# Diagnostic challenges of the idiopathic plasmacytic lymphadenopathy (IPL) subtype of idiopathic multicentric Castleman disease (iMCD): Factors to differentiate from IgG4-related disease

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## ABSTRACT

**Aims and methods** Idiopathic multicentric Castleman disease (iMCD) is currently considered to be classified into three clinical subtypes, including idiopathic plasmacytic lymphadenopathy (IPL), thrombocytopaenia, anasarca, fever, reticulin fibrosis/renal dysfunction, organomegaly (TAFRO) and not otherwise specified (NOS). Among the three, iMCD-IPL closely mimics IgG4-related disease (IgG4-RD). In diagnosing IgG4-RD, it is sometimes challenging to distinguish iMCD-IPL patients that also meet the histological diagnostic criteria for IgG4-RD. In this study, we focused on the number of IgG4-positive cells in the lymph nodes and analysed the relationship with laboratory findings to distinguish iMCD-IPL from IgG4-RD. Thirty-nine patients with iMCD-IPL and 22 patients with IgG4-RD were included.

**Results** Among the cases considered to be iMCD-IPL, 33.3% (13/39) cases also met the histological diagnostic criteria for IgG4-RD and serum IgG4 levels were not different between the two groups. However, the serum IgG4/IgG ratio was significantly higher in IgG4-RD, with a cut-off value of 19.0%. Additionally, a significant positive correlation between serum IgG levels and the number of IgG4-positive cells was observed in iMCD-IPL (p=0.001). The serum IgG cut-off value for distinguishing iMCD-IPL meeting histological criteria for IgG4-RD from other iMCD-IPL was 5381 mg/dL.

**Conclusions** iMCD-IPL cases with high serum IgG levels (>5000 mg/dL) were likely to meet the diagnostic criteria for IgG4-RD because of the numerous IgG4-positive cells observed. A combination of clinical presentations, laboratory values including the serum IgG4/IgG ratios and histological analysis is crucial for diagnosis of IgG4-RD and iMCD-IPL.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Idiopathic multicentric Castleman disease (iMCD)-idiopathic plasmacytic lymphadenopathy (IPL) occasionally meet the histological diagnostic criteria for IgG4-related disease (RD).

### WHAT THIS STUDY ADDS

⇒ iMCD-IPL with high serum IgG (>5000 mg/dL) were more likely to meet the histological diagnostic criteria for IgG4-RD.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A combination of clinical presentation, laboratory findings and histological analysis is crucial to distinguish iMCD-IPL from IgG4-RD.

## INTRODUCTION

Idiopathic multicentric Castleman disease (iMCD) is a lymphoproliferative disorder of unknown etiology characterised by multiple lymphadenopathies without infection of herpesvirus/human herpes virus 8 (KSHV/HHV8).[1]

iMCD is divided into several subtypes based on clinical and histological findings. Currently, iMCD is classified into three clinical subtypes: iMCD-IPL (idiopathic plasmacytic lymphadenopathy), iMCD-TAFRO (thrombocytopaenia, anasarca, myelofibrosis, reticulin fibrosis/renal dysfunction and organomegaly) and iMCD-NOS (not otherwise specified).[2–5] iMCD-IPL was previously recognised as part of iMCD-NOS,[6–8] but it was recently identified as an independent subtype of iMCD based on clinicopathological homogeneity.[9]

In Japan, most iMCD cases are considered iMCD-IPL, characterised by less aggressive clinical course compared with iMCD-TAFRO.[10 11] Clinically, iMCD-IPL presents with anaemia, fatigue and non-specific laboratory abnormalities, including polyclonal hypergammaglobulinaemia, thrombocytosis and high C reactive protein (CRP) level.[8 11 12]

IgG4-related disease (IgG4-RD) is also a systemic disease of unclear etiology, characterised by high serum IgG4 levels and mass lesions with fibrosis and IgG4-positive cell infiltration.[13] The disease involves lesions in various organs, including the pancreas, lacrimal and salivary glands, lungs and lymph nodes.[14]

Since patients with iMCD-IPL and IgG4-RD may present with similar symptoms associated with elevated serum immunoglobulins and

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**Table 1** Clinical findings of patients with iMCD-IPL and IgG4-RD

| | iMCD-IPL (n=39) | IgG4-RD (n=22) | P value |
|---|---|---|---|
| Age | 52.0 (43.5–62.0) | 71.0 (59.8–75.5) | **<0.001*****|
| Sex (M/F) | 22/17 | 7/15 | 0.584 |
| Serum IgG, mg/dL | 4726.0 (4096.5–5970.5) | 3929.0 (2132.0–4156.0)‡ | **0.001**** |
| Serum IgG4, mg/dL | 674.0 (289.0–934.5)† | 907.0 (274.0–1366.2)‡ | 0.684 |
| Serum IgG4/IgG, % | 12.0 (6.4–20.1)† | 28.2 (25.3–40.8)‡ | **<0.001***** |
| Serum IgA, mg/dL | 509.0 (418.0–653.5)† | 165.0 (105.3–202.8)‡ | **<0.001***** |
| Serum IgM, mg/dL | 223.0 (147.3–653.5)† | 62.5 (27.4–98.4)‡ | **<0.001***** |
| Serum IgE, IU/mL | 1975.5 (1418.0–3313.3)† | 761.5 (442.9–1211.5)‡ | **0.027*** |
| CRP, mg/dL | 6.1 (3.1–7.8)† | 0.1 (0.0–0.2)‡ | **<0.001***** |
| ESR, mm/hour | 106.5 (70.5–112.8)† | 16.0 (14.0–78.0)‡ | 0.109 |
| Albumin, g/dL | 3.0 (2.4–3.4)† | 3.8 (3.6–4.0)‡ | **<0.001***** |
| Haemoglobin, g/L | 102 (95–117)† | 129 (118–144) | **<0.001***** |

Values are the median (IQR). Significant p values are in bold. Significance was calculated using the Mann-Whitney U test. The $\chi 2$ test was used for the statistical analysis of nominal scales. Normal ranges: serum IgG, 870–1700 mg/dL; serum IgG4, 4.0–115.7 mg/dL; serum IgA, 90–400 mg/dL; serum IgM, 33–190 mg/dL (male), 46–260 mg/dL (female); serum IgE, 0–170 IU/mL; CRP, 0.0–0.3 mg/dL; ESR, 0–10 mm/hour (male), 0–15 mm/hour (female); albumin, 3.8–5.2 g/dL; haemoglobin, 136–183 g/L (male), 112–152 g/L (female).
***p<0.05, **p<0.01, *p<0.001.
†Serum $IgG_4$, $IgG_4$/IgG, IgA, IgM, IgE, CRP, ESR, albumin and haemoglobin were available for 19, 19, 31, 30, 12, 38, 9, 23 and 38 patients with iMCD-IPL, respectively.
‡Serum IgG, IgG4, IgG4/IgG, IgA, IgM, IgE, CRP, ESR and albumin were available for 15, 17, 12, 12, 12, 6, 18, 5 and 16 patients with IgG4-RD, respectively.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IgG4-RD, IgG4-related disease; iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy.

lymphadenopathy, clinicians sometimes face challenges in differentiating iMCD-IPL from IgG4-RD. Moreover, iMCD-IPL is noted as a disease that should be excluded in the diagnostic criteria for IgG4-RD.[15] In addition, the fifth edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues added IgG4-RD as a new category, which is described with a focus on lymph node lesions.[16] Therefore, the differentiation of the two diseases in lymph nodes is becoming increasingly important. Also, given the difference in treatment strategies, it is crucial to differentiate the two diseases in lymph nodes.[17 18]

In this study, we investigated the relationship between the number of IgG4-positive cells and laboratory parameters to clarify the features of iMCD-IPL that help differentiate it from IgG4-RD.

## MATERIALS AND METHODS

### Patients

Sixty-one Japanese patients with lymph node lesions in iMCD-IPL (n=39) and IgG4-RD (n=22) were included in this study. All cases were retrieved from surgical pathology consultation files from the Department of Pathology (Okayama University, Japan). Thirty cases of iMCD-IPL and 22 cases of IgG4-RD are those included in our previous report.[19]

All IgG4-RD cases met both the comprehensive diagnostic criteria for IgG4-RD and pathological criteria (IgG4-positive cell count >100/high power fields (HPFs) and IgG4/IgG positive cell ratio >40%).[13 20]

All iMCD-IPL cases met the consensus diagnostic criteria for iMCD.[1] According to a previous report,[8] we defined iMCD-IPL as a case meeting all four criteria: (1) prominent polyclonal hypergammaglobulinaemia (gamma globulin >4.0 g/dL or serum IgG level >3500 mg/dL), (2) multicentric lymphadenopathy, (3) an absence of definite autoimmune disease and (4) normal germinal centres (GCs) and a sheet-like infiltration of polyclonal plasma cells in the lymph node lesion. All cases were serologically or immunohistochemically negative for KSHV/HHV8. Patients on immunosuppressants were excluded from the study.

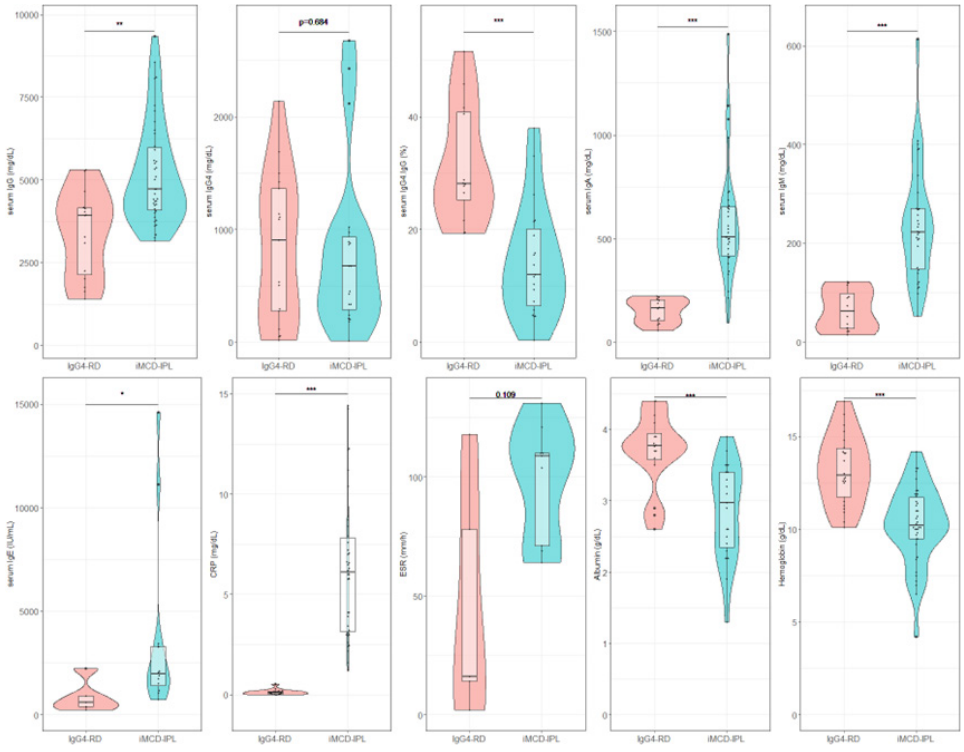


**Figure 1** Comparison of laboratory parameters between iMCD-IPL and IgG4-RD. Significant differences between iMCD-IPL and IgG4-RD in serum IgG, serum IgG4/IgG ratio, serum IgA, serum IgM, serum IgE, CRP, albumin and haemoglobin. *p<0.05, **p<0.01, ***p<0.001. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy; RD, related disease.



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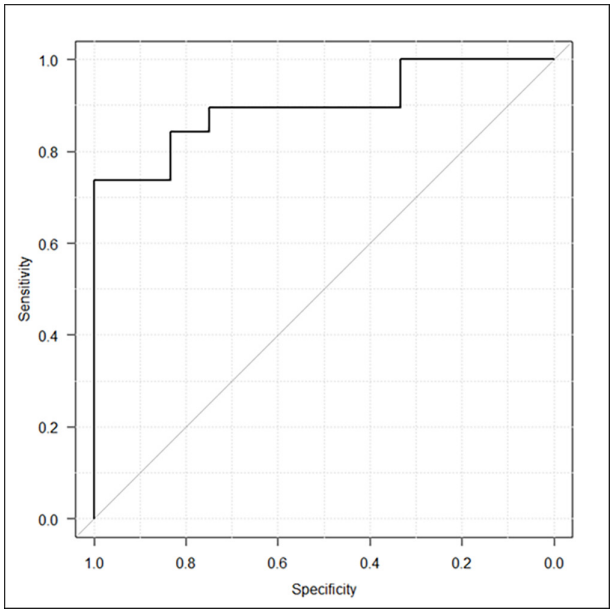


**Figure 2** ROC curve differentiating iMCD-IPL from IgG4-RD based on serum IgG4/IgG ratio (%). The cut-off value of the curve was 19.0%, with sensitivity and specificity of 73.7% and 100.0%, respectively. iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy; RD, related disease; ROC, receiver operating characteristic.

This study cohort included two cases of iMCD-IPL with extranodal lesions (lung and kidney). However, in the two cases, the clinical and histological findings of lymph nodes were consistent with iMCD-IPL, met the IgG4-RD exclusion criteria (continuing elevated serum level of CRP, elevated serum level of IgA, elevated serum level of IgM, sheet-like proliferation pattern of mature plasma cells, high degree of haemosiderin deposition, neutrophilic infiltration)[21] and were strongly positive for IL-6 immunostaining.[22] Thus, they were finally diagnosed as iMCD-IPL.

### Histological evaluation and immunohistochemistry

All samples were lymph node biopsy specimens, which were fixed in 10% formaldehyde and embedded in paraffin. These paraffin-embedded tissue blocks were sliced into 3 µm thick sections, which were stained with HE.

Immunohistochemical staining was performed on an automated Bond Max instrument (Leica Biosystems, Wetzlar, Germany) using IgG4 (MC011, 1:10000; The Binding Site, Birmingham, UK) and IgG (RWP49, 1:600; Novocastra, Newcastle, UK). The number of IgG and IgG4 positive cells was estimated in the interfollicular area with the highest density of IgG4 positive cells. A number of cells in three different HPFs (eyepiece, ×10 and lens, ×40) were counted, and the average was calculated to obtain the number of IgG4 positive cells and the IgG4/IgG positive cell ratio.

### Analysis of the relationship between laboratory data and IgG4-positive cells

Clinical data such as age, gender and laboratory data (CRP, IgG, IgG4, IgA, IgM, IgE, erythrocyte sedimentation rate (ESR), albumin, haemoglobin) were obtained. The correlation between the number of IgG4-positive cells in the lymph nodes and serum immunoglobulin levels, and serum IgG levels and CRP, was examined and compared between iMCD-IPL and IgG4-RD.

The CHAP score, an index to evaluate the disease activity of iMCD, was calculated from the values of CRP score, haemoglobin score, albumin score and performance status score.[23] In iMCD-IPL, the correlation between CHAP score and the number of IgG4-positive cells was investigated.

### Statistical analysis

Statistical analyses were conducted by using SPSS for Windows version V.23.0 (SPSS). Analysis methods included the Mann-Whitney U test, $\chi^2$ test and receiver operating characteristic (ROC) curves. Statistical significance was set at $p<0.05$.

## RESULTS

### Clinical findings

The clinical findings are summarised in table 1 and figure 1.

Twenty-two males and 17 females were diagnosed with iMCD-IPL, and 15 males and seven females were diagnosed with IgG4-RD. The mean age of iMCD-IPL and IgG4-RD patients was 53.2 (range 34–76) and 68.1 (range 47–81) years, respectively. Serum IgG, IgA, IgM and IgE levels were significantly higher in iMCD-IPL patients compared with IgG4-RD ($p<0.05$, $p<0.001$, $p<0.001$ and $p=0.027$, respectively). There was no difference in serum IgG4 levels between the groups ($p=0.684$). In contrast, serum IgG4/IgG ratio was significantly higher in IgG4-RD ($p<0.001$). ROC curves were generated for the serum IgG4/IgG ratio to differentiate iMCD-IPL and IgG4-RD (figure 2). The area under the curve (AUC) was estimated to be 0.899, and the cut-off value of the curve was 19.0%, with sensitivity and specificity of 73.7% and 100.0%, respectively.

Serum CRP levels were significantly higher in patients with iMCD-IPL ($p<0.001$). ESR was higher in patients with iMCD-IPL than with IgG4-RD, but no significant difference was observed. Both albumin and haemoglobin were significantly lower in iMCD-IPL ($p<0.001$ and $p<0.001$, respectively).

### Pathological findings

Pathologically, the lymph nodes in the iMCD-IPL cases showed a tendency of hyperplastic GCs and sheet-like proliferation of mature plasma cells in expanded interfollicular areas (figure 3). In contrast, IgG4-RD cases showed a mixed proliferation of mature to immature plasma cells, eosinophils, small lymphocytes and immunoblasts (figure 4). Additionally, no storiform fibrosis and phlebitis were observed. Vascularity was mild, follicular hyperplasia and interfollicular expansion were also observed in both diseases.

The number of IgG4 positive cells and IgG4/IgG positive cell ratio is shown in table 2. The mean IgG4 positive cells were 134.2/HPF (range 45.7–401.0) in iMCD-IPL and 228.1/HPF (range 117.0–458.0) in IgG4-RD. The number of IgG4-positive cells was significantly higher in IgG4-RD than in iMCD-IPL ($p<0.001$). All IgG4-RD cases showed IgG4-positive cell number >100/HPF. In contrast, there were 22 cases (56.4%) of iMCD-IPL with IgG4-positive cells >100/HPF. The mean IgG4/IgG positive cell ratio was significantly higher in IgG4-RD (81.6%, range 55.2%–97.6%) than in iMCD-IPL (36.8%, range 4.0%–93.7%) ($p<0.001$). Among the iMCD-IPL cases, 13 cases (33.3%) met the histological diagnostic criteria (IgG4 positive cells >100/HPF and IgG4/IgG positive cell ratio >40%) for IgG4-RD.[13] However, the clinical and histological findings in these 13 cases were consistent with iMCD-IPL: continuous elevation of CRP, sheet-like proliferation of mature plasma cells



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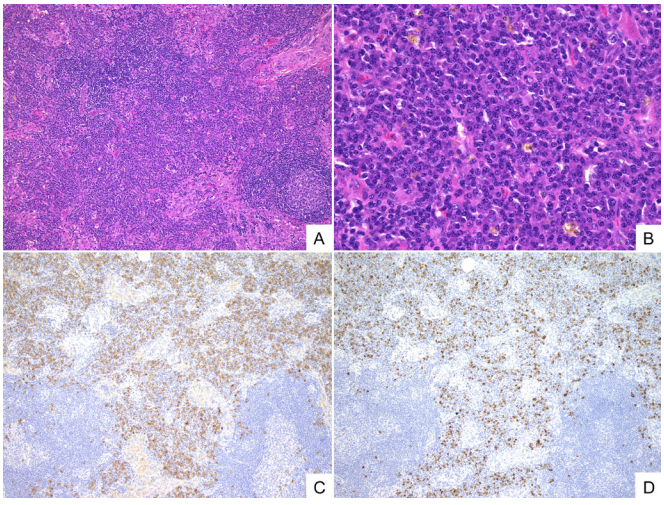


**Figure 3** Pathological findings of iMCD-IPL with numerous IgG4-positive cells. Interfollicular areas are expanded, and the germinal centre shows normal to hyperplastic (A, HE, ×4). Sheet-like proliferation of mature plasma cells in the interfollicular areas and haemosiderin deposition are observed (B, HE, ×60). IgG4/IgG positive cell ratio are >40% in this case (C, IgG; D, IgG4, ×10). iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy.

and haemosidelin deposition . Among them, 12 cases showed no extranodal lesions characteristic of IgG4-RD. One case showed pulmonary involvement, but met the exclusion criteria for IgG4-RD and was strongly positive for IL-6 immunostaining.[21]

### Relationship between laboratory data and the number of IgG4-positive cells

The relationship between the number of IgG4-positive cells and laboratory data is shown in figure 5.

In iMCD-IPL cases, there was a significant positive correlation between serum IgG levels and the number of IgG4-positive cells (r=0.514, p=0.05). While a similar positive correlation was observed in IgG4-RD cases, it was not statistically

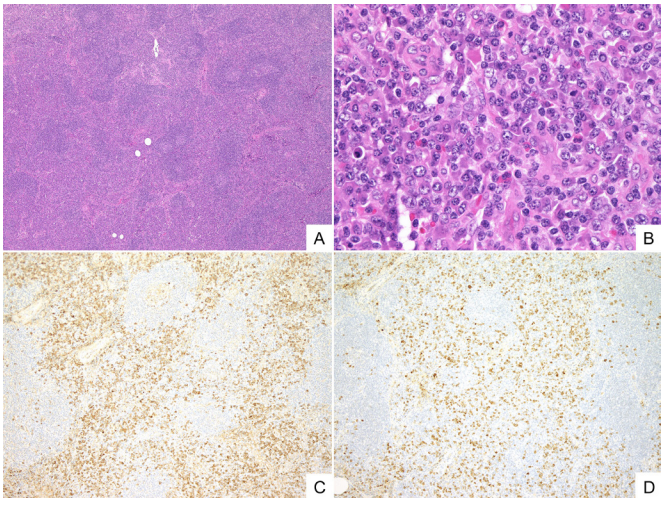


**Figure 4** Pathological findings of IgG4-RD. Interfollicular areas are expanded (A, HE, ×4). In the interfollicular areas, mixed proliferation of mature to immature plasma cells, eosinophils, small lymphocytes and immunoblasts are observed (B, HE, ×60). IgG4/IgG positive cell ratio are >40% (C, IgG; D, $IgG_4$, ×10). RD, related disease.

**Table 2** Pathological findings of iMCD-IPL and IgG4-RD

| | iMCD-IPL (n=39) | IgG4-RD (n=22) | P value |
|---|---|---|---|
| IgG4-positive cells /HPF | 113.7 (67.5–191.8) | 221.5 (175.3–272.5) | **<0.001** |
| >10/HPF, n (%) | 39 (100) | 22 (100) | |
| >50/HPF, n (%) | 34 (87.2) | 22 (100) | |
| >100/HPF, n (%) | 22 (56.4) | 22 (100) | |
| IgG4/IgG-positive cells ratio | 30.2 (19.3–44.3) | 81.4 (71.0–93.9) | **<0.001** |
| >100/HPF and IgG4/IgG-positive cells ratio >40%, n (%) | 13 (33.3) | 22 (100) | |

Values are the median (IQR). Significant p values are in bold. Significance was calculated using the Mann-Whitney U test. The number of $IgG_4$-positive cells (/HPF) is the average of three different HPFs with the highest density in interfollicular area. HPF, high power field; IgG4-RD, IgG4-related disease; iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy.

significant (r=0.506, p=0.054). Serum IgG4 and the number of IgG4-positive cells showed a significant positive correlation in the iMCD-IPL and IgG4-RD cases (r=0.713, p=0.001 and

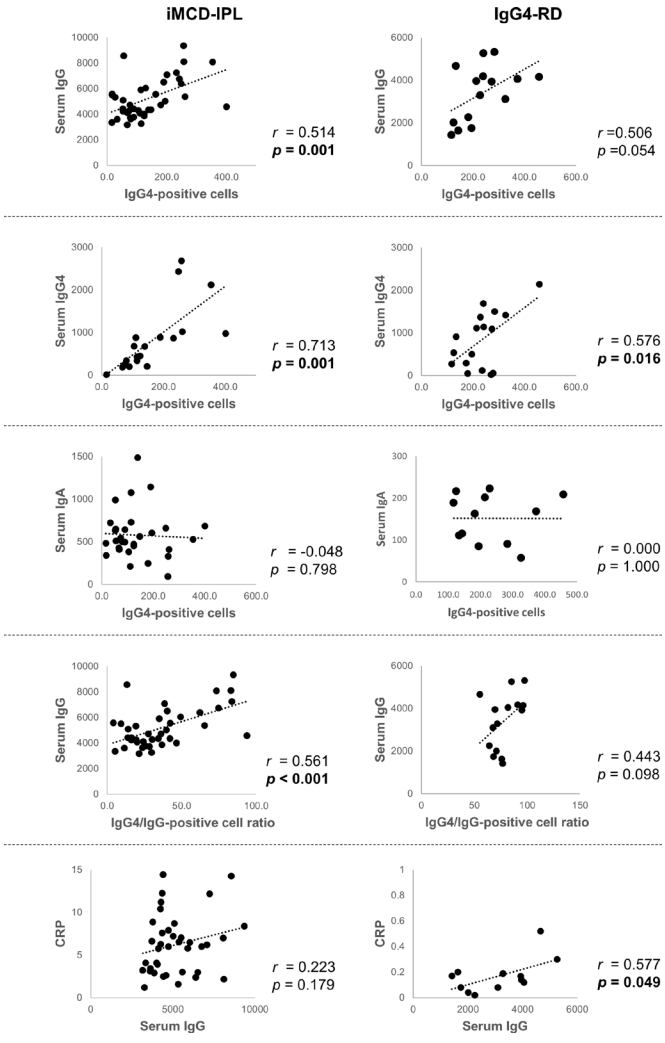


**Figure 5** Comparison of the number of IgG4-positive cells and laboratory data in iMCD-IPL and IgG4-RD. CRP, C reactive protein; iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy; RD, related disease.



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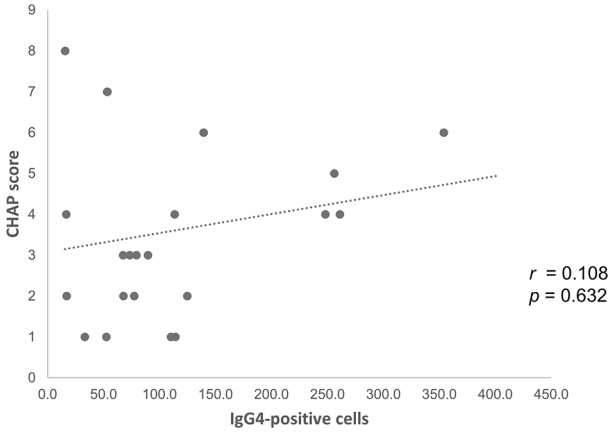


**Figure 6** Comparison of the number of IgG4-positive cells and CHAP score in iMCD-IPL. CHAP, an index calculated from the values of CRP score, haemoglobin score, albumin score and performance status score; CRP, C reactive protein; iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy.

r=0.576, p=0.016, respectively). No relationship was observed between serum IgA levels and the number of IgG4-positive cells in the two groups (r=−0.048, p=0.798 and r=0.000, p=1.000, respectively).

In terms of histological analysis, there was a positive correlation between the IgG4/IgG-positive cell ratio on tissue and serum IgG levels in both groups (r=0.561, p<0.001 and r=0.443, p=0.098, respectively). Comparison of serum IgG and CRP showed a weak positive correlation in both groups (r=0.223, p=0.179 and r=0.577, p=0.049, respectively). No significant relationship was observed between the number of IgG4-positive cells and CHAP score (figure 6).

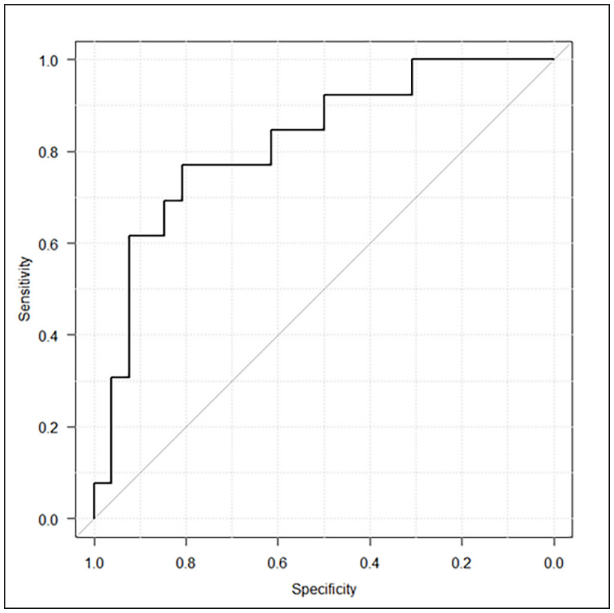


**Figure 7** ROC curves for differential diagnosis between cases of iMCD-IPL that meet histological criteria for IgG4-RD and other iMCD-IPL cases by serum IgG (mg/dL). The cut-off value of the curve was 5381 mg/dL, with sensitivity and specificity of 80.0% and 76.9%, respectively. iMCD-IPL, idiopathic multicentric Castleman disease-idiopathic plasmacytic lymphadenopathy; $IgG_4$-RD, $IgG_4$-related disease; ROC, receiver operating characteristic.

Figure 7 describes the ROC curves to distinguish iMCD-IPL with positive histological criteria for IgG4-RD from iMCD-IPL who did not meet the criteria. The AUC was estimated to be 0.820, and the cut-off value of the curve was 5381 mg/dL, with sensitivity and specificity of 80.0% and 76.9%, respectively.

## DISCUSSION

In this study, we examined the variables to discriminate iMCD-IPL and IgG4-RD. While iMCD is commonly described as a disease with systemic hyperinflammatory symptoms with lymphadenopathy, patients with iMCD-IPL are likely to have indolent clinical course, and histological differentiation between iMCD-IPL with elevated IgG and IgG4, and IgG4-RD can be challenging.

Clinically, the iMCD-IPL group showed significantly higher serum levels of IgG, IgA, IgM and IgE, which is a consequence of polyclonal hypergammaglobulinaemia due to hyper IL-6 in iMCD-IPL.[24] Those with iMCD-IPL tend to have serum IgG4 levels exceeding 135 mg/dL and meet the criteria for IgG4-RD. In the present study, 94.7% (18/19 cases) of iMCD-IPL met the serum IgG4 criteria for IgG4-RD. However, the serum IgG4/IgG ratio was significantly higher in IgG4-RD, with the cut-off value of 19.0%. Given that iMCD-IPL polyclonally increases not only IgG4 but also other subclasses, the serum IgG4/IgG ratio is lower than in IgG4-RD. Therefore, clinicians need to have a comprehensive approach to diagnosing iMCD-IPL based on multiple clinicopathological variables and avoid fixating themselves on the serum IgG4 levels. In addition, CRP, albumin and haemoglobin levels help differentiate between the two diseases. These clinical findings in iMCD-IPL may be affected by hyper IL-6.[25 26]

Immunohistochemically, 33.3% (13/39 cases) of iMCD-IPL met the histological diagnostic criteria for IgG4-RD. Histologically, the diagnosis of IgG4-RD requires the number of IgG4-positive cells and the IgG4/IgG-positive cell ratio. Since less than 50% of iMCD-IPL cases met the criteria for IgG4/IgG-positive cell ratio, it could be an essential indicator to differentiate the two entities. In iMCD-IPL that met the criteria for IgG4-RD, the proposed exclusion criteria for IgG4-RD in 2020 may be accurate enough to rule out.[19 21]

The study cohort included two cases of iMCD-IPL with extranodal lesions. These two cases were clinically and histologically consistent with iMCD-IPL but had pulmonary and kidney lesions. However, the lung and kidney are the common site of iMCD-IPL and IgG4-RD,[22] and it is difficult to distinguish the two by lesion distribution only.

Regarding the relationship between laboratory findings and IgG4-positive cells, high serum IgG cases had higher numbers and percentages of IgG4-positive cells regardless of the primary diseases, making IgG4-positive cell numbers and percentages less useful to differentiate the two. However, serum IgG>5000 mg/dL seems to be a good cut-off value, as none of the patients with IgG4-RD had serum IgG beyond the suggested cut-off.[27–29]

Interestingly, the results showed that the ratio of serum IgG4 increased in cases with higher serum IgG. Among immunoglobulins, IgG4 is a unique antibody, and previous reports showed that IgG4 antibodies are produced late. It usually takes several months of repeated antigen exposure for the IgG4 response to become prominent.[30 31] Furthermore, chronic exposure has been reported to increase serum IgG4 not only in its absolute level but also in its ratio to total IgG.[32 33] Among iMCD-IPL, cases with longer disease duration may cause high serum IgG levels and numerous IgG4-positive cells. Furthermore, these features of



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IgG4 antibodies suggest that cases with higher serum IgG levels are more likely to have increased IgG4/IgG-positive cell ratios.

In addition, the relationship between serum IgG and CRP was examined, but no significant correlation was found in iMCD-IPL. Serum CRP is a parameter of inflammatory symptoms, but it may be difficult to predict disease activity in iMCD-IPL by serum IgG levels because no correlation is observed. On the other hand, a significant positive correlation was observed between serum IgG and CRP in IgG4-RD. However, there are few cases with CRP exceeding the baseline level, which may not reflect the disease condition. Since there was no relationship between CHAP score and the number of IgG4-positive cells, it was possible that the increase in the number of IgG4-positive cells is not clearly related to disease activity in iMCD-IPL.

Interestingly, the frequency of iMCD subtypes may differ from each country. Especially, the ratio of iMCD-IPL is approximately half in our iMCD registry (The Japanese Castleman disease team by the Ministry of Health, Labour and Welfare of Japan), while it is reported to be less than 20% in China.[34] In addition, iMCD-IPL accounts for 12.7% (13/102 cases) of iMCD cases in the Castleman Disease Collaborative Network registry.[35]

These results suggest that there may be differences in the incidence of iMCD-IPL among races and regions. Moreover, since iMCD-IPL is a new subtype of iMCD and has been potentially underdiagnosed. In the future, it is necessary to establish comprehensive diagnostic criteria for iMCD-IPL, and to retrospectively analyse how many patients with iMCD-IPL were misdiagnosed as IgG4-RD.

Our study had several limitations. First, we were not able to investigate the disease duration. Second, the number of IgG4-positive cells and laboratory findings in other IgG4-RD mimickers was not investigated. Third, tissue sampling procedures may affect the number of IgG4-positive cells observed. Future studies are needed to determine if there are differences in serum IgG4 levels and the number of IgG4-positive cells depending on the duration of the condition.

In conclusion, we examined the relationship between IgG4-positive cells and laboratory findings in iMCD-IPL and IgG4-RD. While 33.3% of iMCD-IPL cases met the histological diagnostic criteria for IgG4-RD, those with high serum IgG level (cut-off value: 5381 mg/dL) were more likely to meet the criteria. In such cases, more attention should be paid to the diagnosis. It is necessary to differentiate iMCD-IPL from IgG4-RD by comprehensive assessments of clinical and pathological findings, including a cut-off of Serum IgG4/IgG ratio, without being fixated on serum IgG4 only. Furthermore, the ratio of serum IgG4 increased in cases with higher serum IgG may be associated with chronicity, but the disease duration in this study was unidentified and requires further research.

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