anaplastic large cell lymphoma of B cell type show a somatic mutation in the IgH V region genes. Leukemia 12 : 753-757, 1998
12 Trainor KJ, Brisco MJ, Wan JH, Neoh S, Grist S, *et al.* : Gene rearrangement in B- and T-lymphoproliferative disease detected by the polymerase chain reaction. Blood 78 : 192-196, 1991
13 Kaplan EL, Meier P : Non-parametric estimation from incomplete observation. Am J Stat Assoc 53 : 457-481, 1958
14 Hochberg MC : Updating the American Colledge of Rheumatology revised criteria for the classification of systemic lulus erythematosus. Arthritis Rheum 40 : 1725, 1997
15 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, *et al.* : The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31 : 315-324, 1988
16 Bohan A, Peter JB : Polymyositis and dermatomyositis (First of two parts). New Engl J Med 292 : 344-347, 1975
17 Fujibayashi T, Sugai S, Miyasaka N, Hayashi Y, Tsubota K : Revised Japanese criteria for Sjögren's syndrome (1999) : availability and validity. Mod Rheumatol 14 : 425-434, 2004
18 Picker LJ, Weiss LM, Medeilos LJ, Wood GS, Warnke RA : Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol 128 : 181-201, 1987
19 Ree HJ, Kadin ME, Kikuchi M, Ko YH, Go JH, *et al.* : Angioimmunoblastic lymphoma (AILD-type T-cell lymphoma) with hyperplastic germinal centers. Am J Surg Pathol 22 : 643-655, 1998
20 Attygalle AD, Kyriakou C, Dupuis J, Grogg KL, Diss TC, *et al.* : Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies : clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 31 : 1077-1088, 2007
21 Kojima M, Itoh H, Shimizu K, Saruki N, Murayama K, *et al.* : Malignant lymphoma in patients with systemic rheumatic disease (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and dermatomyositis) : A clinicopathologic study of 24 Japanese cases. Int J Surg Pathol 14 : 43-48, 2006
22 Frizzera G : Atypical lymphoproliferative disorders. *In* : Knowles DM (ed), Neoplastic Hematopathology. 2nd ed. Baltimore, Lippincott Williams & Wilkins, pp. 569-622, 2001
23 Kawano Y, Noma T, Kou K, Yoshizawa I, Yata J : Regulation of human IgG subclass production by cytokines : human IgG subclass production enhanced differentially by interleukin-6. Immunology 84 : 278-284, 1995
24 Kojima M, Sugiura I, Itoh H, Shimizu K, Murayama K, *et al.* : Histological varieties of Epstein-Barr virus-related lymph node lesion resembling autoimmune disease-like clinicopathological findings in middle-aged ane elderly patients. A study of six cases. Pathol Res Pract 202 : 609-615, 2006
25 Kamel OW, van de Rijn M, LeBrun DP, Weiss LM, Warnke RA, *et al.* : Lymphoid neoplasms in patients with rheumatoid arthritis and dermatomyositis : Frequency of Epstein-Barr virus and other features associated with immunosuppression. Hum Pathol 25 : 638-643, 1994
26 Kamel OW : Iatrogenic lymphoproliferative disorders in non-transplantation settings. Semin Diag Pathol 14 : 27-34, 1997
27 Kojima M, Itoh H, Hirabayashi K, Igarashi S, Tamaki Y, *et al.* : Methtrexate-associated lymphoproliferative disorders. A clinicopathological study of 13 Japanese cases. Pathol Res Pract 202 : 679-685, 2006
28 Ioachim HL, Medeiros LJ : Ioachim's lymph node pathology, 4th ed, Philadelphia, PA, Lippincott, Williams & Wilkins, pp. 248-254, 2009

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Multicentric Castleman's disease representing effusion at initial clinical presentation: clinicopathological study of seven cases

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PAPER

Multicentric Castleman's disease representing effusion at initial clinical presentation: clinicopathological study of seven cases

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We present here seven cases of idiopathic multicentric Castleman's disease (MCD) showing effusion at the initial clinical presentation. This series includes a high proportion of middle-aged and elderly females (5/7). Various autoantibodies were detected in six cases. Anemia (Hb < 10 g/dl) was detected in four cases, leukocytosis (WBC > 10×10^9/l) in three and thrombocytopenia (<100×10^9/l) in five. Positivity for C-reactive protein or elevated erythrocyte sedimentation rate was recorded in all seven cases. Elevated serum IgG level (>2000 mg/dl) was recorded in only three cases. Elevated serum interleukin-6 level was recorded in all four cases examined. At the onset of disease, four cases were associated with idiopathic thrombocytic purpura. During the course of disease, one case each was diagnosed as systemic sclerosis + Sjögren's syndrome (SJS) and SJS. Histologically, five lesions exhibited a mixed type of Castleman's disease, and one case each exhibited a hyaline-vascular type and plasma cell type. The non-neoplastic nature of the B-lymphocytes was demonstrated by immunohistochemistry and polymerase chain reaction. There were no human herpes type-8 virus-positive cells in any of the seven lesions. Good responsiveness to glucocorticoid therapy has been seen in all six cases treated. From a therapeutic perspective, it is important to discriminate this subtype of MCD. *Lupus* (2010) **0**, 1–7.

Key words: autoimmune disease; effusion; lymph node; Multicentric Castleman's disease

Introduction

Castleman's disease (CD) is an uncommon lymphoproliferative disorder (LPD).[1] Three disorders bearing the eponym of CD have been identified and were reviewed by Frizzera: localized CD of the hyaline-vascular (HV) type, localized CD of the plasma cell (PC) type, and 'multicentric Castleman's disease' (MCD).[2–4] However, several studies have indicated that MCD is composed of several disease entities,[5,6] including idiopathic MCD and secondary MCD due to human immunodeficiency type-1 (HIV) infection, autoimmune disease-associated lymphadenopathy, POEMS syndrome (polyneuropathy, anasarca, organomegaly, endocrinopathy, M-proteins and skin lesions), and non-Hodgkin's lymphomas.[7–14] Moreover, the involvement of human herpesvirus-8 (HHV-8) infection has been demonstrated in at least 40–50% of MCD unrelated to HIV in western countries.[5,15,16] However, as previously reported by Suda et al. and confirmed by our previous study, HHV-8 appears to be unrelated to the etiology of MCD in Japan.[17,18] Moreover, clinical findings of MCD in Japan are quite different from those of western countries.[18] MCD in western countries exhibits an aggressive and usually fatal disease course associated with infectious complications and risk of malignant tumors; one-third of patients will develop Kaposi's sarcoma and/or B-cell lymphoma.[2–6,8,10,11] MCD in Japan usually exhibits a

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chronic disease course. Moreover, MCD in Japan does not appear to progress to Kaposi's sarcoma or B-cell lymphoma.[18]

We report here clinicopathologic and immunohistochemical findings of MCD representing massive effusion at the initial clinical presentation.

Materials and methods

Seven cases were collected from a series by one of the authors (MK) treated between 1994 and June 2009. Medical records of these seven cases were extensively reviewed. Four cases (nos. 1, 2, 5 and 6) have been reported previously.[19]

The tissue specimens were fixed in formalin, routinely processed and embedded in paraffin. For light microscopy, the sections were stained using hematoxylin-eosin. Paraffin blocks of lymph node biopsies from all seven patients were available. Immunohistochemical studies were performed using the antigen retrieval method on the streptavidin-biotin-peroxidase method, Ventana automated (BenchMark™, Tucson, Arizona, USA) stainer, or Histofine Histostainer (Nichirei Bioscience Inc, Tokyo, Japan) according to the manufacturer's instructions.

A panel of antibodies against human immunoglobulin light chain (kappa and lambda) (Novocastra, New Castle, UK), IgG (Novocastra), IgA (Novocastra), IgM (Novocastra), MCO011 (IgG4; Binding Site, Birmingham, UK), polyclonal-CD3 (Dako; A/S, Glostrup, Denmark), L26 (CD20; Dako), cocktail of 2G9 (CD21; Novocastra) and RB L25 (CD35; Novocastra), Leu7 (CD57; Becton Dickinson, Mountain View, CA, USA), and 137B1 (HHV-8; Novocastra) was used. Sections with known reactivity for antibodies assayed served as positive controls, and sections treated with normal rabbit and mouse serum served as negative controls.

In situ hybridization with EBV-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA in formalin-fixed paraffin-embedded sections using a Ventana automated (BenchMark™) stainer or using the hybridization kit (Dako).

DNA was extracted from paraffin-embedded sections. The variable region (CDR2 and FW3) and VDJ region (CDR3) of the immunoglobulin heavy chain (IgH) gene were amplified by semi-nested PCR, using primers of FR2B, LJH and VLJH, according to a previously described method.[20] Primers were as follows: 5′-CCGG(A/G)AA(A/G)(A/G)GTCTGGAGTGG-3′, as upstream consensus V region primer (FR2B); 5′-TGAGGAGACGGTGACC-3′, as a consensus J region primer (LJH); 5′-GTGACCAGGGT [A/C/G/T] CCTTGGCCCCAG-3′, as a consensus J region primer (VLJH). PCR products were estimated to be 200–300 base pairs in length.

Cases exhibiting major clinical diagnostic criteria for POEMS syndrome including a sensorimotor peripheral polyneuropathy and a monoclonal PC proliferative disorder were excluded.[21]

Results

Clinical findings

The main clinical findings are shown in Tables 1 and 2. There were two males and five females with a median age of 53 years (range 43–68 years). Massive effusion was recorded in five cases (nos. 1, 3, 4–7) (Figure 1), whereas moderate (no. 6) or slight effusion (no. 2) was recorded in one case each. Characteristics of the effusion were recorded in four cases (nos. 2, 4, 5 and 7). Three cases (nos. 2, 5, and 7) demonstrated an exudate and the remaining case (no. 4) demonstrated a transudate.

Analysis of patient lifestyle did not suggest any risk factors for HIV-1 infection, although serological data regarding anti-HIV-1 antibodies were available only in four cases (nos. 3–5 and 7).

Four cases (nos. 1, 4–6) were associated with idiopathic thrombocytic purpura (ITP) at the disease onset. Two patients were associated with systemic autoimmune disease during the course of disease. One case (no. 1) was diagnosed as having systemic sclerosis and Sjögren's syndrome (SJS) 114 months after onset of disease.[22] One case (no. 2) was diagnosed as having SJS 3 months after the onset of disease.[22]

Complete remission was achieved in all seven cases. Two patients (nos. 3 and 5) are not currently receiving treatment. The remaining five cases (1, 2, 4, 6 and 7) are receiving mainly low-dose prednisone (5–15 mg/day).

Pathological and immunohistochemical findings

The sizes of the lesions ranged from 1–1.5 cm in diameter. Pathological and immunohistochemical findings of MCD have been well described.

Briefly, the lymph node biopsies of six patients (nos.1–6) contained numerous lymphoid follicles with atrophic germinal centers (Figure 2a). Three cases (nos. 3–5) demonstrated a few normal germinal centers. However, the majority of the other

Table 1 Summary of clinical findings

No	*Age sex*	*Clinical presentation*	*Site of LA (size/cm)*	*Site of effusion*	*↑H*	*↑S*	*Associated AID*	*Initial therapy and outcome*
1	43/F	Dyspnea, edema	Systemic (1)	Pl, Peri, Ascites	–	+	ITP*+SJS+SS	Prednisone, 50 mg/day, 186 mo alive
2	51/F	Low-grade fever	Systemic (1.5)	Pl	+	+	SJS	Prednisone, 250 mg/day, Recurred in LN at 6 months, alive 35 mo alive
3	52/F	Fever, skin rash, edema	Bil. Axilla & inguinal (1)	Pl, ascites	–	–	–	Prednisone 250 mg/day, 75 mo alive
4	53/F	Fever, fatigue, abdominal distention	Bil. neck & axilla (1)	Pl, Peri, Ascites	–	–	ITP*	Prednisone, 30 mg/day, 29 mo alive
5	55/M	Fever, edema	Bil.axilla & inguinal (1)	Pl, Ascites	+	+	ITP*	Prednisone,60 mg/day 87 mo alive
6	65/F	Low-grade fever, diarrhea, edema	Systemic (1.5)	Pl	+	+	ITP*	Prednisone, 100mg/day +vincristine, 2 mg/day. Recurred in LN at 6 mo. Second recurrence in LN at 46 mo. 113 mo alive
7	68/M	Dyspnea, abdominal distention	Systemic (1.4)	Pl, Peri, Ascites	–	+	–	Prednisone, 3mo alive

LA: lymphadenopathy, ↑H: hepatomegaly, ↑S: splenomegaly, AID: autoimmune disease, Pl: pleural effusion, Peri: pericardial effusion, Bil.: bilateral, ITP: idiopathic thrombocytic purpura, SJS: Sjögren's syndrome, SS: systemic sclerosis, mo: months.
*ITP-associated onset of disease.

Table 2 Summary of laboratory findings

No	*Hb (g/dl)*	*WBC (10^9/L)*	*PL (10^9/L)*	*BMPC (>5%)*	*M-protein*	*CRP (mg/dl)*	*IgG (mg/dl)*	*IL-6 (pg/ml)*	*VEGF (pg/ml)*	*Positivity of autoantibody*
1	10.4	11.2	39	–	–	NE*	2358	+	NE	Anti-PA
2	13.6	9.79	102	–	–	5.6	2124	4.86	NE	SS-A/B antibody, ANA
3	9.1	9.3	105	–	–	1.8	1160	11.6	540	–
4	10.5	10.1	47	NE	–	18.9	1176	NE	NE	PA-IgG, ANA
5	9.5	12.1	12	–	–	14.5	NE	NE	NE	PA-IgG, ANA, RF
6	9.4	5.5	15	–	–	7.3	1596	NE	NE	PA-IgG, Anti-Tbab, Anti-TyPO
7	7.3	5.7	93	–	–	8.44	3272	12.6	135	D-Coombs

Hb: hemoglobin, WBC: white blood cell count, PLT: platelet count, BMPC: bone marrow plasma cytosis, CRP: C-reactive protein, IL-6: interleukin-6, VEGF: vascular endothelial growth factor, anti-PA: antiplatelet antibody, ANA: antinuclear antibody, PA-IgG: platelet associated-IgG, RF: rheumatoid factor, Anti-Tbab: antithyroglobulin antibody, Anti-TyPO: antithyroid peroxidase antibody, D-Cooms: direct-Coombs' test, NE: not examined.
*erythrocyte sedimentation rate was 30 mm/hr.

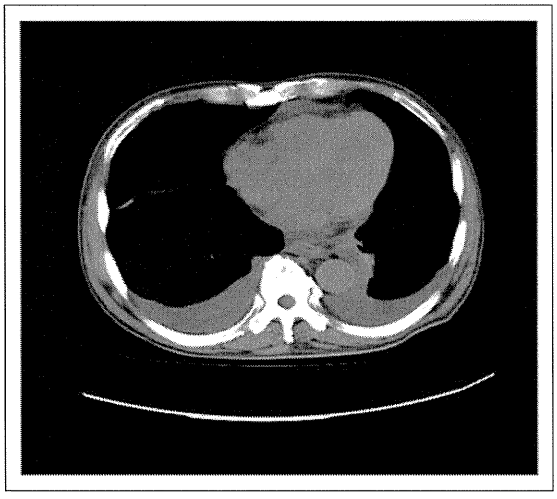

Figure 1 Computed tomographic scan at the onset of disease. Note massive bilateral pleural effusion. Case 7.

follicles were small HV (Figure 2b) and so-called epithelioid types (Figure 2c). The latter type consisted mostly of follicular dendritic cells (FDCs) (Figure 2c). A portion of FDCs demonstrated enlarged nuclei with prominent nucleoli (Figure 2c). The mantle zones were occasionally broad and concentrically arranged in the HV and epithelioid types.

The interfollicular area was characterized by moderate-to-prominent vascularity with short, closely spaced venules containing high numbers of endothelial cells in all lesions (Figure 2d). Moderate-to-large sheets of mature plasma cells were observed in five cases (nos.1, 3–6) (Figure 2d), whereas a few scattered plasma cells were observed in the remaining one case (no. 2). A number of immature plasma cells and a few immunoblasts were observed in one case (no. 6) (Figure 2d). Five cases (nos. 1, 2, 4–6) were

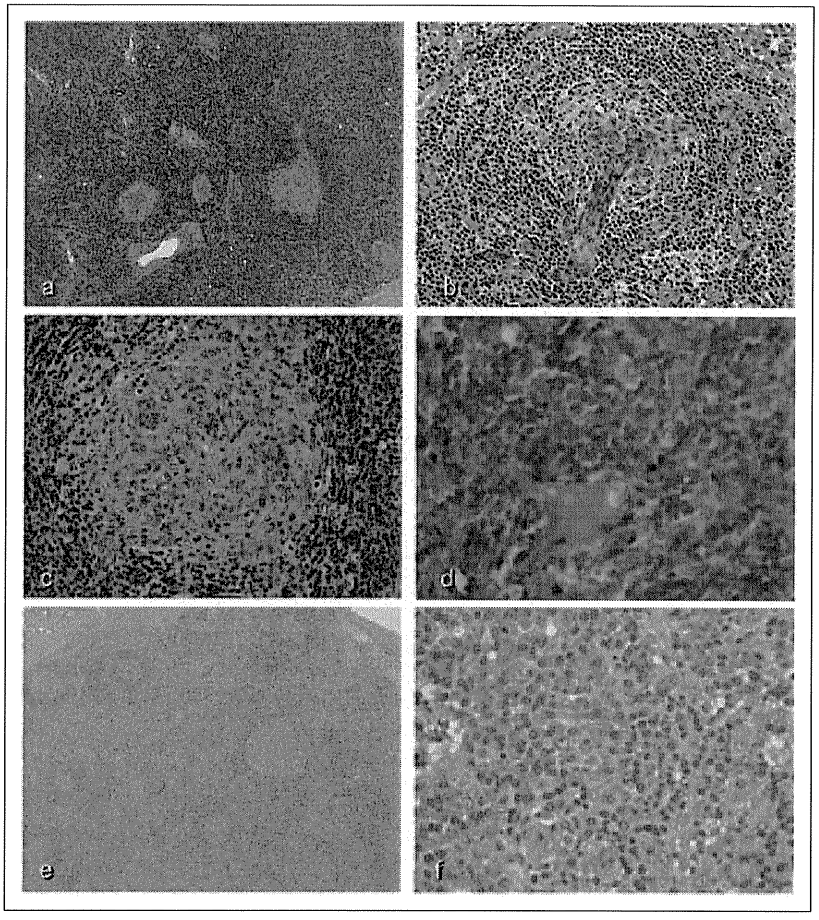

Figure 2 (a) Medium-power field of the lymph node. Note numerous abnormal germinal centers and open sinus. Hematoxylin-eosin (HE) × 25. Case 6. (b) High-power field of the germinal center demonstrating a hyaline-vascular type. HE × 100. Case 5. (c) High-power field of the germinal center demonstrating an epithelioid type. Note the nuclear enlargement of follicular dendritic cells. HE × 100. Case 6. (d) High-power field of the interfollicular area. The interfollicular area contained aggregates of mature and immature plasma cells. Note numerous arborizing capillaries and postcapillary venules. HE × 100. Case 6. (e) Medium-power field of the lymph node. Note hyperplastic germinal centers. HE × 25. Case 7. (f) High-power field of the lymph node lesion demonstrated sheet-like proliferation of plasma cells in the interfollicular area. HE × 100. Case 7.

diagnosed as mixed type and one (no.3) as HV type according to Flendrig.[23]

The remaining case (no. 7) demonstrated numerous lymphoid follicles with normal germinal centers (Figure 2e). The interfollicular area was characterized by sheets of proliferating mature plasma cells (Figure 2f). This case was diagnosed as the PC type.

The immunoglobulin light chain reactivity of plasma cells and their precursors was polyclonal with a kappa to lambda ratio of 2 to 1 (Figure 3a and 3b). Studies of heavy chain antigens in interfollicular plasma cells and their precursors demonstrated that IgG was predominantly expressed in all seven cases. In addition, a moderate number of such cells expressing IgA was also seen in all seven cases. There were only a few IgM-positive cells. IgG4 immunostain also demonstrated only a few positive plasma cells.

Few Leu7+ T-cells were observed in the HV germinal centers and the majority of epithelioid germinal centers (Figure 3c), whereas numerous Leu7-positive cells were predominant in the light zone in the normal reactive germinal centers and a minority of epithelioid germinal centers.

FDCs showed strong immunoreactivity to a cocktail of 2G9 and RB L25 monoclonal antibodies. The majority of the FDC networks showed a tight/concentric or expanded/disrupted pattern (Figure 3d), with the exception of a few follicles and a normal/reactive pattern in six cases (nos. 1–6).[24]

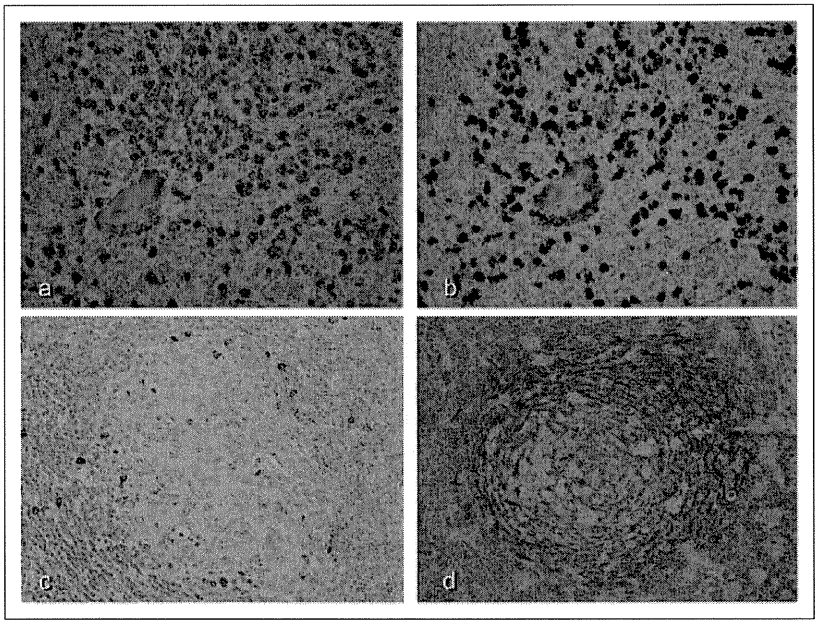

Figure 3 Immunostaining for light chain determinant of immunoglobulins demonstrated the polytypic nature of the plasma cells and their precursors (a) kappa and (b) lambda. × 50, Case 6. (c) Leu7 immunostaining demonstrated only a few positive T cells in an epithelioid germinal center. × 50 (d) A cocktail of 2G9 and RB L25 immunostain demonstrated an expanded/disrupted pattern of the follicular dendritic cell network. × 50.

The FDC networks showed a normal/reactive pattern in one PC-type case (no. 7), with the exception of a few expanded/disrupted follicles in all cases. There were no HHV-8 or EBER-positive cells in any of the seven cases.

Genotypic study

PCR assay for the IgH gene demonstrated only germ line bands with IgH chain probes in all seven cases.

Discussion

In the early 1980s, Mori et al. demonstrated a new clinicopathologic entity, namely idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL) showing normal germinal centers and sheet-like proliferation of polyclonal plasma cells in the lymph node lesion, which are the same pathological findings as the PC type of CD.[25] Later, Frizerra concluded that IPL is identical to MCD.[4,5] However, we have demonstrated at least two subtypes of MCD in Japan, namely the IPL and non-IPL types. IPL appears to be a homogenous disease entity, whereas non-IPL type is a heterogeneous cluster of disease entities.[18]

IPL is characterized by (1) prominent polyclonal hypergammaglobulinemia (gamma globulins > 4.0 g/dl or serum IgG level >3500 mg/dl), (2) multicentric lymphadenopathy, (3) high level of serum IL-6, and (4) the absence of distinct autoimmune disease.[18,25] We found occasional effusion (6/10) in the non-IPL type at the onset of disease.[18]

To further clarify the clinicopathological findings of MCD presenting with effusion at the onset of disease, seven such cases were studied. Interestingly, both IPL and non-IPL types of MCD having effusion showed an elevated serum interleukin-6 (IL-6) level.[18] However, the clinicopathologic findings of the present cases are quite different from those of IPL. Clinically, the seven cases under discussion were characterized by (1) predominance of middle-aged and elderly females (5/7); (2) massive effusion (5/7); (3) multicentric lymphadenopathy (7/7); (4) high frequency of positivity for various autoantibodies (6/7); and (5) frequent association with autoimmune disease (6/7). Histologically, six of seven cases demonstrated the HV type or mixed type of CD according to the Flendrig.[23]

Autoimmune disease frequently occurs in middle-aged women and occasionally shows serositis, particularly in systemic lupus erythematosus (SLE).[22] Four cases (nos. 1, 4–6) were associated with ITP

at disease onset. Moreover, two cases (nos. 1 and 2) were associated with systemic autoimmune disease (SS + SJS and SJS). Indeed, autoimmune diseases including rheumatoid arthritis (RA) and SLE showing clinicopathological findings of MCD have been reported.[12,14] Moreover, high serum levels of IL-6 have been recorded in RA and SLE.[5] As initially proposed by Frizzera et al., a portion of idiopathic MCD was considered an ill-defined autoimmune disease.[2,3] The present seven cases indicated that at least a portion of the non-IPL type of MCD presenting with effusion appears to be autoimmune disease-associated LPDs in Japan.

POEMS syndrome is an important differential diagnostic problem.[9,21] However, none of our seven patients exhibited monoclonal plasma cell proliferation such as the presence of M-proteins and sensory motor neuropathy, which are minimal clinical diagnostic criteria for POEMS syndrome, during the course of follow-up.[21] Histologically, lymph node lesions in POEMS syndrome frequently show the mixed type of CD.[7] Moreover, immunohistochemical study demonstrated monotypic plasma cell nature.[7] However, the non-neoplastic nature of B-cells in lymph node lesions was demonstrated by immunohistochemistry and PCR.

In Japan, lymph node lesions in IgG4-related disorders appear to be another important differential diagnostic problem.[26] Lymph node lesions of IgG4-related disorders are characterized by reactive follicular hyperplasia and prominent interfollicular plasmacytosis.[26] However, there were only a few IgG4+ plasma cells in our seven cases.

In conclusion, the present seven cases may be a unique subtype of MCD in Japan. As previously indicated, the chronic disease course in these cases appears to be related to negativity for HHV-8 infection among Japanese.[5,15–18] There was a good response to glucocorticoid therapy in all six cases treated. From a therapeutic perspective, it is important to discriminate this subtype of MCD.

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Conflict of interest

The authors declare that they have no conflicts of interest.

References

1 Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer* 1956; 9: 822–830.
2 Frizzera G, Massarelli G, Banks BM, Rosai J. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease. Pathological findings in 15 patients. *Am J Surg Pathol* 1983; 7: 211–231.
3 Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castlemamn's disease. Clinical findings and clinicopathological correlations in 15 patients. *J Clin Oncol* 1985; 3: 1202–1216.
4 Frizzera G. Castleman's disease and related disorders. *Sem Diag Pathol* 1988; 5: 346–364.
5 Frizzera G. Atypical lymphoproliferative disorders. In: Knowles DM (ed.), *Neoplastic Hematopathology*, 2nd ed. Lippincott Williams & Wilkins; 2001. p. 569–622.
6 Ioachim HL, Medeiros LJ. *Ioachim's Lymph Node Pathology*, 4th ed. Lippincott, Williams & Wilkins; 2009. p. 227–237.
7 Kojima M, Sakuma H, Mori N. Histopathological features of plasma cell dyscrasia with polyneuropathy and endocrine disturbances with special referemce to germinal center lesions. *Jpn J Clin Oncol* 1983; 13: 557–576.
8 Tanda F, Massareli G, Constantzi G. Multicentric giant lymph node hyperplasia: an immunohistochemical study. *Hum Pathol* 1983; 14: 1053–1058.
9 Nakanishi T, Soube I, Toyokura Y, *et al.* The Crow-Fukase syndrome. a study of 102 cases in Japan. *Neurology* 1984; 34: 712–720.
10 Kessler E. Multicentric giant lymph node hyperplasia: a report of seven cases. *Cancer* 1985; 56: 2446–2451.
11 Weisenberger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric angiofollicular lymph node pyperplasdia: a clinicopathologic study of 16 cases. *Hum Pathol* 1985; 16: 162–172.
12 Ben-Chetrit E, Flusser D, Okon E, Ackerman Z, Rubinow A. Multicentric Castleman's disease assocoiated with rheumatoid arthritis: a possible role of hepatitis B antigen. *Ann Rheum Dis* 1989; 48: 326–330.
13 Ioachim HL, Cronin W, Roy M, Maya M. Persistent lymphadenopathies in people at high risk for HIV infection. Clinicopathologic correlations and long-term follow-up in 79 cases. *Am J Clin Pathol* 1990; 93: 208–218.
14 Kojima M, Nakamura S, Itoh H, *et al.* Systemic lupus erythematosus (SLE) lymphadenopathy presenting with histopathologic features of Castleman's disease: A clinicopathologicstudy of five cases. *Pathol Res Pract* 1997; 193: 565–571.
15 Cesarman E, Knowles DM. The role of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in lymphoproliferative diseases. *Sem Cancer Biol* 1999; 9: 165–174.
16 Dupin N, Diss TL, Kellam P, *et al.* HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked HHV-8-positive plasmablastic lymphoma. *Blood* 2000; 95: 1406–1412.
17 Suda T, Kanato H, Delsol G, *et al.* HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. *Pathol Int* 2001; 51: 671–679.
18 Kojima M, Nakamura N, Tsukamoto N, *et al.* Clinical implications of idiopathic multicentric Castleman's disease among Japanese. A report of 28 cases. *Int J Surg Pathol* 2008; 16: 391–398.
19 Kojima M, Nakamura S, Nishikawa M, Itoh H, Miyawaki S, Masawa N. Idiopathic multicentric Castleman's disease. A clinicopathologic and immunohistochemical study of five cases. *Pathol Res Pract* 2005; 202: 325–332.
20 Kuze T, Nakamura N, Hashimoto Y, Abe M. Most of CD30+ anaplastic large cell lymphoma of B cell type show a somatic mutation in the IgH V region genes. *Leukemia* 1998; 12: 753–757.
21 Dispenzieri A, Kyle RA, Lacy MQ, *et al.* POEMS syndrome: definitions and long-term outcome. *Blood* 2003; 101: 2496–2506.
22 Kumar V, Cotran RS, Robbins SL. *Basic Pathology*, 7th ed. WB Saunders; 2003. p. 103–164.

23 Flendrig JA. Benign giant lymphoma:clinicopathologic correlation study. In: Clark RL, Gumley RW (eds), *The Year Book of Cancer*. YearBook Medical Publishers; 1970. p. 296–299.
24 Nguyen DT, Diamond LW, Hansmann ML, *et al.* Castleman's disease. differences in follicular dendritic network in the hyaline vascular and plasma cell variants. *Histopathology* 1994; 24: 437–443.
25 Mori S, Mohri N, Uchida T, Shimamine T. Idiopathic plasmacytic lymphadenopathy with polyclonal hyperuimmunoglobulinemia: a syndrome related to giant lymph node hyperplasia of plasm cell type. *J Jpn Soc Res* [Suppl] 1980; 20: 55–65 (in Japanese).
26 Sato Y, Kojima M, Takata K, *et al.* Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. *Mod Pathol* 2009; 22: 589–599.

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Cytological findings of IgG4-related pleural effusion: a case report

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Dear Editor, We report here the cytological findings of a case of an immunoglobulin G4 (IgG4)-related pleural lesion showing massive pleural effusion. IgG4 is the least common of the four subclasses of IgG (IgG1, IgG2, IgG3 and IgG4) and comprises only 3–6% of the entire IgG fraction. IgG4-related disease is a recently recognized entity characterized clinically by tumour-like enlargement of one or more exocrine glands or other extranodal sites by lymphoplasmacytic infiltrates and sclerosis, accompanied by increased IgG4-positive plasma cells in the tissues and elevated IgG4 titre in the serum.[1–3] The most common manifestations of IgG4-related disease are autoimmune pancreatitis, chronic sclerosing sialoadenitis of the submandibular gland and chronic sclerosing dacryoadenitis.

A 57-year-old Japanese man presented with a 2-month history of dyspnoea. Chest radiograph and computed tomography demonstrated massive bilateral pleural effusions and pleural thickening. The results of a complete blood count and differential analysis were normal. Total serum protein was 7.7 g/dl, and serum protein electrophoresis demonstrated a polyclonal hypergammaglobulinaemia (30%). The serum IgG4 level (970 mg/dl; normal <135 mg/dl) and interleukin-2 (IL-2) receptor level (1710 U/ml; normal <500 U/ml) were markedly elevated. However, C-reactive protein (CRP) was negative and the serum lactate dehydrogenase (LDH) level was within the normal range (189 IU/l; normal <220 IU/l). The patient responded well to steroid therapy and remained well at 12 months of follow-up.

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The Giemsa-stained smears obtained from the pleural effusion contained numerous small lymphocytes admixed with plasma cells, plasmacytoid cells and large immunoblasts showing plasma cell differentiation, together with a few mesothelial cells (Figure 1a–c). Binucleated plasma cells were also observed (Figure 1a). The nuclei of the small lymphocytes were usually round (Figure 1a). The immunoblasts contained one or two prominent, central, basophilic nucleoli and broad basophilic cytoplasm (Figure 1b). The smear also contained a few grape cells and eosinophils (Figure 1c). Haemophagocytic histiocytes were occasionally observed (Figure 1c).

Pleural biopsy specimens demonstrated pleural thickening with prominent lymphoplasmacytic infiltration and a few eosinophils (Figure 2a). Using formalin-fixed, paraffin-embedded sections, immunohistochemical study for light chain determinant demonstrated the polytypic nature of plasma cells and their precursors. There were numerous IgG4-positive plasma cells in the lesion, comprising more than 40% of the IgG-positive plasma cells (Figures 2b,c). Polymerase chain reaction assay for the immunoglobulin heavy chain gene demonstrated only germline bands.[4]

The pathological findings of IgG4-related pleural lesion characterized by pleural thickening and prominent polyclonal lymphoplasmacytic infiltration have been well described.[1,3,5] However, little is known about the cytological findings of pleural effusion in IgG4-related pleural lesion.[5] The presence of numerous plasma cells and their precursors appears to result from prominent pleural infiltration of plasma cells, their precursors and small lymphocytes. Moreover, Giemsa-stained specimens demonstrated a few eosinophils, which is one of the characteristic histomorphological findings of IgG4-related disease.[2,3] The laboratory findings of the present case, such as increased serum IgG4 level and IL-2 receptor level, normal serum LDH level and negativity of CRP, are characteristic.[2,3]

IgG4-related disease more frequently affects Asian populations.[2,3] In the literature, reactive plasmacytosis in serous effusion has been reported in chronic inflammatory processes[6] and the majority of IgG4-related

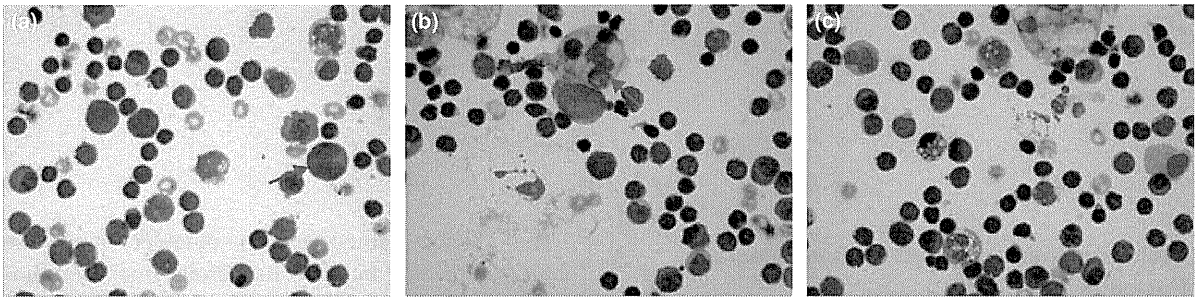

Figure 1. Pleural fluid cytology. (a) Numerous small lymphocytes admixed with plasma cells, plasmacytoid cells and large immunoblasts showing plasma cell differentiation together with a few mesothelial cells. Arrow indicates a binucleated plasma cell. The nuclei of the small lymphocytes were usually round (Giemsa, ×150). (b) Immunoblasts containing one or two prominent, central, basophilic nucleoli and broad basophilic cytoplasm. Arrow indicates a haemophagocytic histiocyte (Giemsa, ×150). (c) Numerous plasma cells, plasmacytoid cells, small lymphocytes and haemophagocytic histiocytes. A grape cell and an eosinophil can be seen (Giemsa, ×150).

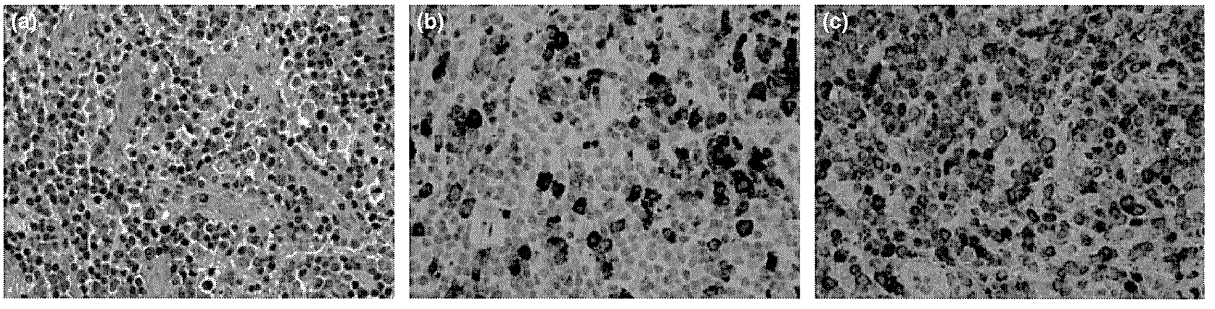

Figure 2. Pleural biopsy. (a) Numerous mature plasma cells and small lymphocytes with a few eosinophils (haematoxylin and eosin, ×100). Immunoperoxidase (×100): (b) IgG4-positive plasma cells comprising more than 40% of IgG-positive plasma cells (c).

disease appears to be benign. However, occasionally, the disease can be complicated by the development of malignant lymphoma.[2,3,6] Cheuk *et al.*[7] reported two cases of ocular adnexal extranodal marginal zone B-cell lymphoma showing sclerosing inflammation in the background and numerous IgG4-positive monotypic plasma cells. Several cases of pancreatic adenocarcinoma have been described in association with IgG4-related sclerosing pancreatitis.[3] Moreover, rarely, pulmonary adenocarcinoma has also been reported with features of IgG4-related disease.[3]

Finally, IgG4 disease must be differentiated from malignant pleural effusions including multiple myeloma, and carcinomatous and lymphomatous effusions that may include numerous plasma cells and their precursors.[6] However, immunohistochemical and genotypic studies demonstrated the polytypic nature of the plasma cells and their precursors in the pleural lesions.

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References

1. Zen Y, Inoue D, Kitao A *et al.* IgG4-related lung and pleural disease: a clinicopathologic study of 21 cases. *Am J Surg Pathol* 2009;**33**:1886–93.

2. Sato Y, Notohara K, Kojima M *et al.* IgG4-related disease: historical overview and pathology of hematological disorders. *Pathol Int* 2010;**60**:247–58.
3. Cheuk W, Chan JKC. IgG4-related sclerosing disease. A critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 2010;**12**:303–32.
4. Kuze T, Nakamura N, Hashimoto Y, Abe M. Most of CD30+ anaplastic large cell lymphoma of B cell type show a somatic mutation in the IgH V region genes. *Leukemia* 1998;**12**:753–7.
5. Rossi G, Marchioni A, Guicciardi N, Cadoili A, Cavazza A. Recurrent pleural and pericardium effusions in a white woman with IgG4-related syndrome. *Am J Surg Pathol* 2009;**33**:802–3.
6. Naylor B. Pleural, peritoneal, and pericardial effusions. In: *Comprehensive Cytopathology*, 3rd edn. Bibbo M, Wilbur S (eds). Philadelphia, PA: Saunders; 2008: pp. 515–77.
7. Cheuk W, Yuen HK, Chan ACL *et al.* Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008;**32**:1159–67.

INTERNAL MEDICINE

□ CASE REPORT □

Visual Field Deficit: A Rare Initial Symptom of Autoimmune Pancreatitis

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Abstract

An autoimmune pancreatitis (AIP) patient with metachronous and multiple extrapancreatic lesions is reported. Initial symptoms were proptosis, oculomotor deficits, and a visual field deficit of the left eye, and swelling of bilateral lacrimal glands. Swelling of the right salivary gland and elevated serum levels of hepatobiliary enzymes were detected. AIP associated with IgG4-related orbital pseudotumor, IgG4-related sclerosing dacryoadenitis and sialadenitis, and IgG4-related sclerosing cholangitis was diagnosed. All symptoms and lesions improved with steroid therapy. Although an orbital pseudotumor is a rare extrapancreatic lesion of AIP, we should know that AIP patients may describe unusual symptoms such as abnormal visual field.

Key words: autoimmune pancreatitis, IgG4, orbital pseudotumor, sclerosing sialadenitis, sclerosing dacryoadenitis

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Introduction

Autoimmune pancreatitis (AIP) is a peculiar type of pancreatitis of presumed autoimmune etiology. It is characterized clinically by a preponderance of elderly males, jaundice as a frequent initial symptom, and responsiveness to steroid therapy; serologically by elevation of serum IgG or IgG4 levels; radiologically by enlargement of the pancreas and irregular narrowing of the main pancreatic duct; and histopathologically by dense fibrosis with lymphoplasmacytic infiltration in the pancreas (1, 2). Other prominent features of this disease involve a variety of extrapancreatic complications (1-3).

We found dense fibrosis with abundant infiltration of T lymphocytes and IgG4-positive plasma cells and obliterative phlebitis in extrapancreatic lesions associated with AIP, such as sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, and retroperitoneal fibrosis. Furthermore, we also found dense infiltration of IgG4-positive plasma cells and T lymphocytes in various organs of AIP patients, such as the periportal area of the liver, gastric mucosa, colonic mucosa, dermis, lymph nodes, and bone marrow (1, 2, 4, 5). Therefore, we proposed the existence of a novel clinicopathological entity, "IgG4-related sclerosing disease" (1, 2, 4), which is a systemic disease characterized by extensive IgG4-positive plasma cell and T lymphocyte infiltration of various organs. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (1, 2).

From this point of view, both AIP and the extrapancreatic lesions of AIP may occur randomly. We report an AIP patient who developed a visual field deficit of the left eye and swelling of bilateral salivary glands, which were metachronously associated with sclerosing sialadenitis and sclerosing cholangitis.

Case Report

A 76-year-old man noticed swelling in the left upper eyelid in October 2007 and visited another hospital. The patient was suspected to be having an allergic reaction at the initial

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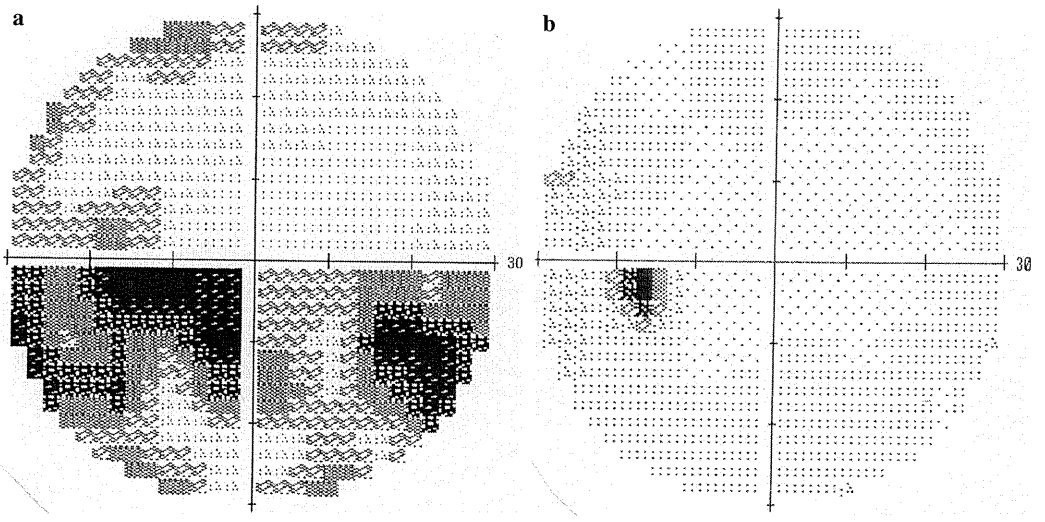

Figure 1. (a) Visual field examination shows lower visual field deficit of the left eye before steroid therapy. (b) The visual field deficit improved significantly after steroid therapy.

visit, but the eyelid swelling gradually increased. In April 2009, the patient felt proptosis, oculomotor deficits, and a visual field deficit of the left eye, as well as swelling of bilateral lacrimal glands. The left orbital lesion was biopsied on suspicion of malignant tumor, but there was no malignancy, and he was followed without treatment. In June 2009, swelling of the right salivary glands and elevated serum levels of hepatobiliary enzymes were detected. He was referred to our hospital for further examination.

The physical findings on admission included proptosis and oculomotor deficits of the left eye and painless swelling of bilateral lacrimal glands and the right salivary gland. No superficial lymphadenopathy, hepatomegaly, or splenomegaly was noted. The visual acuity of the right eye was 1.2, left eye was 0.2. The ophthalmologic examinations showed a lower visual field deficit (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA) (Fig. 1a) and an omnidirectional ocular motility disorder of the left eye.

Laboratory examinations showed elevation of serum hepatobiliary enzyme levels: alanine aminotransferase, 307 (normal range, 5-40) IU/L, aspartate aminotransferase, 319 (5-35) IU/L, alkaline phosphatase, 1191 (80-260) IU/L, γ-glutamyl transpeptidase, 988 (5-70) IU/L, lactic dehydrogenase, 205 (115-245) IU/L, and leucine aminopeptidase 193 (<170) IU/L. Hepatitis B surface antigen and antibody to hepatic C virus were negative. Immunologically, the serum IgG level was 4,135 (<1,700) mg/dL and IgG4 level was 2,490 (<135) mg/dL; antinuclear antibody(ANA) was positive (×80). Anti-Ro antibody (SS-A), anti-La antibody (SS-B), anti-mitochondrial antibody, and anti-smooth muscle antibody were all negative.

Head magnetic resonance imaging (MRI) showed proptosis of the left eye due to an orbital tumor and swelling of bilateral lacrimal glands (Fig. 2a, b). There were no sites of involvement on head MRI. Re-examination of the biopsied piece of the orbital tumor in the previous hospital revealed abundant infiltration of IgG4-positive plasma cells and lymphocytes, and focally storiform-like fibrosis (Fig. 3a-d). There were no findings of obliterative phlebitis or MALT-lymphoma.

Abdominal computed tomography (CT) and MRI revealed diffuse pancreatic enlargement and mild thickening of the gallbladder and bile duct wall (Fig. 4a). An endoscopic retrograde cholangiopancreatography indicated diffusely irregular narrowing of the main pancreatic duct and stenosis of the lower bile duct. The patient was diagnosed as having AIP according to the Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis 2006 (6).

Percutaneous liver biopsy performed for liver dysfunction after admission to our hospital revealed dense infiltration of lymphocytes and IgG4-positive plasma cells and mild fibrosis in the periportal area of the liver (Fig. 5).

The patient was diagnosed as having AIP associated with IgG4-related sclerosing dacryoadenitis, orbital pseudotumor, IgG4-related sialadenitis, and IgG4-related sclerosing cholangitis. He was begun on treatment for systemic IgG4-related disease with 30 mg prednisolone daily for 2 weeks. The dose was tapered by 2.5-5 mg every two weeks. Four weeks after starting steroid therapy, findings on abdominal CT/MRI (Fig. 4b) and blood tests improved. The visual acuity, lower visual field deficit, and omnidirectional ocular motility disorder of the left eye also improved significantly (Fig. 1b), along with improvement of proptosis and lacrimal gland swelling (Fig. 2c, d).

Discussion

AIP patients frequently have significantly elevated serum IgG4 levels and various extrapancreatic lesions. AIP and its extrapancreatic lesions show similar histopathological findings and good responsiveness to steroid therapy. Currently, they are recognized as organs clinically involved in IgG4-

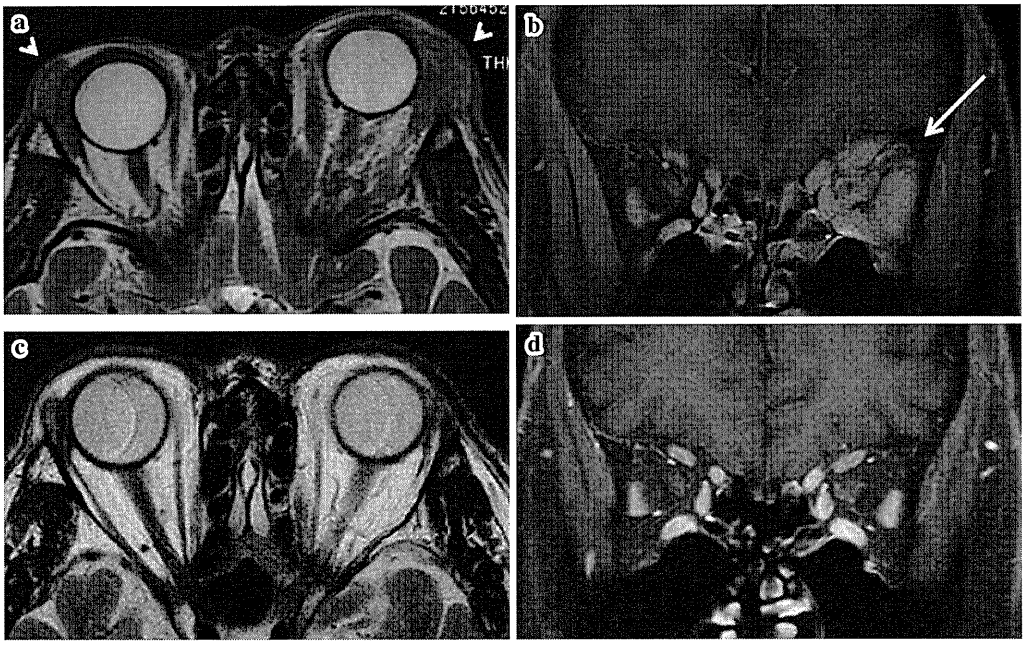

Figure 2. **Magnetic resonance imaging of orbit reveals swelling of bilateral lacrimal grands (short arrow) (a, axial T2-weighted imaging) and an orbital floor pseudotumor (long arrow) (b, coronal T1-weighted fat-suppressed imaging). (c, d) These lesions improved markedly after steroid therapy.**

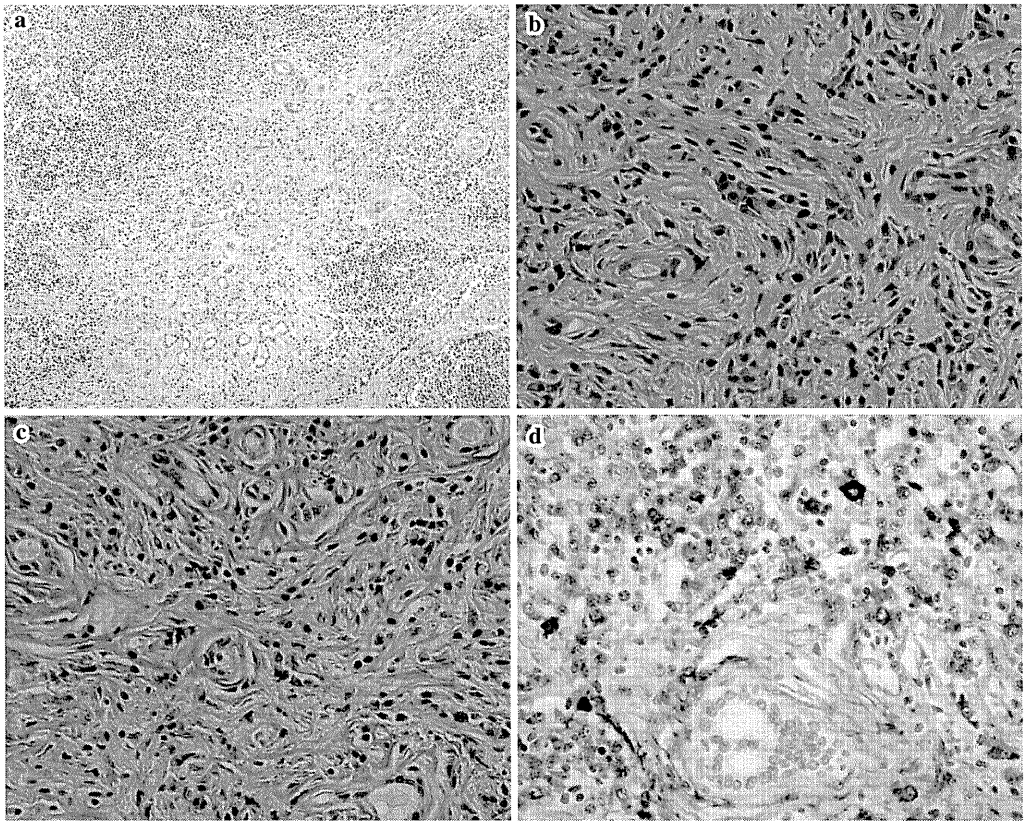

Figure 3. **Histology of the biopsied orbital tumor showing lymphoplasmacytic infiltration and focally storiform-like fibrosis [(a) lower power view, Hematoxylin and Eosin staining; (b) high power view, Hematoxylin and Eosin staining; (c) Elastica Van Gienson staining]. (d) Immunohistochemically, abundant infiltration of IgG4-positive plasma cells was detected (IgG4-immunostaining).**

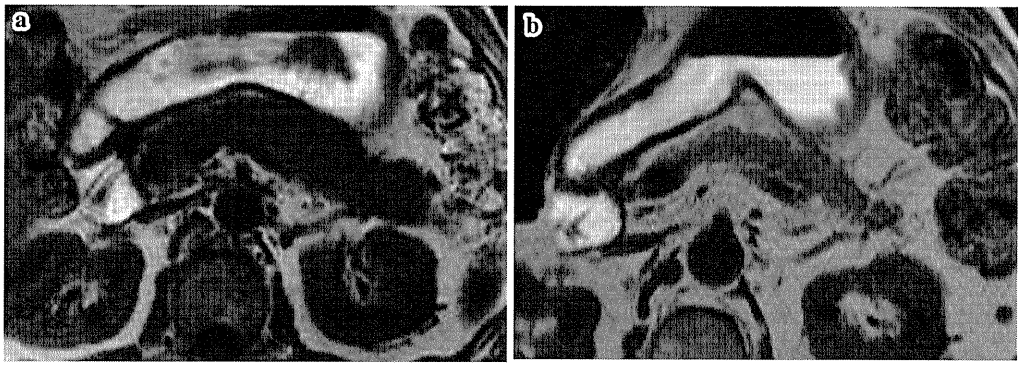

Figure 4. (a) Magnetic resonance imaging showing diffuse enlargement of the pancreas. (b) The pancreatic enlargement improved after steroid therapy.

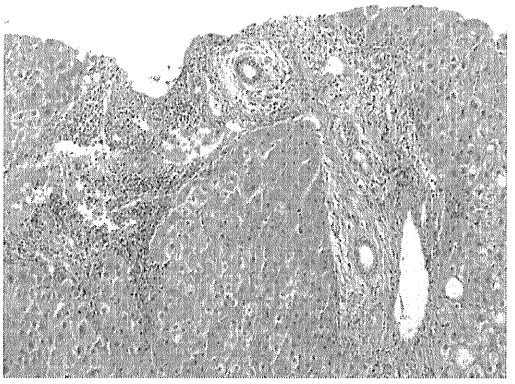

Figure 5. Histology of liver biopsy showing dense lymphoplasmacytic infiltration and mild fibrosis in the periportal area of the liver (Hematoxylin and Eosin staining).

related systemic sclerosing disease. In some cases, only 1 or 2 organs are clinically involved, while in others, 3 or 4 organs are affected (1, 2). Cases with significantly higher serum IgG4 levels, as in this patient, show higher AIP activity and frequently have associated extrapancreatic lesions (7). Extrapancreatic lesions with AIP sometimes appear metachronously. In our previous study, sclerosing sialadenitis, swelling of the lacrimal glands, lymphadenopathy, and retroperitoneal fibrosis were found to be the extrapancreatic lesions preceding AIP, while sclerosing cholangitis occurs synchronously (8). It is unclear why the onset period of each lesion differs in IgG4-related systemic sclerosing disease. AIP occurs most frequently with obstructive jaundice due to associated sclerosing cholangitis (1-3). Compared with AIP, swelling of the salivary or lacrimal glands can be easily noticed even without symptoms. AIP might exist subclinically when preceding salivary or lacrimal gland lesions are diagnosed.

In the present case, the visual acuity, lower visual field deficit, and omnidirectional ocular motility disorder of the left eye improved along with improvement of proptosis. There was no abnormality of the optic nerve and brain on head MRI. Therefore, these ophthalmic symptoms would have been caused by an orbital pseudotumor. Orbital pseudotumor is an idiopathic, benign, inflammatory condition that accounts for approximately 10% of all orbital mass lesions (9, 10). The etiology of orbital pseudotumor is unknown (11). The presentation may be acute or subacute and may occasionally exhibit chronic progression. Orbital pseudotumor may be unifocal or diffuse and may affect any part of the orbit (12). It is usually unilateral, but it may occasionally be bilateral. Chirapapaisan et al. reported that the presenting symptoms included proptosis (80%), oculomotor deficits (61%), pain (51%), lid swelling or a mass (45%), ptosis (25%), and chemosis (18%) in 49 patients with orbital pseudotumor (13). Some patients with orbital pseudotumor may have decreased visual acuity due to optic nerve compression (14). Orbital pseudotumor is sometimes difficult to differentiate from MALT-lymphoma, there was no finding of lymphoma in the biopsy specimen of this case. Multifocal fibrosclerosis is an uncommon fibroproliferative systemic disorder with multiple manifestations, including retroperitoneal fibrosis, sclerosing cholangitis, and salivary gland fibrosis. There are some reports that multifocal fibrosclerosis was complicated by fibrotic orbital pseudotumor (15-17). We have reported a close relationship between AIP and multifocal fibrosclerosis (5). Some orbital pseudotumors including the present case appear to be orbital lesions involved in IgG4-related systemic disease.

Lacrimal gland swelling is also a rare extrapancreatic lesion of AIP. Lacrimal gland swelling was detected in 3.6% of 56 cases in our study (8). Hamano et al (18) reported that lacrimal gland swelling was detected in 8 (12.5%) of 64 AIP patients, and 6 of them had salivary gland swelling. Recently, it was reported that serum IgG4 levels were elevated, and abundant infiltration of IgG4-positive plasma cells with fibrosis was detected in the lacrimal glands in patients with Mikulicz's disease (19, 20), which is a unique condition that refers to bilateral, painless, symmetrical swelling of the lacrimal, parotid, and submandibular glands (21). Mikulicz's disease is currently recognized as the lacrimal and salivary gland lesions of IgG4-related systemic disease (20).

IgG4-related sclerosing cholangitis is frequently associated with AIP, and the stenosis is usually located in the lower part of the common bile duct (1-3). In cases with stenosis of the lower bile duct, thickening of the bile duct

wall consists of fibrosis with infiltration of IgG4-positive plasma cells that sometimes spread extensively to the upper bile duct (1, 2). In the present patient, infiltration of mononuclear cells, including IgG4-positive plasma cells, and mild fibrosis were observed in the periportal area obtained by liver biopsy.

AIP sometimes develops with various symptoms due to associated extrapancreatic lesions. According to the classification (head and neck, thoracic, hepatic and pancreatobiliary, retroperitoneal, and systemic group) of IgG4-related disease by Zen and Nakanuma (22), the present case would be classified into systemic group with multiple lesions not restricted to 1 area. However, a visual field deficit due to orbital pseudotumor appears to be quite rare. An AIP patient who developed a visual field deficit of the left eye and swelling of bilateral salivary glands, which was metachronously associated with sclerosing sialadenitis and sclerosing cholangitis, was reported.

The authors state that they have no Conflict of Interest (COI).

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References

1. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. J Gastroenterol **41**: 613-625, 2006.
2. Kamisawa T, Takuma K, Tabata T, et al. Autoimmune pancreatitis and IgG4-related sclerosing disease. Nat Rev Gastroenterol Hepatol **7**: 401-409, 2010.
3. Ohara H, Nakazawa T, Sano H, et al. Systemic extrapancreatic lesion associated with autoimmune pancreatitis. Pancreas **31**: 232-237, 2005.
4. Kamisawa T, Funata N, Hayashi Y, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol **38**: 982-984, 2003.
5. Kamisawa T, Funata N, Hayashi Y, et al. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. Gut **52**: 683-687, 2003.
6. Okazaki K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol **41**: 626-631, 2006.
7. Kamisawa T, Imai M, Egawa N, Tsuruta K, Okamoto A. Serum IgG4 levels and extrapancreatic lesions in autoimmune pancreatitis. Eur J Gastroenterol **20**: 1167-1170, 2008.
8. Takuma K, Kamisawa T, Anjiki H, et al. Metachronous extrapancreatic lesions in autoimmune pancreatitis. Intern Med **49**: 529-533, 2010.
9. Swamy BN, McCluskey P, Nemet A, et al. Idiopatic orbital inflammatory syndrome: clinical feature and treatment outcome. Br J Opthalmol **91**: 1667-1670, 2007.
10. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. Ophthalmology **111**: 997-1008, 2004.
11. Mombaerts I, Goldschmeding R, Schlingemann RO, et al. What is orbital pseudotumor? Surv Ophthalmol **41**: 66-78, 1996.
12. Smitt MC, Donaldson SS. Radiation therapy for benign disease of orbit. Semin Radiat Oncol **9**: 179-189, 1999.
13. Chirapapaisan N, Chuenkongkaew W, Pornpanich K, Vangveeravong S. Orbital pseudotumor: clinical features and outcomes. Asian Pac J Allergy Immunol **25**: 215-218, 2007.
14. Yan J, Wu Z, Li Y. The differentiation of idiopathic inflammatory pseudotumor from lymphoid tumors of orbit: analysis of 319 cases. Orbit **23**: 245-254, 2004.
15. Aylward GW, Sullivan TJ, Garner A, et al. Orbital involvement in multifocal fibrosclerosis. Br J Ophthalmol **79**: 246-249, 1995.
16. Levine MR, Kaye L, Mair S, et al. Multifocal fibrosclerosis. Report of a case of bilateral idiopathic sclerosing pseudotumor and retroperitoneal fibrosis. Arch Ophthalmol **111**: 841-843, 1993.
17. Rootman J, McCarthy M, White V, et al. Idiopathic sclerosing inflammation of the orbit. A distinct clinicopathologic entity. Ophthalmology **101**: 578-584, 1994.
18. Hamano H, Arakura T, Muraki T, et al. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. J Gastroenterol **41**: 1197-1205, 2006.
19. Takahashi M, Kawano M, Zen Y, et al. IgG4-related chronic sclerosing dacryadenitis. Arch Ophthalmol **125**: 1575-1578, 2007.
20. Yamamoto M, Harada S, Ohara M, et al. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. Rheumatology **44**: 227-234, 2005.
21. Schaffer AJ, Jacobsen AW. Mikulicz's syndrome: a report of ten cases. Am J Dis Child **34**: 327-346, 1927.
22. Zen Y, Nakanuma Y. IgG4-related disease. A cross-sectional study of 114 cases. Am J Surg Pathol **34**: 1812-1819, 2010.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Serum IgG4-negative autoimmune pancreatitis

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Abstract
Background Autoimmune pancreatitis (AIP) is considered to be a pancreatic lesion of IgG4-related systemic disease, but about 20% of AIP patients do not have elevated serum IgG4 levels. This study aimed to clarify the pathophysiology of AIP patients without elevated serum IgG4 levels.
Methods Fifty-eight AIP patients were divided into 2 groups: those with elevated serum IgG4 levels (>135 mg/dl; SIgG4-positive AIP) and those without (SIgG4-negative AIP). The 2 groups' clinical, serological, radiological, and histological findings, as well as salivary and lacrimal gland function, were compared.
Results Serum IgG4 levels were elevated in 45 AIP patients and normal in 13 patients. In SIgG4-negative AIP patients, the female ratio tended to be high; obstructive jaundice was less likely; abdominal pain and acute pancreatitis were more likely; segmental swelling of the pancreatic body and/or tail was more common; sclerosing extrapancreatic lesions, salivary and lacrimal gland dysfunction, and abundant infiltration of IgG4-positive plasma cells in the gastric mucosa were less likely; and conservative follow-up was sometimes implemented. Histological examination of the pancreas of SIgG4-negative AIP showed lymphoplasmacytic sclerosing pancreatitis (LPSP) rather confined to the pancreas ($n = 4$), inadequate material ($n = 2$), and pancreatic fibrosis showing infiltration of lymphocytes without infiltration of IgG4-positive cells or neutrophils ($n = 2$).
Conclusions Clinicopathological features of SIgG4-negative AIP differed from those of SIgG4-positive AIP. Some SIgG4-negative AIP cases are LPSP rather confined to the pancreas. SIgG4-negative AIP may include idiopathic duct-centric pancreatitis (IDCP) or sclerosing pancreatitis other than LPSP or IDCP, but further studies are needed to clarify this issue.

Keywords Autoimmune pancreatitis · IgG4 · Lymphoplasmacytic sclerosing pancreatitis · Idiopathic duct-centric pancreatitis

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Introduction

Autoimmune pancreatitis (AIP) is a distinct entity that is being recognized with increasing frequency worldwide. Since it responds dramatically to steroids, an autoimmune process has been implicated in its etiology. The histological pattern of AIP is called lymphoplasmacytic sclerosing pancreatitis (LPSP), which is characterized by dense

infiltration of IgG4-positive plasma cells and T lymphocytes, storiform fibrosis and obliterative phlebitis [1–3]. Since AIP is frequently associated with various sclerosing extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis, showing similar histological findings to the pancreas, AIP can be considered to be a pancreatic lesion of IgG4-related systemic disease, and its extrapancreatic lesions are clinical manifestations of organs involved in this systemic disease [4–6].

Another characteristic feature of AIP is significant elevation of serum IgG4 levels [1–3]. Hamano et al. [7] reported that the serum IgG4 level was >135 mg/dl in 19 of 20 AIP patients and that an IgG4 cutoff value of 135 mg/dl resulted in high accuracy (97%), sensitivity (95%), and specificity (97%) in distinguishing AIP from pancreatic cancer. However, in a recent study, the sensitivity of an elevated serum IgG4 level was 68% [8] to 81% [1].

From retrospective, histological examination of the resected pancreases of patients with mass-forming chronic pancreatitis, American and European pathologists described another unique histological pattern, which they called idiopathic duct-centric pancreatitis (IDCP) [9] or AIP with granulocyte epithelial lesions (GEL) [10]. It is histologically characterized by ductal epithelial granulocytic infiltration leading to ductal damage and obstruction, a feature not seen in LPSP. The lobular infiltrate contains neutrophils. Obliterative phlebitis is uncommon in IDCP, and the tissue does not generally stain for IgG4-positive cells [3, 9–11]. Although the typical clinical features of IDCP have not yet been clarified, typical serological abnormalities seen in AIP are not seen in IDCP [3]. IDCP is sometimes detected in Western countries, but it is uncommon in Japan and Korea [2].

In this study, to clarify the pathophysiology of AIP patients without elevated serum IgG4 levels (SIgG4-negative AIP), clinicopathological differences detected between AIP patients exhibiting elevated serum IgG4 levels (SIgG4-positive AIP) and SIgG4-negative AIP patients were examined.

Patients and methods

Study patients

Serum IgG4 levels were measured by nephelometry using IgG subclass kits (BS-NIA IgG4, Medical & Biological Laboratories, Nagoya, Japan) in 58 AIP patients [43 males and 15 females; average age 63.2 ± 12.9 (mean ± SD) years] before steroid therapy or surgical resection. They were diagnosed as having AIP according to the Asian diagnostic criteria [12] based on radiological, serological and histological findings, and responsiveness to steroid. The serum IgG4 cutoff value was 135 mg/dl, which has been used widely [7]. Serum IgG4 levels were measured at least more than twice in patients without an elevated serum IgG4 level on the first examination.

Pancreatic resection and bypass operation were performed on suspicion of pancreatic cancer in 7 and 4 patients, respectively; steroid therapy was performed finally in 42 patients; and 6 patients have been followed conservatively. Steroid therapy was started at 0.6 mg/kg/day of prednisolone and gradually tapered to a maintenance dose over a period of 3–6 months. To prevent relapse, steroid maintenance therapy (2.5 mg–5 mg/day) was performed for 1–3 years. Relapse of AIP was defined as reappearance of symptoms with the development or reappearance of pancreatic and/or extrapancreatic abnormalities on imaging studies [13, 14].

Clinical, serological, and radiological analysis

The following clinical factors were retrospectively assessed: age at the time of diagnosis; sex ratio; drinking and smoking habits; present or past history of allergic diseases such as acute allergic rhinitis, atopic dermatitis, and bronchial asthma; and treatment. Drinking habit was defined as drinking more than 80 g of alcohol/day for more than 7 years, and smoking habit was defined as smoking more than 20 pack-years (the number of packages of cigarette per day times years of smoking). Acute pancreatitis was diagnosed when both severe upper abdominal pain and elevated serum amylase levels (>3 times normal) were met. Furthermore, SIgG4-negative AIP patients were subdivided into 2 groups according to the degree of serum IgG4 levels: slightly lower SIgG4 patients (IgG4 70–135 mg/dl) and extremely lower SIgG4 patients (IgG4 <70 mg/dl), and clinical features were compared between the 2 groups.

Serologically, serum IgG levels ($n = 58$), autoantibodies ($n = 56$) including antinuclear antigen and rheumatoid factor, serum IgE levels ($n = 30$), peripheral eosinophil count ($n = 49$), and serum amylase levels ($n = 58$) were reviewed.

Radiologically analyzed findings were as follows: enlargement of the pancreas (diffuse/segmental) and extrapancreatic lesions on CT, fluorine-18 fluorodeoxyglucose (FDG) uptake and maximum standardized uptake value (SUV) on FDG positron emission tomography (PET) ($n = 13$) [15, 16], and high signal intensity and apparent diffusion coefficient (ADC) value on diffusion-weighted magnetic resonance imaging (DWI) ($n = 13$) [17]. The presence of 4 extrapancreatic lesions that were detected with a relatively high frequency in AIP patients (sclerosing cholangitis of the hilar or intrahepatic bile duct, sclerosing

cholecystitis, sclerosing sialadenitis, and retroperitoneal fibrosis) was evaluated. Though stenosis of the lower bile duct occurred frequently in AIP patients, sclerosing cholangitis as an extrapancreatic lesion of AIP was defined as presence of stenosis of the hilar or intrahepatic bile duct on cholangiography to rule out stenosis of the lower bile duct induced by compression by the swollen pancreas. Sclerosing cholecystitis was defined as gallbladder wall thickening of more than 4 mm. The presence of salivary gland swelling and retroperitoneal fibrosis was determined based on the CT findings. FDG uptake was first evaluated visually. A region of interest (ROI) was placed over the entire area of any abnormal FDG uptake. SUVmax (maximum ROI activity/injected dose/body weight) was then computed at the early period [15, 16]. DWI was obtained using a single-shot echo-planar imaging sequence, and the high signal intensity area was assessed. All ADC values were calculated on a workstation with standard software (ShadeQuest; Yokogawa Electric, Tokyo, Japan). The ADC values were determined by measurements of the ROI created on each ADC map [17].

To assess glucose tolerance, fasting serum glucose and glycosylated hemoglobin levels were examined in all patients. *N*-Benzoyl-L-tyrosyl-*p*-aminobenzoic acid (BT-PABA) excretion tests (normal $\geq$70%) were performed on 9 patients to assess pancreatic exocrine function.

Salivary and lacrimal gland functions

If AIP and its extrapancreatic lesions are clinical manifestations of organs involved in IgG4-related systemic disease [4–6], salivary and lacrimal gland functions may be impaired in AIP patients. Therefore, we investigated salivary gland function with sialochemistry and lacrimal gland function with Schirmer's test.

Salivary fluid is normally isotonic with plasma, and Na^+ and Cl^- are extensively resorbed via the ductal system to produce a hypotonic secreted fluid. Salivary Na^+ concentrations are increased in patients with Sjogren's syndrome, since resorption is altered in Sjogren's syndrome by the periductal lymphocytic infiltration [18]. The salivary β2-microglobulin level shows high specificity for inflammation of the salivary glands, and the salivary β2-microglobulin level increases in Sjogren's syndrome [19]. Saliva was collected without stimulation in 25 patients. Patients allowed saliva to drain continuously from the lower lip or spit it out for 30 min in the morning. Salivary concentrations of Na^+ and β2-microglobulin were investigated [20]. The sialochemistry data of 30 normal individuals were used as controls.

To examine tear production as a measure of lacrimal gland function, Schirmer's test was performed prospectively in the 14 AIP patients before steroid therapy. Schirmer's test involves measuring the amount of wetting of a special filter paper, which is 5-mm wide and 35-mm long. First, the filter paper is folded 5 mm from one end and inserted between the middle and outer third of the lower lid. The patient is then asked to keep his eyes open and to blink as necessary. After 5 min, the filter strip is removed, and the amount of wetting from the fold is measured. A normal eye will wet between 10 and 25 mm during that period. Measurements between 6 and 10 mm are considered borderline, and values of 5 or <5 mm are indicative of impaired secretion [21]. A participant with one or both eyes yielding abnormal test results was defined as having tear secretion dysfunction. The lower of the right and left lacrimal gland test results was used for the analysis [22].

Histological and immunohistochemical examination

Surgically resected ($n = 7$) and surgically or US-guided biopsied ($n = 7$) pancreatic specimens, and endoscopic ultrasonography-guided fine-needle aspiration EUS-FNA specimens taken with a 19-gauge needle ($n = 2$) and 21-gauge needle ($n = 5$) were examined histologically and immunohistochemically using anti-CD3, anti-CD20, and anti-IgG4 antibodies. Endoscopically biopsied specimens from the stomach ($n = 24$) were stained with anti-IgG4 antibody, and the number of IgG4-positive plasma cells was counted per high power field (hpf).

Statistical analysis

Data were expressed as mean $\pm$ SD. The data were compared between S. IgG4-positive and S. IgG4-negative AIP. For statistical analyses, Student's t test, Fisher's exact probability test, and Mann-Whitney's U test were employed. A value of <0.05 was considered statistically significant. When repeated comparisons were made, a value of <0.01 was considered significant.

Results

Clinical, serological, and radiological differences

Serum IgG4 levels were elevated in 45 (78%) of the 58 AIP patients (604.2 $\pm$ 526.0 mg/dl) and ranged from 11 to 123 mg/dl in the other 13 patients. No significant differences in age, presence of drinking and smoking habit, and allergic disease history were found. The female ratio tended to be higher in SIgG4-negative AIP patients, but the difference was not significant. As an initial symptom, obstructive jaundice was significantly more frequent in SIgG4-positive AIP patients (71%, $p = 0.002$), and abdominal pain was