

IgG4-related Lung and Pleural Disease: A Clinicopathologic Study of 21 Cases

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Abstract: Immunoglobulin G4 (IgG4)-related disorders can occur in the respiratory system. However, the clinicopathologic characteristics have not been well clarified. In this study, we examined clinical and pathologic features of, and follow-up data on, IgG4-related lung and pleural lesions. The patients group consisted of 17 males and 4 females with an average age of 69 years (range: 42 to 76). Pulmonary lesions in 16 patients and pleural lesions in 5 patients were examined. Histologically, all lesions showed diffuse lymphoplasmacytic infiltration. Irregular fibrosis and obliterative vascular changes were more common in solid areas. Nine cases (43%) had eosinophilic infiltration with more than 5 cells per high-power field. Immunostaining revealed numerous IgG4-positive plasma cells in inflamed areas. Sclerosing inflammation was distributed with intrapulmonary connective tissue. Pulmonary lesions showed a variety of morphologic changes according to the predominant area of inflammation. Serum IgG4 concentrations were elevated in 9 of 11 patients tested (average 6.9 g/L; range 0.3 to 18.0 g/L; normal range < 1.35 g/L). Extra-pulmonary and extra-pleural IgG4-related lesions were identified in 9 patients (43%), and developed simultaneously or asynchronously during follow up. All patients treated with steroids responded, but some radiologic abnormalities remained in 3 patients. Interestingly, 1 patient was found to have a primary adenocarcinoma against a background of IgG4-related lung disease during follow up. In conclusion, IgG4-related diseases show a greater variety of pulmonary and pleural lesions than previously thought. It is important, therefore, to know the morphologic variety and clinicopathologic characteristics of this disorder.

Key Words: IgG4, inflammatory pseudotumor, interstitial pneumonia, autoimmune pancreatitis, lung cancer

(*Am J Surg Pathol* 2009;33:1886–1893)

Recently, much attention has focused on immunoglobulin G4 (IgG4)-related diseases. In 2001, Hamano et al⁷ reported that patients with sclerosing pancreatitis,

also called autoimmune pancreatitis, have high-serum IgG4 concentrations. IgG4-related lesions similar to autoimmune pancreatitis have also been identified in the bile duct (sclerosing cholangitis),²² salivary gland (chronic sclerosing sialadenitis or Küttner tumor),¹⁴ lacrimal gland (chronic sclerosing dacryoadenitis),² retroperitoneum (retroperitoneal fibrosis),⁸ and aorta (inflammatory aneurysm).¹³ Irrespective of the organ affected, IgG4-related diseases show similar clinicopathologic features. IgG4-related diseases are clinically characterized by a common occurrence in adults, male predominance, elevation of the serum IgG4 concentration, and frequent association with IgG4-related conditions in other organs.¹ The affected organs are focally or diffusely swollen, and sometimes show tumorous lesions (inflammatory pseudotumor).²² IgG4-related diseases are pathologically characterized by diffuse lymphoplasmacytic infiltration with marked interstitial fibrosis, eosinophilic infiltration, and obliterative phlebitis of the vein branches.^{2,5,8,13,14,22} In addition, numerous IgG4-positive plasma cells can be identified by immunostaining.^{2,5,8,13,14,22} Usually, IgG4-related diseases are effectively treated with corticosteroid.¹

There are several reports with regard to IgG4-related lung diseases.^{16,18,23} Recently, we reported that IgG4-related pulmonary disease can show a variety of radiologic abnormalities.⁹ However, the pathologic characteristics of IgG4-related pulmonary and pleural lesions have not been well documented. Another issue is the relationship between IgG4-related disease and malignancy. Cheuk W et al⁴ suggested that IgG4-related sclerosing dacryoadenitis can progress to malignant lymphoma. In addition, there have been several reports of autoimmune pancreatitis associated with pancreatic cancer.^{6,10} However, no such associations have been documented in pulmonary lesions.

In this study, we examined the clinicopathologic features of 21 patients with IgG4-related pulmonary or pleural disease to characterize this newly designated disease entity.

PATIENTS AND METHODS

Patients

A total of 21 cases were selected from the pathology files of the Division of Pathology, Kanazawa University

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Financial support: nothing to declare

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Hospital, and affiliated hospitals in Japan, and the consultation file of 1 author (Y.Z.) for the period between 1990 and 2009. The cases after 2004 were originally diagnosed as IgG4-related lung and pleural disease. The cases before 2004 were searched on the pathology files by the term of inflammatory pseudotumor, and retrospectively rediagnosed as IgG4-related disease on the basis of characteristic histologic features described below. All patients underwent histologic examinations of lung or pleural tissues. The patients group consisted of 17 males and 4 females with an average age of 69 years (range: 42 to 76 y). Nine of the 21 patients underwent surgical resection because they were suspected of having or to exclude neoplasm (2 patients, lobectomy; 7 patients, partial resection). Eight and 4 patients underwent video-assisted thoracic surgery (VATS) and a biopsy (1 needle and 3 bronchoscopic), respectively. Pathologic specimens were used for the study. Eight patients were used in our earlier study.²³

Classification of IgG4-related Pulmonary and Pleural Lesions

Out of 21 patients, 16 had pulmonary lesions and 4 had pleural lesions. The remaining patient had both intrapulmonary and pleural lesions, but was treated as a pleural case because only the pleural specimen was available for pathologic examination.

On the basis of radiologic features, pulmonary lesions were classified into 4 subtypes⁹: (1) Solid nodular type having a solitary nodule resembling primary lung cancer; (2) Bronchovascular type showing a thickening of bronchovascular bundles and interlobular septa; (3) Alveolar interstitial type showing a diffuse reticular shadow in both lower lobes with bronchiectasia resembling interstitial pneumonia; and (4) Round-shaped ground-glass opacity (GGO) type characterized by multiple round-shaped GGO resembling bronchioloalveolar carcinoma. Regarding pleural lesions, 3 patients had nodular lesions in the visceral pleura; whereas, nodular lesions in 2 patients involved the parietal pleura and chest wall.

Pathologic Examination

Diagnosis of IgG4-related Lung and Pleural Diseases

Formalin-fixed and paraffin-embedded specimens were prepared for histopathologic and immunohistochemical examinations. Sections 4 μ m thick were cut for hematoxylin and eosin, elastica van Gieson, and immunohistochemical staining. IgG4-related disease was diagnosed on the basis of the pathologic features reported to date, such as diffuse lymphoplasmacytic infiltration, irregular fibrosis, occasional eosinophilic infiltration, and obliterative vasculitis.^{2,14,22,23} Some IgG4-positive plasma cells can be detected in several inflammatory disorders; however, the diffuse infiltration of numerous IgG4-positive plasma cells is characteristic of IgG4-related disease. In addition, it has been suggested that an elevated IgG4-positive to IgG-positive plasma cell ratio (IgG4/IgG ratio) is helpful in distinguishing IgG4-related from

non-IgG4-related inflammatory conditions. Our earlier studies revealed that most IgG4-related diseases had an IgG4/IgG-positive plasma cell ratio of more than 30%.^{14,22,23} In contrast, the ratio was less than 10% in non-IgG4-related diseases. Therefore, we diagnosed with IgG4-related lesions, patients having characteristic hematoxylin and eosin findings, diffuse IgG4-positive plasma cell infiltration, and an IgG4/IgG-positive cell ratio greater than 30%.

Immunohistochemistry

Immunostaining of IgG and IgG4 was performed with an Autostainer (HX System Benchmark, Ventana Medical Systems, Tucson, AZ) as per the manufacturer's instructions. Primary antibodies used were a rabbit polyclonal antibody against human IgG (Dako Cytomation, Glostrup, Denmark) and a mouse monoclonal antibody for human IgG4 (Zymed Laboratory, Inc, San Francisco, CA). Sections were pretreated with proteinase (IgG and IgG4). In cases associated with primary lung cancer, immunostaining of cytokeratin (AE1/3) was also performed using a mouse monoclonal (Dako Cytomation).

In Situ Hybridization

In situ hybridization of κ -chain and λ -chain was performed with HX System Benchmark (Ventana Medical Systems). Specific probes for κ -chain and λ -chain were obtained from Ventana Medical Systems. Specimens of gastric marginal zone B-cell lymphoma (MALToma) and tonsillitis were used as positive and negative controls, respectively.

Serological Examination

Serum concentrations of IgG and IgG4 were examined in 13 and 11 patients, respectively.

RESULTS

Clinical Features

Clinical features of the patients are summarized in Table 1. No significant difference was observed among the subtypes of lesions. Out of 21 patients, 17 (81%) were male. All patients were adults. Nine patients (43%) had allergic predispositions: 6 with bronchial asthma, 1 with allergic rhinitis, 1 with drug allergy, and 1 with chronic sinusitis. Ten patients had subjective pulmonary symptoms like cough and bloody sputum. In contrast, 11 patients were found to have pulmonary or pleural lesions during a routine medical check or work up for extrapulmonary IgG4-related diseases. There was no particular correlation between subjective symptoms and subtypes of IgG4-related lung and pleural lesions.

Nine patients (43%) had IgG4-related diseases in other organs. Autoimmune pancreatitis was observed in 3 patients; chronic sclerosing sialadenitis in 4; retroperitoneal fibrosis in 2; a renal lesion in 1; and a bile duct lesion in 1. One patient was found to have 5 extrapulmonary lesions (pancreatitis, cholangitis, sialadenitis, retroperitoneal fibrosis, and a renal lesion)

TABLE 1. Clinical Features of 21 Patients With IgG4-related Lung or Pleural Lesions

	Pulmonary Lesions				
	Nodular (n = 9)	Bronchovascular (n = 4)	Interstitial (n = 2)	Round GGO (n = 1)	Pleural Lesions (n = 5)
Average age (range)	60 (43-72)	57 (42-70)	66 (59-73)	43	62 (49-76)
Sex (M/F)	6/3	3/1	2/0	1/0	5/0
Pathological specimen (surgical/VATS/biopsy)	7/1/1	1/2/1	0/1/1	0/1/0	1/3/1
Allergic disorders	3 (33%)	4 (100%)	1 (50%)	0	1 (20%)
Extrapulmonary lesions	2 (22%)	3 (75%)	1 (50%)	0	3 (60%)
High-serum IgG concentration	3/4 (75%)	4/4 (100%)	1/1 (100%)	1/1 (100%)	3/3 (100%)
High-serum IgG4 concentration	1/1 (100%)	3/3 (100%)	2/2 (100%)	1/1 (100%)	2/4 (50%)
Association with premalignant or malignant lesions within IgG4-related lesions	0	1 (AAH)	1 (adenoca)	0	0

AAH indicates atypical adenomatous hyperplasia; adenoca, adenocarcinoma; IgG4, immunoglobulin G4; interstitial, alveolar interstitial type; Nodular, solid nodular type; round GGO, round-shaped ground-glass opacity type; VATS, video-assisted thoracic surgery.

asynchronously during follow up. Extrapulmonary and extrapleural lesions in 4 of 9 patients occurred before the pulmonary episodes (6 mo to 5 y before). In contrast, 1 patient showed extrapulmonary lesions in the kidney, retroperitoneum and salivary glands 6 years after the pulmonary episode. Extrapulmonary and extrapleural lesions in the remaining 4 patients were found at the same time as the pulmonary and pleural lesions.

Serum Concentrations of IgG and IgG4

Thirteen and 11 patients underwent serological examinations of IgG and IgG4, respectively. All patients except 1 (a solid nodular type) had high IgG concentrations (average 24.6 g/L; range 15.6 to 41.1 g/L; normal range 8.7 to 17.0 g/L). IgG4 concentrations were elevated in all patients except 2 (both pleural lesions) (average 6.9 g/L; range 0.3 to 18.0 g/L; normal range < 1.35 g/L).

Pathologic Features

Macroscopic Findings

Surgical specimens of the solid nodular type showed relatively discrete nodular lesions gray in color. Nodules ranged from 0.9 to 5.0 cm. In 6 of 9 cases, the lesions were located in the peripheral lung parenchyma, whereas in 3 cases the lesions involved the hilar bronchus and were associated with obstructive pneumonia. The VATS specimen of an alveolar interstitial-type case revealed firm lung parenchyma and pleural thickening. Specimens of the bronchovascular type showed focal irregular fibrosis. Seven VATS specimens taken from a patient with the

round-shaped GGO type revealed ill-defined nodular lesions up to 1.5 cm in diameter. Pleural specimens showed nodular pleural thickening with fibrous extension into subpleural connective tissue (in cases of parietal lesions) and lung parenchyma (in cases of visceral lesions).

Microscopic Findings

All types of lesions were histologically characterized by diffuse lymphoplasmacytic infiltration. Irregular fibrosis was also a characteristic feature especially in pulmonary lesions of the solid nodular type and pleural lesions.

In solid nodular lesions, alveolar structures were severely distorted because of diffuse sclerosing inflammation (Figs. 1A, B). Lymphoplasmacytic infiltration was also identified in the alveolar interstitium around or away from the nodular lesions. Sclerosing inflammation was observed in the wall of the large bronchus in patients with hilar lesions (Fig. 1C). Nodular sclerosing inflammation involving bronchial glands was a characteristic feature. Inflammation occurred within the bronchial wall, and did not involve the bronchial epithelium.

In the bronchovascular type, inflammatory cells were observed in pulmonary connective tissue including the bronchovascular bundles, alveolar interstitium, interlobular septa, and pleura (Figs. 1D–G). Interestingly, severe inflammatory cell infiltration was observed around bronchi with mucoid impaction in a patient with bronchial asthma (Fig. 1H). In addition, 1 case was associated with

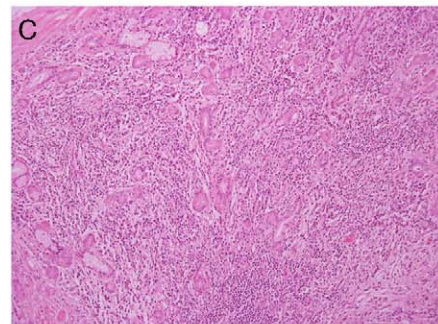
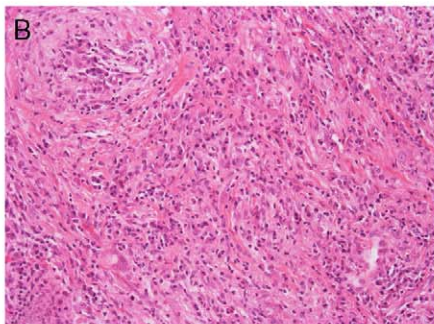
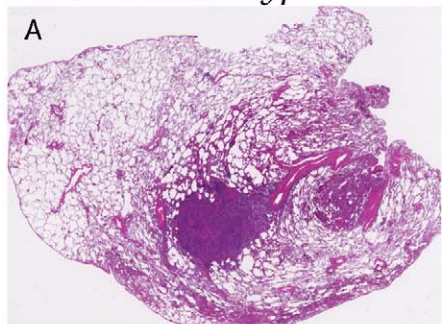
FIGURE 1. Histopathology of immunoglobulin G4 (IgG4)-related lung disease. A, A solid nodular-type lesion shows a relatively discrete mass. The interstitium around the nodule is slightly thickened. (Hematoxylin and eosin (H&E); loupe view); (B) The nodule showed diffuse lymphoplasmacytic infiltrates with fibrosis. (H&E; $\times 100$); (C) Sclerosing inflammation involves the bronchial glands. (H&E, $\times 100$); (D–F) Inflammatory cell infiltration is observed around the bronchus and bronchioles, and in the alveolar interstitium. (H&E; D and E, $\times 100$; F, $\times 200$); (G) Inflammatory cells consist of lymphocytes, plasma cells, and some eosinophils. (H&E; $\times 400$); (H) Inflammation is pronounced in the bronchus with a mucus plug. (H&E; $\times 40$); (I) Many IgG4-positive plasma cells are identified. (IgG4 immunostaining; $\times 400$); (J) The alveolar interstitium shows relatively homogeneous thickening. (H&E; $\times 100$); (K) Lymphocytes and plasma cells infiltrate the alveolar interstitium. (H&E; $\times 400$); (L) IgG4-positive plasma cells are present in the alveolar interstitium. (IgG4 immunostaining; $\times 400$).

an atypical adenomatous hyperplasia (AAH) measuring 0.7 cm.

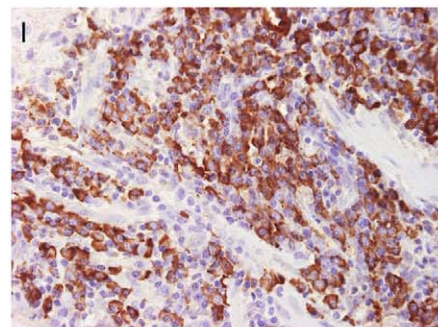
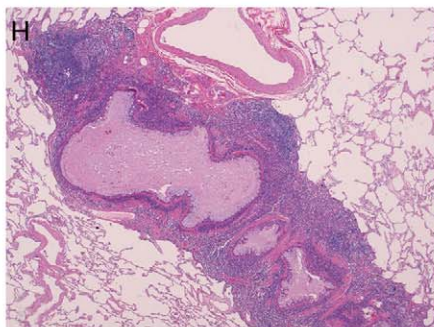
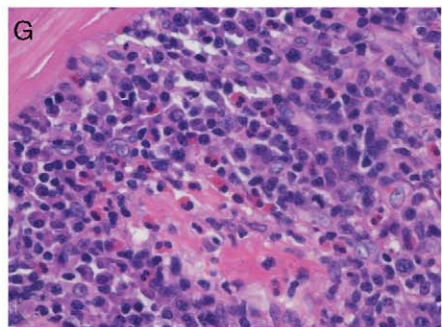
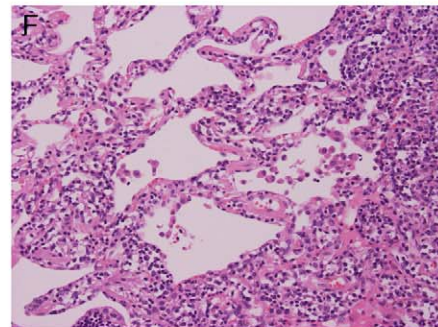
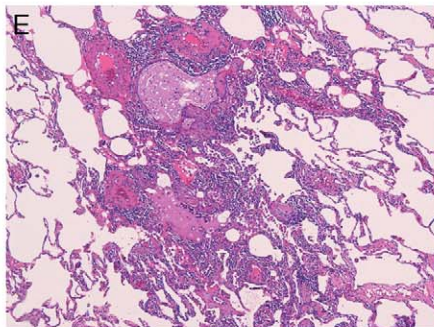
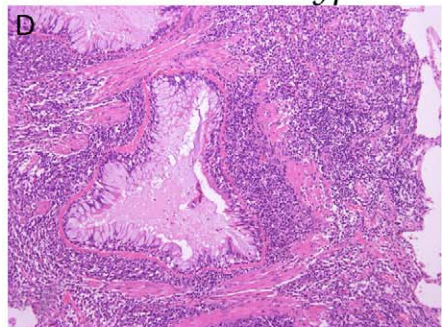
In alveolar interstitial and round-shaped GGO types, lymphoplasmacytic infiltration was observed in

the alveolar interstitium (Figs. 1J, K). Inflammation and thickening of the alveolar interstitium were relatively monotonous, and these histologic features corresponded to the nonspecific interstitial pneumonia (NSIP) pattern.

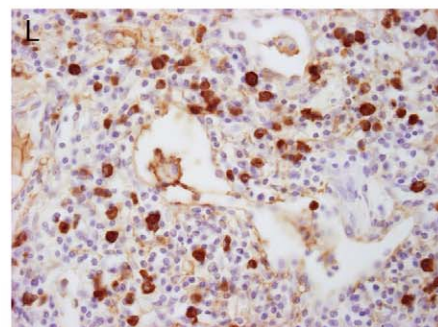
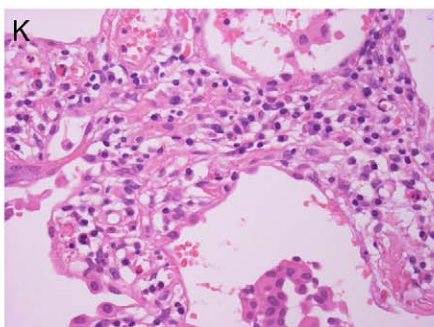
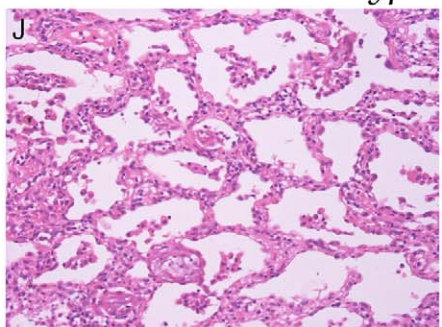
Solid nodular type



Bronchovascular type



Alveolar interstitial type



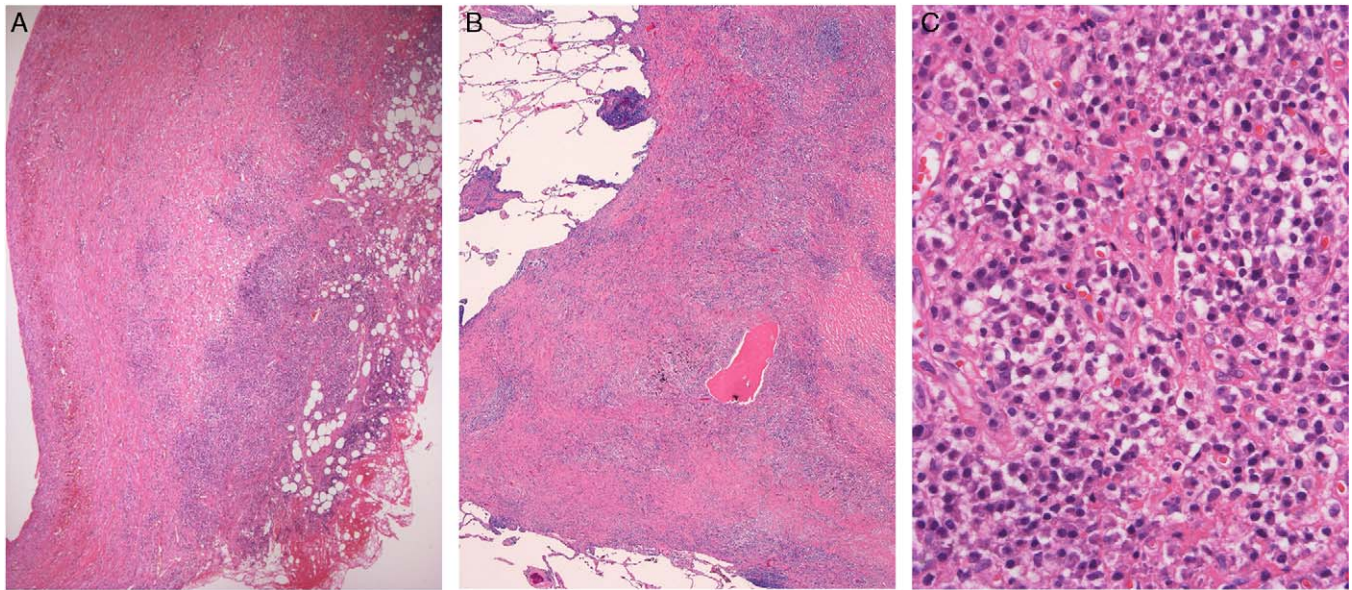


FIGURE 2. Histopathology of immunoglobulin G4-related pleural lesions. A, Parietal pleura shows nodular thickening, at the deep part of which inflammation extends into adipose tissue. [Hematoxylin and eosin (H&E); $\times 20$]; (B) Sclerosing inflammation of visceral pleura involves subpleural lung parenchyma. (H&E; $\times 20$); (C) Inflammatory cells consist mainly of lymphocytes and plasma cells. (H&E; $\times 200$). [full color online](#)

Regarding pleural lesions, pleura were severely thickened by diffuse sclerosing inflammation (Fig. 2). Fibrosis was more pronounced on the side of the pleural cavity. In the parietal lesion, sclerosing inflammation extended into subpleural fibrous and adipose tissue. Visceral pleural lesions severely involved subpleural lung parenchyma. Those parenchymal lesions resembled the solid nodular type.

Eosinophilic infiltration (more than 5/high-power field) was identified in 9 cases (43%) (Figs. 1G, K). Lymphoid follicles were identified in 11 cases (52%). The presence and absence of those 2 features were not related to the subtype of lesion. Obliterative phlebitis was more commonly observed in the pulmonary lesions of the solid nodular type and pleural lesions than the other 3 subtypes (93% in the solid nodular type and pleural lesions; 14% in other subtypes; $P < 0.001$) (Fig. 3A). Similarly, obliterative arteritis (sclerosing inflammation involving arterial branches) was identified in 50% of the solid nodular type and pleural lesions, but not in any cases of other subtypes ($P = 0.01$) (Fig. 3B). Several multinucleated giant cells were identified in the alveolar space in 5 cases (2 solid nodular, 1 alveolar interstitial, and 2 pleural cases), although a discrete epithelioid granuloma was not identified in any cases. Neutrophilic infiltration was rare.

Immunohistochemistry and In Situ Hybridization

IgG4 immunostaining revealed numerous IgG4-positive plasma cells distributed diffusely within the nodular lesion, and along with the alveolar interstitium, bronchovascular bundles, interlobular septa, and pleura (Figs. 1I, L). Proportions of IgG4-positive plasma cells among IgG-positive plasma cells were 39% to 88%.

Interestingly, numerous IgG4-positive plasma cells were identified in the alveolar interstitium of AAH. In situ hybridization of immunoglobulin light chains showed no clonal nature in any cases.

Treatment and Follow-up Data

Out of 9 patients with the nodular type, 8 underwent surgical resection on suspicion of pulmonary tumors. No patients have had any recurrent pulmonary lesions to date. The remaining case was diagnosed by bronchoscopic biopsy, and effectively treated with corticosteroid. Out of 4 patients with the bronchovascular type, 3 were treated effectively with corticosteroid, although several reticular shadows remained in 1 patient. The remaining patient was not treated because of an absence of pulmonary symptoms. The patient with the round-shaped GGO type was treated with a low dose of steroids after VATS. The treatment slightly diminished the size of remaining lesions.

Both of the patients with alveolar interstitial-type lesions were treated with corticosteroid after histologic diagnosis. One patient responded completely to the therapy. The other patient with more significant lesions also responded, but some of the radiologic changes remained. In addition, this patient was found to have a nodular lesion within the reticular shadow in the right lower lobe 2 years after starting steroid therapy. Bronchoscopic biopsy revealed a moderately differentiated adenocarcinoma. The specimen from the right lower lobectomy showed a nodular lesion 2.4 cm in diameter against a background of interstitial pneumonia and mild emphysema. The tumor was a histologically moderate differentiated adenocarcinoma of mixed subtypes. It was pathologically stage 3A (pT1N2M0).

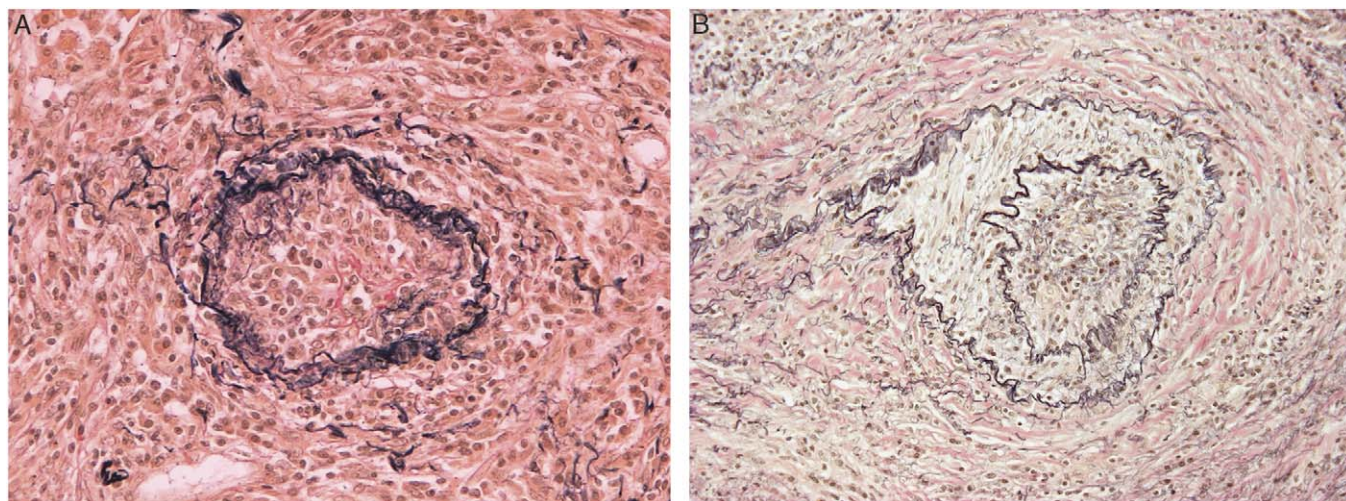


FIGURE 3. Vascular changes of immunoglobulin G4-related lung disease. A, Obliterative phlebitis. (Elastica van Gieson; $\times 400$); (B) Obliterative arterial lesion. (Elastica van Gieson; $\times 200$). [full color online](#)

Immunostaining revealed many IgG4-positive plasma cells within a tumor and a background of interstitial pneumonia (Fig. 4).

Regarding the pleural lesions, 3 of 4 patients underwent surgical resection. The remaining patient, in whom the lesion on the parietal pleura was diagnosed on the basis of a needle biopsy, did not receive any treatment because he did not have symptoms.

DISCUSSION

The results obtained can be summarized as follows.

(1) IgG4-related pulmonary lesions show a variety of

morphologic changes, and can be classified into 4 subtypes. (2) There was no significant clinical difference between the subtypes. (3) All the lesions showed similar histologic features, but the incidence of obliterative vascular changes was more common in the solid nodular pulmonary lesions or pleural lesions. (4) Consistent with other IgG4-related disorders, extrapulmonary and extra-pleural lesions were common. (5) Steroid therapy was effective, but some radiologic abnormalities remained. (6) Two cases were associated with primary lung cancer or a premalignant lesion.

There were some histologic differences regarding obliterative vascular changes among subtypes. However,

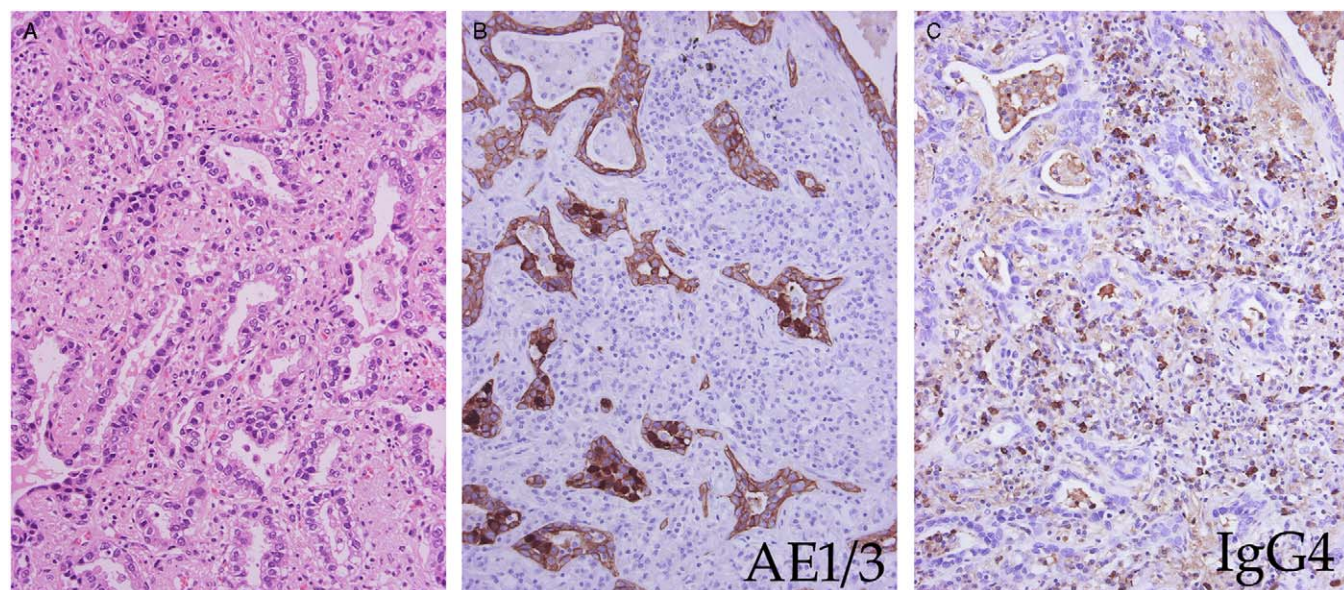


FIGURE 4. Histopathology of adenocarcinoma arising against a background of immunoglobulin G4-related lung disease. A, Adenocarcinoma shows the acinar pattern. (Hematoxylin and eosin, $\times 200$); (B and C) Immunoglobulin G4-positive plasma cells are intermixed with carcinoma cells. (Immunostaining, $\times 100$; at almost the same fields). [full color online](#)

this is probably because the diffuse sclerosing inflammation was more pronounced in the solid nodular type of pulmonary lesions and pleural lesions. It is important to know whether the subtypes of lung and pleural lesions reflect different pathologic processes. Histologic features except for vascular changes, clinical characteristics and the association with extrapulmonary lesions did not differ among subtypes. Therefore, all lesions could be different manifestations of a single disease entity named IgG4-related lung and pleural disease. It is of interest whether different morphologic types of pulmonary lesions can occur or only the same type of lesions can develop at the time of recurrence.

Distinguishing multicentric Castleman disease from IgG4-related lung disease is important because the 2 differ in their responsiveness to steroids. Histologically, immunostaining of IgG4 would be useful; however, the degree of infiltration by IgG4-positive plasma cells in classical Castleman disease is still unclear. Careful examination is necessary to discriminate the 2 diseases on the basis of a lymph node biopsy, because IgG4-related lymphadenopathy sometimes shows Castleman-like features.³ Serologically, interleukin-6 and IgG4 would be useful for a differential diagnosis. However, Yamamoto et al²⁰, recently reported borderline cases not clearly classified as either into Castleman disease or IgG4-related disease. Another report also described elevated serum IgG4 concentrations in patients with multicentric Castleman disease.¹¹ Further examination using larger numbers of cases of multicentric Castleman disease and IgG4-related disease seems mandatory.

Lymphomatoid granulomatosis (LYG) is another differential diagnosis, because IgG4-related lung disease morphologically resembles grade 1 lesion of LYG with the presence of interstitial inflammation and obliterative arterial changes.^{15,21} Features suggestive IgG4-related lung disease rather than LYG include lack of atypical cells, a high percentage of IgG4-positive plasma cells, and negative for Epstein-Barr virus-encoded small RNA.^{15,21} It is also of interest that the alveolar interstitial type showed the NSIP pattern. Immunostaining of IgG4 should be recommended, when we diagnose NSIP with unusual histologic features like prominent eosinophilic infiltration, obliterative vascular changes, or lymph follicle formation despite the absence of extrapulmonary autoimmune disorders. In addition, it is another important issue whether or not IgG4-related disease can also manifest usual interstitial pneumonia or desquamative interstitial pneumonia patterns.

Regarding the relationship to inflammatory pseudotumor, we earlier reported that hepatic inflammatory pseudotumor can be classified into 2 types: IgG4-related (lymphoplasmacytic) and non-IgG4-related (fibrohistiocytic) types.²⁵ IgG4-related lymphoplasmacytic type histologically corresponded to so-called plasma cell granuloma. We speculate this classification can be applied for pulmonary inflammatory pseudotumor.²³ That is, a part of, but not all, pulmonary inflammatory pseudotumors would be included in IgG4-related lung disease. It is more important to discriminate IgG4-related disease from inflammatory myo-

fibroblastic tumor. Inflammatory myofibroblastic tumor is different from IgG4-related disease in true neoplastic nature and the presence of fascicular proliferation of spindle cells. The number of IgG4-positive plasma cells is also useful for this discrimination. Interestingly, however, we have found a case of typical inflammatory myofibroblastic tumor of the lung associated with many IgG4-positive plasma cells.

The radiologic features of the bronchovascular type resembled sarcoidosis.¹² Serum angiotensin converting enzyme levels would be useful for distinguishing the 2, because there has been no report of a patient with IgG4-related disease and an elevated level of angiotensin converting enzyme to the best of our knowledge. Epithelioid granuloma histologically seems most important for this differential diagnosis. IgG4-related disease is rarely associated with granulomas, but they are usually small and vague, and histologically different from the granulomas typically observed in sarcoidosis. Conversely, diffuse lymphoplasmacytic infiltration is rare in cases of sarcoidosis. However, it might be difficult to differentiate the 2 by a bronchoscopic biopsy. Interestingly, Tsushima et al¹⁹ recently reported that IgG4 levels in bronchoalveolar lavage were also higher in patients with IgG4-related lung disease than those with sarcoidosis. They suggested that some patients with IgG4-related lung disease had a small airway limitation on pulmonary function testing.¹⁹

Long-term follow-up data on IgG4-related diseases are still lacking. But, it was reported that several patients with autoimmune pancreatitis had pancreatic cancer.^{6,10} In this study, 2 patients had AAH or primary lung cancer. It seems difficult at this point to conclude that IgG4-related disease increases the risk of pulmonary adenocarcinoma. Especially, because IgG4-related disease usually occurs in adult patients, careful analysis is necessary to conclude this issue. However, it should be noted that the adenocarcinoma developed within IgG4-related pulmonary lesions in 1 patient. In addition, there have been 2 reports describing a relationship between IgG4-related disease and malignant lymphoma.^{4,17} It is necessary to follow the history of patients with IgG4-related lung disease for longer to accurately reveal the risk of lung cancer and malignant lymphoma. After the steroid therapy, some radiologic features remained. This is probably because the lungs contain air. Fibrosis could be more pronounced in an air-containing organ compared with a solid organ like the pancreas.

The pathologic features of large bronchi were characteristic. Sclerosing inflammation involved bronchial glands. Despite severe inflammation, the bronchial epithelium was relatively preserved. Those features resembled IgG4-related sclerosing cholangitis, in which bile ducts show diffuse, homogeneous, and transmural thickening like a tube.²² Th2-dominant immune reactions and activated regulatory T cells were involved in the pathogenesis of IgG4-related sclerosing cholangitis.²⁴ A similar pathologic process might be involved in the bronchial lesion. A high prevalence of allergic predisposition among the patients might be related to the Th2-dominant immune reaction in IgG4-related lung disease.

In conclusion, this study revealed clinicopathologic characteristics of IgG4-related pulmonary and pleural disorders. This disease entity shows a greater variety of lung and pleural lesions than previously thought. It is important, therefore, to know the morphologic variety and clinicopathologic characteristics of this disorder.

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