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Multicentric Castleman's disease with abundant IgG4-positive cells: a clinical and pathological analysis of six cases

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ABSTRACT

Background Differentiation between multicentric Castleman's disease and systemic immunoglobulin (Ig) G4-related lymphadenopathy is sometimes difficult. It has been suggested that measurement of the IgG4-/IgG-positive cell ratio is useful for the differential diagnosis of the two diseases. However, the authors present a detailed report of six patients with multicentric Castleman's disease with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%).

Results In the present series, the patients showed systemic lymphadenopathy, polyclonal hypergammaglobulinaemia and elevated serum interleukin-6 (IL-6) and C-reactive protein levels. Further, anaemia, hypoalbuminaemia, hypocholesterolaemia and thrombocytosis were observed. These findings were consistent with those of multicentric Castleman's disease. Although five patients showed elevated serum IgG4 levels, only two patients showed an increased serum IgG4/IgG ratio. However, the two patients showed highly elevated serum IgG4 levels, but the serum IgG4/IgG ratios were, although increased, not very high. Also, a patient with increased serum IgG4/IgG ratio showed a good response to antihuman IL-6 receptor monoclonal antibody (tocilizumab). Histologically, the germinal centres were mostly small and regressive, and frequently penetrated by hyalinised blood vessels, and there was no eosinophil infiltration. These findings were different from those of IgG4-related lymphadenopathy.

Conclusions The authors conclude that multicentric Castleman's disease sometimes occurs with abundant IgG4-positive cells and elevated serum IgG4 levels. Therefore, the two diseases cannot be differentially diagnosed by immunohistochemical staining alone. Laboratory findings, especially IL-6 level, C-reactive protein level and platelet count, are important for the differential diagnosis of the two diseases.

INTRODUCTION

Castleman's disease is a rare atypical lymphoproliferative disorder¹ classified according to the histopathological findings of the affected lymph nodes as plasma-cell type, hyaline-vascular type or a mixed-type variant of the former two types.^{2,3} Patients with the plasma-cell type or mixed-type Castleman disease frequently show systemic manifestations (multicentric Castleman's disease (MCD)) such as fever, fatigue and loss of appetite and weight. Abnormal laboratory and clinical

findings include elevated C-reactive protein (CRP) level, hypergammaglobulinaemia, anaemia, hypoalbuminaemia, hypocholesterolaemia and thrombocytosis.²⁻⁵ These symptoms are closely related to high interleukin (IL)-6 levels, and therefore MCD is considered as a hyper-IL-6 syndrome. Idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia is considered the same as MCD in Western countries.^{6,7} Although idiopathic plasmacytic lymphadenopathy and MCD have a similar clinicopathology, the former has a significantly better 5-year survival rate than the latter.^{6,7}

Immunoglobulin (Ig) G4-related diseases have recently been confirmed, which show unique and interesting clinicopathological features.⁸ Together with a group of researchers, we revealed that IgG4-related lymphadenopathy sometimes shows systemic lymphadenopathies and polyclonal hypergammaglobulinaemia,^{8,9} and is often clinically and/or histologically suspected to be MCD.⁸ Recently, we reported the clinical and pathological findings of systemic IgG4-related lymphadenopathy; these findings overlapped only partially with those of MCD.⁸

On the basis of immunohistochemical findings, Cheuk *et al*⁹ previously suggested an IgG4-/IgG-positive cell ratio of >40% to be the diagnostic criterion for IgG4-related lymphadenopathy. However, we experienced six patients with MCD with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%).

In the present study, we conducted a detailed examination of six patients with MCD with abundant IgG4-positive cells to further clarify the differences in the clinicopathological findings of the present study on MCD and those presented in previous reports on IgG4-related lymphadenopathy, and sought to establish differential diagnostic criteria for the two diseases.

MATERIALS AND METHODS

Patients and materials

We clinicopathologically examined six Japanese patients with MCD with abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%). The cases were retrieved from the surgical pathology consultation files of the authors (YS, MK and TY).

Clinical information was obtained from the patient medical records, referring pathologists or clinicians.

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All data and samples from the patients were collected with their informed consent.

Histological examination and immunohistochemistry

Surgically biopsied lymph node specimens were fixed in 10% formaldehyde and embedded in paraffin. Serial sections (4 µm) were cut from each block of paraffin-embedded tissue, and several selected sections were stained with H&E. The sections were immunohistochemically stained using an automated BenchMark XT slide stainer (Ventana Medical Systems, Tucson, Arizona). The tissue sections were subjected to standardised heating pretreatment for antigen retrieval prior to the immunohistochemical procedure. The following primary antibodies were used: CD20 (L26; 1:200; Novocastra, Newcastle, UK), CD3 epsilon (PS1; 1:50; Novocastra), CD5 (4C7; 1:100; Novocastra), CD10 (56C6; 1:50; Novocastra), CD21 (1F8; 1:20; Dako, Carpinteria, California), CD138 (MI15; 1:100; Dako), Bcl-2 oncoprotein (3.1; 1:200; Novocastra), IgG (polyclonal; 1:20000; Dako), IgG4 (HP6025; 1:400; The Binding Site, Birmingham, UK), κ light chain (kp-53; 1:100; Novocastra), Lambda light chain (HP-6054; 1:200; Novocastra) and human herpesvirus type 8 (137B10; 1:50; Novocastra).

The number of IgG4- or IgG-positive cells was estimated in areas with the highest density of IgG4- or IgG-positive cells, respectively. Five different high-power fields (HPFs; eyepiece, ×10; lens, ×40) were examined in each section, and the average number of IgG4- or IgG-positive cells per HPF was calculated.⁸

PCR for the detection of Ig heavy-chain gene rearrangement

Ig heavy-chain gene rearrangement was analysed by PCR. The reaction was performed according to the standard procedures described previously.^{8 10 11} The primers used for Ig heavy-chain gene amplification were as follows^{8 10 11}: 5'-TGG [A/G]TC CG[C/A] CAG [G/C]C[T/C] [T/C]C[A/C/G/T] GG-3' as an upstream consensus V-region primer; 5'-TGA GGA GAC GGT GAC C-3' as a consensus J-region primer; and 5'-GTG ACC AGG GT[A/C/G/T] CCT TGG CCC CAG-3' as a consensus J-region primer.

Statistical analyses

All statistical analyses were performed using the Mann-Whitney U test with SPSS software (version 14.0). A p value of <0.05 was considered statistically significant.

RESULTS

Clinical and laboratory findings

The clinical and laboratory findings are summarised in tables 1, 2 respectively. The study subjects comprised five men and one woman with a median age of 52.0 years (range 43.0–68.0 years). All the patients showed systemic lymphadenopathy and were clinically and/or histologically suspected to have MCD, and/or malignant lymphoma previously. The size of the lymph nodes ranged from 1.0 to 2.5 cm. Analysis of the lifestyles of the patients did not indicate any risk factors for HIV infection; antihuman immunodeficiency virus 1 antibody was negative in the three patients examined. Various autoantibodies were detected in three of the six patients examined (table 1). Hypergammaglobulinaemia was detected in all the patients. The IgG level (mean±SD 5354.33±2278.67 mg/dl) was elevated in all the patients. The serum IgA level (mean±SD 708.35±241.65 mg/dl) was elevated in five patients, and the serum IgM level (mean±SD 172.37±241.65 mg/dl) was elevated in two patients. Further, five patients showed elevated serum IgG4 levels (mean±SD 492.83±538.40 mg/dl). However, only two patients showed an increased serum IgG4/IgG ratio; this was because the patients showed significantly elevated levels of other IgG subclasses. The IL-6 level (mean±SD 22.35±8.77 pg/ml) and CRP level (mean±SD 7.50±2.70 mg/dl) were significantly elevated in all the patients. Moreover, our patients showed anaemia (haemoglobin level: mean±SD 10.30±2.37 g/dl), hypoalbuminaemia (albumin level: mean±SD 2.7±0.73 g/dl), hypocholesterolaemia (total cholesterol: mean±SD 113.40±18.98 mg/dl) and thrombocytosis. Lactate dehydrogenase level was not found to be elevated (mean±SD 116.50±19.26 IU/l) in any patient. In contrast, the soluble IL-2 receptor level was significantly elevated (mean±SD 2111.67±918.87 U/ml) in all patients.

Compared with our previous study on systemic IgG4-related lymphadenopathy,⁸ the present study on MCD showed significantly elevated IL-6 and CRP levels, anaemia, hypoalbuminaemia and hypocholesterolaemia. The differences in the above-mentioned findings between the groups were statistically significant (table 3).

Pathological and immunohistological findings of lymph nodes

Histopathological findings of the biopsied lymph nodes of the patients were very similar (figures 1–3). Lymphoid follicles were

Table 1 Clinical findings and IgG4/IgG-positive cell ratio in six patients with multicentric Castleman's disease

Patient no	Age/sex	Presentation	Autoantibodies	Treatment and clinical outcome (follow-up period in months)	IgG4-/IgG-positive cell ratio (%)
1	43/M	Fatigue, systemic lymphadenopathy, thrombocytosis	ANA (borderline) RF (+)	Follow-up; stable disease (10)	45.2
2	68/M	No subjective symptoms, systemic lymphadenopathy, thrombocytosis	ANA (borderline) RF (–) Anti-SS-A/anti-SS-B (–) Anti-dsDNA (–)	Follow-up; stable disease (11)	54.7
3	47/F	Fatigue, skin purpura, renal dysfunction, systemic lymphadenopathy, thrombocytosis	ANA (+) RF (+) Anti-SS-A/anti-SS-B (+) Anti-dsDNA (+)	Steroid; partial remission, worsening of symptoms on reduced dose of steroid (26)	46.5
4	50/M	Fever, renal dysfunction, systemic lymphadenopathy, multiple lung nodules, bone marrow plasmacytosis, thrombocytosis	ANA (+) Anti-dsDNA (+)	Steroid; complete remission, disappearance of lymph node swelling and multiple lung nodules, negative test results for autoantibodies (31)	48.8
5	65/M	No subjective symptoms, incidental finding of systemic lymphadenopathy since several years	ANA (borderline)	Follow-up; stable disease (10)	76.6
6	54/M	No subjective symptoms, incidental finding of systemic lymphadenopathy since 15 years, multiple lung nodules, thrombocytosis	ANA (–) RF (–) Anti-SS-A/anti-SS-B (–) Anti-Sm (–)	Tocilizumab; complete remission, disappearance of lymph node swelling and multiple lung nodules, improvement in laboratory data (13)	43.4

ANA, antinuclear antibody; dsDNA, double-stranded DNA; F, female; Ig, immunoglobulin; M, male; RF, rheumatoid factor; SS, Sjögren syndrome; Sm, Smith antigen; Tocilizumab, anti-human interleukin-6 receptor monoclonal antibody.

Table 2 Laboratory data on patients with multicentric Castleman's disease

Patient no	IgG1 (mg/dl) (320–748)*	IgG2 (mg/dl) (208–754)*	IgG3 (mg/dl) (6.6–88.3)*	IgG4 (mg/dl) (4.8–105)*	IgG4/IgG (%) (3–6)*	IgG (mg/dl) (870–1700)*	IgA (mg/dl) (110–410)*	IgM (mg/dl) (35–220)*	IgE (IU/ml) (<170)*	CRP (mg/dl) (<0.3)*	IL-6 (pg/ml) (<4.0)*	LDH (IU/l) (119–229)*	sIL-2R (U/ml) (220–530)*	Hb (g/dl) (male, 13.5–17.6)* (female, 11.3–15.2)*	Alb (g/dl) (4.0–5.0)*	T-cho (mg/dl) (150–219)*
1	1830	1810	270	93	2.3	4003	620.1	139.2	ND	2.84	8.6	119	1812	12.7	3.4	142
2	2080	1270	94	147	4.1	3591	1049	135	1670	9.3	19.6	143	1080	13.2	3.6	103
3	ND	ND	ND	154	4.9	3113	352	106	ND	7.21	27.4	103	2137	7.5	2.2	117
4	3290	1310	168	314	6.2	5082	898	229	ND	9.3	31.2	133	3797	8.1	1.8	114
5	ND	ND	ND	1460	17.4	8380	638	263	ND	10.06	30	91	1644	10.9	2.2	ND
6	3810	2210	55.8	789	11.5	7957	693	162	ND	6.26	17.3	110	2200	9.4	3.0	91

*Normal range or value (in the respective unit).

Alb, albumin; CRP, C-reactive protein; Hb, haemoglobin; Ig, immunoglobulin; IL-6, interleukin-6; LDH, lactate dehydrogenase; ND, not determined; sIL-2R, soluble interleukin-2 receptor; T-cho, total cholesterol.

diffused throughout the cortex of the lymph node. The follicles showed variable degrees of regressive changes in the germinal centres with a distinct mantle zone, decreased number of centroblasts and tangible body macrophages. The germinal centres were mostly small and regressive, and frequently penetrated by hyalinised blood vessels. These findings were different from those of IgG4-related lymphadenopathy.^{8 12 13} The inter-follicular area was characterised by sheets of proliferating mature plasma cells with a slight-to-moderate increase in vascular proliferation, and there was no eosinophil infiltration. These histological findings were consistent with those of MCD rather than of IgG4-related lymphadenopathy.^{8 12–16}

The majority of CD21-positive follicular dendritic cells formed networks similar to those in the germinal centres.

The IgG4-/IgG-positive cell ratio ranged from 43.4% to 76.6%, with an average of 52.0%.

There were no human herpesvirus type 8 antibody-positive cells and no Ig light-chain restriction.

Ig heavy-chain gene rearrangement

No Ig heavy-chain gene rearrangement was observed in any case.

DISCUSSION

MCD is a rare lymphoproliferative disorder and often refractory to even corticosteroid treatment or chemotherapy; consequently, the prognosis of patients with this disease is poor.^{5–7} In Japan, some patients showed a less aggressive or sometimes self-limiting clinical course of a disease. Moreover, the disease is often sensitive to conventional therapies such as those with corticosteroids and cytotoxic agents.^{6 7 17 18} These cases befit the disease entity of idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia. Our patients showed an indolent or good clinical course and tested negative for human herpesvirus type 8 antibody. Thus, our patients might have idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia rather than multicentric Castleman disease.^{6 7 18}

In our present study, the patients showed abundant IgG4-positive cells (IgG4-/IgG-positive cell ratio, >40%), and the histological findings were partially similar to those of IgG4-related lymphadenopathy. However, our patients showed elevated serum IL-6 levels and the related biological effect, that is, elevated CRP levels, and thrombocytosis. Therefore, they were considered to have hyper-IL-6 syndrome.^{5 8 16–19} Moreover, the patients showed anaemia, hypoalbuminaemia, hypocholesterolaemia and elevated serum IgA levels. These findings were consistent with those of MCD and quite different from those of IgG4-related lymphadenopathy.^{5 8 16–19} IgG4-related lymphadenopathy is not characterised by elevated serum IL-6 and CRP levels.^{8 16 19} Moreover, histological findings show normal-to-hyperplastic germinal centres and eosinophil infiltration.^{8 12 13 16} However, our cases usually showed small and regressive germinal centres, and no eosinophil infiltration was observed there (table 3). These histological findings were consistent with those of MCD.^{8 12–16}

IL-6 is an interleukin produced by a variety of cells, including T cells, macrophages and B cells, and has multiple biological functions.^{5 17} It induces the final maturation of activated B cells to produce plasma cells (Ig-producing cells).^{5 17} Continuous IL-6 production induces polyclonal hypergammaglobulinaemia.^{20–22} Moreover, IL-6 increases the serum levels of IgG4 and other IgG subclasses.^{22–24} A previous study reported a case of MCD with elevated serum IgG4 level.²⁵ Therefore, we suggest that the number of IgG4-positive cells increases in MCD. In our study, although five patients showed elevated serum IgG4 levels, three

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Table 3 Clinical and pathological findings of multicentric Castleman's disease and systemic IgG4-related lymphadenopathy

Findings	Multicentric Castleman's disease (present series)	Systemic IgG4-related lymphadenopathy (data from Sato <i>et al</i> ⁶)	p Value*
Clinical findings			
Systemic lymphadenopathy	Yes	Yes	—
Polyclonal hypergammaglobulinaemia	Yes	Yes	—
Elevated serum IgG level	Yes (mean±SD 5354.33±2278.67 mg/dl)	Yes (mean±SD 3651.8±1214.1 mg/dl)	NS
Elevated serum IgA level	Yes (mean±SD 708.35±241.65 mg/dl)	No (mean±SD 228.5±135.73 mg/dl)	0.003
Elevated serum IL-6 level	Yes (mean±SD 22.35±8.77 pg/ml)	No (mean±SD 8.45±11.61 pg/ml)	0.039
Elevated CRP level	Yes (mean±SD 7.50±2.70 mg/dl)	No (mean±SD 0.29±0.25 mg/dl)	0.001
Anaemia	Yes (haemoglobin level: mean±SD 10.30±2.37 g/dl)	No (haemoglobin level: mean±SD 12.96±1.61 g/dl)	0.034
Hypoalbuminaemia	Yes (albumin level: mean±SD 2.7±0.73 g/dl)	No (albumin level: mean±SD 3.71±0.48 g/dl)	0.011
Hypocholesterolaemia	Yes (total cholesterol: mean±SD 113.40±18.98 mg/dl)	No (total cholesterol: mean±SD 163.1±28.11 mg/dl)	0.009
Thrombocytosis	Yes	No	—
Pathological findings			
Germinal centre	Small and regressive	Normal—hyperplastic	—
Interfollicular area	Sheets of proliferating mature plasma cells	Proliferation of mature plasma cells with plasmacytoid cells and immunoblasts	—
Eosinophil infiltration	No	Yes	—

*p<0.05 was considered statistically significant.

CRP, C-reactive protein; Ig, immunoglobulin; IL-6, interleukin-6; NS, not significant.

of these patients (patient nos 2, 3 and 4) did not show an increased serum IgG4/IgG ratio. The remaining two of the five patients (patients no 5 and 6) showed highly elevated serum IgG4 levels (1460 mg/dl and 789 mg/dl, respectively), but the

serum IgG4/IgG ratios were, although increased, only 17.4% and 11.5%, respectively. This was because the patients had elevated levels of not only IgG4 but also IgG1, IgG2 and IgG3 (table 2). Serum IgG1 levels, in particular, were significantly elevated.

Figure 1 Histopathological findings of patient no 1. Expansion of the interfollicular area was observed, and lymphoid follicles showed variable degrees of regressive changes in the germinal centres with a distinct mantle zone (A, B). Blood vessels penetrated into the germinal centres (C). The interfollicular area was characterised by sheets of proliferating mature plasma cells, and there was no eosinophil infiltration (D). (E) Immunostaining of IgG4. (F) Immunostaining of IgG. The IgG4-/IgG-positive cells ratio was 45.2%, but the serum IgG4 level was not elevated. (A–D) H&E staining; (A) ×40, (B) ×100, (C) ×200, (D) ×400, (E, F) ×100.

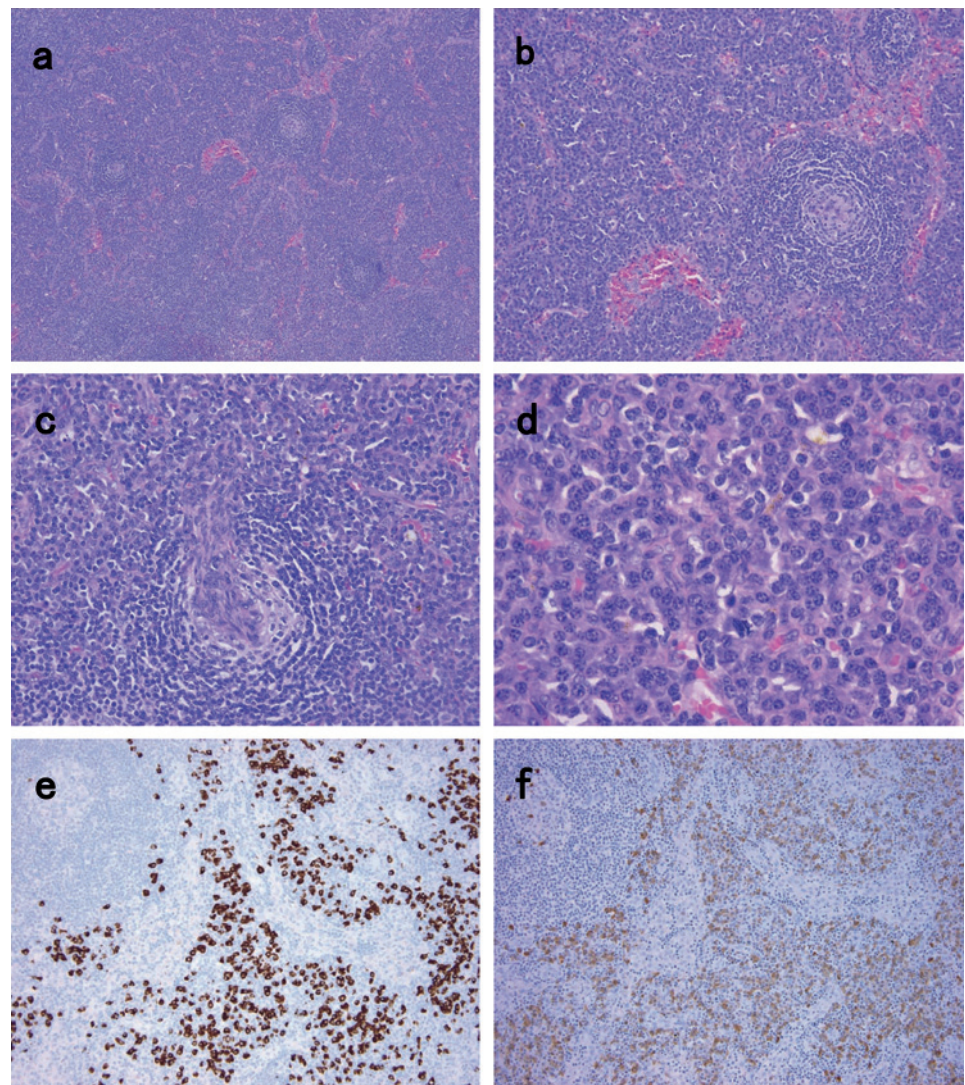
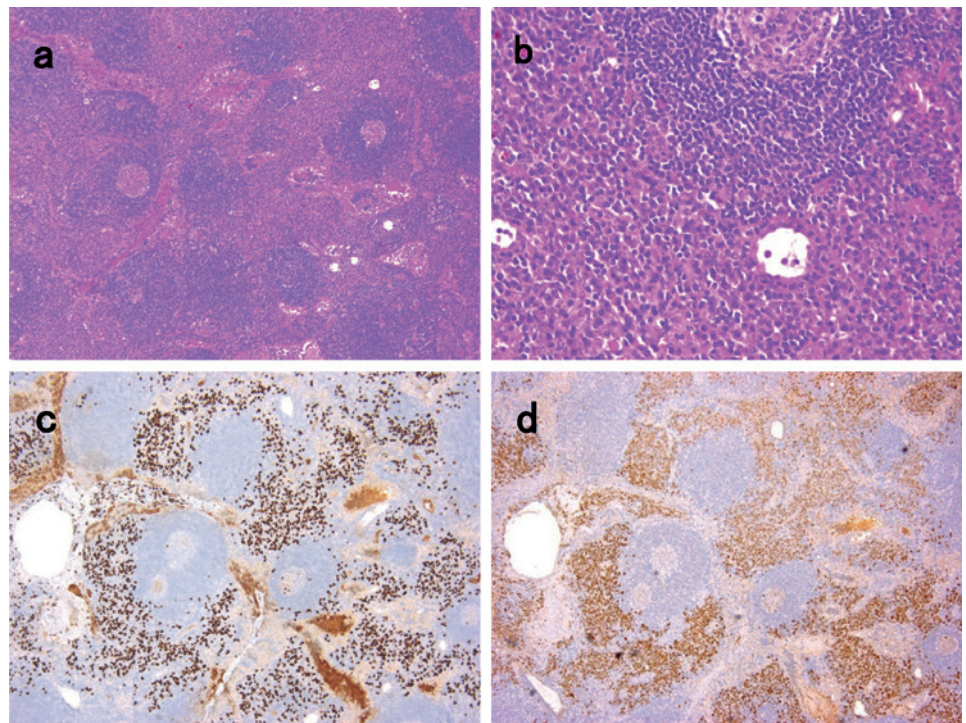


Figure 2 Histopathological findings of patient no 2. Small germinal centres and expansion of the interfollicular area were observed (A). Sheets of proliferating mature plasma cells were observed in the interfollicular area (B). (C) Immunostaining of IgG4. Immunostaining of (D) IgG. The IgG4-/IgG-positive cell ratio was 54.7%. The serum IgG4 level was elevated, but the serum IgG4/IgG ratio was not increased. (A, B) H&E staining; (A) $\times 40$, (B) $\times 200$, (C, D) $\times 40$.



Interestingly, patient no 6 showed a good response to anti-human IL-6 receptor monoclonal antibody (tocilizumab), with disappearance of lymph node swelling and multiple lung nodules. Therefore, the case of this patient was considered to be that of a hyper-IL-6 syndrome, that is, MCD.

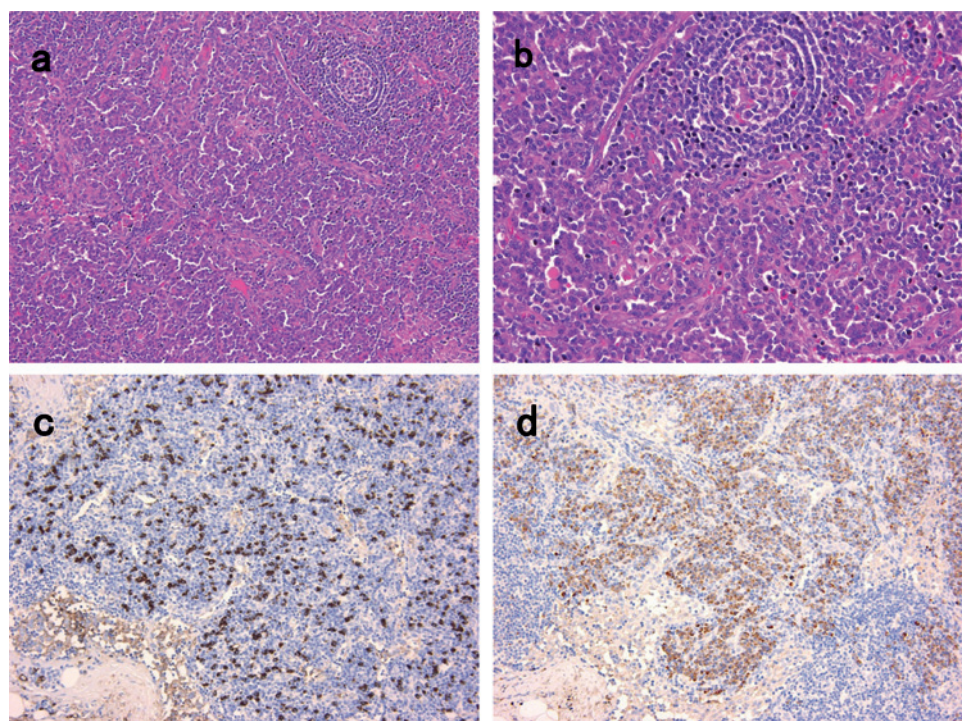
Patient no 1 showed an increased IgG4-/IgG-positive cell ratio, but serum IgG4 level was not elevated. Thus, this case indicated that the IgG4-/IgG-positive cell ratio and serum IgG4 level are not always correlated.

According to recently reports, IgG4-related diseases are characterised by elevated serum IgE level and eosinophil infiltration in the affected tissue,^{8 16 19 26} probably due to upregulated T

helper 2 (Th-2) cytokine production.²⁷ In our series, eosinophil infiltration in the affected tissue was not observed, but two patients examined showed elevated serum IgE levels. As mentioned above, IL-6 polyclonally increases Ig level^{20–24} and is related to IgE synthesis.²¹ Thus, we suggest that the elevated serum IgE levels in two patients were due to IL-6. Previous reports have described that serum IgE level is elevated in MCD and idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia.^{17 18}

On the basis of immunohistochemical findings, Cheuk *et al*⁹ reported the diagnostic criterion for IgG4-related lymphadenopathy to be an IgG4-/IgG-positive cell ratio of $>40\%$.

Figure 3 Histopathological findings of patient no 6. Small germinal centres, moderate increase in vascular proliferation and sheets of proliferating mature plasma cells were observed (A, B). (C) Immunostaining of IgG4. (D) Immunostaining of IgG. The IgG4-/IgG-positive cell ratio was 43.4%. The serum IgG4 level was highly elevated (789 mg/dl), but the serum IgG4/IgG ratio was only 11.5%. Moreover, a good response to tocilizumab was observed. (A, B) H&E staining; (A) $\times 40$, (B) $\times 100$, (C, D) $\times 100$.



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Take-home messages

- In Japan, idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinaemia is considered identical to multicentric Castlemans disease (MCD).
- We examined six patients with MCD with the presence of abundant IgG4-positive cells.
- MCD and systemic IgG4-related lymphadenopathy cannot be differentially diagnosed by immunohistochemical staining alone.
- Histologically, MCDs usually showed small and regressive germinal centres, and this finding were different from IgG4-related lymphadenopathy.

However, our results of immunohistochemical staining showed IgG4/IgG-positive cell ratios of >40% in MCD. Therefore, we concluded that in some cases, differential diagnosis of IgG4-related lymphadenopathy and MCD is difficult only by immunohistochemical staining of lymph node lesions.

Moreover, recently report have mentioned that pancreatic carcinoma and cutaneous Rosai–Dorfman disease show an increased number of IgG4-positive cells and elevated serum IgG4 level.^{28–30} Therefore, it is not appropriate to diagnose IgG4-related diseases only by immunohistochemical staining.

In conclusion, MCD sometimes occurs with abundant IgG4-positive cells and elevated serum IgG4 levels. Therefore, MCD and systemic IgG4-related lymphadenopathy cannot be differentially diagnosed only by immunohistochemical staining. Clinical features and laboratory data, especially IL-6 level, CRP level and platelet count, are important for a differential diagnosis of the two diseases.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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