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Review Article

Idiopathic plasmacytic lymphadenopathy: A conceptual history along with a translation of the original Japanese article published in 1980

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The current consensus on Castleman disease is that it is a group of several distinct lymphoproliferative disorders with different underlying pathogenesis and clinical outcomes. In 1980, Mori *et al*. proposed the concept of idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL), a disease of unknown etiology, characterized by severe polyclonal hypergammaglobulinemia and generalized superficial lymphadenopathy. After Frizzera *et al*.'s landmark report in 1983, the term multicentric Castleman disease (MCD) gradually became established, and for a time, IPL was regarded as identical to MCD. However, with the subsequent recognition of human herpesvirus 8 (HHV8)-related MCD in the 1990s and the contributions by Kojima *et al*. in the 2000s, in which non-HHV8-related MCD (now called idiopathic MCD) was at least subclassified into IPL and others (non-IPL), it is now clear that the original distinctiveness of IPL is still maintained in MCD, which is a diverse collection of diseases.

Keywords: idiopathic plasmacytic lymphadenopathy, IPL, MCD, iMCD, TAFRO syndrome

CASTLEMAN DISEASE

The current consensus on Castleman disease is that it is a group of several distinct lymphoproliferative disorders with different underlying disease pathogenesis and clinical outcomes.[1] According to the lesion distribution, the disorders are classified as unicentric or multicentric. Unicentric Castleman disease (UCD) is further subdivided into hyaline-vascular and plasma cell[2,3] types (Figures 1A, 1B, 2, and 3). The hyaline-vascular unicentric subtype, the prototype Castleman disease originally reported by Benjamin Castleman in the early 1950s (Figure 1A),[4,5] is now considered a neoplasm of follicular dendritic cells (FDCs), based on the findings that FDC proliferation and dysplastic FDCs can be observed in the lesion, clonal karyotypic and genetic abnormalities are reported, and approximately 7% of FDC sarcomas arise in the background hyaline-vascular Castleman disease.[6] Multicentric Castleman disease (MCD) encompasses a spectrum of disorders with overlapping clinicopathological manifestations,[7] but this name was not widely known until the early 1980s. Although several researchers had reported and suggested a multicentric form of Castleman disease characterized by multiple lymphoid tissue lesions, it had not yet been established as a disease concept.

IDIOPATHIC PLASMACYTIC LYMPHADENOPATHY

In 1978, Shigeo Mori and his mentor, Noboru Mohri, presented a paper with the title "Clinicopathological study of systemic nodal plasmacytosis associated with severe polyclonal hyperimmunoglobulinemia" (translated from Japanese) at the 67th Annual Meeting of the Japanese Society of Pathology (from April 5 to 7, Kumamoto, Japan).[8] They reported four patients with severe polyclonal hypergammaglobulinemia, lymphadenopathy, hepatomegaly, a high erythrocyte sedimentation rate, mild anemia, and hypocholesterolemia. The patients were all male, aged between 10 and 30 years, and there were no obvious triggers for the disease. The initial symptoms included generalized fatigue and mild fever. The serum gammaglobulin and IgG levels were 4 to 6 times higher than normal, and the IgA and IgM levels were also elevated, but M-protein was absent. The disease condition did not markedly worsen, and although the symptoms could be relieved by using steroids, they were not curable. The patients were followed up in outpatient clinics for 3–15

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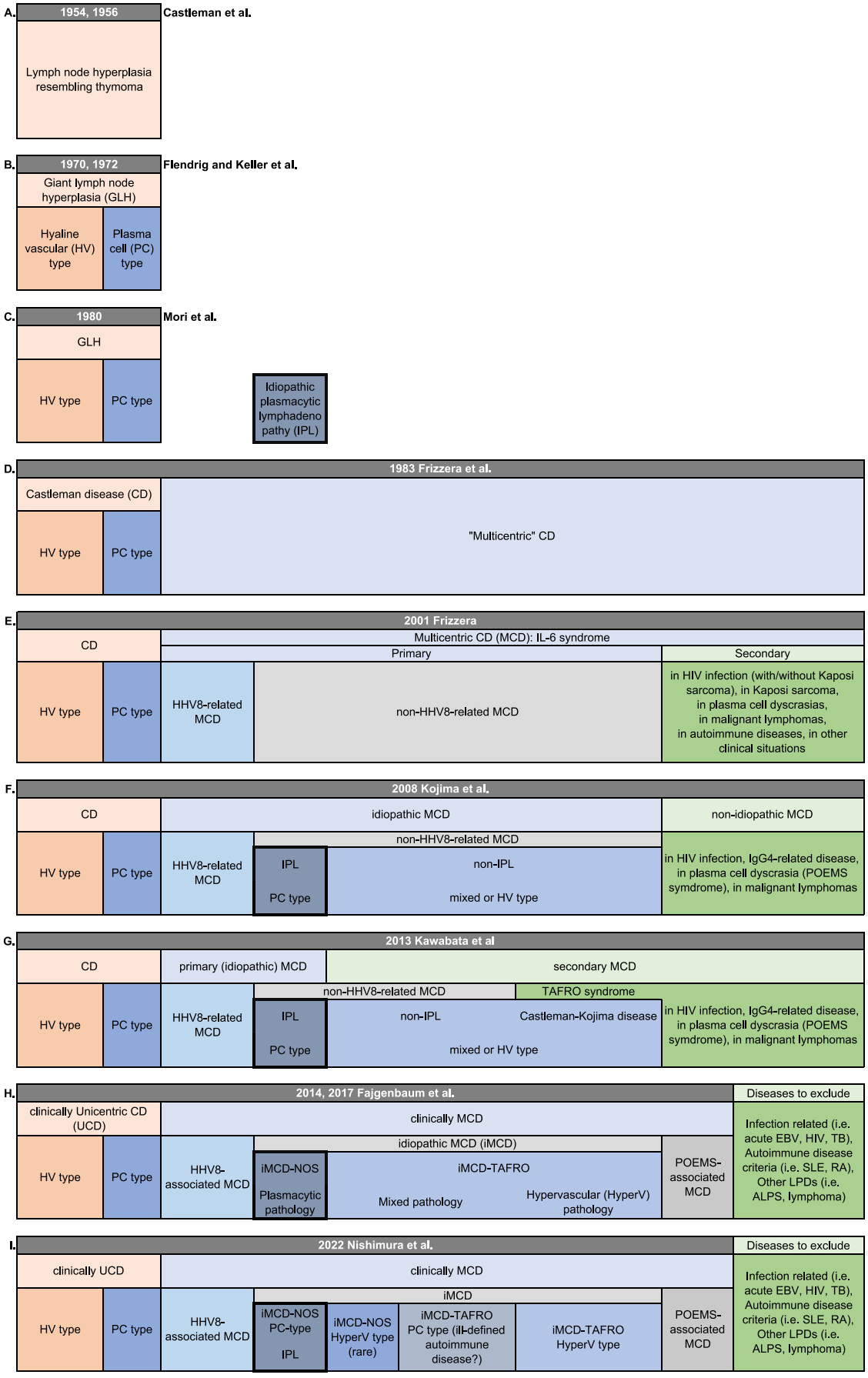

Fig. 1. Evolution of the concept of Castleman disease

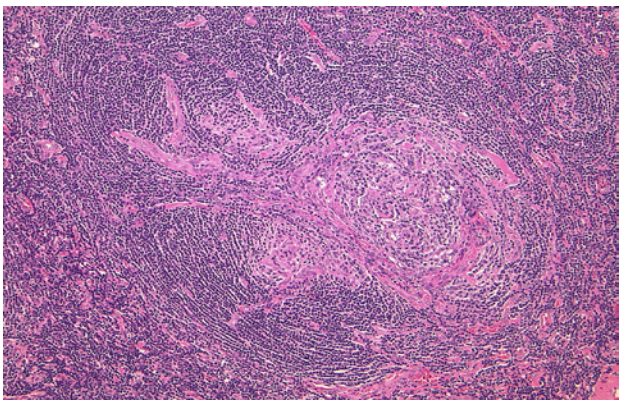

Fig. 2. Histopathology of Castleman disease, hyaline vascular-subtype
Branched vessels with focal hyalinization are observed in the follicle. In this follicle, several regressive germinal centers are grouped by fusion of the thick mantle zones, in which small lymphocytes are concentrically arranged.

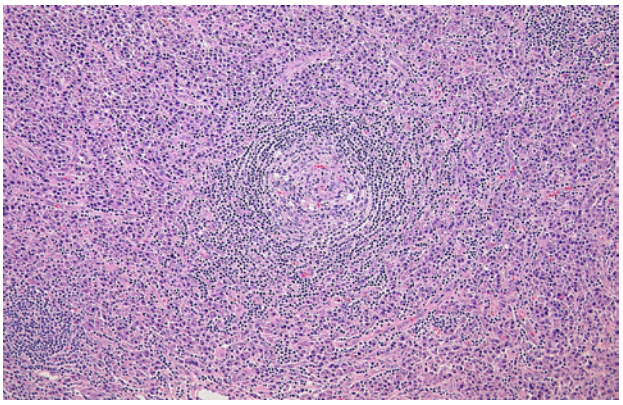

Fig. 3. Histopathology of Castleman disease, plasma cell-subtype
The germinal center is well-demarcated from the mantle zone and does not harbor highly branched and hyalinized vessels, clearly different from the vascular changes in the germinal centers of Castleman disease, hyaline vascular-subtype. The mantle zone constitutes concentrically arranged small lymphocytes but is not very thick. Plasmacytosis is observed immediately adjacent to the mantle zone, associated with vascular proliferation.

years. No foci of infection or localized bulky lymphadenopathy was found despite a detailed workup. The histological features of the 12 lymph node biopsies were nearly identical. There was a marked increase in the number of plasma cells from the subcapsular region to the deep medulla. The basic lymph node architecture was preserved, but it was difficult to distinguish the cortex from the medulla, and the follicles appeared as islands in a sea of plasma cells. Lymph follicles were composed of a relatively well-developed germinal center and a thin mantle zone and were present from the cortex to the medulla. Vascular proliferation was present in the interfollicular areas but not in the germinal centers. Immunoblasts and hyaline deposits were absent. Paracortical areas were atrophic but present. The plasma cells were a mixture of κ- and λ-positive cells.

In 1980, the term "idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL)" was proposed by Mori *et al*. as a generic term for an enlarged cohort of 10 cases of unknown etiology characterized by severe polyclonal hypergammaglobulinemia and generalized superficial lymphadenopathy (Figure 1C).[9] Patients with IPL have the clinical and histological features of plasma cell-type Castleman disease.[2,3,9] Nevertheless, Mori *et al*. stated that IPL should not be recognized as the same disease entity as plasma cell-type Castleman disease because IPL did not have localized mass formation but presented with generalized lymphadenopathy.[9] Therefore, they did not use the existing terms "giant lymph node hyperplasia," "Castleman disease," or "Castleman lymphoma" but coined the term "IPL." Mori *et al*. also pointed out that IPL and plasma cell-type Castleman disease may share common pathogenic mechanisms.[9]

MULTICENTRIC CASTLEMAN DISEASE

At the 1980 Annual Meeting of the United States/Canadian branch of the International Academy of Pathology, Glauco Frizzera and his colleagues reported the histopathology and clinical features of the multicentric form in 10 patients. They demonstrated several clinical differences between the localized and multicentric forms. In 1983, they described their morphological observations of the nodal and extranodal involvement of the multicentric form in an enlarged cohort of 15 patients and discussed its etiology and relation to other lymphoproliferative diseases, especially the unicentric form (Figure 1D).[10] After this report, the term MCD gradually became established.

IPL AND MCD

In 1988, Frizzera stated that he borrowed the pathology slides of IPL cases from Mori and concluded on a personal review that IPL and MCD were identical.[11] Correspondingly, in 1991, Mori also stated that the disorder reported by Frizzera *et al*. was identical to what he and his colleagues reported as IPL.[12] However, considering current knowledge, there appears to be a fundamental difference between the 10 cases of Mori *et al*.[9] and the 15 cases of Frizzera *et al*.[10] in terms of histopathologic and clinicopathologic diversity. This difference may be attributed to differences in the case collection criteria. Frizzera *et al*. collected cases based on histopathologic similarities to UCD, whereas Mori *et al*. collected cases based on strict clinical criteria, including polyclonal hypergammaglobulinemia, excluding collagen disease and malignancy (Table 1).

The histopathology of the 10 cases of Mori *et al*.[9] was highly consistent and very similar to that of plasma cell-type UCD reported by Keller *et al*.[2] The mass of plasma cell-type UCD showed a lymph node structure, with a high degree of plasmacytosis in the interfollicular areas, occasional residual sinuses, normal or slightly hyperplastic germinal centers, and occasional vascularization of the germinal centers, all of which were consistent with the histology of lymph nodes in IPL.[9] IPL was also unique in the prognosis, as most patients had an indolent course but were not completely cured.[9]

Table 1. Criteria for IPL

Original criteria (Mori *et al*. 1980)
1. Polyclonal hypergammaglobulinemia with serum IgG >4,500 mg/dL, without M-protein
2. Generalized superficial lymphadenopathy, the largest of which should be the size of a fingertip on palpation or more than 1.8 cm in the greatest diameter by actual measurement, and a high degree of plasmacytosis on histology, with little or no destruction of the architecture
3. No known diseases that could be associated with hyperglobulinemia (infectious diseases, collagen diseases, rheumatoid arthritis and its subtypes, Sjogren syndrome, various allergies including drug allergies, hypersensitivity, so-called adjuvant diseases, myasthenia gravis, hyperthyroidism, hepatitis, liver cirrhosis, and malignant tumors including lymphomas)
Modified criteria (Kojima *et al*. 2008)
1. Prominent polyclonal hypergammaglobulinemia (γ-globulin >4.0 g/dL or serum IgG level >3,500 mg/dL)
2. Multicentric lymphadenopathy
3. Absence of definite autoimmune disease
4. Normal germinal centers and sheet-like infiltration of polyclonal plasma cells in the lymph node lesion
Non-IPL type was defined by multicentric lymphadenopathy and lymph node lesions containing normal, hyaline vascular (HV), and epithelioid germinal centers as described by Frizzera *et al*. (1983). Cases demonstrating prominent polyclonal hyperimmunoglobulinemia with HV germinal centers were classified as the non-IPL type.

Abbreviations: IPL, idiopathic plasmacytic lymphadenopathy

In contrast, more histopathologic and clinicopathologic diversity was observed among the 15 MCD cases of Frizzera *et al*.[10] They subdivided the histological findings of 82 lymph nodes obtained from 15 patients into four types: patterns A, B, C, and D. Pattern C, which was observed in eight lymph nodes (10%) and was characterized primarily by the diffuse, uniform accumulation of plasma cells surrounding secondary follicles, appears similar to the lymph node findings of IPL. As for the prognosis, seven patients had an indolent course characterized by repeated exacerbations and remissions, eight patients had an aggressive course, and nine of the 15 patients died, all but one directly resulting from lymphoproliferative disease or its complications, including two with Kaposi sarcoma and one with lymphoma.[10] According to Frizzera *et al*.,[10,13] patient 14 was a 54-year-old female who presented with fever, weakness, and cough. Her serum IgG level was 5,200 mg/dL. She underwent four lymph node biopsies, all showing pattern C, and was alive 156 months after the onset.[10,13] Patient 14's disease appears consistent with IPL, but the remaining 14 patients showed various lymph node findings and clinical symptoms that may or may not be consistent with IPL.

In addition, several clinical and laboratory features of the 15 patients of Frizzera *et al*. were similar to those of a "collagen disease" to the point that in some of them a diagnosis of rheumatoid arthritis, Sjogren syndrome, or systemic lupus erythematosus was made, although Frizzera described that the overall clinical picture never fitted completely any of these syndromes.[10] In contrast, patients with known diseases associated with hyperglobulinemia, including collagen diseases, were excluded from the study by Mori *et al*.[9]

These findings indicate that IPL is not identical to MCD but is a more homogeneous disease that is part of MCD, in which characteristic histological and clinicopathological features are shared. Several lines of evidence strongly suggest that interleukin (IL)-6 may mediate these similarities. Frizzera presented the idea that MCD should be designated IL-6 syndrome or, when referring specifically to its pathologic changes, as IL-6 lymphadenopathy, and he subclassified MCD/IL-6 syndrome into primary and secondary forms (Figure 1E).[14]

HHV8 AND MCD

In the early 1980s, the first case officially identified as acquired immunodeficiency syndrome (AIDS) was reported. Subsequently, the association between MCD, Kaposi sarcoma, and AIDS was noted. In 1995, Soulier *et al*. identified human herpesvirus 8 (HHV8)-like sequences in 14 of 14 HIV-positive MCD cases and in 7 of 17 (41%) HIV-negative cases.[15] In terms of a putative association with HHV8, two of the 15 cases in the Frizzera *et al*. series had Kaposi sarcoma,[10] suggesting that cases classified today as HHV8-associated MCD would have been included. In 1999, Mori *et al*. developed a rabbit polyclonal antibody against recombinant ORF73 protein/LANA,[16] and in 2001, examined the prevalence of HHV8 in 75 cases of MCD in the Japanese population and in seven French patients with MCD.[17] One Japanese patient and two French patients had AIDS. HHV8 was detected only in these three AIDS patients, suggesting that HHV8 was unrelated to most MCD in HIV-negative Japanese patients.

IPL, non-IPL, AND TAFRO SYNDROME

Subsequently, Masaru Kojima "reintroduced" the concept of IPL, which even its discoverer had given up referring to and called by another name with some resignation. In 2004, Kojima *et al*. examined 16 cases of IPL that were confirmed to be negative for HHV8 by immunohistochemistry and suggested that IPL was distinct from the MCD reported in Western countries.[18] Compared with 46 Western patients

with MCD in the literature, 16 Japanese patients with IPL had a significantly better 5-year survival rate.[18] Histologically, IPL is characterized by the sheet-like proliferation of plasma cells in the interfollicular area and lymphoid follicles with active germinal centers.[9] In contrast, most reported Western cases of MCD were of the mixed type, with features of hyaline-vascular lymph follicles, sheets of plasma cells, and interfollicular vascular proliferation. The 16 IPL cases reported by Kojima *et al*. showed neither hyaline-vascular germinal centers nor prominent vascular proliferation in the interfollicular area.[18] In response to this report by Kojima *et al*.,[18] a letter describing the first recognized Western IPL case of a 35-year-old man was published.[19]

In 2008, Kojima *et al*. examined 28 Japanese patients with idiopathic MCD (Figure 1F).[20] Note that the term idiopathic MCD, first officially used by Kojima in 2008, was defined differently from the same term proposed by Fajgenbaum *et al*. in 2014 (Figure 1H) and used today, in that the former referred to both HHV8-related and HHV8-negative MCD[20,21] whereas the latter indicated only HHV8-negative MCD.[22] Kojima's idiopathic MCD is a concept identical to Frizzera's primary MCD (Figure 1E).[14,21] However, as mentioned above, HHV8 is positive exclusively in the MCD of HIV-positive patients in Japan; therefore, regardless of either definition, idiopathic MCD almost always refers to HHV8-negative MCD in the MCD of HIV-negative Japanese patients. Among the 28 cases, Kojima *et al*. identified 18 cases of IPL using their modified criteria (Table 1). In the remaining 10 non-IPL patients, eight were diagnosed as the mixed type and two cases as the hyaline-vascular type. The non-IPL cases exhibited a significant female predominance, higher age distribution, and higher incidence of leukocytosis, thrombocytopenia, pleural effusion, ascites, and autoimmune disease.[20] In 2011, Kojima *et al*. described IPL as a homogenous disease entity, whereas non-IPL-type MCD was a heterogeneous cluster of disease entities.[23] Among the non-IPL-type MCD cases highlighted by Kojima *et al*., the disease in a distinct group of cases was later named Castleman-Kojima disease[21] and was found to present TAFRO syndrome, which another group, Takai *et al*., independently reported in 2010 (Figure 1G).[24]

CONCLUSIVE REMARKS

The original article by Mori *et al*. was published in *The Journal of the Japanese Society for Lymphoreticular Tissue Research*[9] in 1980, which was the predecessor of the *Journal of Clinical and Experimental Hematopathology*. Because it was published in Japanese, the original paper, which would have been epoch-making if it had been published in English, has unfortunately not been widely read worldwide. I am not confident that the authors' passion, sincerity, and modesty in trying to be as accurate as possible when proposing a new disease concept, which were evident in the original paper, are expressed in my English translation (Supplemental data). The 10 original cases, collected according to strict clinical criteria (Table 1), were highly homogeneous. Therefore, IPL maintains its distinctiveness as an independent entity, corresponding to plasma cell-type idiopathic MCD, not otherwise specified,[25] in the diverse disease concepts of MCD today (Figure 1H)[22,26] and even in the evolving concept (Figure 1I).[27] Kojima, who passed away at 62 in 2018, would have felt the same way and hoped to keep the concept of IPL from fading away so that researchers worldwide could revisit it.

CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the content of this article.

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Supplementary Materials

Idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia: A syndrome related to giant lymph node hyperplasia of plasma cell type#

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TRANSLATOR'S NOTES

– The original Japanese paper was published in The Journal of the Japanese Society for Lymphoreticular Tissue Research (the predecessor of Journal of Clinical and Experimental Hematopathology) in 1980 (20(suppl):55-65). This English translation by Kengo Takeuchi in 2022 is a dedication to his mentor, Shigeo Mori (1943-).
– # As the English title, *"A group of patients with marked polyclonal hyperimmunoglobulinemia and severe plasma cell hyperplasia in the systemic lymph nodes: differences from plasma cell-type Castleman lymphoma"* seemed to be closer to the meaning of the title of the original Japanese paper; the English title listed as reference 23 in the following paper was adopted in the present translation.
Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathologic correlations in 15 patients. J Clin Oncol. 1985;3:1202-1216.
– Japanese journal names in References were translated according to the ICHUSHI database (https://www.jamas.or.jp/).
– Obvious errors in the original text have been corrected by the translator as appropriate.

INTRODUCTION

Keller *et al*. (1972)[1] classified giant lymph node hyperplasia (GLH, also known as Castleman lymphoma) into two subtypes: the hyaline vascular (HV) and plasma cell (PC) types. They described the clinicopathological features of the two subtypes and noted that while both had their own unique characteristics, many cases had characteristics of both types. They considered that the PC type might be an earlier, more active phase and the HV type may be a late phase, or that the two might be different phenotypes of a single disease. Since then, many PC-type GLHs have been reported, although it is questionable whether these reported cases are consistent with the PC-type GLH described by Keller *et al*.

Apart from GLH, since 1977, we have been interested in the existence of cases of unknown etiology characterized by extremely severe polyclonal hyperglobulinemia and swelling of the superficial systemic lymph nodes, and thus we have been compiling cases.[2] It is unclear whether the etiology of these cases is the same, and whether they can be considered a single syndrome remains to be investigated. However, they share many characteristic clinical and histopathological findings and present a unique picture in terms of the outcome and prognosis, in that they have an indolent course, and no cases have been cured. In addition, when the clinicopathological characteristics of these cases were compared with those of PC-type GLH, almost all of the features were found to be consistent, except that the present cases did not have a localized mass. This article compares the clinical and histopathological data of the present cases [designated hereafter as idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL)] with those of PC-type GLH and considers the distinctiveness of PC-type GLH.

1. Cases

The cases considered to be IPL in this article met the following criteria:
(1) Polyclonal hyperimmunoglobulinemia with serum IgG > 4,500 mg/dl and no M-protein.
(2) Generalized superficial lymphadenopathy, the largest of which should be the size of a fingertip on palpation or ≥ 1.8 cm in maximum diameter when actually measured, as well as a high degree of plasmacytosis shown by histology, with little or no destruction of the architecture.
(3) No known diseases associated with hyperglobulinemia.

Patients with the following diseases were excluded as described above (3):
Various infectious diseases

Collagen diseases, rheumatoid arthritis and its subtypes, Sjogren syndrome, various allergies, including drug allergies, hypersensitivity, so-called adjuvant diseases, myasthenia gravis, and hyperthyroidism
Hepatitis and liver cirrhosis
Hodgkin disease, non-Hodgkin malignant lymphoma, and other malignant tumors
Immunoblastic lymphadenopathy (polyclonal immunoblastosis)

Ten patients met the criteria described above (Table 1). Eight of these cases were from the University of Tokyo and Nihon University, and two (VI and X) were provided by Kanto-Teishin Hospital and Kawasaki Medical School. Cases I[3], II,[2] III,[2] VII,[4] and X[5] have been reported. Cases with markedly increased immunoglobulins and lymph nodes less than the size of a fingertip, as well as cases with IgG < 4,500 mg/dl were excluded from the present study.

2. Clinical findings of IPL and comparison with PC-type GLH

The clinical data for the ten IPL cases are summarized in Table 1. As shown in the table, the patients were mainly young adults at the time of consultation, and there was no remarkable medical or family history. In terms of occupation, cases I and II were a chemist and glassworker, respectively. The others were students, housewives, office workers, cab drivers, etc. The chief complaints were not severe at the time of the visit, and often consisted of a persistent low-grade fever or feeling somewhat tired. Some patients visited the clinic for a thorough examination after being diagnosed with increased blood sedimentation during a physical examination. In other words, almost all patients were discovered by chance and the actual point of onset could not be confirmed.

Physical examinations revealed enlarged superficial lymph nodes in all of the patients. The lymph nodes rarely exceeded the size of a thumbtack, and in terms of location, they were not confined to any part of the body but were systemic. In addition, hepatosplenomegaly was observed in many cases, and as a noteworthy sign, erythema of the skin often appeared in case II.

The laboratory findings showed marked hypergammaglobulinemia and hyperimmunoglobulinemia in all of the patients. In the fractions, IgG was increased to more than three times the standard value in all cases, whereas IgA and IgM increased markedly in eight cases but were noticeably lower in two cases. M protein was negative in all cases. Urinary Bence-Jones protein was detected in four cases, consisting of both κ and λ chains. In addition, in most cases, the α2-globulin levels increased slightly and the serum cholesterol levels decreased.

Hematological examination revealed mild-to-moderate anemia in the majority of cases. The anemia was normomicrocytic or normo-hypochromic. The serum iron levels were often low. In many cases, the number of plasma cells in the bone marrow increased.

Other relatively common laboratory abnormalities included increased erythrocyte sedimentation rate, strong positive C-reactive protein (CRP), positive direct Coombs reaction, and negative dinitrochlorobenzene (DNCB) skin reaction. Other abnormal findings among those omitted from the table were a small number of cases with elevated serum fibrinogen levels (cases II and IV), elevated serum copper levels (I and V), slightly increased leucine aminopeptidase (LAP) (V and VIII), and markedly decreased serum transferrin (I and VII). On the other hand, there were a few cases in which the rheumatoid arthritis (RA) reaction and various viral antibody titers were elevated, but these values fluctuated constantly with repeated testing, suggesting a pseudopositive biological reaction.

In most cases, the peripheral white blood cell fraction was normal. The lymphocyte counts were within normal limits. The T and B lymphocyte fractions were examined in cases I, II, VI, and IX and these were within normal limits. Peripheral lymphocyte function tests were performed in cases I and IV under the care of Professor Yata of the Department of Pediatrics, Tokyo Medical and Dental University, who reported that the peripheral T-cell suppressor function was enhanced in both cases.

The courses of many IPL cases remained unchanged or showed a slight exacerbation tendency (specifically, a gradual increase in serum gamma-globulin and serum immunoglobulin) for several years or more. During this period, only minor complaints, such as fatigability and feverishness, appeared, and the globulin levels were suppressed with small doses of steroids but returned to high levels after discontinuation. No patient achieved complete remission. Cases VII and VIII deserve special mentions in terms of their clinical courses and outcomes. As described above, case VII was a glass worker. A physical examination revealed the presence of abnormal chest shadows. He was referred for further testing and was found to have hyperproteinemia and hyperglobulinemia. He died after 16 years of treatment and observation. The patient was autopsied, and a significant plasmacytic interstitial pneumonia was found. In case VIII, their polyclonal immunoglobulin level continued to rise for six years. The corresponding polyclonal IgG-producing plasma cells infiltrated all reticuloendothelial organs of the body, initially reactively and later in an almost tumor-invasive manner, leading to their death. In both cases, the outcome was more progressive and uncontrolled until death, compared with the other cases of controllable hyperglobulinemia with no or slow progression.

Next, the clinical manifestations and IPL data described above were compared with PC-type GLH. The left side of Table 2 lists all the clinical findings for PC-type GLH in the original publication by Keller *et al*. The right side shows the frequency of these findings in IPL.

As shown in Table 2, many of the clinical findings for PC-type GLH were also observed in IPL. Both conditions shared the following 15 abnormalities: male predominance, fever and fatiguability, splenomegaly, superficial lymph node swelling, accelerated blood sedimentation, anemia, thrombocytosis, bone marrow plasmacytosis, hypergammaglobu-

Table 1. Clinical data of the ten cases of IPL

Case No.	Age	Sex	Obsevation time (years)	Outcome	Chief complaints at the first visit	Hepatomegaly	Splenomegaly	Lymph node swelling	Erythrocyte sedimentation rate/h	Peripheral blood				Bone marrow plasma cell (%)
										Red blood cell count ($x10^4/mm^3$)	White blood cell count ($/mm^3$)	Lymphocyte count ($/mm^3$)	Platelet count ($x10^4/mm^3$)	
I	32	M	6	Stable	Fatigability	++	++	+++	172	327	3500	770	30	4.4
II	22	M	4	Stable	Nothing in particular (health check)	+	++	+	150	401	7000	2520	30	3.2
III	34	M	11	Stable	Fatigability, mild fever	++	++	+++	168	191	3600	900	13	13.0
IV	28	F	4	Slightly progressive	Fever	++	++	+++	125	298	7300	1970	41	9.0
V	20	M	5	Stable	Fatigability, fever	-	-	+++	158	350	7000	1400	30	7.0
VI	57	M	6	Stable	Lymph node swelling	+++	-	++	152	430	7000	2000	35	1.0
VII	26	M	16	Death	Abnormal chest X-ray	++	+	++	120	330	3300	890	13	6.6
VIII	28	F	6	Death	Fever, hepatosplenomegaly	++	++++	+++	140	260	5500	275	20	3.6
IX	35	M	2	Stable	Health check	-	-	+++	103	510	6000	150	25	0.8
X	31	F	6	Stable	Fever, lymph node swelling	+	-	++		347	5300	1590	30	3.3

	Serum protein							Serum iron	Serology							
	Total protein (g/dl)	α2G (g/dl)	γ-G (g/dl)	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	Total cholesterol (mg/dl)		CRP	Direct Coombs test	Tuberculin test	DNCB skin test	Antinuclear antibody	Agglutination test for rheumatoid factor detection	Antiviral antibody	Antitoxoplasma antibody
I	11.5	0.80	5.6	7800	1100	350	100	32	6+	+	+	-	-	-	EBV↑, other↑	-
II	13.4	0.74	5.7	6800	950	271	125	80	6+	+	++	+	-	-	Rubella↑	-
III	12.0		6.0	↑↑↑	↑	↑↑	96		6+		+	-	-	-	-	-
IV	12.0	1.20	5.9	6900	433	533	126	14	6+	-	±	-	-	++	EBV↑, other↑	-
V	9.0	1.32	5.4	4550	350	400	140	102	6+	-	+		-	-	-	-
VI	9.0	w.n.l	5.2	4500	800	250	130		2+	-	-		-	-	-	
VII	13.9	0.72	6.2	8500	2080	490	90		6+	-	+		-	+	-	-
VIII	13.4	↓	9.6	9600	150	73	65	43	4+	-			-	-	-	
IX	9.6		5.0	5120	121	59	131		-	+	+		-	-		
X	8.9		4.2	5200	472	246	116	18		+			-	+		

Table 2. Comparison between the clinical data of PC-GLH and IPL

Features observed in PC-type Castleman disease	Frequency in IPL
Male predominance	yes
Fever, fatigability	6/10
Splenomegaly	6/10
Superfacial lymph node swelling	10/10
Increased erythrocyte sedimentation rate	10/10
Anemia	9/10
Leukocytosis	0/10
Thrombocytosis	1/10
Plasmacytosis in bone marrow	8/10
Hypergammaglobulinemia	10/10
Hyperalpha2globulinemia	5/7
Hyperfibrinogenemia	2/3
Elevated alkaline phosphatase	6/9
Abnormal BSP retention	0/0
Low serum iron	5/6
Low serum transferrin level	3/3
High serum copper	2/4
High serum ceruloplasmin level	0/0
increased leucine aminopeptidase level	2/4
Localized mass formation in one area of the body	0/10
Relieved with mass removal	not done

linemia, hyper-α2-globulinemia, hyperserum fibrinogen, elevated serum alkaline phosphatase, low serum iron, low serum transferrin, elevated serum copper, and elevated LAP. On the other hand, elevated white blood cell and platelet counts, which were usually seen in PC-type GLH, were rarely seen in IPL. In addition, in all cases of PC-type GLH, there was a localized mass in one area of the body, and removal of the mass often relieved the clinical symptoms. However, in IPL, although there was generalized lymphadenopathy, a localized mass in one region of the body was not found, despite careful workup.

3. Histology of IPL lesions and comparison with the histology of PC-type GLH

Twenty-eight lymph nodes biopsied from ten IPL cases and the excised spleen from case VIII were re-examined for histology.

The histological images of the lymph nodes were very similar, except for the late-stage lymph node of case VIII, which showed an extreme form of reactive plasmacytosis, with varying degrees of change depending on whether the patient was on steroid therapy. These lymph nodes were enlarged, mostly between 1.5 and 2.5 cm at the maximum diameter, without destruction of the underlying structure. The most conspicuous feature was the marked expansion through the interfollicular areas and medulla, which was filled with mature plasma cells. These plasma cells were found to be polyclonal through immunohistochemistry using the peroxidase anti-peroxidase (PAP) method, with a mixture of cells possessing various heavy and light chains. In many cases, small lymphocytes were present among the plasma cells, and a few large blasts were observed in some cases. The area of plasmacytosis extended from just below the capsule to the deep medulla. Therefore, in many cases, it was not easy to distinguish between the cortex and medulla (Figures 1, 2), resulting in follicles appearing as islands in the sea. However, in patients undergoing treatment, the area of plasmacytosis could be identified as the medulla (Figure 3).

The sinus was identified in all cases when observed carefully, although the size of the sinus varied from case to case and from specimen to specimen, even within an individual. The sinus was narrowed by plasma cells and was difficult to identify in many cases. In cases III and VII, many small nests of large histiocyte-like cells appeared in the sinuses, which appeared to be epithelioid.

The number of follicles increased considerably, except in the late stage of case VIII (Figures 1-4). They were distributed just below the capsule to the deep medulla. The germinal centers were in the form of reactive hyperplasia. The cells in the germinal centers were mainly centroblasts, centrocytes, and macrophages, which are normal germinal center components. The germinal centers were well-demarcated from the mantle zone. In nine of ten cases, blood vessels entered the germinal centers from outside the follicles (Figures 7 and 8). In seven of nine cases, the vessel wall was slightly thickened. However, there were no highly-branched, dendritic, or sclerotic vessels, clearly distinguishing them from the vascular changes in the germinal center of HV-type GLH.

The layer of small lymphocytes constituting the mantle zone was not very thick (Figures 4-8). In many cases, small lymphocytes in the mantle zone were arranged in concentric circles and often formed a single file pattern. Areas of plasmacytosis were observed immediately adjacent to the mantle zones (Figures 6 and 10).

Blood vessels also proliferated in the areas where plasma cells proliferated (Figure 5). Many of these vessels had a post-capillary-venule-like morphology.

In all cases, so-called tertiary follicles (translator's note: nodular aggregates of T cells in the cortex) were found mainly under the capsule, but they were not well developed.

In contrast, the histopathology of case VIII was unique. The lymph node biopsied two years before death showed a histology almost consistent with that described above, with no destruction of the architecture, and the infiltrating plasma cells were mature and completely polyclonal, as shown by immunohistochemistry using the PAP method. The simultaneously excised spleen was massive (2,135 g) and showed a high degree of mature plasma cell proliferation in the medulla and paracortical regions. Two years later, autopsy revealed marked infiltration of mature plasma cells into various organs, including the lymph nodes and bone marrow. Although the lymph nodes were difficult to observe due to autolysis, there appeared to be mild destruction of the architecture, which is considered a form of neoplastic infiltration. However, these plasma cells still possessed polyclonal IgG antibodies.

A comparison of the histology of IPL lymph nodes

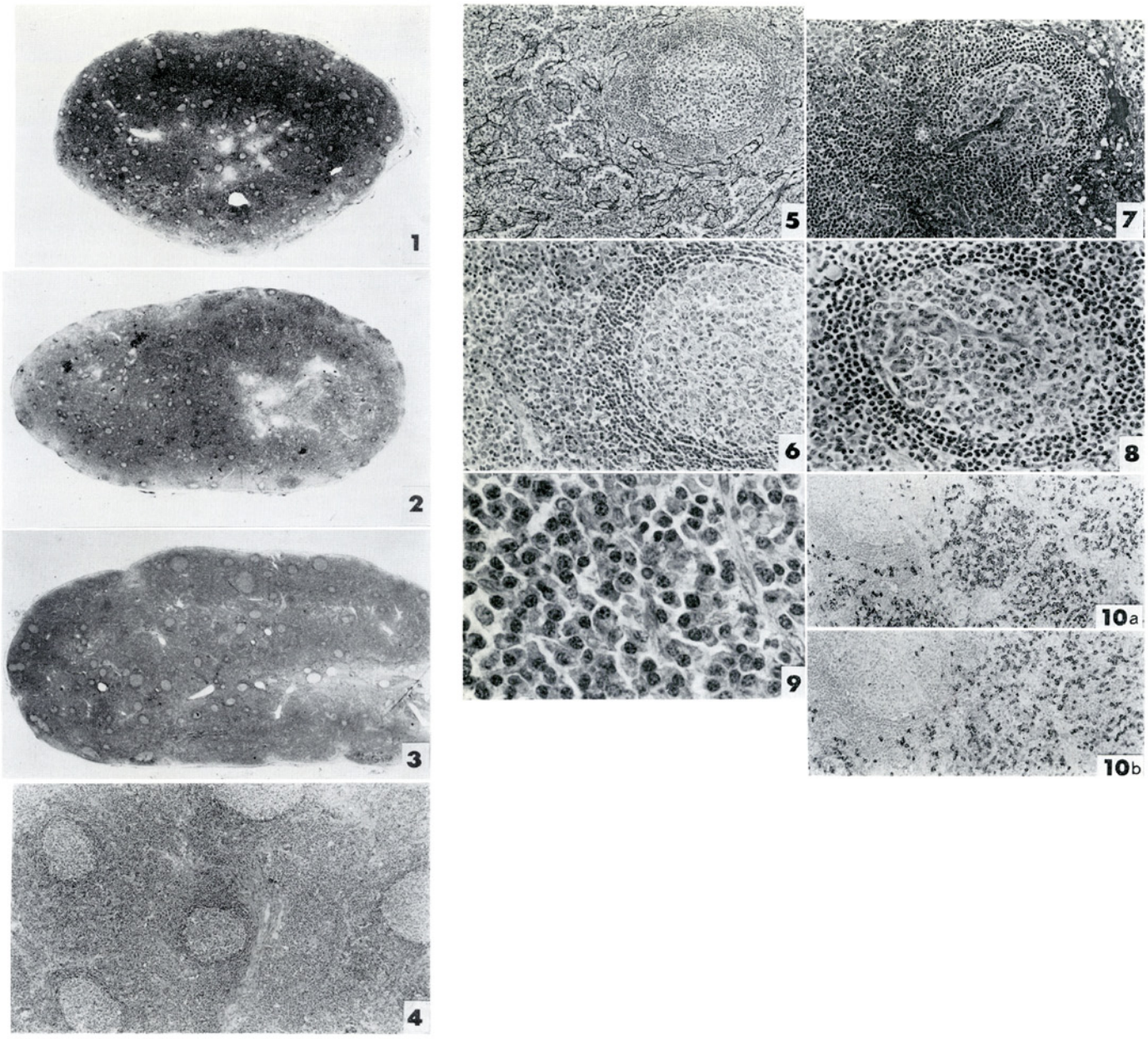

Figure
(Translator's note: The Japanese text in the blank space above Figure 1, including the Japanese calendar year of Showa 55, means "1980 Volume 20 Supplement". The original Japanese article has been cited in several papers as having been published in 1980 or 1981, causing some confusion, but 1980 is the correct year.)
1: Lymph node in IPL, enlarged to 2.4 cm at the maximum diameter. The interfollicular area is highly hyperplastic. The follicles are also hyperplastic and distributed in an insular pattern throughout the lymph node. The sinusoids are compressed and difficult to see. (Case IV)
2: Same as Figure 1. (Case X, maximum diameter 2.2 cm)
3: Lesser degree of change, with marked hyperplasia of the follicle and interfollicular area, but the sinuses are clearly visible. (Case I, ×8)
4: Well-developed germinal centers, thin mantle zone, and enlarged parafollicular area. (Case IV, ×50)
5: There is a marked increase in the number of blood vessels in the parafollicular area. (Case II, silver impregnation stain, ×60)
6: There is a marked increase in plasma cells in the parafollicular area, which is in contact with the mantle zone. (Case I, ×120)
7: Vascular penetration into the germinal center; in IPL, the vessels in the germinal centers show only this level of development at best. (Case VIII, ×60)
8: Barely Hassall-like structure in the germinal center, which is significantly less developed than those in HV-type GLH. (Case IX, ×180)
9: Proliferating plasma cells are of a mature type. A small number of small lymphocytes are admixed. (Case VII, ×600)
10: PAP immunostaining, ***a***: anti-kappa, ***b***: anti-lambda, kappa-, and lambda-chain-bearing cells mixed in the same field of view.

described here with that of PC-type GLH in the original publication by Keller *et al*. is shown in Table 3.

As shown in the table, there was no distinction between the two conditions at the histological level. In PC-type GLH, the mass had a lymph node structure with a high degree of plasmacytosis between the follicles, occasional residual sinuses, normal or slightly hyperplastic germinal centers, and occasional vascularization of the germinal centers, all of which are consistent with the histology of the lymph nodes in IPL. In contrast, the maximum diameter of the masses ranged from 3 to 11 cm in PC-type GLH, and the individual components of the fused masses ranged from 2.5 to 7 cm. This is considerably larger than the lymph nodes in untreated IPL cases, which range from 2.0 to 3.3 cm.

DISCUSSION

The essential pathogenesis of the cases reported in this paper is clinically polyclonal hyperimmunoglobulinemia of unknown etiology, with the exception of a particularly severe form of reactive polyclonal plasmacytosis in the lymph nodes. Most of the clinical manifestations of IPL described in this paper are considered to be ancillary to essential conditions. Systematic searches for such a group of cases have rarely been reported, with only a few sporadic case reports.[2-7]

It is dangerous to assume that all ten cases of IPL described here are a single entity. In addition, the criteria in this article for IPL are highly artificial, and it is undisputed that there are many cases with similar clinicopathological features but to milder degrees. Nevertheless, we are interested in this group of cases and collected them for two reasons. First, patients with this condition share common clinical symptoms, courses, and outcomes, and we hope that this will provide guidance in formulating a treatment plan and estimating the prognosis when we encounter such patients in the future. The other reason is that we believe that some of these cases may have a common etiology, specifically failure of the B-cell proliferation mechanism, and we are seeking clues to the pathogenesis, including this possibility. We hope to accumulate more such cases in the future and deepen the clinical, histological, and cellular immunological data.

Table 3. Histological comparison between the nodules of PC-type GLH and the lymph nodes of IPL

PC-type GLH	IPL
In all cases, the mass shows a lymph node structure (the mass consists of lymph node(s)).	Lymph nodes.
Marked plasmacytosis in the interfollicular area.	Consistent.
The sinuses can rarely be clearly observed.	In many cases, it was difficult to identify the sinuses.
Usual-sized or large germinal centers are present.	Consistent.
There is usually no marked vascularization or hyalinization of the germinal centers.	Very mild vascularization of the germinal centers was seen in 9 of 10 cases. No hyalinization or arborizing vessels were seen.

Next, we will discuss the relationship between GLH and IPL, which is a key theme of the present study. Keller *et al*.[1] were the first to define PC-type GLH. They considered GLH a distinct entity and subclassified it into HV- and PC-types. This classification was based on clinicopathological characteristics and not on etiology or pathogenesis. Therefore, when discussing PC-type GLH, it is necessary to assume that only those cases that fit their clinicopathological definition should be referred to as such. The basic clinical and histopathological features of PC-type GLH, as described by Keller *et al*., are that there is a localized mass formation in one area of the body where the mass is a lymph node (or tissue with a lymph node structure) with markedly increased polyclonal plasma cells in the interfollicular area, and that the various clinical abnormalities,[1,8-11] including hypergammaglobulinemia, disappear with removal of the mass.

The clinicopathological features of IPL were compared with those of PC-type GLH. While there are fundamental differences in the size of the enlarged lymph nodes and whether they are localized, and relatively minor differences in the presence or absence of leukocytosis and thrombocytosis, the other abnormalities are almost completely consistent. In other words, if the criteria for localized masses were removed from the Keller *et al*. criteria for PC-type GLH, and systemic PC-type GLH was allowed to exist, at least the majority of IPLs would fall into this category. However, as mentioned above, we assumed that GLH should not exceed the definition of Keller *et al*. without limitations, and therefore, the two diseases should be distinguished. The multifaceted similarities between the two diseases pose a question when considering the etiology and pathogenesis of GLH. This similarity raises the possibility that common factors may be involved in the pathogenesis of both diseases (GLH and IPL). It is possible that the same factors that act locally in GLH or processes similar to those occurring locally in GLH may be involved on a systemic scale in at least some IPL cases. However, it would be fruitless to discuss this hypothesis further unless the pathogenesis mechanism of PC-type GLH is further elucidated.

Lastly, one of the authors (Uchida) reported a thought-provoking case with hyperimmunoglobulinemia and peculiar histology of the lymph nodes, in which the patient died after a lapse of approximately one year.[12] The histology of the lymph nodes in this case, taken at a relatively early stage, showed markedly increased vascularity in the germinal centers, as well as onion-skin fibrosis and hyalinosis of the adventitia of the vessels, giving rise to a Hassall body-like structure. The interfollicular area showed small vessel proliferation and fibrosis, and moderate proliferation of polyclonal mature and immature plasma cells was observed. In the late stage, polyclonal plasma cells (mainly immature) markedly increased in number and took a form that could be described as neoplastic proliferation with mild structural destruction, while the germinal centers were markedly atrophic. The histology of the early resected lymph nodes showed a combination of histological features of both HV-

and PC-type GLH, although immature cells were present in the interfollicular area. It is interesting that such morphological changes can occur in systemic lymph nodes. In addition, the histology of the lymph nodes at the end of the disease was interesting because it was thought that the plasma cells remained polyclonal and grew in a tumor-like manner, suggesting similarity to case VIII in the present report. Furthermore, this case was not included in the present report because the serum IgG level was 3,500 mg/dl, but it can be assumed that such cases are very similar to the group of ten typical cases of IPL in the present report.

CONCLUDING REMARKS

We described the clinical and pathological characteristics of ten patients with severe polyclonal hyperimmunoglobulinemia and extremely high levels of polyclonal plasmacytosis in systemic lymph nodes of unknown etiology (IPL) and compared these characteristics with those of plasma cell-type giant lymph node hyperplasia (PC-type GLH).

We showed that IPL has the majority of the abnormal clinical findings and histological features of PC-type GLH and that the two diseases are clinicopathologically similar. In contrast to PC-type GLH, where the mass is localized and clinical symptoms disappear when the mass is removed, IPL lacks such a localized mass, which is a distinct difference between the two diseases.

We argued that PC-type GLH and IPL should not be regarded as the same disease entity at this time and pointed out that they may share some common pathogenesis mechanisms.

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