(IgG4+MOLPS) の確立のための研究」班．「IgG4 関連疾患包括診断基準 2011」．日本内科学会誌 in press, 2012

8. Kamisawa T, Funata N, Hayashi Y, *et al.* A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol.* 38:982-984, 2003
9. Kamisawa T, Nakajima H, Egawa N, *et al.* IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology* 6:132-137 2006
10. Okazaki K, Uchida K, Miyoshi H, *et al.* Recent Concepts of Autoimmune Pancreatitis and IgG4-Related Disease. *Clin Rev Allergy Immuno.* 2011
11. Okazaki K, Uchida K, Koyabu M, *et al.* Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol.* 46:277-288, 2011
12. Yamamoto M, Ohara M, Suzuki C, *et al.* Elevated IgG4 concentrations in serum of patients with Mikulicz's disease. *Scand J Rhumatol.* 33:432-433, 2004
13. Masaki Y, Dong L, Kurose N, *et al.* Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome: Analysis of 64 cases of IgG4-related disorders. *Ann. Rheum.* 63:1310-1315, 2009
14. Dahlgren M, Khosroshahi A, Nielsen GP, *et al.* Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. *Arthritis Care Res.* (Hoboken) 62, 1312-1318, 2010
15. Kitagawa S, Zen Y, Harada K, *et al.* Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am J Surg Pathol.* 29:783-791, 2005
16. Hamano H, Kawa S, Ochi Y, *et al.* Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 359:1403-1404, 2002
17. Zen Y, Onodera M, Inoue D, *et al.* Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol.* 33:1833-1839, 2009
18. Zen Y, Kitagawa S, Minato H, *et al.* IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. *Hum Pathol.* 36:710-717, 2005
19. Saeki T, Saito A, Yamazaki H, *et al.* Tubulointerstitial nephritis associated with IgG4-related systemic disease. *Clin Exp Nephrol.* 11:168-173, 2007
20. Saeki T, Nishi S, Imai N, *et al.* Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int.* 78:1016-1023, 2010
21. Zen Y, Inoue D, Kitao A, *et al.* IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol.* 33:1886-1893, 2009
22. Inoue D, Zen Y, Abo H, *et al.* Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology* 251:260-270, 2009
23. Sato Y, Notohara K, Kojima M, *et al.* IgG4-related disease: historical overview and pathology of hematological disorders. *Pathol Int.* 60:247-258, 2010
24. Yamamoto M, Takahashi H, Suzuki C, *et al.* Analysis of serum IgG subclasses in Churg-Strauss syndrome-the meaning of elevated serum levels of IgG4. *Intern Med.* 49:1365-1370, 2010
25. Masaki Y, Sugai S, and Umehara H. IgG4-related Diseases Including Mikulicz's Disease and Sclerosing Pancreatitis: Diagnostic Insights. *J Rheumatol.* 37, 2010
26. Shimosegawa T, Chari ST, Frulloni L, *et al.* International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 40: 352-358, 2011
27. Kawano M, Saeki T, Nakashima H, *et al.* Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol.* 15:615-626, 2011

Hindawi Publishing Corporation
International Journal of Rheumatology
Volume 2012, Article ID 357071, 9 pages
doi:10.1155/2012/357071

Review Article

Are Classification Criteria for IgG4-RD Now Possible? The Concept of IgG4-Related Disease and Proposal of Comprehensive Diagnostic Criteria in Japan

Kazuichi Okazaki[1] and Hisanori Umehara[2]

[1] *Division of Gastroenterology and Hepatology, The Third Department of Internal Medicine, Kansai Medical University, Shinmachi, Hirakata, Osaka 573-1197, Japan*
[2] *Division of Hematology and Immunology, Department of Internal Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Kanazawa, Japan*

Correspondence should be addressed to Kazuichi Okazaki, okazaki@hirakata.kmu.ac.jp

Received 9 November 2011; Accepted 25 March 2012

Academic Editor: Vikram Deshpande

Recent studies suggest simultaneous or metachronous lesions in multiorgans characterized by elevated serum levels of IgG4 and abundant infiltration of IgG4-positive plasma cells with various degrees of fibrosis. Two Japanese research committees for IgG4-RD, one from fibrosclerosis (Okazaki team) and the other from lymph proliferation (Umehara team) supported by the "Research Program for Intractable Disease" of the Ministry of Health, Labor, and Welfare of Japan, have agreed with the unified nomenclature as "IgG4-RD" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD. Validation of the CDC demonstrated satisfactory sensitivity for the practical use of general physicians and nonspecialists but low sensitivity in the organs to be difficult in taking biopsy specimens such as type1 autoimmune pancreatitis (IgG4-related AIP), compared with IgG4-related sialadenitis/dacryoadenitis (Mikulicz's disease) and IgG4-related kidney disease. Although the diagnostic criteria covering all IgG4-RD are hard to be established, combination with the CDC and organ-specific diagnostic criteria should improve sensitivity.

1. Introduction

Recent studies have suggested simultaneous or metachronous lesions in multiorgans characterized by elevated serum levels of IgG4 and abundant infiltration of IgG4-positive plasma cells with various degrees of fibrosis, which lead us to propose the concept of a systemic disease [1, 4, 10, 23, 24]. However, there are many synonyms suggesting a systemic disease, such as IgG4-related autoimmune disease [1], IgG4-related sclerosing disease [4], IgG4-related plasmacytic syndrome (SIPS) [23], IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [10], and systemic IgG4-related disease, all of which may refer to the same conditions [24, 25] (Table 1). To simplify these conditions, members of two Japanese research committees for IgG4-related disease, one from view of fibrosclerosis (Chaired by Prof. Okazaki) [24] and the other from lymph proliferation (Chaired by Professor. Umehara H) [25], both of which are supported by the "Research for Intractable Disease" Program from the Ministry of Health, Labor, and Welfare of Japan, have agreed with unification of different nomenclatures as "IgG4-related disease (IgG4-RD)" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD [15]. As it still remains unclear whether pathogenetic mechanisms in each involved organ-are same or not, the term IgG4-RD was appointed as minimally reflecting these conditions to avoid misdiagnosis of malignancy as much as possible.

2. The Concept of IgG4-Related Disease

The two Japanese research committees independently analyzed the clinical features and conditions of IgG4-RD and finally resulted in the following consensus with close collaboration [15, 24, 25]. (1) Patients with IgG4-RD show

Table 1: Nomenclatures of IgG4-related conditions.

Nomenclature	Authors	(year)
IgG4-related autoimmune disease	Kamisawa et al. [1]	(2003)
IgG4-associated multifocal systemic fibrosis	van der Vliet and Perenboom [2]	(2004)
IgG4-related systemic disease	Kamisawa et al. [3]	(2004)
IgG4-related sclerosing disease	Kamisawa et al. [4–7]	(2006)
Hyper-IgG4 disease	Neild et al. [8]	(2006)
IgG4-related disease	Zen et al. [9]	(2007)
Systemic IgG4 plasmacytic syndrome (SIPS)	Masaki et al. [10]	(2009)
IgG4-related multiorgan Lymphoproliferative syndrome (IgG4-MOLPS)	Masaki et al. [10]	(2009)
IgG4-associated disease	Geyer et al. [11]	(2010)

diffuse/focal organ enlargement, with mass-forming or nodular/thickened lesions in various organs, including the central nervous system [26], lachrymal/salivary glands [10, 23], thyroid gland [27, 28], lungs [29], pancreas [30, 31], biliary duct [32], liver [33], gastrointestinal tract [34, 35], kidneys [36], prostate gland [37], retroperitoneum [38], skin [39], lymph nodes [5, 40, 41], and artery [42, 43]. These conditions are quite similar to multifocal idiopathic fibrosclerosis (MIF) [44]. (2) These multiorgan lesions may occur synchronously or metachronously, with the prominent infiltration of lymphocytes and IgG4-positive plasmacytes with fibrosis. (3) IgG4-RD mainly affects middle-aged to elderly men except for IgG4-related dacryoadenitis/sialadenitis. Although clinical symptoms depending on involved organs are relatively mild, some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions; hydronephrosis due to retroperitoneal fibrosis; respiratory symptoms due to pulmonary lesions. (4) Steroid treatment is effective in many patient with IgG4-RD. However, prognosis and risk factors of recurrence still remain unclear. (5) Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 characteristic of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of pancreatic, biliary tract, and retroperitoneal lesions but are rarely observed in lachrymal/salivary glands or lymph nodes.

3. IgG4-Related Disease (IgG4-RD) as the Comprehensive Nomenclature [24, 25]

In addition to MIF, there are many synonyms, such as IgG4-related autoimmune disease [1], "IgG4-related sclerosing disease" [4], IgG4-related plasmacytic disease (SIPS) [23], and "IgG4 + sMOLPS" [10], all of which may refer to the same conditions. It has been debated which one is the most appropriate. Storiform fibrosis and obliterative phlebitis are characteristic of biliopancreatic, retroperitoneal, and renal lesions, but rarely observed in lachrymal/salivary glands and lymphnodes [24, 25]. Then, the nomenclature of "IgG4-related sclerosing disease" is mainly based on the fibrous swollen organs, whereas those of "IgG4-SIPS" and "IgG4-MOLPS" are based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis [24, 25]. Although most patients have multiorgan lesions synchronously or metachronously, about 10–20% of the patients show a solitary organ involved without confirming other organ involvement [24, 25]. Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not. In addition to IgG4-RD, IgG4-associate conditions such as high serum levels of IgG4 or abundant infiltration of IgG4-positive cells were reported in some patients with malignancy; pancreatic [6, 45], biliary [46] and salivary cancer [47], gastrointestinal sarcoma [48], and ocular adnexal lymphoma [49–51]. Therefore, the term "systemic" may lead us to misdiagnosis of other organ lesions showing IgG4-related conditions in cases of malignancy [51]. Based on these findings, the members of Umehara and Okazaki teams have agreed that the term "IgG4-related disease" is appointed as minimally accepting these conditions at this moment.

4. Comprehensive Diagnostic Criteria for IgG4-RD [15, 24, 25]

The patients with IgG-4-related disease show organ enlargement or nodular/hyperplastic lesions in organs in the entire body, synchronously or metachronously, due to the prominent infiltration and fibrosis of lymphocytes and plasmacytes; however, the causes of the disease are still not clear. The organs known to be affected include the central nervous system, lacrimal/salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tracts, kidneys, prostate gland, retroperitoneum, skin, arteries, and lymph nodes. Although it remains unclear whether this disease is the same as multifocal fibrosclerosis, that is a possibility. Clinical symptoms vary depending on the organ in which the lesions are located, which suggests that it is hard to establish criteria covering all patients with IgG4-RD. Therefore, specific diagnostic criteria are required for each involved organ such IgG4-related Mikulicz's disease (IgG4-related dacryoadenitis/sialadenitis [12] (Table 2), type 1 AIP (IgG4-related pancreatitis) [13] (Table 3), and IgG4-related kidney disease [14, 41] (Table 4). However, these organ-specific criteria do not cover other organs or are not familiar to general clinicians and specialists. Moreover, to avoid misdiagnosis of malignancy, all physicians have to know this emerging disease entity and can make a diagnosis of IgG4-RD. Therefore, the CDC for IgG4-RD, containing three major criteria (clinical, hematological and histopathological examinations), have been proposed for practical use of general physicians and nonspecialist [15] (Table 5). Although sensitivity of the CDC for definitive IgG4-RD is low in the organs to be difficult in taking biopsy specimens, it can detect possible cases of IgG4-RD. In the probable or possible cases, organ specific criteria should be used concurrently.

Table 2: Diagnostic criteria for IgG4+ Mikulicz's disease [12] (approved by the Japanese Society for Sjögren's Syndrome, 2008).

(1) Symmetrical swelling of at least 2 pairs of lachrymal, parotid, and submandibular glands continuing for more than 3 months,

(2) elevated serum IgG4 (>135 mg/dL),

or

(3) histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 50%) with typical tissue fibrosis or sclerosis.

Differential diagnosis is necessary from other disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. Although the diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different.

(1) *Clinical Examination.* Physical examinations and imaging on US/CT/MRI can show the characteristic diffuse/localized swelling, masses, or thickness in single or multiple organs (Figure 1).

(2) *Immunological Examination*

(a) *Increase of Serum Levels of IgG4.* The cutoff value for serum IgG4 concentration, 135 mg/dL, was based on receiver operating characteristic (ROC) curves, and its validity was confirmed in patients with autoimmune pancreatitis [7] (Table 6). In patients with single-organ involvement and serum IgG4 concentration less than 135 mg/dL, the IgG4/IgG ratio may be helpful in making a diagnosis.

However, elevated IgG4 may be also observed in other diseases (e.g., atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease), especially in about 10% of malignancy, which suggests that high serum IgG4 is not necessarily specific marker of IgG4-RD [6]. Although a high cutoff value with >270 mg/dL of IgG4 increases specificity but decreased sensitivity of IgG4-RD differing from pancreatic cancer [45]. Therefore, at present, the significance of elevated IgG4 in the pathogenesis/pathophysiology of IgG4-RD still remains unknown.

(b) *Other Immunological Markers.* In addition to increased serum levels of IgG4, high serum levels of polyclonal γ-globulin, IgG, and IgE are often, and hypocomplementemia may occur [52]. As these markers are less sensitive for IgG4-RD, they are not included as a diagnostic criterion.

(3) *Histopathologic Examination.* Although tissue biopsies are difficult to obtain from some organs, including the pancreas, retroperitoneum and ocular cavity, histopathological examination is important.

(a) *Marked Lymphocyte and Plasmacyte Infiltration and Fibrosis.* Storiform or swirling fibrosis or obliterative phlebitis is Characteristic of IgG4-RD and may be important in its diagnosis.

(b) *Infiltration of IgG4-Positive Plasma Cells.* IgG4/IgG-positive cells more than 40% [53] or 50% [12] have been reported in lymphnodes of the patients with IgG4-RD. On the other hand, more than 10 IgG4-positive plasma cells are recommended that in diagnosis of type 1 AIP [13]. Based on these findings, the CDC for IgG4-RD recommend both the ratio of IgG4/IgG-positive cells >40% and infiltration of >10 IgG4-positive plasma cells/HPF for the definitive diagnosis [15]. Eosinophilic infiltration is often observed along with infiltration of IgG4-positive cells. It is noted that reactive infiltration of IgG4-positive cells and fibrosis may be observed in various diseases and clinical conditions, such as rheumatoid synovitis, inflammatory oral and skin lesions, and around cancer. However, it is noted that some additional immune-mediated conditions with increased serum interleukin-6 (IL-6) such as multicentric Castleman's disease may show elevated serum IgG4 and/or IgG4+/IgG+ plasma cell ratios >40%.

(4) *Prohibition of Facile Steroid Treatment in the CDC for IgG4-RD.* Patients with malignant lymphoma or paraneoplastic lesions can sometimes be improved by steroid administration. Therefore, steroid trials should be strictly avoided. Efforts should be made to collect tissue samples for diagnosis. However, patients having disease in organs difficult to biopsy, such as the pancreas, retroperitoneum, and pituitary, and respond to steroids may possibly have IgG4-RD. In accordance with the guidelines for treatment of autoimmune pancreatitis, patients should be started on 0.5-0.6 mg/kg/day/prednisolone. If patients do not respond to the initial steroid therapy, the diagnosis should be reviewed again.

(5) *Diseases to be Excluded or Differentiated*

(a) *Malignancies (e.g., Cancer, Lymphoma).* In cases of malignancy in the involved organs, it is essential to determine whether malignant cells are present histopathologically.

(b) *Similar Diseases.* Other similar benign diseases including Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, idiopathic retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome should be differentially diagnosed using the diagnostic criteria for each disease. It is noted that multicentric Castleman's disease, one of hyper IL-6 syndromes should be excluded from IgG4-RD, even if the CDC for IgG4-RD are fulfilled.

Table 3: International Consensus Diagnostic Criteria (ICDC) for autoimmune pancreatitis [13].

Diagnosis	Primary basic for diagnosis	Imaging Evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt
*Level 2 D is counted as level 1 in this setting.			
	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical†): segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm)
S	Serology	IgG4, >2× upper limit of normal value a or b	IgG4, 1-2× upper limit of normal value a or b
OOI	Other organ involvement		
		(a) Histology of extrapancreatic organs:	(a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct‡:
		any three of the following: (1) marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration; (2) storiform fibrosis; (3) obliterative phlebitis; (4) abundant (>10 cells/HPF) IgG4-positive cells.	both of the following: (1) marked lymphoplasmacytic infiltration without granulocytic infiltration; (2) abundant (>10 cells/HPF) IgG4-positive cells.
		(b) Typical radiological evidence at least one of the following: (1) segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture; (2) retroperitoneal fibrosis;	(b) Physical or radiological evidence: at least one of the following: (1) symmetrically enlarged salivary/lachrymal glands; (2) radiological evidence of renal involvement described in association with AIP.
H	Histology of the pancreas	LPSP (core biopsy/resection): at least 3 of the following: (1) periductal lymphoplasmacytic infiltrate without granulocytic infiltration; (2) obliterative phlebitis; (3) storiform fibrosis; (4) abundant (>10 cells HPF) IgG4-positive cells.	LPSP (core biopsy): any 2 of the following: (1) periductal lymphoplasmacytic infiltrate without granulocytic infiltration; (2) obliterative phlebitis; (3) storiform fibrosis; (4) abundant (>10 cells/HPF) IgG4-positive cells.
			Diagnostic steroid trial
Response to steroid (Rt)*	Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations		

Table 4: Diagnostic criteria for IgG4-related kidney disease [14].

(1) Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG or IgE or hypocomplementemia

(2) Abnormal renal radiologic findings:

(a) multiple low-density lesions on enhanced computed tomography;

(b) diffuse kidney enlargement;

(c) hypovascular solitary mass in the kidney;

(d) hypertrophic lesion of the renal pelvic wall without irregularities of the renal pelvic surface.

(3) Elevated serum IgG4 level (>135 mg/dL)

(4) Histological findings in the kidney:

(a) dense lymphoplasmacytic infiltration by >10 IgG4-positive plasma cells/high power field (HPF) and/or IgG4+/IgG+ positive plasma cells > 40%;

(b) characteristic (sclero-) fibrosis surrounding nests of lymphocytes and/or plasma cells;

(5) Histological findings in extrarenal organ(s):

dense lymphoplasmacytic infiltration by >10 IgG4-positive plasma cells/HPF and/or IgG4/IgG-positive plasma cells > 40%

Definite: (1) + (3) + (4) (a), (b)
(2) + (3) + (4) (a), (b)
(2) + (3) + (5)
(1) + (3) + (4) (a) + (5)

Probable: (1) + (4) (a), (b)
(2) + (4) (a), (b)
(2) + (5)
(3) + (4) (a), (b)

Possible: (1) + (3)
(2) + (3)
(1) + (4) (a)
(2) + (4) (a)

Appendix:

(1) Clinically and histologically, the following diseases should be excluded:
Wegener's granulomatosis, Churg-Strauss syndrome, and extramedullary plasmacytoma.

(2) Radiologically, the following diseases should be excluded:
Malignant lymphoma, urinary tract carcinomas, renal infarction, and pyelonephritis.

(Rarely, Wegener's granulomatosis, sarcoidosisand metastatic carcinoma)

Table 5: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011 [15].

[Concept]

IgG4-related disease (IgG4-RD) shows organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously, due to marked infiltration of lymphocytes and IgG4-positive plasma cells, as well as fibrosis of unknown etiology. IgG4-RD affects various organs, including the pancreas, bile duct, lacrimal gland, salivary gland, central nervous system, thyroid, lung, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, others show involvement of a single organ. Clinical symptoms vary depending on the affected organ, and some patients may experience serious complications, such as obstruction or compression symptoms due to organomegaly or hypertrophy and organ dysfunction caused by cellular infiltration or fibrosis. Steroid therapy is often effective.

[Comprehensive clinical diagnostic criteria for IgG4-RD, 2011]

(1) Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs.

(2) Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dL).

(3) Histopathologic examination shows;

(1) marked lymphocyte and plasmacyte infiltration and fibrosis

(2) infiltration of IgG4-positive plasma cells: ratio of IgG4/IgG positive cells > 40% and > 10 IgG4-positive plasma cells/HPF.

Definite: (1) + (2) + (3), Probable: (1) + (3), Possible: (1) + (2)

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome) by additional histopathological examination. Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4RD.

Table 6: Sensitivity and specificity of serum levels of IgG4 in patients with type 1 AIP.

	Cut-off	Sensitivity		Specificity	
	mg/dL	n	Median/(range)	n	(vs cancer)
Japan	135				
Okazaki et al. [16]		71	80% 410 (3–3670)	101	98%
Okazaki et al. [17]		52	73% 505 (43–1540)		NS
Kawa et al. [18]		64	92% 618 (8–2855)	80	98%
Korea	135				
Choi et al. [19]		30	73% 473 (10–1764)	76	99%
USA	140				
Ghazale et al. [20]		45	76% 550 (16–2890)	135	90%
Raina et al. [21]		26	44% (8–825)	NS	
Italy	135				
	(focal)	55	66% 267		NS
Frulloni et al. [22]	(diffuse)	32	27% 78		

Table 7: Validation of a combination of CDC and organ-specific criteria for type 1 AIP.

Compared with pancreas cancer, the sensitivity of comprehensive criteria for definite/probable AIP was 0%, but 78% for possible AIP, and specificity was 100% in any groups. Although it is hard to take an enough size of specimen in diagnosis of AIP malignancy can be usually denied by EUS-FNA. Therefore, the CDC are enough for detecting possible AIP, but not for definite/probable AIP.

AIP (n = 60) PaCa (n = 17) Total (n = 77)	JPS 2006	ICDC for type 1 AIP	CDC for IgG4-RD	
Diagnosis of AIP	Definite AIP	Definite/probable AIP	Definite/probable AIP	Possible
sensitivity	70%	97%	0%	78%
specificity	100%	100%	100%	100%
PPV	100%	100%	0%	100%
NPV	49%	8%	100%	57%
accuracy	77%	95%	22%	83%

PaCa: pancreas cancer, PPV: positive predictive value, NPV: negative predictive value.

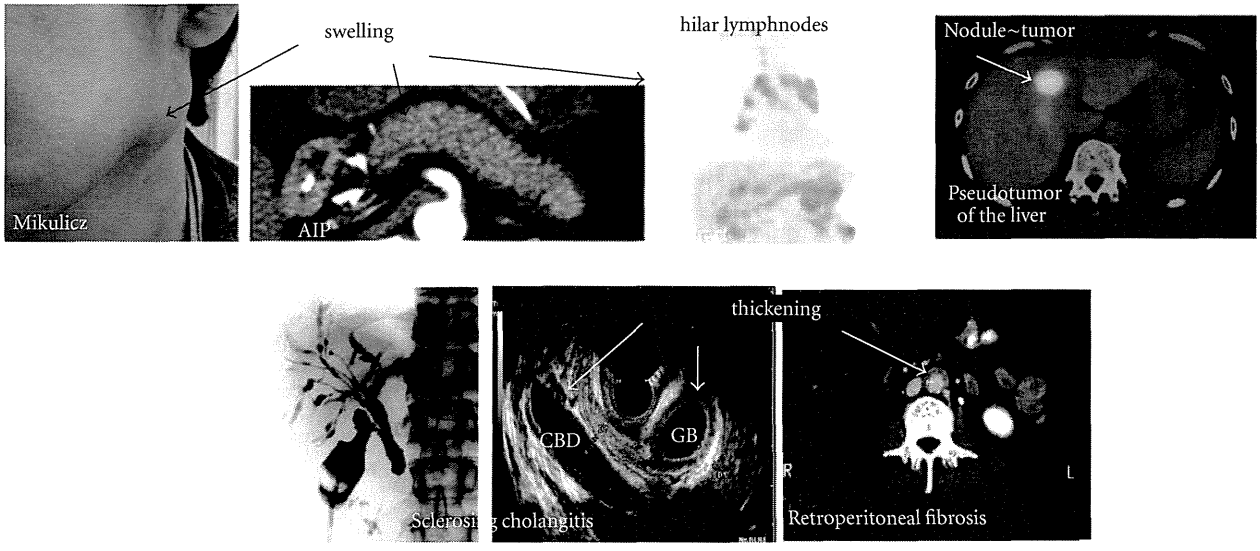

Figure 1: Clinical findings of IgG4-related disease. Physical examinations and imaging on US/CT/MRI can show the characteristic diffuse/localized swelling, masses, or thickness in single or multiple organs.

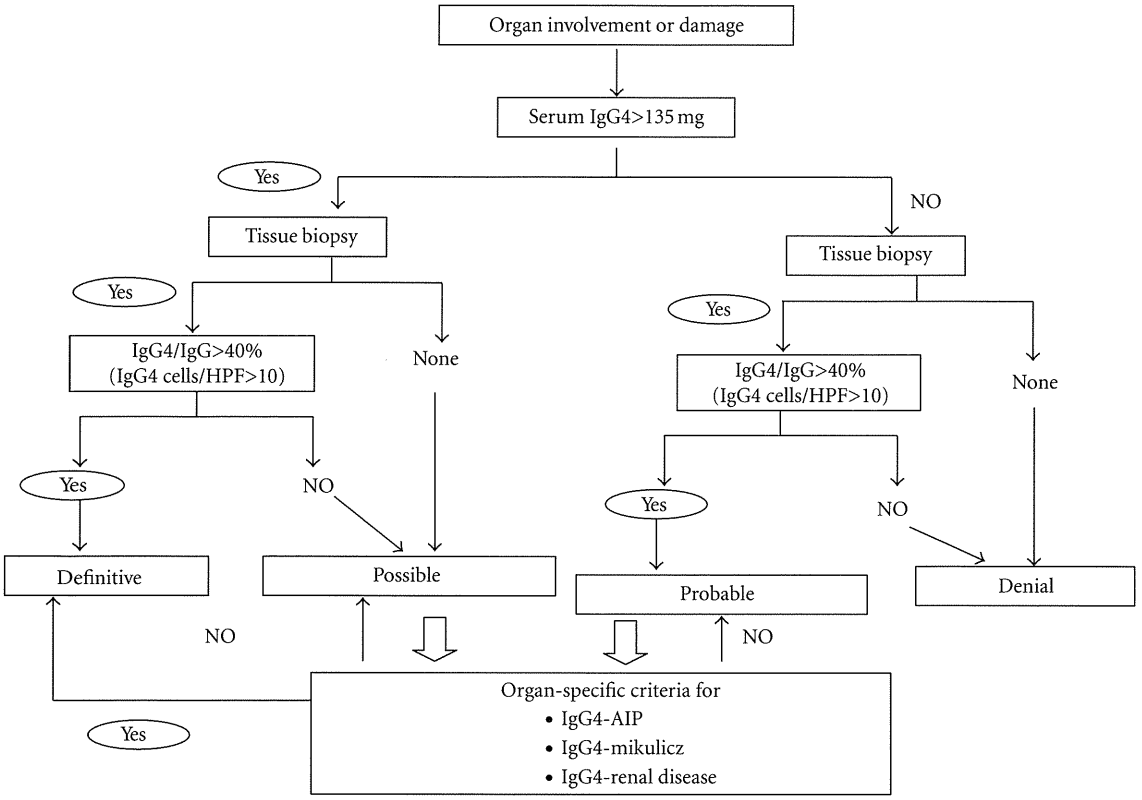

FIGURE 2: Diagnostic algorithm for IgG4-RD in Japan.

5. Sensitivity and Specificity of the CDC Criteria and Diagnostic Algorithm for IgG4-RD

The sensitivity of CDC for definitive/probable IgG4-RD is satisfactory in IgG4-related MD [12] and IgG4-related KD [14], but not in type 1 AIP [6, 13]. The major reason of low sensitivity in type 1 AIP is that enough biopsy samples of the pancreas are not easily obtained in most of these patients. In addition, endoscopic ultrasonography (EUS), guide fine needle aspiration (FNA), is available in a few of institutes in Japan, for examples only 16 of 226 (7%) board member institutes in Kink district of Japan Gastroenterological Endoscopy Society (JGES). On the other hand, the sensitivity of the CDC for possible IgG4-RD is satisfactory in type 1 AIP (Table 7). In contrast, patients with type 1 AIP could not be diagnosed by the comprehensive diagnostic criteria (0%) for definite, because biopsies could not be obtained from most of these patients. Therefore, combination of the CDC and organ-specific criteria should increase the sensitivity of diagnosis, even in the possible cases of IgG4-RD.

Based on these findings, a diagnostic algorithm for IgG4-RD in combination with the CDC and other organ-specific criteria has been proposed, although they have a limitation to the utility of the criteria proposed [15] (Figure 2). In patients with (a) organ enlargement, mass or nodular lesions, or organ dysfunction, performing of both (b) measurement of serum IgG4 and (c) tissue biopsy is recommended. In the cases with >135 mg/dL of IgG4, diagnostic histopathological findings of >10 IgG4 cells/HPF and an IgG4/IgG cell ratio >40 can diagnose them as definitive AIP. In possible or probable cases fulfilling criterion (a) with (b), or (c), organ-specific criteria for each disease should be applied. It is important to differentiate IgG4-RD from malignant tumors of each organ (e.g., cancer, lymphoma) and similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, and Churg-Strauss syndrome) by additional histopathological examination. Future studies including other organ diseases similar to IgG4-RD are needed to establish the diagnostic efficacy of CDC.

6. Conclusion

"All Japan Research Team for IgG4-RD" unified the nomenclatures as "IgG4-related disease (IgG4-RD)" and proposed the comprehensive diagnostic criteria (CDC) for IgG4-RD. The CDC for IgG4-RD was made for the practical use and for general physicians to differentiate IgG4-RD from malignancy or similar diseases as much as possible. Although sensitivity of the CDC for definitive IgG4-RD is low in the organs to

be difficult in taking biopsy specimens, it can detect possible cases of IgG4-RD. In the probable or possible cases, organ-specific criteria should be used concurrently.

Authors' Contribution

K. Okazaki and H. Umehara declare that they equally contributed to this work.

Disclosure

Japanese Research Committee of IgG4-RD (The Working Group of Japanese Research Committee of IgG4-RD) is supported by the Ministry of Health, Labor, and Welfare of Japan.

Acknowledgments

This study was partially supported by: (1) a Grant-in-Aid for Scientific Research (C) of the Ministry of Culture and Science of Japan (23591017); (2) Health and Labor Sciences Research grants (K.O.) for Intractable Diseases, from the Minister of Labor and Welfare of Japan; (3) grants-in-aid from CREST Japan Science and Technology Agency.

References

[1] T. Kamisawa, N. Funata, Y. Hayashi et al., "A new clinicopathological entity of IgG4-related autoimmune disease," *Journal of Gastroenterology*, vol. 38, no. 10, pp. 982–984, 2003.

[2] H. J. van der Vliet and R. M. Perenboom, "Multiple pseudotumors in IgG4-associated multifocal systemic fibrosis," *Annals of Internal Medicine*, vol. 141, no. 11, pp. 896–897, 2004.

[3] T. Kamisawa, N. Funata, and Y. Hayashi, "Lymphoplasmacytic sclerosing pancreatitis is a pancreatic lesion of IgG4-related systemic disease," *The American Journal of Surgical Pathology*, vol. 27, no. 8, pp. 1119–1127, 2003.

[4] T. Kamisawa and A. Okamoto, "Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease," *Journal of Gastroenterology*, vol. 41, no. 7, pp. 613–625, 2006.

[5] T. Kamisawa, H. Nakajima, N. Egawa, N. Funata, K. Tsuruta, and A. Okamoto, "IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy," *Pancreatology*, vol. 6, no. 1-2, pp. 132–137, 2006.

[6] T. Kamisawa, P. Y. Chen, Y. Tu et al., "Pancreatic cancer with a high serum IgG4 concentration," *World Journal of Gastroenterology*, vol. 12, no. 38, pp. 6225–6228, 2006.

[7] K. Okazaki, S. Kawa, T. Kamisawa et al., "Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal," *Journal of Gastroenterology*, vol. 41, no. 7, pp. 626–631, 2006.

[8] G. H. Neild, M. Rodriguez-Justo, C. Wall, and J. O. Connolly, "Hyper-IgG4 disease: report and characterisation of a new disease," *BMC Medicine*, vol. 4, article 23, 2006.

[9] Y. Zen, T. Fujii, Y. Sato, S. Masuda, and Y. Nakanuma, "Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease," *Modern Pathology*, vol. 20, no. 8, pp. 884–894, 2007.

[10] Y. Masaki, L. Dong, N. Kurose et al., "Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders," *Annals of the Rheumatic Diseases*, vol. 68, no. 8, pp. 1310–1315, 2009.

[11] J. T. Geyer, J. A. Ferry, N. L. Harris et al., "Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease," *American Journal of Surgical Pathology*, vol. 34, no. 2, pp. 202–210, 2010.

[12] Y. Masaki, S. Sugai, and H. Umehara, "IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights," *Journal of Rheumatology*, vol. 37, no. 7, pp. 1380–1385, 2010.

[13] T. Shimosegawa, S. T. Chari, L. Frulloni et al., "International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the international association of pancreatology," *Pancreas*, vol. 40, no. 3, pp. 352–358, 2011.

[14] M. Kawano, T. Saeki, H. Nakashima et al., "Proposal for diagnostic criteria for IgG4-related kidney disease," *Experimental Nephrology*, vol. 15, no. 5, pp. 615–626, 2011.

[15] H. Umehara, K. Okazaki, Y. Masaki et al., "Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011," *Modern Rheumatology*, vol. 22, no. 1, pp. 21–30, 2012.

[16] K. Okazaki, S. Kawa, T. Kamisawa et al., "Japanese clinical guidelines for autoimmune pancreatitis," *Pancreas*, vol. 38, no. 8, pp. 849–866, 2009.

[17] K. Okazaki, K. Uchida, M. Matsushita, and M. Takaoka, "How to diagnose autoimmune pancreatitis by the revised Japanese clinical criteria," *Journal of Gastroenterology*, vol. 42, supplement 18, pp. 32–38, 2007.

[18] S. Kawa, K. Okazaki, T. Kamisawa, T. Shimosegawa, and M. Tanaka, "Japanese consensus guidelines for management of autoimmune pancreatitis: II. Extrapancreatic lesions, differential diagnosis," *Journal of Gastroenterology*, vol. 45, no. 4, pp. 355–369, 2010.

[19] E. K. Choi, M. H. Kim, T. Y. Lee et al., "The sensitivity and specificity of serum immunoglobulin G and immunoglobulin G4 levels in the diagnosis of autoimmune chronic pancreatitis: Korean experience," *Pancreas*, vol. 35, no. 2, pp. 156–161, 2007.

[20] A. Ghazale, S. T. Chari, T. C. Smyrk et al., "Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer," *American Journal of Gastroenterology*, vol. 102, no. 8, pp. 1646–1653, 2007.

[21] A. Raina, D. Yadav, A. M. Krasinskas et al., "Evaluation and management of autoimmune pancreatitis: experience at a large us center," *American Journal of Gastroenterology*, vol. 104, no. 9, pp. 2295–2306, 2009.

[22] L. Frulloni, C. Scattolini, M. Falconi et al., "Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients," *American Journal of Gastroenterology*, vol. 104, no. 9, pp. 2288–2294, 2009.

[23] M. Yamamoto, M. Ohara, C. Suzuki et al., "Elevated IgG4 concentrations in serum of patients with Mikulicz's disease," *Scandinavian Journal of Rheumatology*, vol. 33, no. 6, pp. 432–433, 2004.

[24] K. Okazaki, K. Uchida, H. Miyoshi, T. Ikeura, M. Takaoka, and A. Nishio, "Recent concept of autoimmune pancreatitis and IgG4-related disease," *Clinical Reviews in Allergy and Immunology*, vol. 41, no. 2, pp. 126–138, 2010.

[25] H. Umehara, K. Okazaki, Y. Masaki et al., "A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details," *Modern Rheumatology*, vol. 22, no. 1, pp. 1–14, 2012.

[26] A. Shimatsu, Y. Oki, I. Fujisawa, and T. Sano, "Pituitary and stalk lesions (Infundibulo-hypophysitis) associated with

immunoglobulin G4-related systemic disease: an emerging clinical entity," *Endocrine Journal*, vol. 56, no. 9, pp. 1033–1041, 2009.

[27] M. Dahlgren, A. Khosroshahi, G. P. Nielsen, V. Deshpande, and J. H. Stone, "Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum," *Arthritis Care and Research*, vol. 62, no. 9, pp. 1312–1318, 2010.

[28] M. Kojima, M. Hirokawa, H. Kuma et al., "Distribution of IgG4- and/or IgG-positive plasma cells in Hashimoto's thyroiditis: an immunohistochemical study," *Pathobiology*, vol. 77, no. 5, pp. 267–272, 2010.

[29] Y. Zen, D. Inoue, A. Kitao et al., "IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases," *American Journal of Surgical Pathology*, vol. 33, no. 12, pp. 1886–1893, 2009.

[30] K. Yoshida, F. Toki, T. Takeuchi, S. I. Watanabe, K. Shiratori, and N. Hayashi, "Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis," *Digestive Diseases and Sciences*, vol. 40, no. 7, pp. 1561–1568, 1995.

[31] H. Hamano, S. Kawa, A. Horiuchi et al., "High serum IgG4 concentrations in patients with sclerosing pancreatitis," *The New England Journal of Medicine*, vol. 344, no. 10, pp. 732–738, 2001.

[32] T. Nakazawa, H. Ohara, H. Sano et al., "Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis," *Gastrointestinal Endoscopy*, vol. 60, no. 6, pp. 937–944, 2004.

[33] S. Eguchi, M. Takatsuki, M. Hidaka et al., "De novo autoimmune hepatitis after living donor liver transplantation is unlikely to be related to immunoglobulin subtype 4-related immune disease," *Journal of Gastroenterology and Hepatology*, vol. 23, no. 7, part 2, pp. e165–e169, 2008.

[34] T. Fujita, T. Ando, M. Sakakibara, W. Hosoda, and H. Goto, "Refractory gastric ulcer with abundant IgG4-positive plasma cell infiltration: a case report," *World Journal of Gastroenterology*, vol. 16, no. 17, pp. 2183–2186, 2010.

[35] K. Ueno, T. Watanabe, Y. Kawata et al., "IgG4-related autoimmune pancreatitis involving the colonic mucosa," *European Journal of Gastroenterology and Hepatology*, vol. 20, no. 11, pp. 1118–1121, 2008.

[36] Y. Uchiyama-Tanaka, Y. Mori, T. Kimura et al., "Acute tubulointerstitial nephritis associated with autoimmune-related pancreatitis," *American Journal of Kidney Diseases*, vol. 43, no. 3, pp. e18–e25, 2004.

[37] I. Nishimori, T. Kohsaki, S. Onishi et al., "IgG4-related autoimmune prostatitis: two cases with or without autoimmune pancreatitis," *Internal Medicine*, vol. 46, no. 24, pp. 1983–1989, 2007.

[38] H. Hamano, S. Kawa, Y. Ochi et al., "Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis," *The Lancet*, vol. 359, no. 9315, pp. 1403–1404, 2002.

[39] A. Miyagawa-Hayashino, Y. Matsumura, F. Kawakami et al., "High ratio of IgG4-positive plasma cell infiltration in cutaneous plasmacytosis—is this a cutaneous manifestation of IgG4-related disease?" *Human Pathology*, vol. 40, no. 9, pp. 1269–1277, 2009.

[40] W. Cheuk, H. K. L. Yuen, S. Y. Y. Chu, E. K. W. Chiu, L. K. Lam, and J. K. C. Chan, "Lymphadenopathy of IgG4-related sclerosing disease," *American Journal of Surgical Pathology*, vol. 32, no. 5, pp. 671–681, 2008.

[41] Y. Sato, M. Kojima, K. Takata et al., "Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease," *Modern Pathology*, vol. 22, no. 4, pp. 589–599, 2009.

[42] S. Kasashima, Y. Zen, A. Kawashima et al., "Inflammatory abdominal aortic aneurysm: close relationship to IgG4-related periaortitis," *American Journal of Surgical Pathology*, vol. 32, no. 2, pp. 197–204, 2008.

[43] J. H. Stone, A. Khosroshahi, A. Hilgenberg, A. Spooner, E. M. Isselbacher, and J. R. Stone, "IgG4-related systemic disease and lymphoplasmacytic aortitis," *Arthritis and Rheumatism*, vol. 60, no. 10, pp. 3139–3145, 2009.

[44] D. E. Comings, K. B. Skubi, J. van Eyes, and A. G. Motulsky, "Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease," *Annals of Internal Medicine*, vol. 66, no. 5, pp. 884–892, 1967.

[45] A. Ghazale, S. T. Chari, T. C. Smyrk et al., "Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer," *American Journal of Gastroenterology*, vol. 102, no. 8, pp. 1646–1653, 2007.

[46] B. K. Straub, I. Esposito, D. Gotthardt et al., "IgG4-associated cholangitis with cholangiocarcinoma," *Virchows Archiv*, vol. 458, no. 6, pp. 761–765, 2011.

[47] J. Gill, N. Angelo, M. L. Yeong, and N. McIvor, "Salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland," *Human Pathology*, vol. 40, no. 6, pp. 881–886, 2009.

[48] M. Joo, S. H. Chang, H. Kim, J. M. Gardner, and J. Y. Ro, "Primary gastrointestinal clear cell sarcoma: report of 2 cases, one case associated with IgG4-related sclerosing disease, and review of literature," *Annals of Diagnostic Pathology*, vol. 13, no. 1, pp. 30–35, 2009.

[49] W. Cheuk, H. K. L. Yuen, A. C. L. Chan et al., "Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease," *American Journal of Surgical Pathology*, vol. 32, no. 8, pp. 1159–1167, 2008.

[50] T. Kubota, S. Moritani, T. Yoshino, H. Nagai, and H. Terasaki, "Ocular adnexal marginal zone B cell lymphoma infiltrated by IgG4-positive plasma cells," *Journal of Clinical Pathology*, vol. 63, no. 12, pp. 1059–1065, 2010.

[51] M. Yamamoto, H. Takahashi, T. Tabeya et al., "Risk of malignancies in IgG4-related disease," *Modern Rheumatology*. In press.

[52] T. Muraki, H. Hamano, Y. Ochi et al., "Autoimmune pancreatitis and complement activation system," *Pancreas*, vol. 32, no. 1, pp. 16–21, 2006.

[53] Y. Zen, K. Harada, M. Sasaki et al., "Distribution of IgG4- and/or IgG-positive plasma cells in Hashimoto's thyroiditis: an immunohistochemical study," *Pathobiology*, vol. 77, no. 5, pp. 267–272, 2010.

Ⅲ. 分担研究報告

厚生労働科学研究費補助金　難治性疾患等克服研究事業
IgG4 関連疾患に関する調査研究
分担研究報告書

IgG4 関連疾患　胆膵分科会報告

研究分担者　　岡崎和一　　関西医科大学　内科学第三講座　教授

研究要旨：IgG4 関連疾患（IgG4-RD）は日本発の疾患概念として国際的にも新規疾患として認められつつあるが、病変は全身多臓器に及ぶため、各臓器病変の病態解明について、臓器毎の分科会が組織された。胆膵分科会では１型自己免疫性膵炎（AIP）、IgG4 関連硬化性胆管炎（IgG4-SC）を中心に、肝・消化管病変を含む IgG4 関連消化器疾患について、わが国での実態を明らかにするために活動を開始した。

共同研究者：
下瀬川　徹[1)]、神澤 輝実[2)]、川　茂幸[3)]、能登原憲司[4)]、日比 紀文[5)]、島津 章[6)]、乾　和郎[7)]、大原 弘隆[8)]、中沢 貴宏[9)]、太田 正穂[10)]、西野隆義[11)]、伊藤 鉄英[12)]、浜野 英明[13)]、吉田 仁[14)]、平野 賢二[15)]、水野 伸匡[16)]、渡邉 智裕[17)]、児玉 裕三[17)]、窪田 賢輔[18)]、洪　繁[19)]、木梨達雄[20)]、内田一茂[21)]
（東北大学消化器内科[1)]、東京都立駒込病院内科[2)]、信州大学総合健康安全センター[3)]、倉敷中央病院病理検査科[4)]、慶応義塾大学医学部消化器内科[5)]、国立病院機構京都医療センター臨床研究センター[6)]、藤田保健衛生大学坂文種報徳會病院消化器内科[7)]、名古屋市立大学大学院地域医療教育学[8)]、名古屋市立大学大学院医学研究科消化器・代謝内科学[9)]、信州大学医学部法医学教室[10)]、東京女子医科大学八千代医療センター消化器内科[11)]、九州大学大学院医学研究院病態制御内科学[12)]、信州大学医学部附属病院医療情報部・消化器内科[13)]、昭和大学医学部内科学講座消化器内科学部門[14)]、東京大学医学部附属病院消化器内科[15)]、愛知県がんセンター中央病院消化器内科部[16)]、京都大学医学研究科消化器内科学講座[17)]、横浜市立大学附属病院内視鏡センター[18)]、慶応義塾大学医学部坂口記念システム医学講座[19)]、関西医科大学生命化学研究所・分子遺伝学講座[20)]、関西医科大学内科学第三講座[21)]）

A．研究目的

肝胆膵・消化管領域を含めた高 IgG4 血症、IgG4＋細胞浸潤を認める病変を対象に IgG4 関連消化器病変との異同や実態について検討する。

1）IgG4 関連硬化性胆管炎の診断基準の評価
2）胆膵領域 IgG4 関連疾患の重症度分類
3）他消化器領域における IgG4 関連疾患
4）高 IgG4 血症、IgG4＋細胞浸潤を認めるその他の胆膵疾患

B．研究方法

1）IgG4 関連硬化性胆管炎の診断基準の評価
血中 IgG4 値のカットオフ値の妥当性の評価についてワーキンググループを組織して検討する。

2）胆膵領域 IgG4 関連疾患の重症度分類
胆膵領域疾患の重症度の定義と分類を分科会で検討する。

3）他消化器領域における IgG4 関連疾患
コンセンサスのない肝（自己免疫性肝炎）、消化管病変（食道・胃・乳頭・大腸）について各臓器のワーキングチームを組織する。

4）高 IgG4 血症、IgG4＋細胞浸潤を認める他の胆膵疾患
膵癌(含閉塞性膵炎)、胆管癌、PSC の一部の IgG4 陽性細胞浸潤を認める症例に関する調査を行う。

（倫理面への配慮）
本研究のために新たな検査はせず、通常の診療で得られる所見を用いて解析する。また、画像、病理組織を含めた検査所見の本研究への利用については患者本人の承諾を得ると共に解析にあたっては年齢と性別のみの人情報が対象となるため個人が特定されることはない。

C．研究結果
1） IgG4 関連硬化性胆管炎の診断基準の評価
血中 IgG4 値のカットオフ値の妥当性の評価についてワーキンググループを組織して検討し、182 mg/dL が胆管癌や原発性硬化性胆管炎との鑑別に有用であった。
2） 重症度の定義（重症、(中等症)、軽症）
AIPで実際にステロイドが効かないのは２％程度であり、患者数にするとステロイドの効かない患者はAIP3000人中60人、IgG4全体もAIPと同じ頻度と仮定すると1～2万人中200～400人程度がステロイドの効かない患者数となる。ステロイド治療歴のある患者の再燃率はAIPでは1年以内が30%、3年以内が90%程度といのが日本のデータなのでこれらはほぼ全員ステロイド再投与となり中等症以上ということになるが、重症患者は実質上あまり増えないと思われることより
軽症：治療介入不要、中等症以上：要治療介入、重症：ステロイド治療依存性あるいはステロイド抵抗性で、治療しても臓器機能障害が残存する。
5） 他消化器領域における IgG4 関連疾患
上部消化管（食道、胃、十二指腸）：都立駒込病院　神澤先生、下部消化管（小腸、大腸）：慶応大　日比先生、肝：信州大　川先生がチームリーダーとなって文献症例と参加施設症例の検討をする予定となった。
6） 高 IgG4 血症、IgG4＋細胞浸潤を認める他の胆膵疾患
膵癌(含閉塞性膵炎)、胆管癌、PSC の一部の IgG4 陽性細胞浸潤を認める症例に関する調査を行う。

E．結論
胆膵分科会では１型自己免疫性膵炎（AIP)、IgG4 関連硬化性胆管炎（IgG4-SC）を中心に、肝・消化管病変を含む IgG4 関連消化器疾患について、わが国での実態を明らかにするために活動を開始した。

F．研究発表
1． 論文発表

1. Ikeura T, Takaoka M, Uchida K, Shimatani M, Miyoshi H, Kusuda T, Kurishima A, Fukui Y, Sumimoto K, Satoi S, Ohe C, Uemura Y, Kwon AH, Okazaki K. Autoimmune pancreatitis with histologically proven lymphoplasmacytic sclerosing pancreatitis with granulocytic epithelial lesions. Intern Med. 2012;51(7):733-7
2. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012 Feb;22(1):21-30
3. Uchida K, Kusuda T, Koyabu M, Miyoshi H, Fukata N, Sumimoto K, Fukui Y, Sakaguchi Y, Ikeura T, Shimatani M, Fukui T, Matsushita M, Takaoka M, Nishio A, Okazaki K. Regulatory T cells in type 1 autoimmune pancreatitis. Int J Rheumatol. 2012;2012:795026. Epub 2012 Mar 28.
4. Yamashina M, Nishio A, Nakayama S, Okazaki T, Uchida K, Fukui T, Okazaki K. Comparative Study on Experimental Autoimmune Pancreatitis and Its Extrapancreatic Involvement in Mice. Pancreas. 2012;41(8):1255-62.

5. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. Int J Rheumatol. 2012;2012:358371.
6. Fukui Y, Uchida K, Sumimoto K, Kusuda T, Miyoshi H, Koyabu M, Ikeura T, Sakaguchi Y, Shimatani M, Fukui T, Matsushita M, Takaoka M, Nishio A, Shikata N, Sakaida N, Uemura Y, Satoi S, Kwon AH, Okazaki K. The similarity of Type 1 autoimmune pancreatitis to pancreatic ductal adenocarcinoma with significant IgG4-positive plasma cell infiltration. J Gastroenterol. 2012 Oct 5.

2. 学会発表

1. Kimi Sumimoto, Kazushige Uchida, Yuri Fukui, Takeo Kusuda, Hideaki Miyoshi, Norimasa Fukata, Masanori Koyabu, Yutaku Sakaguchi, Tsukasa Ikeura, Masaaki Shimatani, Toshiro Fukui, Mitsunobu Matsushita, Makoto Takaoka, Akiyoshi Nishio, Kazuichi Okazaki. Comparison of International Consensus Diagnostic Criteria and Major Diagnostic Criteria for Autoimmune Pancreatitis. DDW2012 San Diego, California, USA 2012/05
2. Kazushige Uchida, Kazuichi Okazaki. Recent Advances in Autoimmune Pancreatitis. 第 98 回日本消化器病学会総会 東京 2012/04
3. 池浦司，高岡亮，内田一茂，島谷昌明，三好秀明，楠田武生，岡崎和一 疼痛症状のある慢性膵炎患者に対する_成分栄養剤（エレンタール®）の有用性 第98回日本消化器病学会総会 東京 2012/04
4. 富山 尚、内田一茂、岡崎和一 自己免疫性膵炎 におけるステロイドパルス療法の有用性 第98回日本消化器病学会総会 東京 2012/04
5. 内田 一茂，楠田 武生，小藪 雅紀，三好秀明，住本 貴美，福井 由理，池浦 司，島谷 昌明，高岡 亮，岡崎 和一 IgG4関連胆・膵病変におけるIgG4産生機序と制御性T細胞の意義 第109回日本内科学会講演会 京都 2012/04
6. 山科雅央、西尾彰功、岡崎 敬、中山新士、福井寿朗、内田一茂、岡崎和一 自己免疫性膵炎発症マウスにおける膵外病変の検討 第29 回日本胆膵病態・生理研究会 京都 2012/06
7. 楠田武生、内田一茂、岡崎和一 IgG4関連疾患としての自己免疫性膵炎（AIP type 1;LPSP）と好中球病変（AIP type 2;IDCP）における免疫学的相違に関する検討 第29回日本胆膵病態・生理研究会 京都 2012/06
8. 富山 尚、内田一茂、岡崎和一 1型自己免疫性膵炎（type 1 AIP）に対する初期治療としてのステロイドパルス療法の検討 第29回日本胆膵病態・生理研究会 京都 2012/06
9. 住本貴美，内田一茂，福井由理，三好秀明，坂口雄沢，池浦 司，島谷昌明，高岡 亮，岡崎和一 当科における自己免疫性膵炎の診断能に関する検討 第39回日本膵臓学会大会 山形 2012/06
10. 山科雅央、西尾彰功、岡崎 敬、中山新士、福井寿朗、内田一茂、岡崎和一 自己免疫性膵炎マウスにおける膵外病変の検討 第39回日本膵臓学会大会 山形 2012/06
11. 中山新士、西尾彰功、山科雅央、岡崎 敬、福井寿朗、内田一茂、坂口雄沢 アルコール性慢性膵炎の発症における自然免疫／獲得免疫の関与の検討 第39回日本膵臓学会大会 山形 2012/06
12. 内田一茂、池浦 司、岡崎和一 自験例よりみた自己免疫性膵炎の長期予後 第39回日本膵臓学会大会 山形 2012/06

13. 内田一茂、西尾彰功、岡崎和一 IgG4関連肝胆膵疾患における制御性T細胞に関する検討 第49回日本消化器免疫学会 鹿児島 2012/06
14. 内田一茂、岡崎和一、正宗　淳、下瀬川徹 IgG4 関連疾患における性差について第 8 回消化器病における性差医学・医療研究会 京都 2012/08
15. 内田一茂、岡崎和一 IgG4 関連胆膵疾患における ICOS 陽性制御性 T 細胞による IgG4 産生機序に関する検討 第 40 回日本臨床免疫学会 東京 2012/09

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

厚生労働科学研究費補助金難治性疾患克服研究事業
IgG4 関連疾患に関する調査研究
分担研究報告書

膵癌における IgG4 陽性形質細胞の包括診断基準を基にした検討

研究分担者　岡崎和一　関西医科大学　内科学第三講座　教授

研究要旨：近年膵癌周囲に IgG4 陽性細胞が浸潤しているとい報告がなされているのがその詳細については不明である。今回我々は 21 例の膵癌と 9 例の 1 型自己免疫性膵炎（AIP）の手術標本を用いて、IgG4 陽性細胞と制御性 T 細胞（Treg）の関係について検討した。癌部、癌周囲、閉塞性膵炎における IgG4 陽性細胞の数、IgG4/IgG 陽性細胞の比は AIP と比べ有意に低かった（$p<0.05$）。膵癌症例では、IgG4/IgG 比と浸潤単核球に対する Foxp3 陽性細胞は癌部で有意に高値であった（$p<0.05$）。癌部では 9 例（43%）、癌周囲 6 例（29%）、閉塞性膵炎 3 例（14%）で、包括診断基準の IgG4/IgG 比 40%以上を満たしていた。EUS-FNA などの微小検体において、膵癌と AIP の鑑別には注意が必要である。

共同研究者
内田一茂、福井由里、住本貴美、池浦司、光山俊行、坂尾将幸、高岡亮
（関西医科大学内科学第三講座）

A．研究目的

1 型自己免疫性膵炎(AIP)のうち、限局性を呈する自己免疫性膵炎は膵癌との鑑別で苦慮する例が少なくない。2011 年に公表された IgG4 関連包括診断基準では、IgG4/IgG 陽性細胞比 40%以上、かつ IgG4 陽性細胞が 10/HPF を超えるという項目がある。そこで我々は自験例において 1 型自己免疫性膵炎と膵癌とそれに伴う膵炎において浸潤する IgG4 陽性細胞について検討した。

B．研究方法

対象は 1992 年から 2010 年にかけて本学で手術された膵癌患者(PDA) 21 例(女性 7 名、男性 14 名；平均年齢 67 歳)、1 型自己免疫性膵炎患者(AIP) 9 例(女性 5 名、男性 4 名；平均年齢 65 歳)である。

方法は IgG、IgG4、Foxp3 陽性細胞について免疫組織学的方法を用いて検討した。

（倫理面への配慮）

本研究のために新たな検査はせず、過去の手術標本を用いた。解析にあたっては年齢と性別のみの個人情報が対象となるため個人が特定されることはない。

C．研究結果

IgG4/IgG 陽性細胞の比率は AIP 62.4%±5.9、癌部 29.1%±4.5、膵癌隣接部位 25.9%±5.4、膵癌上流の閉塞性膵炎 21.0%±4.8 と AIP で有意に高値であった。

IgG4 陽性細胞数は AIP 21.667±2.436、癌部 5.183±1.061、膵癌隣接部位 2.250±0.431、膵癌上流の閉塞性膵炎 4.033±0.005 個と AIP が有意に高値であった。

IgG4/IgG 陽性細胞比 40%以上の症例が癌部で 21 例中 9 例(43%)、膵癌隣接部位で 21 例中 6 例(29%)、膵癌上流の閉塞性膵炎で 21 例中 3 例(14%)認めた。IgG4/IgG 陽性細胞比 40%以上かつ IgG4/HPF10 を超える症例は膵癌上流の閉塞性膵炎で 21 例中 1 例(5%)に認めた。

Disease	IgG4 >10/hpf	IgG4/IgG > 40 %	IgG4 > 10/hpf かつ IgG4/IgG > 40 %
1 型 AIP	9/9 (100 %)	8/9 (89 %)	8/9 (89 %)
膵癌			
癌部	1/21 (5 %)*	9/21 (43 %)**	1/21 (5 %)*
癌周囲	0/21 (0 %)*	6/21 (29 %)**	0/21 (0 %)*
閉塞性膵炎	2/21 (10 %)*	3/21 (14 %)*†	1/21 (5 %)*

（表 1）各疾患と IgG4 陽性細胞数。

* $p < 0.001$; ** $p < 0.01$ versus Type 1 AIP, † $p < 0.05$ versus main lesion. hpf :high power field

IgG4 と Foxp3 の相関関係は膵癌上流の閉塞性膵炎において相関関係が認められた(R= 0.733)。癌部、膵癌隣接部位では相関関係は認められなかった。

D．考察

膵癌において IgG4/IgG 比率が 40%を超え IgG4 陽性細胞数が 10/HPF を超える症例が認められた。このうち癌細胞のない閉塞性膵炎において 5%に認められた。ただし IgG4 陽性細胞の分布は AIP ではび漫性に膵癌では限局性に認められており、この分布の違いは鑑別に有用となる可能性がある。膵癌と AIP を鑑別する上で FNA など少量の検体で診断する場合は、陽性細胞を数えるのみではなくその分布についても十分な検討が必要であると考えられた。

IgG4 陽性細胞の誘導に関しては、膵癌上流の閉塞性膵炎において AIP と同様に IgG4 と Foxp3 は相関関係が認められた。このことは AIP と同様の機序で IgG4 産生が誘導されている可能性があるが、膵癌隣接部位、膵癌上流の閉塞性膵炎領域において相関関係は認められなかったことより、腫瘍近傍においては異なる機序で IgG4 が産生されている可能性もあり、この点については今後更なる検討が必要であると考えられた。

E．結論

膵癌と AIP の鑑別において IgG4/IgG 陽性細胞比率および IgG4 陽性細胞数を用いることは注意が必要である。

F．研究発表

1．論文発表

1. Ikeura T, Takaoka M, Uchida K, Shimatani M, Miyoshi H, Kusuda T, Kurishima A, Fukui Y, Sumimoto K, Satoi S, Ohe C, Uemura Y, Kwon AH, Okazaki K. Autoimmune pancreatitis with histologically proven lymphoplasmacytic sclerosing pancreatitis with granulocytic epithelial lesions. Intern Med. 2012;51(7):733-7
2. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012 Feb;22(1):21-30
3. Uchida K, Kusuda T, Koyabu M, Miyoshi H, Fukata N, Sumimoto K, Fukui Y, Sakaguchi Y,

Ikeura T, Shimatani M, Fukui T, Matsushita M, Takaoka M, Nishio A, Okazaki K. Regulatory T cells in type 1 autoimmune pancreatitis. Int J Rheumatol. 2012;2012:795026. Epub 2012 Mar 28.

4. Yamashina M, Nishio A, Nakayama S, Okazaki T, Uchida K, Fukui T, Okazaki K. Comparative Study on Experimental Autoimmune Pancreatitis and Its Extrapancreatic Involvement in Mice. Pancreas. 2012;41(8):1255-62.
5. Uchida K, Masamune A, Shimosegawa T, Okazaki K. Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009. Int J Rheumatol. 2012;2012:358371.
6. Fukui Y, Uchida K, Sumimoto K, Kusuda T, Miyoshi H, Koyabu M, Ikeura T, Sakaguchi Y, Shimatani M, Fukui T, Matsushita M, Takaoka M, Nishio A, Shikata N, Sakaida N, Uemura Y, Satoi S, Kwon AH, Okazaki K. The similarity of Type 1 autoimmune pancreatitis to pancreatic ductal adenocarcinoma with significant IgG4-positive plasma cell infiltration. J Gastroenterol. 2012 Oct 5.

2. 学会発表

1. Kimi Sumimoto, Kazushige Uchida, Yuri Fukui, Takeo Kusuda, Hideaki Miyoshi, Norimasa Fukata, Masanori Koyabu, Yutaku Sakaguchi, Tsukasa Ikeura, Masaaki Shimatani, Toshiro Fukui, Mitsunobu Matsushita, Makoto Takaoka, Akiyoshi Nishio, Kazuichi Okazaki. Comparison of International Consensus Diagnostic Criteria and Major Diagnostic Criteria for Autoimmune Pancreatitis. DDW2012 San Diego, California, USA 2012/05
2. Kazushige Uchida, Kazuichi Okazaki. Recent Advances in Autoimmune Pancreatitis. 第 98 回日本消化器病学会総会 東京 2012/04
3. 池浦司，高岡亮，内田一茂，島谷昌明，三好秀明，楠田武生，岡崎和一 疼痛症状のある慢性膵炎患者に対する_成分栄養剤（エレンタール®）の有用性 第98回日本消化器病学会総会 東京 2012/04
4. 富山 尚、内田一茂、岡崎和一 自己免疫性膵炎 におけるステロイドパルス療法の有用性 第98回日本消化器病学会総会 東京 2012/04
5. 内田 一茂，楠田 武生，小藪 雅紀，三好秀明，住本 貴美，福井 由理，池浦 司，島谷 昌明，高岡 亮，岡崎 和一 IgG4関連胆・膵病変におけるIgG4産生機序と制御性T細胞の意義 第109回日本内科学会講演会 京都 2012/04
6. 山科雅央、西尾彰功、岡崎 敬、中山新士、福井寿朗、内田一茂、岡崎和一 自己免疫性膵炎発症マウスにおける膵外病変の検討 第29 回日本胆膵病態・生理研究会 京都 2012/06
7. 楠田武生、内田一茂、岡崎和一 IgG4関連疾患としての自己免疫性膵炎（AIP type 1;LPSP）と好中球病変（AIP type 2;IDCP）における免疫学的相違に関する検討 第29回日本胆膵病態・生理研究会 京都 2012/06
8. 富山 尚、内田一茂、岡崎和一 1型自己免疫性膵炎（type 1 AIP）に対する初期治療としてのステロイドパルス療法の検討 第29回日本胆膵病態・生理研究会 京都 2012/06
9. 住本貴美，内田一茂，福井由理，三好秀明，坂口雄沢，池浦 司，島谷昌明，高岡 亮，岡崎和一 当科における自己免疫性膵炎の診断能に関する検討 第39回日本膵臓学会大会 山形 2012/06
10. 山科雅央、西尾彰功、岡崎 敬、中山新士、福井寿朗、内田一茂、岡崎和一 自己免疫性膵炎マウスにおける膵外病変の検討 第39回日本膵臓学会大会 山形 2012/06

11. 中山新士、西尾彰功、山科雅央、岡崎　敬、福井寿朗、内田一茂、坂口雄沢 アルコール性慢性膵炎の発症における自然免疫／獲得免疫の関与の検討 第39回日本膵臓学会大会 山形 2012/06
12. 内田一茂、池浦　司、岡崎和一 自験例よりみた自己免疫性膵炎の長期予後 第39回日本膵臓学会大会 山形 2012/06
13. 内田一茂、西尾彰功、岡崎和一 IgG4関連肝胆膵疾患における制御性T細胞に関する検討 第49回日本消化器免疫学会 鹿児島 2012/06
14. 内田一茂、岡崎和一、正宗　淳、下瀬川徹 IgG4 関連疾患における性差について第 8 回消化器病における性差医学・医療研究会 京都 2012/08
15. 内田一茂、岡崎和一 IgG4 関連胆膵疾患における ICOS 陽性制御性 T 細胞による IgG4 産生機序に関する検討 第 40 回日本臨床免疫学会 東京 2012/09

G．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

厚生労働科学研究費補助金　難治性疾患等克服研究事業
IgG4 関連疾患に関する調査研究
分担研究報告書

IgG4 関連疾患における悪性疾患合併率の全国調査

研究分担者　　岡崎和一　　関西医科大学　内科学第三講座　教授

研究要旨：IgG4 関連疾患については日本発の疾患概念であるが、その予後については不明である。そこで今回我々は、IgG4 関連疾患における悪性疾患の合併率について全国調査を行った。

共同研究者　内田一茂
（関西医科大学内科学第三講座）

A．研究目的

IgG4 関連疾患については日本発の疾患概念であるが、その予後については不明である。そこで今回我々は、IgG4 関連疾患における悪性疾患の合併率について全国調査を行うこととした。

B．研究方法

IgG4 関連の全身性疾患（自己免疫性膵炎・IgG4 関連唾液腺炎・IgG4 関連眼疾患・IgG4 関連肺疾患・IgG4 関連腎臓病・IgG4 関連後腹膜線維症・IgG4 関連リンパ節腫大・その他の IgG4 関連疾患）の患者数について悪性疾患の合併患者数を調査した。対象施設は自己免疫性膵炎の全国調査に回答した 250 施設の呼吸器内科、耳鼻科、眼科、リウマチ・膠原病科、泌尿器科と千葉班班員の施設に受診中の患者数についてアンケートを送付した。

（倫理面への配慮）

患者数についての調査であり個人情報は一切含まれていない。

C．研究結果

自己免疫性膵炎は 1008 例の患者の回答がありうち悪性疾患を合併したものは 127 例（12.6%）内訳は、舌癌 3 例・喉頭癌 2 例・甲状腺癌 5 例・肺癌 18 例・胃癌 26 例・十二指腸癌 1 例・肝臓癌 4 例・胆管癌 2 例・膵臓癌 12 例・大腸癌 18 例・腎臓癌 5 例・膀胱癌 8 例・前立腺癌 13 例・卵巣癌 1 例・脂肪肉腫 1 例・悪性黒色腫 1 例・白血病 2 例・悪性リンパ腫 2 例・詳細不明 3 例であった。IgG4 関連唾液腺炎は 470 症例のうち 27 例(5.7%)で舌癌 1 例・喉頭癌 1 例・唾液腺癌 1 例・MALT リンパ腫 1 例・悪性リンパ腫 3 例・乳癌 5 例・肺癌 1 例・胃癌 1 例・肝臓癌 1 例・大腸癌 6 例・前立腺癌 2 例・子宮癌 1 例・悪性中皮腫 2 例・悪性黒色腫 1 例であった。IgG4 関連肺疾患は 100 例中 11 例（11.0%）で肺癌 3 例・大腸癌 2 例・腎臓癌 1 例・卵巣癌 2 例・子宮癌 1 例・MALT リンパ腫 1 例であった。IgG4 関連腎臓病は 117 例中 20 例（17.1%）で肺癌 1 例・胃癌 9 例・大腸癌 5 例・腎臓癌 3 例・前立腺癌 1 例であった。IgG4 関連眼疾患は 317 例中 37 例（11.7%）で胃癌 2 例・膵臓癌 1 例・前立腺癌 1 例・乳癌 2 例・悪性リンパ腫 19 例・MALT リンパ腫 12 例であった。IgG4 関連リンパ節腫大は４９例中 3 例（6.1%）で前立腺癌 1 例・悪性リンパ腫 2 例であった。IgG4 関連後腹膜線維症は 115 例中 12 例（10.4%）で肺癌 1 例・大腸癌 3 例・膀胱癌 2 例・腎臓癌 1 例・前立腺癌 3 例・乳癌 1 例・悪性リンパ腫 1 例であった。その他の IgG4 関連疾患は 86 例 13 例（14.0%）で肺癌 2 例・食道癌 2 例・胃癌 2 例・胆管癌 1 例・膵臓癌 1 例・大腸癌 2 例・膀胱癌 1 例・詳細不明 1 例であった。