

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.

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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

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

of Diff-Quik stainTM (Dade Behring, Newark, DE, USA). The pellets in the BALF were analyzed for lymphocyte subsets by flow cytometry at the Special Reference Laboratory).

Statistics

All results are reported as means $\pm$ standard deviation (SD), with the P-MD and L-MD groups compared using the Mann–Whitney *U*-test or Fisher's exact test, as appropriate. *P* values of <0.05 were considered statistically significant.

Results

Patient profiles

Patient profiles are summarized in Table 1. Ages at the time of diagnosis ranged from 24 to 80 years, with a mean of 60 ± 15 years. Of the 25 patients, 11 (44.0%) had a history of allergic rhinitis or sinusitis, and 7 (28.0%) had bronchial asthma. Allergic rhinitis (46.2 vs. 36.3%) and bronchial asthma (38.5 vs. 9.0%) were more common in the P-MD than in the L-MD group. Thirteen patients (52.0%) visited the hospital because of swelling of the lacrimal, parotid, and/or submandibular glands, and 7 (28.0%) complained of respiratory problems such as cough or dyspnea or had abnormal findings on chest X-ray.

Details of the 13 patients in the P-MD group are shown in Table 2. At diagnosis of MD, 7 (53.8%) of these patients had extra-pulmonary lesions, including 3 with AIP (patients 3, 4, and 13 in Table 2), 1 with retroperitoneal fibrosis (patient 2), 3 with interstitial nephritis (patients 4, 8, and 12), and 1 with hypophysitis (patient 5).

Laboratory findings

All 25 patients had abnormally high serum concentrations of total protein, IgG, and IgG4, with mean concentrations of 8.4 g/dl, 2872 mg/dl, and 926 mg/dl, respectively. In addition, 21 patients (84%) had high serum IgE concentrations, averaging 897 IU/ml. IgA and IgM concentrations, however, were within normal ranges in all patients. All patients were negative for anti-SS-A and anti-SS-B antibodies, but 6 (24%) and 7 (28%) were positive for rheumatoid factor (RF) and antinuclear antibodies (ANA), respectively. Laboratory results in the P-MD and L-MD groups are summarized in Table 3.

Serum total protein, IgG, IgG4, and sIL-2R concentrations were each significantly higher, and CH50 was significantly lower, in the P-MD than in the L-MD group. The 6 patients positive for immune complexes were all in the P-MD group. IgE concentrations did not differ significantly between the P-MD and L-MD groups.

Imaging analysis

Chest CT images of PM-D patients showed various abnormalities in the bronchi, bronchovascular bundles, alveolar septa, pleura, and hilar lymph nodes (Table 4; Fig. 1). CT showed thickening of the bronchial wall in 8 patients (61.5%, Fig. 1a), consolidation in 4 (30.8%, Fig. 1b), nodule(s) in 4 (30.8%, Fig. 1c), ground glass opacity in 3 (23.1%), interlobular thickening in 2 (15.4%), pleural thickening and/or effusion in 3 (23.1%), and mediastinal lymphadenopathy in 10 (76.9%, Fig. 1d), with many patients showing more than one of these findings. Thickening of the bronchial wall was observed in all five patients with asthmatic symptoms.

Table 1 Clinical and demographic characteristics of patients with Mikulicz's disease

	All (<i>n</i> = 25)	P-MD (<i>n</i> = 13)	L-MD (<i>n</i> = 11)
Age (years)	60 $\pm$ 15	61 $\pm$ 17	63 $\pm$ 9
Sex	M 18:F 7	M 11:F 2	M 6:F 5
Allergic history	11 (44.0%)	7 (53.8%)	4 (36.3%)
Rhinitis/sinusitis	9 (36.0%)	6 (46.2%)	3 (27.3%)
Bronchial asthma	7 (28.0%)	5 (38.5%)	1 (9.0%)
Both of them	5 (20.0%)	4 (30.1%)	1 (9.0%)
Chief complaint			
Glandular swelling	13 (52.0%)	3 (23.1%)	10 (91.0%)
Cough	5 (20.0%)	5 (38.5%)	
Dyspnea	1 (4.0%)	1 (7.7%)	
Abnormal chest X-ray	1 (4.0%)	1 (7.7%)	
Others	5 (20.0%)	3 (23.1%)	1 (9.0%)

P-MD Mikulicz's disease with pulmonary and/or mediastinal lesions, *L-MD* Mikulicz's disease limited to the lacrimal and/or salivary glands

Table 2 Clinical features of 13 MD patients with pulmonary lesions

Age (years)	Sex	Extra-pulmonary lesions	IgG (mg/dl)	IgG4 (mg/dl)	IgE (IU/ml)	CH50 (U/ml)	Chest CT findings	Histological findings of pulmonary lesions	BALF		
									TCC	Lym (%)	CD4/8
1 71	F		2386	615	2585	34	Bronchial thickening	Chronic bronchitis, IgG <10/HPF	1.5	12.4	0.9
2 69	M	RPF	2731	269	975	14	Small nodules				
3 25	M	AIP	4859	3405	1100	13	Diffuse reticular shadows, consolidation, bronchial thickening	Lymphoplasmacytic infiltration IgG4/IgG >50%	2.3	20	0.6
4 41	M	AIP, nephritis	6361	776	1123	17	Diffuse reticular shadows, bronchial thickening				
5 75	M	Hypophysitis	2373	241	1868	28	Multiple masses	Inflammatory pseudotumor IgG4/IgG >40%	1.2	24.9	2.5
6 75	M		8361	4075	44	37	Focal infiltration	Interstitial lymphoplasmacytic infiltrate, IgG4 cells <10/HPF	1.2	41	2.2
7 58	M		4307	2490	223	34	Pleural effusion, consolidation				
8 74	M	Nephritis	4387	1320	560	5	Hilar lymphadenopathy				
9 35	M		1617	485	108	44	Hilar lymphadenopathy				
10 69	M		1955	991	853	37	Bronchial thickening	Chronic bronchitis, IgG4/G >50%	1.6	23.4	2.6
11 71	M		5117	384	1141	7	Hilar lymphadenopathy, pleural thickening	Chronic bronchitis, IgG4/G >50%	2.7	5.8	0.9
12 66	F	Nephritis	4174	1260	100	35	Interstitial lobular thickening, bronchial thickening, pleural thickening	Chronic bronchitis, IgG4/G >50%	4.8	18.5	1.6
13 59	M	AIP	2456	1850	1160	29	Bronchial thickening				

BALF bronchoalveolar lavage fluid CT computed tomography HPF high-power field, TCC total cell count ($\times 10^5$ cells/ml), RPF retroperitoneal fibrosis, AIP autoimmune pancreatitis, Lym lymphocytes

Table 3 Laboratory findings in the P-MD and L-MD groups

	P-MD (<i>n</i> = 13)	L-MD (<i>n</i> = 11)	<i>P</i>
Age (years)	61 ± 17	58 ± 14	
Sex (male/female)	13/2	6/5	0.193
Total protein (g/dl)	9.1 ± 1.8	7.5 ± 0.5	0.006
Serum IgG (mg/dl)	3930 ± 1956	1716 ± 434	<0.001
Serum IgG4 (mg/dl)	1347 ± 1227	428 ± 197	0.008
CH50 (U/ml)	25.7 ± 12.9	43.4 ± 7.2	0.003
IgE (IU/ml)	842 ± 757	1010 ± 1039	0.160
sIL-2R (U/ml)	1625 ± 1195	525 ± 238	<0.001
Immune complex	63.7%	0%	0.013
RF	30.7%	18.2%	0.640
ANA	33.3%	9.1%	0.317

sIL-2R soluble interleukin-2 receptor, *RF* rheumatoid factor, *ANA* antinuclear antibodies

Table 4 Chest CT findings

	<i>n</i> = 13
Bronchial wall thickening	8 (61.5%)
Consolidation	4 (30.8%)
Nodule/mass	4 (30.8%)
Ground glass opacity	3 (23.1%)
Interlobular thickening	2 (15.4%)
Pleural thickening/effusion	3 (23.1%)
Lymphadenopathy	10 (76.9%)

Ga-67 scintigraphy was performed in 11 P-MD patients and FDG-PET in 2. Of these 13 patients, 10 (76.9%) showed Ga-67 or 18F-FDG accumulation in mediastinal lymph nodes, 2 (15.4%) showed diffuse Ga-67 accumulation in bilateral lung fields (patients 3 and 4), and 2 (15.4%) showed patchy accumulation in the lesions (patients 5 and 12).

Histopathological findings

Histological examination of the bronchus and/or lung was performed in 7 patients, all of whom showed numerous lymphoplasmacytic infiltrates in the bronchial mucosa, peri-bronchovascular bundles (Fig. 2a), and alveolar septa. We also observed invasion by IgG4-positive plasma cells (Fig. 2b). Typical sclerosing inflammation was found in only one patient, who had an inflammatory pseudotumor (patient 5, Fig. 2c, d).

BALF findings

BALF was analyzed in 7 patients in the PM-D group. The mean total cell count was somewhat high ($2.2 \pm 1.3 \times 10^5/\text{ml}$) with a lymphocyte predominance

($20.9 \pm 11.1\%$), but there was no increase in the CD4/CD8 lymphocyte ratio (1.61 ± 0.8).

Clinical outcomes

Of the 25 patients, 17 (11 PM-D, 5 L-MD, and 1 MD with arthritis) were treated with prednisolone (initial dose 20–50 mg/day), with all rapidly responding to steroid therapy. Three years after the initiation of the steroid therapy, however, one patient (patient 3) experienced a recurrence as an intra-orbital tumor during maintenance therapy (7.5 mg/day). One other patient (the one who had MD with arthritis) developed arthropathy 8 years after the initiation of the steroid therapy, and was treated with prednisolone (10 mg/day) and salazosulfapyridine (2 g/day) [22].

Discussion

After the first description of the relationship between MD and IgG4 in 2004 [5], IgG4-related MD, also called IgG4-positive multi-organ lymphoproliferative disorder, was found to be a systemic disease accompanied by coexisting autoimmune pancreatitis (AIP), interstitial nephritis, and interstitial pneumonia [7]. MD has now been recognized as a representative feature of IgG4-related disease.

Although respiratory involvement has been reported in IgG4-related disease, most patients have been described as having complications of AIP [23–26]. As IgG4-related disease can present with various conditions in various organs, we focused on respiratory involvement in patients with IgG4-related MD.

We found that 44% of our patients with IgG4-MD had a history of allergic rhinitis and/or bronchial asthma, and that 28% complained of respiratory symptoms. In comparison, the incidence of allergic rhinitis in the general population

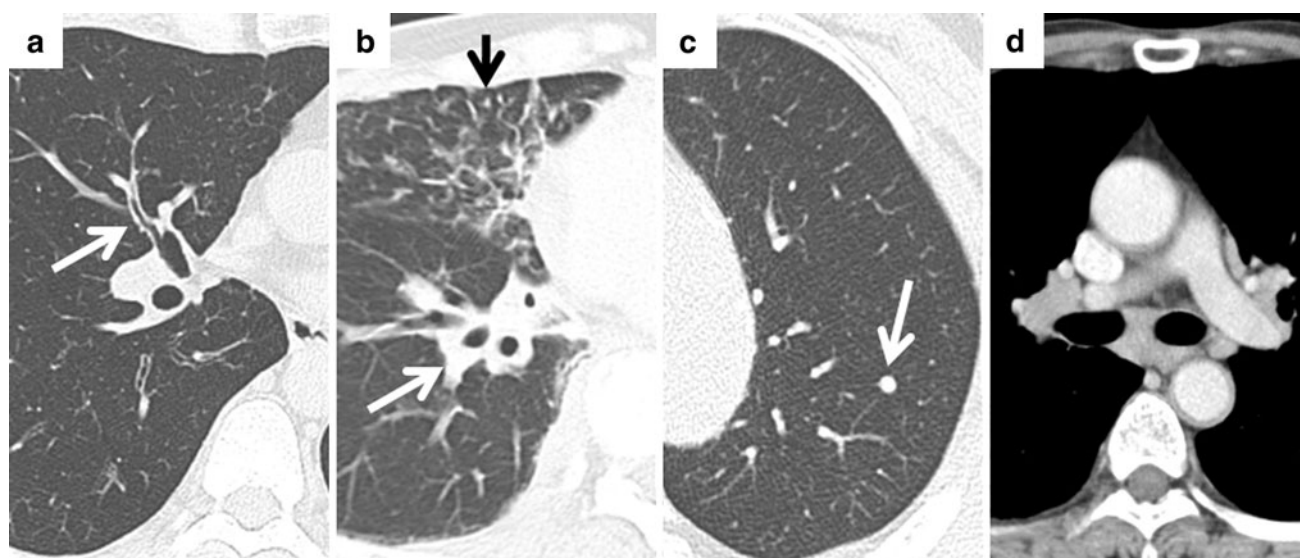
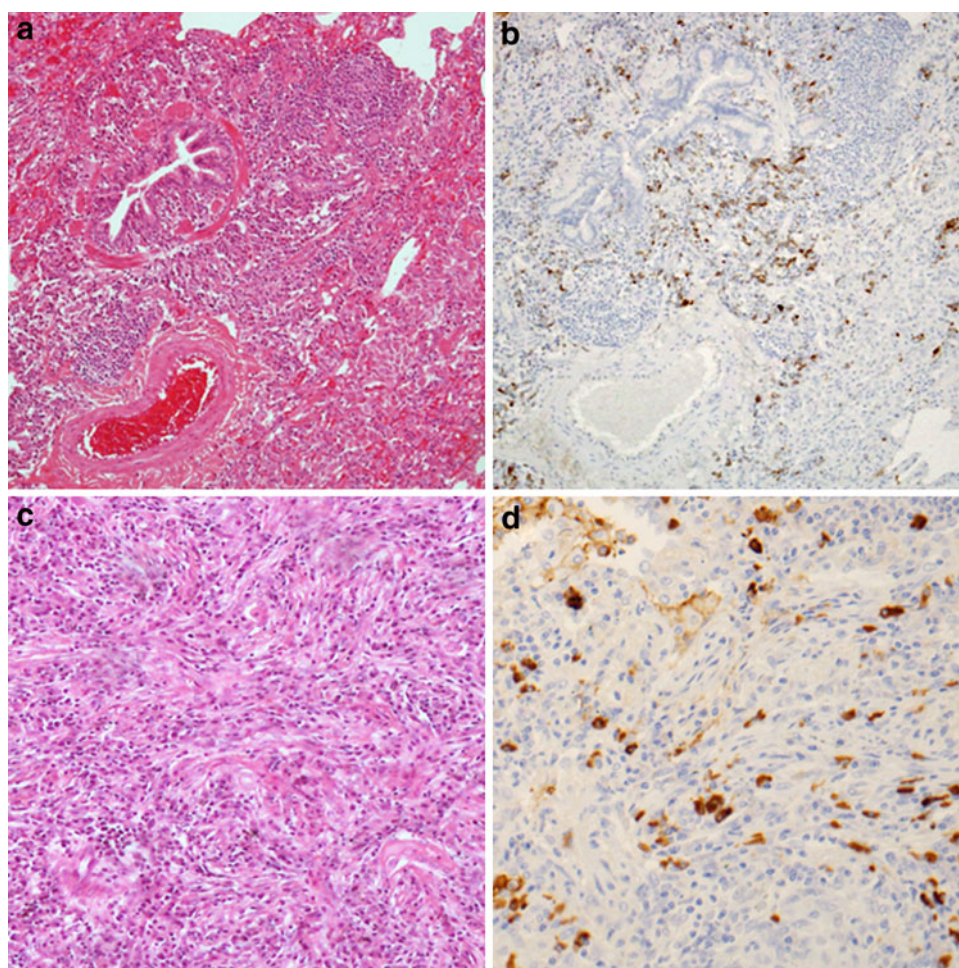


Fig. 1 Chest computed tomography (CT) findings, showing **a** bronchial thickening (*white arrow*) in the right upper lobe; **b** interlobular thickening (*black arrow*) in the right middle lobe, and thickening of

the bronchovascular bundle (*white arrow*) in the right lower lobe; **c** a solid small nodule (*white arrow*) in the left upper lobe; and **d** mediastinal lymphadenopathy

Fig. 2 Histopathology of pulmonary lesions, showing **a** peri-bronchial inflammation with lymphocytes (H&E, $\times 100$ original magnification); **b** increased numbers of IgG4-positive plasma cells among the inflammatory infiltrates (IgG4, $\times 100$); **c** fibrosis with a storiform pattern (H&E, $\times 200$); and **d** infiltrates of IgG4-positive plasma cells among proliferating fibroblasts. (IgG4, $\times 200$)



of Japanese aged around 60 years, including individuals with cedar pollinosis, is about 20–30% [27]. Thus, the frequency of allergic symptoms such as rhinitis and asthma in patients with MD, especially those with P-MD, was higher than that in the general Japanese population.

Allergic rhinitis has been found to be more common in patients with MD than in those with typical Sjögren's syndrome (40.6 vs. 14.1%) [7]. The reason for the higher incidence of allergy is unclear, but the expression of Th2 cytokines and regulatory cytokines was found to be upregulated in lesions containing IgG4-positive plasma cell infiltrates [9]. Th2 cytokines play important roles in the pathogenesis of allergic disorders such as allergic rhinitis and bronchial asthma, suggesting that the pathogenesis of allergic disorders and that of IgG4-related diseases are closely related [28].

We found that most of our patients with IgG4-MD had elevated serum concentrations of total protein, IgG, IgG4, and IgE, and that patients with P-MD showed significantly higher concentrations of total protein, IgG, IgG4, and sIL-2R than those with L-MD. Moreover, patients with P-MD tended to show disorders in many organs and had hypocomplementemia. The mean serum IgG and IgG4 concentrations in patients with AIP and pulmonary involvement have been reported to be 2747 and 1185 mg/dl, respectively [25]. Hypocomplementemia has been observed in 17–36% of patients with AIP and has been regarded as being associated with disease activity [29]. These reports and our results suggest that disease activity is high in patients with MD or AIP with pulmonary involvement, and that pulmonary involvement may be associated with disorders of other organs. Conversely, the combination of hypergammaglobulinemia and hypocomplementemia may indicate multi-organ involvement, including pulmonary lesions, in MD. Careful investigations are necessary to diagnose conditions associated with IgG4-related disease.

Of our 25 patients, 13 (52%) had IgG4-related abnormalities on chest CT, including abnormalities in the bronchi, bronchovascular bundles, alveolar septa, pleura, and hilar lymph nodes. Findings of hilar and mediastinal lymphadenopathy on CT were supported by Ga-67 and/or FDG-PET accumulation. Lung lesions have been reported in 51.2% of patients with AIP, with hilar lymphadenopathy in 78.3% [30]. Our findings suggest that Ga-67 scintigraphy and FDG-PET may be useful tools for detecting the presence and distribution of these lesions [31]. As their radiologic features and distributions resembled those of sarcoidosis [25, 32], we measured serum angiotensin-converting enzyme (ACE) concentrations in our P-MD group and serum IgG4 in 13 patients with sarcoidosis. We found that the mean serum ACE concentration in the P-MD group was 13.8 ± 4.2 IU/ml, within the normal range of

7.0–25.0 IU/ml, and the mean concentration of serum IgG4 in the sarcoidosis patients was 41.2 ± 23.2 mg/dl, also within the normal range. BALF in the P-MD group showed lymphocyte predominance, but, in contrast to the findings in patients with sarcoidosis, the CD4/CD8 lymphocyte ratio was not altered. Measurements of serum ACE and IgG4 concentrations and CD4/CD8 in BALF should be sufficient to distinguish IgG4-MD from sarcoidosis when either disease is suspected on chest CT or radioisotope images.

Histopathological examination of transbronchial or surgical lung biopsy samples showed infiltrates of lymphocytes and plasma cells in the bronchial mucosa and peri-bronchovascular bundles. Findings characteristic of AIP, such as obliterative phlebitis and storiform fibrosis, were seen only in the 1 patient (patient 5) with inflammatory pseudotumor of the lung. A study of 21 patients with IgG4-related lung and pleural disease showed that irregular fibrosis and obliterative vascular changes were observed in almost all the solid nodules and pleural lesions [33]. Although two of our patients (patients 1 and 6) showed chest CT abnormalities with abundant infiltration of IgG4-positive plasma cells in their salivary glands, biopsy samples of the respiratory apparatus showed few IgG4-positive plasma cells (<10 cells per high-power field [HPF], with each having a mean of 8 cells per HPF) among many lymphocytes with tissue fibrosis. One of these patients (patient 1) had received short-term oral steroid therapy for bronchial asthma 1 month before bronchial biopsy, suggesting that short-term steroid therapy had removed IgG4-positive plasma cells from the bronchial mucosa. In the other patient (patient 6), the infiltrative shadow on CT disappeared spontaneously within a few weeks after transbronchial lung biopsy. Spontaneous remission of lesions has been observed in patients with IgG4-related diseases. Patients with AIP and duodenal papilla negative for IgG4 (mean, 6.6 cells per HPF, range 0–17 cells per HPF) appeared to have a high frequency of remission without steroid therapy [34], suggesting that our patient 6 may have presented with the same clinical condition (i.e., AIP and duodenal papilla negative for IgG4).

Corticosteroid therapy has been regarded as effective for IgG4-related disease [35, 36]. Although all of our patients who received steroid therapy responded to treatment, 2 developed either extra-glandular or extra-pulmonary lesions several years after the initiation of the steroid therapy.

To our knowledge, this report is the first to describe respiratory involvement associated with IgG4-MD. We found that almost 50% of IgG4-MD patients presented with abnormal findings on chest CT, and that IgG4-MD patients with pulmonary disorders frequently had allergic symptoms and presented with marked hypergammaglobulinemia

when compared with IgG4-MD patients with lesions limited to the lacrimal and/or salivary glands. Furthermore, the initial clinical manifestations of pulmonary disease differed in patients with IgG4-MD and those with AIP, although imaging and laboratory findings were the same. Pulmonary physicians should include IgG4-related disease in the differential diagnosis of asthmatic patients with hypergammaglobulinemia. Rheumatologists and hematologists should perform tests for respiratory lesions when patients with MD present with persistent cough.

In conclusion, pulmonary involvement associated with IgG4-MD is not rare. The careful diagnosis of IgG4-related MD should exclude other similar diseases, such as sarcoidosis, bronchial asthma, Castleman's disease, Sjögren's syndrome, and malignant lymphoma. As IgG4-related disease is still a developing entity, the details of each organ condition should be clarified.

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Conflict of interest None.

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