□ CASE REPORT □

IgG4-associated Multifocal Systemic Fibrosis Complicating Sclerosing Sialadenitis, Hypophysitis, and Retroperitoneal Fibrosis, but Lacking Pancreatic Involvement

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Abstract

A 71-year-old man was admitted with malaise, mild fever, anorexia, body weight loss, lower back pain, thirst, and polydipsia. He showed bilateral swelling of the submandibular glands. Examinations showed panhypopituitarism and a high serum IgG4 concentration. Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed uptake in the pituitary gland, bilateral submandibular gland, bilateral hilar and mediastinal lymph nodes, and a mass consistent with retroperitoneal fibrosis, but not in the pancreas. Biopsy specimens from the submandibular gland and retroperitoneal mass indicated sialadenitis and retroperitoneal fibrosis respectively, and showed severe fibrosis and inflammation with marked lymphoplasmacytic infiltration and IgG4-positive plasma cell infiltration. Hormone replacement therapy with hydrocortisone resulted in marked clinical improvement. Systemic involvement found in this patient possibly corresponded to the new concept of IgG4-associated multifocal systemic fibrosis.

Key words : panhypopituitarism, FDG-PET, IgG4-associated multifocal systemic fibrosis, IgG4-related autoimmune disease, multifocal fibrosclerosis, autoimmune pancreatitis

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Introduction

A high serum IgG4 concentration and abundant IgG4-bearing plasma cell infiltration are characteristic features of autoimmune pancreatitis (1, 2). This disease is also characterized by a variety of extra-pancreatic lesions, such as sclerosing cholangitis, sialadenitis, and retroperitoneal fibrosis (2, 3). A new concept has been proposed for these conditions with special reference to the contribution of IgG4, such as IgG4-related autoimmune disease or IgG4-associated multifocal systemic fibrosis (3, 4). A recent report indicated the additional complication of a pituitary lesion in patients

with autoimmune pancreatitis (5). In this report, we presented the case that corresponded to the IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. The present case report supports the new disease concept of IgG4-associated multifocal systemic fibrosis. In addition, we discuss whether FDG-PET could detect systemic multiple lesions in this case.

Case Report

In January 2004, a 71-year-old man was admitted to Shinshu University Hospital with malaise, mild fever, anorexia,

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Figure 1. Gadolinium-enhanced brain MR imaging showed swelling of the pituitary gland consistent with hypophysitis (a). After the hormone replacement therapy, swelling of the pituitary gland (b) was ameliorated (sagittal section).

Figure 2. Cervical CT images revealed bilateral swelling of the submandibular glands (arrows).

Figure 3. Axial enhanced contrast CT revealed a mass encompassing the abdominal artery and the bilateral common iliac artery, radiologically consistent with retroperitoneal fibrosis.

body weight loss, lower back pain, thirst, and polydipsia. He had no family history of pancreatic disease, collagen disease, or fibrotic illness. Examination revealed bilateral swelling of the submandibular glands. Serum electrolyte values were as follows: sodium, 120 mEq/L; potassium, 5.0 mEq/L; chloride, 84 mEq/L. Immunological tests indicated elevated serum levels of IgG (3,015 mg/dl), IgG4 (405 mg/dl), soluble interleukin-2 receptor (700 U/ml), and β_2 -microglobulin (5.5 mg/dl), but levels of other serological markers, including antinuclear antibody (ANA), rheumatoid factor (RF), anti-double-stranded DNA antibody, anti-RNP antibody, anti-Sjögren's syndrome (SS)-A antibody, and

anti-SS-B antibody, were close to normal. Panhypopituitarism was found, including secondary hypothyroidism (TSH 0.128 μ IU/ml; free T4 2.11 pg/ml; free T3 0.45 ng/dl), secondary hypoadrenalism (ACTH 15.3 pg/ml; cortisol 0.9 μ g/dl; urinary 17-ketosteroids 1.2 mg/24 h; urinary 17-hydroxysteroids 1.0 mg/24 h) and lower levels of other pituitary hormones (GH 0.3 ng/ml; FSH <1.0 mIU/ml; LH <0.2 mIU/ml). HLA typing revealed the DRB1* 0405-DQB1* 0401 haplotype, which is consistent with that of autoimmune pancreatitis. MR imaging showed swelling of

Figure 4. Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed intense uptake in the pituitary gland [arrow (b)], bilateral submandibular glands [arrows (a)], bilateral hilar and mediastinal lymph nodes, and a mass consistent with retroperitoneal fibrosis. [(a) coronal section, (b) sagittal section].

Figure 5. Abdominal CT imaging revealed no swelling of the pancreas.

the pituitary gland consistent with hypophysitis (Fig. 1a) and the submandibular gland (Fig. 2). Abdominal CT scan revealed a mass encompassing the abdominal artery and the bilateral common iliac artery, radiologically consistent with retroperitoneal fibrosis (Fig. 3). FDG-PET revealed intense uptake in the pituitary gland, bilateral submandibular glands, bilateral hilar and mediastinal lymph nodes, and a mass consistent with retroperitoneal fibrosis (Fig. 4). This pituitary lesion could not be detected on Gallium-67 scintigraphy.

Figure 6. Abdominal magnetic resonance cholangiopancreatography (MRCP) imaging revealed no irregular narrowing of the pancreatic duct (a). Abdominal MR imaging (T2WI) revealed no irregular narrowing of the pancreas duct [arrows, (b-e)].

However, abdominal CT and MR images revealed no swelling of the pancreas (Fig. 5) and no irregular narrowing of the pancreatic duct (Fig. 6). In addition, FDG-PET also showed no accumulation in the pancreas. Biopsy specimens from the submandibular gland and retroperitoneal mass indicated sialadenitis and retroperitoneal fibrosis, respectively, indicating dense fibrosis and chronic inflammation with marked lymphoplasmacytic infiltration and IgG4-positive plasma cell infiltration (Fig. 7).

Based on the diagnosis of panhypopituitarism, we began hormone replacement therapy with hydrocortisone at 30 mg/day and thyroxine at 25 µg/day, which resulted in marked clinical and laboratory improvement. In addition, the swelling of the bilateral submandibular glands was reduced gradually. CT and MR images showed reductions in size of the pituitary gland (Fig. 1b), submandibular gland, and the mass lesion of retroperitoneal fibrosis. FDG-PET showed reduced uptake in all of the multiple lesions. Since then, he has continued hormone replacement therapy with hydrocortisone and thyroxine, and had no recurrence.

Discussion

A high serum IgG4 concentration and abundant IgG4-bearing plasma cell infiltration are characteristic features of autoimmune pancreatitis (1, 2). This disease is also characterized by a variety of extra-pancreatic lesions, such as sclerosing cholangitis, sialadenitis, and retroperitoneal fibrosis, as observed in this patient (2, 3). These extra-pancreatic le-

Figure 7. Transcutaneous biopsy specimens obtained from the submandibular gland indicated dense fibrosis and chronic inflammation with marked lymphoplasmacytic infiltration and IgG4-positive plasma cell infiltration [(a) HE stain $\times 400$, (b) stained with IgG4 monoclonal antibody $\times 400$].

Table 1. Laboratory Data on Admission

Peripheral blood examination		Blood chemical examinations	
WBC	4,800/ μ l	Na	120 mEq/l
neutrophils	49.0%	K	5.0 mEq/l
eosinophils	4.0%	Cl	84 mEq/l
monocytes	9.0%	Ca	9.6 mg/dl
lymphocytes	38%	BUN	25 mg/dl
RBC	3.39×10^3 /mm ³	Creatinine	0.89 mg/dl
Hemoglobin	10.2g/dl	Uric acid	3.0 mg/dl
Hematocrit	30.1%	Total protein	8.1 g/dl
Platelet	26.0×10^4 / μ l	Albumin	3.7 g/dl
Serum examinations		ZTT	18.5 k.u.
CRP	3.72 mg/dl	TTT	17.7 k.u.
β_2 -microglobulin	5.5 mg/dl (0.8-1.8)	T-Bilirubin	0.53 mg/dl
sIL-2R	700 U/ml (135-483)	ALP	194 U/l
IL-6	0.889 pg/ml (0.221-4.62)	γ -GTP	17 U/l
ACE	11.9 U/l (7.0-25.0)	Choline-E	240 U/l
IgA	205 mg/dl	AST	29 U/l
IgM	33 mg/dl	ALT	16 U/l
IgG	3015 mg/dl	LDH	172 U/l
IgG1	1400 mg/dl (538-1244)	CPK	112 U/l
IgG2	1250 mg/dl (254-820)	Amylase	68 U/l
IgG3	200 mg/dl (<117)	Glucose	93 mg/dl
IgG4	405 mg/dl (<70)	Ferritin	610 ng/ml
IgE	95 IU/ml	Endocrinology	
FANA	(-)	TSH	0.128 μ IU/ml (0.2-4.0)
RF	(-)	Free T4	2.11 pg/ml (1.0-2.0)
Anti-RNP	(-)	Free T3	0.45 ng/dl (2.5-4.2)
Anti-Sm	(-)	ACTH	15.3 pg/ml (9-60)
Anti-SSA	(-)	Cortisol	0.9 μ g/dl (5-15)
Anti-SSB	(-)	Urinary17-ketosteroids	1.2 mg/24 h
Anti-Scl-70	(-)		(4.6-16.4)
Anti-Jo-1	(-)	Urinary17-hydroxysteroids	1.0 mg/24 h
Coagulation systems			(2.9-11.6)
PT	13.6 s	GH	0.3 ng/ml (<5.0)
APTT	44.1 s	FSH	<1.0 mIU/ml (2.9-8.2)
Fibrinogen	887.2 mg/dl	LH	<0.2 mIU/ml (1.8-5.2)

sions as well as the pancreatic lesion respond favorably to corticosteroid treatment (1-3). The spectrum of systemic lesions seen in autoimmune pancreatitis corresponds well to that of systemic multifocal fibrosclerosis, which includes sclerosing cholangitis, retroperitoneal fibrosis, mediastinal fibrosis, Riedel's thyroiditis, and pseudotumor of the orbit

(4), and autoimmune pancreatitis has been regarded as a systemic disease (2, 3).

The present case had a variety of systemic lesions, such as sclerosing sialadenitis, panhypopituitarism due to hypophysitis, and retroperitoneal fibrosis. In addition, the patient had a high serum IgG4 concentration and showed abundant IgG4-bearing plasma cell infiltration in involved tissues of the submandibular gland and retroperitoneal mass. Accordingly, IgG4 will open the way for the diagnosis of these lesions. Though this patient lacked pancreatic involvement, the spectrum of systemic involvements together with IgG4 contribution corresponded to the extra-pancreatic lesions of autoimmune pancreatitis, and suggested the presence of systemic disease as mentioned above. In this patient, glucocorticoid treatment for hypopituitarism probably induced the amelioration of the systemic lesions. A recent report indicated the additional complication of a pituitary lesion in patients with autoimmune pancreatitis, as observed in this case (5).

A new disease concept has been proposed for these conditions with special reference to the contribution of IgG4, such as IgG4-related autoimmune disease or IgG4-associated multifocal systemic fibrosis (3, 5). This new concept covers an equivalent disease spectrum to that of systemic multifocal fibrosclerosis, but stresses the contribution of IgG4. In particular, IgG4-associated multifocal systemic fibrosis includes pituitary lesion as found in the present case. If this new concept is legitimate, it will allow various combinations of systemic inflammatory lesions, and will theoretically suggest the presence of a disease complex without pancreatic involvement, similar to that seen in this patient. Thus, the present case supported the new disease concept of IgG4-associated multifocal systemic fibrosis, and demonstrated a variety of combinations of systemic lesions. In addition, the present case highlights the usefulness of serum IgG4 measurements to search for systemic involvement, including lesions of hypophysitis, sialadenitis, mediastinal pseudotumor, sclerosing cholangitis, and retroperitoneal fibrosis, which

can be found in association with this disease complex.

Chronic sclerosing sialadenitis has also been known as Mikulicz's disease and Küttner tumor. A previous study reported that chronic sclerosing sialadenitis of the submandibular gland could be associated with idiopathic retroperitoneal fibrosis and other idiopathic fibrosing diseases as found in this case (6). Furthermore, these conditions of sclerosing sialadenitis were reported to be closely associated with high serum IgG4 concentration and IgG4 bearing plasma cell infiltration (7, 8). Accordingly, it is possible that the present case is regarded as Mikulicz's disease with systemic involvement.

FDG-PET is a powerful molecular imaging technique for the human body. As altered glucose metabolism is characteristic of many malignancies, FDG-PET is used mostly in oncology for staging and therapy control. Although FDG-PET is a sensitive tool for detecting malignancy, FDG uptake is not tumor specific and can also be seen in healthy tissue or in benign disease, such as inflammation or posttraumatic repair (9). For example, Pfadenhauer et al reported that inflammation of the arterial wall was demonstrated by FDG-PET imaging in patients with Takayasu's and temporal ar-

teritis as systemic disease (10). However, their report was of a rare case in which FDG-PET was useful to judge the extension of benign systemic disease, as shown in the present case. Based on the results of FDG-PET, we initially suspected that the present case was a malignant lymphoma. However, a final diagnosis of IgG4-associated systemic multifocal fibrosis was made based on the analysis of biopsy specimens from the submandibular gland and retroperitoneal mass. This case highlights the usefulness of FDG-PET to judge the accurate extension and the effects of therapy in such systemic multiple lesions.

In conclusion, this patient was admitted to the hospital with a variety of systemic involvements including hypophysitis, sialadenitis, mediastinal pseudotumor, and retroperitoneal fibrosis, which responded to hydrocortisone. He also showed a high serum IgG4 concentration and abundant IgG4 bearing plasma cell infiltration in the lesions of sialadenitis and retroperitoneal fibrosis, suggesting that the patient's condition corresponded to the new disease concept of IgG4-associated multifocal systemic fibrosis. FDG-PET simultaneously revealed a variety of systemic lesions.

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