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④ IgG4関連眼疾患分科会	東京医科大学	後藤　浩
⑤ IgG4関連腎臓病分科会	金沢大学	川野充弘
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Research Article

Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009

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The number of patients with autoimmune pancreatitis who visited hospitals in Japan in 2007 was approximately 2709 (95% confidence interval; range 2540–3040). Because IgG4-related disease is a new clinical entity, there are no data with regard to its prevalence. To estimate the number of patients with IgG4-related disease in Japan, we randomly selected hospitals using stratification and asked them how many patients they had with IgG4-related disease in 2009. The number of patients with Mikulicz's disease, IgG4-related retroperitoneal fibrosis, IgG4-related renal disease, IgG4-related pulmonary disease, and IgG4-related lymphadenopathy who visited hospitals in Japan in 2009 was approximately 4304 (95% confidence interval; range 3360–5048), 272 (95% confidence interval; range 264–306), 57 (95% confidence interval; range 47–66), 354 (95% confidence interval; range 283–424), and 203 (95% confidence interval; range 187–240), respectively. The total number of patients with IgG4-related disease without autoimmune pancreatitis in Japan was approximately 5190 (95% confidence interval; range 4141–6084). The male : female ratio was 1 : 0.77, and the average of age of disease onset was 58.8 years. The total number of patients with IgG4-related disease in Japan in 2009, including autoimmune pancreatitis, was approximately 8000.

1. Introduction

IgG4-related disease (IgG4-RD) has recently been proposed as a new disease entity, and a number of case reports and studies evaluating the clinical characteristics of IgG4-RD have appeared in the literature. In 1995, Yoshida et al. proposed autoimmune pancreatitis (AIP) [1]. Hamano et al. reported that these patients showed elevated serum IgG4 [2]. Recently, autoimmune pancreatitis has been distinguished variously as type 1 and type 2 [3]. Type 1 AIP is characterized by IgG4. On the other hand, type 2 AIP is characterized by neutrophil infiltration. Type 1 AIP is commonly complicated with other organ involvement (OOI) [4, 5]. Kamisawa et al. proposed IgG4-related sclerosing disease [6]. This concept is based on sclerosing fibrosis. Systemic IgG4-related plasmacytic syndrome (SIPS) and IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) were proposed based on lymphoproliferation [7, 8]. The Research Program for Intractable Disease by the Ministry of Health, Labor and Welfare (MHLW) has agreed to use the term "IgG4-related disease (IgG4-RD)" [9]. The most common OOIs are the well-known Mikulicz's disease, IgG4-related retroperitoneal fibrosis, IgG4-related renal disease, IgG4-related pulmonary disease, and IgG4-related lymphadenopathy. However, there has been no epidemiological report regarding the prevalence of IgG4-RD, even in a restricted area. We conducted a national survey for IgG4-RD, based on a national survey for AIP in 2009.

2. Methods

In 2006, the Japan Pancreas Society first proposed the diagnostic criteria for AIP [10, 11]. In 2007, using these criteria, a second nationwide survey for AIP was conducted and estimated the prevalence of AIP in Japan [12]. Briefly, following the guidelines of the Nationwide Epidemiological

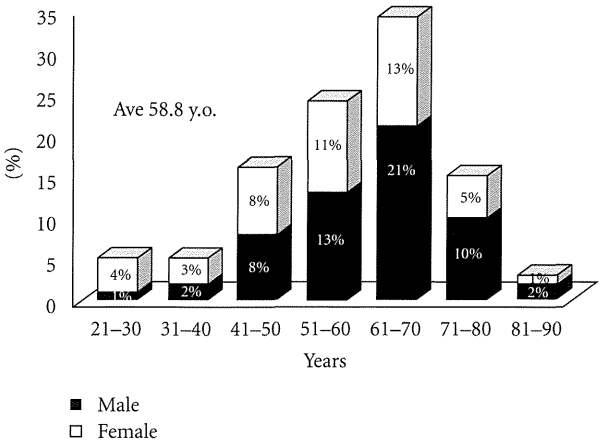
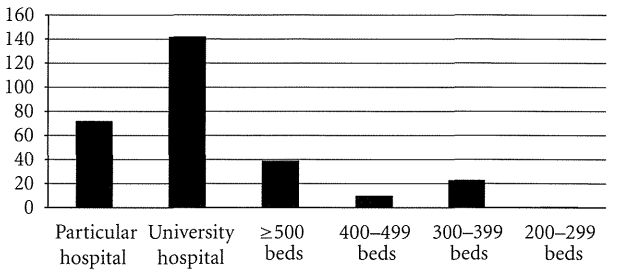


FIGURE 1: Sex and age of onset of IgG4-related disease. The male : female ratio was 1 : 0.77, and the average of age of disease onset was 58.8 years.



	Estimated patients	Lower limits	Upper limits
Dept. of Respiratory Medicine	21.8	13.6	30
Rheumatology	151.4	136.3	166.6
Internal Medicine	726.7	663.8	789.6
Otolaryngology	354.2	322.7	385.9
Ophthalmology	297.9	277.8	448.4
Total	1552.1	1283.7	1820.5

FIGURE 2: Mikulicz' disease without autoimmune pancreatitis. The number of patients with Mikulicz's disease without autoimmune pancreatitis, who visited hospitals in Japan in 2009, was approximately 4304 (95% confidence interval; range 3360–5048).

Survey Manual issued by the Research Committee on the Epidemiology of Intractable Diseases, [13] hospitals using stratification were randomly selected according to the number of beds in each; the more beds a hospital had, the greater the probability that it would be selected. Furthermore, 37 departments in hospitals in a particular stratum which were considered to have recorded AIP cases for research purposes and 317 departments in university hospitals were stratified separately. Next, the following departments were selected: Internal Medicine, Gastroenterology, Surgery, and Gastroenterological Surgery. From these selections, 2972 departments were nominated. A questionnaire was sent to the selected departments along with the diagnostic criteria for AIP, and respondents were asked to provide the number and sex of AIP patients who had visited the hospital in 2007. This survey included questions about sex, age of disease onset, and the diagnostic basis for AIP. According to this national survey of AIP, the number of AIP patients who visited a hospital in Japan in 2007 was estimated to be 2790 (95% confidence interval; range 2540–3040). AIP in the Japanese population was estimated as 0.82 per 100,000. The number of newly contracted patients in one year was 1,120 patients (95% confidence interval; range 1,000–1,240). Japanese vital statics of the Ministry of Health, Labor and Welfare for 2007 showed the total population to be 127,771,000 people (adult population, 104,197,000). 36.05% of the autoimmune pancreatitis patients were in the 250 hospitals who responded to the autoimmune pancreatitis nationwide survey in Japan. It was assumed that 2.773 times the number of presumptive patients in these 250 hospitals would be the number of estimated patients for the whole country. There were many experiences of autoimmune pancreatitis in these 250 hospitals. It seemed that patients with IgG4-related disease gathered a lot in these 250 hospitals. A questionnaire was sent to selected departments (Respiratory Medicine, Rheumatology, Internal Medicine (except Gastroenterology), Otolaryngology, Ophthalmology, and Urology) in these 250 hospitals, and respondents were asked to provide the number of IgG4-RD patients who had visited the hospital in 2009. This survey included questions about sex, age of disease onset, and the diagnostic basis for IgG4-RD.

3. Results

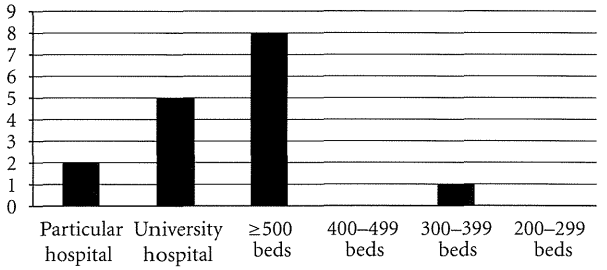
In these patients, the male : female ratio was 1 : 0.77. Figure 1 shows the distribution of the age of these patients at disease onset. The average of age of disease onset was 58.8 years. The peak was in the age range 61–70 years, and the disease-onset age in approximately one-third of the patients (33%) was 61–70 years. Interestingly, the number of patients with a disease-onset age of less than 40 years was dramatically lower, as most of the patients (90%) started to show IgG4-RD after the age of 40.

A total of 301 (26.8%) of 1250 departments responded to the questionnaire (Table 1). Based on these results, the number of patients with Mikulicz's disease without autoimmune pancreatitis who visited hospitals in Japan in 2009, was approximately 4304 (95% confidence interval; range 3360–5048) (Figure 2). The number of patients with IgG4-related retroperitoneal fibrosis without autoimmune pancreatitis who visited hospitals was approximately 272 (95% confidence interval; range 246–303) (Figure 3). The number of patients with IgG4-related renal disease without autoimmune pancreatitis, who visited hospitals was approximately 57 (95% confidence interval; range 47–66) (Figure 4). The number of patients with IgG4-related pulmonary disease without autoimmune pancreatitis who visited hospitals was approximately 354 (95% confidence interval; range 283–424) (Figure 5). The number of patients with IgG4-related lymphadenopathy without autoimmune pancreatitis who visited hospitals was approximately 203 (95% confidence interval;

Table 1: Stratification and selection of hospitals and survey results.

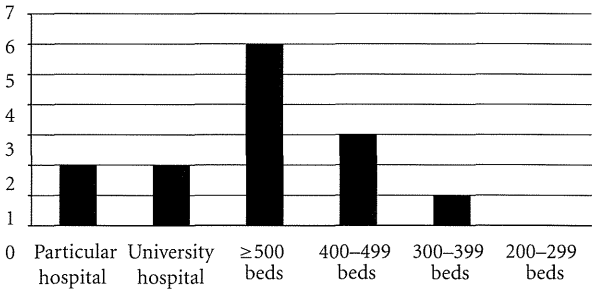
Stratification	Hospitals nominated	Department nominated	Departments replying	Reply rate (%)
University hospital	49	245	58	23.7
Particular hospital[a]	55	275	96	34.9
≥500 beds	72	360	99	27.5
400–499 beds	33	165	38	23.0
300–399 beds	27	135	33	23.0
200–299 beds	12	60	10	16.7
100–199 beds	1	5	0	0
≤99 beds	1	5	0	0
Total	250	1250	301	26.6

[a]Hospitals considered to have collected AIP cases for research purposes.



	Estimated patients	Lower limits	Upper limits
Dept. of Rheumatology	18.2	11.1	25.4
Internal Medicine	30.2	26.9	33.8
Urology	50	49.5	50.4
Total	98.2	95.3	109.1

Figure 3: IgG4-related retroperitoneal fibrosis without autoimmune pancreatitis. The number of patients with IgG4-related retroperitoneal fibrosis without autoimmune pancreatitis, who visited hospitals in Japan in 2009 was approximately 272 (95% confidence interval; range 246–303).



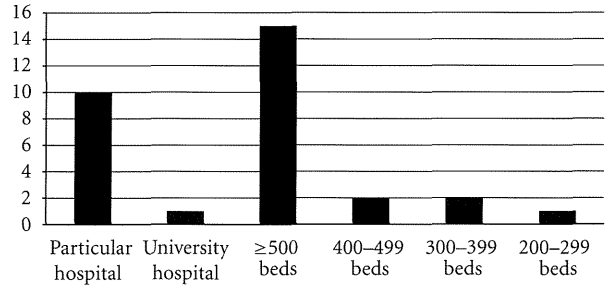
	Estimated patients	Lower limits	Upper limits
Dept. of Rheumatology	20.4	17.1	23.8

Figure 4: IgG4-related renal disease without autoimmune pancreatitis. The number of patients with IgG4-related renal disease without autoimmune pancreatitis, who visited hospitals in Japan in 2009, was approximately 57 (95% confidence interval; range 47–66).

range 187–240) (Figure 6). The total number of patients with IgG4-related disease without autoimmune pancreatitis in Japan was estimated to be approximately 5190 (95% confidence interval; range 4141–6084).

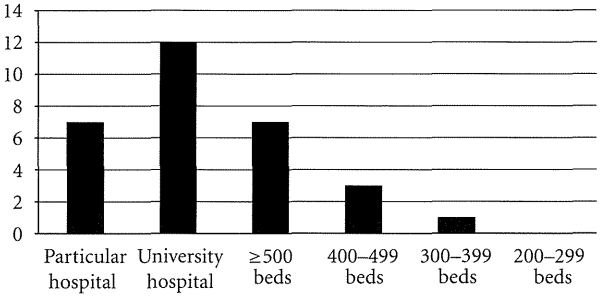
4. Discussion

This is one of several nationwide surveys conducted to elucidate the number of AIP patients in Japan and also the first such survey to be conducted worldwide. It is difficult to ascertain the number of patients with IgG4-RD, the awareness of this disease is low, and its symptoms are varied. Another national survey in Japan was reported by Umehara et al. [9]. They have estimated the number of individuals with IgG4-RD throughout Japan by using the number of patients in Ishikawa Prefecture as an example. Populations in Ishikawa Prefecture contains 1.16 million people, with little population inflow/outflow. In Ishikawa Prefecture, there are two University Hospitals, Kanazawa Medical University Hospital and Kanazawa University Hospital. Assuming that new patients with IgG4-RD would visit one of the two university hospitals, it was estimated that the incidence of this disease throughout Japan is 0.28–1.08/100,000 population with 336–1,300 patients newly diagnosed per year from 2003 to 2009. Since the median age of onset of IgG4-RD is 58 years and the clinical symptoms are relatively mild, with slow progression and good response to steroid therapy, life expectancy after diagnosis has been estimated at 20 years. Thus, it has been estimated that there are approximately 6,700 to 26,000 patients in Japan who have developed IgG4-RD over the past 20 years. From our national survey, the total number of patients with IgG4-RD without autoimmune pancreatitis in Japan was approximately 5190 (95% confidence interval; range 4141–6084). The number of AIP patients who visited a hospital in Japan was estimated to be 2790 patients. Therefore, the total number of patients with IgG4-related disease including autoimmune pancreatitis in Japan in 2009 was approximately 8000. Our estimate is somewhat lower than another national survey from Umehara et al. There are several possibilities of reasons for this matter. In this survey, we estimated the number of IgG4-RD patients based on the hospitals' treatment of AIP. On the other hand, Umehara et al.'s result was estimated from the two university hospitals



	Estimated patients	Lower limits	Upper limits
Dept. of Respiratory Medicine	127.6	102.2	152.9

FIGURE 5: IgG4-related pulmonary disease without autoimmune pancreatitis. The number of patients with IgG4-related pulmonary disease without autoimmune pancreatitis, who visited hospitals in Japan in 2009, was approximately 354 (95% confidence interval; range 283–424).



	Estimated patients	Lower limits	Upper limits
Dept. of Rheumatology	73.1	67.4	86.8

FIGURE 6: IgG4-related lymphadenopathy without autoimmune pancreatitis. The number of patients with IgG4-related lymphadenopathy without autoimmune pancreatitis, who visited hospitals in Japan in 2009, was approximately 203 (95% confidence interval; range 187–240).

(Department of Rheumatology) in Ishikawa Prefecture. From these two national surveys, it is suggested that total number of patients with IgG4-related disease including autoimmune pancreatitis in Japan was approximately about 10,000 and the average of age of disease onset was 58 years.

It has been reported the ratio of male patients in autoimmune pancreatitis [5]. In this survey, the male : female ratio was 1 : 0.77. Most patients have Mikulicz's disease without autoimmune pancreatitis. In Mikulicz's disease, the male : female ratio was 1.30 : 1. This is the reason that the deference is few at male and female ratio compared with autoimmune pancreatitis. Answer rate of this survey is not so high. One reason is guessed that IgG4-RD is not familiarized, therefore the patients with IgG4-RD are concentrated on the hospital that answered this survey. In 2011, the comprehensive diagnostic criteria for IgG4-RD are established by all Japan G4 team [14]. It will be necessary to familiarize general physicians with this new disease concept.

Acknowledgments

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The similarity of Type 1 autoimmune pancreatitis to pancreatic ductal adenocarcinoma with significant IgG4-positive plasma cell infiltration

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Abstract
Background High serum immunoglobulin G4 (IgG4) levels and infiltration of IgG4-positive cells are characteristic of Type 1 autoimmune pancreatitis (AIP). We previously reported that increased regulatory T cells (Tregs) may regulate IgG4 production in AIP. Although an increased serum IgG4 concentration is observed in some patients with pancreatic ductal adenocarcinoma (PDA), clarification is still necessary. We have therefore studied the correlations between IgG4-positive cells and Tregs in patients with PDA.
Subjects and methods A total of 21 PDA and nine AIP patients were enrolled in our study. The numbers and ratios of Tregs, IgG4-positive, and IgG-positive cells immunohistochemically stained with anti-Foxp3, IgG4, and IgG antibodies, respectively, were counted in three areas of resected pancreata in PDA, peritumoral pancreatitis (PT), and obstructive pancreatitis (OP).
Results In PDA, PT, OP area, the number of IgG4-Positive cells (5.183 ± 1.061, 2.250 ± 0.431, 4.033 ± 1.018, respectively; $p < 0.05$) and the ratio of IgG4/IgG (0.391 ± 0.045, 0.259 ± 0.054, 0.210 ± 0.048, respectively; $p < 0.05$) were significantly lower than those in AIP (21.667 ± 2.436 and 0.306 ± 0.052, respectively). The numbers of IgG4-positive cells did not differ significantly among the three areas of resected pancreata examined. However, the IgG4/IgG (0.391 ± 0.045) and Foxp3/monocyte (0.051 ± 0.008) ratios in PDA area were significantly ($p < 0.05$) higher than those in OP area (IgG4/IgG: 0.210 ± 0.048; oxp3/monocyte: 0.0332 ± 0.005), but not in PT area. Of the 21 cases of PDA, the ratio of IgG4/IgG was >40 % in nine (43 %), six (29 %) and three (14 %) cases in PDA, PT and OP area, respectively. Foxp3 and IgG4 were positively correlated in OP area, but not in PDA and PT area.
Conclusions Clinicians should be careful when basing a differential diagnosis of PDA and AIP on the numbers of IgG4-positive cells and the ratio of IgG4/IgG, especially when determined using a small biopsied sample.

Keywords Autoimmune pancreatitis · IgG4 · Regulatory T cells · Forkhead box P3 · Pancreatic ductal adenocarcinoma

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Introduction

In 1961, Sarles et al. [1] first observed a case of idiopathic chronic pancreatitis with hypergammaglobulinemia, in which an autoimmune mechanism was supposedly involved. In 1991, Kawaguchi et al. [2] defined the pathologic feature as lymphoplasmacytic sclerosing pancreatitis (LPSP), and in 1995, Yoshida et al. [3] proposed the concept of "autoimmune pancreatitis (AIP)." In 2001, Hamano et al. [4] reported that elevated serum

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immunoglobulin G4 (IgG4) levels were highly specific and sensitive for the diagnosis of AIP. Kamisawa et al. [5] subsequently suggested that AIP is a systemic disease, based on the findings that the pancreas and other involved organs showed an abundant infiltration of IgG4-positive plasma cells. Thereafter, many AIP cases have been reported by Japanese investigators, and AIP has been accepted as a new clinical entity [6–9].

Reports from Europe [10] and the USA [11] describe unique histological patterns in the resected pancreata of patients with mass-forming chronic non-alcoholic pancreatitis with epithelial destruction by granulocytes. This disease has been called idiopathic duct centric pancreatitis (IDCP) [11], AIP with granulocyte epithelial lesions (AIP with GEL), or Type 2 AIP [12]. In 2011, the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis (ICDC) was published. According to ICDC, AIP can be either a Type 1 AIP (LPSP) or a Type 2 AIP (IDCP) [13]. Most of the Japanese AIP cases reported to date are LPSP, with very few reports of IDCP [14].

Patients with AIP commonly present with a mass in the head of the pancreas and may also have jaundice from associated bile duct strictures. Thus, they are often presumed to have a pancreatic ductal adenocarcinoma (PDA) and may undergo pancreatic resection without a definitive preoperative diagnosis. High serum IgG4 concentrations (135 mg/dL) may be helpful in distinguishing AIP from PDA preoperatively [4]. However, about 10 % of the cases with elevated serum IgG4 levels have been reported as PDA [15]. Moreover, infiltration of IgG4-positive cells into the tissue is characteristic of Type 1 AIP [5, 16–22]. It has clearly been shown that cases of Type 1 AIP may have numerous IgG4-positive plasma cells within the periductal inflammatory infiltrate, leading to various density thresholds have been suggested as useful markers in distinguishing Type 1 AIP from chronic pancreatitis. There have been a few recent reports of IgG4-positive cells in PDA [19, 22, 23]. However, the ratio of IgG4-positive cells to infiltrated IgG-positive cells (IgG4/IgG) in PDA remains unclear. The use of the IgG4/IgG ratio has proved to be a more valuable marker than the absolute counts of IgG4-positive cells.

Great attention has been focused on the relation between various autoimmune disease and regulatory T cells (Tregs) [24–30]. Recently, a few reports have suggested that Forkhead box P3 (Foxp3)-positive cells have been seen in PDA [31–33]. We previously reported that increased quantities of Tregs may influence IgG4 production in Type 1 AIP [34–36]. However, the relationship between IgG4 and Foxp3 in PDA is still obscure. We compared the relationship between IgG4-positive cells and Tregs in PDA and Type 1 AIP.

Methods

Subjects

We examined nine patients with Type 1 AIP (5 women and 4 men; mean age 65 years, range 42–81 years) and 21 patients with PDA (7 women and 14 men, mean age 67 years, range 51–78 years) (Table 1). All patients were treated between 1992 and 2010 at Kansai Medical University and represent surgery cases. All Type 1 AIP cases were suspected as PDA prior to the operation, and these patients were diagnosed histopathologically as LPSP post-surgery. There was no PDA case with an AIP background, either clinically or histopathologically. This study was approved by Kansai Medical University's ethics committee, and all patients gave informed consent.

Histopathology and immunohistochemistry

We counted infiltrating cells in three categorized areas (Fig. 1a) from the resected pancreas of each patient with PDA: (1) the PDA area, where adenocarcinoma cells had infiltrated; (2) the peritumoral pancreatitis (PT) area; (3) the obstructive pancreatitis (OP) area, characterized by upstream dilatation of the main pancreatic duct (MPD) with obstruction by the cancer [37, 38] and inter- and intralobular fibrosis [39]. The OP and PDA areas (Fig. 1a) were selected from different sections, but the PT area was selected from the same section as the PDA area. Three pathologists diagnosed the PDA, PT and OP areas independently. Infiltrating cells in Type 1 AIP were counted in the active inflammatory area. We counted the numbers of immunohistochemically identifiable IgG, IgG4, and Foxp3-positive cells and mononuclear cells in each area with three different fields per high power field (hpf) (400×). The cell numbers in the three different fields were averaged and compared among according to PDA, PT, OP area and AIP. The fields with the highest density of IgG4 and Foxp3-positive cells were evaluated. IgG-positive cells were counted with the same three fields used for counting IgG4-positive cells.

Table 1 Clinical profile and characteristics of the patient and control groups

Clinical profile	*n*	Sex (male/female)	Age (years)[a]
PDA	21	14/7	67 ± 2 (51–78)
Type 1 AIP	9	4/5	65 ± 2 (56–75)

PDA Pancreatic ductal adenocarcinoma, *Type 1 AIP* Type1 autoimmune pancreatitis

[a] Values are given as the mean ± standard error of the mean (SEM), with the range in parenthesis

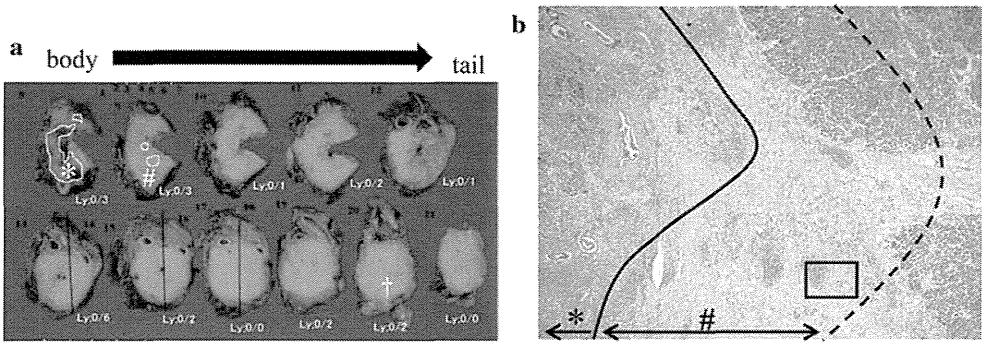

Fig. 1 **a** Macro-photograph of distal pancreatectomy. *From left to right* Pancreatic body to the pancreatic tail. Area *enclosed* by *white line* (*asterisk*) is the pancreatic ductal adenocarcinoma (PDA) area, *hash symbol* marks the peritumoral pancreatitis (PT) area, *dagger symbol* marks the obstructive pancreatitis (OP) area. **b** Hematoxylin and eosin (H&E) staining in PDA (×20). *Area left of solid black line* (*asterisk*) PDA area, *area between the solid line and dotted line* (*hash symbol*) PT area *square* PT area enlarged in Fig. 3

Formalin-fixed and paraffin-embedded specimens were prepared and used for histopathologic and immunohistochemical studies. Sections 4-μm thick were cut for hematoxylin and eosin (H&E), Elastica van Gieson (EvG), and immunohistochemical staining. Formalin-fixed paraffin embedded pancreatic sections were deparaffinized and rehydrated using xylene and a graded descending series of alcohol. Endogenous peroxidase activity was blocked for all sections in 3 % H_2O_2/methanol for 10 min. After washing in distilled water, the slides for IgG and IgG4 were treated by proteinase (Sigma, St. Louis, MO) for 15 min at room temperature, and the slides for Foxp3 were exposed to microwave pretreatment in a target retrieval solution (Dako Japan, Kyoto, Japan) at 100 °C for 20 min to enhance antigenicity. All slides were incubated for 10 min in protein blocking reagent without serum (ProTaqs Biocyc GmbH & Co., Berlin, Germany). The slides were then incubated at 4 °C overnight with primary antibodies. The primary antibodies used were a goat polyclonal antibody against human IgG (Vector laboratories, Burlingame, CA), a mouse monoclonal antibody against human IgG4 (Zymed Laboratories, San Francisco, CA), and a biotin labeled rat polyclonal antibody against human Foxp3 (eBioscience, San Diego, CA). The slides for IgG and IgG4 were then incubated with secondary antibodies using the Elite ABC goat IgG kit (Vector Laboratories) and Chem Envision kit/HRP (Dako Japan), following the manufacturers' instructions. The slides for Foxp3 were treated with avidin-biotinylated peroxidase complex (Vector Laboratories). Finally, antibody binding was detected using 3, 3′-diaminobenzidine (DAB) (Dojindo, Kumamoto, Japan). Sections were counterstained with hematoxylin [35]. Negative controls were evaluated by replacing the primary antibody with similarly diluted nonimmunized serum.

Results

Immunohistochemical findings on IgG and IgG4-positive cells

The ratio of IgG4-positive cells to infiltrated mononuclear cells (IgG4/Mono) was significantly higher in Type 1 AIP (0.135 ± 0.018; Fig. 5c, d) than in the PDA area (0.048 ± 0.010; $p < 0.0001$; Fig. 2c, d), in the PT area (0.027 ± 0.006; $p < 0.0001$; Fig. 3c, d), and in the OP area (0.033 ± 0.008; $p < 0.0001$; Figs. 4c, d, 6a). The ratio of IgG-positive cells to infiltrated mononuclear cells (IgG/Mono) was significantly higher in Type 1 AIP (0.306 ± 0.052; Fig. 5e, f) than in the PDA area (0.156 ± 0.015; $p < 0.0001$; Fig. 2e, f), in the PT area (0.119 ± 0.015; $p < 0.0001$; Fig. 3e, f), and in the OP area (0.147 ± 0.016; $p < 0.0001$; Figs. 4e, f, 6b). The ratio of IgG4-positive cells to IgG-positive cells (IgG4/IgG) was significantly higher in Type 1 AIP (0.624 ± 0.059) than in the PDA area (0.391 ± 0.045; $p = 0.0075$), in the PT area (0.259 ± 0.054; $p < 0.0001$), and in the OP area (0.210 ± 0.048; $p < 0.0001$; Fig. 6c). The ratio of IgG4/IgG was significantly higher in the PDA area than in the OP area ($p = 0.0092$). Of the 21 cases of PDA, nine (43 %) in the PDA area, six (29 %) in the PT area, and three (14 %) in the OP area showed >40 % IgG4-positive cells per IgG-positive cells (Fig. 6c; Table 2). The number of IgG4-positive cells (IgG4/hpf) in Type 1 AIP (21.667 ± 2.436; Fig. 5d) was significantly higher than that in the PDA area (5.183 ± 1.061; $p < 0.0001$; Fig. 2d), PT area (2.250 ± 0.431; $p < 0.0001$; Fig. 3d), and OP area (4.033 ± 0.005; $p < 0.0001$; Figs. 4d, 6d).

Immunohistochemical findings on Foxp3-positive cells

The ratio of Foxp3-positive cells to infiltrated mononuclear cells (Foxp3/Mono) in Type 1 AIP (0.097 ± 0.009;

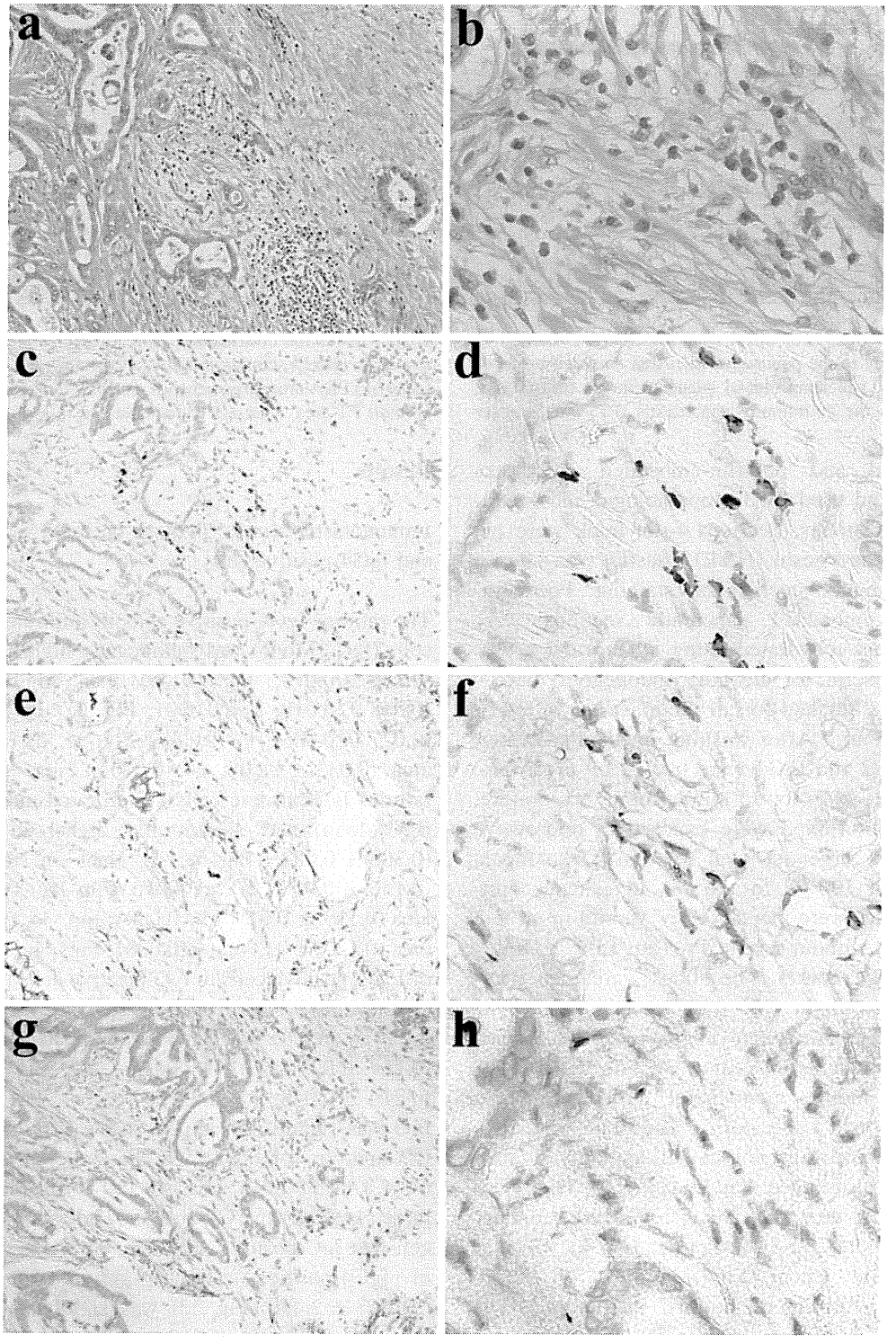

Fig. 2 Histopathologic and immunohistochemical findings in the PDA area. H&E staining. **a** ×100, **b** ×400. Inflammatory cells' infiltrate was evident in tumor stroma: Immunoglobulin G4 (IgG4)-positive cells (H&E; **c** ×100, **d** ×400) and IgG-positive cells (H&E; **e** ×100, **f** ×400) were abundant, whereas Foxp3-positive cells (H&E; **g** ×100, **h** ×400) were scattered

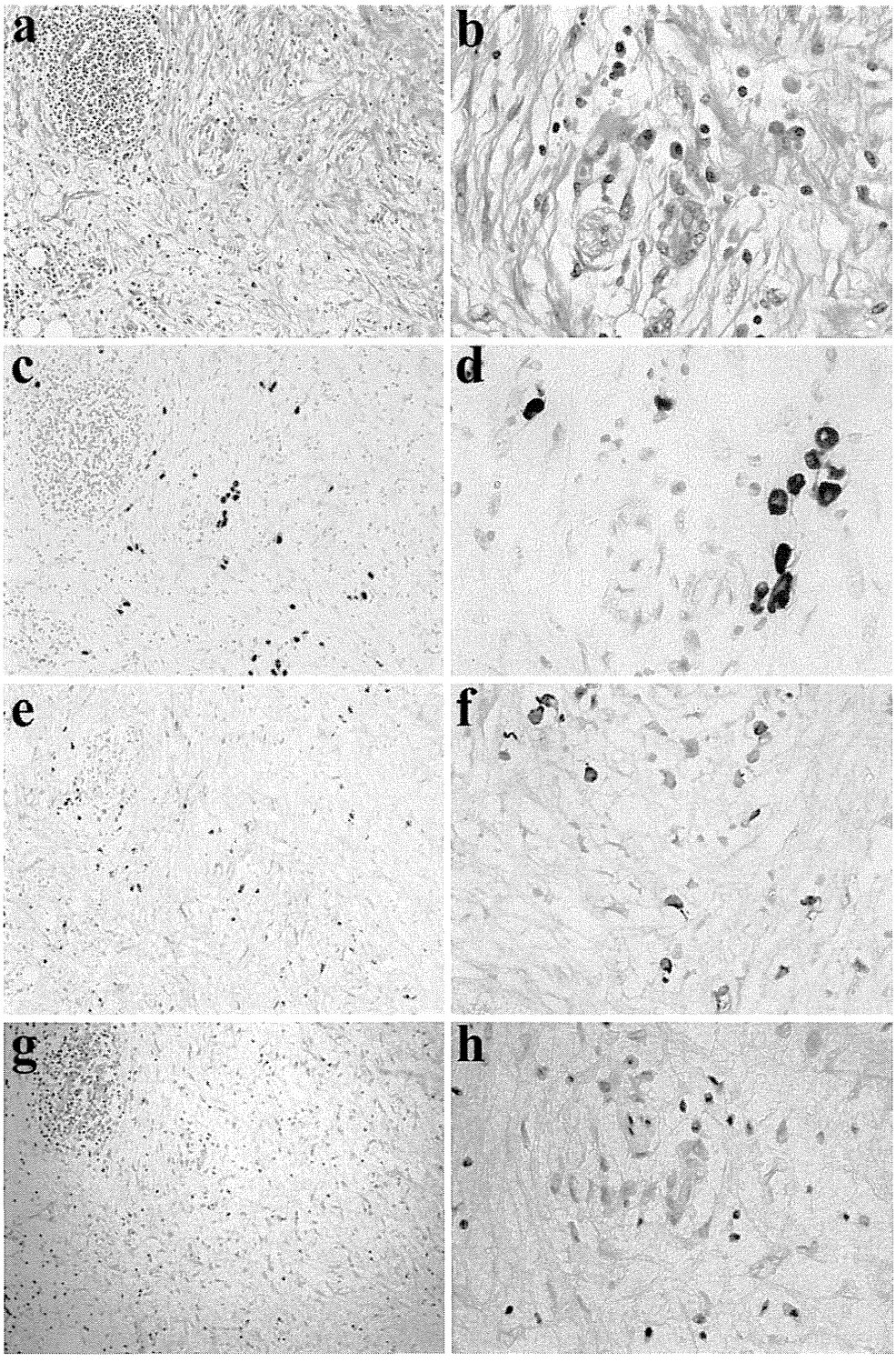

Fig. 3 Histopathologic and immunohistochemical findings in the PT area. H&E staining. **a** ×100, **b** ×400. Inflammatory cells' infiltrate was evident in tumor stroma. IgG4-positive cells (**c** ×100, **d** ×400) and IgG-positive cells (**e** ×100, d ×400) were abundant, whereas Foxp3-positive cells (**g** ×100, **h** ×400) were scattered

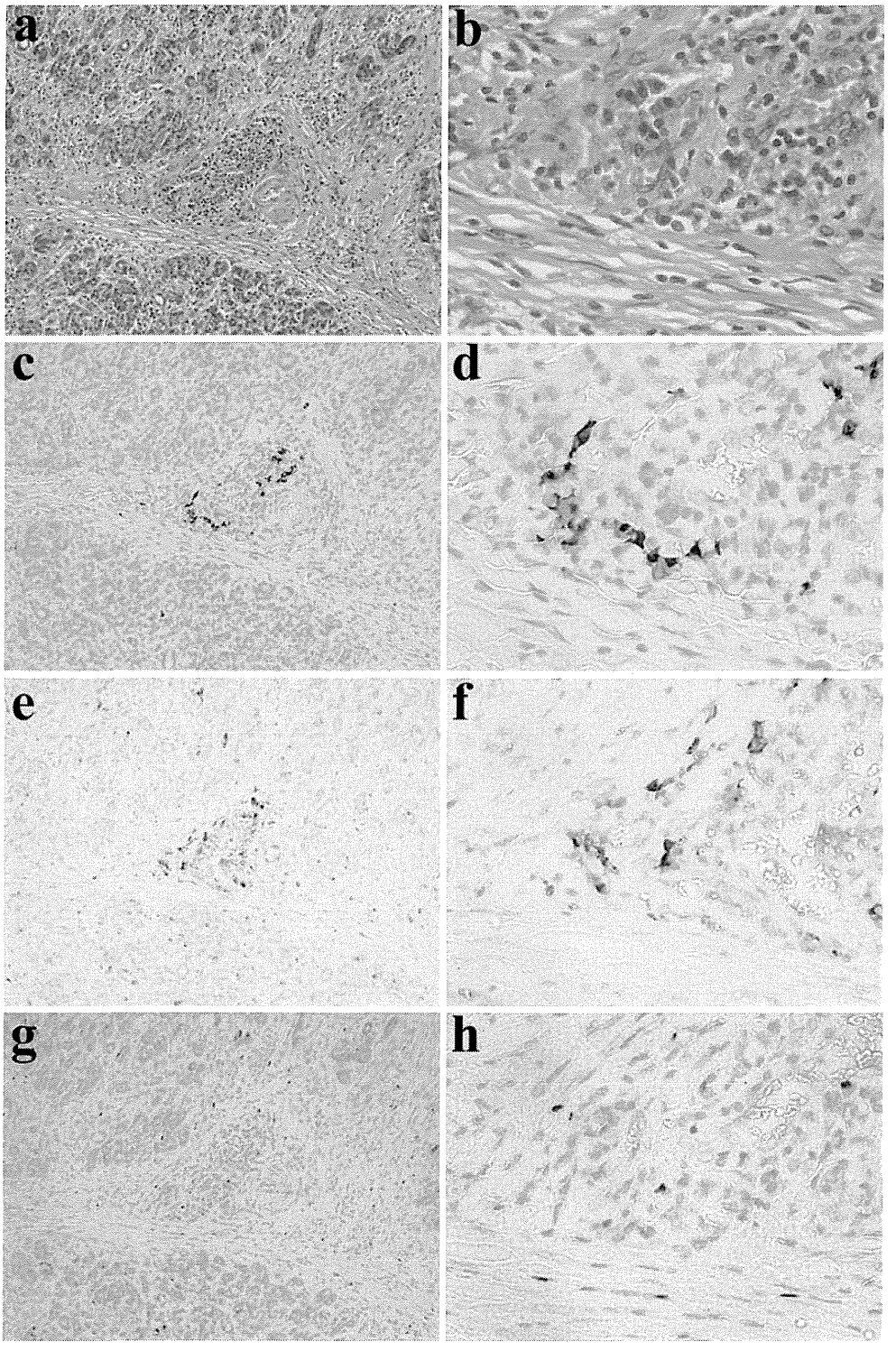

Fig. 4 Histopathologic and immunohistochemical findings in the OP area. H&E staining. **a** ×100, **b** ×400. Inflammatory cells' infiltrate was evident in interlobular position. IgG4-positive cells (**c** ×100, **d** ×400), IgG-positive cells (**e** ×100, d ×400), and Foxp3-positive cells (**g** ×100, **h** ×400) were abundant

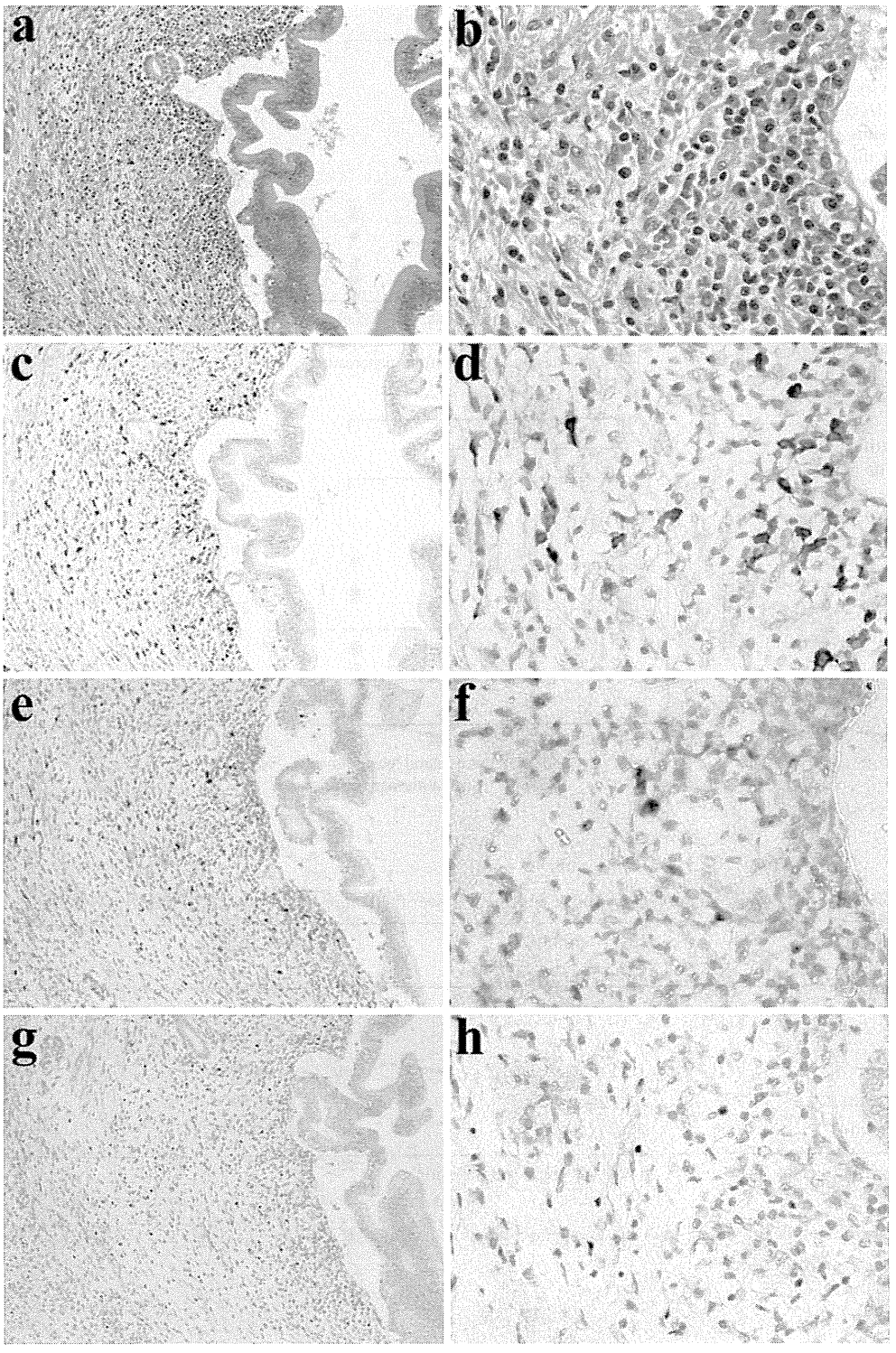

Fig. 5 Histopathologic and immunohistochemical findings in Type 1 autoimmune pancreatitis (AIP). H&E staining. **a** ×100, **b** ×400. Inflammatory cells' infiltrate was evident around the pancreatic duct. IgG4-positive cells (**c** ×100, **d** ×400), IgG-positive cells (**e** ×100, d ×400), and Foxp3-positive cells (**g** ×100, **h** ×400) were abundant

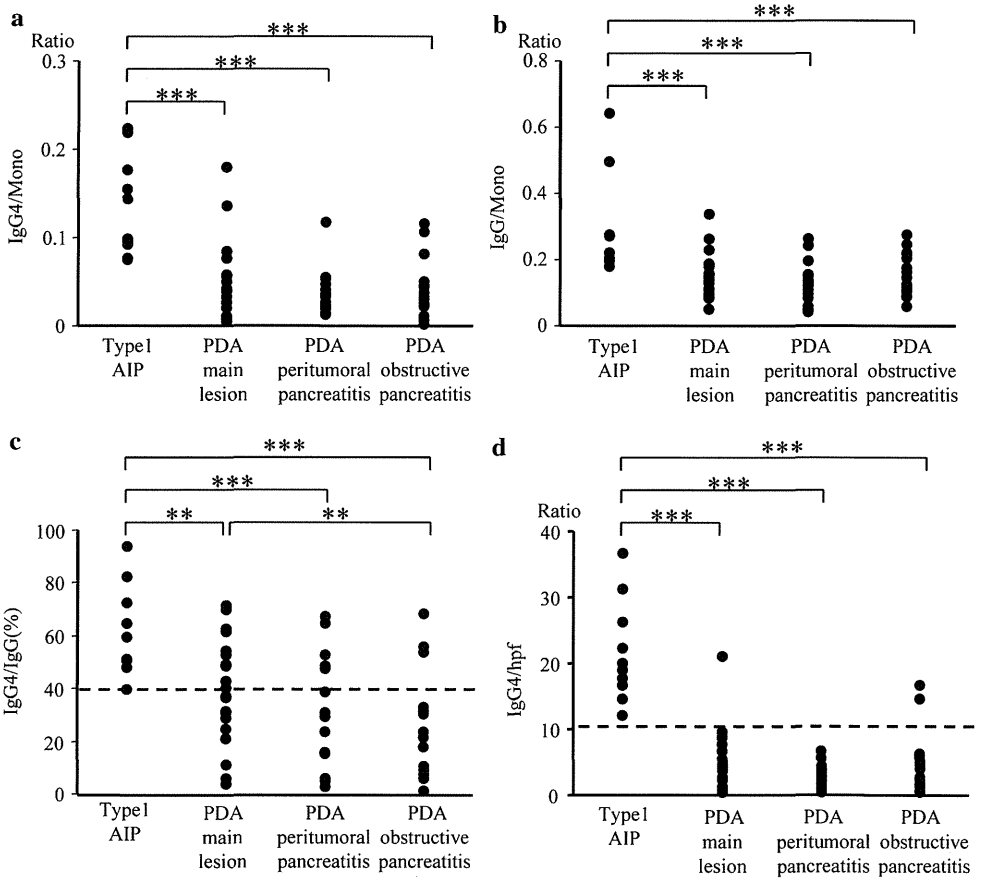

Fig. 6 The ratios of infiltrated IgG4, IgG, and IgG4/IgG positive cells. **a** The ratio of IgG4-positive cells to infiltrated mononuclear cells (*IgG4/Mono*) in Type 1 AIP patients was significantly higher than others. **b** The ratio of IgG-positive cells to infiltrated mononuclear cells (*IgG/Mono*) in Type 1 AIP patients was significantly higher than others. **c** The ratio of IgG4-positive cells to IgG-positive cells (*IgG4/IgG*) in Type 1 AIP patients was significantly higher than others. The ratio of IgG4/IgG was significantly higher in the PDA area than in the obstructive pancreatitis area. **d** IgG4-positive cells per high-power field in Type 1 AIP were significantly higher than others. A small but significant part of the PDA area showed >10 IgG4-positive cells per high-power field. Data are expressed as the mean ± standard error of the mean (SEM). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Table 2 Number of cases with more than ten IgG4-positive cells/high power field and a more than 40 % IgG4/IgG ratio in PDA and Type 1 AIP

Disease	IgG4 >10/hpf	IgG4/IgG > 40 %	IgG4 > 10/hpf and IgG4/IgG > 40 %
Type 1 AIP	9/9 (100 %)	8/9 (89 %)	8/9 (89 %)
PDA			
Main lesion	1/21 (5 %)*	9/21 (43 %)**	1/21 (5 %)*
Peritumoral pancreatitis	0/21 (0 %)*	6/21 (29 %)**	0/21 (0 %)*
Obstructive pancreatitis[a]	2/21 (10 %)*	3/21 (14 %)*,†	1/21 (5 %)*

* $p < 0.001$; ** $p < 0.01$ versus Type 1 AIP, † $p < 0.05$ versus main lesion

hpf High power field

Data are presented as the number of cases, with the percentage given in parenthesis

[a] DISTAL sites from pancreatic cancer

Fig. 5g, h) was significantly higher than that in the PDA area (0.051 ± 0.008; $p < 0.0001$; Fig. 2g, h), the PT area (0.035 ± 0.005; $p < 0.0001$; Fig. 3g, h), and the OP area (0.032 ± 0.005; $p < 0.0001$; Figs. 4g, h, 7). The ratio of IgG4/IgG was significantly higher in the PDA area than in the OP area ($p = 0.0358$).

Correlation between the Foxp3/Mono and IgG4/Mono ratio in OP

The Foxp3/Mono and IgG4/Mono ratios were positively correlated in the OP area ($R = 0.733$), but not in other areas (PDA: $R = 0.102$; PT: $R = 0.09$; Fig. 8a). The

Foxp3/Mono and IgG4/Mono ratios were positively correlated in Type 1 AIP ($R = 0.92$; Fig. 8b), but there was no correlation in the other areas (data not shown).

Discussion

In an attempt to clarify the pathophysiological differences between PDA and AIP, in our study we focused on the number of IgG4-positive cells and the ratio of IgG4/IgG. The ratio of cases with >10 positive cells/hpf of IgG4-positive cells was 5 % (1/21) in the PDA area and 10 % (2/21) in the OP area (Table 2). Our study of distribution of IgG4-positive cells in PDA revealed scattered or focal findings (Figs. 3, 4, 5). To date, only a few studies have evaluated IgG4 staining in PDA. In a study by Deshpande et al. [19], IgG4-positive cells (>1 positive cells/×20) were identified in 11 of 19 PDA cases, and documentation of increased numbers of tissue IgG4 positive plasma cells, although not an entirely specific marker for AIP, may provide ancillary evidence for the diagnosis of an IgG4-related systemic disease. It is not possible to compare our results with previous ones due to the different methods used to count positive cells, but it is clear that an increased number of tissue IgG4-positive cells is not a specific marker for Type 1 AIP.

According to the report of Zhang et al. [22], three of 25 resected PDA showed moderate to marked numbers(>10 positive cells/hpf) of IgG4-positive cells, and the distribution of IgG4-positive cells was patchy; moreover, there was no increased staining in areas of chronic pancreatitis adjacent to the tumor. This result relating to the IgG4-positive cell count of the PT area depended on each specimen. Therefore, in the future, it would seem necessary to require a more accurate assessment of the number of samples collected. Dhall et al. [23] reported that diffuse and dense staining (>50 positive cells/hpf) for IgG4 is specifically seen in LPSP and that very little and scattered or focal staining for IgG4 was seen in PDA. These results depended on each stage of the specimen. In our study, the distribution of IgG4-positive cells produced a similar finding, but the number of IgG4-positive cells was less obvious in Type 1 AIP. This difference in distribution might be useful for distinguishing Type 1 AIP from PDA.

We investigated the ratio of IgG4/IgG and found it to range from 0 to 0.71 (mean 0.39) in the PDA area, from 0 to 0.67 (mean 0.26) in the PT area, and from 0 to 0.68 (mean 0.21) in the OP area (Fig. 6c). Many investigators have examined the ratio of IgG4/IgG in inflammatory diseases [40–44], but few studies have evaluated the ratio of IgG4/IgG in PDA [45, 46]. Strehl et al. [46] reported that the ratio of IgG4/IgG in ten adenocarcinomas (4 pancreas, 2 colon, 2 lung, 2 breast) ranged between 0 and 0.48 (mean 0.21). Sepehr et al. [45] reported that the IgG4/IgG ratio of the ampulla in 30 invasive ductal adenocarcinomas ranged between 0 and 0.16 (mean 0.03). To date, there has been no detailed report of IgG4/IgG exceeding 40 % in PDA. In the 2011 comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), pathological findings of marked IgG4-positive cell infiltration (>10 cells/hpf) and an IgG4/IgG ratio of >40 % are considered to be diagnostic of IgG4-RD [47]. In our study, the ratio of IgG4/IgG exceeding 40 % in

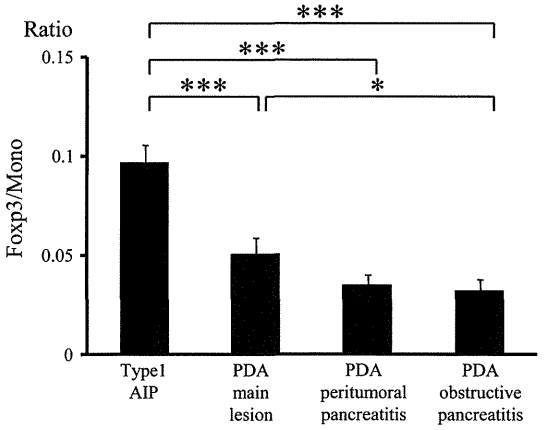

Fig. 7 Ratio of infiltrated Foxp3-positive cells in Type 1 AIP and PDA. The ratio of Foxp3-positive cells to infiltrated mononuclear cells (*Foxp3/Mono*) was significantly higher in Type 1 AIP than others. The ratio of IgG4/IgG was significantly higher in the PDA area than in the obstructive pancreatitis area. Data are expressed as the mean ± SEM. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$

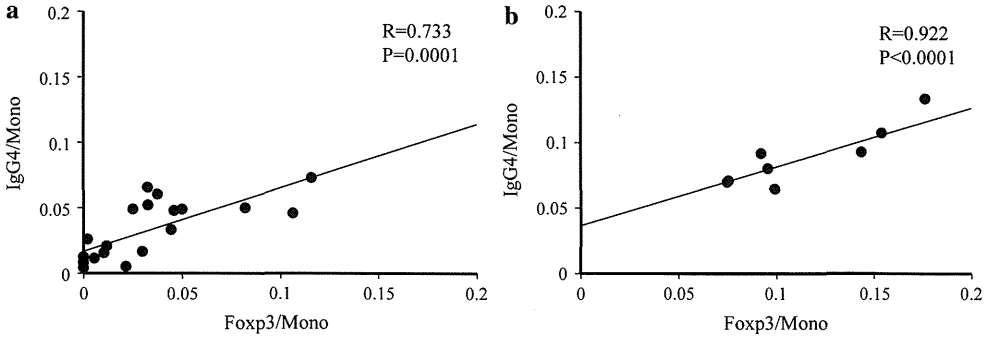

Fig. 8 Correlation between Foxp3- and IgG4-positive cells: **a** OP area, **b** Type 1 AIP. The Foxp3/Mono and IgG4/Mono ratios were positively correlated in the OP area ($R = 0.733$) and in Type 1 AIP ($R = 0.922$)

the PDA area was much higher than expected. Although the ratio decreased with distance from the PDA area; 14 % (3/21) of the cases showed dense staining in the OP area (>40 % IgG4/IgG) (Table 2). Since only 5 % (1/21) of cases fulfilled IgG4 >10/hpf and IgG4/IgG ratio >40 % in the OP area, clinicians should be careful when basing their differential diagnosis of PDA and AIP on the number of IgG4-positive cells and the ratio of IgG4/IgG.

In the OP area, Foxp3/Mono and IgG4/Mono were positively correlated. Apart from pathogenesis, in terms of disease activity suppression, Tregs have been reported to be increased in the periphery or inflammatory sites in patients with such chronic inflammatory diseases as viral hepatitis B/C [48, 49] or *Helicobacter pylori* gastritis [50]. Our previous studies showed positive correlations between IgG4 and Tregs in patients with AIP using peripheral blood [36], pancreas tissues [34], and extra pancreatic lesions [35], suggesting that Tregs may promote the production of IgG4 via interleukin-10 (IL-10) secreted from Tregs. In the present study, there was a significant relationship between IgG4-positive cells and Tregs, although only a few Tregs and IgG4-positive cells infiltrated into the OP area of PDA compared with AIP. Taken together, our findings suggest a similar mechanism producing IgG4 in AIP and OP of PDA. However, further studies are required to clarify this mechanism. In the PT and PDA area, Foxp3/Mono and IgG4/Mono were not correlated. IgG4 may be produced in both the PT and PDA area by a mechanism different from that in Type 1 AIP. There have been several reports of Foxp3-positive cells in PDA [31–33]. In a study by Hiraoka et al. [33], the expression of Foxp3 was increased by the presence of a poorly differentiated tumor for the purpose of providing protection against tumoral immunity. In our study, all of the tumors were moderately differentiated tumors; hence, we could not investigate the difference of degree of differentiation. In an immunohistochemistry using an anti-Foxp3 antibody (PCH101; eBioscience) that detected the n-terminal residues of Foxp3, Hinz et al. [32] reported that they detected Foxp3 expression in tumor cells of 24/39 cases of PDA. In this study, with same anti-Foxp3 antibody (PCH101; eBioscience), tumor-infiltrating lymphocytes were detectable, but malignant epithelial cells were not (data not shown). Foxp3 may, therefore, develop against tumor immunity, unlike Type 1 AIP in PDA.

In conclusion, our findings suggest that the infiltration of IgG4-positive cells is also found in obstructive pancreatitis along with PDA. Therefore, clinicians should be very careful making a differential diagnosis of PDA and AIP based on the number of IgG4-positive cells and the ratio of IgG4/IgG, especially with a small biopsied sample taken by fine needle aspiration.

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Conflict of interest The authors declare that they have no conflict of interest.

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Review Article

Treatment of Autoimmune Pancreatitis with the Anecdotes of the First Report

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The first case that led researchers to put forward a new concept of autoimmune pancreatitis (AIP) was treated with steroids by gastroenterologists in Tokyo Women's Medical University. It is important to differentiate AIP from pancreatic cancer before treatment with steroids is started. Today, steroids are standard therapy for AIP worldwide. In the Japanese consensus guidelines, steroid therapy is indicated for symptomatic AIP. After management of glucose levels and obstructive jaundice, oral prednisolone is initiated at 0.6 mg/kg/day for 2–4 weeks and is gradually tapered to a maintenance dose of 2.5–5 mg/day over 2-3 months. To prevent relapse, maintenance therapy with low-dose prednisolone is used. For relapsed AIP, readministration or increased doses of steroids are effective. The presence of proximal bile duct stenosis and elevated serum IgG4 levels may be predictive of relapse of AIP. It is necessary to verify the validity of the Japanese regimen of steroid therapy for AIP. The necessity, drugs, and duration of maintenance therapy for AIP need to be clarified by prospective studies.

1. Introduction

The first case that led researchers to put forward a new concept of autoimmune pancreatitis (AIP) was treated with steroids by gastroenterologists (Professor Tadashi Takeuchi) in Tokyo Women's Medical University, and the concept was proposed by Yoshida, a member of the group, in 1995 [1]. This paper describes the anecdotes of treatment of the first case that led researchers to put forward a new concept of AIP and reviews current strategies for treatment of this disorder.

2. Anecdotes of Treatment of the First AIP Case

In 1993, a 68-year-old woman who had undergone exploratory laparotomy for jaundice and an abdominal tumor at another hospital, but she was found to have advanced pancreatic cancer that was inoperable, and one month after being discharged she came to Tokyo Women's Medical University Hospital to be treated for pancreatic cancer.

Her general condition was good, and during that 1-month period her jaundice had spontaneously improved without any treatment. Based on the physical examination, the laboratory results, and the findings obtained by diagnostic imaging, AIP would come to mind today, but there was no concept of AIP in those days.

As far as steroid therapy is concerned, we have to pay attention to side effects or complications such as steroid-induced pancreatitis. However, it was fortunate that steroid therapy was dramatically effective without any side effects in this patient; her physical findings, laboratory data, and diagnostic imaging findings became normal, and she was discharged uneventfully.

The 8-week steroid therapy was effective, with the results that hyperglobulinemia and positive autoantibody were normalized, and swelling of the pancreas and irregular narrowing of the main pancreatic duct were also normalized. Those were clearly attributable to an autoimmune mechanism, and we proposed autoimmune pancreatitis.