

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<sup>+</sup> plasma cells accounting for more than 50% of IgG4<sup>+</sup> 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.<sup>1</sup> Since the original description, Castleman's disease (CD) has been extended to include two types, the classical hyaline vascular (HV) type and plasma cell (PC) type.<sup>2-4</sup>

The HV type of CD accounts for approximately 90% of cases.<sup>2-4</sup> 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.<sup>2-4</sup> Histologically, the PC type of CD is defined by numerous lymphoid follicles with an active germinal center (GC) and interfollicular polyclonal plasmacytosis.<sup>2-4</sup>

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.<sup>5-8</sup> IgG-related sclerosing disease is defined by elevated serum IgG4 levels (> 135 mg/dL) and/or numerous IgG4<sup>+</sup> plasma cells accounting for more than 50% of IgG<sup>+</sup> cells in the affected organs.<sup>8</sup>

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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.<sup>9</sup> 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.<sup>9</sup> 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™) stainer according to the manufacture's instructions. The panel of antibodies included human immunoglobulin light chains ( $\kappa$  and  $\lambda$ ) (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

(BenchMark™) 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.*<sup>10</sup>

## 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.<sup>11</sup>

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

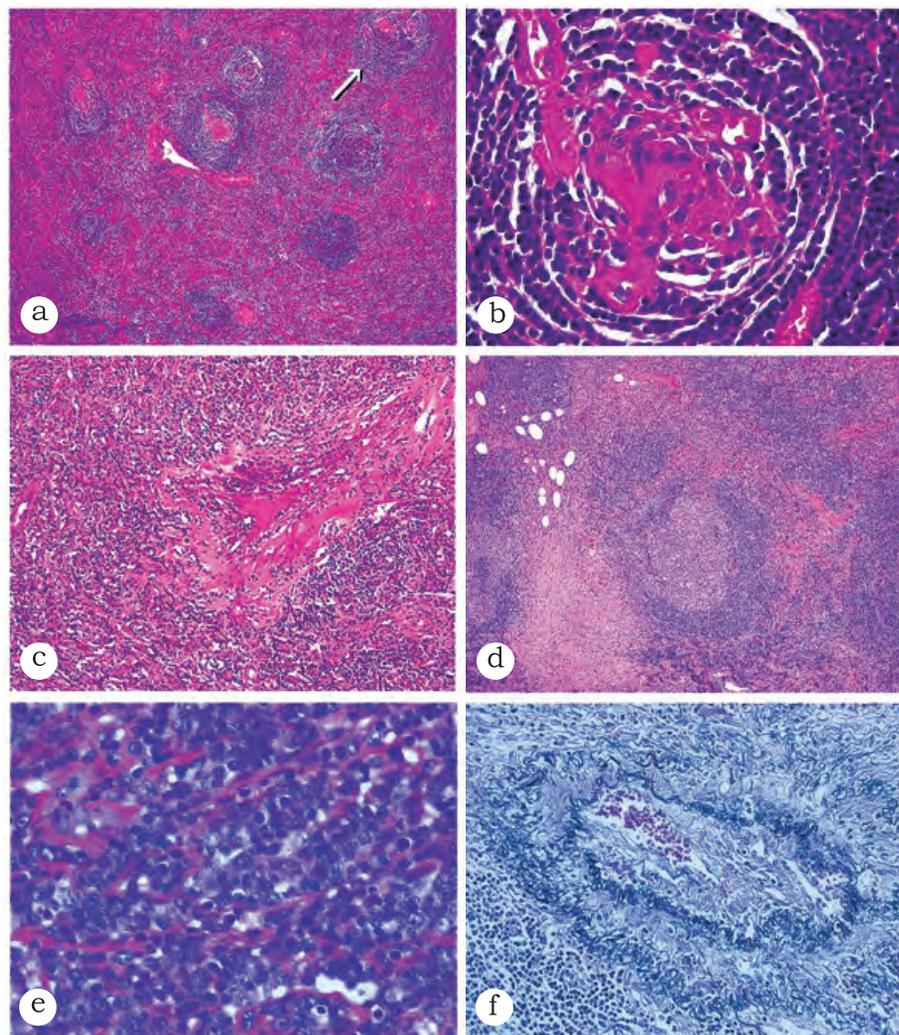
F, female; M, male; IL-6, interleukin-6; NE, not examine; A(-), alive without disease; A(+), alive undertreatment; HV, hyaline-vascular; PC, plasma cell; \*, Normal range < 135 mg/dL; \*\*, Normal range < 4.62 pg/mL

**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. (*Ia*) 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,  $\times 10$ . (*Ib*) High-power field of a GC of Fig. 1a. Note the nuclear enlargement of follicular dendritic cells (FDCs). Case 1, H&E stain,  $\times 100$ . (*Ic*) Medium-power field of the lesion. Note marked small vessel proliferation and sclerosis in the interfollicular area. Case 4, H&E stain,  $\times 25$ . (*Id*) 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,  $\times 10$ . (*Ie*) 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,  $\times 100$ . (*If*) Elastic-van Gieson stain demonstrating phlebitis in Case 6.  $\times 10$ .

cells contained multiple small atrophic GC with increased vascularity (multiple GC pattern) (Fig. 1a)<sup>3</sup>; (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).<sup>3</sup> 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).

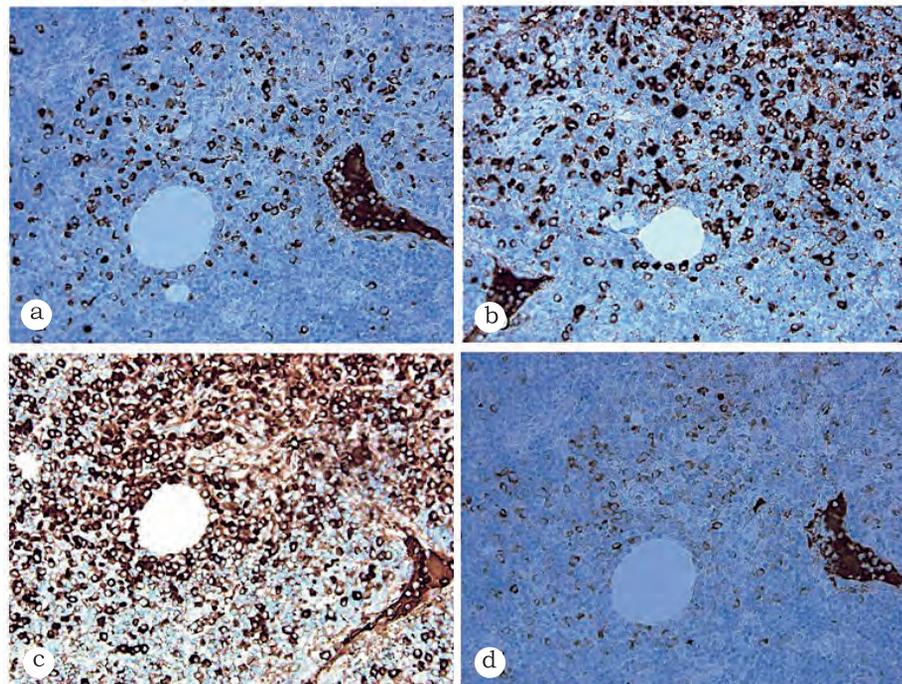
The results of immunohistochemical studies of these patients were similar to those described in previous reports.<sup>4,12</sup> Briefly, mantle cells in the primary follicular and multiple GC patterns were CD20<sup>+</sup>, sIgM<sup>+</sup>, sIgD<sup>+</sup>, CD3<sup>-</sup>, CD10<sup>-</sup>, CD43<sup>-</sup>, bcl-2<sup>+</sup> and cyclin D1<sup>-</sup>.<sup>4,12</sup> 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.*<sup>13</sup> There were only a few IgG<sup>+</sup> 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 lymphoplasma-cytic 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)  $\alpha$ -light chain in Case 3. (2b)  $\lambda$ -light chain in Case 3. (2c) There were numerous IgG<sup>+</sup> cells in the paracortical area in Case 3. (2d) Fifty percent of the IgG<sup>+</sup> plasma cells were IgG4-positive in Case 3. (2a), (2b), (2c) and (2d), Counterstained with hematoxylin,  $\times 100$ .

2b).<sup>9</sup> There were numerous IgG<sup>+</sup> plasma cells with scattered IgA<sup>+</sup> or IgM<sup>+</sup> plasma cells in all four cases. IgG4<sup>+</sup> cells comprised 50-60% of IgG<sup>+</sup> plasma cells in three cases (Nos. 3, 5, and 7) (Figs. 2c and 2d), whereas Case 6 contained only a few IgG4<sup>+</sup> 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<sup>+</sup> or cyclin D1<sup>+</sup> small B-cells in either lesion. There were no CD56<sup>+</sup> plasma cells in any of the four lesions.

There were no HHV-8<sup>+</sup> and EBER<sup>+</sup> 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.<sup>2,4</sup> The majority of the CD located in the retroperitoneum were the HV type of CD.<sup>14,15</sup> 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.<sup>2,4</sup> 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.<sup>16-18</sup> When sclerosis is prominent, the term "sclerosing variant of FL" has previously been applied.<sup>18</sup> FL rarely shows lymphoid follicles mimicking the HV type of CD.<sup>16,19</sup> One of our four cases of HV type CD showed prominent interfollicular sclerosis. However, lymphoid follicles of the present four HV type were CD10<sup>+</sup>.<sup>16,17</sup> 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.<sup>16,17,20</sup> However, immunohistochemical and genotypic studies demonstrated polytypic nature of the B-lymphocytes. Moreover, there were no CD43<sup>+</sup> centrocyte-like cells and/or CD56<sup>+</sup> plasma cells in any of the four lesions.<sup>16,17,20,21</sup>

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

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- $\gamma$ -globulinemia may be related to a high level of IL-6 in the PC type of CD.<sup>22</sup> 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.<sup>2,3,22,23</sup>

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,<sup>7</sup> whereas PC type of CD is occasionally resistant to corticosteroid therapy.<sup>23</sup> From a therapeutic perspective, it is important to discriminate IgG4-related disorder from PC type of CD.

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