Comparison of Plasma Cell Type of Castleman's Disease and IgG4-Related Sclerosing Disease: A Histopathological and Immunohistochemical Study

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Key Words

Castleman's disease · IgG4-related sclerosing disease · Plasma cell · Immunohistochemistry

Abstract

Objectives: Castleman's disease (CD) is a group of rare atypical lymphoproliferative disorders classified as hyaline vascular (HV) and plasma cell (PC) types. CD may be closely mimicked by IgG4-related sclerosing disease (IgG4-SD) involving the lymph nodes. We retrospectively analyzed findings in patients with CD to elucidate the relationship between CD and IgG4-SD. **Methods:** Clinicopathological and immunophenotypical characteristics, including IgG+ and IgG4 expression by plasma cells, were analyzed in 87 consecutive patients diagnosed with CD from 1999 to 2010 at two major Korean hospitals. **Results:** The numbers of IgG+ ($p < 0.001$) and IgG4+ ($p < 0.001$) cells and the IgG4:IgG ratio ($p = 0.003$) were significantly higher in the PC than in the HV group. The mean IgG4+:IgG+ plasma cell ratio in the PC group was 25.1%, with 10 patients having a ratio $>40\%$, the threshold IgG4:IgG ratio in patients with IgG4-SD. **Conclusions:** Patients with the PC form of CD and IgG4-related lymphadenopathy share some features, including the pattern of plasma cell distribution and high-level infiltration of IgG4+ cells. Some patients thought to have the PC form of CD could be reclassified as showing IgG4-related lymphadenopathy.

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Objectives

Since Kamisawa et al. [1] proposed the concept of IgG4-related sclerosing disease (IgG4-SD) to explain that autoimmune pancreatitis is a pancreatic manifestation of a systemic disease, various organs have been reported to be involved: lung, breast, central nervous system, liver and intestine [2–6]. Some idiopathic fibrosing diseases such as retroperitoneal fibrosis [7, 8] and sclerosing mediastinitis [9] can be explained by this concept. When IgG4-SD involves multiple lymph nodes presenting as systemic lymphadenopathy, it can show some overlapping features with multicentric Castleman's disease (CD) [10] such as hyalinized blood vessels, increased high endothelial venules, and many plasma cells in the interfollicular region [11].

Table 1. Clinical characteristics of patients with CD

Factor	n
Age, years	11–87 (mean 41.9)
Gender	
Male	54 (62.1%)
Female	33 (37.9%)
Site	
Neck	35 (40.2%)
Abdominal cavity	12 (13.8%)
Mediastinum	5 (5.7%)
Retroperitoneum	6 (6.9%)
Specific organ (lung, kidney, etc.)	8 (9.0%)
LN other than neck	21 (24.1%)
Size of LN, cm	1.1–15.0 (median 3.2)
Multicentricity	
Single	57 (65.5%)
Multiple	30 (34.5%)

LN = Lymph node.

In this study, we evaluated the numbers and the distribution pattern of IgG-positive (IgG+) and IgG4-positive (IgG4+) plasma cells in CD to find relationship between CD and IgG4-SD.

Patients and Methods

Data from 87 patients with CD, including 55 consecutive patients diagnosed at the Asan Medical Center, Seoul, Korea, from 1999 to 2010, and 32 consecutive patients diagnosed at Seoul National University from 2001 to 2010, were analyzed in the study. The medical records of each patient were reviewed and clinical histories as well as follow-up data were recorded, including patient age, gender, original tumor site, tumor size and evidence of human immunodeficiency virus (HIV) infection. The multicentricity was assessed using the results of computed tomography; it was defined as a multicentric case when enlarged lymph nodes were identified in at least three different sites. Laboratory tests evaluated the presence in serum of human herpes virus 8 (HHV8) and serum concentrations of IgG and IgG4 if available. The histological features of each patient were used to reclassify patients into two groups, a hyaline vascular (HV) and a plasma cell (PC) group. Patients in the PC group showed at least one region with sheets of plasma cells and mixed cell types.

To preserve nodal structures, we made multispecimen blocks [12] from formalin-fixed paraffin-embedded tissue sections and incubated these blocks with antibodies to IgG (1:200; Dako, Glostrup, Denmark) and IgG4 (1:2,000; Binding Site, Birmingham, UK). Immunohistochemical staining results were evaluated by determining the distribution patterns of IgG+ plasma cells, the numbers of IgG+ and IgG4+ plasma cells, and the ratio of IgG4+ to IgG+ plasma cells. The distribution patterns of IgG+ plasma

cells were classified into a diffuse type, if at least one high-power field (HPF) was filled with IgG+ plasma cells, and a focal type, if IgG+ plasma cells were present, but not to the extent seen in the diffuse type. If no IgG+ cells were evident, the sample was classified as negative. The numbers of IgG+ and IgG4+ cells were counted using the UTHSCSA Image Tool (University of Texas Health Science Center, San Antonio, Tex., USA). The average numbers of IgG+ and IgG4+ cells per HPF were evaluated by enumeration of three areas showing the highest densities of positive cells. Samples were also immunostained with antibodies to κ (1:100; Dako) and λ (1:4,000; Dako) light chains to exclude the possibility of malignant lymphoma. Epstein-Barr virus (EBV) status was assessed by in situ hybridization for EBV-encoded RNA, and the samples were also immunostained with antibody to HHV8 (1:20; Cell Marque, Rocklin, Calif., USA).

The χ^2 test was used to assess the relationships among multicentricity, distribution patterns of IgG+ cells and the new subgroups of CD. Student's *t* test was employed to compare the numbers of IgG+ and IgG4+ cells per HPF and the ratio of IgG4+ to IgG+ cells in subgroups. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, Ill., USA).

Results

The 87 patients consisted of 54 males and 33 females, with a median age of 41.9 years (range: 11–87 years). The most common site of involvement was the neck lymph nodes (35 patients, 40.2%), followed by nodes of the abdominal cavity (12 patients, 13.8%). Involved lymph nodes were highly variable in size, ranging from 1.0 to 15.0 cm in the greatest dimension (mean 4.3 cm). Thirty patients (34.5%) showed multicentricity, including a patient with involvement of whole body lymph nodes and the bone marrow. Table 1 summarizes the clinicopathological characteristics of patients with CD.

Of the 87 patients, 51 were diagnosed with HV type, 24 with PC type and 12 with mixed-type disease. Patients with the HV type of disease showed classic node morphology, with thick hyalinized vessels and either absence of IgG+ or IgG4+ cells, or focal presence of such cells in interfollicular areas. In contrast, distinctive thick vessels were absent in patients with the PC type of disease, and interfollicular areas were expanded with sheets of plasma cells. Immunohistochemical staining showed that such plasma cells were diffusely positive for IgG and a significant portion of them was also positive for IgG4. In mixed-type patients, the characteristic vessels were less prominent, but features of both the HV and PC types were seen (fig. 1). Obliterating phlebitis was not identified in any patient.

Based on the presence of plasma cells, we reclassified the patients into two groups, an HV group (51 patients,

Fig. 1. Microscopic findings of three types of CD, as shown by immunohistochemical staining for IgG and IgG4. The hyaline vascular type (a) shows a typical hyalinized vascular pattern without IgG+ (d) or IgG4+ (g) cells. Interfollicular areas of the plasma cell type (b) are expanded with sheets of plasma cells positive for IgG (e), with some plasma cells also positive for IgG4 (h). The mixed type (c) shows regions of both the hyaline vascular and plasma cell types, with some IgG+ (f) and IgG4+ (i) cells.

Table 2. Multicentricity and the pattern of IgG+ cells in subgroups of patients with CD

Factor	Number of patients		p
	HV group	PC group	
Multicentricity	11/51 (21.6)	19/36 (52.8)	0.011
Pattern of IgG+ cells			
Diffuse	12/51 (23.5)	27/36 (75.0)	<0.001
Focal	28/51 (54.9)	9/36 (25.0)	
Negative	11/51 (21.6)	0/36 (0.0)	

Figures in parentheses are percentages.

Table 3. IgG+ and IgG4+ cells in subgroups of patients with CD

Factor	Mean		p
	HV group	PC group	
IgG+ cells/HPF	73.3	214.5	<0.001
IgG4+ cells/HPF	13.3	54.6	<0.001
IgG4+ cells/IgG+ cells	9.9	25.3	0.002

Table 4. Clinicopathological characteristics of the cases with high IgG4/IgG ratio (>40%)

Case	Age years	Sex	Site	Multicentricity	Dx	HHV8	IgG pattern	IgG/ HPF	IgG4/ HPF	IgG4/ IgG, %	Serum IgG4 mg/dl	Serum IgG mg/dl	CRP mg/dl
22	24	female	neck	single mass	HV	negative	diffuse	136	98	72.1	–	–	0.05
42	34	male	mediastinum	single mass	HV	negative	diffuse	176	69	39.2	–	–	–
44	34	male	neck	single mass	HV	negative	diffuse	120	48	40.0	–	–	–
75	38	male	abdominal cavity	single mass	HV	negative	focal	69	37	53.6	–	–	–
84	57	male	neck	single mass	HV	negative	diffuse	194	101	52.1	–	–	–
9	52	female	kidney	single mass	PC	negative	diffuse	249	236	94.8	–	–	–
31	15	female	neck	multicentric	PC	negative	diffuse	237	142	59.9	–	–	0.44
45	29	male	inguinal LN	single mass	PC	negative	diffuse	280	162	57.9	0.84	1,490	–
51	38	male	inguinal LN	multicentric	PC	negative	diffuse	230	134	58.3	–	–	10.11
53	49	male	neck	multicentric	PC	NA	focal	62	50	81.0	0.42	2,250	–
71	54	male	abdominal cavity	multicentric	PC	negative	focal	43	18	41.9	–	–	–
74	26	male	mediastinum	multicentric	PC	negative	diffuse	205	178	86.8	–	–	–

Dx = Diagnosis; LN = lymph node.

Table 5. Clinicopathological characteristics of the cases with serum IgG level

Case	Age years	Sex	Site	Multicentricity	Dx	HHV8	IgG pattern	IgG/ HPF	IgG4/ HPF	IgG4/ IgG, %	Serum IgG4 mg/dl	Serum IgG mg/dl	CRP mg/dl
11	13	male	neck	multicentric	PC	negative	diffuse	275	42	15.3	–	1,080	19.39
27	47	male	inguinal LN	multicentric	PC	negative	diffuse	290	73	25.2	–	1,270	1.26
32	38	male	retroperitoneum	multicentric	HV	positive	diffuse	290	20	6.9	–	1,920	6.84
45	29	male	inguinal LN	single mass	PC	negative	diffuse	280	162	57.9	0.84	1,490	–
53	49	male	maxillary sinus	multicentric	PC	negative	focal	62	50	80.6	0.42	2,250	–
59	68	male	neck	single mass	HV	negative	focal	68	25	36.8	–	1,325	–
60	51	male	neck	single mass	PC	negative	focal	130	15	14.6	–	1,399	–
78	50	male	inguinal LN	multicentric	PC	negative	diffuse	232	21	9.1	–	3,087	–

Dx = Diagnosis; LN = lymph node.

58.6%) and a PC group (36 patients, 41.4%). The PC group included patients with at least one region showing sheets of plasma cells. Multicentricity was significantly more common in the PC (19/36 patients, 52.8%) than in the HV (11/51 patients, 21.6%) group ($p = 0.003$). The pattern of IgG+ plasma cells was focal or negative in most patients of the HV group (37/51, 72.6%), whereas the pattern was diffuse in most of those in the PC group (27/36, 75.0%) (table 2).

The mean numbers of IgG+ cells/HPF (214.5 vs. 73.3, $p < 0.001$) and IgG4+ cells/HPF (54.6 vs. 13.3, $p < 0.001$) were significantly higher in the PC than in the HV group. In addition, the mean ratio of IgG4+ to IgG+ cells was significantly greater in the PC than in the HV group (25.3 vs. 9.9%, $p = 0.002$) although the ratio in the PC group ranged from 0 to 94.8%.

When we analyzed the patients with an IgG4 to IgG ratio >40% [11], we found that patient age, tumor size, original site or multicentricity did not differ between the two groups. However, when we compared patients with multicentric and unicentric CD, we found that the former patients were significantly older (mean age, 47.3 vs. 39.1 years, $p = 0.050$) and had a higher mean serum IgG concentration (1,921 vs. 1,404 mg/dl, $p = 0.226$). We also found that the mean numbers of IgG+ (152 vs. 121, $p = 0.220$) and IgG4+ (33 vs. 29, $p = 0.659$) plasma cells per HPF, as well as the IgG4 to IgG ratio (19.7 vs. 14.5%, $p = 0.323$), were slightly higher in the multicentric group. The clinicopathological characteristics of these patients are summarized in table 4.

Immunohistochemical staining showed that samples from 25 patients expressed κ and λ light chains, but none

showed restrictions, indicating that none of these patients had malignant lymphoma. Five patients were positive for EBV by in situ hybridization, but there was no relationship between EBV status and diagnosis ($p = 0.355$). The serum of 5 patients was positive for HHV8, with 3 also being positive on immunohistochemical staining.

Serum concentrations of IgG and IgG4 were evaluated in 8 patients, and found to range from 1,080 to 3,087 mg/dl. Of these 8 patients, 6 (75.0%) belonged histologically to the PC group and 5 (62.5%) were multicentric. The mean IgG4 to IgG ratio in these patients was 30.6%. No patient showed other features suggesting IgG4-SD during the follow-up period. Table 5 shows the clinicopathological characteristics of these patients.

Discussion

CD is a group of rare atypical lymphoproliferative disorders, classified as HV, PC and mixed types [13]. The HV type is characterized by the presence of distinctive follicles with an expanded mantle zone and prominent vessels in the germinal centers associated with hyalinization, whereas the histological features of the PC type are less distinctive. In the lymph nodes, the PC type is characterized by variable germinal center hyperplasia with expanded mantle zones and a marked paracortical plasmacytosis [14, 15].

Because of this last feature (paracortical plasmacytosis), CD has been re-evaluated to consider IgG4+ cell infiltration [11, 16]. The lymphadenopathy of IgG4-SD has been described as CD like, with follicular hyperplasia and an interfollicular expansion pattern [11]. Moreover, the lymphadenopathy of IgG4-SD with a CD-like pattern showed an intact nodal architecture with many reactive follicles and moderate-to-large numbers of mature plasma cells in the interfollicular zone. The number of IgG4+ plasma cells ranged from 17 to 877 per HPF (median 383), with 43–99% (median, 58%) of IgG+ cells in lymph nodes being IgG4+ cells. In patients with the CD-like pattern, the number of IgG4+ cells per HPF was rather high (mean 521), with a mean of 50% of IgG+ plasma cells being IgG4+.

We observed higher numbers of IgG4+ cells per HPF in the PC than in the HV group, with the ratio of IgG4+ to IgG+ cells being significantly higher in the PC group. Moreover, of the 35 patients in the PC group, 10 had sufficiently high IgG4+ to IgG+ ratios (41.9–94.8%) to overlap with that seen in IgG4-SD patients [11].

The etiology of CD is probably heterogeneous, although IL-6, a pro-inflammatory cytokine, is involved in the pathogenesis of CD, especially in systemic manifestations thereof [15]. Moreover, treatment of multicentric CD with anti-IL-6 antibody has been shown to be effective [17], indicating that IL-6 plays a role in CD. Elevated serum IL-6 may induce expansion of IgG4-SD to mimic CD [18], although systemic IgG4-related lymphadenopathy can be differentiated from multicentric CD by the older age of patients, and lower C-reactive protein and IL-6 concentrations, in those with the former disease [10].

HHV8-positive rate in this study was low (5.7%) and no patient showed HIV positivity. However, those data were similar to HHV8- and HIV-positive rates in Asian patients in a previous study [19].

As our study was retrospective in design, we have only limited information on included patients. Serum concentrations of IgG were measured in only 6 patients and IgG subclasses were evaluated in only 2. The majority of patients were lost during the follow-up period after the biopsy or the excision of the lesions. However, serum IgG concentrations were very high (1,920–3,087 mg/dl) in 3 of the 6 patients, with 2 having high IgG4+ to IgG+ ratios (58 and 80%). These findings provide further evidence for overlapping features in patients with the PC type of CD and those with IgG4-SD. Multicentric CD and lymphadenopathy in IgG4-SD are rather similar in histological features and the two conditions also share the distribution pattern of IgG+ plasma cells and high IgG4 concentration.

In conclusion, at least some patients with CD may be hard to differentiate from those with IgG4-related lymphadenopathy. Some patients with the PC type of CD should perhaps be reclassified as having IgG4-SD.

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