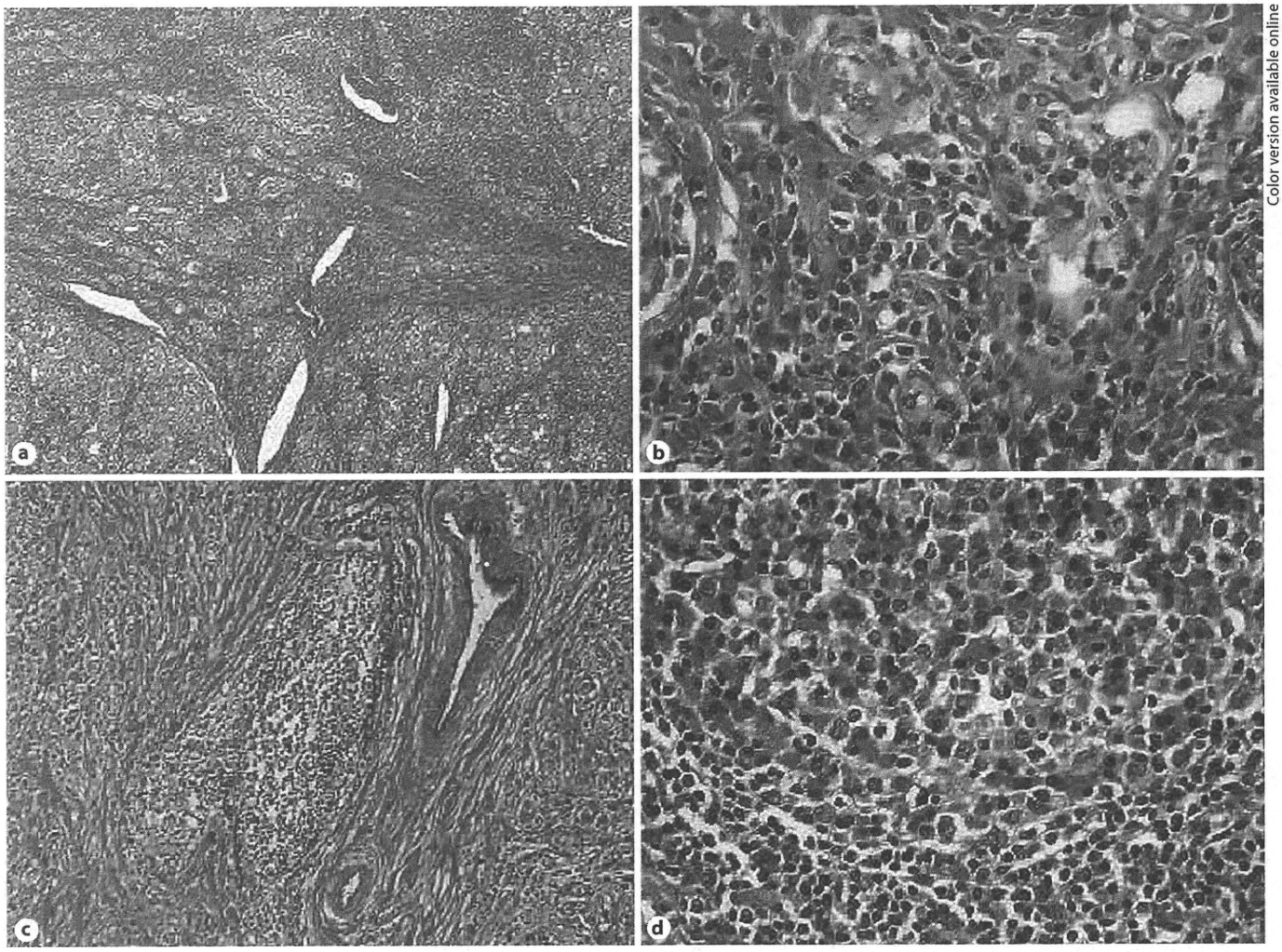

Fig. 1. a On a low-power field, the lesion was characterized by dense inflammatory processes, various degrees of lymphoid follicle formation and stromal fibrosis. HE. ×4. **b** On a high-power field, there were prominent lymphoplasmacytic infiltrations associated with follicular cell degeneration. HE. ×40. **c** On a medium-power field, Victoria blue-HE stain demonstrated obstructive phlebitis. ×20. **d** On a high-power field, numerous plasma cells were seen in the germinal center surrounded by mantle cells. HE. ×40.

the intrafollicular + interfollicular pattern demonstrated kappa light chain-restricted germinal centers. These histological and immunohistological findings are similar to those of follicular colonization of extranodal marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type showing prominent plasma cell differentiation [13]. In comparison with other types of MALT-type lymphoma, plasma cell differentiation is more prominent in thyroid MALT-type lymphoma [14]. Moreover, the majority of thyroid MALT-type lymphomas demonstrated an intracytoplasmic kappa light chain [15]. However, there were no CD20- and CD43-positive CCL cells or lymphoepithelial lesions in either case [14, 16]. Using a cocktail of CD21 and CD35 antibodies, there was no broken follicular dendritic cell network, which is a characteristic immunohistochemical finding of follicular colonization of MALT-type lymphoma in either of the 2 lesions [14, 16]. A few cases of IgG4-producing MALT-type lymphoma have been reported [17]. However, overall these immunohistochemical findings suggested that these 2 lesions differed from MALT-type lymphoma.

Riedel's thyroiditis has commonly been reported as a thyroid involvement of IgG4-related sclerosing disease by some researchers [18]. In this study, a small number

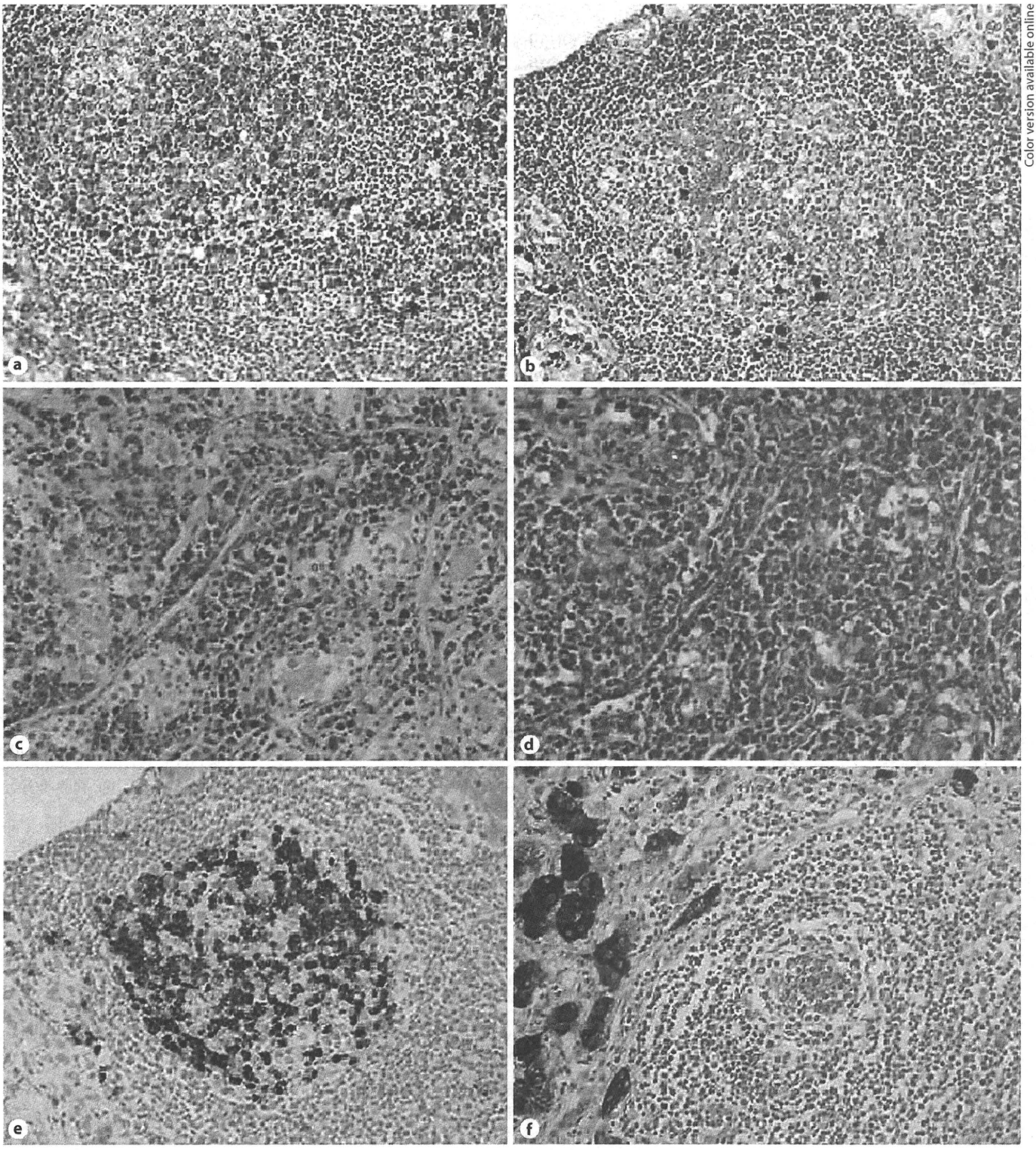

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Fig. 2. In an immunohistochemical study, intrafollicular plasma cells demonstrated marked kappa light chain predominance (kappa/lambda ratio was greater than 10/1): kappa (**a**) and lambda (**b**). Same case as in figure 1c. ×20. IgG4-positive plasma cells comprised more than 30% of IgG-positive plasma cells in the interfollicular area: IgG4 (**c**) and IgG (**d**). ×20. **e** Note numerous IgG4-positive plasma cells in the germinal center. ×20. Same case as figure 1c. **f** Thyroglobulin was detected by a cocktail of CD21 and CD35 antibody-positive follicular dendritic cell networks in germinal centers as well as in follicular epithelium. ×10.

of IgG4 HT and non-IgG4 HT cases (IgG4 HT = 2, non-IgG4 HT = 4) demonstrated obstructive phlebitis which is a characteristic histological finding of Riedel's thyroiditis and IgG4-related sclerosing disease [3–5, 19]. However, there was no extrathyroid fibrosis, which is another characteristic histological finding of Riedel's thyroiditis [3, 5]. Thyroglobulin was detected at the follicular dendritic cell networks in germinal centers as well as in the follicular epithelium, which is seen in HT [20]. Furthermore, in a previous study, Harach and Williams [6] characterized plasma cell subsets in Riedel's thyroiditis by immunohistochemistry, demonstrating that IgA plasma cells but not IgG plasma cells were predominant in Riedel's thyroiditis. Therefore, as previously suggested by Li et al. [8, 9], we also considered that Riedel's thyroiditis is unrelated to IgG4-related sclerosing disease.

In conclusion, the present study demonstrated that the majority of cases with IgG4 HT and non-IgG HT showed an interfollicular distribution pattern of IgG4- and/or IgG-positive plasma cells. Moreover, a minority of IgG4 HT (7%) and non-IgG4 HT contained IgG/kappa light chain-restricted germinal centers. However, the number of these cases is too limited to clarify the clinicopathological significance at present.

Acknowledgments

This work was supported by the Intractable Diseases, the Health and Labour Sciences Research Grants from Ministry of Health, Labor and Welfare.

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J Clin Exp Hematopathol
Vol. 50, No. 1, May 2010

Original Article

Castleman's Disease of the Retroperitoneum : With Special Reference to IgG4-Related Disorder

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Localized Castleman's disease (CD) has been divided two types, the classical hyaline vascular (HV) type and the rare plasma cell (PC) type. Recently, we have reported two cases of IgG4-related disorder of the retroperitoneum showing PC type of CD. To further clarify the clinicopathological findings of CD of the retroperitoneum, eight such cases have been studied. A single lesion was located in the retroperitoneum (n = 3), ureter (n = 2) and renal hilum (n = 2). One case had bilateral ureter lesions. The HV type of CD accounts for approximately 90% of cases. However, 50% (n = 4) of our cases were the PC type of CD. Three of the four lesions of HV type had lymph node lesions, whereas all four PC type of CD were soft tissue masses. These clinicopathologic findings appear quite different from previous descriptions. Immunohistochemical study demonstrated numerous IgG4$^+$ plasma cells accounting for more that 50% of IgG4$^+$ cells in three cases of the four PC type of CD. Moreover, serum IgG4 concentration was increased in two of the four cases of PC type of CD that were examined. The serum interleukin-6 levels were within the normal range in two cases of PC type that were examined. The present study suggests that a majority of the PC type of CD arising in the retroperitoneum appears to be an IgG4-related disorder. [*J Clin Exp Hematopathol 50(1) : 39-44, 2010*]

Keywords: Castleman's disease, retroperitoneum, hyaline vascular type, plasma cell type, IgG4-related disorder

INTRODUCTION

In 1956, Castleman *et al.* described an entity involving localized mediastinal lymph node hyperplasia that resembled thymoma.[1] Since the original description, Castleman's disease (CD) has been extended to included two types, the classical hyaline vascular (HV) type and plasma cell (PC) type.[2-4] The HV type of CD accounts for approximately 90% of cases.[2-4] This type is usually localized to a single lymph node, is asymptomatic, and shows a benign clinical course. Histologically, HV type of CD is characterized by abnormal lymphoid follicles and interfollicular vascularity. The PC type of CD is occasionally multifocal and may be associated with systemic problems such as fever, weight loss, hemolytic anemia and hypergammaglobulinemia.[2-4] Histologically, the PC type of CD is defined by numerous lymphoid follicles with an active germinal center (GC) and interfollicular polyclonal plasmacytosis.[2-4]

IgG4 is the least common subclass of IgG, normally accounting for only 3% to 6% of the IgG in the serum (normal range ; 4.8-105 mg/dL). IgG4-related sclerosing disease is a recently recognized syndrome characterized clinically by tumor-like enlargement of one or more exocrine glands or extranodal tissues and raised serum IgG4 levels. It is characterized pathologically by lymphoplasmacytic infiltration and sclerosis, as well as an increased frequency of IgG4-secreting plasma cells.[5-8] IgG-related sclerosing disease is defined by elevated serum IgG4 levels (> 135 mg/dL) and/or numerous IgG4$^+$ plasma cells accounting for more than 50% of IgG$^+$ cells in the affected organs.[8]

Received : June 9, 2009
Revised : July 14, 2009
Accepted : July 29, 2009

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Recently, we have reported two cases of IgG4-related disorder of the retroperitoneum showing histological findings of PC type of CD.[9] To further clarify the clinicopathological findings of CD of the retroperitoneum, we have examined eight such cases.

MATERIALS AND METHODS

Eight cases were collected from a series by one of the authors (M. K.) treated between January 1988 and June 2009. Medical records of eight cases were extensively reviewed. Two cases (Nos. 5 and 7) have been reported previously.[9] Surgical specimens were fixed in formalin, routinely processed and embedded in paraffin. For light microscopic examination, the sections were stained with hematoxylin-eosin and elastica-van Gieson stain.

Immunohistochemical studies were performed using the antigen retrieval method on the avidin-biotin-peroxidase method or Ventana automated (BenchMark^{TM}) stainer according to the manufacture's instructions. The panel of antibodies included human immunoglobulin light chains (κ and λ) (Dako A/S, Glostrup, Denmark), IgA (Dako), IgD (Dako), IgG (Novocastra, Newcastle, UK), MCO011 (IgG4 ; Binding Site, Birmingham, UK), IgM (Dako), PS-1 (CD3 ; Immunotech, Marseille, France), 56C6 (CD10 ; Novocastra), L26 (CD20 ; Dako), cocktail of 2G9 (CD21 ; Novocastra) and RB L25 (CD35 ; Novocastra), DFT-1 (CD43 ; Dako), 1B16 (CD56 ; Novocastra), SP-4 (Cyclin D1 ; Nichirei Co. Tokyo, Japan), 124 (bcl-2 ; Dako) and 137B1 (human herpes virus type-8 [HHV-8] ; Novocastra). 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 Epstein-Barr virus (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 (BenchMarkTM) stainer or using the hybridization kit (Dako).

Paraffin-embedded tissues from the operatively resected specimen were prepared for polymerase chain reaction (PCR), and the rearranged *immunoglobulin heavy*-chain (*IgH*) genes were amplified using the seminested PCR method as described by Wan *et al.*[10]

RESULTS

The main clinicopathological findings are shown in Table 1.

Clinical findings

The patients, three men and five women, ranged in age from 21 to 75 years with a median age of 58.5 years. "B" symptoms such as fever were recorded in only one patient (No. 7). The tumor was located in the retroperitoneum in three cases (Nos. 1, 2 and 4), in the periureter tissue in three cases (Nos. 3, 6 and 7) and in the renal hilum in two cases (Nos. 5 and 8). Case 3 had bilateral periureter tissue tumors. The other cases had a single solitary lesion. In one patient (No. 3), there was an association of chronic sclerosing sialoadenitis which belongs to the IgG4-related disease.[11]

Postoperatively, the serum IgG4 levels were examined in four cases (Nos. 3, 5-7), and serum IgG4 levels were increased in two cases (Nos. 3 and 7). The serum interleukin-6 (IL-6) levels were within normal range in two cases examined (Nos. 3 and 7). One patient (No. 3) was given prednisolone after the tumor biopsy and the remaining six patients did not receive medication. Follow-up data were obtained in all patients except one patient (No. 4). Seven patients were alive during the follow-up period, ranging four to 108 mon (median 12 mon).

Table 1. Summary of main clinicopathological findings of eight cases

No. of case	Age/ Gender	Site of the tumor	Size of the lesion (cm)	Systemic symptom	IgG4* (mg/dL)	IL-6** (pg/mL)	Therapy	Outcome	Histology
1	21/F	Right retroperitoneum	5	-	NE	NE	Resection	17 mon A(-)	HV
2	46/F	Retroperitoneum	5	-	NE	NE	Resection	4 mon A(-)	HV
3	47/F	Bilateral ureters	1.5	-	478	1.6	Biopsy + Prednisone	6 mon A(+)	PC
4	59/M	Retroperitoneum	5	-	NE	NE	Resection	Lost	HV
5	68/F	Left renal hilum	3	-	101	NE	Resection	11 mon A(-)	PC
6	71/F	Left ureter	3.5	-	75.9	NE	Resection	12 mon A(-)	PC
7	73/M	Left ureter	3.5	fever	412	2.33	Resection	22 mon A(-)	PC
8	75/M	Left renal hilum	2	-	NE	NE	Resection	108 mon A(-)	HV

F, female ; M, male ; IL-6, interleukin-6 ; NE, not examine ; A(-), alive without disease ; A(+), alive undertreatment ; HV, hyaline-vascular ; PC, plasma cell ; *, Normal range < 135 mg/dL ; **, Normal range < 4.62 pg/mL

Pathological, immunohistochemical and EBV findings

The size of the lesion ranged from 1.5 to 5 cm in diameter (mean = 3.6 cm). Macroscopically, all eight lesions were solitary and firm, and were relatively well circumscribed.

1) HV type

Under low magnification, the lesions in four cases (Nos. 1, 2, 4 and 8) was found to contain numerous lymphoid follicles. Three types of the lymphoid follicles were further delineated into the following groups : (i) Lymphoid follicles with normal hyperplastic GCs ; (ii) Large nodules of mantle

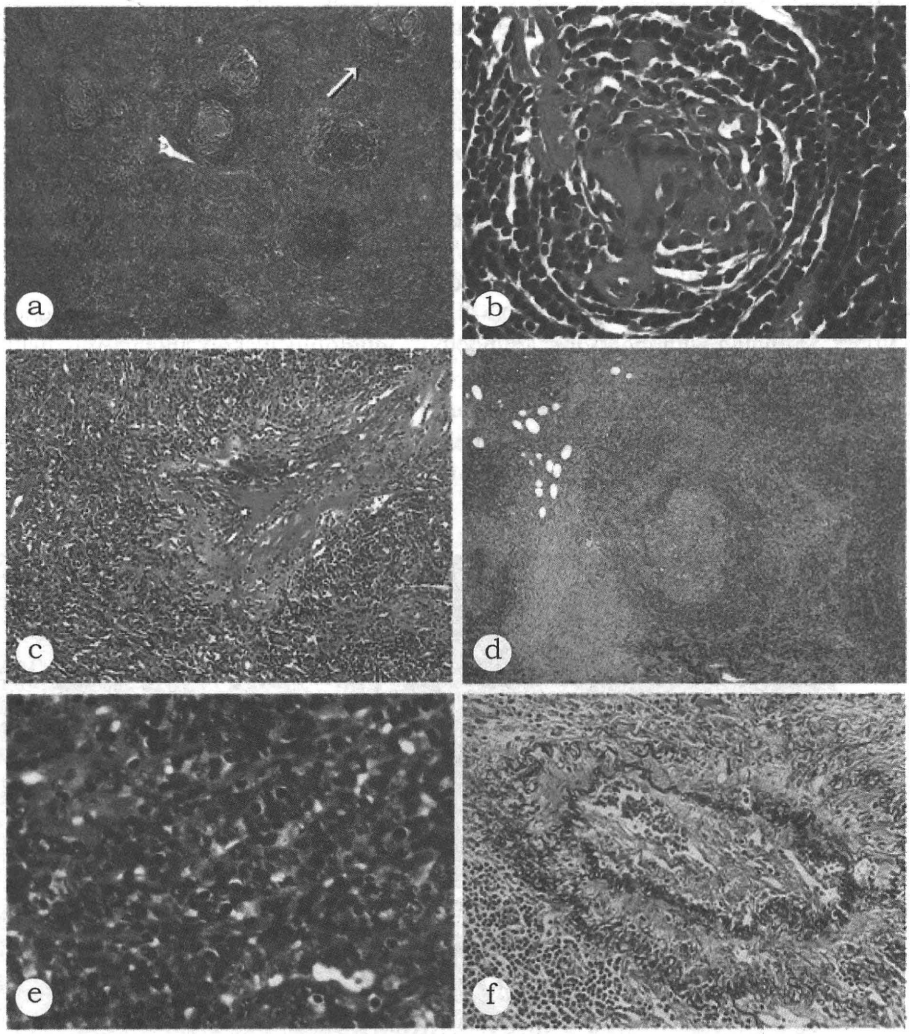

Fig. 1. Pathological findings of Castleman's disease of the retroperitoneum. (***1a***) Low power field of the affected lymph node. There were nodules of mantle cells with inconspicuous germinal centers (GCs). These nodules were penetrated by small vessels. Note a large nodule of mantle cells containing multiple small atrophic GCs (*arrow*). Case 1, H&E stain, ×10. (***1b***) High-power field of a GC of Fig. 1a. Note the nuclear enlargement of follicular dendritic cells (FDCs). Case 1, H&E stain, ×100. (***1c***) Medium-power field of the lesion. Note marked small vessel proliferation and sclerosis in the interfollicular area. Case 4, H&E stain, ×25. (***1d***) On low-power field, numerous lymphoid follicles with active GCs were present. Note the fibrous sclerosis in the interfollicular area. Case 3, H&E stain, ×10. (***1e***) On high-power field, numerous infiltrating plasma cells including Mott cells were seen in the interfollicular area. There was no sign of marked proliferation of blood vessels. Case 3, H&E stain, ×100. (***1f***) Elastica-van Gieson stain demonstrating phlebitis in Case 6. ×10.

cells contained multiple small atrophic GC with increased vascularity (multiple GC pattern) (Fig. 1a)[3] ; (iii) Large, often irregularly shaped nodules of mantle cells with inconspicuous GCs. Frequently, these nodules were radically penetrated by small vessels and somewhat resembled primary follicles (primary follicular pattern).[3] A portion of follicular dendritic cells (FDCs) in these GCs demonstrated enlarged nuclei with prominent nucleoli (Fig. 1b). The majority of the lymphoid follicles in all four cases showed the primary follicular pattern and/or multiple GC pattern. There were no plasmacytoid dendritic cells in any of the four lesions. Marked small vessel proliferation and perivascular fibrous masses were observed in all four subjects (Fig. 1c). There were interfollicular sclerosis in all four lesions and it was especially prominent in one case (No. 4) (Fig. 1c).

The results of immunohistochemical studies of these patients were similar to those described in previous reports.[4,12] Briefly, mantle cells in the primary follicular and multiple GC patterns were $CD20^+$, $sIgM^+$, $sIgD^+$, $CD3^-$, $CD10^-$, $CD43^-$, $bcl\text{-}2^+$ and cyclin $D1^-$.[4,12] Staining with monoclonal antibody cocktail of 2G9 and RB L25 highlighted the meshwork of FDCs. The FDC networks of the primary follicular pattern and multiple GC pattern showed a tight/concentric pattern or expanded/disrupted pattern as previously described by Nguyen *et al.*[13] There were only a few $IgG4^+$ plasma cells in all four lesions. There were no HHV-8 or EBER-positive cells in any of the four cases.

2) PC type

All four lesions were composed of a dense lymphoplasmacytic infiltration. The inflammatory process extended to the periureter adipose tissue. Numerous lymphoid follicles with active GCs were also observed (Fig. 1d). The interfollicular area was characterized by sheets of proliferating mature plasma cells (Fig. 1e). A few immature plasma cells and immunoblasts were intermingled with mature plasma cells. Many plasma cells containing numerous basophilic rounded cytoplasmic inclusions (Mott cells) were seen in Case 7. However, there were no Dutcher bodies, centrocyte-like cells or amyloid deposition in any of the four lesions. In the interfollicular area, there was no marked proliferation of blood vessels in any of the four lesions. However, in the interfollicular area, there were marked fibrous sclerosis in two lesions (Nos. 3 and 6). Partially obstructive phlebitis was observed in the two lesions (Nos. 5 and 6) (Fig. 1f).

The immunoglobulin light chain reactivity of plasma cells showed a polyclonal pattern in all four lesions (Figs. 2a and

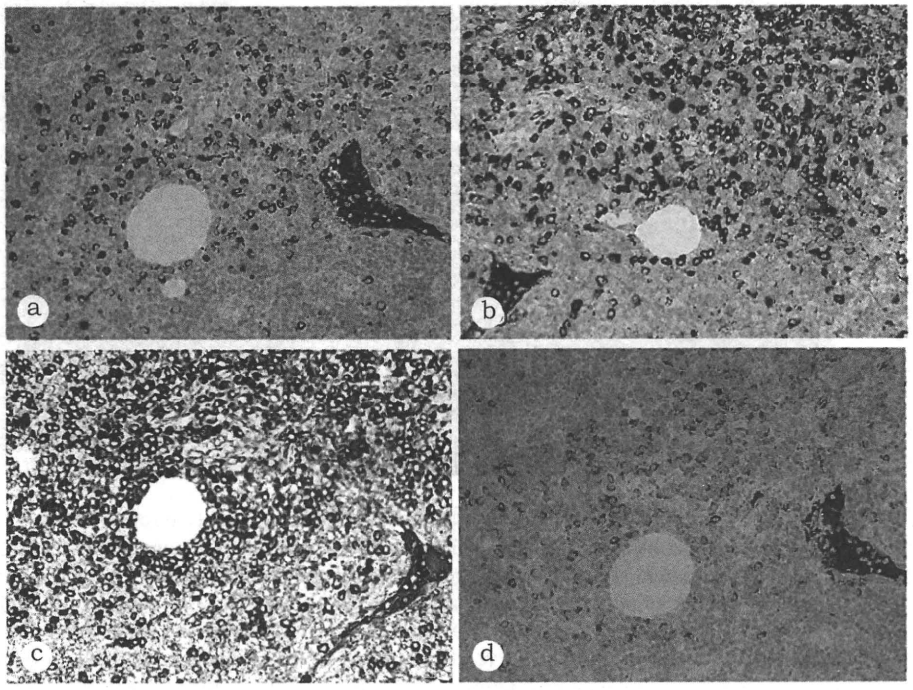

Fig. 2. Immunostaining for light chain determinant of the immunoglobulin demonstrating the polytypic nature of mature plasma cells. (***2a***) κ-light chain in Case 3. (***2b***) λ-light chain in Case 3. (***2c***) There were numerous IgG^+ cells in the paracortical area in Case 3. (***2d***) Fifty percent of the IgG^+ plasma cells were IgG4-positive in Case 3. (***2a***), (***2b***), (***2c***) and (***2d***), Counterstained with hematoxylin, ×100.

2b).[9] There were numerous IgG^+ plasma cells with scattered IgA^+ or IgM^+ plasma cells in all four cases. $IgG4^+$ cells comprised 50-60% of IgG^+ plasma cells in three cases (Nos. 3, 5, and 7) (Figs. 2c and 2d), whereas Case 6 contained only a few $IgG4^+$ plasma cells. CD20 immunostaining demonstrated that there were no intraepithelial B-lymphocytes in the renal pelvis or ureter mucosa. B-cells in the GCs were bcl-2 negative in both lesions. There were no $CD43^+$ or cyclin $D1^+$ small B-cells in either lesion. There were no $CD56^+$ plasma cells in any of the four lesions.

There were no $HHV\text{-}8^+$ and $EBER^+$ cells in any of the four cases.

Genotypic study

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

DISCUSSION

The HV type of CD accounts for approximately 90% of cases.[2-4] The majority of the CD located in the retroperitoneum were the HV type of CD.[14,15] However, in the present series, four of the eight cases of retroperitoneal CD were the PC type of CD. It has been reported that the majority of the PC type of CD were located in the peripheral lymph nodes.[2,4] However, all four cases of PC type of CD in this study were extranodal lesions. These clinicopathological findings are quite different from previous descriptions.

Some degree of sclerosis is common in follicular lymphoma (FL), particularly in those involving in retroperitoneum and groin.[16-18] When sclerosis is prominent, the term "sclerosing variant of FL" has previously been applied.[18] FL rarely shows lymphoid follicles mimicking the HV type of CD.[16,19] One of our four cases of HV type CD showed prominent interfollicular sclerosis. However, lymphoid follicles of the present four HV type were $CD10^-$.[16,17] Moreover, genotypic studies demonstrated polytypic nature of the B-lymphocytes.

The PC type of CD should be differentiated from low-grade B-cell lymphoma showing prominent plasma cell differentiation, particularly marginal zone B-cell lymphoma and multiple myeloma involving extramedullary organs.[16,17,20] However, immunohistochemical and genotypic studies demonstrated polytypic nature of the B-lymphocytes. Moreover, there were no $CD43^+$ centrocyte-like cells and/or $CD56^+$ plasma cells in any of the four lesions.[16,17,20,21]

Interestingly, immunohistochemical studies demonstrated numerous $IgG4^+$ plasma cells accounting for more than 50% of IgG^+ cells in three (Nos. 3, 5 and 7) of the four lesions.[8] Obstructive phlebitis, which is one of the characteristic histological findings of IgG4-related disorders, was observed in one case (No. 6).[4-7] The fibrous sclerosis in the interfollicular area was also seen in Case 3.[4-8]

Serum IgG4 concentration was increased in two cases (Nos. 3 and 7) whereas serum IgG4 concentration was within the normal range in Case 5. However, postoperatively serum IgG4 levels may have decreased levels to the normal range in Case 5. These three cases appear to be IgG4-related disorders. Yoshizaki *et al.* demonstrated that abnormal clinical findings such as general fatigue, anemia and polyclonal hyper-γ-globulinemia may be related to a high level of IL-6 in the PC type of CD.[22] However, serum IL-6 levels were within the normal range in two cases (Nos. 3 and 7). Moreover, there were no clinical characteristics of PC type of CD in any of the four cases.[2,3,22,23]

The remaining case (No. 6) showed similar histopathological findings of other three cases including thrombophlebitis and fibrous sclerosis in the interfollicular area. This case indicated that at least a portion of PC type of CD is unrelated to the IgG4 related disorder. In other words, PC type of CD contains a heterogeneous disease entity.

Good responsiveness to glucocorticoid therapy is seen in IgG4-related disorder,[7] whereas PC type of CD is occasionally resistant to corticosteroid therapy.[23] From a therapeutic perspective, it is important to discriminate IgG4-related disorder from PC type of CD.

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

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Lupus published online 21 October 2010
DOI: 10.1177/0961203310381510

The online version of this article can be found at:
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Lupus (2010) 0, 1–7
http://lup.sagepub.com

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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Received 7 December 2009; accepted 20 July 2010

10.1177/0961203310381510

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.

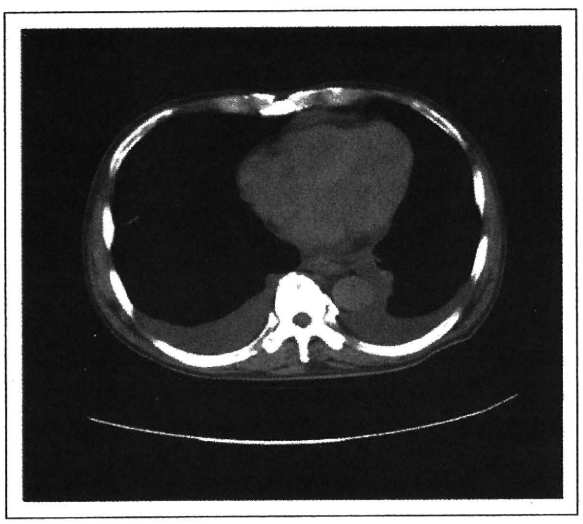

Figure 1 Computed tomographic scan at the onset of disease. Note massive bilateral pleural effusion. Case 7.

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

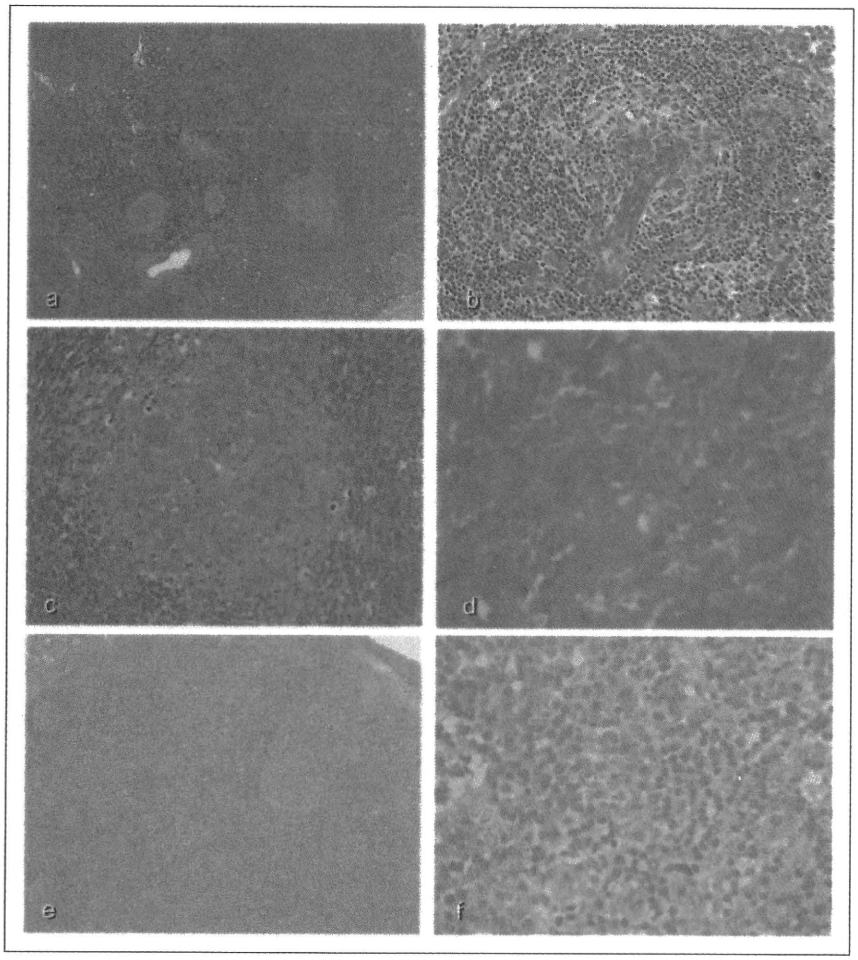

Figure 2 (a) Medium-power field of the lymph node. Note numerous abnormal germinal centers and open sinus. Hematoxylin-eosin (HE) × 25. Case 6. (b) High-power field of the germinal center demonstrating a hyaline-vascular type. HE × 100. Case 5. (c) High-power field of the germinal center demonstrating 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]

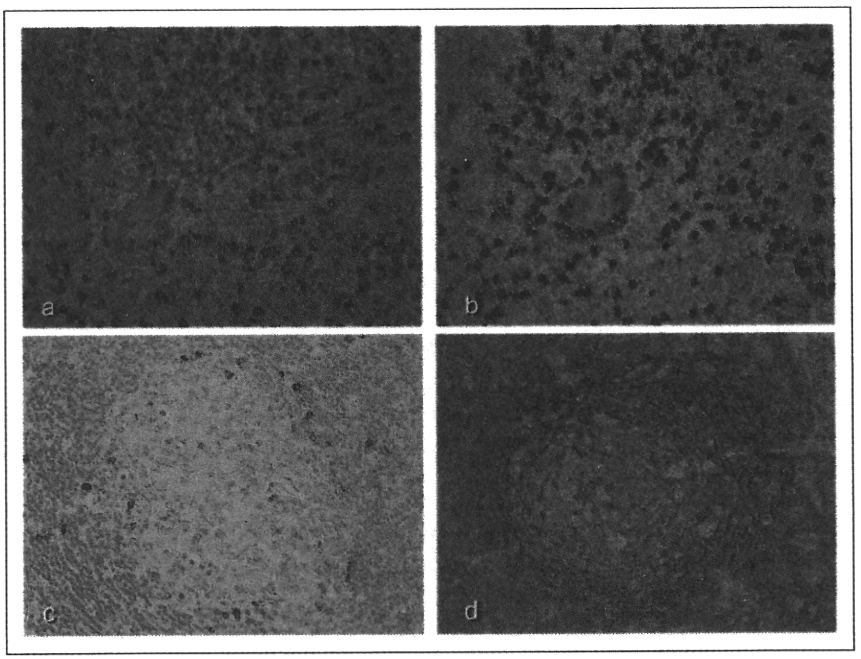

Figure 3 Immunostaining for light chain determinant of immunoglobulins demonstrated the polytypic nature of the plasma cells and their precursors (a) kappa and (b) lambda. × 50, Case 6. (c) Leu7 immunostaining demonstrated only a few positive T cells in an epithelioid germinal center. × 50 (d) A cocktail 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.

Funding

This work was supported by the Intractable Diseases, the Health and Labor Sciences Research Grants from Ministry of Health, Labor and Welfare.

Conflict of interest

The authors declare that they have no conflicts of interest.

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nature REVIEWS

July 2010 volume 7 no. 7
www.nature.com/reviews

GASTROENTEROLOGY & HEPATOLOGY

Autoimmune pancreatitis and IgG4-related sclerosing disease

Terumi Kamisawa, Kensuke Takuma, Naoto Egawa, Koji Tsuruta and Tsuneo Sasaki

Reprinted from NR Gastroenterology & Hepatology, Vol. 7 #7, 2010

Autoimmune pancreatitis and IgG4-related sclerosing disease

Terumi Kamisawa, Kensuke Takuma, Naoto Egawa, Koji Tsuruta and Tsuneo Sasaki

Abstract | Autoimmune pancreatitis (AIP) is a unique form of pancreatitis in which the pathogenesis is suspected to involve autoimmune mechanisms. AIP sometimes mimics pancreatic cancer in its presentation, but as AIP responds dramatically to steroid therapy, accurate diagnosis is necessary. AIP is currently diagnosed on the basis of a combination of characteristic clinical, serological, morphological and histopathological features. However, its diagnosis remains a clinical challenge and there are no internationally agreed diagnostic criteria. Another type of AIP called 'idiopathic duct-centric chronic pancreatitis' or 'AIP with granulocytic epithelial lesion' has been reported in Western countries. IgG4-related sclerosing disease is a systemic disease in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs. Organs with tissue fibrosis and obliterative phlebitis, such as the pancreas, salivary gland and retroperitoneum, show clinical manifestations; AIP seems to represent one manifestation of IgG4-related sclerosing disease. As a mass is formed in most cases of IgG4-related sclerosing disease, a malignant tumor is frequently suspected on initial presentation. Clinicians should consider IgG4-related sclerosing disease in the differential diagnosis to avoid unnecessary surgery.

Kamisawa, T. *et al. Nat. Rev. Gastroenterol. Hepatol.* **7**, 401–409 (2010); published online 15 June 2010; doi:10.1038/nrgastro.2010.81

Introduction

Autoimmune pancreatitis (AIP) (also known as lymphoplasmacytic sclerosing pancreatitis; LPSP) is a form of pancreatitis with a presumed autoimmune etiology.[1–3] Sarles *et al.*[4] first reported pancreatitis associated with hypergammaglobulinemia in 1961. These authors suggested autoimmunity as one of the etiologies of pancreatitis.[4] In 1995, Yoshida *et al.*[5] first proposed the concept of AIP. Since then, AIP has been increasingly documented and is now recognized as a distinct entity.[3,6]

We conducted a histological and immunohistochemical analysis of various organs and extrapancreatic lesions of patients with AIP. On the basis of these findings, we proposed a new clinicopathological entity, 'IgG4-related sclerosing disease', and suggested that AIP is one manifestation of this systemic disease.[7–10] In this Review, we focus on the clinical and pathophysiological features of AIP and IgG4-related sclerosing disease.

Autoimmune pancreatitis

Prevalence

A nationwide Japanese survey conducted in 2002 reported 900 individuals with AIP, and the prevalence rate was estimated as 0.82 per 100,000 individuals.[11] The prevalence of AIP among patients with chronic pancreatitis was estimated at about 2%. The male:female ratio was 2.85. 47% of patients were between 61 and 70 years old at disease onset and patients older than 46 years accounted for 95% of all patients.[11] A more recent survey in Japan predicted that the number of patients with AIP had increased to 3,000.[12] In three studies in the USA, 43 of 1,808 (2.4%) pancreatic resections were reported to have LPSP on histological examination.[13–16] These data suggest that the number of reported cases of AIP is increasing with a growing global awareness of this disease.

Pathogenesis

Despite a great deal of effort, the pathogenetic mechanisms of AIP remain unclear. Human leukocyte antigen (HLA) haplotype DRB1*0405-DQB1*0401 is associated with AIP in the Japanese population,[17] but not in Korean patients.[18] However, substitution of aspartic acid to nonaspartic acid at DQβ1 57 may represent a key genetic factor for relapse of AIP in Korean patients.[18] *CTLA4* (cytotoxic T-lymphocyte-associated protein 4), which encodes a protein that acts as a negative regulator of T-cell responses, has also been reported to be a susceptibility factor for AIP.[19,20]

An antibody specific to AIP has not been identified. However, lactoferrin, carbonic anhydrase II and pancreatic secretory trypsin inhibitor have been suggested as candidate target antigens in AIP.[21,22] Endo *et al.*[23] reported that an autoantibody against amylase α-2A was a novel marker for both AIP and fulminant type 1 diabetes mellitus. Frulloni *et al.*[24] found a novel antibody associated with AIP that showed a homology with plasminogen-binding protein of *Helicobacter pylori*.

With regard to cellular immunity, the effector cells of AIP have not been established. Activated $CD4^+$ and $CD8^+$ T cells bearing HLA-DR and CD45RO are increased in the peripheral blood of patients with AIP.[21] T-helper-1

Competing interests
The authors declare no competing interests.

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Key points

- Autoimmune pancreatitis (AIP) should be diagnosed on the basis of a combination of characteristic clinical, serological, morphological and histopathological features
- Given than AIP responds dramatically to steroid therapy, accurate differentiation from pancreatic cancer is important
- IgG4-related sclerosing disease is a systemic disease, in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs
- AIP may be one manifestation of IgG4-related sclerosing disease

(T_H1) cells predominate over T_H2 cells in the peripheral blood,[21] whereas T_H2 cells dominate within the involved organs of patients with AIP.[25] Okazaki *et al.*[26] suggested that T_H1 cytokines induce AIP and T_H2 cytokines progress the disease. It has also been reported that circulatory regulatory T (T_{REG}) cells are significantly increased, and naive T_{REG} cells are significantly decreased in patients with AIP.[26,27] Zen *et al.*[25] demonstrated overproduction of T_H2 and increased expression of $CD4^+CD25^+$ forkhead box protein 3 (Foxp3) T_{REG} cells in the organs of patients with AIP. They suggested that T_{REG} cells might be involved in the *in situ* production of interleukin (IL)-10, which induces IgG4 class switching, and transforming growth factor β (TGF-β), which induces fibroplasia.[25] Upregulation of T_H2 cells and T_{REG} cells is related to allergic disorders rather than classical autoimmune diseases.[25] In our study,[28] 44% of patients with AIP had a history of allergic disease, and these patients frequently had elevated serum IgE levels and peripheral eosinophilia. Allergic mechanisms may be related to the occurrence of AIP.[28]

High serum levels of circulating immune complex linked to increased serum IgG1, decreased levels of C3 and C4 and normal levels of mannose binding lectin (MBL) in patients with AIP and a lack of IgG4 binding capacity to C1q suggest that complement activation through the IgG1-triggering classical pathway is likely to be involved in the pathogenesis of AIP.[29] Kawa *et al.*[30] suggested that IgG4 or IgG4 immune complexes may not be pathogenetic but anti-inflammatory factors in AIP.

In summary, we believe that the pathogenesis of AIP involves an initial response to self-antigens induced by a decrease in levels of naive T_{REG} cells and T_H1 cytokines, and that the disease is progressed by memory T_{REG} cells and T_H2 immune response, which results in fibrosis and production of IgG4.

Clinical findings

AIP mainly occurs in elderly males;[31] in our series the mean age was 66.5 years (range 25–83 years) and 75% of patients were male.[10] In a US series by Chari *et al.*[32] the mean age was 61 years and 85% of patients were male. The initial symptom of AIP is usually obstructive jaundice induced by sclerosing cholangitis (74% in our series,[10] 82% in the UK,[33] and 88% in the USA[32]). The severity of the jaundice sometimes fluctuates. Other symptoms can include abdominal or back pain, weight loss and anorexia. Diabetes mellitus, usually type 2, was detected in 50% of patients in our series[10] and in 45% of Korean cases.[34] In most patients diabetes and AIP are diagnosed simultaneously, but some patients show exacerbation of pre-existing diabetes with the onset of AIP.[35] Mild or moderate pancreatic exocrine dysfunction is frequently detected.[35,36] Symptoms associated with extrapancreatic lesions, such as swelling of salivary glands, hydronephrosis and lymphadenopathy, are sometimes observed.[37]

Laboratory findings

Increased serum levels of biliary enzymes have been observed in 77% of patients with AIP.[21] Elevated levels of serum pancreatic enzymes were detected in 41% of patients and these levels rarely became abnormally high.[21] Peripheral eosinophilia (≥600 cells/mm^3) and increased serum levels of IgE were detected in 11% and 34% of patients in our series, respectively.[28] Elevated serum IgG levels were detected in 56% of patients.[10] Antinuclear antibody (ANA) tests and rheumatoid factor tests produced positive results in 44% and 16% of patients, respectively.[10] Increased serum IgG4 levels (≥135 mg/dl) are frequently detected in patients with AIP, and serum IgG4 levels are closely associated with disease activity.[38] The sensitivity of increased serum IgG4 levels to identify patients with AIP was 77% (30 of 39) in our series,[39] 81% (39 of 48) in the USA[32] and 68% (25 of 37) in Korea;[34] the cut-off values used were 135 mg/dl in our series and the Korean series, and 140 mg/dl in the US series. However, increased serum IgG4 levels in patients with pancreatic cancer were detected in 4% (5 of 116) in our series[39] and 7% (5 of 71) in the University of Pittsburgh Medical Center series.[40] Ghazale *et al.*[41] reported that serum IgG4 levels were increased (>140 mg/dl) in 10% (13 of 135) patients with pancreatic cancer, but only 1% had IgG4 levels >280 mg/dl compared with 53% of patients with AIP.

Radiological findings

Diffuse enlargement of the pancreas and effacement of the lobular contour of the pancreas are typical pancreatic findings of AIP. Delayed-phase dynamic CT and MRI enhancement of the enlarged pancreas is characteristic of AIP (Figure 1a).[42–44] Affected pancreatic lesions show reduced intensity on T_1-weighted images compared with the liver.[43,45] As fibroinflammatory changes involve the peripancreatic adipose tissue, a capsule-like rim surrounding the pancreas, which appears as a low-density area on CT (Figure 1a) and as a hypointense area on a T_2-weighted MRI, is rather specific in patients with AIP.[42–44] The clinical utility of diffusion-weighted MRI (DW-MRI) for differentiating AIP from pancreatic cancer has been clarified.[46] On DW-MRI, AIP and pancreatic cancer were detected as high signal-intensity areas, but the high signal-intensity areas were diffuse ($n = 3$), solitary ($n = 5$), and multiple ($n = 3$) in patients with AIP (Figure 1b), while all 40 patients with pancreatic cancer showed solitary areas. The apparent diffusion coefficient (ADC) values for AIP were significantly lower than for pancreatic cancer and for the normal pancreas; an ADC cut-off value of 1.093×10^{-3} mm^2/s was useful to distinguish AIP from pancreatic cancer.[46]

An enlarged hypoechoic pancreas with hyperechoic spots can be seen on ultrasound examination.[42,23] Diffuse