

Review Article

Historical and pathological overview of Castleman disease

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Castleman disease consists of several lymphoproliferative subtypes that share some histological features in the lymph nodes. On the other hand, numerous clinical findings and etiologies make the disease challenging to understand. The origin of the disease is the hyaline vascular-type unicentric Castleman disease (UCD), first reported by Benjamin Castleman *et al.* in 1954. Although UCD is characterized by localized lesions and lack of symptoms, multicentric Castleman disease (MCD) with multiple lesions and systemic symptoms was reported by Frizzera in 1983. MCD is further divided according to KSHV/HHV8 infection status. In KSHV/HHV8-related MCD, viral infection signals lead to excessive cytokine production, and cause clinical and pathologic abnormalities. Some cases of plasma cell-type KSHV/HHV8-negative MCD can be found in association with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin changes), which is a paraneoplastic syndrome. The others are idiopathic MCD, which are currently considered a heterogeneous group of diseases with overlapping pathological and clinical features. In this article, we summarize the historical evolution of Castleman disease to help understand the disease concept. We also review the latest ideas and definitions of the subtypes within the MCD spectrum and summarize the histopathological findings.

Keywords: Castleman disease, idiopathic multicentric Castleman disease, TAFRO syndrome, idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia

INTRODUCTION

Castleman disease (CD) is a rare lymphoproliferative disorder that consists of several subtypes with different etiologies, clinical manifestations, and histological features. CD has become a current heterogeneous group of diseases over the past seven decades since the disease was first described.

The term CD has its origins in a case report published in 1954 by Castleman *et al.*¹ This initial case report was soon followed by a more detailed analysis of patients having isolated mediastinal lymphadenopathy.² In these initial publications, Castleman and colleagues described what is currently defined as hyaline vascular (HV)-type unicentric Castleman disease (HV-UCD).^{1,2}

Later, Flendrig *et al.*³ and Keller *et al.*⁴ reported the existence of a histological type in which mature plasma cells proliferate in the interfollicular area, and the plasma cell (PC)-type was established as the histological subtype of CD. In 1980, Mori *et al.* reported a group of disorders with histologi-

cal similarities to PC-type CD, but with generalized lymphadenopathy rather than a localized disease as previously reported. Clinically, these cases exhibited hypergammaglobulinemia and were termed as idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL).⁵ In 1983, Frizzera *et al.* also reported an entity with PC-type CD-like histology, presenting with generalized lymphadenopathy and systemic symptoms, and defined it as multicentric CD (MCD).⁶

In the early 1980s, with the increase in the acquired immunodeficiency syndrome (AIDS) epidemic, the link between Kaposi's sarcoma and MCD became recognized.⁷⁻⁹ In 1995, it was demonstrated that Kaposi's sarcoma-associated herpesvirus/human herpes virus 8 (KSHV/HHV8) is associated with the pathogenesis of MCD.¹⁰ Indeed, several patients reported by Frizzera *et al.* developed Kaposi's sarcoma, suggesting case of KSHV/HHV8-associated MCD.⁶ In the West, the recognition of HHV8-negative MCD took time because of the prevalence of HHV8-associated MCD,


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whereas in Japan, a concept corresponding to HHV8-negative MCD was reported earlier.^{5,11}

In 2017, the first international consensus diagnostic criteria for idiopathic (KSHV/HHV-8 negative) multicentric Castleman disease (iMCD) were published,¹² bringing the concept worldwide attention. iMCD is a heterogeneous disease concept that can be further divided into at least two subtypes based on differences in clinical presentation. One distinct subtype is iMCD with TAFRO (thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly) symptoms (iMCD-TAFRO).¹³ Although TAFRO symptoms are characteristic, over-reliance on clinical symptoms may lead to misdiagnosis. It is necessary to exclude other diseases that may also present with TAFRO symptoms, such as autoimmune diseases, infections, and malignancies, by histological examination.¹⁴ iMCD without TAFRO symptoms is termed iMCD-not otherwise specified (iMCD-NOS). Currently, IPL is considered to be included in the iMCD-NOS and is a less heterogeneous disease concept.¹⁵

This review explains how this heterogeneous group of diseases was formed by summarizing the historical background in order to help understand the complicated disease concept. In addition, this review emphasizes iMCD, and describe its diagnostic criteria and histological findings based on the latest reports.

HISTORICAL BACKGROUND OF CD

The history of CD is summarized in Figure 1.

I. The first description of CD

In 1954, Castleman and Towne first described a 40-year-old man who presented with fever, weakness, and nonproductive cough, and was found to have a large mediastinal mass on chest X-ray.¹ Subsequently, Castleman described a series of twelve additional patients with enlarged mediastinal lymph nodes that resembled thymic tumors grossly and microscopically.² The two major histological features of these lesions were hyperplasia of lymphoid follicles and marked capillary proliferation with endothelial hyperplasia. These intrafollicular capillaries had thick hyalinized walls, and disease with these features is the current entity of HV-UCD.

Later, in 1970, Flendrig reported a different type in which mature plasma cells infiltrated the interfollicular area.³ In 1972, Keller and Castleman *et al.* analyzed 81 cases and established the two histological types, HV and PC.⁴ They reported that the PC-type was rare, with only 9/81 cases, and was more often associated with systemic symptoms, which improved with the removal of the lesion.

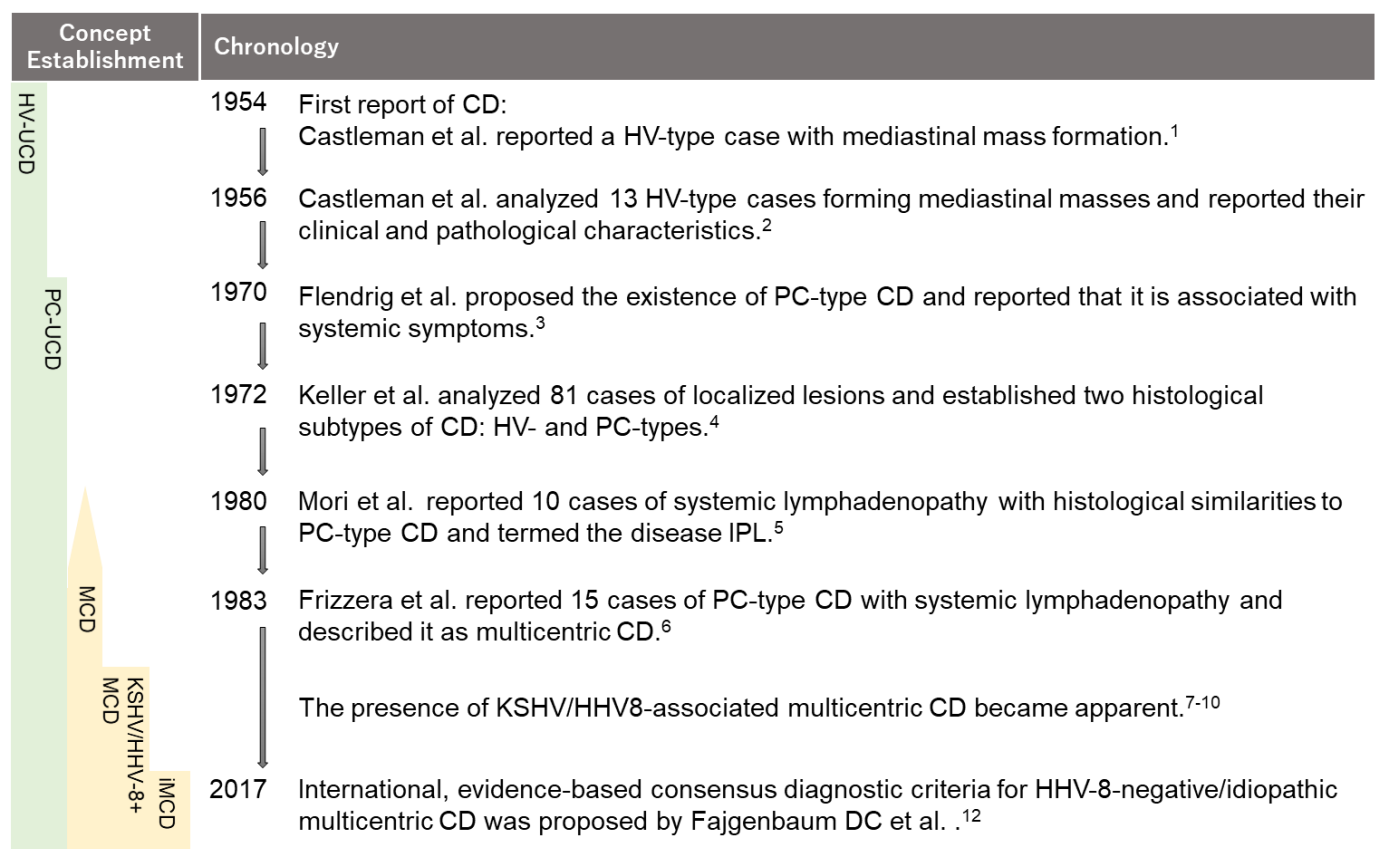


Fig. 1. Chronological history of Castleman disease (reference numbers: 1-10, 12).

Abbreviations: CD, Castleman disease; HV, hyaline vascular; PC, plasma cell; UCD, unicentric CD; iMCD, idiopathic multicentric CD; Kaposi sarcoma associated herpesvirus/human herpes virus 8.

II. MCD

Both HV- and PC-type CD described by Castleman *et al.* and Keller *et al.* were localized types and were associated with asymptomatic to mild symptoms.^{2,4} In 1983, Frizzera *et al.* defined MCD by reporting 15 cases with histological features similar to PC-type CD, presenting with generalized lymphadenopathy and systemic symptoms.⁵ Among these cases, there were two cases associated with Kaposi's sarcoma, suggesting that the cases included the equivalent of what is now termed KSHV/HHV8-associated MCD. In addition, some of the cases they reported exhibited clinical and laboratory findings characteristic of systemic lupus erythematosus (SLE), Sjögren's syndrome, or both.¹⁶ Thus, these cases may be regarded as ill-defined autoimmune diseases.^{11,17} Thus, MCD has been a heterogeneous group.

In the early 1980s, with the increasing AIDS epidemic, the association between Kaposi's sarcoma and MCD was recognized by clinicians, and the frequent coexistence of the two diseases was described.⁷⁻⁹ The etiology and pathogenesis of MCD were first linked to KSHV/HHV8 in 1995 when Soulier *et al.* detected KSHV/HHV8 sequences in all human immunodeficiency virus (HIV)-positive MCD cases and 41% of HIV-negative MCD.¹⁰ This led to the establishment of the disease entity "KSHV/HHV8-associated MCD".

III. IPL

In 1980, Mori *et al.* reported 10 cases with systemic lymphadenopathy and marked polyclonal hypergammaglobulinemia, demonstrating non-neoplastic plasma cell proliferation on lymph node biopsy, and termed them IPL.⁵ Mori *et*

al. noted the following characteristics of IPL; 1: polyclonal hypergammaglobulinemia without M-protein, 2: systemic superficial lymphadenopathy, with a high degree of plasma cell proliferation on histology but without destruction of lymph node architecture, and 3: exclusion of known diseases associated with hypergammaglobulinemia such as infections, collagen diseases, hyperthyroidism, allergic diseases, hepatitis, liver cirrhosis, Hodgkin lymphoma, and non-Hodgkin lymphoma. The article also compared the clinicopathological features of PC-type UCD and IPL, noting the similarities in pathological mechanisms.

The 10 cases of IPL reported by Mori *et al.* were more homogeneous than the cases reported by Frizzera *et al.*, as Mori *et al.* strictly excluded mimickers, such as autoimmune diseases, and all 10 cases followed indolent and uniform clinical courses.

In 2008, Kojima *et al.* reported that there are at least two subtypes of PC-type iMCD, corresponding to IPL and non-IPL, the latter being more likely to exhibit thrombocytopenia, fluid retention, positive autoantibodies, and relatively marked clinical symptoms.¹¹ Kojima *et al.* also noted that non-IPL may be an ill-defined autoimmune disease.

Based on these considerations, IPL is considered to be a part of the current PC-type iMCD, and is a more homogeneous entity (Figure 2).^{12,15} The concept of IPL may help better understand iMCD and extract more uniform cases for recent genetic analysis.

IV. The emergence of the concept of iMCD

After KSHV/HHV8 was identified as one of the etiological agents of MCD, the role of viruses in MCD pathogenesis

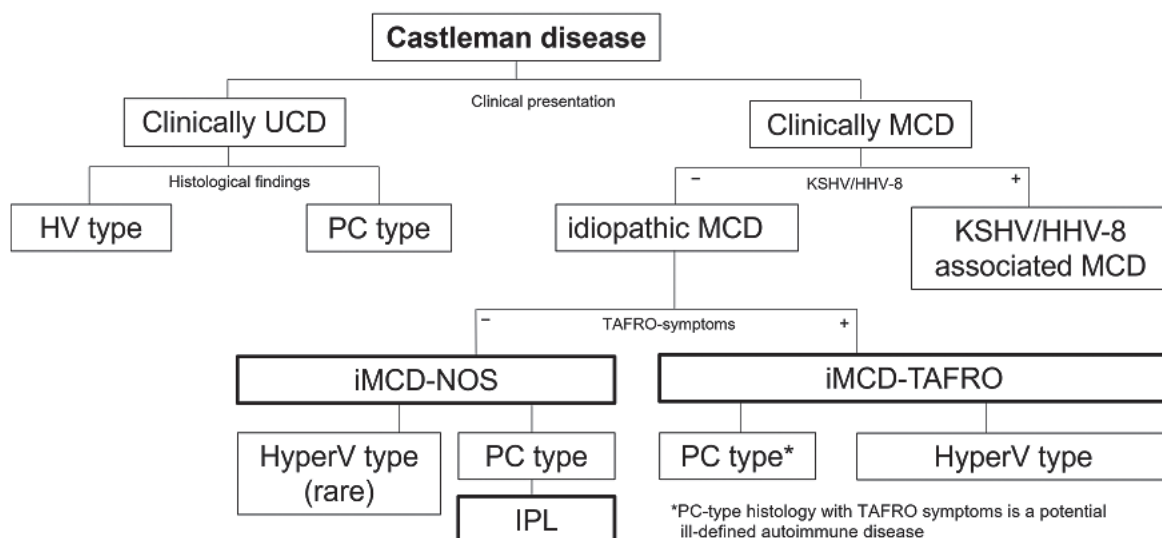


Fig. 2. Classification of Castleman disease (CD).

CD is divided into several subtypes according to its clinical presentation, histological findings, and etiology. iMCD itself encompasses a heterogeneous group of diseases. iMCD with TAFRO symptoms has been established as an independent entity, and it usually shows hypervascular-type histology. iMCD without TAFRO-symptoms is defined as iMCD-NOS, and usually shows plasma cell-type histology with varying degrees of vascularization.

Abbreviations: UCD, unicentric CD; MCD, multicentric CD; HV, hyaline vascular; PC, plasma cell; iMCD, idiopathic MCD; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin changes; KSHV/HHV-8, Kaposi sarcoma associated herpesvirus/human herpes virus 8; TAFRO, thrombocytopenia, anasarca, myelofibrosis, renal dysfunction and organomegaly; NOS, not otherwise specified; HyperV, hypervascular; IPL, idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia.

was highly investigated; however, the etiology of KSHV/HHV8-negative MCD (iMCD) has remained obscure and the concept itself was not established until recently. Between 2015 and 2016, a working group of pathologists and clinicians led by Dr. Fajgenbaum reviewed 244 cases with clinical data and 88 lymph node tissue specimens to develop the first international consensus diagnostic criteria for iMCD in 2017.¹²

This consensus on clinicopathological diagnostics led to the standardization of diagnosis and improved algorithms for clinical management.

OVERVIEW OF CLASSIFICATION OF CD

Eventually, over nearly 70 years, the term CD came to include heterogeneous conditions with different etiologies, and clinical and histological presentations. The current subtype classification of CD is summarized in Figure 2.

CD is divided into several subtypes according to its clinical presentation, histological findings, and etiology. According to the number of involved lymph node areas, CD can be classified into two subtypes: UCD and MCD. UCD involves only one lymph node region and is usually asymptomatic, whereas MCD is associated with systemic symptoms and multiple lymph node involvement. UCD can be further divided into two subtypes (HV-type and PC-type) based on histological features, with the former being the majority (74.4 - 91.4%).^{4,19-21}

MCD is divided according to KSHV/HHV8 infection status. In KSHV/HHV8-related MCD, viral infection signals lead to excessive cytokine production, and cause clinical and pathological abnormalities. In KSHV/HHV8-negative MCD, some cases of PC-type can be found in association with POEMS syndrome, a paraneoplastic syndrome caused by an underlying plasma cell neoplasm.²²⁻²⁵ The CD-like histology in the lymph nodes of patients with POEMS syndrome is thought to be caused by cytokines produced by the underlying monoclonal plasma cell population.²⁶⁻²⁸ The other type of KSHV/HHV8-unrelated CD, excluding POEMS-associated MCD, is defined as iMCD. Although iMCD is currently considered a heterogeneous group of diseases with overlapping pathological and clinical features, iMCD with TAFRO symptoms has recently been established as an independent entity.^{13,29} iMCD with TAFRO symptoms typically presents with hypervascular (HyperV)-type histology, which is somewhat unique from iMCD-NOS.

Frizzera *et al.* proposed a “mixed type” of MCD, which is a mixture of the HV- and PC-type known at the time.³⁰ However, there are no clear criteria to define which features and extent are regarded as mixed type.^{15,16,30,31} Therefore, it may be better to not use the term “mixed type” to avoid confusion until the pathogenesis of each type of iMCD is further clarified by advanced analyses such as proteomics and genomics (presumed by the authors).

HISTOLOGICAL FEATURES

The histopathological findings observed in CD can occur under many reactive and neoplastic situations.¹² Therefore, the diagnosis of CD always requires clinical and laboratory findings. This is true for all subtypes of CD, but it is especially important in possible MCD patients. Potential mimics of CD include autoimmune diseases (rheumatoid arthritis, SLE, hemophagocytic lymphohistiocytosis, adult-onset Still disease), IgG4-related diseases, infectious diseases (acute Epstein-Barr virus infection, acute human immunodeficiency virus infection, and other viral infection), and malignancies (Hodgkin lymphoma, non-Hodgkin lymphoma, follicular dendritic cell sarcoma), among others.¹²

Immunoglobulin gene rearrangement and flow cytometry to investigate the clonal lymphoid cell proliferation help to exclude malignancy. A diagnosis of CD should be made using whole excisional lymph node biopsies and small materials, such as needle biopsies, are insufficient for diagnosis.

Unicentric Castleman disease

UCD, HV-type

HV-type constitutes the majority (74.4%-91.4%) of UCD.^{4,19-21} It occurs in individuals of a broad range of ages, and equally in men and women.^{20,32-35} As the lesions are localized to a single location and lack symptoms, they are often detected incidentally on imaging studies. The site and frequency of disease may vary depending on access to imaging studies. At the time of the report by Castleman and Keller *et al.*, the overwhelming majority of cases were of mediastinal origin detected on chest radiography. However, we recently reported that intra-abdominal and retroperitoneal origins are more frequent than previously thought.³⁶ In the cohort of 38 cases, the most common location was the abdominal cavity (34.2%), followed by mediastinal (23.7%) and retroperitoneal (15.8%) regions.³⁶ In the abdominal cavity, the mesenteric origin is the most common and is often clinically excised due to suspicion of gastrointestinal stromal tumor, leiomyoma, or neurogenic tumor. The mean size of the lesions is approximately 5.0 cm,^{35,36} which is larger than the lymph nodes observed in MCD.

Histologically, the involved lymph nodes exhibit varying degrees of follicular and interfollicular changes (Figure 3). The follicles may increase in density and the germinal center is atrophic. There is increased vascularity with hyalinization of the vessel wall in the interfollicular area (Figure 3a). Based on CD21 immunostaining, the follicular dendritic cells are retained and prominent (Figure 3b). The sclerotic blood vessels penetrate the atrophic germinal center (Figure 3c), and they may appear radial and dendritic in shape (Figure 3d). Small and mature lymphocytes are arranged in concentric circles around the germinal center (Figure 3c), exhibiting an onion-skin-like appearance. This concentric mantle zone and the penetrating blood vessels in the germinal center are sometimes referred to as the lollipop appearance (Figure 3c). Twinning, in which two or more germinal centers are com-

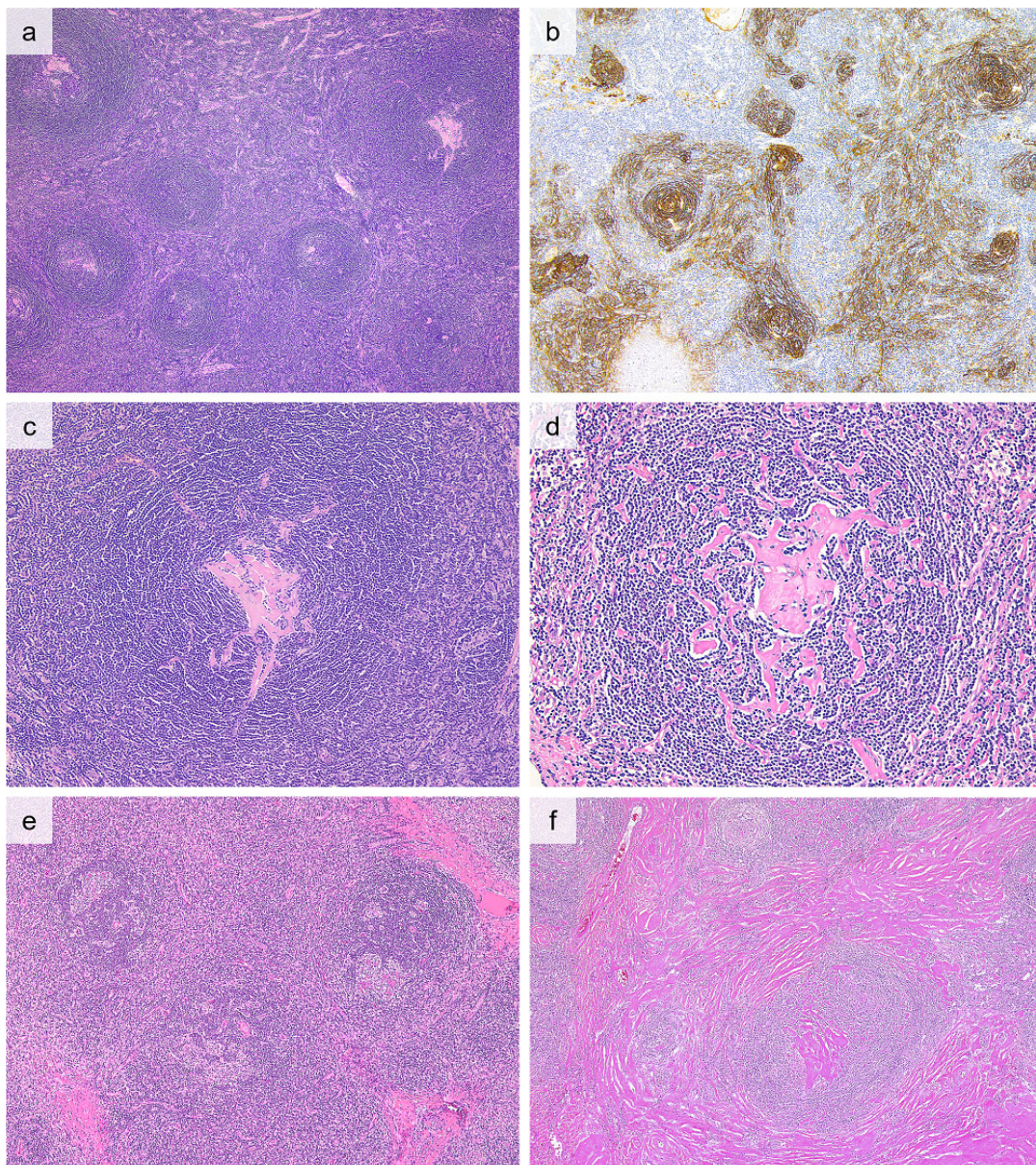


Fig. 3. Histological findings of HV-UCD. (*a*, H&E) Follicles with an atrophic germinal center and increased vascularity in the interfollicular area are shown. (*b*, CD21 staining) CD21 immunostaining reveals prominent follicular dendritic cells. (*c* and *d*, H&E) The atrophied germinal center is penetrated by blood vessels with hyalinized walls, and the vessels often show radial or dendritic morphology. (*e*, H&E) Altered follicle structures with expanded mantle zones are shown. (*f*, H&E) Broad hyalinized collagen fibers are present in the lesion.

bined and surrounded by lymphocytes in the mantle zone, and progressive transformation of the germinal center-like pattern, which presents as an altered follicle structure with expanded mantle zone, are sometimes observed (Figure 3e). Broad hyalinization (Figure 3f) and thick hyalinized collagen fibers surrounding large blood vessels are also observed, and these hyalinized areas may be accompanied by calcification. Scattered polyclonal plasma cells may be present but are not widely aggregated. In approximately one-fourth of cases, atypical dendritic cells can be found in the germinal center (Figure 4a) and interfollicular area (Figure 4b), often multinucleated and resembling Warthin-Finkeldey cells.³⁶ These cells are positive for follicular dendritic cell markers such as CD21 (Figure 4c) and CXCL13 (Figure 4d).^{15,36-40}

UCD, PC-type

PC-type accounts for the minority of cases (9-26%) of UCD^{3,4,19-21} and demonstrates prominent plasmacytosis similar to that observed in MCD. PC-type UCD (PC-UCD) exhibits a localized distribution of lesions, but the mass is often composed of several adjacent lymph nodes rather than a single node.^{4,30} Unlike HV-UCD, almost all PC-UCD patients present with symptoms, such as fever, night sweats, fatigue, and abnormal laboratory findings, but they are not as marked as in MCD.^{15,41} Patients with PC-UCD often benefit from resection of the lesion, being distinct from MCD.^{21,35} Infiltrating plasma cells are generally polyclonal,³⁰ but may exhibit light chain restriction, predominantly lambda

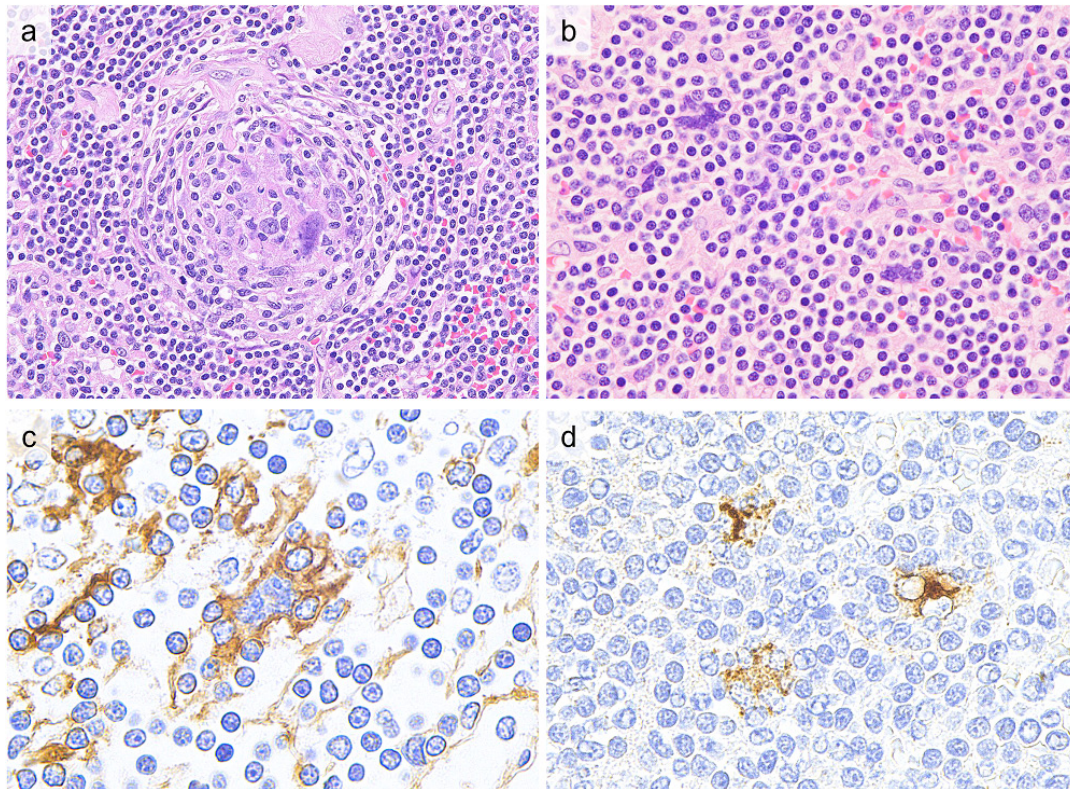


Fig. 4. Atypical dendritic cells in the germinal center and interfollicular area are seen in HV-UCD. (*a* and *b*, H&E) Multinucleated giant cells resembling Warthin–Finkeldey cell are observed in the germinal center area and interfollicular area. These cells are positive for CD21 (*c*) and CXCL13 (*d*) and correspond to dysplastic dendritic cells.

expression.⁴²⁻⁴⁴

Multicentric Castleman disease

CD variant of POEMS syndrome

POEMS syndrome was first described by Crow *et al.* in 1956 and is characterized by polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin changes.⁴⁵ POEMS syndrome is a paraneoplastic syndrome due to an underlying plasma cell neoplasm, and bone marrow biopsy reveals monoclonal plasma cell populations in two-thirds of cases.^{28,46} Nearly all POEMS cases are λ chain restricted.⁴⁶ Lymphadenopathy with CD-like histology is observed in 11-30% of patients with POEMS syndrome, and is thought to be caused by cytokines produced by monoclonal plasma cells.⁴⁷⁻⁵¹ The histological image of lymph node biopsy of a patient with a plasma cell neoplasm associated with POEMS syndrome is shown in Figure 5. Plasma cell proliferation and hypervascularization were observed in the interfollicular area, and lambda light chain restriction was present on *in situ* hybridization (Figure 5). Cytokines proposed to drive POEMS symptoms include vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-12, transforming growth factor-1 β , and tumor necrosis factor- α .^{26,28,52} Among cases of POEMS syndrome with CD-like histology, there are some without underlying clonal plasma cell proliferation disorder,²² which can be diagnosed as CD variant of POEMS.⁵³

It is essential to exclude POEMS syndrome when PC-type CD-like histology is noted, as treatment of the underlying neoplasm is required. To exclude POEMS syndrome, a thorough history and physical examination, blood tests (measurement of VEGF),^{26,54-57} and radiographic assessment of the bones⁵⁸⁻⁶⁰ may be helpful.

KSHV/HHV8-associated MCD

Some cases of MCD, especially in immunosuppressed patients due to HIV infection, are caused by KSHV/HHV8 infection, leading to systemic cytokine dysregulation.^{18,61,62} IL-6 plays a major role in the pathogenesis of MCD with or without KSHV/HHV8 infection. KSHV/HHV8 encodes a viral homologue of an early lytic antigen, viral IL-6, which binds directly to the IL-6 receptor (gp130) without requiring its coreceptor gp80, and can stimulate the known human IL-6-induced signaling pathways via the shared cytokine signaling receptor gp130.⁶³

Lymph node histology is similar to iMCD and is characterized by abundant polyclonal plasmacytosis in the interfollicular area.⁶⁴ The structure of the lymph node is preserved, and interfollicular vascularization is observed. In the mantle zone surrounding the follicles, abundant medium to large plasmablasts are observed (Figure 6a), which are positive on immunostaining for HHV8 (monoclonal antibodies to the latent nuclear antigen-1) (Figure 6b).⁶⁵ These KSHV/HHV8-infected plasmablasts express lambda restricted

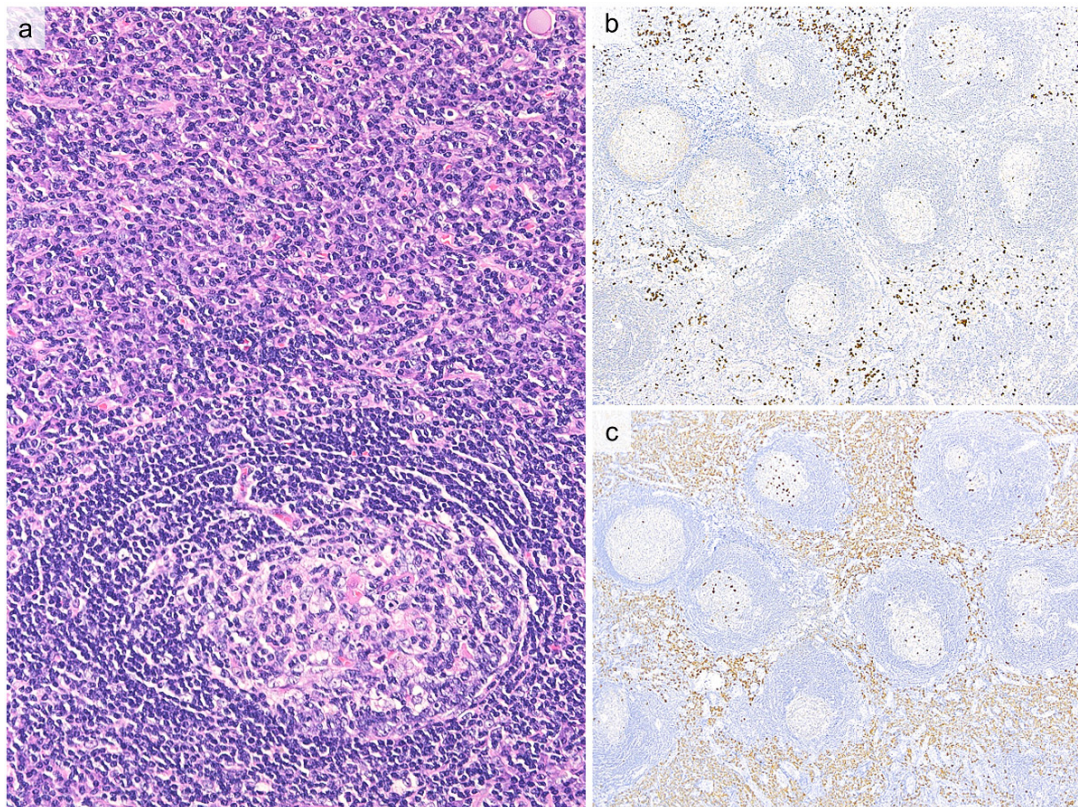


Fig. 5. Lymph node histology in a patient with a plasma cell neoplasm associated with POEMS syndrome. (*a*, H&E) Prominent plasma cell proliferation and hypervascularization in the interfollicular area are observed. *In situ* hybridization for Igκ (*b*) and Igλ (*c*) revealed lambda light chain restriction.

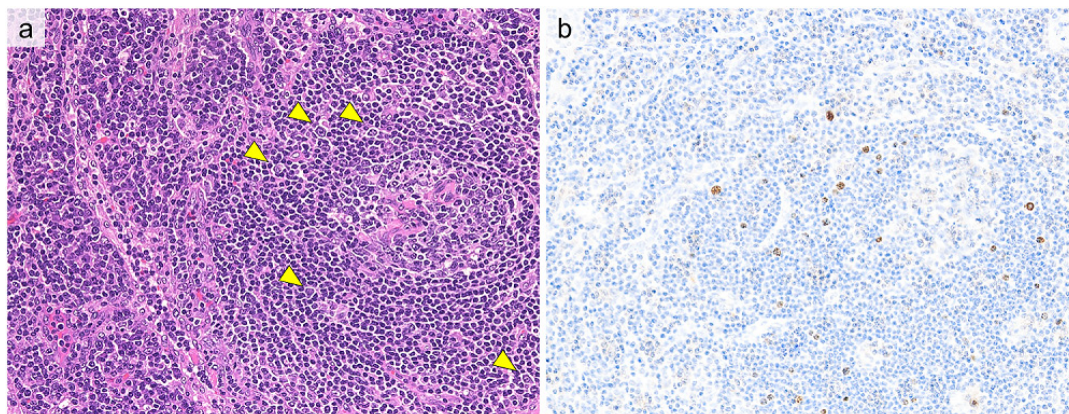


Fig. 6. Histological findings of KSHV/HHV8-associated MCD. (*a*, H&E) Increased number of plasmablasts (arrowheads) in the mantle cell zones is observed. (*b*, HHV8-encoded latent nuclear antigen-1) Immunostaining for HHV8 highlights the infected plasmablasts.

IgM.³¹

Idiopathic MCD

Dysregulation of cytokines plays an important role also in iMCD pathogenesis, but the etiology that drives this process has not been elucidated in iMCD. iMCD itself is a heterogeneous group of diseases that can be further classified into several subtypes. In this section, we will discuss the differences in clinical manifestations and histology of some conditions currently considered as subtypes of iMCD.

1) iMCD-TAFRO

TAFRO syndrome is a recently recognized systemic disease, named after the acronym for its characteristic symptoms: thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly. The average age of patients with TAFRO syndrome is 50-59 years, with no apparent difference between males and females.^{13,14,66} Its development in young patients (14-22 years old) has also been reported.⁶⁶⁻⁶⁹ TAFRO syndrome has an acute to subacute clinical course

and is sometimes fatal.^{13,14}

It is important to note that TAFRO syndrome is not a specific type of iMCD, but is a heterogeneous clinical entity that can also be caused by conditions such as malignancy, autoimmune disorders, and infections (Figure 7).¹⁴

After excluding other conditions that may cause TAFRO syndrome, the diagnosis of iMCD-TAFRO should be made by a combination of clinical and histological findings. The validated international definition of TAFRO-iMCD proposed in 2021 requires histological findings from a lymph node biopsy specimen that are compatible with iMCD-TAFRO, in addition to all four clinical criteria (thrombocytopenia, anasarca, fever or hyperinflammatory status, and organomegaly).¹⁴

In patients with iMCD-TAFRO, lymph node enlargement is reported to be mild, usually with diameters ranging from 6 mm to 14 mm (median 9 mm).¹³ Histologically, the involved lymph nodes exhibit marked vascular proliferation with plump endothelial cells in the interfollicular areas, with a lesser degree of plasmacytosis (Figure 8a-8d).¹⁵ The histology typically observed in iMCD-TAFRO is called HyperV-type.¹² Although the HyperV-type of iMCD shares some features with the HV-type of UCD, the terms are distinguished in the context of clinical presentation (MCD vs. UCD). Another distinction is that lymph nodes involved in MCD with HyperV-type histology are often only slightly enlarged, whereas those with HV-type UCD form a larger localized mass. There is no association with viral infections such as KSHV/HHV8 and Epstein-Barr virus.

In bone marrow specimens of iMCD-TAFRO, hypercellular marrow with megakaryocytic hyperplasia is observed (Figure 8e, 8f). Megakaryocytes exhibit slight atypia, with micro- and multi-separated nuclear megakaryocytes. Silver impregnation staining highlights reticulin fibrosis (Figure 8g).

For comparison, histological images of lymph nodes in a patient with SLE accompanied by TAFRO symptoms are

shown (Figure 9). Abundant plasma cell infiltration is atypical for iMCD-TAFRO, but is rather similar to the features of PC-type iMCD. It has been reported that patients with rheumatoid arthritis and SLE present with lymphadenopathy resembling CD histologically,^{11,70,71} and Frizzera *et al.* also noted that iMCD may include undiagnosed autoimmune diseases.^{6,16,17} These autoimmune diseases need to be excluded in the diagnosis of iMCD.

2) iMCD-NOS

iMCD without TAFRO (iMCD-NOS) generally presents as PC-type with marked plasmacytosis in the interfollicular area. The degree of vascularization is variable, and any of the four levels of vascularization (normal, mildly, moderately, and very prominent) defined by the consensus diagnostic criteria¹² can be observed. PC-type histology is characterized by sheet-like proliferation of mature plasma cells between expanded interfollicular area, and hemosiderin deposition is observed to varying degrees (Figure 10a, 10b).⁷² The plasma cells are polyclonal. Russel bodies, which are intracellular inclusions filled with globulin aggregates, are frequently observed (Figure 10c). IL-6 staining is strongly positive in interfollicular plasma cells and cells of the germinal center (Figure 10d).⁷³

In patients with PC-type iMCD, polyclonal hypergammaglobulinemia due to the overproduction of IL-6 often results in high serum IgG4 levels and increased numbers of IgG4-positive plasma cells in tissues. Therefore, differentiation between PC-type iMCD and IgG4-related diseases may be difficult in some cases.^{74,75} Several clinical and histological findings are useful in differentiating between the two groups:^{73,76,77} high serum levels of CRP, IgA, and IgM, an increased number of IgA-positive cells, and strong IL-6 positivity in tissue are supportive of PC-type iMCD, whereas increased eosinophils in tissue are supportive of IgG4-related disease.

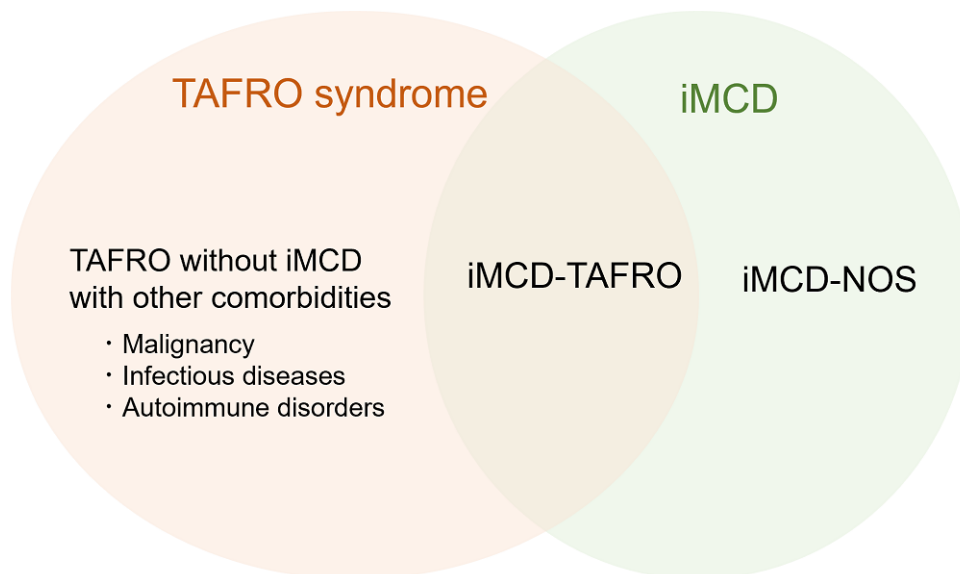


Fig. 7. Concepts of TAFRO syndrome and iMCD-TAFRO. “TAFRO syndrome” includes iMCD-TAFRO and a group associated with other comorbidities.

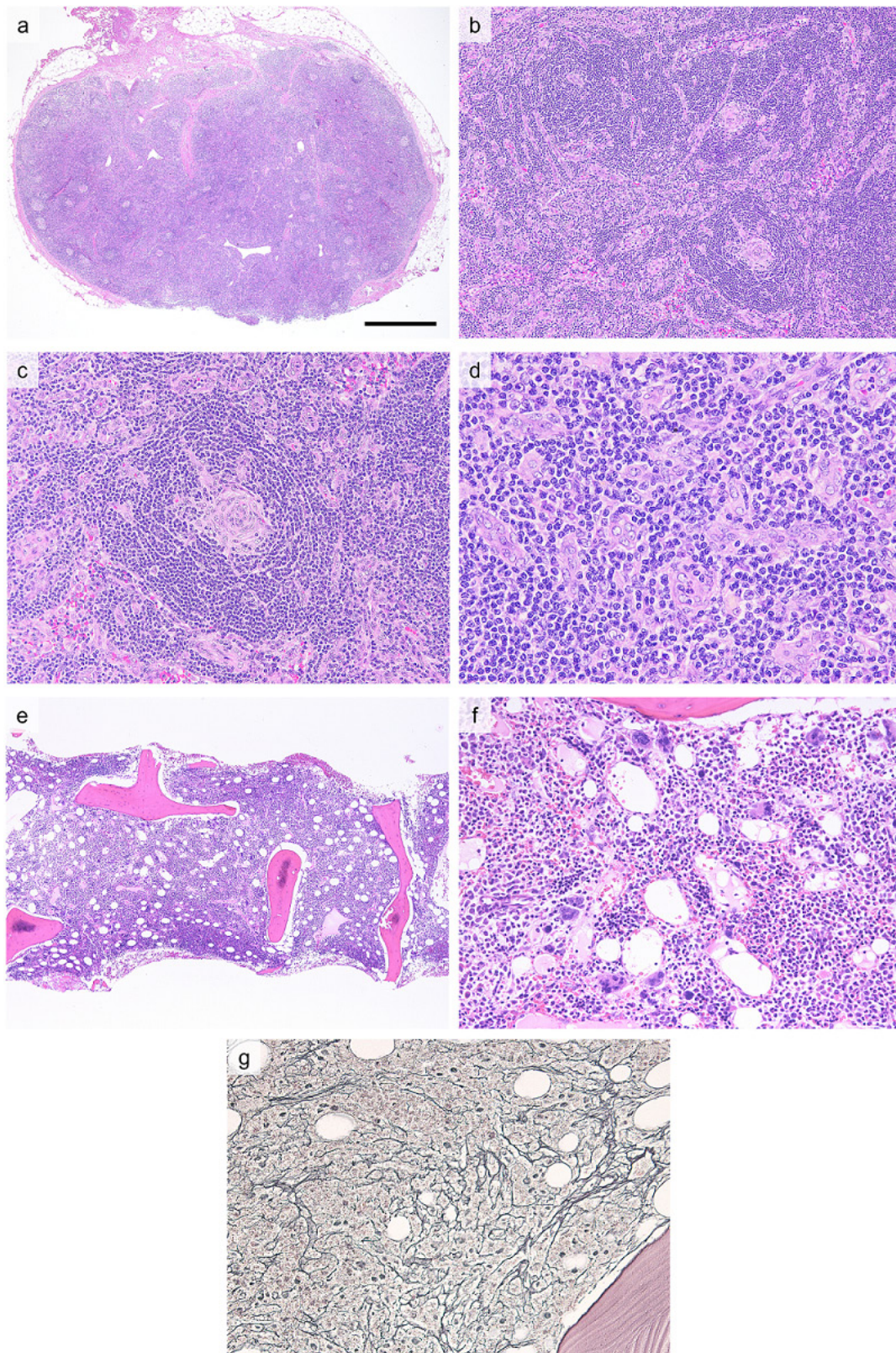


Fig. 8. Histological findings of iMCD-TAFRO. (*a*, H&E) The involved lymph node is mildly enlarged (scale bar: 1000 μm). (*b-d*, H&E) Regressed germinal center and marked hypervascularization with plump endothelial cells in the interfollicular area are shown. Hyalinization of vessel wall is not apparent. (*e*, H&E) Hypercellular bone marrow. (*f*, H&E) Megakaryocytic hyperplasia is observed. (*g*, Silver impregnation staining) Silver staining highlights reticulin fibrosis.

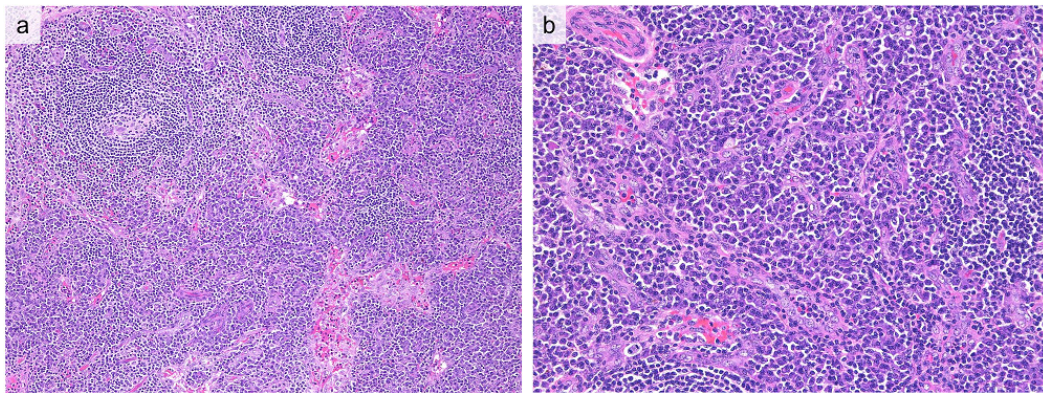


Fig. 9. Histological findings in a patient with systemic lupus erythematosus. (*a* and *b*, H&E) Lymph node biopsy revealed an atrophic germinal center. In the expanded interfollicular area, prominent vascular proliferation and sheet-like plasmacytosis are observed.

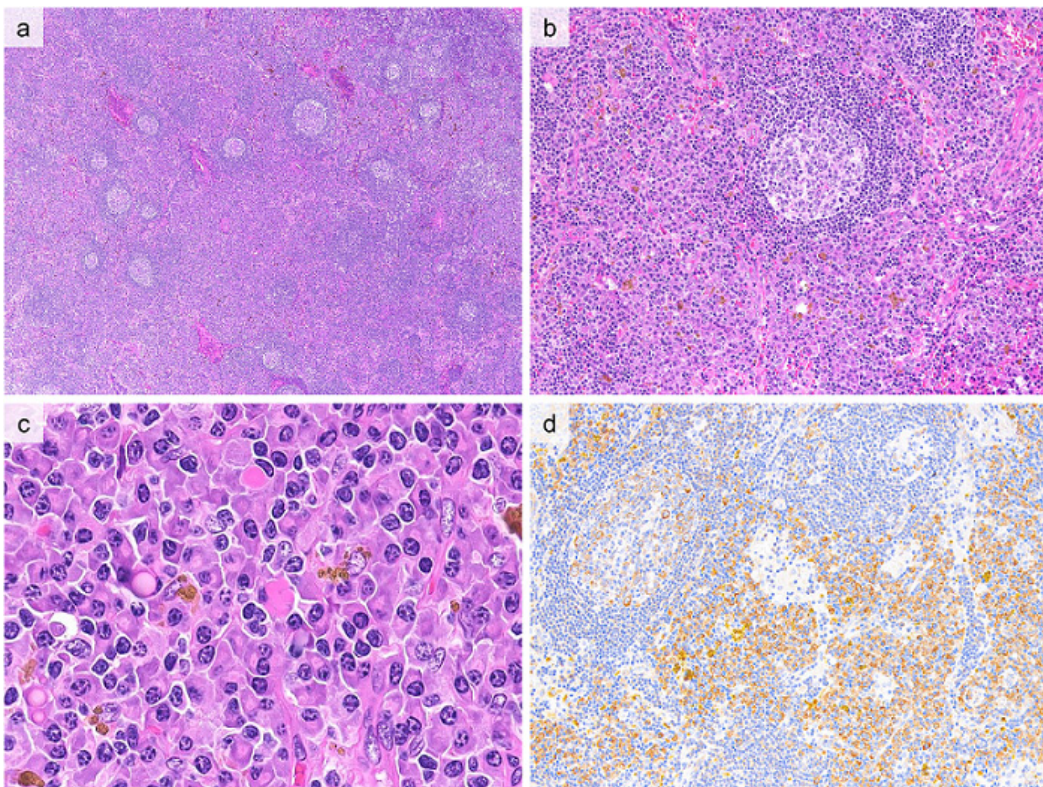


Fig. 10. Histological findings of iMCD-NOS (plasma cell-type iMCD). (*a*, H&E) The interfollicular area is markedly expanded. (*b*, H&E) Sheet-like plasma cell proliferation is seen in the expanded interfollicular area, accompanied by hemosiderin deposition. (*c*, H&E) Russel bodies (center of the image) are often observed, reflecting increased immunoglobulin production. (*d*, IL-6 immunostaining) Immunostaining of IL-6 is strongly positive in plasma cells in the interfollicular area and in B cells in the germinal center.

In summary, iMCD can be histologically divided into PC-type and HyperV-type, with the latter commonly presenting TAFRO symptoms. PC-type iMCD consists of at least two clinically distinct groups: those with and without TAFRO symptoms. PC-type iMCD with TAFRO symptoms is included in the so-called TAFRO syndrome, and is frequently associated with positive autoantibodies such as anti-cardiolipin and anti-SS-A antibodies.⁷⁸ However, such cases are possibly autoimmune-related disorders that do not meet the existing classification criteria.¹¹ PC-type iMCD without

TAFRO symptoms demonstrates hypergammaglobulinemia and thrombocytopenia, corresponding to IPL. The classification of iMCD according to histological findings and the presence of TAFRO symptoms is summarized in Table 1.

CONCLUSIONS

The term CD has been used to cover a spectrum of diverse lymphoproliferative disorders, with different clinical manifestations, disease etiologies, and histopathological fea-

Table 1. Current classification of idiopathic multicentric Castleman disease (iMCD)

	Plasma cell-type		Hypervascular-type
TAFRO symptoms	Absent	Present	Present
Pleural effusion/ascites	Absent	Present	Present
Platelet count	Increased ~ Normal	Decreased	Decreased
Hypergammaglobulinemia	Present	Usually absent	Absent
Autoantibody positivity rate	Low	High (especially aCL, anti-SSA/Ro)	Low
Histological findings	Lymph nodes	Lymph nodes	Lymph nodes
	Normal to hyperplastic GC Expanded interfollicular area Sheet-like plasmacytosis	Expanded interfollicular area Vascular proliferation Plasma cell proliferation	Atrophic GC Prominent vascular proliferation Plump endothelial cells Bone marrow Megakaryocytic hyperplasia Reticulin fibrosis
	Corresponding to IPL	Corresponding to iMCD-TAFRO	
		*Note that plasma cell-type histology with TAFRO symptoms is a potential ill-defined autoimmune disease	

Abbreviations: TAFRO, thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly; aCL, anticardiolipin antibody; GC, germinal center; IPL, idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia.

tures. UCD and HHV8-related MCD are considered clinicopathologically homogeneous disease entities, whereas iMCD is considered heterogeneous. In this review, we summarized the complex disease concept by explaining its historical background. iMCD can be classified into more uniform units when combined with pathomorphological findings and the presence of TAFRO symptoms. In the future, molecular analysis is expected to improve our understanding of the pathogenesis and pathophysiology, and the development of therapies. In this regard, accurate classification of diseases based on detailed clinical and histological findings will help select targets for the analysis.

AUTHOR CONTRIBUTIONS

Conceptualization, M.F.N. and Y.S.; writing—original draft preparation, M.F.N.; writing—review and editing, Y.N., A.N., Y.S.; funding acquisition, Y.S.; Supervision, Y.S. and T.Y. All authors read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors report no potential conflicts of interest.

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