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Review

Multicentric Castleman disease and the evolution of the concept

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Summary
The term multicentric Castleman disease (MCD) encompasses a spectrum of conditions that share some overlapping clinicopathological manifestations. The fundamental pathogenetic mechanism involves dysregulated cytokine activity, causing systemic inflammatory symptoms as well as lymphadenopathy. Some of the histological changes in lymph nodes resemble the histology of unicentric Castleman disease (UCD). However, based on current knowledge, the use of this shared nomenclature is unfortunate, since these disorders differ in pathogenesis and prognosis. In Kaposi sarcoma-associated herpesvirus (KSHV)-associated MCD, cytokine overactivity is caused by viral products, which can also lead to atypical lymphoproliferations and potential progression to lymphoma. In idiopathic MCD, the hypercytokinemia can result from various mechanisms, which ultimately lead to different constellations of clinical presentations and varied pathology in lymphoid tissues. The authors review the evolving concepts and definitions of the various conditions under the eponym of multicentric Castleman disease.

Key words: Castleman disease, Kaposi sarcoma-associated herpesvirus, human herpesvirus type 8, interleukin-6, TAFRO syndrome

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Multicentric Castleman Disease (MCD) - Juan Rosai and the evolution of the concept

The term Castleman disease began with a single case discussed at the recurring clinicopathological conferences (CPC's) of the Massachusetts General Hospital and published in 1954 [1]. It was an example of what we now consider unicentric Castleman disease (UCD). Ultimately two histological and clinical variants were identified [2]. One subtype had prominent hyalinization, regressive changes in follicles, with increased vascularity (hyaline vascular type), while the second had an increase in plasma cells and was more often associated with systemic symptoms (plasma cell type). However, both forms presented with localized mass lesions.

In 1980 Glauco Frizzera, working with Juan Rosai, presented a paper at the USCAP meeting, then known as the United States and Canadian Branch of the International Academy of Pathology, describing 10 patients with a multicentric lymphoid disorder with histological features resembling UCD. They expanded on their observations in a manuscript published in 1983, describing a systemic lymphoproliferative disorder with morphological features of Castleman's disease [3]. Their pivotal description mainly pertained to lymph nodes, but splenomegaly was present in most of the 15 patients, and the authors also reported the histological findings in the spleen from 4 cases.

All patients presented with constitutional symptoms including fever, night sweats, weight loss and generalized lymphadenopathy. An important clue to the pathogenesis was that two patients had Kaposi sarcoma. Other clinical features included anemia, thrombocytopenia, and polyclonal hypergammaglobulinemia. The clinical evolution of the disease was variable, with four patients having a fatal outcome in 5-14 months, while other patients had a chronic, indolent course, with remissions and exacerbations. At the time of publication, six patients were still alive after 39-156 months. The causes of death were multifactorial, with five patients dying of sepsis, and one developing lymphoma. Based on what we know today, it is likely that many of the reported patients had Human Herpesvirus 8 (HHV8) [also known as Kaposi sarcoma-associated herpesvirus (KSHV)]-associated MCD, while others with more protracted and chronic disease may have had idiopathic MCD (iMCD). Rosai and colleagues also noted similarities to "collagen vascular diseases" [3], and speculated on similarities to what was known at the time as angioimmunoblastic lymphadenopathy (AIL) and T-zone lymphoma. Their landmark article helped set the stage for the discovery of KSHV/HHV8 in patients with Kaposi sarcoma in 1984, and was an important step in defining the clinical and pathological features of the various conditions included in the concept of MCD [4]. MCD is not a single disease entity, but the overlapping features of vascular proliferation, plasmacytosis, and immune dysfunction may be related to similarities in pathophysiology as we will discuss below.

KSHV associated MCD

HHV8: an etiologic agent for multiple hematologic diseases

HHV8, also known as KSHV, was first isolated from Kaposi sarcoma in 1984 by Chang et al. [5]. Subsequently, it was determined to be causally related to MCD [6]. Uncontrolled HHV8 infection causes approximately 50% of MCD cases and is ubiquitous in HIV-associated Castleman disease. (Fig. 1) HHV8 is also the etiologic agent of primary effusion lymphoma (PEL) [7]. Latent HHV8 infection is overwhelmingly common. HHV8 seroprevalence ranges from 6% to 50%, depending on the geographic regions and subpopulations [8]. However, HHV8 remains in a dormant state in most cases. Only a minority of infected individuals develop HHV8-associated MCD and other diseases years or even decades later, emphasizing the role of cofactors in determining the development of such diseases. In this respect, immunodeficiency is the primary risk factor for developing HHV8-associated diseases, with HIV infection being the most common underlying immunocompromised state.

Like all other members of the herpesvirus family, HHV8 establishes lifelong infection in the host. Due to its large, complex genome, this virus can sustain chronic infection through skillful immune evasion and low-copy replication by frequent switching between latent and lytic replication cycles. Lymphoid and endothelial cells serve as major latent reservoirs of HHV8 [9], although HHV8 can also infect and persist in other types of cells, such as monocytes, dendritic cells, and epithelial cells. During latency, a large portion of the HHV8 genome is kept silenced through multiple epigenetic modifications [10]. Transcription is limited to a few latency-associated genes, including the latency-associated nuclear antigen-1 (LANA-1), the most abundantly expressed protein consistently detected in all HHV8-infected tumors. The restricted expression of viral antigens aids the virus in avoiding recognition by the host immune system while allowing for long-term viral persistence [11,12]. Therefore, the human immune system can suppress the infection yet never eliminate this pathogen. Under appropriate conditions, the latently infected cells can be induced to enter the lytic cycle. Some of the well-established factors that activate lytic replication of HHV8 include immune suppression and co-pathogenic infections, as well as cellular stress, hypoxia, and inflammation. The lytic phase is characterized by the expression of a highly ordered cascade of genes that ensures efficient replication of virions [13-15].

It should be noted that the expression of HHV8 genes does not always follow the latency-versus-lytic-replication paradigm. Certain viral genes that are typically expressed during lytic cycles can be activated by host transcriptional machinery, independent of full lytic activation [16]. For instance, the expression of HHV8-encoded viral IL-6 (vIL-6) was shown to be induced by the X-box binding protein-1 (XBP-1), a transcription factor highly expressed in the B-cell lineage [17]. The extra layer of regulation adds to the heterogeneity of viral gene expression profiles among different HHV8-associated diseases. For example, in Kaposi sarcoma, most tumor cells have latent infection, while lytic proteins are expressed in a small percentage of cells. A greater proportion of cells in PEL express lytic proteins, while MCD demonstrates the highest frequency of lytic replication (up to 25%) [18-20]. Conceivably, the heterogeneity in viral gene expression profiles contributes to the wide clinicopathological spectrum of HHV8-associated diseases, ranging from subclinical to progressive disease, from localized to systemic illness, and from reactive hyperplasia or benign scarring to overt malignancy.

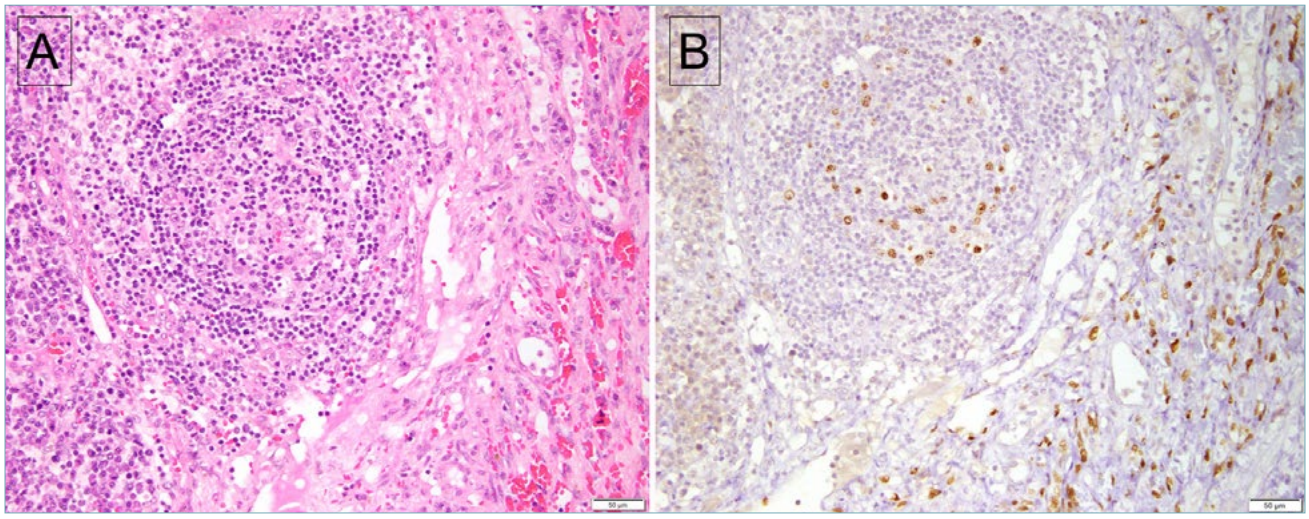

Figure 1. Lymph node involved by both MCD and KS. (A) The follicle shows regressive changes, with an adjacent spindle cell proliferation associated with extravasated red blood cells. (B) Staining for LANA-1 is positive in both lymphoid cells within the follicle as well as the spindle cells of KS. However, the spindle cells of KS are negative for vIL-6 (not shown).

Pathogenesis of HHV8-associated MCD

Speculation abounds over whether MCD is an autoimmune, infectious, reactive, or clonal disease [21]. Despite some early obstacles and lingering controversies, a new conceptual framework of MCD pathogenesis has been proposed: both the nodal and systemic manifestations are reactive changes to elevated levels of IL-6 and, to a lesser extent, other circulating factors in the cytokine and chemokine storm [21]. MCD can be further subcategorized based on the presence of HHV8 into HHV8-associated MCD and HHV8-negative iMCD. Although the underlying mechanisms responsible for the cytokine storm in iMCD cases remains hypothesis-generating, the prominent pathogenic role of HHV8 is undisputed in HHV8-associated MCD cases. In these patients, immunosuppression enables HHV8 to escape host immune control. The increased lytic replication triggers antiviral signaling cascades that lead to excessive production of human IL-6 (hIL-6) and other cytokines, including IL-10, tumor necrosis factor-α (TNF-α), and IL-1.

Notably, the HHV8 genome is known to encode for homologs of several human regulatory proteins involved in cell proliferation, survival, and immune response [22,23]. In particular, the production of vIL-6, a "pirate" cytokine with optimized and unregulated IL-6 functions, is thought to be a critical disease driver of HHV8-associated MCD, and the circulating level of vIL-6 correlates with disease activity [24,25]. Although vIL-6 shares only 25% sequence identity with and demonstrates lower signaling potency than its human counterpart, hIL-6 [23,26,27], it is capable of stimulating all of the known hIL-6-induced signaling pathways in a similar manner [28,29]. Furthermore, vIL-6 functions in a wider variety of cell types since it is able to signal merely by engaging the ubiquitously expressed gp130 subunit of IL-6 receptor. In contrast, signaling of hIL-6 requires the full IL-6 receptor (both gp130 and gp80) [28, 30].

Both vIL-6 and hIL-6 play a pleiotropic role in MCD: they stimulate the proliferation of B cells and plasmablasts, activate angiogenesis, and mediate systemic inflammatory symptoms [31-33]. Consequently, these mechanisms lead to the characteristic pathologic changes and clinical manifestations, described in greater detail in the following section. Foremost is hIL-6, which exerts a potent chemotactic activity and attracts plasmablasts to cluster around small vessels, producing an environment that is more conducive to cross-infection and paracrine signaling among these cells. This process amplifies the plasmablasts and is followed by massive viral replication, cell lysis, and excessive cytokine production, which reciprocally augments cell-to-cell transmission and cell proliferation. The ultimate outcome of such a vicious circle is an exponential escalation of hIL-6 and vIL-6, both locally and systemically.

At the cellular level, the binding of hIL-6 and vIL-6 to IL-6 receptors results in activation of JAK/STAT and MAPK pathways [34]. Both pathways serve a key role in orchestrating the expansion of the two infective compartments – plasmablasts and lymphovascular

endothelial cells. The effects of cytokines on local target-cell populations are manifested by lymphoid hyperplasia and, consequently, increased immunoglobulin production. The effects are also manifested by activation of endothelial cells and vascular endothelial growth factor (VEGF) production, resulting in neo-angiogenesis with the formation of penetrating vessels. Additionally, the lytic replication of HHV8 leads to the destruction of endothelial cells, resulting in hyalinized scars and temporary lymph node swelling.

At the systemic level, both hIL-6 and vIL-6 exert a potent proinflammatory effect; their cooperative effect with other cytokines released into the circulation during disease flares results in the systemic inflammatory response syndrome [24,35,36]. In addition, these cytokines can deregulate host immunity against co-infecting pathogens, such as HIV and EBV. Human herpesvirus 8 and the co-infecting microbes can build a mutually beneficial relationship to promote expansion and enhance the pathogenic activity of one another through multifaceted interactions, such as the direct interplay between microbial products and indirect modulation of the microenvironment. The undesirable synergistic interactions not only accelerate the progression of HHV8-associated MCD, but also aggravate the pathologies associated with the coinfections [37,38]. Hence, the development and severity of HHV8-associated MCD are deeply influenced by host factors and complementing viral infections [39].

Advances in the understanding of the pathogenesis of HHV8-associated MCD have provided useful insights into new therapeutic strategies. Agents targeting the essential cytokine pathways, such as antibodies against IL-6/IL-6R and antagonists of the IL-1 receptor, have been proven effective in alleviating systemic manifestations [32,40]. Targeting both infected cellular reservoirs (lymphoid and endothelial cells) is emerging as a novel therapeutic concept. For example, anti-CD20 and anti-CD19 strategies can comprehensively destroy the lymphoid reservoir of HHV8 and have been shown to improve patient outcomes of HHV8-associated MCD [41]. While multimodal approaches targeting both lymphoid and endothelial compartments have not been translated into routine clinical practice, promising preclinical results are expected to pave the way for successful implementation of this approach in the near future [42].

Characterizing pathology and clinical presentations of HHV8-associated MCD

HHV8-positive MCD is assigned as a separate group of MCD owing to its viral etiology, variable clinical course, and high likelihood of resulting in HHV8-positive lymphomas. Patients with MCD typically present with systemic symptoms that are often severe and can be life-threatening without proper treatment [24]. Clinical manifestations of HHV8-associated MCD mainly fall into three categories. First and foremost, this disease often demonstrates episodic exacerbation of systemic inflammatory response, which includes constitutional symptoms, organomegaly, cytopenia, multiple organ dysfunction, elevated levels of acute-phase proteins, hypergammaglobulinemia, and hypoalbuminemia. The hemophagocytic syndrome can occur in up to 50% of HHV8-associated MCD cases. Second, hypoalbuminemia may lead to prominent fluid overload, manifesting as edema, ascites, pleural or pericardial effusions, and seizures. Finally, patients may suffer from symptoms related to complications or comorbidities, such as HIV (in 82% of patients)[43] and other infections, Kaposi sarcoma (in 48% of patients) [6], lymphoma, and paraneoplastic pemphigus. It is important to bear in mind that none of the symptoms are exclusively discriminatory for MCD; they all overlap with symptoms of other diseases, including viral infection, rheumatic or vasculitic disease, and malignancies. A lymph node biopsy is of the utmost importance in establishing the correct diagnosis, since current pathological diagnostic criteria of MCD are based on histologic findings in lymph nodes, although extranodal sites can also be involved. It is of interest that severe inflammatory symptoms with similar laboratory findings as seen in HHV8-associated MCD can be observed in a subset of patients that have no significant nodal disease (KSHV inflammatory cytokine syndrome or KICS) [44,45], as well as in patients that are starting anti-retroviral therapy as part of their immune reconstitution (KSHV-IRIS) [46].

Lymph nodes involved in HHV8-associated MCD show regressive changes in follicles and increased vascularity (Fig. 2). The nodes typically reveal relatively preserved lymph node architecture, with involuted follicles and penetrating venules. The interfollicular zone is characterized by vascular proliferation and prominent plasmacytic infiltrates. A unique and invariable feature of this form of MCD is the presence of HHV8-infected “plasmablasts”, located primarily in the mantle zones but also seen randomly in the interfollicular area. In some cases, these plasmablasts expand to form larger collections, previously described as microlymphomas [47-49], which may invade or replace the germinal centers (GC). These cells are characteristically medium to large with vesicular nuclei, one or more nucleoli, and amphophilic cytoplasm. Like normal plasma cell precursors, they are uniformly positive for MUM1; variably express CD20 and CD79a;

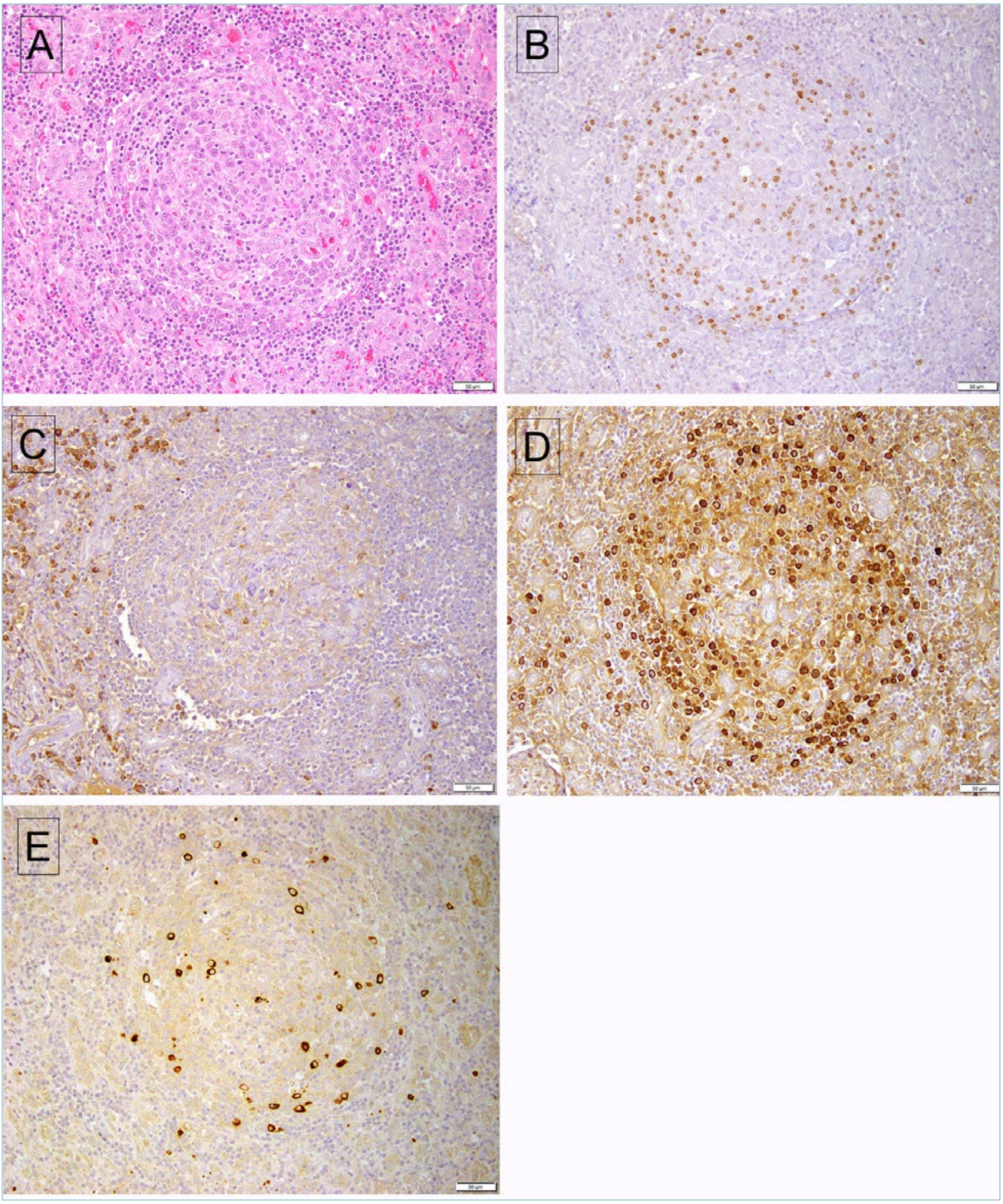

Figure 2. HHV8-associated MCD involving lymph node. (A) The follicle shows an attenuated mantle cuff, with increased vascularity most evident in the interfollicular area. (B) A stain for LANA-1 shows positive cells mainly at the periphery of the affected follicle. (C) A stain for kappa light chain shows positivity in interfollicular plasma cells, while the HHV8-infected plasma cells (D) stain for lambda light chain. (E) The HHV8-positive cells also express vIL-6.

lack PAX5, BCL6, and CD138; and are negative for EBV. The plasmablasts exclusively express IgM and lambda light chain; however, they show a polyclonal or oligoclonal pattern of immunoglobulin gene rearrangement at the DNA level [50].

Human herpesvirus 8 exemplifies a pathogen that can alter immunoglobulin diversity by reprogramming its host cells. The enigmatic restriction of HHV8 infection to IgM lambda-expressing B cells is a long-recognized feature of MCD; however, understanding of the underlying mechanisms remains incomplete. It is thought to be driven by the viral manipulation of human signaling pathways. The plasmablasts appear to originate from pre-GC naïve B cells, as they do not harbor somatic mutations in the rearranged immunoglobulin genes [49]. It has been postulated that HHV8 viral latent products may be able to transform IgM-positive naïve B cells into plasmablasts in the absence of GC reactions, possibly by mediating signaling events that normally occur in GC reactions. Thus, the infected plasmablasts lack class switching recombination and remain IgM-positive. Furthermore, HHV8-encoded proteins, such as vFLIP, can act as an NF-κB activator; NF-κB signaling is essential for generating lambda light chain-expressing B cells following unsuccessful kappa gene rearrangement in normal B-cell development [51]. Thus, HHV8 likely reinduces immunoglobulin rearrangement in the originally kappa-expressed cells through induction of human NF-κB transcriptional activity.

Relationship of HHV8-associated MCD with other HHV8-associated lymphoproliferative disorders

It has been well-established that HHV8-associated MCD is associated with a heightened risk for non-Hodgkin lymphoma [47,48,52]. The incidence of non-Hodgkin lymphoma in patients with HIV-associated MCD is reported to be about 15-fold higher than that in the general HIV-infected population [47]. The most common type of non-Hodgkin lymphomas arising in the background of MCD is designated as HHV8-positive diffuse large B-cell lymphoma (DLBCL), not otherwise specified in the WHO classification. Human herpesvirus 8-positive DLBCL is characterized by destruction of nodal architecture and sheets of plasmablastic cells, displaying an immunophenotype that is virtually identical to that of the HHV8-infected plasmablasts in MCD; in particular, these cells also strongly express IgM with lambda light-chain restriction [50]. However, the development of frank lymphoma is characterized by clonal immunoglobulin gene rearrangements, in contrast to the polyclonal or oligoclonal nature of the plasmablasts in MCD. These observations have led to the conclusion that HHV8-positive DLBCL likely represents a selective clonal expansion of HHV8-infected plasmablasts following polyclonal activation. One convincing piece of evidence for this hypothesis comes from the observation that, in rare cases, there was a sequential progression of MCD with individual plasmablasts to “microlymphomas” and finally HHV8-positive DLBCL. Upon closer examination, additional genetic abnormalities were found in the “microlymphomas” [53]. In this respect, it is important to note that although the so-called “microlymphomas” pose the potential to transition to overt lymphoma, only a fraction of these cases progresses to frank lymphoma. Additionally, a clear clonal relationship has not been established between the “microlymphoma” and concomitant or subsequent lymphoma [26]. Therefore, such cases are probably best regarded as a variant of MCD or no more than a non-committed precursor of lymphoma.

Synchronous or metachronous PEL represents another HHV8-associated malignancy in patients with MCD. Primary effusion lymphoma typically presents as effusions in the absence of a tumor mass. The neoplastic cells are pleomorphic with features of immunoblastic, plasmablastic, or anaplastic cells. While EBV infection is not a prerequisite for PEL development, the vast majority of PEL cases are coinfected with EBV that exhibits restricted gene expression [54]; the small subset of PEL without coinfection of EBV is usually seen in immunocompetent patients [50]. In comparison to HHV8-positive DLBCL, it is not as well-established whether PEL arising in the setting of MCD originates from HHV8-infected plasmablasts. Conceptually, the transformation of a node-based disease into an effusion-based lymphoma seems counterintuitive.

Indeed, MCD and PEL are different in many aspects: First, the phenotype of PEL differs from that of the plasmablasts in MCD in that PEL is often positive for activation markers and occasionally expresses T-cell markers but usually lacks surface and cytoplasmic immunoglobulin but. Second, PEL cells show evidence of rearranged immunoglobulin genes and high levels of somatic mutations [55]. They also exhibit a gene expression profile between that of DLBCL and plasma cells [56,57]. These features seem to indicate that PEL is derived from a transition stage between antigen-selected GC B cells and terminally differentiated plasma cells, in contrast to HHV8-associated MCD, which likely originates from naïve B cells. This model fits best with current knowledge of immunophenotypic and genetic features of PEL, but an alternative pathway is also considered. According to the second scenario, both MCD and PEL originate from the same HHV8-infected subtype of B cells, while additional pathogenic factors

in PEL influence the disease genetics, phenotype, and manifestations. One important cooperative factor to consider is coinfecting EBV, which is known to imitate GC biology and could conceivably be responsible for clonal evolution toward a post-GC phenotype [58,59]. Furthermore, the discovery of lambda-restricted HHV8-infected plasmablastic cells in body fluids introduces a novel concept of a "liquid form" of MCD [60] and lays a foundation for the transformation of HHV8-associated MCD into an effusion-based lymphoma.

Germinotropic lymphoproliferative disorder (GLPD)

Besides PEL, coinfection by HHV8 and EBV has been identified in germinotropic lymphoproliferative disorder (GLPD). This entity was first described in 2002 [61]; so far, fewer than 20 cases have been reported in the literature [62]. In sharp contrast to PEL, as well as the other HHV8-associated diseases, GLPD affects mainly immunocompetent individuals, presents as localized lymphadenopathy without obvious systemic symptoms, and has a favorable clinical course. This finding leads to an intriguing question: Why do the same oncogenic factors (HHV8 and EBV) diverge into two diseases that have such vastly different outcomes (PEL and GLPD)? Speculations on possible mechanisms include host immune status and microenvironment (effusion vs. GC), which may influence key aspects of lymphomagenesis. The unanswered questions highlight gaps in knowledge that must be filled in by future research; genomic and epigenomic comparison of different HHV8-related lymphoproliferative disorders may be an attractive research direction.

Histologically, GLPD is characterized by aggregates of plasmablasts coinfected by HHV8 and EBV that preferentially colonize GCs but may also extend into the interfollicular regions (Fig. 3). The plasmablasts are positive for MUM-1 but lack expression of CD45, CD138, and B-cell markers. Like MCD, the plasmablastic cells show monotypic light chain expression but are polyclonal at the molecular level. The lymph nodes often show features resembling Castleman disease, such as atrophic and hyalinized follicles, vascular proliferation, and marked plasmacytosis [63,64].

The distinction between GLPD and HHV8-MCD requires the integration of clinical and pathological data. Namely, GLPD is coinfected by HHV8 and EBV. In this regard, GLPD is different from MCD, which is almost always EBV-negative. Second, in GLPD, plasmablasts primarily infiltrate GC, whereas in MCD, they involve the mantle zones. Third, GLPD shows monotypic kappa or lambda light chains, while MCD is only positive for IgM lambda. Lastly, localized involvement in immunocompetent individuals is more compatible with a diagnosis of GLPD.

Idiopathic MCD HHV8-negative MCD and other Castleman-like conditions

Approximately half or more of the MCD cases are negative for HHV8, mostly in HIV-negative patients. The etiology of the HHV8-negative MCD is largely unknown, and these cases have been referred to as iMCD [65]. Among them, a subgroup of patients presents with a characteristic constellation of symptoms/signs including thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction, and organomegaly, which gives rise to the acronym TAFRO syndrome. This subset of iMCD is now considered a specific entity (TAFRO-iMCD) with clinical and histologic presentations distinct from other non-TAFRO iMCD cases, although both entities are driven by cytokine hypersecretion. Additionally, an MCD-like presentation can also be caused by paraneoplastic mechanisms, such as in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes) syndrome. Several other conditions, such as lymphoid malignancies and IgG4-related disease, may mimic MCD in both the clinical presentation and histopathology, adding further complexity in differential diagnosis.

TAFRO syndrome and TAFRO-associated iMCD (TAFRO-iMCD)

TAFRO syndrome is a systemic inflammatory disorder first reported in Japan [66], and was later also described in Caucasian patients [67]. The Japanese TAFRO Syndrome Research Team proposed the diagnostic criteria of TAFRO syndrome in 2015, which was further updated in 2019 [68,69]. The diagnostic criteria include clinical and laboratory parameters, as well as disease conditions to be excluded. The pathological findings of TAFRO syndrome often resemble those of Castleman disease. However, a lymph biopsy is not always available in patients of TAFRO syndrome, often due to anasarca, bleeding tendency, or the minor extent of lymphadenopathy. Thus, lymph node biopsy was listed only as a minor diagnostic criterion. Despite some overlapping features, many clinical manifestations are distinct from those of iMCD, and TAFRO syndrome is considered a distinct disorder by many investigators. To distinguish from non-TAFRO iMCD, another research group proposed

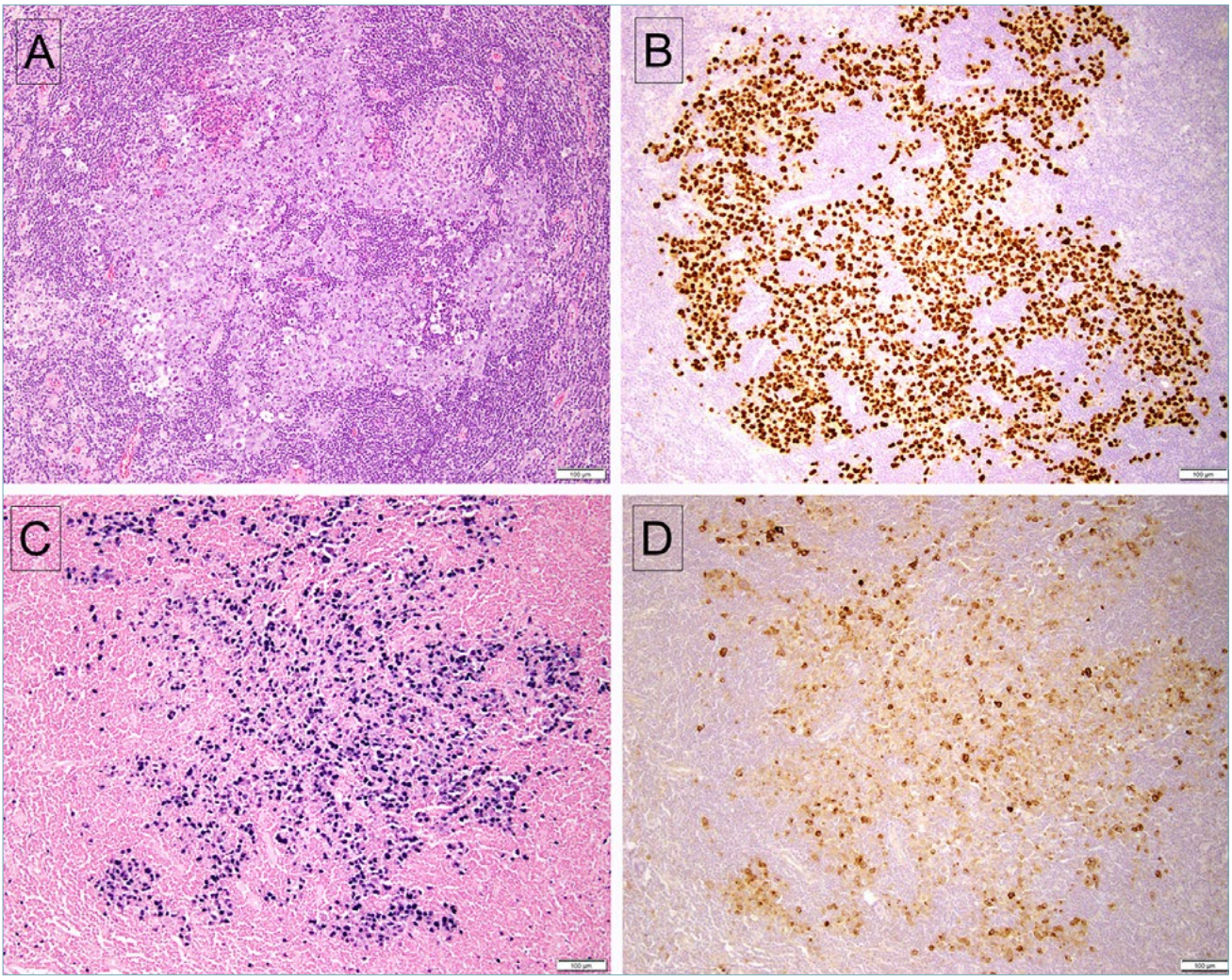

Figure 3. Germinotropic lymphoproliferative disorder. (A) The affected follicle shows irregular cords and sheets of atypical large lymphoid cells. (B) The lesional cells are positive for LANA-1, and also positive for EBV, with EBER in situ hybridization (C). D. The affected cells are also positive for vIL-6.

separate diagnostic criteria for TAFRO syndrome-associated iMCD (TAFRO-iMCD) [70], in which the characteristic histopathological findings of iMCD in lymph nodes are essential for diagnosis. Applying these diagnostic criteria, iMCD is divided into two categories: TAFRO-associated iMCD (TAFRO-iMCD) and iMCD not otherwise specified (iMCD-NOS). It is noteworthy that those cases of TAFRO syndrome without proven iMCD by lymph node biopsy share similar clinical, laboratory and prognostic features as TAFRO-iMCD, while distinct from iMCD-NOS [71], suggesting that TAFRO syndrome and TAFRO-iMCD defined by different diagnostic criteria represent the same clinical entity, and both require prompt diagnosis and intensive treatment.

In addition to those disease-defining symptoms/signs such as thrombocytopenia, anasarca, fever, reticulin fibrosis/renal dysfunction, and organomegaly, TAFRO-iMCD exhibits additional clinical and laboratory features that are distinct from iMCD-NOS, such as hypogammaglobulinemia (in contrast to hypergammaglobulinemia in iMCD-NOS), higher neutrophil counts, elevated transaminases, alkaline phosphatase and γ-glutamyl transpeptidase, and higher C-reactive protein levels [65,71,72]. Patients with TAFRO-iMCD usually have more aggressive clinical course, with significantly longer lengths of hospitalization. Based on the severity classification proposed by the Castleman Disease Collaborative Network (CDCN), the severe iMCD cases often present with the TAFRO-iMCD sub-

type and have higher mortality rate especially during the first few months [71,73-75].

The lymphadenopathy in TAFRO-iMCD is usually milder than in iMCD-NOS. Approximately 40% of patients do not develop radiographically enlarged lymph nodes [72]. Histologically, the involved lymph nodes usually exhibit fewer plasma cells than seen in other forms of iMCD. There is often marked vascular proliferation in the interfollicular areas, and the germinal centers are often atrophic with increased vessels lined by plump endothelial cells with enlarged nuclei and less hyalinization (Fig. 4). Bone marrow biopsies often show megakaryocyte hyperplasia with slight atypia such as multiple and separated nuclei. Mild loose reticulin fibrosis and occasional megakaryocytic emperipolesis are also common findings, while significant plasmacytosis is not observed [70,76].

The distinct clinical presentation suggests that TAFRO-iMCD may have a unique pathogenesis different from iMCD-NOS. For example, IL-6, which is a hallmark cytokine that is elevated in iMCD, is often only mildly elevated in TAFRO-iMCD. The common clinical features associated with IL-6 hypersecretion, such as thrombocytosis and hypergammaglobulinemia, are not observed in TAFRO-iMCD, in contrast to the iMCD-NOS patients [70], suggesting that elevated serum IL-6 might not be the primary pathogenesis driving the inflammatory responses in TAFRO-iMCD. A recent plasma proteomic study identified a distinct proteomic profile in TAFRO-iMCD versus iMCD-NOS, further supporting the notion that these iMCD subtypes may be diverse chemokines/cytokines driving the symptomatology [77]. Another genetic study by next generation sequencing using a target panel of ~500 genes further shed light in the genetic basis of TAFRO-iMCD. A somatic MAP2K2 (MEK2) mutation and a germline RUNX1 mutation were identified in two patients with TAFRO-iMCD. In both patients, ERK was significantly activated, suggesting a potential role of the MAPK signaling in the pathogenesis of TAFRO-iMCD [78].

iMCD-NOS

International evidence-based consensus criteria were proposed for iMCD [4]. According to this scheme, the diagnosis of iMCD requires enlarged lymph nodes with histopathologic features of CD, plus at least two clinical and/or laboratory features as minor criteria. Five main pathologic features were highlighted, namely regressed germinal centers, follicular dendritic cell (FDC) prominence, vascularity, hyperplasic germinal centers and plasmacytosis. iMCD cases exhibit a spectrum of histopathologic features. On one end of the spectrum is the hypervascular" histopathologic subtype that shows features resembling the unicentric hyaline vascular Castleman disease, with regressed germinal centers and prominence of FDC, while the "plasmacytic" subtype lies on the other end of the spectrum, typified by marked plasmacytosis but with residual hyperplastic germinal centers (Fig. 5). Many patients actually show a "mixed" subtype. As discussed above, most TAFRO-iMCD cases demonstrate hypervascular or mixed histopathology, but there are also iMCD-NOS patients with similar histopathology that do not have the TAFRO clinical manifestations.

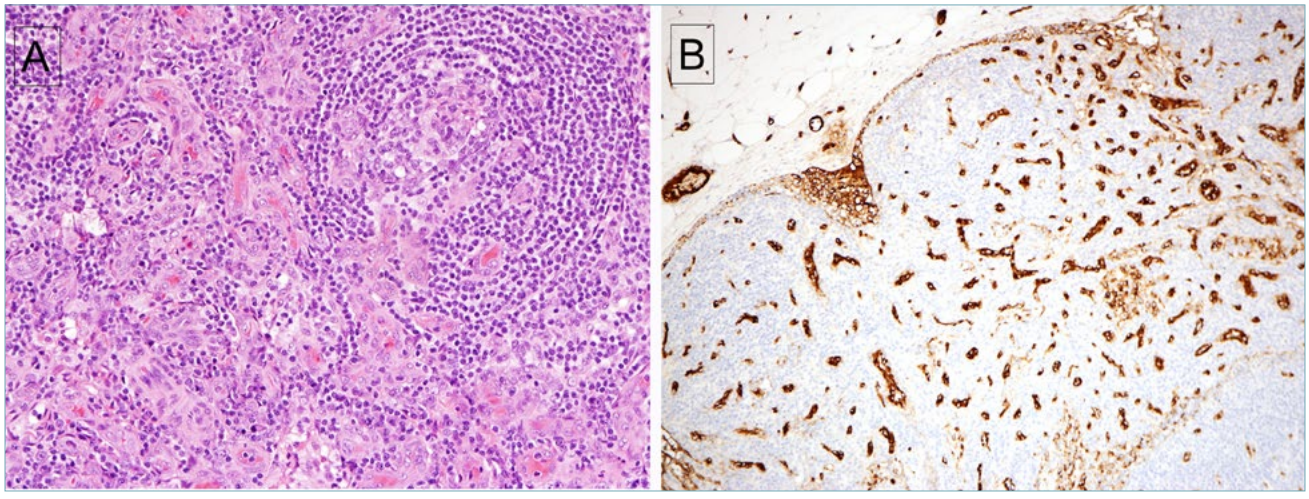

Figure 4. Idiopathic MCD with features of TAFRO. (A) The follicle shows regressive changes with markedly increased vascularity in the paracortex. (B) Staining for Factor VIII highlights the prominent vascularity.

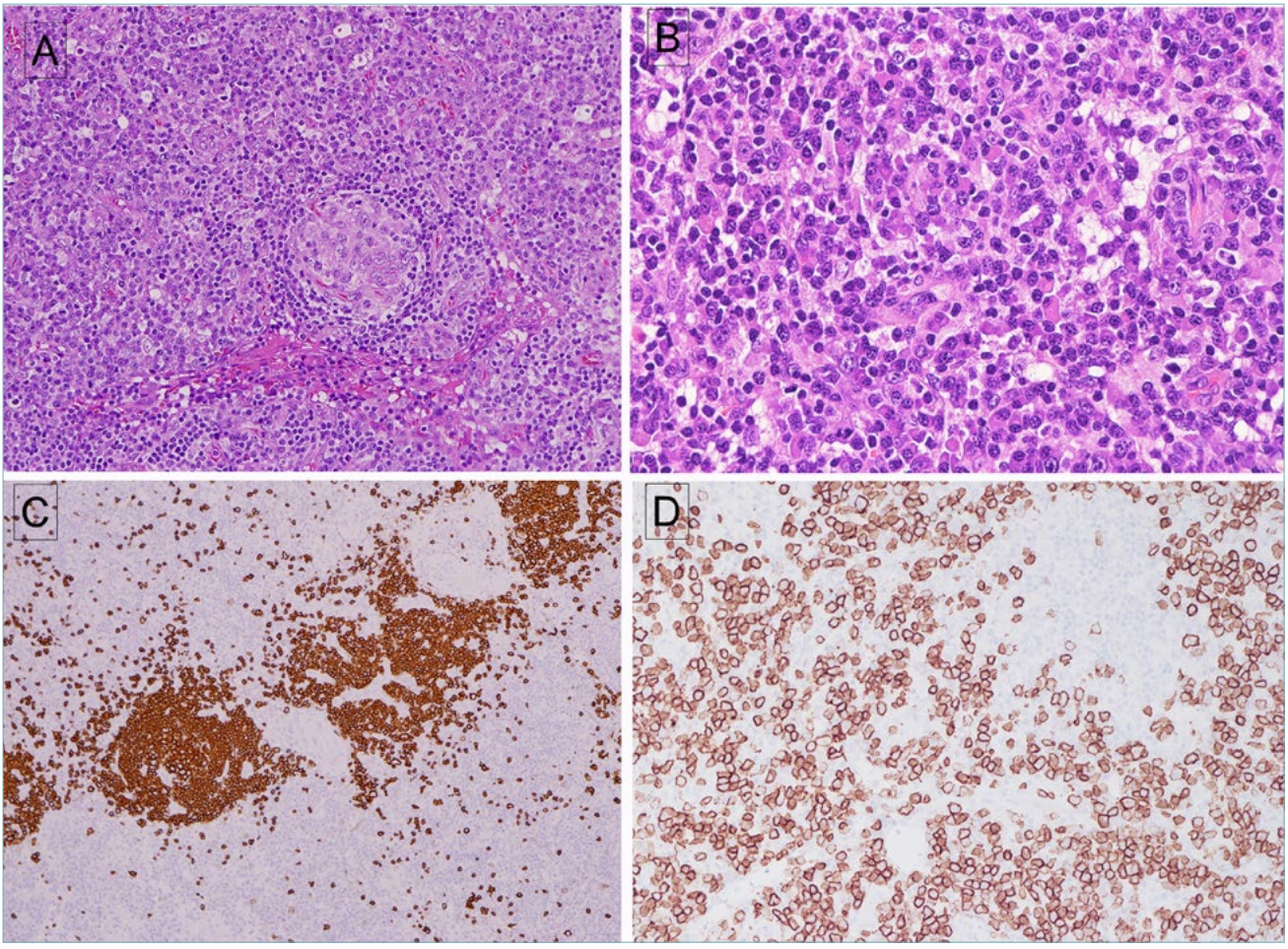

Figure 5. Idiopathic MCD, plasma cell type. (A) A small follicle with attenuated mantle cuff is surrounded by numerous mature plasma cells. (B) Plasma cells have mature nuclear features, with some cells containing Russell-body inclusions. (C) A stain for CD20 is positive in follicles but negative in plasma cells. Some increase in vascularity within the follicles is evident. (D) Abundant plasma cells are positive for CD138. Plasma cells were polytypic for kappa and lambda (not shown).

The histopathologic subtyping of iMCD into hypervascular, plasmacytic, and mixed subtypes provides a diagnostic scheme to encompass the heterogeneity in the histopathologic presentation of iMCD. Early data from the randomized controlled trial of siltuximab, an anti-IL-6 therapy, showed that all responders had either plasmacytic or mixed histopathologic subtypes, while none of the patients who achieved a durable response to siltuximab were classified as hypervascular subtype by central review [79]. Based on the data, the National Comprehensive Cancer Network (NCCN) had issued guidance recommending first-line siltuximab therapy for iMCD, except for patients with the hypervascular histopathology [80]. However, recent data from CDCN showed that the histopathologic subtypes are often inconsistently assigned among pathologists, with only 23% concordance rate in three pathologic reviews at local site, central review and a CDCN expert panel in the study [81]. This inconsistency has limited the clinical utility of the histopathologic iMCD subtyping. Additionally, the real-world data showed that severe iMCD patients, including cases of TAFRO-iMCD and iMCD-NOS of hypervascular subtype, may respond to anti-IL-6 therapy. Therefore, currently there is insufficient evidence to guide treatment based solely on the iMCD histopathologic subtype [81].

As in HHV8-associated MCD, iMCD is also characterized by proinflammatory hypercytokinemia, in particular IL-6. The pathophysiologic significance of IL-6 in iMCD has been confirmed by the efficacy of anti-IL-6 therapy. Currently the anti-IL-6 monoclonal antibody (siltuximab or tocilizumab) with or without

corticosteroids, is the preferred first-line therapy for iMCD, as recommended by the international consensus treatment guideline proposed by CDCN [75]. While the anti-IL-6 therapy represented a significant breakthrough in the treatment of iMCD, a substantial portion of patients remain refractory. For those patients, the second-line therapy includes rituximab in combination with immunomodulatory agent and steroid. Cytotoxic chemotherapy is generally reserved for patients with severe iMCD who fail to respond to the initial therapies. The resistance to anti-IL-6 therapy suggests that additional pathways may underlie the pathogenesis of iMCD and may serve as important targets for future iMCD therapies. Studies have shown that the mTOR signaling may be one potential target. Activation of mTORC1 has been found in iMCD lymph nodes by immunohistochemical studies for pS6, p4EBP1, and p70S6K. A proteomic signature of increased mTORC1 signaling was also detected in serum from iMCD patients by gene set enrichment analysis [82]. Another serum-based proteomic study also identified PI3K/Akt/mTOR pathway activation in anti-IL-6-refractory TAFRO-iMCD cases, and the administration of sirolimus, an mTOR inhibitor, was able to induce remission in these patients [83,84]. These data provide the rationale for therapeutic targeting of mTOR pathway in iMCD, and clinical trials of sirolimus for anti-IL-6-resistant iMCD are currently underway [85,86].

Despite the progress in understanding cytokine and signal pathway activation in iMCD, the underlying genetic mechanisms that drive the diseases processes have not been elucidated. There have been few studies investigating the genetic abnormalities. A recent whole-exome sequencing study on 22 patients of iMCD identified somatic alterations in five genes (*NCOA4*, *DARS2*, *MTCL1*, *RABPE1* and *DNAH11*), which are associated with unfavorable clinical outcomes [87]. Among them, *NCOA4* mutation was identified in 5 of 22 iMCD patients (23%), including 4 patients (18%) showing a same L261F mutation. Comparison of the mutation frequencies across different cancers has revealed that iMCD has the highest incidence of *NCOA4* mutations, and the *NCOA4* L261F mutation has not been reported in other cancers, suggesting that this genetic mutation might play an essential role in the pathogenesis of iMCD. *NCOA4* encodes the nuclear receptor co-activator 4, which is a co-activator of a variety of nuclear receptors. Structural modeling predicts that the L261F mutation results in instability of the protein and may change the conformation and phenotype. However, further studies are needed to confirm the roles of NCOA4 in iMCD. Additionally, alterations in genes involved in chromatin organization, including *SETD1A*, *ASH1L*, *KMT2E* and *DNMT3A*, have also been found in a subset of iMCD patients [88]. Another unanswered question is the cell types that are responsible for driving the iMCD pathogenesis and producing the cytokines. A subset of iMCD patients responds to rituximab, supporting B cells as an important contributor at least in some iMCD patients. Other cell types, including other lymphocytes, plasma cells, monocytes, endothelial cells, and follicular dendritic cells are likely also involved, as B-cell depletion is not effective in all patients [89].

POEMS syndrome

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes) is a paraneoplastic syndrome due to an underlying monoclonal plasma cell neoplasm. The clinical manifestations are thought to be caused by hypersecretion of proinflammatory and angiogenic cytokines, including vascular endothelial growth factor that is abundantly present in the plasma cells (both clonal and polyclonal) in patients of POEMS syndrome [90]. Chan et al. working with Juan Rosai, described some of the distinctive vascular lesions seen in POEMS [91]. Patients usually present with sclerotic bone lesions, rather than the typical osteolytic lesions seen in multiple myeloma. Most patients have a λ light chain-expressing plasma cell clone in their bone marrow, with highly restrictive usage of two λ variable (V) domains (IGLV1-40 and IGLV1-44) [92]. Half of patients show lymphoid aggregates in the bone marrow biopsy, with distinctive rimming by plasma cells. Megakaryocyte hyperplasia and clustering is also a frequent finding [93].

Up to 30% of POEMS patients to have lymphadenopathy with Castleman-like histology, and the presence of Castleman disease is one of the major criteria for the diagnosis of POEMS syndrome [94,95]. Thus, all patients presenting with iMCD, especially the plasmacytic histologic subtype, should be carefully surveyed to exclude the possibility of POEMS syndrome, since the treatment is entirely different from that of iMCD, and requires eradication of the culprit plasma cell clone.

Other disease conditions with histopathology mimicking iMCD

A variety of neoplastic and non-neoplastic conditions are known to exhibit a Castleman-like histomorphology, causing diagnostic challenges. Both Hodgkin and non-Hodgkin lymphomas may display Castleman-like features. Classic Hodgkin lymphoma can show hyaline sclerosis or florid plasmacytosis reminiscent of Castleman disease [96]. These Castle-

man-like histologic features likely represent a non-specific immune response to the immunologic stimuli in the tumor microenvironment. In some cases, the Castleman-like histology is caused by cytokine-producing lymphoma cells, as reported in cases of intravascular large B-cell lymphoma secreting IL-6 [97]. Angioimmunoblastic T-cell lymphoma often shows atrophic germinal centers and proliferation of high endothelial venules, which may mimic the hyaline vascular or hypervascular subtype of iMCD. A rare variant of follicular lymphoma can show Castleman-like morphology, including neoplastic follicles with onion-skin-like mantle zones and penetrating hyalinized blood vessels, but features of follicular lymphoma are usually evident to make the correct diagnosis [98]. Additionally, various non-neoplastic conditions, such as acquired immunodeficiency syndrome, syphilis and autoimmune disorders may also give rise to a Castleman-like morphology. Another differential diagnosis of iMCD is IgG4-related disease, which is a systemic inflammatory disorder characterized by sclerosing inflammation rich in IgG4-expressing plasma cells. iMCD patients may have an elevated serum IgG4 level, while some cases of IgG4-related disease may show Castleman-like morphology. Both conditions present with systemic lymphadenopathy with extranodal involvement, and sometimes the differentiation can be difficult [99]. In general, patients of IgG4-related disease tend to be older than patients of iMCD. The affected organs overlap between two conditions, but the presence of pancreatitis or sialo-dacryoadenitis suggests IgG4-related disease. Histologically, both conditions may be rich in plasma cells, but the plasma cells are often arranged in sheets in iMCD, while more commonly admixed with lymphocytes in IgG4-related disease. Serum IgG4 levels or absolute number of IgG4-positie cells in tissue are not useful for discriminating between the two conditions; the serum IgG4/IgG ratio and the ratio of IgG4/IgG-positive cells in tissue are more reliable discriminators [100].

Concluding remarks

In this article, we reviewed the evolving concepts and definitions of the various conditions under the eponym of MCD and summarize current knowledge regarding the histopathology and pathogenesis of lesions within the MCD spectrum. The current belief is that both the nodal and systemic manifestations are reactive changes to elevated levels of IL-6 and other circulating factors in the cytokine and chemokine storm; the hypercytokinemia can result from various mechanisms, which ultimately leads to different constellations of clinical presentations and pathological features.

Despite growing knowledge about the clinicopathological features of these conditions and the underlying dysregulated cytokine activity, diagnosis and accurate classification of MCD remains challenging. The clinical presentation is highly heterogeneous, and the pathological findings are not specific. Secondly, these patients are at a high risk of developing lymphoproliferative disorders, which can greatly confound the differential diagnoses. Thirdly, a lymph biopsy is not always available, which has sparked the interest of investigators to explore alternative diagnostic approaches. Additionally, our understanding of the underlying molecular mechanisms that drive the diseases processes is still at its infancy. Genomic and epigenomic characterization of MCD and related lymphoproliferative disorders may represent an attractive future research area that potentially leads to advances in diagnosis and therapy.

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Author's contribution

All authors contributed to drafting of the manuscript and review and editing of the final text. The figures were provided by Drs. Pittaluga and Jaffe.

Ethical consideration

All studies were in compliance with an IRB approved protocol and institutional guidelines for the study of human tissues.

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