 3c) and pulmonary hilar lymph nodes. Swelling of the parotid glands and prostate (Fig. 3d) recovered slowly in two months after the administration of PSL. There was a marked decrease in pancreatic swelling,

the stricture of the pancreatic duct, the dilatation on the tail side and the thickness of the bile duct and gall bladder walls on US (Fig. 3e). ERCP revealed a marked decrease in the irregular surface pattern on the pancreatic duct and common bile duct wall along with narrowing of the pancreatic duct (Fig. 3f); however, the stricture in the common bile duct did not fully recover after four weeks of PSL treatment and improved six months after the administration of PSL. The serum IgG4 concentrations gradually decreased to 612 mg/dL within four weeks, after which they continuously decreased to reach 150 mg/dL within three months. Normal levels were maintained thereafter. No relapse of disease activity has been observed as of September 2012.

These data suggest that the disease activity and response to PSL in the various affected organs were significantly related to the serum IgG4 level in this case.

Discussion

IgG4-related disease is a relatively new disease entity. In 2001, Hamano et al. reported an increased frequency of high serum IgG4 levels in patients with autoimmune pancreatitis (1). The term IgG4-related disease was chosen for this condition at an international symposium in 2011. Six characteristic features have been identified to date: systemic involvement; solitary or multiple lesions showing diffuse or localized swelling, masses, nodules and/or wall thickening on imaging; a high serum IgG4 level (>135 mg/dL); abundant infiltration of lymphoplasmacytes and IgG4-bearing plasma cells; a positive response to corticosteroid therapy; and complications similar to those seen in other IgG4-related diseases (2-5). Kamisawa et al. recognized the condition as being a systemic disease exhibiting sclerosing changes in various extrapancreatic organs, including the periorbital tissues, salivary glands, meninges, lymph nodes, thyroid glands, lungs, aorta, retroperitoneum, kidneys, pancreas, biliary tree, gall bladder, liver and prostate (9). Fujinaga et al. summarized 90 cases of autoimmune pancreatitis and analyzed the imaging features of extrapancreatic lesions for the differential diagnosis from lesions of corresponding organs. They found extrapancreatic lesions in 92.2% of the cases, including lachrymal and salivary gland lesions (47.5%), lung hilar lymphadenopathy (78.3%), bile duct wall thickness (77.8%), peri- and para-aortic lymphadenopathy (56.0%) and so on (10). Zen et al. reported the organ-specific pathological features of IgG4-related disease. They found head and neck, thoracic, hepatic and pancreatobiliary, retroperitoneal and systemic lesions in 20.1%, 14%, 23.7%, 11.4% and 30.7% of cases, respectively (11). Since the symptoms are characterized by the organs affected by inflammation, e.g., involvement of the periorbital tissues and salivary glands resembles the symptoms of Mikulicz's syndrome, this information is useful for the differential diagnosis of other diseases and might be related to the response to the administration of PSL. Indeed, our patient showed a slower response in the parotid glands, prostate and common bile duct, most likely due to the organ-specific features of this disease entity. Histologically, IgG4-related disease is characterized by dense lymphoplasmacytic infiltrates rich in IgG4-positive cells that show fibroinflammatory changes. The laboratory data of the case reported here revealed elevated serum IgG and IgG4 levels. The activity of systemic lesions is known to be related to the IgG level (2). Hamano et al., in a review of 64 cases, reported that involvement of one, two, three and four extrapancreatic organs was identified in 31.3%, 26.6%, 21.9% and 9.4% of cases, respectively, and showed that patients with three extrapancreatic lesions appear to have significantly higher IgG4 levels than those without lesions. This result suggests that patients with multiple extrapancreatic lesions have an active disease. Interestingly, no cases showed involvement of more than five organs, and in 10.9% of the cases, no extrapancreatic lesions

were found (6). A similar result was reported by Ohara et al., suggesting that a high level of IgG4 may indicate the existence of extrapancreatic lesions (12). Therefore, conducting systemic screening and initiating the administration of PSL is necessary if a high level of IgG4 is found. The case described here is a rare and unique case showing involvement of as much as 10 organs at the onset of disease with a high level of serum IgG4.

The relationship between the IgG4 levels and relapse was described by Kawa et al., who suggested that the IgG and IgG4 levels may be a marker of disease relapse (8). In the case reported here, no evidence of relapse has been found to date, and the patient's IgG4 level has remained within the normal range for more than 11 months with oral PSL therapy. However, due to the significantly high IgG4 level and the presence of multiple lesions with various associated symptoms, providing careful follow-up, including measuring the serum IgG4 levels and performing imaging studies such as CT, US and MRI, is necessary.

IgG4-related disease is a relatively new entity. In addition to PSL (13), B-cell depletion therapy with rituximab may be effective in some, but not all, cases of recurrent or refractory IgG4-RD (14). Further evaluation of cases of IgG4-related disease is required in order to provide a comprehensive understanding of this disease, which will aid the development of a standard therapy.

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

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