

Castleman's disease: one disease, multiple etiologies

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Abstract

Castleman disease (CD) comprises a heterogeneous group of rare lymphoproliferative disorders characterized by similar morphological features in nodal biopsies. Since Benjamin Castleman's initial description in 1956, our understanding of CD has progressed substantially. The intricate mechanisms underlying the four recognized subtypes of multicentric CD (MCD) have been studied thoroughly during recent decades. Major disease contributors include the identification of certain viral infections, namely human herpes virus-8 (HHV-8) and HIV; and the discovery of molecular and genetic mechanisms driving disease development and progression and the consequent development of biological targeted therapies, notably siltuximab and rituximab. The CD has been associated with autoimmune, autoinflammatory, and hematological disorders. Along with epidemiological data, the current classification of CD encompasses unicentric CD and MCD. MCD is further subdivided into HHV-8-associated MCD, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin (POEMS)-associated MCD, and idiopathic MCD (iMCD), which includes thrombocytopenia, anasarca, fever, reticulín TAFRO-iMCD, and iMCD-not-otherwise-specified (iMCD-NOS). While these subtypes share common histological and similar clinical manifestations, they represent distinct conditions. In this review, we discuss the differences in epidemiology, pathophysiology, histology, clinical presentation, and treatment for all distinct CD subtypes. We focus on the role of viral infections in CD development and epidemiology. We finally end by acknowledging areas where further research is needed to uncover the complex nature of CD.

Keywords

Antiretroviral therapy. HHV-8. Kaposi's sarcoma. HIV. Interleukin-6. Lymphoma.

Introduction

Castleman disease (CD) encompasses a heterogeneous group of rare lymphoproliferative disorders characterized by shared morphological features in nodal biopsies¹. The unicentric form was first described in 1956 by Castleman et al., based on a series of cases

initially misdiagnosed as thymomas². By 1984, systemic or multicentric cases had been documented, along with their association with Kaposi's sarcoma (KS)³. In 1995, the presence of human herpes virus 8 (HHV-8) was identified in patients with HIV and CD, including those without KS⁴. At the end of the 1990s, CD was described alongside a monoclonal gammopathy with typical clinical manifestations, nominated as

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POEMS syndrome – polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes¹.

By the late 2000s, a particular profile of idiopathic multicentric CD (iMCD), which included thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly was characterized and named as thrombocytopenia, anasarca, fever, reticulin fibrosis (TAFRO)-iMCD⁵. Since then, our understanding of CD has substantially improved, in part due to the development of biological therapies that target cytokines, such as interleukin (IL)-6, and rituximab⁶⁻⁸. Their efficacy has shed light on the pathological mechanisms behind the disease. Furthermore, the discovery of the role that certain viral infections play, namely HHV-8 and HIV, and the association with certain autoimmune, autoinflammatory, and hematological diseases, has led to a new classification for the disease¹. It is now understood that CD is most likely a common histological picture, with similar clinical and pathological manifestations, shared by distinct etiological conditions.

According to the underlying cause, physiopathology, and clinical manifestations, CD can be classified as unicentric CD (UCD) and MCD. The latter includes three different diseases, HHV-8-associated MCD, POEMS-associated MCD, and iMCD, which can be further divided into TAFRO-iMCD and iMCD-not-other-wise-specified (iMCD-NOS)^{5,9}. Figure 1 records graphically the updated CD classification. In this review, we describe the differences in the epidemiology, physiopathology, histology, clinical manifestations, and treatment for different CD subtypes, with a special focus on the role of certain viral infections.

CD epidemiology: current landscape and perspectives

The CD has historically been challenged from an epidemiological perspective^{1,10,11}. A dedicated international disease code was not implemented until 2016 with the ICD-10. The diagnostic criteria for iMCD were not established until 2017⁹. As a result, earlier data were fragmentary and often reliant on scattered case series and reports⁶. These limitations have been, especially, pronounced in low and middle-income countries, as well as in sub-Saharan Africa, where reliable incidence and prevalence estimates remain scarce⁶. Furthermore, an inherent limitation of existing literature is that a large proportion of cases originate from the same geographical regions, raising questions about the influence of ethnicity on clinical manifestations and whether current data may be generalized worldwide¹².

Consequently, precise figures on the global incidence, prevalence, and proportion of each CD subtype remain uncertain.

Recent large-scale studies have begun to clarify the current epidemiology of CD, underscoring key regional and subtype-specific differences. In the United States, a 2022 study that used the newly implemented ICD-10 code and updated iMCD diagnostic criteria found a national incidence of 5.5-5.8 cases per million inhabitants during the 2017-2018 period, lower than in previous estimates¹³. Approximately 35% of patients were classified as having UCD and 65% as MCD. Among all CD cases, iMCD alone accounted for 57.4%, whereas only 4% tested positive for HHV-8 and 5% for HIV, suggesting that previous studies might have overestimated HHV-8 rates by disproportionately reporting HHV-8-positive cases¹³. In contrast, the largest retrospective study to date, conducted in China in 2023, comprising 1,634 patients, found a greater proportion of UCD (55.7%) compared with MCD (44.3%)¹¹. Of those classified as MCD, 80.7% were iMCD, and 19.3% were categorized as “aMCD,” representing patients who lacked significant inflammation or hypercytokinemia but still had multicentric lymphadenopathy. Notably, only 1.64% of patients in this Chinese MCD cohort were HHV-8-positive, and all patients were HIV-negative. Moreover, among the iMCD group, the severe TAFRO variant made up only 7% of cases, being the rest classified as iMCD-NOS¹¹. These discrepant results in the USA and China point out a distinctive geographic pattern.

The epidemiology of CD continues evolving alongside advances in diagnosis and treatment¹⁴. For MCD, the introduction of rituximab as an effective drug and more recently the approval of siltuximab have led to great advances in therapeutic options⁷. As effective treatments emerge and patient outcomes improve, the disease will likely be better characterized and tracked over time.

The epidemiological picture of CD has become increasingly clear due to standardized diagnostic criteria, a dedicated ICD-10 code, and recently published data using these tools¹¹. Nevertheless, key questions remain regarding regional variation, particularly in areas with limited health-care infrastructure¹. Altogether, advances in subtype-specific therapies may further shift the distribution of CD and improve outcomes¹⁴. Identifying risk factors, defining genetic and immune correlates, and elucidating potential ethnic differences are crucial steps to better understand and treat CD¹.

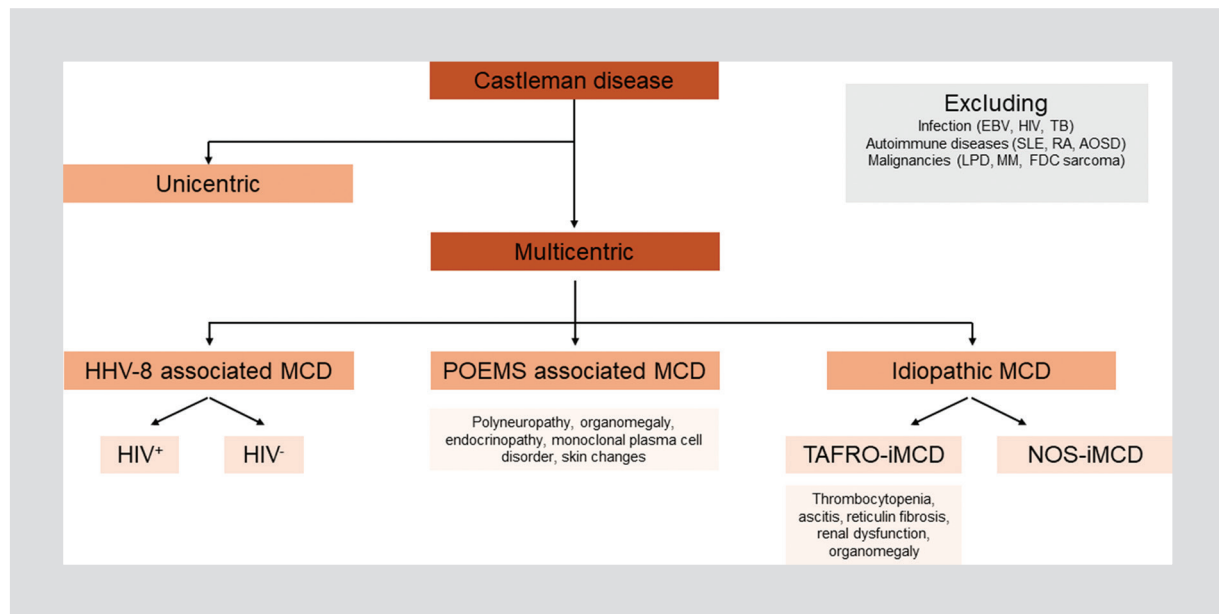


Figure 1. Classification of Castleman disease. EBV: Epstein–Barr virus; TB: tuberculosis; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; AOSD: adult-onset Still disease; LPD: lymphoproliferative disorders; MM: multiple myeloma; FDC: follicular dendritic cell; HHV-8: human herpesvirus 8; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes; TAFRO: thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly; NOS: not otherwise specified. Adapted from Fajgenbaum et al.⁹

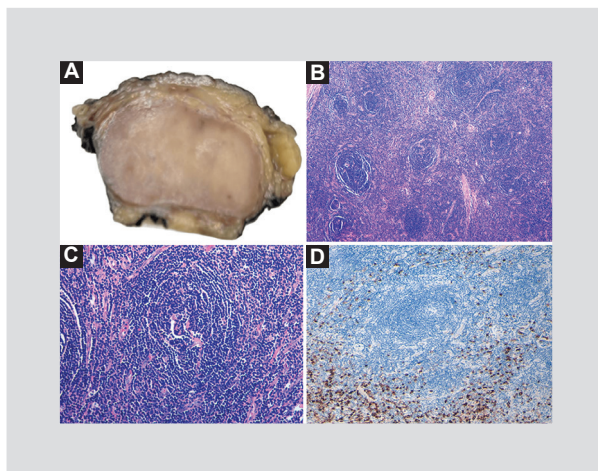


Figure 2. Lymph node with Castleman disease. **A:** retroperitoneal lesion of 7 cm. **B:** regressed germinal centers. **C:** a follicle shows a hyaline-vascular lesion (also known as a lollipop lesion). **D:** plasmacytosis (interfollicular plasma cells CD138+).

Histopathology of CD

The diagnosis of all types of CD requires a complete biopsy of an affected lymph node (Fig. 2A). Until 2017, the histology of CD was classified into three simple categories always requiring clinical/radiographic correlation: Hyaline vascular (HV), plasmocytic, and mixed¹. However, advances in the understanding of the clinical manifestations and epidemiology of the disease led to a

different categorical classification for the MCD¹. While the histopathology of the different subtypes of CD shares some common characteristics, each form is also associated with distinct features that emphasize their differences and unique pathological roots. Consequently, a work group of expert pathologists and clinicians proposed, in addition to criteria for the diagnosis of iMCD, a scoring system that examines specific histopathological features to provide a more nuanced classification⁹. This system assesses five parameters: regression of germinal centers (Fig. 2B), follicular dendritic cell (FDC) prominence, vascularity (Fig. 2C), hyperplastic germinal centers, and plasmacytosis (Fig. 2D); each one is scored from 0 to 3. Each of these parameters is used to then classify the histopathological subtype of the biopsy. Grade 2 or 3 regressed germinal centers or plasmacytosis is required for the diagnosis of iMCD, associated with clinical, laboratory, and exclusion criteria fulfilled.

In both clinicopathological subtypes, the morphological findings are a spectrum ranging from hyper-vascular to mixed to plasmocytic, and they overlap with those seen in UCD, MCD associated with POEMS syndrome, and Kaposi Sarcoma Herpesvirus (KSHV)/HHV8-associated MCD¹⁵. Hence, as there is no clear link between pathological classification and treatment (specifically IL-6 blockade) or prognosis, histopathologic findings are of limited use¹⁶. Moreover,

when evaluated by different experts, the same cases are often not classified as the same subtype, with only 23% agreement in one study, highlighting the complexity of classifying the disease histologically¹⁷.

Findings related to HV and hypervascular subtypes

HV UCD shows follicles increased in number and size. Germinal centers are lymphocyte-depleted and enriched in FDCs, occasionally with dysplasia. Mantle zones are expanded with lymphocytes arranged in concentric (onion-skin) rings around germinal centers¹⁵. These are infiltrated by hyaline-vascular lesions (lollipop lesions). Fibrous bands compartmentalize the surrounding lymph node structure, and the interfollicular areas often show increased vascular proliferation⁹.

While the HV pattern dominates in UCD, a similar hypervascular (or HyperV) histology is also observed in iMCD, particularly in cases with TAFRO syndrome^{9,16}. However, in iMCD-TAFRO, the node architecture is typically less disrupted, and sinus integrity is preserved, highlighting subtle differences between localized and systemic disease presentations¹⁶. This latter group of patients who present with iMCD and HV-like histopathologic features are considered HyperV instead of HV, to avoid confusion⁹.

Findings related to plasmocytic subtype

Plasmocytic UCD presents interfollicular zones that are densely infiltrated by sheets of plasma cells (PCs) accompanied by follicles that range from large and hyperplastic to small with regressive changes¹⁵. Lymph node architecture and FDCs are preserved (unlike in the hyaline UCD subtype)¹⁷. Hyaline-vascular follicles may be present, but they are poorly formed¹⁵.

A distinguishing feature in HHV-8-associated MCD is the presence of large immunoblasts or plasmoblasts KSHV/HHV8-positive by immunostaining, within the mantle zones often forming small clusters (microlymphomas) or larger sheets. These HHV-8-infected cells express monotypic IgM- λ and viral proteins like viral IL-6, driving systemic inflammatory symptoms¹.

In plasmocytic histology linked to iMCD and POEMS, the PCs remain polyclonal, but cytokine dysregulation, particularly of IL-6, plays a significant pathogenic role¹⁶. This pattern is frequently seen in systemic forms of CD, such as HHV-8-associated MCD, iMCD, and POEMS-associated MCD¹. This subtype rarely appears in UCD but often reflects systemic disease processes¹⁶.

Findings related to mixed subtype

The mixed subtype represents a convergence of HV and plasmocytic features, creating a histological pattern incorporating regressed germinal centers characteristic of HV and extensive interfollicular plasmocytosis typical of the plasmocytic variant¹. However, some authors argue against this term, as there are no clear criteria to define it, and they recommend not using the term "mixed type" to avoid confusion¹⁶. The World Health Organization classifies both subtypes together as mixed/plasmocytic subtypes.

UCD

Etiopathogenesis

UCD involves a single lymph node or group of nodes within one lymphatic region¹. Most recent data suggest that UCD is more likely a clonal neoplastic process, with the probable cell of origin being stromal cells, specifically FDCs⁸. No association has been found with viral infections (HIV or HHV-8)¹⁸. A recent study utilizing next-generation sequencing on lymph node tissue from UCD cases revealed mutations in platelet-derived growth factor receptor β 9 (PDGFR- β 9), with gain-of-function conferring proliferative and survival advantages, in nearly 20% of cases; these mutations are located in CD45- cells, which likely represent stromal cells⁸.

Epidemiology

The unicentric variant accounts for 35-55% of all CD cases^{11,13}. UCD can be seen at any age, but it is often diagnosed in the fourth decade, with a slightly higher incidence reported in women¹⁰.

Clinical findings and diagnosis

While UCD is often an incidental finding, some patients may present with compression-related symptoms, and a subset (especially those with plasmocytic or mixed histopathological subtypes, accounting for 10-20% of cases) may experience inflammatory symptoms like those seen in iMCD⁶. The diagnosis of UCD generally does not impact life expectancy⁸. However, it is associated with an increased risk of developing some serious complications, such as paraneoplastic pemphigus (PNP), a severe autoimmune blistering disorder often associated with the HV subtype.

PNP frequently manifests alongside progressive and potentially fatal bronchiolitis obliterans (BO). In addition, UCD has been associated with FDC sarcoma, and occasionally with lymphomas, including Hodgkin and non-Hodgkin types¹¹.

With respect to approaching UCD, it is essential to perform a differential diagnosis to distinguish it from certain infectious diseases, autoimmune conditions, PC neoplasms, lymphomas, and stromal and vascular neoplasms, given the clinical and histological similarities and their prognostic and therapeutic implications⁸. Therefore, it is essential to study a broad and high-quality histological sample. Unfortunately, there is no specific biomarker for UCD available to date. However, vascular endothelial growth factor (VEGF) and PDGF could be used to discern UCD from other lymphoproliferative disorders¹¹.

Management

The preferred treatment for UCD is complete surgical excision, which results in the resolution of symptoms and associated abnormalities in approximately 90% of cases¹. The presence of PNP and BO warrants prompt management since resection of the UCD lesion has been shown to often halt or reverse their progression⁸. In cases involving large, vascular lymph nodes, or when surgery is not feasible, presurgical embolization may be used. After surgery, follow-up should include computed tomography scans, physical examinations, and laboratory tests at 12-month intervals⁸. If symptoms persist or new or recurrent lymphadenopathies appear after complete lymph node removal, alternative diagnoses, and histopathological review, should be considered.

For patients experiencing compression-related symptoms, signs of systemic inflammation, such as night sweats, fevers, anorexia, weight loss, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or the recurrence of symptoms after surgical removal, medical treatments may be effective after reconfirming the diagnosis^{6,8}. Options include rituximab alone or in combination with steroids, or anti-IL-6 monoclonal antibody therapy.

For patients with unresectable but asymptomatic disease or mild, non-severe compressive symptoms, watchful observation is an appropriate option⁶. Observation is also a suitable choice for patients who become asymptomatic following treatment with rituximab/steroids or anti-IL-6 monoclonal antibodies. However, for those who remain symptomatic, radiotherapy or embolization may be tried.

Additional treatment options include immunomodulatory or immunosuppressive therapies, such as corticosteroids, cyclosporine A, or sirolimus⁸.

MCD

The multicentric variant of CD comprises a highly diverse group of entities, including HHV-8-associated and POEMS-associated forms, as well as idiopathic forms with TAFRO or pure variants (iMCD-NOS), which share a relatively common hallmark histopathology (Fig. 1)¹⁶. However, despite the apparent similarities, the term makes reference to three distinct conditions with significant clinical and, more importantly, etiopathogenic differences, as illustrated in table 1¹⁹. Understandably, the differences in causal mechanisms and pathophysiology explain why treatment varies drastically depending on the type of MCD: HHV-8-associated MCD, POEMS-associated MCD, or iMCD¹, as shown in figure 3.

Overall, MCD is a disease with a slight male predominance, typically presenting in the fifth or sixth decade of life^{1,6,20}. Given the systemic (lymphoproliferative and inflammatory) nature of the condition, MCD has a severe clinical course characterized by lymphadenopathy across multiple regions, general symptoms, and organ dysfunction caused by excessive release of cytokines and/or inflammatory proteins^{1,11}. The most common manifestations of MCD at diagnosis include fever, night sweats, unintentional weight loss, fluid accumulation, and organomegaly, although these symptoms vary depending on the disease subtype.

HHV-8-associated MCD

HHV-8, also known as KSHV, is the etiologic agent of HHV-8-associated MCD, a lymphoproliferative disorder with systemic manifestations caused by uncontrolled HHV-8 replication^{19,21}. Only a small percentage of individuals infected with HHV-8 eventually develop MCD, and it is believed that immunodeficiency, most notably HIV infection, is a necessary risk factor for disease development^{1,21}. Indeed, approximately 50% of HHV-8-MCD cases occur in HIV-positive individuals, highlighting the critical role of co-infection as a disease driver²¹. Overall, the link between CD, especially HHV-8-associated MCD, and other infections highlights the key role of viruses in the pathogenesis of lymphoproliferative disorders²².

Table 1. Main differences of multicentric Castleman disease types

Features	HIV+ HHV-8+ MCD	HIV—HHV-8+ MCD	POEMS-associated	iMCD-TAFRO	iMCD-NOS
Age onset	Fourth decade	Seventh decade	Fifth decade	Fifth decade	Fifth to sixth decade
Organomegaly	*/absent	*†/absent	†	†	†
Systemic symptoms	Fever, hemophagocytic syndrome, fluid effusions	Fever, hemophagocytic syndrome, fluid effusions.	Fever, hepatomegaly, splenomegaly, extravascular volume overload	High fever, hepatomegaly, splenomegaly	High fever, hepatomegaly, splenomegaly
Markers	‡CRP, ESR, ferritin, hIL-6, vIL-6, IL-10, hypergammaglobulinemia, hypoalbuminemia, anemia, thrombocytopenia, pancytopenia	†CRP, ESR, ferritin, hIL-6, vIL-6, IL-10, hypergammaglobulinemia, hypoalbuminemia, anemia, thrombocytopenia, pancytopenia	†IL-12, IL-6, monoclonal gammopathy, CRP, ESR, ferritin, thrombocytosis, VEGF, anemia	†IL-6, CRP, ESR, ferritin, Thrombocytopenia, normal/mild gammaglobulins, anemia, procalcitonin, liver dysfunction	†IL-6, CRP, ESR, ferritin, thrombocytosis, polyclonal hypergammaglobulinemia, anemia, liver dysfunction
Complications and related diseases	Lymphoproliferative disorders Kaposi sarcoma, KICS		Peripheral neuropathy, endocrine (thyroid, adrenal, pituitary, and gonadal axes), abnormal pulmonary function tests, papilledema, sclerotic bone lesions	Anasarca, renal dysfunction, intravascular coagulation, fibrinolysis, malignancies	Peripheral neuropathy, immune thrombocytopenia, autoimmune hemolytic anemia, interstitial lung disease, malignancies, and lymphoma
Clinical course	†Aggressive	*Aggressive	†Aggressive	†Aggressive	Variable
Diagnosis	Nodal LANA-1 or serum HHV-8 PCR		Polyradiculoneuropathy + monoclonal gammopathy + VEGF/sclerotic bone lesion	Reticulin fibrosis Hyper/homoplasia of megakaryocytes High alkaline phosphatase	Exclusion
Treatment	Rituximab, steroids Etoposide/doxorubicin Valganciclovir? ART	Rituximab, steroids Etoposide/doxorubicin Valganciclovir?	MM therapy of bone lesions, radiation, ASCT. iMCD-like therapy if not bone lesions	Siltuximab Tocilizumab Steroids Rituximab, CIN	Siltuximab Tocilizumab Steroids Rituximab

*Mild.

†Moderate.

‡Marked.

MCD: multicentric Castleman disease; HHV-8: human herpesvirus 8; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TAFRO: thrombocytopenia, anasarca, fever, reticulocytosis, and organomegaly; NOS: not otherwise specified; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; KICS: Kaposi sarcoma-associated herpesvirus inflammatory cytokine syndrome; LANA-1: latency-associated nuclear antigen; PCR: polymerase chain reaction; ART: antiretroviral therapy; VEGF: vascular endothelial growth factor; MM: multiple myeloma; ASCT: autologous stem cell transplant; CIN: calcineurin inhibitor; iMCD: idiopathic multicentric Castleman disease.

Data compiled from Dispenzier et al.,¹ Faigenbaum et al.,⁴⁵ Caballero et al.,⁴² and Nishimoto et al.⁴¹

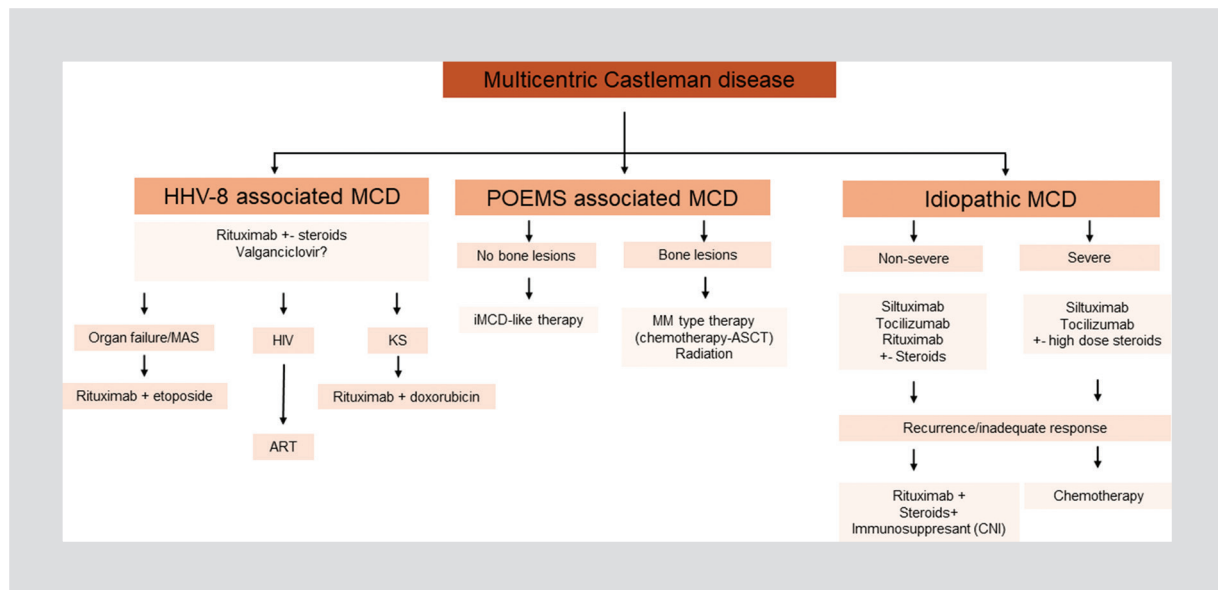


Figure 3. Management of multicentric Castleman disease. MCD: multicentric Castleman disease; HHV-8: human herpesvirus 8; MAS: macrophage activation syndrome; ART: antiretroviral therapy; KS: Kaposi sarcoma; iMCD: idiopathic multicentric Castleman disease; ASCT: autologous stem cell transplant; CIN: calcineurin inhibitor (data adapted and compiled from Jurczynski et al.³⁴ Van Rhee et al.⁷ and Pria et al.²⁸).

Etiopathogenesis

Uncontrolled HHV-8 infection is recognized as the principal etiological driver of this entity¹. HHV-8-associated MCD is a rare condition that affects both HIV-positive and HIV-negative individuals, with immunosuppression serving as the critical factor in disease progression^{20,23}. While HHV-8-associated MCD may develop in individuals with controlled HIV replication under antiretroviral therapy, immunosuppression markedly amplifies the severity of MCD²³.

The lifecycle of HHV-8 is central to its pathogenicity, as the virus alternates between latency and lytic phases⁶. During latency, HHV-8 expresses a limited number of proteins, such as the latency-associated nuclear antigen 1 (LANA-1), which is essential for maintaining the viral genome within infected cells. In the lytic phase, the virus produces a broader array of proteins, including viral IL-6 (vIL-6), viral interferon regulatory factor 1, and viral protein kinase, which are directly implicated in the pathogenesis of HHV-8-MCD²⁴. These lytic proteins facilitate viral replication and evasion from the host's immune response, therefore enabling persistent infection and contributing to the inflammatory and oncogenic milieu noticed in HHV-8-associated MCD⁶.

A defining feature of HHV-8-associated MCD is the overexpression of vIL-6, a homolog of human IL-6 (hIL-6), which is a key driver of disease progression⁶. vIL-6 is

predominantly expressed in plasmoblasts surrounding lymphoid follicles and serves as a cornerstone in sustaining the inflammatory microenvironment²⁵. Concurrently, hIL-6 is overexpressed in FDCs within germinal centers and in PCs, further amplifying the pro-inflammatory and pro-proliferative signals. Both vIL-6 and hIL-6 enhance B-cell proliferation and plasmoblast survival, with vIL-6 demonstrating a unique ability to directly activate the gp130 subunit of the IL-6 receptor independently of the gp80 subunit⁶. This direct activation contributes significantly to the cytokine dysregulation seen in HHV-8-MCD.

The cytokine profile in HHV-8-associated MCD extends beyond IL-6. It also includes elevated levels of IL-10, IL-1 β , tumor necrosis factor α (TNF- α), and VEGF, all of which act as significant contributors to disease progression²⁶. These cytokines, many of which are upregulated by viral proteins such as LANA-1, contribute to the hallmark clinical manifestations of HHV-8-associated MCD, such as systemic inflammation, anemia, fever, and hypoalbuminemia^{1,25}. VEGF is of particular importance, as it serves as a pivotal factor in angiogenesis, a process that not only characterizes the histopathology of HHV-8-associated MCD but also is involved in its progression⁶.

Epidemiology

Based on its etiopathogenesis, the epidemiology of MCD depends on the prevalence of HHV-8 and HIV

within the general population. In sub-Saharan Africa, where the HHV-8 rate in some countries can exceed 50%, there is a strong association between MCD and HIV co-infection, leading to a greater incidence of HHV-8-associated MCD⁶. In 2008, a large prospective database in the United Kingdom, which included 56,202 HIV-positive individuals, compared the incidence of HHV-8-associated MCD with KS in the pre-antiretroviral (ART) era (1983-1996), the early ART era (1997-2001), and the late ART era (2002-2007). The incidence of HHV-8-associated MCD was 2.3, 2.8, and 8.3/10,000 PY, respectively, representing a significant increase over time, with an overall incidence of 4.3/10,000 PY²³. The explanation for this increase is uncertain, with factors such as greater awareness of CD, a higher index of suspicion, and improved diagnostic accuracy being suggested. Hypothetically, subtle forms of immune dysfunction in HIV, despite being controlled under ART, along with a complex interaction between HIV and HHV-8, could be significant²³.

In HIV-positive individuals with HHV-8-associated MCD, the average age at diagnosis typically ranges from 30 to 40 years, with the majority being white males²⁰. By contrast, HIV-negative patients with MCD are typically diagnosed much later in life, around the age of 60, possibly due to age-related immune decline or other factors that predispose to viral replication and immune dysregulation^{20,23}.

Clinical findings and diagnosis

HHV-8-associated MCD is clinically characterized by recurrent episodes of systemic inflammation, hypoalbuminemia leading to fluid effusions, and complications arising from underlying infections, including Epstein-Barr virus (EBV) infection (Table 1)^{6,22,27}. Patients typically exhibit significant systemic inflammation, with elevated levels of inflammatory mediators or markers such as ESR, CRP, hIL-6, vIL-6, and IL-10, accompanied by increased viral loads in peripheral blood mononuclear cells¹. These findings indicate active viral replication and immune dysregulation. In HIV-positive individuals, immunosuppression facilitates viral reactivation and lytic gene expression, leading to more severe manifestations, including fever, splenomegaly, and hemophagocytic syndrome²⁶. In contrast, in HIV-negative patients, other immunosuppressive conditions, such as age-related immune decline or underlying deficiencies, may contribute to unchecked viral replication and disease progression¹. Laboratory findings consistently reveal elevated acute-phase reactants, hypergam-

maglobulinemia, and hypoalbuminemia. Furthermore, HIV-positive patients with HHV-8-associated MCD experience the poorest prognosis among all MCD subtypes, demonstrating the severe impact of co-infection on disease course and outcomes²⁰.

Among the lymphoproliferative complications of MCD, particularly in individuals co-infected with HIV^{28,29}, the most challenging are the development of plasmoblastic lymphoma (HHV-8 positive large B-cell lymphoma), HHV-8-associated germinotropic lymphoproliferative disorder, and primary effusion lymphoma (PEL). These disorders are characterized by neoplastic plasmoblastic cells with complex immunophenotypes, often co-infected with EBV^{22,27}. HHV-8 plays a central role in their pathogenesis through viral proteins such as vIL-6, which drives VEGF expression and angiogenesis, and LANA-1, which supports tumor cell survival³⁰.

Kaposi sarcoma-associated herpesvirus inflammatory cytokine syndrome (KICS) is another related complication, marked by high viral loads and cytokine profiles similar to MCD but with faster progression and overlapping symptoms such as fever and weight loss³¹. In addition, KS frequently coexists with HHV-8-associated MCD, driven by shared mechanisms of angiogenesis and cytokine-mediated inflammation⁶. These overlapping pathologies underscore the intricate interplay between HHV-8, immune dysregulation, and lymphoproliferative disorders.

The diagnosis of HHV-8-associated MCD is based on clinical features and histology consistent with MCD, with either a positive LANA-1 test on the lymph node biopsy or a positive polymerase chain reaction (PCR) for circulating HHV-8 confirming the diagnosis of HHV-8-associated MCD⁹.

Treatment

Therapeutic options for HHV-8-associated MCD have evolved significantly, with rituximab-based therapy serving as the cornerstone (Fig. 3)^{28,32}. Rituximab, a monoclonal antibody targeting CD20, was identified as a highly effective treatment in 2007²⁹. Treatment strategies, however, are tailored based on the patient's disease severity, comorbidities, and the presence of coexisting conditions, such as Kaposi sarcoma or life-threatening organ dysfunction³³. In people living with HIV, ART is a critical component of treatment²⁸. Therefore, ART should be initiated or continued in all patients, with close attention to potential pharmacological interactions between ART and cancer-directed therapies²⁸.

For patients with life-threatening disease, poor performance status, or concurrent KS, combination therapy with rituximab and chemotherapy is recommended³². In cases of organ failure without KS, etoposide is the most frequently added chemotherapy agent to enhance treatment efficacy^{28,32}. Conversely, for patients with concurrent KS, pegylated liposomal doxorubicin is typically used alongside rituximab, as this approach addresses both conditions simultaneously^{28,32}. Notably, while rituximab is highly effective, it may exacerbate or unmask KS, necessitating careful monitoring and the addition of doxorubicin in such cases.

Despite the high response rates and improvement of long-term survival achieved with rituximab-based therapy, relapse is common²⁸. However, it can usually be managed successfully with additional courses of rituximab²⁸. Maintenance therapy has emerged as a promising strategy to prevent relapse, with a combination of valganciclovir and zidovudine demonstrating improved outcomes. Despite it, as first-line therapy, anti-herpesvirus agents such as valganciclovir and zidovudine have shown limited success, with responses that are often short-lived³³.

Efforts to target HHV-8 vIL-6, a key contributor to HHV-8-associated MCD pathogenesis, have included the use of tocilizumab, an IL-6 receptor antagonist³³. Unfortunately, single-agent tocilizumab has demonstrated only transient responses, with limited efficacy observed in small studies³³.

An additional challenge in managing HHV-8-associated MCD is the elevated risk of lymphoma, which affects up to 20% of patients and stands as a leading cause of mortality in this population. Commonly observed lymphomas include PEL and plasmoblastic lymphoma, both of which are associated with poor prognoses²⁷. These lymphomas are often positive for HHV-8 and require tailored therapeutic approaches. Furthermore, KS frequently coexists with HHV-8-associated MCD, either preceding, coinciding with, or following the diagnosis. Its management should be integrated into the treatment of HHV-8-associated MCD, particularly with the use of combination therapy^{22,27}.

Despite substantial advances in the management of HHV-8 MCD, challenges remain in confronting relapses, mitigating lymphoma risk, and addressing the coexistence of KS, highlighting the necessity for continued research and personalized patient care²².

POEMS-associated MCD

HHV-8 negative MCD can sometimes occur simultaneously with POEMS syndrome, a term derived from a

systemic disorder caused by monoclonal and polyclonal PCs through a mechanism that is not yet fully understood³⁴⁻³⁹.

Etiopathogenesis

Monoclonal PCs are considered the primary etiological drivers of POEMS-associated MCD^{35,36,39,40}. However, the precise distinctions in cellular and cytokine profiles between POEMS-associated MCD and classic POEMS syndrome remain uncertain. In classic POEMS syndrome, excessive production of VEGF and IL-12 due to somatic mutations in PCs is well established as a critical driver of disease pathology^{35,36}. Notably, these cytokines appear to be produced at levels even higher than those observed in iMCD, suggesting a unique pathogenic signature in POEMS-related disorders³⁵. Both cytokines are implicated in vascular permeability, angiogenesis, and immune dysregulation, processes that are central to the clinical manifestations of POEMS-associated MCD³⁶. Increased levels of VEGF and other proinflammatory cytokines, including IL-1 β , TNF- α , and IL-6, also seem to play an important role in POEMS-associated MCD³⁵. The mechanisms linking somatic mutations in PCs to the excessive production of these cytokines remain a critical area for future research³⁹. Hypothetically these mutations might disrupt normal cytokine regulatory networks, leading to unchecked production of VEGF and IL-12, which in turn could drive systemic inflammation and organ dysfunction.

Epidemiology

The epidemiology of POEMS syndrome has not been thoroughly investigated^{34,38,40}. Diagnostic challenges, coupled with its low incidence, present significant obstacles to obtaining accurate estimates of its incidence and prevalence³⁸. Despite these limitations, studies suggest that MCD develops in POEMS syndrome in 11%-64% of cases³⁴. In addition, it is known that POEMS syndrome typically manifests around the fifth decade of life and is more prevalent in males, with a male-to-female ratio of approximately 1.5:2^{34,40}. A Japanese study estimated the prevalence at 0.3/100,000 inhabitants⁴⁰.

Clinical findings and diagnosis

POEMS syndrome does not strictly follow the clinical features included in the acronym (Table 1)¹. It typically

presents with polyneuropathy that begins with pain and hyperesthesia, progressing to symmetrical and ascending motor weakness³⁷. Elevated VEGF levels can lead to extravascular fluid overload, as well as mild to moderate renal dysfunction^{36,37}. Patients may also experience pulmonary abnormalities and subclinical cardiac dysfunction^{34,37}. Organomegaly is usually asymptomatic³⁷. Endocrinopathies, particularly hypogonadism, are common. Sclerotic bone lesions are also frequently observed. In addition, thrombosis may occur in about half of cases, sometimes serving as the initial manifestation and potentially leading to stroke due to VEGF-induced vasculopathy³⁴.

POEMS syndrome is primarily diagnosed using clinical criteria (Table 2)³⁴. The diagnosis requires the presence of both mandatory criteria, one of the three major criteria, and one of the six minor criteria.

The median survival of patients with POEMS syndrome who receive treatment is 13.7 years, while untreated cases are associated with a grim prognosis³⁷. The Japanese study reported a 10-year survival rate of 93%, whereas other studies have reported lower survival rates, including an 82% 10-year survival rate and a disease progression-free survival rate at 10 years of only 53%^{38,40}.

Management

The rarity of POEMS syndrome has led to the absence of standardized treatment guidelines, and therapeutic approaches are often adapted from existing schedules for iMCD (Fig. 3)³⁷. When bone lesions are present, treatment regimens typically follow those used for myeloma³⁴. In the absence of bone marrow involvement and with fewer than three bone lesions, the standard treatment is radiotherapy combined with corticosteroids and autologous stem cell transplantation (ASCT)³⁷. ASCT can be considered upfront or after induction chemotherapy, depending on the patient's clinical status and eligibility criteria³⁴. For individuals with bone marrow involvement or extensive bone lesions, high-dose melphalan with ASCT has been the cornerstone of treatment for over two decades^{1,34}. However, given their anti-angiogenic properties, immunomodulatory drugs such as thalidomide, lenalidomide, and bortezomib have rapidly gained prominence in POEMS syndrome treatment. Caution should be exercised with thalidomide and bortezomib due to their potential to induce or exacerbate neuropathy. This is why lenalidomide is currently the first-line treatment³⁷.

Table 2. Diagnostic criteria for POEMS syndrome

Mandatory (required)
1. Clonal plasma cell dyscrasia.
2. Polyneuropathy.
Major (at least one)
1. Castleman disease.
2. VEGF elevation.
3. Osteosclerotic lesions.
Minor (at least one)
1. Organomegaly: spleno-hepatomegaly, lymphadenopathy.
2. Endocrinopathy.
3. Extravascular volume overload: edema, pleural effusion, ascites.
4. Skin changes: hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, white nails.
5. Papilledema.
6. Polycythemia/thrombocytosis.

VEGF: vascular endothelial growth factor.

Adapted from Jurczyszyn et al.³⁴

iMCD

iMCD is a clinic-pathologically similar entity to HHV-8-associated MCD, but it lacks LANA-1 in lymph node tissue or circulating HHV-8. Therefore, it represents a completely distinct etiopathogenic condition^{1,6,20} (Fig. 1). At present, this group is further divided into TAFRO-associated iMCD and iMCD-NOS, with notable clinical differences (Table 1).

Etiopathogenesis

The etiology and pathogenesis of iMCD remain significantly less understood compared to HHV-8-associated MCD or POEMS-associated MCD. Several theories have been proposed to explain the underlying mechanisms driving iMCD^{1,18,41,42}. These include polyclonal lymphoproliferation and hypercytokinemia triggered by autoinflammatory or autoimmune mechanisms, paraneoplastic processes involving clonal cell populations, or an unidentified viral infection. However, despite extensive research efforts, none of these hypotheses have been definitively proven, highlighting the enigmatic nature of this disease¹⁹.

One of the most prominent features of iMCD pathogenesis is the presence of a cytokine storm^{5,41}. Elevated levels of circulating cytokines, particularly IL-6, are a hallmark of the disease, and clinical improvements with IL-6 inhibition underscore its critical role⁴¹.

This cytokine, which is produced by various inflammatory cells, fibroblasts, endothelial cells, and some cancer cells, has pleiotropic effects that influence immune regulation, inflammation, and hematopoiesis. Its overproduction mirrors observations in mouse models with elevated IL-6 levels, where the resulting phenotype closely aligns with the clinical features of iMCD⁴³. In addition to IL-6, other cytokines, and growth factors, including VEGF, IL-1, IL-2, chemokine CXCL13, and TNF- α , are implicated in iMCD pathogenesis⁴⁴. These mediators collectively contribute to the unique systemic inflammation, vascular abnormalities, and lymphoproliferation noticed in iMCD.

Beyond cytokines, recent evidence points to the involvement of dysregulated signaling pathways^{41,44}. Aberrant activation of pathways such as the mammalian target of rapamycin (mTOR), signal transducer and activator of transcription 3 (JAK-STAT3), and type I interferon (IFN- γ) signaling has been observed in iMCD⁴⁵. These pathways, which play central roles in cellular growth, survival, and immune modulation, may act as amplifiers of the disease's pathogenic processes, offering potential therapeutic targets for future interventions⁴⁵.

The possibility of a viral etiology for iMCD has been an area of research, given the well-established role of HHV-8 in HHV-8-associated MCD¹⁹. However, recent findings challenge the plausibility of this hypothesis¹⁸. In a study utilizing a hybrid RNA sequencing and virome capture platform to analyze samples from 25 patients with CD, no new viruses were identified¹⁸. Among the 11 patients with iMCD and 12 with UCD, HHV-8 was notably absent, and no other vertebrate viruses were discovered. These results suggest that, unlike HHV-8-associated MCD, iMCD is unlikely to be driven by a viral infection. The lack of association with known or novel viruses represents a critical divergence between the pathogenesis of iMCD and HHV-8-associated MCD, redirecting the focus toward other potential mechanisms¹⁸.

Although no significant increase in TAFRO syndrome or iMCD cases was observed during the COVID-19 pandemic, isolated reports suggest a potential link between the cytokine storm induced by COVID-19 or its vaccine and the onset of these conditions⁴⁶. TAFRO hyperinflammatory states, driven by elevated cytokines like IL-6, VEGF, and CXCL10, are also central to severe COVID-19 and its complications, highlighting overlapping mechanisms⁴⁶. In patients with long COVID, elevated levels of inflammatory cytokines persist⁴⁶. Post-COVID-19 immune dysregulation, including conditions such as

multisystemic inflammatory syndrome in children and adults, shares clinical features with TAFRO syndrome, suggesting a potential link⁴⁶. In addition, mRNA vaccines, which elicit strong immune responses, have been associated with elevated cytokines such as IL-6, IFN- γ , and CXCL10⁴⁷, potentially acting as triggers for TAFRO syndrome in predisposed individuals⁴⁶. Further research is needed to clarify the relationship between COVID-19, mRNA vaccines, and TAFRO syndrome development, as well as to explore the role of autoimmunity and cross-immune reactions in its pathogenesis⁴⁸.

Autoimmune processes provide another compelling explanation for the pathogenesis of iMCD^{1,42,49}. The clinical and pathological overlap between iMCD and autoimmune conditions supports this hypothesis. Approximately one-third of iMCD patients exhibit autoantibodies⁴², and genetic studies have revealed an increased frequency of polymorphisms in the IL-6 receptor (IL-6R) among iMCD patients compared to healthy controls⁴⁹. These findings suggest that alterations in immune regulation and cytokine signaling may predispose individuals to the disease. Nevertheless, more extensive studies are required to establish the role of autoimmunity in iMCD and to delineate its mechanisms of action.

Finally, the hypothesis that iMCD may be driven by neoplastic processes is gaining attention¹⁹. Patients with iMCD exhibit a higher risk of malignancy compared to age-matched controls, and the clinicopathological features of the disease often overlap with hematologic malignancies such as Hodgkin lymphoma and myelofibrosis¹. While no definitive clonal population has been identified in iMCD, the higher malignancy risk and the histopathological similarities with neoplastic conditions suggest that further investigation is warranted.

Taken together, these observations highlight the multifactorial nature of iMCD pathogenesis. While the precise mechanisms remain elusive, the evidence points to a convergence of cytokine dysregulation, immune system perturbations, and possibly paraneoplastic processes^{18,19,42}. Although the role of viruses in iMCD is unlikely, the parallels between viral-driven HHV-8-associated MCD and iMCD raise intriguing questions about shared downstream pathogenic pathways, such as cytokine storms and immune dysregulation^{45,49}. Future investigations should explore innovative approaches to clarify these mechanisms, with the goal of refining diagnostic precision and expanding therapeutic possibilities.

1. Major criteria (both needed)	
1. Histopathological lymph node consistent with the iMCD spectrum	
2. Enlarged lymph nodes in ≥ 2 lymph node stations	
2. Minor criteria (≥ 2 , with at least 1 laboratory criteria)	
1. Laboratory	
Elevated C reactive protein	
Anemia	
Thrombocytopenia or thrombocytosis	
Hypoalbuminemia	
Renal dysfunction	
Polyclonal hypergammaglobulinemia	
2. Clinical criteria	
Constitutional symptoms	
Large spleen/liver	
Fluid accumulation	
Eruptive cherry angiomas or violaceous papules	
Lymphocytic interstitial pneumonitis	
3. Additional features supportive, but not needed for diagnosis	
Elevated IL-6, sIL-2R, VEGF, IgA, IgE, LDH, and/or B2M	
Reticulin fibrosis of bone marrow (particularly in TAFRO)	
Paraneoplastic pemphigus, BOOP, autoimmune cytopenias, polyneuropathy, glomerular nephropathy, inflammatory myofibroblastic tumor	
Exclusion criteria (must rule out)	
1. Infection-related disorders	
HHV-8 infection or Kaposi sarcoma	
EBV-associated lymphoproliferative disease	
Inflammation or adenopathy by others (CMV, HIV, TB, toxoplasma...)	
2. Autoimmune/autoinflammatory diseases	
Systemic lupus erythematosus	
Rheumatoid arthritis	
Adult-onset Still disease	
Juvenile idiopathic arthritis	
Autoimmune lymphoproliferative syndrome	
3. Malignant/lymphoproliferative disorders	
Lymphoma	
Multiple myeloma	
Primary lymph node plasmacytoma	
Follicular dendritic cell sarcoma	
POEMS syndrome	

Figure 4. Consensus diagnostic criteria for idiopathic multicentric Castleman disease. iMCD: idiopathic multicentric Castleman disease, VEGF: vascular endothelial growth factor; LDH: lactate dehydrogenase; B2M: β -2-microglobulin; TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; BOOP: bronchiolitis obliterans organizing pneumonia; HHV-8: human herpesvirus 8; EBV: Epstein-Barr virus; CMV: cytomegalovirus; TB: tuberculosis; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (adapted from Fajgenbaum et al.⁹).

Epidemiology

A 2022 study from the USA estimated an incidence of around five cases per million patient-years for iMCD, accounting for 55-80% of all MCD cases¹³. In addition, in a 2023 report from China, only 7% of iMCD cases were classified as TAFRO, whereas the rest were iMCD-NOS¹¹. iMCD generally presents in the fifth to seventh decades of life and exhibits a slight male predominance^{11,13,14}. TAFRO patients tend to be slightly younger and more frequently male compared to NOS patients¹⁴.

Clinical findings and diagnosis

Like other forms of MCD, iMCD is characterized by systemic symptoms that typically progress rapidly, accompanied by organomegaly and elevated inflammatory markers in the blood (Table 1)¹. This group of patients may also experience autoimmune phenomena, adding complexity to the differential diagnosis⁴⁹. In addition, iMCD patients demonstrate an increased

incidence of myeloid and solid malignancies compared to the general population, a phenomenon likely associated with IL-6-mediated immune suppression⁵⁰.

iMCD diagnosis relies on meeting consensus criteria established in 2017, which include distinct lymph node pathology, multicentric lymphadenopathy, clinical and laboratory criteria, and exclusion of alternative infectious, malignant, or autoimmune conditions (Fig. 4)⁹.

Further classification of iMCD into iMCD-NOS and iMCD-TAFRO is recommended due to their distinct therapeutic management^{5,9,42}. Patients with iMCD-NOS may develop peripheral neuropathy, immune thrombocytopenia, autoimmune hemolytic anemia, interstitial lung disease, and an increased risk of malignancies and lymphoma^{6,50}. These patients typically exhibit a less aggressive clinical course, better corticosteroid responsiveness, thrombocytosis, less frequent anasarca, lower alkaline phosphatase levels, and higher γ -globulin levels¹.

In contrast, TAFRO syndrome represents a severe subtype of iMCD, characterized by thrombocytopenia, ascites, reticulin fibrosis in the bone marrow, renal

Table 3. Proposed diagnostic criteria for TAFRO-iMCD

1. Histopathological (all needed)
Characteristic TAFRO lymph node histology*
Negative LANA-1 for HHV-8
2. Major criteria
≥ 3 TAFRO symptoms
Thrombocytopenia
Anasarca
Fever
Reticulin fibrosis
Organomegaly
Absence of hypergammaglobulinemia
Small volume lymphadenopathy
3. Minor criteria (at least 1)
Hyper/normoplasia of megakaryocytes
High alkaline phosphatase without markedly elevated transaminases

*Atrophic germinal centers with enlarged nuclei of endothelial cells, proliferation of endothelial venules with enlarged nuclear in the interfollicular zone, and small numbers of mature plasma cells.

TAFRO: thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly; LANA-1: latency-associated nuclear antigen; HHV-8: human herpes virus 8; iMCD: idiopathic multicentric Castleman disease.

Adapted from Iwaki et al.⁵

dysfunction, and organomegaly (collectively termed TAFRO), and typically normal immunoglobulin levels⁴². Patients with TAFRO experience aggressive inflammatory responses involving complex signaling pathways, with diagnostic criteria established in 2015 (Table 3). In these patients, platelet counts often mirror disease activity, with decreases indicating potential flares⁵.

While the clinical course of iMCD-NOS may vary and is not always aggressive, TAFRO syndrome is typically severe from onset^{5,42}. Severe cases, particularly iMCD-TAFRO, can escalate to life-threatening cytokine storms, resulting in multiorgan dysfunction⁵. Patients under 30 and over 60 years of age are more likely to experience severe disease¹⁴. Overall, 76% of patients present with severe disease at diagnosis, including 93% of TAFRO patients¹⁴. The estimated 3-year survival rate for TAFRO patients is 66%, compared to 85-99% for iMCD-NOS patients¹¹.

Management

Patients with iMCD should be stratified according to disease severity, in line with the criteria proposed by van Rhee et al. (Fig. 3)^{7,9,50}. Despite the severity of TAFRO syndrome, its description is relatively recent, and there are no studies or registries that distinguish its treatment outcome from iMCD-NOS. Consequently,

the current approach considers both subtypes to have the same treatment protocols.

For non-severe iMCD, frontline therapy with siltuximab, an anti-IL-6 monoclonal antibody, is recommended^{1,7}. If siltuximab is unavailable or not approved, tocilizumab may be used as an alternative option. Steroids can serve as adjunctive therapy, with dosages tailored to the severity of the disease^{6,11,50}. For patients who respond to anti-IL-6 monoclonal antibody therapy, treatment should be continued indefinitely. In cases of mild clinical presentation, a limited course of rituximab may be an alternative option.

Patients unresponsive to anti-IL-6 targeted therapy should be considered for rituximab-based therapy combined with steroids, with the possible addition of immunomodulatory or immunosuppressive agents^{7,13}. Second- or third-line therapy options include thalidomide, cyclosporine A, sirolimus, anakinra, or bortezomib. At this stage, consultation with an expert is strongly recommended to guide treatment decisions.

For severe iMCD, close monitoring is essential due to the risk of life-threatening complications. Treatment should start with siltuximab, or tocilizumab if not available, and high-dose steroids^{6,7,13,50}. If there is no clear response within 1 week, or if the patient's condition worsens at any moment, combination chemotherapy should be initiated⁷. Expert guidance is advised to identify the most appropriate treatment approach. Examples of chemotherapy regimens include rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab, bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (R-VDT-PACE), or etoposide/cyclophosphamide/rituximab. Further treatment should be individualized based on the patient's response and clinical status⁵⁰.

Conclusion

Despite the common clinical and histopathological features, CD is now recognized as a highly heterogeneous condition with multiple etiologies, clinical presentation, prognosis, and treatment. Recent advances in understanding pathogenic mechanisms, such as the role of HHV-8 in KSHV-associated MCD and IL-6 in iMCD, have enabled the development of targeted therapeutic regimes for each subtype. This progress has led to the establishment of a more comprehensive, precise, and individualized classification of MCD, which includes HHV-8-associated MCD, POEMS-associated MCD, as well as TAFRO-iMCD and iMCD-NOS. Unique diagnostic criteria for these entities are now available, and more

sophisticated and specific therapeutic approaches have led to significant improvements in prognosis. Nevertheless, despite the progress made in recent years, significant gaps remain in our understanding of the epidemiology and pathophysiology of this complex group of conditions.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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