



Original contributions

# IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung

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Interstitial pneumonia;  
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**Summary** The association between IgG4 dysregulation and inflammatory pseudotumor (IPT) was first reported in sclerosing pancreatitis. Recently, we described IPTs of the liver and breast, into both of which many IgG4-positive plasma cells had infiltrated. In this study, we examined the clinical and histological features of 9 cases of IPT (histologically corresponding to plasma cell granuloma) of the lung with an emphasis on IgG4-positive plasma cell infiltration. The lesions were characterized histologically by dense lymphoplasmacytic infiltrates intermixed with fibrosis and, in some cases, prominent eosinophilic infiltration, irregular narrowing of bronchioles entrapped in nodules, and an interstitial pneumonia pattern at the boundaries of nodules. Obliterative phlebitis was easily found in all cases, and 5 lesions also had obliterative arteritis. Immunostaining revealed many IgG4-positive plasma cells diffusely distributed within nodules, and the ratios of IgG4-positive to other plasma cells were extraordinarily high. Of the 9 patients, 8 underwent surgical treatment and in 1 patient, lesion was diagnosed on transbronchial biopsy and effectively treated with corticosteroid. Two cases were associated with chronic sclerosing sialadenitis or lymphadenopathy, in which many IgG4-positive plasma cells were also identified by immunostaining. The clinicopathologic similarities between IPT of the lung and sclerosing pancreatitis suggest that IgG4-related immunopathologic processes might be involved in the pathogenesis of the pulmonary lesions.

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## 1. Introduction

Inflammatory pseudotumors (IPTs) occur in almost all major organs, including the lung [1-3]. An IPT is characterized histologically as an irregular proliferation of myofibroblasts intermixed with an infiltrate of inflammatory

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cells, mainly lymphocytes and plasma cells [1-3]. Currently, IPT is regarded as a heterogeneous disease and is subcategorized histologically into the following: (1) cellular type (inflammatory myofibroblastic tumor), (2) plasma cell-rich type (plasma cell granuloma), and (3) fibrohistiocytic type (with numerous macrophages or xanthoma cells) [1]. The possible involvement of viral infection and true neoplastic proliferation of mesenchymal or dendritic cells have been reported in some inflammatory myofibroblastic tumors [4,5], although little is known about the pathogenesis of the plasma cell granuloma type.

There is now increasing evidence for a close relationship between IPT and IgG4-positive plasma cells. Sclerosing pancreatitis, also called autoimmune pancreatitis or lymphoplasmacytic sclerosing pancreatitis [6-8], is a unique form of pancreatitis effectively treatable with corticosteroid [9]. Sclerosing pancreatitis is characterized by an irregular narrowing of the pancreatic duct and/or prominent swelling of the pancreatic parenchyma, occasionally presenting as a mass lesion corresponding to IPT of the pancreas [8,9]. More than 90% of patients with sclerosing pancreatitis have high serum IgG4 levels, and unnecessary operation due to an erroneous diagnosis of pancreatic carcinoma is now avoidable by measuring serum IgG4 [10]. In addition, many IgG4-bearing plasma cells are histologically demonstrable in the lesions [11]. On the basis of these clinicopathologic characteristics, sclerosing pancreatitis is now considered an IgG4-related disorder.

Recently, we reported IgG4-related IPTs in extrapancreatic tissues such as the liver and breast [11,12]. Interestingly, all of these lesions had histological features similar to those of sclerosing pancreatitis. Histologically, they were characterized by severe lymphoplasmacytic infiltrates with irregular fibrosis, scattered eosinophils, and obliterative phlebitis. Many IgG4-positive plasma cells were demonstrated. In addition, the patient with IPT of the breast presented a high serum concentration of IgG4 [12]. We hypothesized that IgG4 dysregulation was involved in the pathogenesis of these IPTs of the liver and breast, such as in sclerosing pancreatitis. This prompted us to study IPT of the lung (IPT-L) with regard to IgG4 dysregulation. In this study, we analyzed the involvement of IgG4-positive plasma cells in IPT-L and the clinicopathologic similarities between IPT-L and sclerosing pancreatitis. The goal of this study was to determine whether IPT-L is an IgG4-related disease.

## 2. Materials and methods

### 2.1. Case selection

Clinical and pathological features of 9 cases of IPT-L were examined. Seven cases of idiopathic interstitial pneumonia (IIP) were used as a disease control. All cases were collected from the files of the Pathology Departments

of Kanazawa University Hospital, Ishikawa Prefectural Central Hospital, Kouseiren Takaoka Hospital, and Fukui Saiseikai Hospital, Japan, the patients being seen between 1988 and 2004. The age and sex of the patients were as follows: IPT-L, 42 to 76 years, 5 men and 4 women; IIP, 52 to 65 years, 6 men and 1 woman.

IIP was chosen as a control because it is an idiopathic chronic inflammatory disorder suspected to involve immune-mediated processes. All IIP cases showed bilateral reticular shadows with or without ground-glass opacities, honeycombing, and decreased lung volumes on radiological images, and all patients underwent video-assisted partial lung resections for definitive diagnoses. Histological specimens of 5 cases showed patchy interstitial fibrosis with subpleural or paraseptal distribution. Interstitial fibrosis was temporally heterogeneous and contained fibroblastic foci and lymphoplasmacytic infiltrate. The remaining 2 cases showed interstitial chronic inflammation, consisting mainly of lymphocytes and plasma cells. Interstitial inflammation and fibrosis were relatively uniformly distributed without fibrous foci or a honeycomb pattern. The former 5 cases were considered usual interstitial pneumonia and the latter 2 nonspecific interstitial pneumonia with a cellular pattern.

### 2.2. Laboratory data

The following laboratory data of all IPT-L cases were analyzed: C-reactive protein,  $\gamma$ -globulin, IgG, antinuclear antibodies (ANAs), and tumor markers (carcinoembryonic antigen, neuron-specific enolase, squamous cell carcinoma antigen, and cytokeratin 19 fragment). Serum IgG4 levels were not measured.

### 2.3. Histological evaluation

Tissue samples from each surgically resected or biopsied specimen were fixed in neutral formalin and embedded in paraffin. Resected specimens of the left submandibular gland (case 1) and regional lymph nodes (cases 1 and 2) were similarly processed. More than twenty 4- $\mu$ m sections were cut from each paraffin block. Some of them were stained with hematoxylin-eosin and elastica-van Giesson, and the remaining sections were used for immunohistochemistry studies. The histological features were assessed by 2 pathologists (Y. Z. and Y. N.).

### 2.4. Immunohistochemistry staining for IgG, IgA, IgM, and IgG4

Immunostaining for IgG, IgA, IgM, and IgG4 was performed using mouse monoclonal antibodies against human IgG (Dako Cytomation, Glostrup, Denmark), human IgA (Dako), human IgM (Dako), and human IgG4 (ZYMED Laboratory, San Francisco, Calif). According to the data sheet, the antibody against IgG4 was confirmed to react specifically with the epitope expressed in the Fc region

**Table 1** Age, sex, lesion location, nodule size, treatment, and complications in IPT-L

| Case | Age (y) | Sex | Location                      | Size (cm) <sup>a</sup> | Treatment                 | Complication                                     |
|------|---------|-----|-------------------------------|------------------------|---------------------------|--------------------------------------------------|
| 1    | 72      | M   | Left upper lobe, hilar        | 5.0                    | Lobectomy                 | Chronic sclerosing sialadenitis, lymphadenopathy |
| 2    | 43      | M   | Right lower lobe, hilar       | 4.5                    | Lobectomy                 | Lymphadenopathy                                  |
| 3    | 76      | F   | Left upper lobe, peripheral   | 1.2                    | Partial resection         | Lung cancer                                      |
| 4    | 51      | M   | Left lower lobe, peripheral   | 2.0                    | Partial resection         |                                                  |
| 5    | 63      | M   | Right upper lobe, peripheral  | 1.0                    | Partial resection         |                                                  |
| 6    | 44      | F   | Right upper lobe, peripheral  | 1.1                    | Partial resection         |                                                  |
| 7    | 72      | F   | Right lower lobe, peripheral  | 1.8                    | Partial resection         |                                                  |
| 8    | 42      | F   | Right middle lobe, peripheral | 0.9                    | Partial resection         |                                                  |
| 9    | 48      | M   | Left lower lobe, peripheral   | 1.8                    | Biopsy and corticosteroid |                                                  |

<sup>a</sup> Nodule sizes were measured from pathological specimens in resected cases and from radiological images in biopsied case.

of human IgG4. In the preliminary study, its specificity was confirmed by absorption testing using purified human IgG4 (Athens Research and Technology, Athens, Ga). Deparaffinized sections used for IgG, IgM, and IgG4 studies were microwaved for 20 minutes in citrate buffer (pH 6.0) (IgG and IgM) or EDTA buffer (pH 8.0) (IgG4). The sections for IgA were treated with proteinase K (Dako) for 6 minutes. After blocking of the endogenous peroxidase, the sections were incubated in normal goat serum for 20 minutes and then incubated overnight at 4°C with primary antibodies. These sections were incubated for 1 hour at room temperature with goat antimouse immunoglobulins, which were conjugated to peroxidase-labeled polymer (Envision+, Dako). Diaminobenzidine tetrahydrochloride was used as the chromogen, followed by light counterstaining with hematoxylin. Negative controls were evaluated by substituting similarly diluted nonimmunized mouse serum for the primary antibody.

The IgG-, IgA-, IgM-, and IgG4-positive plasma cells were counted in 10 high-power fields (HPFs) ( $\times 10$  eyepiece and  $\times 40$  lens) in the more prominently inflamed areas in surgically resected cases or in the most inflamed field in the biopsied cases in all IPT-L and IIP lesions, and the numbers were compared. The ratios of IgG4-positive to IgG-positive cells were also calculated in each case.

## 2.5. Statistics

Values are given as mean  $\pm$  SD. The mean values of the 2 groups were compared with the Mann-Whitney *U* test.  $P < .05$  was regarded as significant.

## 3. Results

### 3.1. Clinical history

The clinical histories of the patients with IPT-L are summarized in Table 1. Two patients presented with symptoms (chest pain in case 4, hemoptysis in case 9), whereas the remaining 7 asymptomatic patients were found to have abnormal shadows on chest radiographs during

routine examinations. Chest radiographs and computed tomography revealed solitary nodules in the hilar parts of the lungs (cases 1 and 2) or in the peripheral pulmonary fields (cases 3-9) (Table 1). Endobronchial nodules were seen in the left upper segmental bronchus in case 1 and the right lower segmental bronchus in case 2, and obstructive pneumonia was also observed in individual lobes. The remaining patients showed relatively well-circumscribed nodules in the peripheral lung fields. Positron emission tomography, which was performed only in case 7, revealed marked uptake by the pulmonary nodule and the hilar lymph nodes.

Case 1 had a history of painless swelling of the left submandibular gland 20 months before the pulmonary episode (at the age of 70 years). He underwent surgical resection of the left submandibular gland with the clinical diagnosis of a salivary gland tumor. Pathological examination of the resected specimen revealed a well-circumscribed nodule 3.0 cm in diameter with a severe lymphoplasmacytic infiltrate and irregular proliferation of stromal cells associated with marked atrophy of the

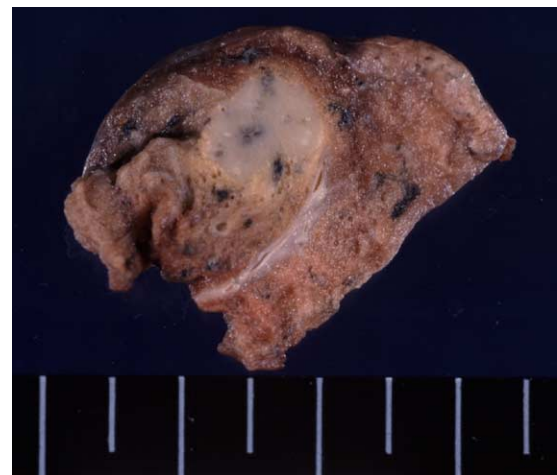


**Fig. 1** Macroscopic picture of surgically resected IPT-L in case 3. Gray nodule with relatively well-circumscribed boundary is seen. Foci of anthracosis are present within and outside nodular lesion.

glandular tissues. A diagnosis of chronic sclerosing sialadenitis (Kuttner's tumor) was made. No recurrence had been observed after follow-up for 10 years. Case 5 had a history of cancer in the left lung (contralateral to the IPT-L) 27 months before the episode of IPT-L (at the age of 60 years). He underwent a left lower lobectomy. Pathological examination of the resected specimen showed a well-differentiated papillary adenocarcinoma in the peripheral parenchyma without lymph node metastasis (pT2 N0 M0, stage I). No recurrence had been observed after a follow-up of 8 years.

### 3.2. Laboratory data

Elevated C-reactive protein was detected in all cases to variable degrees (range, 0.3-10.78 mg/dL; normal, <0.2 mg/dL). Hypergammaglobulinemia was observed in 4 cases (2, 5, 6, and 8) (range, 22.4%-48.7% of serum protein; normal, <20.4%). Serum IgG and ANA levels were examined only in case 8; the patient was noted to have a

high serum IgG concentration (3.11 g/dL; reference range, 0.8-1.6 g/dL) and a 1:80 ANA titer. No tumor markers (carcinoembryonic antigen, neuron-specific enolase, squamous cell carcinoma antigen, and cytokeratin 19 fragment) were detected in any case. Elevated levels of pancreatic enzymes (lipase and amylase) or hepatobiliary enzymes (transaminases, alkaline phosphatase, and  $\gamma$ -glutamyltransferase) were not observed.

### 3.3. Treatment

All IPT-L cases were clinically suspected to be pulmonary neoplasms, especially lung cancers. All patients except case 9 underwent surgical treatment: lobectomy (cases 1 and 2) or partial resection of the lung (cases 3-8). Cases 1 and 2 had enlarged parabronchial (hilar and lobar) lymph nodes, which were surgically removed with suspicion of metastasis. Cases 3 through 8 were found to be IPT at frozen section diagnosis and underwent only partial resection of the lung. Case 9 underwent transbronchial lung biopsy,

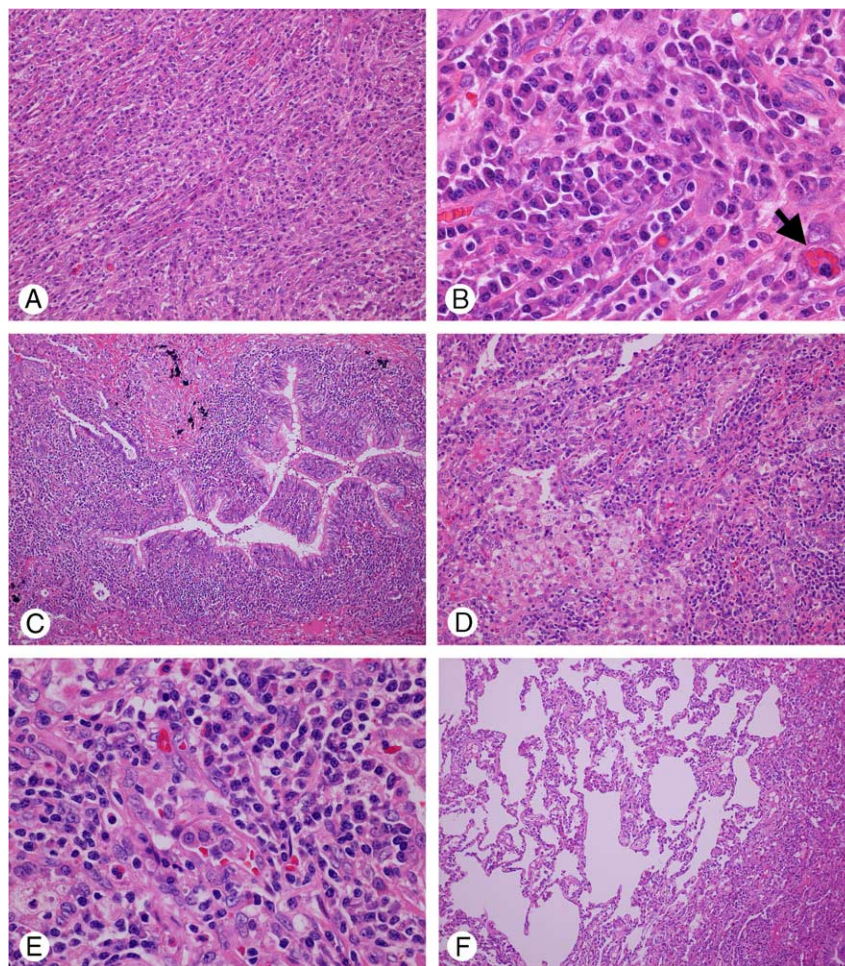


**Fig. 2** Histopathology of IPT-L. A, Lesion consists of severe lymphoplasmacytic infiltrate with irregular fibrosis. B, Plasma cells are predominant components of infiltrating inflammatory cells. Associated Russell bodies are also seen (arrow). C, Bronchiole entrapped in nodule shows irregular stenosis surrounded by lymphoplasmacytic infiltration. D, Alveolar spaces are focally preserved and contain foamy macrophages. E, Prominent eosinophilic infiltrate is observed. F, Interstitial pneumonia pattern at boundary of nodule (nodule is in right lower area) (hematoxylin-eosin, original magnification  $\times 200$  [A],  $\times 600$  [B],  $\times 100$  [C],  $\times 200$  [D],  $\times 600$  [E],  $\times 100$  [F]).

**Table 2** Histological findings of IPT-L

| Feature                                                                     | Cases                     |
|-----------------------------------------------------------------------------|---------------------------|
| Marked infiltration of plasma cells and lymphocytes with irregular fibrosis | 1, 2, 3, 4, 5, 6, 7, 8, 9 |
| Interstitial pneumonia pattern at boundary of nodule                        | 1, 3, 4, 5, 6, 8          |
| Stenotic bronchioles entrapped in nodule                                    | 1, 4, 5, 6, 7, 8          |
| Alveolar spaces containing foamy macrophages                                | 1, 3, 4, 6, 7, 8          |
| Accumulation of neutrophils in entrapped bronchioles or alveoli             | 3, 6                      |
| Prominent eosinophil infiltration (>5 cells per HPF)                        | 4, 6, 9                   |
| Lymph follicles                                                             | 4, 5, 6, 8                |
| Russell bodies                                                              | 1, 2, 3, 4, 5, 6, 7, 8, 9 |
| Multinucleated giant cells                                                  | 1, 3                      |
| Obliterative phlebitis                                                      | 1, 2, 3, 4, 5, 6, 7, 8, 9 |
| Obliterative arteritis                                                      | 1, 2, 4, 5, 6             |

which was diagnosed as IPT-L. He was treated with corticosteroid (30 mg daily) for 1 month, during which time, hemospitum resolved and the pulmonary nodule diminished markedly in size. Only a small fibrous scar was observed on computed tomographic images after steroid therapy. He had no respiratory complaints during a follow-up of 12 years.

### 3.4. Macroscopic findings

All IPT-L lesions were solitary tan and firm nodules, which were relatively well circumscribed without fibrous capsules (Fig. 1). Nodules of cases 1 and 2 showed endobronchial polypoid masses with slight extensions to the parabronchial parenchyma and also had obstructive pneumonia in their regional lobes. No necrosis or daughter nodules were observed in any cases. The size of each nodule is shown in Table 1.

### 3.5. Histological findings

Histological findings are shown in Fig. 2 and Table 2. Histologically, the lesions consisted of severe infiltrates of plasma cells and lymphocytes intermixed with irregular fibrosis (Fig. 2A). Plasma cells and lymphocytes appeared mature without any cellular or nuclear atypia (Fig. 2B). Lymph follicles were also found in 4 cases. Russell bodies (globular, eosinophilic, cytoplasmic, immunoglobulin inclusions) were easily seen in all cases. Bronchioles were entrapped in nodules in 7 cases, and they were stenotic, associated with lymphoplasmacytic infiltration (Fig. 2C). Alveolar spaces were focally preserved within the nodules in 6 cases, and they contained foamy macrophages (Fig. 2D). A few neutrophilic accumulations (microabscesses) were observed in the bronchioles and alveolar spaces in 2 cases. Remarkable eosinophilic infiltration

(>5 eosinophils per HPF) and multinucleated giant cells were also observed in 3 and 2 cases, respectively (Fig. 2E). At the boundaries of the nodules, the inflammatory process extended to adjacent parenchyma, showing fibrous thickening of alveolar septa with lymphoplasmacytic infiltration (interstitial pneumonia pattern) in 6 cases (Fig. 2F). In all cases, plasmacytic infiltration was the most conspicuous feature compared with myofibroblastic proliferation or histiocytic infiltration, and they all corresponded histologically to the plasma cell-rich type of IPT (plasma cell granuloma).

The elastica-van Giesson staining revealed obliterative phlebitis in all cases. In addition, obliterative arteritis was found in 5 cases (Fig. 3).

### 3.6. Immunohistochemistry examination for IgG, IgA, IgM, and IgG4

The results of immunohistochemistry studies for IgG, IgA, IgM, and IgG4 are shown in Table 3. Among plasma cells infiltrating both IPT-L and IIP, most were positive for IgG, but the numbers of IgG-positive plasma cells were significantly higher in IPT-L ( $P < .01$ ). Only a few IgA- or IgM-positive plasma cells were observed in either IPT-L or IIP.

Immunostaining for IgG4 revealed many positive plasma cells diffusely distributed within nodules in all IPT-L cases (Fig. 4). In addition, IgG4-positive plasma cells surrounded the bronchioles or vessels entrapped in nodules. Very few IgG4-positive plasma cells were found in the parenchyma away from nodules. The number of IgG4-positive plasma cells in IPT-L cases ranged from 62 to 235 cells per HPF

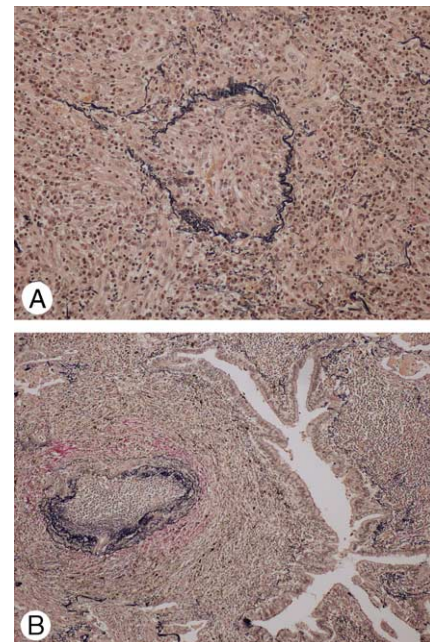


**Fig. 3** Obliterative phlebitis (A) and obliterative arteritis (B) in IPT-L (elastica-van Giesson, original magnification  $\times 200$  [A] and  $\times 100$  [B]).

**Table 3** Numbers of IgG-, IgA-, IgM-, and IgG4-positive plasma cells per HPF and ratios of IgG4-positive to IgG-positive plasma cells in IPT-L and IIP

|       | IgG               | IgA           | IgM           | IgG4              | IgG4/IgG (%)     |
|-------|-------------------|---------------|---------------|-------------------|------------------|
| IPT-L | 241.4 $\pm$ 67.9* | 0.5 $\pm$ 0.9 | 1.0 $\pm$ 1.4 | 138.2 $\pm$ 52.4* | 56.5 $\pm$ 12.5* |
| IIP   | 14.5 $\pm$ 10.3   | 0.6 $\pm$ 1.0 | 1.2 $\pm$ 2.1 | 0.5 $\pm$ 1.3     | 3.4 $\pm$ 0.4    |

\*  $P < .05$  versus IIP.

(138.2  $\pm$  52.4 cells per HPF) in surgically resected cases. In the biopsied case (case 9), several IgG4-positive plasma cells were found in the most inflamed field (35 cells per HPF). In the IIP cases, in which several plasma cells were observed histologically, IgG4-positive plasma cells were scarce (range, 0-7 cells per HPF; average, 0.5  $\pm$  1.3 cells per HPF). The numbers of IgG4-positive plasma cells were significantly higher in IPT-L than in IIP ( $P < .01$ ). In addition, the ratios of IgG4-positive to IgG-positive plasma cells were significantly higher in IPT-L than in IIP ( $P < .01$ ) (Table 3).

Many IgG4-positive plasma cells were found in the interfollicular area of the regional lymph nodes (cases 1 and 2) and also in the chronic sclerosing sialadenitis of the left submandibular gland (case 1). The ratios of IgG4-positive to IgG-positive plasma cells in the lymph nodes and the submandibular gland were 54.2%  $\pm$  23.6% in lymph nodes (cases 1 and 2) and 64.8%  $\pm$  12.3% in the left submandibular gland (case 1).

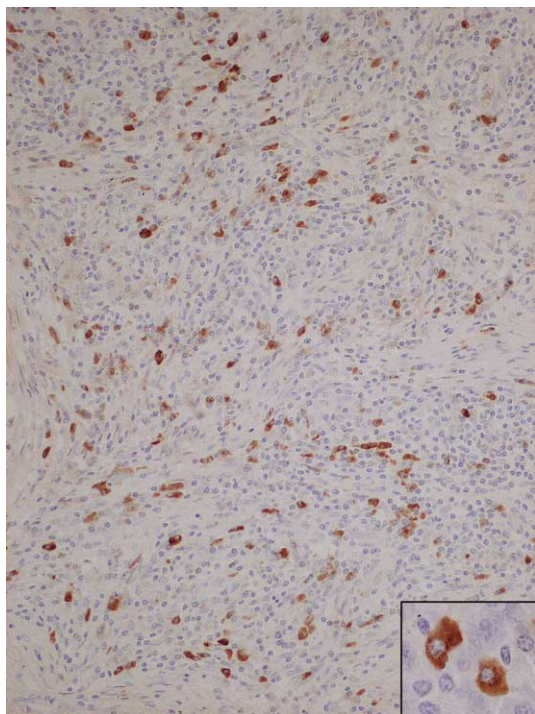


**Fig. 4** Immunostaining of IgG4 in IPT-L. Many IgG4-positive plasma cells are observed (original magnification  $\times 200$ ). IgG4 is present within cytoplasm of plasma cells (inset, original magnification  $\times 600$ ).

## 4. Discussion

Histological findings of sclerosing pancreatitis were first reported as lymphoplasmacytic sclerosing pancreatitis in 1991 [7], and several additional reports confirmed them [11,13,14]. These findings can be summarized as follows: (1) dense lymphoplasmacytic infiltrate with fibrosis, (2) irregular narrowing of entrapped pancreatic ducts, (3) severe acinar atrophy, (4) notable eosinophilic infiltration or granuloma formation in some cases, (5) sclerosing inflammation extending to the peripancreatic adipose tissue, (6) obliterative phlebitis, and (7) many IgG4-positive plasma cells diffusely distributed within the lesions. These features are similar to those of IPT-L obtained in this study, suggesting that similar pathogenetic processes are involved in these 2 conditions. On the other hand, IPT-L had several unique histological findings. The first was the accumulation of foamy macrophages or neutrophils (microabscess), which is uncommon in sclerosing pancreatitis. We speculate that it might be explained by pulmonary anatomic characteristics such as direct continuity with the environment. Indeed, neutrophils and macrophages preferentially accumulated within airways such as bronchioles or alveolar spaces entrapped in the lesions of IPT-L. The second unique finding was obliterative arteritis. Obliterative phlebitis is one of the important features of IgG4-related disorders, including sclerosing pancreatitis [7,11-13], whereas obliterative arteritis has not been reported so far in IgG4-related disorders to the best of our knowledge. Target antigens for the IgG4-related abnormal immune response might be expressed in arteries or arterioles in the lung, although this is only speculative at this time.

IPT of the lung also has clinical characteristics similar to those of sclerosing pancreatitis. The disease more frequently affects males, as does sclerosing pancreatitis [15]. In addition, patients with sclerosing pancreatitis sometimes have extrapancreatic lesions such as cholangitis, sialadenitis, retroperitoneal fibrosis, and lymphadenopathy [16-19]. Many IgG4-positive plasma cells were identifiable in those extrapancreatic lesions, and it is suggested that similar pathogenetic processes are involved in both pancreatic and extrapancreatic lesions in these complicated cases [11,18,19]. Similarly, 2 cases of IPT-L in this study were associated with extrapulmonary lesions, namely, chronic sclerosing sialadenitis (case 1) and lymphadenopathy (cases 1 and 2), in which IgG4-positive cells were identifiable on immunostaining. Recently, it was reported that

IgG4-related disorders, including sclerosing pancreatitis, are closely related to multifocal fibrosclerosis [19]. Thus, IPT-L might be one of the manifestations of IgG4-related multifocal fibrosclerosis.

Sclerosing pancreatitis usually presents with jaundice secondary to marked swelling of the pancreatic parenchyma [9]. Sclerosing pancreatitis responds well to steroid therapy, although pancreatic cancer is clinically suspected, sometimes leading to surgery [9]. In 2002, Hamano et al [10] reported that serum IgG4 levels were specifically elevated in patients with sclerosing pancreatitis. Because of this finding, measuring serum IgG4 levels may make surgery unnecessary by distinguishing sclerosing pancreatitis from pancreatic cancer. The effectiveness of steroid therapy also has been suggested for IPT-L [20,21], as is shown by case 9 in this study, although it is necessary to diagnose IPT-L correctly without surgery before starting steroid therapy. Given the clinicopathologic similarities between sclerosing pancreatitis and IPT-L, serum IgG4 levels might be elevated in patients with IPT-L and become a diagnostic marker for this disease.

There have been only 2 reported cases of sclerosing pancreatitis with pulmonary complications. Taniguchi et al [22] described a patient who was found to have interstitial pneumonia of the lower lung fields bilaterally during a medical follow-up for sclerosing pancreatitis. A trans-bronchial biopsy showed marked thickening of the alveolar septum with significant infiltration of lymphocytes and plasma cells. Immunostaining for IgG4 revealed many positive plasma cells in the alveolar septa. Corticosteroid therapy for 2 weeks markedly improved the sclerosing pancreatitis and the interstitial pneumonia. Nieminen et al [23] also reported a patient who had idiopathic pancreatitis, sclerosing cholangitis, sialadenitis, and nodular interstitial pneumonia. We speculate that the pancreatitis of this patient was sclerosing pancreatitis because he had an autoimmune abnormality (positive rheumatoid factor) and complications of extrapancreatic sclerosing lesions, although his serum IgG4 level was not examined and he was not said to have sclerosing pancreatitis in the original report. The pulmonary lesions of this patient diminished markedly, along with improvement of pancreatitis and cholangitis, on medical therapy. It is interesting that these 2 cases manifested as interstitial pneumonia. All cases of IPT-L in this study were suspected to be lung tumors and not interstitial pneumonia, although interstitial pneumonia patterns were observed at the boundaries of the nodules in 6 of the 9 cases. It is difficult to determine whether these 2 conditions are different diseases or different manifestations of a single disease entity. Further histological examination of the interstitial pneumonia associated with sclerosing pancreatitis is needed to clarify this issue.

IgG4 is the least abundant of the IgG subclasses, accounting for less than 6% of the total IgG fraction in the serum of a healthy subject [24]. Serum IgG4 is

elevated in the limited number of conditions such as allergic or autoimmune disorders [25,26]. In bronchial asthma, IgE participates in the reaction to allergens, whereas IgG4 becomes prominent only late during chronic antigenic stimulation [25]. Therefore, it is suggested that IgG4-producing plasma cells might behave as “memory cells” in allergic patients. In pemphigus vulgaris, the patients have autoantibodies against desmosomes in keratinocytes, and IgG4 is the predominant type of autoantibody detected [27].

Recent studies have revealed that sclerosing pancreatitis and sclerosing pancreatitis-related lesions are characterized by predominant infiltrates of IgG4-positive plasma cells and the former also by elevation of serum IgG4 [10-12]. However, little is known about how IgG4 participates in the pathogenesis of sclerosing pancreatitis. It was found in this study that IPT-L cases showed predominant infiltration of IgG4-positive plasma cells and a higher proportion of IgG4-positive plasma cells among the IgG-positive plasma cells in the lesions of the lungs, submandibular gland (case 1), and lymph nodes (cases 1 and 2). The ratios of IgG4-positive plasma cells to IgG-, IgA-, and IgM-positive plasma cells were significantly higher in IPT-L than in IIP. These data suggest that predominant infiltration of IgG4-positive plasma cells in pulmonary and extrapulmonary lesions in IPT-L does not reflect simply plasma cell activation but rather a dysregulated IgG4-related immune response.

IPT is given different names in various organs. Most of these tumors are subcategorized as plasma cell granulomas (plasma cell-rich type) or inflammatory myofibroblastic tumors (more fibrous type) [1-3]. Some cases have both of these histological characteristics and cannot easily be subcategorized into either group. All IPT-L cases examined in this study corresponded to plasma cell granulomas histologically. In addition, all IgG4-related IPT cases of the liver and breast, as mentioned above, also corresponded to plasma cell granulomas [11,12]. We now speculate that IgG4-related diseases might also be plasma cell granulomas in other organs.

The IPT-L cases examined in this study were all adults, although it is well-known that IPT-L can occur in children [1]. Any clinical or histological differences between adult and pediatric cases have not been elucidated so far. It might be interesting to determine whether IgG4-related IPT-L could exist in a pediatric case, because IgG4-related diseases, including sclerosing pancreatitis, are now believed to occur only in adults, especially persons older than 30 years [9].

In conclusion, dense lymphoplasmacytic infiltrates containing many IgG4-positive plasma cells intermixed with fibrosis and obliterative phlebitis characterized IPT-L (plasma cell granuloma type). Interestingly, these features were similar to those of sclerosing pancreatitis, suggesting that IgG4-related immunopathologic processes might be involved in the pathogenesis of IPT-L.

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