Original Article

Idiopathic multicentric Castleman disease with positive antiphospholipid antibody: atypical and undiagnosed autoimmune disease?

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Idiopathic multicentric Castleman disease (iMCD) is a systemic disorder characterized by systemic inflammation and organ dysfunction associated with an increase in pro-inflammatory cytokines. Some patients with iMCD are positive for autoantibodies, although their significance and relationship with specific associated autoimmune diseases are unclear. This study retrospectively analyzed the clinicopathological features of iMCD patients focusing on autoantibodies. Among 63 iMCD patients in our database, 19 were positive for at least one autoantibody. Among the 19, we identified five with plasma cell type (PC)-iMCD lymph node histopathology and positive anti-phospholipid antibodies. These patients were likely to have thrombocytopenia, anasarca, fever, reticulin fibrosis or renal insufficiency, organomegaly (TAFRO) symptoms, and thrombotic events. The present study suggests that patients with undiagnosed or atypical autoimmune diseases, including anti-phospholipid syndrome (APS), were treated for iMCD. APS may present with thrombocytopenia or even multi-organ failure, which overlap with clinical presentations of iMCD. Due to differences in the treatment regimen and follow-up, recognition of the undiagnosed autoimmune disease process in those suspected of iMCD is essential. Our study highlights the importance of complete exclusion of differential diagnoses in patients with iMCD in their diagnostic workup.

Keywords: idiopathic plasmacytic lymphadenopathy; multicentric Castleman disease; autoimmune, anti-phospholipid syndrome

INTRODUCTION

Idiopathic multicentric Castleman disease (iMCD) is a rare, clinicopathologically heterogeneous disorder with systemic inflammation and/or multi-organ dysfunction related to a high pro-inflammatory cytokine status.[1] Since Fajgenbaum *et al.* proposed the international consensus diagnostic criteria for iMCD, there has been less confusion regarding diagnostic and treatment approaches for the disorder.[2]

However, iMCD has considerable heterogeneity.[3] Pathologically, iMCD is divided into plasma cell (PC) type,

hypervascular (HV) type, and a mixed variant, although the histological definition of the mixed variant is unclear. The pathology of PC-type iMCD (PC-iMCD) is characterized by atrophic to hyperplastic germinal centers, interfollicular plasmacytosis, and mild to severe vascularity. Clinically, patients with iMCD are further classified into iMCD not otherwise specified (iMCD-NOS) or thrombocytopenia, anasarca, fever, reticulin fibrosis, renal insufficiency, and organomegaly clinical subtype (iMCD-TAFRO). TAFRO syndrome is a heterogeneous entity with a constellation of the aforementioned symptoms, including infectious diseases,

malignancies, and rheumatologic disorders, and was first reported in 2010.[4] Attention needs to be paid to the principle that iMCD-TAFRO is one of the causes of TAFRO syndrome, and they are not interchangeable. Some researchers argue that iMCD-NOS should be further classified into idiopathic lymphoplasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia (IPL) and other (non-IPL).[1,2] IPL was first described by Mori *et al.* in 1980 as systemic lymphadenopathy and hypergammaglobulinemia with increased inflammatory markers and serum interleukin-6 (IL-6) with indolent clinical courses.[5-21] In 2008, Kojima *et al.* reported 28 iMCD cases (18 IPL and 10 non-IPL).[22] Of note, 40% of the non-IPL patients were diagnosed with autoimmune diseases, such as Sjögren's syndrome (SjS) and immune thrombocytopenic purpura, and they exhibited thrombocytopenia, anasarca, fever, reticulin fibrosis or renal insufficiency, and organomegaly (TAFRO) symptoms. A systematic literature review also revealed that patients with iMCD have a high prevalence of autoantibodies.[23]

To date, there have been several reports describing that autoimmune diseases, such as SjS and systemic lupus erythematosus (SLE), present as TAFRO syndrome without iMCD.[24-32] At the same time, these reports raise a concern that there may be cases of overlooked autoimmune diseases misdiagnosed as iMCD. Considering the difference in treatment strategies, detecting atypical autoimmune diseases among iMCD is essential. We performed an exploratory analysis of iMCD patients in our database to investigate their clinicopathological characteristics, focusing on autoantibodies and co-existing autoimmune disorders.

MATERIALS AND METHODS

Design and study population

In this retrospective observational study, we performed an exploratory analysis of iMCD patients in our database. All cases were retrieved from surgical pathology consultation files from the Department of Pathology, Okayama University, in Okayama, Japan, which included 63 iMCD cases. All patients underwent surgical lymph node resection. We reviewed electric health records to assess the compatibility of the cases with the international diagnostic criteria of iMCD. We asked consultees to search for rheumatoid factor, antinuclear antibody (ANA), anti-double strand DNA antibody (dsDNA), anti-Smith antibody, anti-Ro/SS-A antibody (SS-A), anti-La/SS-B antibody (SS-B), anti-citrullinated protein antibody, anti-U1-ribonucleoprotein antibody (U1-RNP), anti-Scl-70 antibody, anti-aminoacyl tRNA synthetase antibody, anti-phospholipid antibodies (anti-cardiolipin (CL) or anti-cardiolipin-β2-glycoprotein-1 complex antibodies), anti-mitochondrial antibody, and anti-platelet antibodies, in addition to proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) and myeloperoxidase-ANCA (MPO-ANCA). All patients had negative viral serologies for hepatitis B, hepatitis C, and human immunodeficiency virus.

Clinical analysis

The following data of the patients were collected: age, sex, laboratory data including autoimmune panels, clinical courses, presence of thrombosis, and treatment.

Histological examination and immunohistochemistry

All lymph node specimens were fixed in 10% formaldehyde and embedded in paraffin. These paraffin-embedded tissue blocks were sliced into 3-μm thick sections and stained with hematoxylin and eosin (H&E). Immunohistochemical staining was performed on an automated Bond Max instrument (Leica Biosystems, Wetzlar, Germany) using the following primary antibodies: HHV-8 (13B10, 1:40; LifeSpan Biosciences, Seattle, WA, USA), CD20 (L26; 1:200; Novocastra, Newcastle, UK), and CD3 (PS1; 1:50; Novocastra). *In situ* hybridization was also performed for the κ and λ light chains (Leica Biosystems).

ETHICAL CONCERNS

The Institutional Review Board of Okayama University approved the study (reference number: 2007-033). We performed all study processes in accordance with the Declaration of Helsinki. Informed consent was received from all subjects involved in the study.

RESULTS

Baseline demographics and laboratory findings

Among the 63 iMCD patients, 19 had were positive for at least one autoantibody and only 5 were positive for anti-phospholipid antibodies. The baseline demographics and key laboratory and clinical findings are summarized in Table 1. Patients aged 48–73 years old had variable white blood cell and platelet counts, whereas two patients (cases 3 and 4) had severe thrombocytopenia attributable to TAFRO syndrome. Except for case 1, all patients had high alkaline phosphatase levels. Cases 2–4 had acute kidney injury, and case 4 required hemodialysis due to the severity of the disease. Although cases 1 and 2 had hi high immunoglobulin G (IgG) levels, the others had only marginally increased or normal serum IgG. Serum inflammatory markers were increased to some extent in all patients. Of note, cases 1, 2, and 5 developed acute thrombotic events during their clinical courses. Case 1 had left common femoral vein deep venous thrombosis. Case 2 had splanchnic venous thrombosis. Case 5 had adrenal infarction.

Autoantibodies

The autoantibodies of the five patients are shown in Table 2. Case 1 had high ANA and dsDNA titers, whereas the others had negative or weak positive results. Rheumatoid factor, PR3-ANCA, MPO-ANCA, and U1-RNP were negative in all patients. They all had negative serum and urine protein electrophoresis. Cases 1 and 4 had a considerably high

Table 1. Clinical Features of the Patients

Case No.	Age/Sex	WBC (x 10³)	Plt (x 10³)	ALP (U/L) (Ref < 113)	Cr (mg/dL)	CrCl (mL/min/ 1.73 m²)	IgG (mg/dL)	CRP (mg/dL) (Ref < 0.5)	IL-6 (pg/mL) (Ref < 4.0)	Thrombosis*	Anasarca	Fever (BT > 37.5°C)	Reticulin fibrosis	Organomegaly
1	73/F	4.0	133	94.2	0.53	94	3335	10.2	71.6	+	+	+	+	+
2	49/M	20.6	198	153	1.94	39	4935	4.2	13.8	+	+	+	N/A	+
3	48/M	5.7	14	384	1.76	45	1813	8.0	10.7	-	+	+	N/A	+
4	67/M	5.2	4	250	1.53	46	1859	15.7	579	-	+	+	+	+
5	51/F	13.9	99	1437	0.86	78	1257	10.0	91.8	+	+	+	+	+

Abbreviations: ALP, alkaline phosphatase; Cr, creatinine; CRP, C-reactive protein; IgG, immunoglobulin G; IL-6, interleukin-6; N/A, not available; Plt, platelet; WBC, white blood cell
* Case 1 had left common femoral vein deep venous thrombosis. Case 2 had splanchnic venous thrombosis. Case 5 had left adrenal infarction.

Table 2. Autoantibodies in the Included Patients

Case No.	ANA	dsDNA (IU/mL) (Ref < 12)	PR3-ANCA (U/mL) (Ref < 3.5)	MPO-ANCA (U/mL) (Ref < 3.5)	SS-A (U/mL) (Ref < 10)	SS-B (U/mL) (Ref < 10)	RNP (U/mL) (Ref < 10)	Direct Coombs	Anti-CL (U/mL) (Ref < 3.5)
1	1:1280	45.1	N/A	N/A	60	< 0.5	2.7	+	21.9
2	< 1:40	5.8	1.38	0.89	2.66	1.7	3.8	-	20.2
3	< 1:40	-	< 1.0	< 1.0	N/A	N/A	N/A	-	13.2
4	1:80	2.0	< 0.5	< 0.5	240	72	3.6	-	13.0*
5	1:80	6.0	1.0	1.0	N/A	N/A	-	+	25.0

* Titer of anti-cardiolipin-β2-glycoprotein-1 complex antibody (ref < 3.5 U/mL)
Abbreviations: ANA, anti-nuclear antibody; Anti-CL, anti-cardiolipin antibody; dsDNA, anti-double strand DNA antibody; MPO-ANCA, anti-myeloperoxidase antibody; PR3-ANCA, anti-proteinase-3 antibody; RNP, anti-ribonucleoprotein antibody; SS-A, anti-SS-A/Ro antibody; SS-B, anti-SS-B/La antibody.

SS-A, and case 4 also had a positive SS-B. All patients were positive for anti-CL or anti-cardiolipin-β2-glycoprotein-1 complex antibodies.

Treatment regimen

The treatment regimens for the included patients are described in Table 3. Except for case 1, all patients required additional treatment after high-dose corticosteroids (prednisolone 1 mg/kg). Of note, cases 4 and 5 had refractory disease activity even after treatment with tocilizumab (TCZ), and were administered rituximab (RTX) and cyclosporin.

Histopathological Analysis

The pathological findings of the included patients are summarized in Table 4. Lymph node specimens demonstrated numerous lymphoid follicles with atrophic to normal germinal centers and interfollicular expansion. The expanded interfollicular area consisted of the sheet-like proliferation of mature plasma cells and varying degrees of vascular proliferation (Figure 1). A high degree of hemosiderin deposition was observed in only case 1, and hyaline globulus of immunoglobulin was observed in cases 1 and 2. There were no light chain restrictions or HHV-8 positive cells. These histological findings were consistent with PC-iMCD. All patients had hypercellular marrow except for cases 1 and 4, who had a dry tap. No abnormalities were noted on karyotype testing.

DISCUSSION

This study retrospectively examined the clinicopathological features of iMCD patients, focusing on autoimmune panels and co-existing autoimmune disorders. We found five patients with PC-iMCD histopathology, positive anti-phospholipid antibodies, and similar clinical presentations, including TAFRO symptoms. The present study suggests that some of those diagnosed with iMCD are undiagnosed or have atypical autoimmune diseases. In particular, anti-phospholipid syndrome (APS) may be an important yet uncovered primary etiology of TAFRO syndrome masquerading as iMCD.

APS is a systemic autoimmune disease often characterized by thrombosis, loss of pregnancy, and the expression of anti-phospholipid antibodies (aPL).[33] APS is sometimes associated with other rheumatic diseases such as SLE and SjS. Patients with APS often present with deep venous thrombosis, livedo reticularis, or stroke, but also thrombocytopenia, myocardial infarction, and rarely, catastrophic APS, which may be fatal and requires strong immunosuppression and targeted therapies with RTX or eculizumab.[34,35] Mizuno *et al.* reported that patients with TAFRO syndrome can have thrombotic microangiopathy (TMA)-like glomerulopathy, which may be noted in APS.[36,37] Future studies are warranted to confirm if APS is the underlying etiology of TAFRO syndrome with TMA-like glomerulopathy.

TAFRO syndrome is also a heterogeneous entity including iMCD-TAFRO, malignancy, infection, and autoimmune disease.[38] Clinically, it is essential to sufficiently character-

Table 3. Treatment Regimens

Case No.	1st line	2nd line	3rd line	4th line
1	Prednisolone 1 mg/kg	-	-	-
2	Prednisolone 0.5 mg/kg	Melphalan-prednisolone	-	-
3	Prednisolone 1 mg/kg	Methylprednisolone pulse	-	-
4	Prednisolone 1 mg/kg	TCZ	RTX	CyA
5	Prednisolone 1 mg/kg	TCZ	RTX	-

Abbreviations: CyA, cyclosporin; RTX, rituximab; TCZ, tocilizumab

Table 4. Histological Findings of the Included Patients

Case No.	Germinal centers	Interfollicular area	Vascularity	High degree of hemosiderin deposition	Hyaline globulus of immunoglobulin
1	Atrophic	Expansion and sheet-like proliferation of mature plasma cells	mild	+	+
2	Normal to hyperplastic	Expansion and sheet-like proliferation of mature plasma cells	moderate	-	+
3	Atrophic	Expansion and mixed infiltration of mature plasma cells and immunoblasts.	moderate to severe	-	-
4	Normal to atrophic	Expansion and sheet-like proliferation of mature plasma cells	moderate	-	-
5	Normal to atrophic	Expansion and sheet-like proliferation of mature plasma cells	moderate to severe	-	-
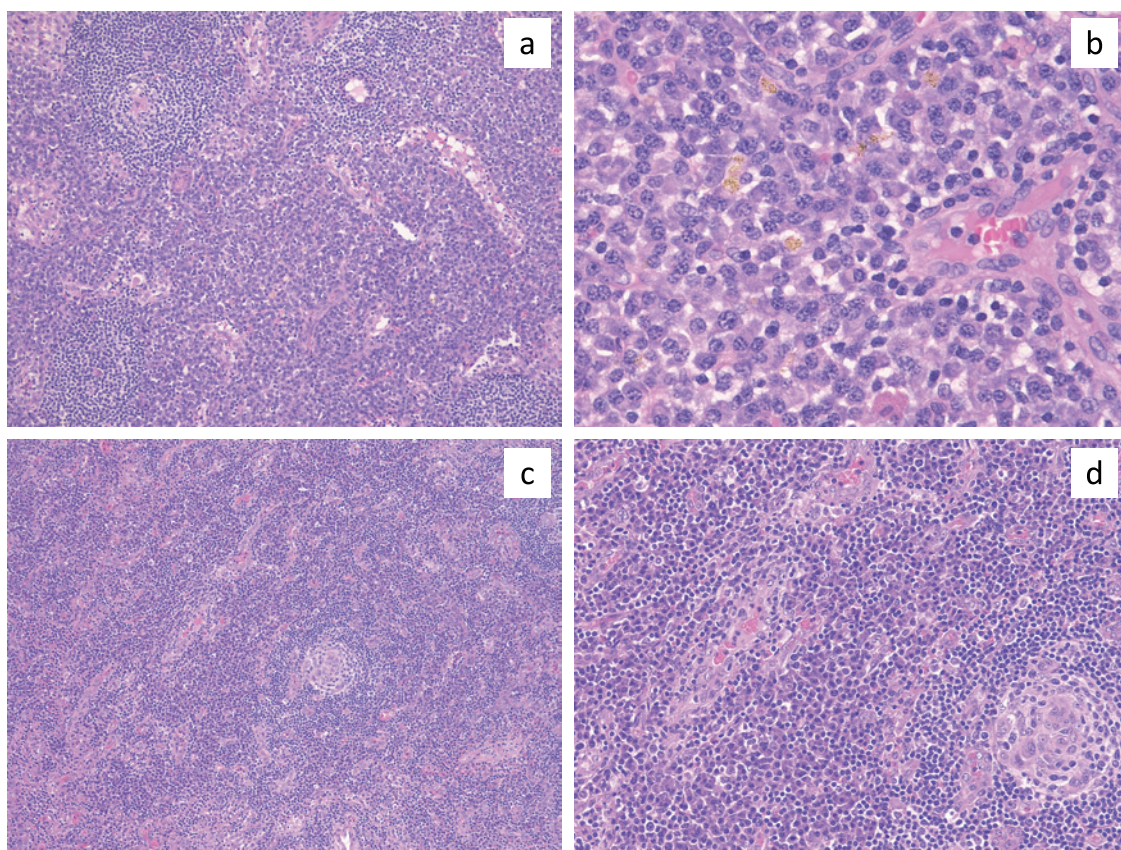
Fig. 1. Pathological findings of the included patients
Case 1: Atrophic germinal center and expanded interfollicular area with mildly vascular proliferation (*a*, HE, ×100). The sheet-like proliferation of mature plasma cells with marked hemosiderin deposition. (*b*, HE, ×400) Case 5: Atrophic germinal centers and expansion of interfollicular area are observed (*c*, HE, ×100). The interfollicular area exhibits moderate to severely vascular proliferation and sheet-like infiltration of mature plasma cells (*d*, HE, ×200).
Abbreviations: HE, hematoxylin and eosin.

ize the primary etiology of TAFRO syndrome due to differences in treatment and follow-up plans. Currently, iMCD is treated using corticosteroids, anti-interleukin-6 monoclonal antibodies, such as tocilizumab, RTX, cyclosporin, or chemotherapy.[1] Immunosuppressants or immunomodulatory medications are considered the first line for autoimmune diseases, and antiplatelet or anticoagulation therapy may be required for APS. Although challenging, the complete exclusion of primary autoimmune diseases is essential before making a diagnosis of iMCD.

Our study has a few limitations that need to be considered upon reviewing the results. First, we performed the pathological analysis of patients at a single Japanese university hospital, which reduces the generalizability of the results to patients with iMCD from other countries and ethnicities. Second, due to the rarity of the disease, we were only able include a small number of patients; further collection is necessary. Third, lymph node biopsy is not a regular diagnostic test for patients with APS. Future studies are required to examine and compare the lymph node histopathology of well-defined APS and PC-iMCD. Furthermore, aPLs may not be disease-specific to APS. Long-term follow-up and re-evaluation of aPLs are necessary.

Regardless of these limitations, our retrospective study provides valuable insight on the clinicopathological characteristics of iMCD from an autoimmune standpoint. Both clinicians and pathologists need to recognize the heterogeneity of iMCD and perform diagnostic workups to pinpoint the primary etiology as close as possible to prevent premature closure in their decision-making.

AUTHOR CONTRIBUTIONS

FUNDING

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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