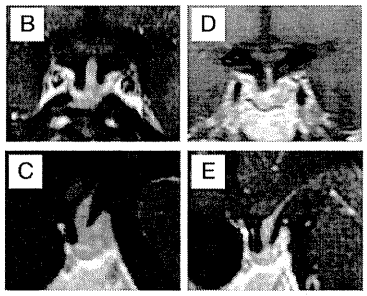
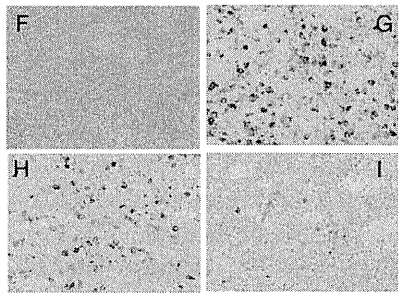
A

(min)	0	30	60	90	120
TSH (uIU/mL)	1.350	8.120	7.630	6.420	5.450
PRL (ng/mL)	11.78	74.67	56.31	42.05	35.50
LH (mIU/mL)	1.92	6.42	9.21	10.42	10.92
FSH (mIU/mL)	8.22	11.36	14.21	15.93	18.61
ACTH (pg/mL)	18	34	34	47	45
Cortisol (ug/dL)	7.68	12.12	13.39	12.69	12.93

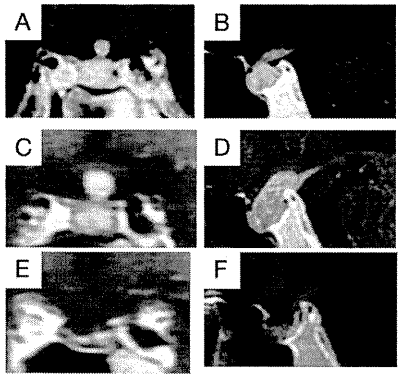




J

(weeks)	0	4	8
IgG4 (mg/mL)	170	123	UD[1)]
IgG (mg/mL)	1520	1060	1050
IgE (IU/mL)	523	342	163
LH (mIU/mL)	2.49	3.27	4.17
FSH (mIU/mL)	7.74	14.34	17.38
GH (ng/mL)	0.118	0.042	0.033
IGF-1 (ng/mL)	43.6	59.3	76.8

Fig. 1 Hormonal data and MRI findings of Case 1.
(A) Pituitary hormone responses to the secretagogues (500μg of TRH, 100μg of LHRH, and 100μg of CRH) are shown. Blood samples were obtained before and after stimulation as indicated.
(B to E) Pituitary images of Case 1 before (B and C) and after (D and E) prednisolone treatment. Note that the enlarged pituitary gland and stalk, which are well enhanced with the gadolinium contrast media and remarkably reduced after two weeks of treatment with prednisolone.
(F to I) Histological findings of a cervical lymph node from Case 1. There is no apparent infiltration of histiocytes or neoplastic cells, and no granuloma formation is seen (F). Infiltration of plasma cells (G), IgG-positive cells (H), and IgG4-positive cells (I). Hematoxylin and eosin (F: x200). Immunostaining with anti-CD 38 antibody (G), anti-IgG antibody (H), anti-IgG4 antibody (I) (G to I: x400).
(J) Immunological and hormonal parameters before and after prednisolone therapy. [1)]UD; Undetermined.



G

(min)	0	30	60	90	120
TSH (uIU/mL)	1.083	7.471	6.148	4.745	3.623
	0.024	0.068	0.092	0.084	0.067
PRL (ng/mL)	3.0	13.1	9.1	6.4	5.1
	18.5	28.65	27.63	24.94	22.70
LH (mIU/mL)	5	16.4	17.0	16.1	14.3
	0.70	2.12	3.17	3.28	3.02
FSH (mIU/mL)	10.9	13.9	14.9	15.7	15.3
	1.44	1.83	2.49	2.74	2.69
ACTH (pg/mL)	29.3	73	50.3	36.2	30.1
	7	13	16	14	12
Cortisol (ug/dL)	7.88	17.58	16.36	11.05	9.39
	0.25	0.45	0.86	0.81	0.59

H

(weeks)	0	4	8
IgG4 (mg/mL)	159	121	UD[1)]
IgG (mg/mL)	1975	1750	1421
IgE(IU/mL)	120	72.9	38.1
LH (mIU/mL)	0.52	<0.1	0.32
FSH (mIU/mL)	1.47	0.54	1.27
GH (ng/mL)	0.019	0.046	UD
IGF-1 (ng/mL)	57.3	97.3	116

Fig. 2 Hormonal data and MRI findings of Case 2.
(A to F) Pituitary images of Case 2 obtained at the initial presentation at 68 years of age (A and B), and before (C and D) and after (E and F) prednisolone treatment. Note the gradual progression of the enlargement of the pituitary gland and its stalk, which are well enhanced with the gadolinium contrast media and remarkably reduced after two weeks of treatment with prednisolone.
(G) The pituitary hormone responses to the secretagogues (500μg of TRH, 100μg of LHRH, and 100μg of CRH) are shown. Blood samples were obtained before and after stimulation as indicated. Data above the lines were obtained at the initial presentation and those below were obtained seven years after the initial presentation.
(H) Immunological and hormonal parameters before and after prednisolone therapy. The reduction of LH and FSH after prednisolone therapy was most likely due to initiation of sex steroid replacement. [1)]UD; Undetermined.

pituitary gland was not apparent. The pituitary lesion was clinically suspected to be IgG4-related pituitary disease. Two weeks after treatment with 30 mg/day of prednisolone, there was a dramatic reduction in the swelling of the pituitary and its stalk (Fig. 2E and F). A reduction of the serum levels of IgG4 and slight increase of IGF-1 (Fig. 2H) were also observed during the tapering of prednisolone (prednisolone was reduced 5 mg/day every two weeks) down to a maintenance dose of 10 mg/day without apparent relapse for longer than three months.

Retrospective survey of our database

Because of the similarity of the MRI findings of the pituitary gland and its stalk between Case 1 and 2, we reviewed the MRI findings of the previous cases admitted to our department and determined the serum levels of IgG4 by using the stock sera of the cases with compatible MRI findings.

Methods

We reviewed the charts of 95 patients who were admitted to our department from January of 2000 to June of 2008. These patients were selected from our database by using keywords such as pituitary, panhypopituitarism, diabetes insipidus, ACTH, adenohypophysitis and infundibuloneurohypophysitis. We were able to find 4 cases other than the above-described Case 1 and 2 with pituitary MRI findings of a diffuse swelling of the entire pituitary and/or its stalk enhanced with gadolinium. In patients receiving corticosteroid replacement, the serum levels of IgG4 (SRL Inc., Tokyo, Japan) were determined by using the stock sera obtained before the start of treatment. Serum levels of IgG4 >135 mg/dL were considered significantly high [1-3].

Results

Four of the identified cases (Cases 3-6 in Table 1) had been clinically diagnosed with either lymphocytic adenohypophysitis or infundibuloneurohypophysitis, and showed clinical and laboratory findings of insufficient production of either anterior or posterior pituitary hormone(s). Serum levels of IgG4 were elevated in two of four cases (Cases 3 and 4). The pituitary MRI findings of these cases are shown in Figure 3. When Cases 1 and 2 were included, there was no male preponderance (2 males and 2 females), but the age of onset remained fairly late (average 68.5 years old). Central diabetes insipidus was seen in three and impaired anterior pituitary function in two cases at the initial presentation. Other organ manifestations seen were interstitial pneumonitis and pachymeningitis in Case 3. No other organ manifestation was been detected in Case 4 per se. We were not able to find any differences in clinical presentation or MRI findings between patients with or without elevated serum levels of IgG4.

Discussion

Our cases reported here were suspected of having IgG4-related pituitary disease based on characteristic MRI findings along with high serum levels of IgG4. Since we did not examine the pituitary tissue, the major concern was the differential diagnosis. It has been shown that an elevated serum level of IgG4 (>135 mg/dL) is a sensitive marker for a diagnosis of AIP [13, 14], and, therefore, this is included as one of the diagnostic criteria for IgG4-related disease [1-3]. However, it should be stressed that in some patients with pancreatic cancer, an important condition in the differential diagnosis of AIP, high serum levels of IgG4 (>140 mg/dL) were indeed found and a higher cut-off (>280 mg/dL) has been suggested to improve specificity [15]. In addition, serum levels of IgG4 can be elevated in Wegener granulomatosis, multicentric Castleman's disease, and idiopathic plasmacytic lymphoadenopathy [1]. Thus, high serum levels of IgG4 alone can not be used to make a diagnosis of IgG4-related disease. In our index cases, such disorders were excluded by blood tests, including assays for negative anti-neutrophil cytoplasmic antibodies and systemic CT, and by the biopsy findings from the cervical lymph nodes and retroperitoneal masses.

Swelling of the pituitary and its stalk is seen in conditions such as lymphocytic hypophysitis, sarcoidosis, tuberculosis and Wegener's granulomatosis. Among these, lymphocytic hypophysitis (LYH) is an important disorder to be differentiated, since LYH is occasionally diagnosed solely based on the MRI findings [16, 17]. LYH is characterized by lymphocytic infiltration leading to the destruction of the pituitary gland in association with an impaired pituitary function, either in the anterior pituitary and/or posterior lobe [16, 18]. LYH is common in young females, particularly in association with late pregnancy or the postpartum period (~60% of the cases with LYH), and peaks in inci-

Table 1 Clinical presentations and serum levels of IgG4 of the cases with pituitary enlargement.

Case #	Age/Sex	Presentation[1)]	IgG	IgG4	Other organ involvement
1	74/F	ACTH,LH, FSH, GH ADH	1520	**170**	cervical and hilar lymph nodes
2	68/M	ADH	**1975**	**159**	cervical and hilar lymph node, and retroperitoneal fibrosis
3	72/M	ACTH,TSH	1550	**167**	interstitial pneumonitis, pachymeningitis
4	60/F	ADH	1504	**201**	none
5	80/M	ACTH	**1736**	92	none
6	24/M	ADH	1063	16	none

[1)]Indicates defective pituitary hormone(s) at the initial presentation. The reference ranges are 4.8-105 (mg/dL) for IgG4, and 870-1700 (mg/dL) for total IgG. The values exceeding the reference ranges are shown in bold.

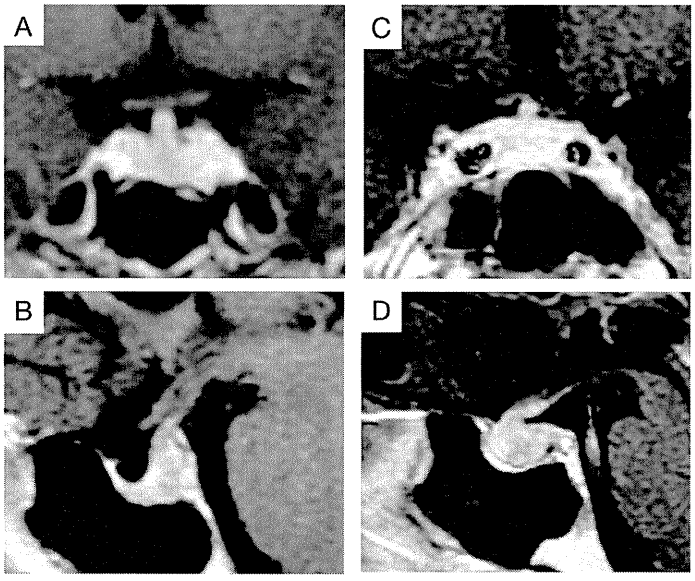


Fig. 3 Pituitary MRI findings of Cases 3 and 4.
Pituitary MRIs with gadolinium contrast media in Cases 3 and 4.
In Case 3 the posterior lobe of the pituitary and the stalk are swollen while the anterior lobe is partially atrophic (A and B). In Case 4 the posterior lobe appears tumorous and compresses the anterior lobe (C and D).

dence in the 4th decade of life [16], but cases of male and olderly individuals have also been reported [16, 18]. It has been shown that some cases with lymphocytic adenohypophysitis can be successfully treated with a small dose of prednisolone, such as 15 to 40 mg per day for 2 weeks to 3 months, but other cases have required high dose methylprednisolone pulse therapy [17]. Based on the clinical picture, our cases may have been diagnosed as late-onset LYH. Indeed, two of the cases with a putative diagnosis of IgG4-related pituitary disease identified in our database (Cases 3 and 4) were originally clinically diagnosed as cases of LYH.

How can LYH and the pituitary lesions associated with IgG4-related disease be differentiated? A pituitary biopsy with IgG4 staining would be the most straightforward method. However, in the absence of such an invasive examination of the pituitary tissue, the patient background and concomitant disorders should be carefully taken into consideration (Table 2). Concomitant autoimmune disorders tend to favor a diagnosis of LYH and allergic disorders, and the organ manifestations seen in IgG4-related disease, such as AIP, strongly suggest IgG4-related pituitary disease.

Table 2 Clinical features associated with lymphocytic hypophysitis and IgG4-related pituitary disease.

	IgG4-Related pituitary disease	Lymphocytic hypophysitis
Age	seventh decade of life	fourth decade of life
Sex	male dominant	female dominant
Pituitary MRI	diffuse swelling	diffuse swelling
Hormonal impairment	anterior and/or posterior	anterior and/or posterior
Associated disorders	allergic disorders	autoimmune disorders
	autoimmune pancreatitis	autoimmune thyroiditis
	Mikulicz disease	type 1 diabetes
	retroperitoneal fibrosis	autoimmune adrenalitis
Serum markers	high IgG4[1)]	anti-pituitary antibodies

Clinical features of these two disorders are summarized based on the literature [1, 12, 18].
[1)] Serum levels of IgG and IgE may also be elevated [1].

Anti-pituitary antibodies may favor a diagnosis of LYH [16], and high serum levels of IgG4 may favor IgG4-related pituitary disease; however, these findings are still non-specific. In this study, therefore, Cases 2 and 3 were considered reasonably likely to be cases of IgG4-related pituitary disease with concomitant disorders and elevated serum levels of IgG4. In Case 1, this diagnosis was suspected based on IgG4-positive cell infiltration in the cervical lymph nodes and by excluding other disorders. The therapeutic response to corticosteroids also supported the diagnosis in Cases 1 and 2. The problematic case would be one with a pituitary lesion with MRI findings suggesting LYH and IgG4-related pituitary disease, but without any concomitant autoimmune or allergic disorders, or any other organ involvement associated with IgG4-related disease, such as in Case 4 in our study. A similar case with central diabetes insipidus, which was assumed to have been caused by a primary tumor or lymphocytic infundibuloneurohypophysitis, was recently reported [11]. After two years of stable clinical course, this case showed rapid development of panhypopituitarism associated with an enlargement of the pituitary, which turned out to be IgG4-related pituitary disease [11]. Therefore, measurement of the serum anti-pituitary antibodies and/or IgG4 would be useful, but still non-specific, for identifying the putative cause of pituitary failure in such cases, and could provide clues to the most appropriate management of the patient. When neither marker is positive, careful observation would be important, including repeated measurement of these markers. When the serum IgG4 levels are elevated, a systemic survey should be considered to detect other organs involved with IgG4-related disease by using gallium scintigraphy and/or FDG-PET [19]. In the cases we reported herein, we did not observe gallium accumulation in the pituitary. We are not certain if this was because gallium scintigraphy is less sensitive than FDG-PET for detecting IgG4-related disease, or whether it was related to the relative size of the lesion and/or the relative degree of inflammation.

In conclusion, we reported four putative cases of IgG4-related pituitary disease. These cases were suspected based on the typical MRI findings and elevated serum levels of IgG4. Our findings suggest that an overall consideration of the clinical picture and measurement of the serum levels of IgG4 may assist in the diagnosis of this disorder.

Acknowledgement

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CASE REPORT

Successful treatment of a patient with IgG4-related disease with a paravertebral mass lesion

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Abstract A 68-year-old woman was admitted with bleary eyes and lacrimal gland swelling. A biopsy specimen from a right paravertebral mass lesion detected by computed tomography showed remarkable IgG4-positive plasma cells. Because serum IgG4 was elevated to 3300 mg/dl, IgG4-related disease was diagnosed, with the assistance of fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT). Administration of 30 mg of oral prednisolone effectively reduced the lacrimal gland swelling and paravertebral mass volume. Nine months after the initiation of prednisolone, serum IgG4 was reduced to 31.4 mg/dl, and there was norecurrence.

Keywords IgG4 · Immunohistochemistry · Paravertebral mass

Abbreviations

AIP	Autoimmune pancreatitis
CT	Computed tomography
FDG	Fluorodeoxyglucose
MD	Mikulicz's disease
PET	Positron emission tomography
sIL2R	Soluble interleukin-2 receptor

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Introduction

Recent reports of IgG4-related disease have described various organ involvements [1–3]. With regard to the elevation of serum IgG4, IgG4-related sclerosing diseases, such as autoimmune pancreatitis (AIP), retroperitoneal fibrosis, and Mikulicz's disease (MD), which presents with enlargement of the lacrimal or salivary glands, are known [4]. Because the disease category has been expanded to include other solid organs, a disease concept, 'IgG4-related disease', was proposed by Masaki et al. [5]. Solid organ involvement often presents with pseudotumors, in which a thick infiltration of IgG4-bearing plasma cells is found [6, 7]. Contrarily, intrathoracic lesions in IgG4-related disease, presenting as retroperitoneal fibrosis, are well known [8]. Because mass formation is also observed in retroperitoneal fibrosis, mass formation could be involved as a variant of retroperitoneal or mediastinal fibrosis. We here report a patient with a paravertebral mass lesion with MD-like gland swelling in IgG4-related disease.

Case report

A 68-year-old woman with a history of bronchial asthma was admitted to Nagasaki Municipal Hospital due to bleary eyes and eyelid swelling. When chest computed tomography (CT) was performed to search for internal organ involvement, a paravertebral mass lesion was detected incidentally (Fig. 1a), with slightly thickened bronchial

walls also being shown. Although the mass covered a large part of the thoracic vertebrae, neither osteolytic change nor invasion into the spinal canal was observed. The patient's total protein and serum IgG were elevated to 9.9 g/dl (normal range 6.7–8.3 g/dl) and 4,195 mg/dl (normal range 870–1700 mg/dl), respectively, with remarkable elevation of serum IgG4, to 3,300 mg/dl (normal range <105 mg/dl). Serum IgE was also elevated, to 625.7 IU/ml (normal range 0–350 IU/ml) with normal angiotensin-converting enzyme or lysozyme. Because malignant lymphoma was initially suspected by CT-guided needle biopsy, with elevation of soluble interleukin-2 receptor (sIL2R) (1257 U/ml; normal range 122–496 U/ml), a thoracoscopic lung biopsy was performed. Although lymphoma and other disorders, including carcinoid and histiocytosis, were excluded based on the pathological study, immunohistochemistry showed dense infiltration of IgG4-positive plasma cells (Fig. 2) in fibrous connective tissue, without the lymphoma cells or caseous necrosis that would have indicated tuberculous granuloma, and the patient had a negative tuberculin reaction. These results caused us to consider the possibility of IgG4-related disease. For detailed examination, the patient was transferred to Nagasaki University Hospital on 9 February 2010.

On admission, the patient complained of back pain, without low-grade fever or musculo-skeletal manifestations. Although no swelling of superficial lymph nodes was observed, obvious bilateral lacrimal gland swelling was shown. Additionally, no enlargement of the submandibular or parotid glands was, observed, and the patient had a slightly dry mouth.

Laboratory findings showed a hemoglobin level of 12.3 g/dl, a total leukocyte count of 5,900/mm^3, and a platelet count of 26.3 × 10^4/mm^3, with elevation of eosinophils (6%; actual count: 354/mm^3). No hepatic or renal dysfunction was found. The findings were negative for C-reactive protein (0.06 mg/dl; normal <0.17), but the erythrocyte sedimentation rate was elevated, to 75 mm/h

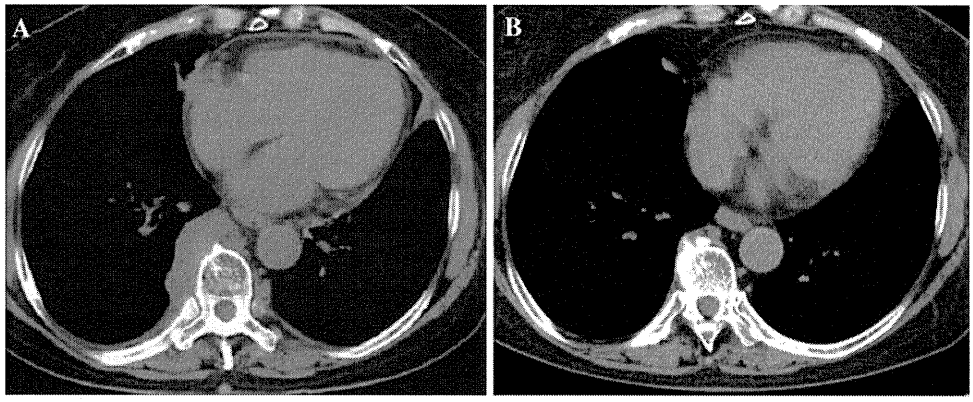

Fig. 1 Uncommon paravertebral mass lesion detected by computed tomography (CT). **a** Before glucocorticoid therapy, a huge mass lesion that covered the thoracic vertebrae was detected. Although the mass lesion covered a large part of the right side of the thoracic vertebrae, no osteolytic change or spinal canal invasion was observed. **b** Nine months after the initiation of glucocorticoid therapy, remarkable reduction of the mass volume was obtained

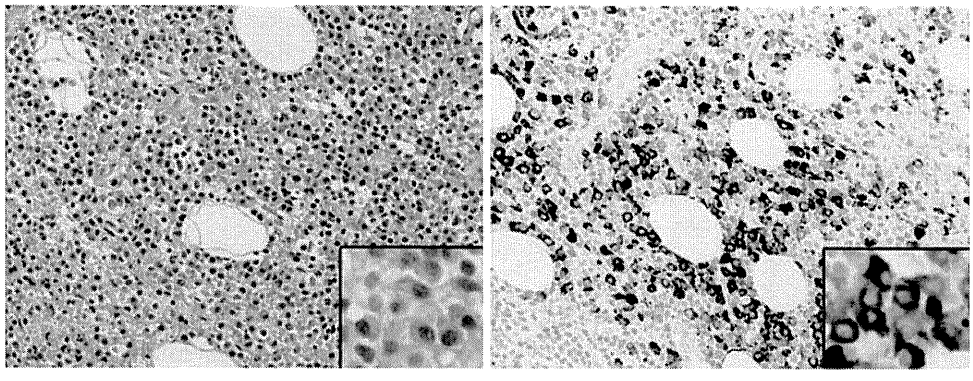

Fig. 2 Hematoxylin and eosin (H&E) staining and IgG4 immunostaining of biopsy specimens. The thoracoscopic lung biopsy specimen was subjected to H&E staining, as shown in the *left panel*. Thick infiltration of mononuclear cells was observed, without malignant cells or caseous necrosis. The *inset* shows the appearance of plasma cells. The *right panel* shows massive infiltration of IgG4-bearing cells in the serial section. The *inset* shows a higher magnification of IgG4-positive plasma cells (original magnifications ×40, inset ×200)

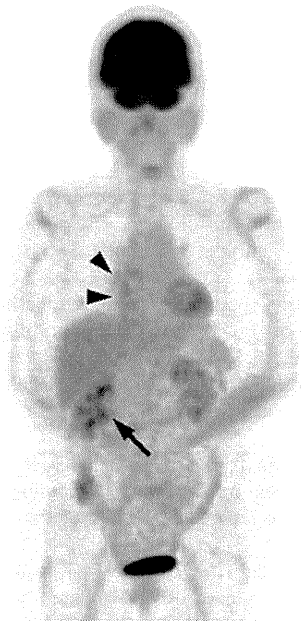

Fig. 3 Fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) was performed for differential diagnosis. Although accumulation of FDG was mainly observed on the right side of the descending thoracic aorta (*arrowheads*), slight accumulation was also observed in the right renal hilus (*arrow*), although no mass was obvious on chest CT

(normal range <15 mm/h). On serology, rheumatoid factor, anti-nuclear antibody, and autoantibodies including anti-SS-A/SS-B antibody, anti-double-stranded deoxyribonucleic acid antibody, anti-ribonucleoprotein antibody, and anti-Sm antibody were negative. The serum complement level was not decreased (37.8 CH50/ml; normal 30–40 CH50/ml). On urinalysis, neither glycosuria nor proteinuria was observed.

For differential diagnosis, fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT was performed (Fig. 3), resulting in the accumulation of FDG on the right side of the descending thoracic aorta, which was in accordance with the previous chest CT findings, without evidence of malignant lymphoma. Although obvious mass formation in the right renal hilus was not detected by CT, slight accumulation in this region was observed on FDG-PET/CT. A diagnosis of IgG4-related disease was made (although it was accompanied by an unreported paravertebral mass), and therefore treatment with 30 mg of oral prednisolone was started, on 22 February 2010.

After the administration of the glucocorticoid, the lacrimal gland swelling was rapidly attenuated, within a month. In November 2010, no exacerbation of lacrimal gland swelling was seen, and serum IgG4 was reduced to 31.4 mg/dl. Follow-up CT in November 2010 showed remarkable reduction of the paravertebral mass volume (Fig. 1b), showing that there had been no recurrence in the period of 9 months after the initiation of glucocorticoid therapy, with 8 mg of oral prednisolone being given at this time. The serum level of sIL2R was also reduced, to 200 U/ml.

Discussion

IgG4-related disease entities can spread to various organs, including solid organs, the peritoneum, and perivascular areas. With respect to intrathoracic lesions in IgG4-related disease, inflammatory aneurysms as well as retroperitoneal fibrosis have been reported recently [9]. However, mass formation in the thorax has not been reported. Although mass formations are usually described as 'pseudotumors,' the masses are usually found in solid organs such as the liver or kidney [10]. We previously reported a similar case, in a patient with AIP with a renal pseudotumor, in 2006 [11]. Most of these cases demonstrated IgG4-positive plasma cell-rich histopathology [12].

The present patient, however, did not present symptoms that were aligned with the previously reported disease concept. Regardless of its similarity to retroperitoneal fibrosis, the pattern in the present case was different from those of the typical cases. Usually, retroperitoneal fibrosis covers the abdominal peritoneum and often involves the ureter or abdominal aorta [13]. The uncommon morphology in the present case may have been a variant of retroperitoneal fibrosis. However, the pathological findings indicated that our case might be related to retroperitoneal fibrosis. More specifically, a dense infiltration of IgG4-positive plasma cells in the paravertebral mass lesion was surrounded by fibrous connective tissue, which showed the possibility that our case might demonstrate 'sclerosing' aspect such as AIP or sclerosing cholangitis [1]. Furthermore, FDG/PET findings showed slight accumulation in the right renal hilus as well as on the right side of the descending thoracic aorta, suggested that the present case showing an aggregated lesion might be associated with a retroperitoneal fibrosis-related condition.

Another possibility is that this patient's disease was a variant of chronic periaortitis. Vaglio et al. [14] reviewed the pathological mechanisms for the onset of this condition, and two possible mechanisms were proposed: (1) T and B lymphocyte recruitment against the presentation of autoantigens such as ceroid and atherosclerotic plaque macrophages develops into periaortic inflammation, and (2) vasculitis of the vasa vasorum extends into the outer retroperitoneum. However, these explanations have no association with IgG4. Based on the above theory, the mass lesion per se must be in contact with periaortitis; however, our case showed no continuity from the thoracic aorta, suggesting a variant of retroperitoneal fibrosis rather than a variant of chronic periaortitis.

In summary, this is the first report that demonstrates an intrathoracic paravertebral mass lesion with MD in a patient with IgG4-related disease. However, the frequency of appearance or distribution of this unique pathological condition remains to be clarified. To elucidate the conceptual broadening of IgG4-related disease, an accumulation of the clinicopathological characteristics and epidemiological surveillance are required.

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Conflict of interest None.

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Case Report

Thyroid papillary carcinoma with solid sclerosing change in IgG4-related sclerosing disease

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IgG4-related sclerosing disease (IgG4-RSD) is an inflammatory and fibrosing disorder characterized by lymphoplasmacytic inflammation with infiltration of various organs, including the pancreas, bile ducts, lung, kidney, and retroperitoneum. As for malignancy in IgG4-RSD, only limited literature is available. We report here a case of thyroid papillary carcinoma showing unique morphology in IgG4-RSD. Solid tumor nests were surrounded by dense IgG4-positive plasma cells and fibrosis at both the primary site and metastatic lymph nodes. In contrast the background thyroid showed focal lymphocytic thyroiditis. IgG4-related sclerosing sialadenitis and autoimmune pancreatitis were also diagnosed, and prednisolone treatment improved symptoms and serum IgG4 abnormality. To the best of our knowledge, this is the first documentation of a malignancy of the thyroid gland occurring in a background of IgG4-RSD. A brief review of the literature on the relationship between IgG4 and malignancy is included.

Key words: chronic thyroiditis, IgG4-related sclerosing disease, papillary carcinoma, thyroid

IgG4-related diseases comprise a recently recognized systemic syndrome characterized histologically by fibrosis, lymphoplasmacytic infiltration of various organs, including the pancreas, bile ducts, lung, kidney, and retroperitoneum, and abundant IgG4-positive plasma cells associated with elevated serum IgG4 levels.[1–12] Regarding malignancy in systemic IgG4 disease and local IgG4 response to malignancy, only a limited number of published reports are available.[13–16]

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We report here a case of thyroid papillary carcinoma showing unique morphology in IgG4-related sclerosing disease (IgG4-RSD). Solid tumor nests were surrounded by dense IgG4-positive plasma cells and fibrosis at both the primary site and metastatic lymph nodes. The literature on the relationship between IgG4 and malignant tumor is reviewed.

CLINICAL SUMMARY

A 72-year-old Japanese man was referred for further evaluation of a bilateral submandibular swelling which had been present for the past several years. An incidental positron emission tomography scan had revealed fluoro-D-glucose uptake in a right thyroid mass and mediastinal lymph nodes. Fine needle aspiration revealed a thyroid papillary carcinoma. Total thyroidectomy and regional lymph node resection were performed. Simultaneously the right submandibular gland was resected to examine the morphology based on the suspicion of IgG4-RSD.

Total serum IgG was elevated (2950 mg/dL; normal: 600–1500), as was the serum IgG4 level (1700 mg/dL; normal: 6–121), confirming the diagnosis of IgG4-RSD. The serum thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were elevated (652 IU/mL; normal: <28 IU/mL; and 93 IU/mL; normal: <16 IU/mL, respectively). Thyroid stimulating hormone (TSH)-receptor antibody (TSHRAb) was negative. Thyroid stimulating antibody (TSAb) was within normal range. Free T3 was 1.67 (normal: 2.30–4.30 pg/mL) and free T4 was 0.88 (normal: 0.9–1.70 ng/dL).

Two months after surgery, the patient started complaining of upper abdominal pain. Further examination disclosed autoimmune pancreatitis (AIP) with sclerosing cholangitis. Diagnosis was made by characteristic imaging on CT and

pancreatography, elevated serum IgG4 levels, and other organ involvement. The main finding of the abdominal CT was a diffusely enlarged pancreas. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography revealed narrowing of the main pancreatic duct throughout the pancreas with irregular diameters. The intrapancreatic and lower biliary ducts were smoothly narrowed and the upper choledochus was dilated. Intrahepatic bile ducts were intact. An obstructive pattern of liver function tests (i.e. an elevated serum alkaline phosphatase 615 IU/L, γ-GTP 349 IU/L) was present. Retroperitoneal lymph nodes were enlarged. Retroperitoneal fibrosis and hydronephrosis were not seen. Prednisolone treatment (30 mg/day) was started for the AIP. One month later serum IgG4 levels and liver function tests returned to normal.

PATHOLOGICAL FINDINGS

The right submandibular gland showed the typical histology of IgG4-related sclerosing sialadenitis. Histologically nodular sclerosis, acinar destruction, lymphoid follicle, dense plasma cell infiltration and phlebitis obliterans were observed (Fig. 1a). Immunostaining revealed strong staining for IgG4 with a mixed infiltrate of lymphocytes, plasma cells, histiocytes and neutrophils (Fig. 1b). Among IgG-positive plasma cells, approximately 90% expressed IgG4.

The thyroid nodule was 2 cm in size and papillary carcinoma showed unusual histology mimicking a mixed solid and sclerosing variant. Solid growth predominated over other structures such as papillary and follicular growth. Solid trabecular growth nests were surrounded by fibrosis, dense plasma cell infiltration and lymphoid follicles (Fig. 2a). Tumor cells had pale eosinophilic cytoplasm and characteristic nuclei of papillary carcinoma, (i.e. clear chromatin, irregular shapes, and nuclear pseudoinclusions; Fig. 2b). Inflammatory cells consisted of plasma cells, lymphocytes, neutrophils and eosinophils. Approximately 90% of IgG-positive plasma cells expressed IgG4 (Fig. 2c). Hyalinized stroma was formed in the dense fibrotic area. Papillary carcinoma cells expressed TGF-β (Fig. 2d). Lymphatic invasion was encountered and confirmed with D2-40 immunostaining; regional lymph node metastasis was observed in eight of 43 nodes (18.6%). Metastatic papillary carcinoma cells were surrounded with IgG4-positive plasma cells (Fig. 2e). The background thyroid gland showed focal lymphocytic thyroiditis without significant follicular destruction and fibrosis (Fig. 2f). In addition, only a few IgG4-positive plasma cells were accompanied with lymphoid follicles. Lymphoid follicles expressed both CD20 and CD3. Positive TgAb, TPOAb, low free T3, and lymphocytic infiltration were sufficient to confirm Hashimoto's thyroiditis (chronic autoimmune thyroiditis) in this case.[17]

Immunohistochemical studies were conducted with the following antibodies applied to 4 μm paraffin sections: rabbit polyclonal antibody against human IgG (DakoCytomation, Glostrup, Denmark; dilution 1:8000); mouse monoclonal antibody against human IgG4 (Binding Site, Birmingham, UK; dilution 1:2000); and TGF-β (Novocastra, Newcastle, UK; dilution 1:50). Tonsil tissue was used as a positive control. For the counting of IgG4-positive and IgG-positive plasma cells, areas with the highest density of positive cells were evaluated. Five high-power fields (HPF) in each section were counted and the ratio of IgG4-positive plasma cells to IgG-positive plasma cells was calculated.

DISCUSSION

IgG4-RSD was first reported with regard to AIP by Hamano *et al.* in 2001.[1] Until now, a spectrum of sites involved in this systemic disease has been reported, including the pancreas, biliary tract, gallbladder, liver, salivary gland, retroperitoneum, lung, kidney, prostate, breast, orbit, lymph node, lacrimal gland and adventitia of the aorta.[2–12] All share histopathological characteristics such as diffuse lymphoplasmacytic infiltration, progressive fibrosis, occasional eosinophilic infiltration and obliterative phlebitis. Most importantly, these sclerosing lesions are characterized by abundant IgG4-positive plasma cell infiltration and are usually associated with an increased level of serum IgG4. For instance, diagnosis of IgG4-RSD is characterized by both elevated serum IgG4 (>135 mg/dL) and histopathological features including lymphocyte and IgG4-positive plasma cell infiltration (IgG4-positive plasma cells/IgG-positive plasma cells >40% checked on a highly-magnified slide in five fields).[18] In this case bilateral sialadenitis of the submandibular glands (Kuttner tumor), pancreas, and biliary tract were involved and serum IgG4 was significantly high (1700 mg/dL).

The association of malignant tumors in IgG4-RSD has been sporadically reported. Adenocarcinomas in the pancreas and salivary gland have been complications in both AIP and IgG4-related sclerosing sialadenitis.[13,14] Also, malignant lymphomas and other lymphoproliferative disorders have appeared in sclerosing dacryoadenitis in the ocular adnexa.[15,16] These tumors arose in organs with IgG4-related sclerosing inflammation. To the best of our knowledge, the present case is the first documentation of malignancy of the thyroid gland in IgG4-RSD. However the role of IgG4 in IgG4-RSD is not known, as well as what immune responses are involved in the pathogenesis. Conceivably, TGF-β may be a key molecule involved in the two major histological findings of IgG4-RSD: IgG4 class switch; and diffuse fibrosis.[19,20] TGF-β is potent in directing B cells to produce IgG4 and inducing a strong fibrogenic function.

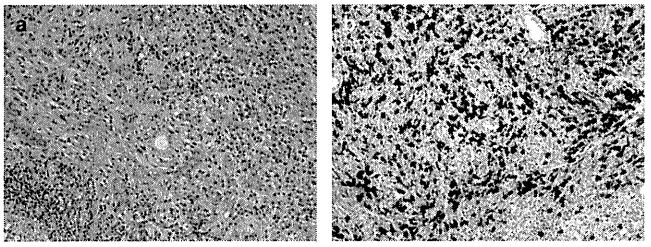

Figure 1 Histology of IgG4-related chronic sialadenitis. (**a**) Lymphoplasmacytic infiltration and fibrosis giving rise to storiform fibrosis. (HE). (**b**) Numerous IgG4-positive plasma cells were identified on immunostaining. (IgG4 immunohistochemistry).

Papillary carcinomas often produce peritumorous fibrosis and scarring. High levels of TGF-β were reported in the invasion front of papillary carcinoma and strong fibrotic area.[21,22] Immunostaining for TGF-β in our case confirmed that papillary carcinoma cells expressed TGF-β.

Recently Hashimoto's thyroiditis has been classified into two groups according to involvement of IgG4-positive plasma cells: IgG4 thyroiditis (IgG4-related, IgG4-positive plasma cell-rich thyroiditis); and non-IgG4 thyroiditis (non-IgG4-related, IgG4-positive plasma cell-poor thyroiditis).[23,24] IgG4 thyroiditis presents with severe lymphoplasmacytic

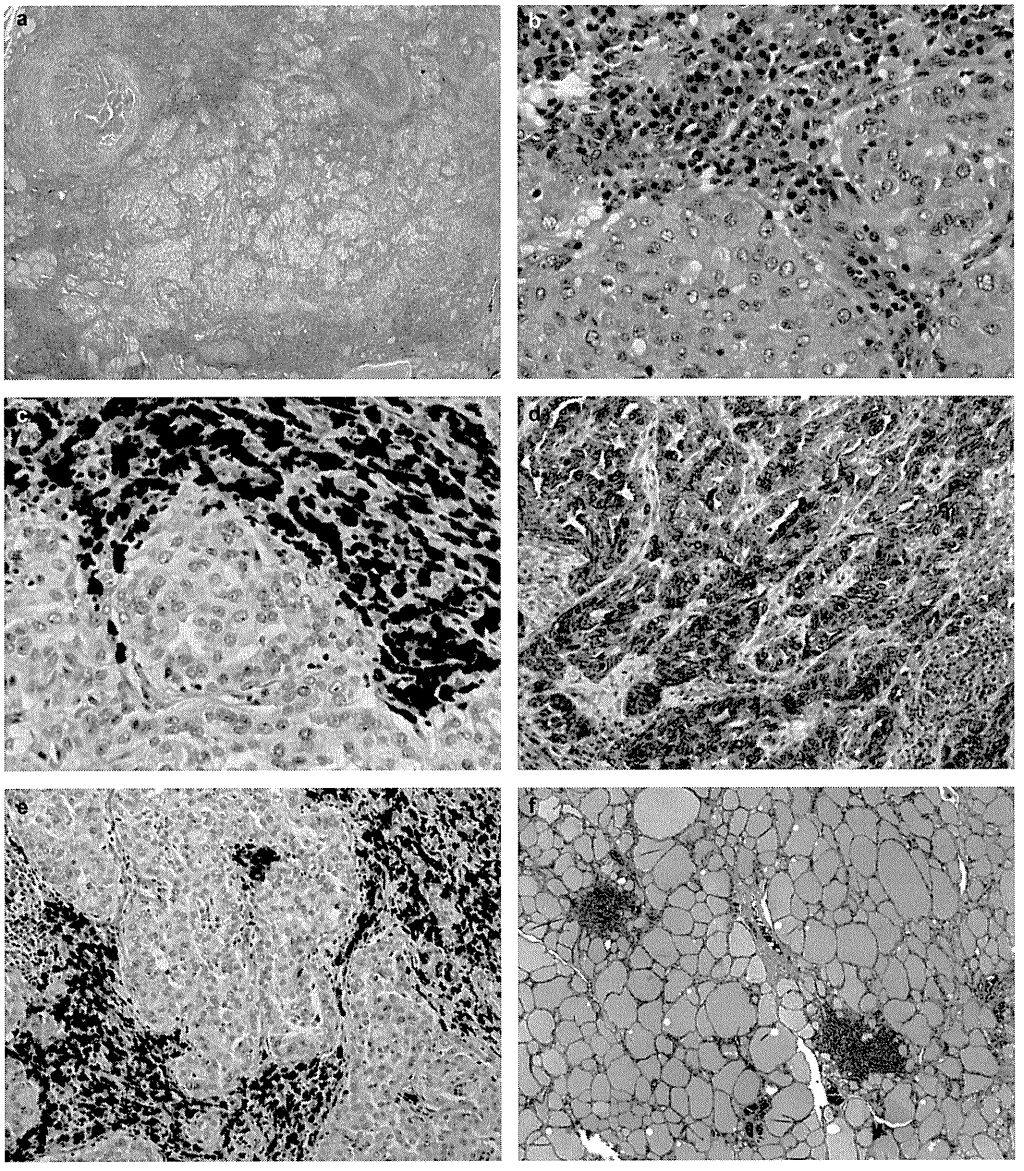

Figure 2 Microscopic findings of thyroid papillary carcinoma. (**a**) Tumor nests were surrounded by dense plasma cells with intermingling fibrosis and lymphoid follicles. (HE). (**b**) Solid-trabecular nests were surrounded by dense plasma cells. Tumor cells had pale eosinophilic cytoplasm and clear and irregular nuclear features of papillary carcinoma. (HE). (**c**) Approximately 90% of plasma cells expressed IgG4. (IgG4 immunohistochemistry). (**d**) Carcinoma cells expressed TGF-β on immunohistochemistry. (TGF-β immunohistochemistry). (**e**) Metastatic papillary carcinoma in cervical lymph node. Papillary carcinoma cells were surrounded by IgG4-positive plasma cells. (IgG4 immunohistochemistry). (**f**) Background thyroid showed mild lymphocytic thyroiditis. (HE).

infiltration, dense fibrosis, marked follicular cell degeneration, oxyphilic change and lymphoid follicle formation. In contrast, non-IgG4 thyroiditis presents with relatively mild or absence of histopathological characteristics. According to this classification, our case is classified as non-IgG4 thyroiditis, since thyroiditis was focal and mild. IgG4 thyroiditis does not appear to be related to the condition of IgG4-RSD.

In conclusion, we report here a case of thyroid papillary carcinoma showing unique morphology in IgG4-RSD. Solid tumor nests were surrounded by dense IgG4-positive plasma cells at both the primary site and metastatic lymph nodes without a chronic sclerosing background.

ACKNOWLEDGMENTS

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CASE REPORT

A case of IgG4-related pulmonary disease with rapid improvement

Masataka Umeda · Keita Fujikawa · Tomoki Origuchi · Toshiaki Tsukada · Akira Kondo · Shinya Tomari · Yuichi Inoue · Hisashi Soda · Hideki Nakamura · Shoko Matsui · Atsushi Kawakami

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Abstract We report a 72-year-old man with respiratory involvement of immunoglobulin G4 (IgG4)-related disease, who developed dry cough and shortness of breath on effort. The chest computed tomography scan image showed massive and diffuse ground-glass opacity, interlobular thickening, and bronchial wall thickening. The infiltration of IgG4-positive plasma cells in the transbronchial lung biopsy and high serum IgG4 concentrations were found. The patient was treated with 0.6 mg/kg oral prednisolone and showed rapid improvement. This is a case of IgG4-related disease in which the only complication was respiratory involvement.

Keywords IgG4-related disease · Interstitial pneumonia · Respiratory involvement

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Introduction

'Immunoglobulin G4-related disease (IgG4-RD)' is new concept of multi-organ disease that is characterized by infiltration into organs of IgG4-positive plasma cells and high serum IgG4 concentrations [1]. It was first described as autoimmune pancreatitis (AIP), but has subsequently been found that the target organs include not only the pancreas, but also lacrimal and salivary glands, biliary duct, kidney, lung, thyroid, lymph node, retroperitoneum, and aorta [2]. A variety of respiratory involvements in IgG4-RD have been described, namely, bronchial [3], interstitial [4, 5], nodular [6], pleural lesion [7], and mediastinal and/or hilar lymphadenopathy [8]. These respiratory involvements are often complicated with IgG4-RD, but it is rare in patients with IgG4-RD that a pulmonary lesion is the only lesion to be detected [4]. We report a patient with IgG4-RD in whom only the respiratory system was affected and who was treated successfully with oral corticosteroid.

Case report

A 72-year-old man was admitted with a 1-year history of dry cough and shortness of breath on effort. The patient had no history of smoking, habitual drinking, allergy, bronchial asthma, or atopic disorder, but he did have a history of

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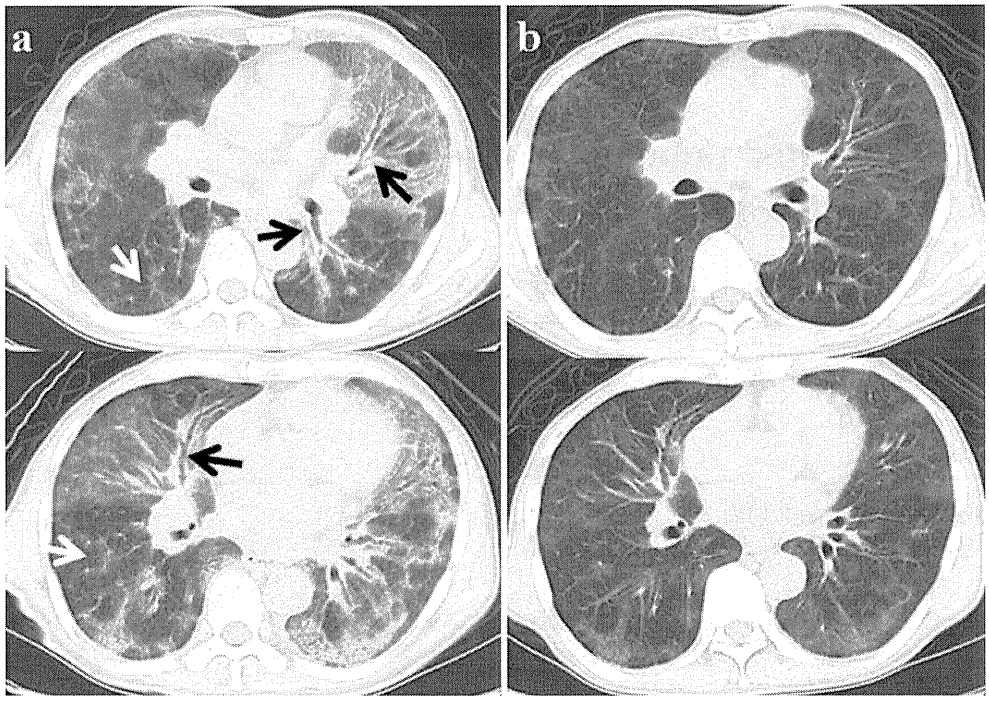

Fig. 1 Chest computed tomography (CT) scan image showed diffuse ground-glass opacity, interlobular thickening (*white arrows*), and bronchial wall thickening (*black arrows*) (**a**). There was rapid improvement within 1 month after treatment initiation (**b**)

aspiration of asbestos. On physical examination, his body temperature was 36.8°C, blood pressure was 117/70 mmHg, pulse was 85 bpm, and respiratory rate was 20 bpm. Oxygen saturation (SpO_2) was 96%. There were fine crackles in auscultation on his back. Laboratory findings revealed the following: leukocytes, 5,150/μl; neutrophils, 2,981/μl; lymphocytes, 1,828/μl; eosinophils, 93/μl; hemoglobin, 8.8 g/dl; platelet, 10.5 × 10^4/μl; C-reactive protein, 6.05 mg/dl (normal <0.10 mg/dl); total protein, 10.2 g/dl (normal 6.7–8.3 g/dl); albumin, 2.5 g/dl (normal 4.0–5.0 g/dl); lactate dehydrogenase, 206 IU/l (normal 119–229 IU/l); angiotensin-converting enzyme, 13.5 IU/l (normal 7.7–29.4 IU/l); ferritin, 273 ng/ml (normal 23–250 ng/ml); soluble interleukin 2 receptor, 1,490 U/ml (normal 124–466); KL-6, 1,471 U/ml (normal <500 U/ml); surfactant protein-A, 61.9 ng/ml (normal <43.8 ng/ml); surfactant protein-D, 129.8 ng/ml (normal <110 ng/ml); CH50, 30 IU/ml (normal 30–45 IU/ml); C3, 82.2 mg/dl (normal 63–134 mg/dl); C4, 8.8 mg/dl (normal 13–36 mg/dl); IgE, 654 IU/ml (normal <300 IU/ml); IgG, 6,690 mg/dl (normal 870–1,700 mg/dl). The serum concentrations of the IgG subclass were as follows: IgG1, 3,820 mg/dl (normal <1,080 mg/dl); IgG2, 2,270 mg/dl (normal <931 mg/dl); IgG3, 166 mg/dl (normal <121 mg/dl); IgG4, 835 mg/dl (normal <108 mg/dl); IgG4/IgG, 11.8%. Although the patient tested positive for antinuclear antibody (ANA; 80×; speckled pattern), test results for rheumatoid factor (RF), anti-SS-A and anti-SS-B antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3 ANCA were all negative. The blood gas analysis was within the normal range. The result of respiratory function tests were as follows: vital capacity was 2.23 l (74.3% predicted), forced expiratory volume in 1 s was 2.06 l (91.2% predicted), and diffusing capacity for carbon monoxide/alveolar volume was 1.74 ml/min/mmHg/l (40.1% predicted).

A chest X-ray showed bilateral infiltration. The chest computed tomography (CT) scan image showed diffuse ground-glass opacity, interlobular thickening, and bronchial wall thickening with hilar and mediastinal lymph-node swelling (Fig. 1a). Fluorodeoxyglucose (FDG) positron emission tomography showed accumulation of 18F-FDG in bilateral lung fields and in the hilar and mediastinal lymph nodes. There was no involvement except the lung in this patient. Bronchoalveolar lavage fluid (BALF) findings were as follows: total cell count, 464.2 × 10^5/ml; alveolar macrophages, 46.2%; lymphocytes, 34.7%; neutrophils, 7.4%; eosinophils, 11.5%; CD4/CD8 ratio, 0.23. The histopathological findings of transbronchial lung biopsy (TBLB) were fibrous thickening of the alveolar septa and lymphoplasmacytic infiltration in the interstitium. Infiltration of IgG4-positive plasma cells was more obvious in the bronchial mucosa than in the alveolar septa (Fig. 2a–c). The number of IgG4-positive plasma cells per high-power field (HPF) was 44.2, and the percentage of IgG4-positive to IgG-positive plasma cells (IgG4+/IgG+) was 76.5%. The number of eosinophil was 1 in 5 HPF. We made a

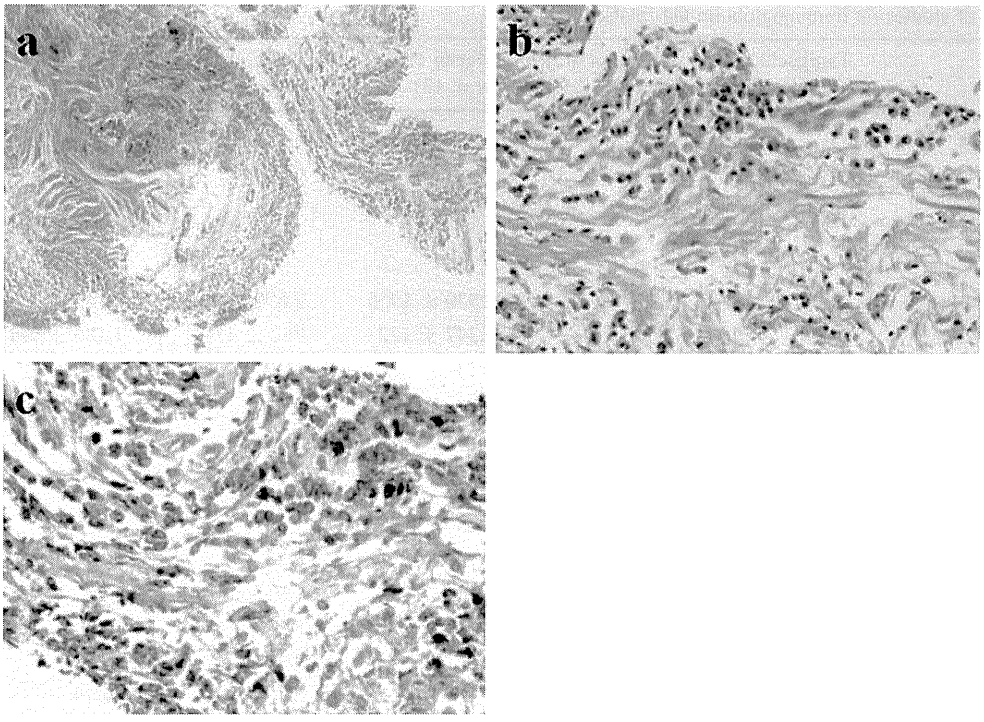

Fig. 2 Immunohistochemical staining of the transbronchial lung biopsy (TBLB). **a**, **b** Hematoxylin and eosin staining (**a** ×20, **b** ×100). **c** Immunostaining for IgG4 (×100) revealed infiltration of immunoglobulin G4-positive plasma cells in bronchial mucosa and alveolar septa

diagnosis of respiratory involvement of IgG4-related disease. The patient was treated with 30 mg (0.6 mg/kg) prednisolone daily. At 1 month after treatment initiation, his respiratory symptoms had improved, there was a marked improvement in lung opacity (Fig. 1b), and the serum concentration of IgG4 had decreased from 853 to 359 mg/dl.

Discussion

In 2001, IgG4-RD was first described as AIP with elevated serum IgG4 concentration [1]. Hirano et al. [9] reported that 13.3% of the 30 AIP patients in their study showed pulmonary complications. Masaki et al. [10] also reported that 9.3% in the 64 Mikulicz's disease patients in their study were complicated with interstitial pneumonitis.

We reviewed the clinical characteristics of pulmonary involvements in IgG4-RD that have been reported to date (Table 1). IgG4-related pulmonary disease (IgG4-PD) often develops in males aged about 60 years. The frequency of allergic predisposition, such as rhinitis and bronchial asthma, in patients with IgG4-PD is higher than that in the general population [11]. A possible relationship between asbestos exposure and IgG4-PD as well as allergic condition has been proposed [12]. The laboratory tests conducted on most of the patients with IgG4-PD reveal high serum concentrations of IgG, especially IgG4. Additionally, hypocomplementemia, high serum IgE, and positivity for RF and ANA are often observed [11, 13, 14]. Various abnormal radiographic patterns, such as bronchial wall thickening, consolidation, nodule(s), ground-glass opacity, interlobular thickening, honeycombing, pleural thickening/effusion, and mediastinal lymphadenopathy, have been observed. Thus, it is difficult to diagnose IgG4-RD solely on the radiographic findings.

In terms of the histopathological findings, the characteristics of IgG4-RD are infiltration of IgG4-positive plasma cells and fibrosis, but the ratio of IgG4/IgG-positive cells in IgG4-PD remains inconclusive. The histopathological findings of IgG4-PD are quite diverse. Early establishment of the IgG4-PD diagnostic guidelines is expected.

In 2004, a case of interstitial pneumonia associated with IgG4-RD, further complicated with AIP, was first reported by Taniguchi et al. [5]. The chest CT scan image showed ground-glass attenuation and honeycombing. The histological findings of TBLB were infiltration of IgG4-positive plasma cells in the alveolar septa. Hirano et al. [9] also reported four patients with AIP complicated with interstitial pneumonia. Inoue et al. [13] reported 13 patients with IgG4-PD and classified the pulmonary lesions of IgG4-RD into four subtypes in terms of radiologic features, namely, solid nodular, bronchovascular, alveolar interstitial, and round-shaped ground-glass opacity type, respectively. These authors also correlated these manifestations with histopathological findings [15], recommending immunostaining

Table 1 Summary of studies on immunoglobulin G4-related disease

	Taniguchi et al. [5] ($n = 1$)	Hirano et al. [9] ($n = 4$)	Matsui et al. [11] ($n = 13$)	Inoue et al. [13] ($n = 13$)	Tsushima et al. [14] ($n = 19$)	Present case ($n = 1$)
Patient characteristics						
Age (years)	63	70 ± 9	61 ± 17	62 ± 11	66 ± 10	72
Sex (no. of male/female)	1/0	3/1	11/2	9/4	15/4	1/0
Laboratory findings						
Serum IgG (mg/dl)	2,350	NA	3,930 ± 1956	2,699 ± 1,087	2,747 ± 1,121	6,690
Serum IgG4 (mg/dl)	1,690	595 ± 570	1,347 ± 1227	752 ± 471	1,185 ± 991	835
Number of patients positive for ANA	0/1	3/4	4/13	6/10	6/19	1/1
Chest CT findings						
Bronchial wall thickening			8/13	9/13		1/1
Consolidation		1/4	4/13			
Nodule/mass			4/13	6/13	8/19	
Ground-glass opacity	1/1	1/4	3/13	12/13	0/19	1/1
Interlobular thickening			2/13	8/13		1/1
Honeycombing	1/1	1/4		2/13		
Pleural thickening/effusion			3/13	6/13	19/19	
Lymphadenopathy			10/13			1/1
Histopathological findings[a]						
Lymphoplasmacytic infiltration	(+)		(+)	(+)	(+)	(+)
Ratio of IgG4/IgG			>40%	>30%		76.5%
Fibrosis			(+)	(+)	(+)	(+)
Eosinophilic infiltration				(+)		(+)
Therapy[b]						
Response to corticosteroid	(+)	(+)	(+)		(+)	(+)
Dose of prednisolone (mg/day)	40	30	20–50		NA	30

Ig Immunoglobulin, *CT* computed tomography, *ANA* antinuclear antibody, *NA* not analyzed

[a] No data available for the Hirano et al. [9] study

[b] No data available for the Inoue et al. [13] study

of IgG4 in non-specific interstitial pneumonia (NSIP) lesions with prominent eosinophilic infiltration, obliterative vascular changes, or lymph follicle formation despite the absence of extrapulmonary autoimmune disorders. In the case of our patient, bronchovascular and interstitial lung lesions were detected in the radiological examination. The pathological and radiological findings suggested that the type of interstitial pneumonia was NSIP, a cellular pattern, but findings atypical of NSIP were also observed, such as bronchial wall changes and distribution of the shadows. Infiltration of IgG4-positive plasma cells was observed in the bronchial mucosa as well as in the pulmonary alveoli. Some eosinophilic infiltrations were also observed, while there was neither obliterative vascular change nor lymph follicle formation. These findings were consistent with the histological features of IgG4-PD reported previously.

For IgG4-PD to be diagnosed, it is necessary to exclude other similar diseases, such as Castleman's disease, sarcoidosis, malignant lymphoma, Sjögren's syndrome, and granulomatous polyangiitis. In addition, IgG4-PD patients with premalignant or malignant lesions within the infiltrated regions of IgG4-positive cells have been reported [15]. Therefore, the histological examination is particularly important. If a diagnosis cannot be reached based on TBLB findings, percutaneous lung biopsy or video-assisted thoracic surgery should be considered. Tsushima et al. [14]

compared BAL findings of patients with pulmonary involvement of AIP with those of patients with pulmonary sarcoidosis and found that the BAL of patients with AIP contained increased total cell counts with a lymphocyte predominance; however, the difference in the cellular subsets, including CD4/CD8 lymphocyte ratio, between the two patient groups was not statistically significant. These authors did observe that IgG4 concentration in the BAL as well as the infiltration of IgG4-positive plasma cells into the pulmonary tissues were significantly higher in patients with AIP than in those with pulmonary sarcoidosis. Since the latter finding was also found in our case, these phenomena appear to be characteristic for IgG4-PD and a helpful marker to exclude other diseases.

Corticosteroid therapy has been regarded as effective therapy for IgG4-RD. Most patients with IgG4-PD respond well to prednisolone at an initial dose of 20–50 mg, but some patients develop extra-pulmonary lesions [11] or experience recurrence of radiologic changes [15]. Further investigation is necessary to determine the optimal initial dose of corticosteroid and collect long-term follow-up data.

To summarize, we describe a case in which the only complication of a patient with IgG4-RD, namely, respiratory involvement, was successfully treated with oral corticosteroid. The IgG4-RD lesions localized in the respiratory system presented with bronchovascular and interstitial pneumonia. The possibility of IgG4-PD in patients with interstitial pneumonia complicated with hypergammaglobulinemia, hypocomplementemia, or allergic predisposition should always be considered. For the diagnosis of IgG4-PD, it is important to determine the infiltrations of IgG4-positive plasma cells pathologically.

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Conflict of interest None.

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ORIGINAL ARTICLE

Respiratory involvement in IgG4-related Mikulicz's disease

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Abstract 'Immunoglobulin G4 (IgG4)-related disease' is a new clinical concept of multi-organ diseases, with Mikulicz's disease (MD) being a clinical phenotype of IgG4-related disease. To clarify the clinical characteristics of respiratory involvement associated with IgG4-related MD, we retrospectively assessed 25 patients with MD, 11 (44%) of whom had allergic symptoms, and 7 (28%) of whom complained of respiratory problems. Thirteen patients (52%) presented with pulmonary and/or mediastinal lesions (P-MD) on chest computed tomography (CT), and 11 (44%) had lesions limited to the lacrimal and/or salivary glands (L-MD). Mean serum total protein, IgG, and IgG4 concentrations were significantly higher and CH50 was significantly lower in the P-MD than in the L-MD group. Immune complex was present only in the P-MD group. Chest CT images showed bronchial wall thickening, consolidation, nodule(s), interlobular thickening, ground glass opacity, pleural thickening/effusion, and mediastinal lymphadenopathy. Five of seven patients who underwent histological examination of the lungs had abundant IgG4-positive plasma cell infiltrates (IgG4/IgG-positive plasma cells >40%), but the other two did not. These findings suggest that respiratory lesions are not rare in patients with IgG4-related MD, and that they present with various manifestations. IgG4-related MD should be differentiated from similar diseases, such as sarcoidosis, bronchial asthma, Sjögren's syndrome, and malignant lymphoma.

Keywords IgG4-related disease · Mikulicz's disease · Respiratory involvement · Autoimmune pancreatitis

Abbreviations

MD	Mikulicz's disease
AIP	Autoimmune pancreatitis
IgG	Immunoglobulin G
CT	Computed tomography
FDG-PET	Positron emission tomography with 18F-fluorodeoxyglucose
BAL	Bronchoalveolar lavage

Introduction

"IgG4-related disease" is a new clinical concept of multi-organ diseases, characterized by high serum IgG4

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concentrations and dense infiltration into organs of IgG4-positive plasma cells. IgG4-related disease was first described as autoimmune pancreatitis (AIP) [1–4], and has since been found to include disorders of various organs, including Mikulicz's disease (MD) [5–7], inflammatory pseudotumor of the lung [8], sclerosing cholangitis [9], tubulointerstitial nephritis [10], prostatitis [11], retroperitoneal fibrosis [12], and inflammatory aortic aneurysm [13]. IgG4-related disease has two major clinical phenotypes, AIP and MD. Although much is known about the clinical features of AIP and extra-pancreatic lesions [14–17], less is known about MD and extra-glandular lesions [18–20].

MD presents as persistent symmetrical swelling of the lacrimal and/or major salivary glands, and histopathologically it presents with sialadenitis/dacryoadenitis characterized by a dense lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells. MD was categorized as a subtype of primary Sjögren's syndrome more than 50 years ago [21] and has not been regarded as systemic. In 2009, however, MD was shown to be a systemic disease, associated with extra-glandular disorders such as allergic rhinitis, interstitial pneumonia, AIP, and interstitial nephritis [7]. To clarify the clinical characteristics of respiratory conditions associated with IgG4-related MD, we retrospectively analyzed 25 patients with this condition.

Patients and methods

Between December 2003 and March 2011, 25 patients (18 men and 7 women, aged 24–80 years) were diagnosed with IgG4-related MD at Toyama University Hospital. Patients were diagnosed with IgG4-MD if they had: (1) symmetrical swelling of at least 2 pairs of lacrimal, parotid, and/or submandibular glands for more than 3 months, (2) a high serum IgG4 concentration (>135 mg/dl), and (3) infiltration of numerous IgG4-positive plasma cells (IgG4-positive plasma cells/IgG-positive plasma cells >50%) into the lacrimal, parotid, and/or submandibular glands with typical tissue fibrosis or sclerosis [18]. Patients with Küttner tumor were excluded.

Of the above 25 patients, 13 were diagnosed by chest computed tomography (CT) with IgG4-related abnormalities in pulmonary and mediastinal lesions (P-MD group). Seven of these patients were histopathologically examined and diagnosed with IgG4-related lesions, and the other 6 were clinically diagnosed. Eleven of the 25 patients had lesions limited to the lacrimal and/or salivary glands (L-MD group). The remaining patient had IgG4-related arthritis with MD [22] and was excluded from the comparison of the P-MD and L-MD groups.

Although 5 of the 25 patients fulfilled the criteria for Sjögren's syndrome, as revised by the Japanese Ministry of Welfare in 1999, none of these patients had sarcoidosis, infections, malignant diseases, or other collagen vascular diseases.

This study conformed to the Declaration of Helsinki, and was approved by the Research Ethics Committee of the University of Toyama.

Serum and plasma assays

At diagnosis of IgG4-related MD, blood was drawn from all patients and serum or plasma was assayed for concentrations of total protein (normal range 6.7–8.3 g/dl), IgG (normal range 863–1589 mg/dl), and CH50 (normal range 30–46 CH50/ml) at Toyama University Hospital; for IgG4 concentrations (normal range 4–108 mg/ml) at the Special Reference Laboratory (Hachioji, Japan); and for IgE (normal range 0–170 IU/ml) and soluble interleukin-2 receptor (sIL-2R) (normal range 122–496 U/ml) at B.M.L. (Kawagoe, Japan).

Imaging

All patients were examined by chest CT, Ga-67 scintigraphy, and/or positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET). CT scans were performed with helical CT scanners (Somatom plus-S [Siemens Japan, Tokyo, Japan] from 2003 to 2004, and with Somatom Sensation cardiac 64 or Somatom Sensation 16 [Siemens Japan], from 2005 to 2011) at Toyama University Hospital. Ga-67 scintigraphy was performed 48 h after the intravenous injection of 111 MBq of Ga-67 citrate, and whole-body FDG-PET scans were performed 60 min after intravenous injection of 18F-FDG (3.7 MBq/kg body weight). The results of chest CT, Ga-67 scintigraphy, and FDG-PET were reviewed by one radiologist (H.S.) and two chest physicians (S.M. and R.H.).

Immunohistochemistry

Immunostaining for IgG and IgG4 was performed using an Autostainer (EnVision System; DAKO, Carpinteria, CA, USA), according to the manufacturer's instructions. Primary antibodies used were a rabbit polyclonal antibody against human IgG (Dako Cytomation, Glostrup, Denmark) and a mouse monoclonal antibody against human IgG4 (Zymed Laboratories, San Francisco, CA,USA).

Bronchoalveolar lavage fluid analysis

Total cell counts in unfractionated bronchoalveolar lavage fluid (BALF) were evaluated using a hemocytometer. The number of BAL cells counted per sample for each differential was 300. Differential counts were obtained using a smear