Multicentric Castleman Disease: Where are we now?

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Abstract

Multicentric Castleman disease (MCD) encompasses a spectrum of conditions that give rise to overlapping clinicopathological manifestations. The fundamental pathogenetic mechanism involves dysregulated cytokine activity, which causes systemic inflammatory symptoms as well as lymphadenopathy. The histological changes in lymph nodes resemble in part the findings originally described in the unicentric forms Castleman disease, both hyaline vascular and plasma cell variants. In MCD caused by Kaposi sarcoma-associated herpesvirus/human herpesvirus-8 (KSHV/HHV8), the cytokine over activity is caused by viral products, which can also lead to atypical lymphoproliferations and potential progression to lymphoma. In cases negative for KSHV/HHV8, so-called idiopathic MCD, the hypercytokinemia can result from various mechanisms, which ultimately lead to different constellations of clinical presentations and varied pathology in lymphoid tissues. In this article, we review the evolving concepts and definitions of the various conditions under the eponym of Castleman disease, and summarize current knowledge regarding the histopathology and pathogenesis of lesions within the MCD spectrum.

Keywords

Castleman disease; multicentric Castleman disease; Kaposi sarcoma-associated herpesvirus; human herpesvirus type 8; interleukin-6; TAFRO syndrome; HIV; acquired immune deficiency syndrome; KICS

Historical Background

In 1954, Castleman and Towne reported the first case of Castleman disease presenting as a large mediastinal mass in a forty-year-old male patient. Histological examination revealed hyperplastic lymphoid tissue with hyalinized germinal centers that mimic Hassall corpuscles. In a subsequent report of twelve more cases, Castleman and colleagues further characterized the clinicopathologic findings. The patients all presented with enlarged mediastinal masses with none or only mild nonspecific systemic symptoms. Two major
Histologic features were recognized: hyalinization of lymphoid follicles and marked capillary proliferation, affecting both the follicles and interfollicular regions. These features later gave rise to the denotation of hyaline vascular type to this entity.

In addition to the prototypic Castleman disease, Flendrig described a different type, which exhibited prominent interfollicular fields of mature plasma cells, and was invariably associated with clinical presentations including fever, lymphadenopathy, splenomegaly and anemia. In 1972, Keller, Hochholzer and Castleman reviewed 81 cases, and established two histological types of Castleman disease: the originally reported hyaline vascular type and the plasma cell type seen more rarely (9 cases). Both types presented as solitary masses, with the plasma cell type more often associated with systemic symptoms.

Subsequently, cases with similar histologic features but involving multiple sites were described. In 1983, Frizzera, Banks, Massarelli and Rosai reported 15 patients of multicentric Castleman disease (MCD), and comprehensively analyzed the morphological, clinical and immunophenotypic features. Clinically, all patients presented with constitutional symptoms such as fever, night sweats or weight loss. Morphologically, the involved lymph nodes were characterized by a histologic triad: 1) diffuse marked plasmacytosis; 2) prominent germinal centers often showing hyaline vascular changes and 3) preserved nodal architecture. In other words, there were features of both hyaline vascular and plasma cell types.

Soon after the acquired immunodeficiency syndrome (AIDS) was described, lymphadenopathy with Castleman-like features was reported to be associated with AIDS. After the human immunodeficiency virus (HIV) was identified as the etiologic agent of AIDS, the association between MCD and HIV infection was further established. However, the bona fide etiologic agent of HIV-associated MCD had been elusive until Soulier et al. identified KSHV/HHV8 sequences in all of the HIV-positive MCD cases and 40% of HIV-negative cases in 1995.

Nonetheless, there remained cases with clinical and histological features resembling MCD cases in HIV-negative patients that were negative for KSHV/HHV8; these cases have been referred to as idiopathic MCD (iMCD). The diagnosis of iMCD is made when clinical and histological manifestations of MCD are observed, but all infectious (including KSHV/HHV8), autoimmune and neoplastic disease known to demonstrate these features have been excluded.

In the end, a spectrum of various conditions has come to be associated with the eponym of Castleman disease (Figure 1). It is clear that these represent several different disease entities, which share some overlapping histological features, but have different etiologies and very different clinical outcomes. Unicentric CD is usually self-limited, contains dysplastic dendritic and stromal elements, and carries a small risk for subsequent follicular dendritic cell sarcoma, whereas MCD associated with KSHV/HHV8 is primarily a lymphoproliferative disorder with risk of progression to lymphoma. The greatest questions remain regarding iMCD, which probably constitutes more than one entity. However, recent data have delineated at least one distinctive syndrome, “thrombocytopenia, anasarca, fever,
reticulin fibrosis and organomegaly” or TAFRO, that had been included in iMCD. In this review, we will summarize the current knowledge regarding the clinical presentation, histopathology and pathogenesis of Castleman disease, focusing on MCD.

Unicentric Castleman Disease

Hyaline vascular Castleman disease

Hyaline vascular type comprises more than 90% of the unicentric Castleman disease. It has a broad range of age distribution from pediatric to elderly patients. There is no predilection for either gender. Most patients present with a localized mass without constitutional symptoms or laboratory abnormalities. The mediastinum is the most common location, although the disease can also occur in extrathoracic sites such as the abdomen or neck. Surgical excision is the treatment of choice, and recurrence is uncommon. The involved lymph nodes are characterized by prominent vascular proliferation and hyalinization. The follicular centers are often atretic, and traversed by radially penetrating vessels that are usually ensheathed by collagenous hyalinization. The germinal centers are surrounded by mantle lymphocytes arranged in layers, imparting an onion-skin appearance. Some of the follicles may group together by fusion of the mantle zones, giving a “twinning” appearance with large irregular follicles containing more than one germinal center (Figure 2A). Between the follicles, there is usually extensive vascular proliferation with perivascular hyalinization. Of note, the follicular dendritic cells sometimes show dysplastic features (Figure 2B), and instances of follicular dendritic cell sarcoma have been described. In fact, recent molecular studies demonstrated clonality in the stromal cells in hyaline vascular Castleman disease, and suggested that genetic alteration in stromal cells including FDCs may be the underlying cause of the disease.

Unicentric Castleman disease, plasma cell type

The plasma cell type comprises around 10% of cases of unicentric Castleman disease. The demographic features resemble those of the hyaline vascular type. However, in contrast to the hyaline vascular type, the plasma cell variant is almost always associated with systemic symptoms and abnormal laboratory findings. The common clinical presentations include fever, night sweats, fatigue, weight loss, splenomegaly, anemia and hypergammaglobulinemia. The disease usually presents as a solitary mass. Surgical excision is curative, and results in disappearance of the associated symptoms and laboratory abnormalities, supporting the localized nature of this entity. The clinically observed mass is often made up by aggregates of multiple discrete lymph nodes characterized by sheets of mature plasma cells in the interfollicular areas. The follicles are usually of normal to large size with hyperplastic germinal centers. There is usually no prominent vascularization or hyalinization, although a portion of the follicles may show hyaline vascular changes. The plasma cells are generally polytypic, although rare cases that exhibit monotypic immunoglobulins, predominantly of light chain, have also been reported.
KSHV/HHV8-associated Multicentric Castleman Disease

Although MCD was initially separated from unicentric CD by its multifocal nature, it is now clear that it represents a different disease with different pathogenesis and much worse clinical outcome. Virtually all MCD cases in HIV-positive patients are associated with KSHV/HHV8, although KSHV/HHV8-positive MCD can also occur in HIV-negative patients. The patients typically present with flares of symptoms including fever, sweats, fatigue, cachexia, lymphadenopathy, splenomegaly, cytopenia and hypoalbuminemia, which are often severe and can be fatal. The diagnostic pathological findings are seen in the lymph nodes, although extranodal sites can also be involved. The involved lymph nodes typically show a mixture of the histologic features of both hyaline vascular and plasma cell types of CD, often with relatively preserved lymph node architecture (Figure 3A). The KSHV/HHV8-infected cells are generally localized in the outer mantle zone or marginal zone. They have moderate amount of amphophilic cytoplasm and a large vesicular nucleus containing one or two prominent nucleoli, and are often described as plasmablasts, although it is debatable whether they truly represent plasmablasts (Figure 3B–D). The KSHV/HHV8-positive ‘plasmablasts’ express OCT2, BLIMP1 and IRF4/MUM1, lack PAX5, BCL6 and CD138, and are negative for EBV. They express high levels of cytoplasmic IgM with monotypic \( \lambda \) light-chain expression (Figure 3E–F), but show a polyclonal pattern of immunoglobulin gene rearrangement. They do not harbor somatic hypermutations in the rearranged IG genes, suggesting a derivation from naïve B cells undergoing extrafollicular plasma cell differentiation.

The monotypic but polyclonal nature of the \( \lambda \)-restricted KSHV/HHV8-infected cells has been enigmatic. Two hypotheses have been proposed, including preferential targeting of \( \lambda \) light chain-expressing B cells by KSHV/HHV8 viruses or selective expansion of \( \lambda \) light chain-expressing B cells in response to viral infection. The detection of \( \kappa \) light chain or its transcript in other KSHV/HHV8-associated lymphoproliferative disorders, such as primary effusion lymphoma (PEL), appears to argue against the first hypothesis. However, a study using \textit{ex vivo} KSHV/HHV8 infection of tonsillar cells showed that latent KSHV/HHV8-infected cells were overwhelmingly enriched in the \( \lambda \) than the \( \kappa \) subset, suggesting that KSHV/HHV8 preferentially targets \( \lambda \) light chain-expressing B cells for stable latent infection. In addition, recent studies demonstrated that the generation of \( \lambda \) light chain-positive B cells is dependent on the NF-\( \kappa B \) signals during normal B cell development. Interestingly, in a transgenic mouse model, targeted expression of KSHV/HHV8 gene vFLIP, which acts as a NF-\( \kappa B \) activator, in B cells resulted in an increase in \( \lambda \) light chain-expressing cells in addition to other MCD features. The data suggest that the intrinsic viral effects (eg. vFLIP) may also be implicated in this enigmatic predilection for \( \lambda \) cells in MCD.

Kaposi sarcoma-associated herpesvirus (KSHV)/Human herpesvirus-8 (HHV-8)

KSHV/HHV-8 was first isolated from Kaposi sarcoma in AIDS patients by Chang et al., and was subsequently established to also be the etiologic agent of primary effusion lymphoma (PEL) and MCD. It is a gamma herpesvirus that has a large double-stranded DNA genome encoding 87 open reading frames (ORFs) and an array of
microRNAs.\textsuperscript{34} It can infect a variety of cells, including endothelial cells, monocytes and B cells. Like all other members of the herpesvirus family, KSHV/HHV8 displays latent and lytic cycles. During latent infection, the viral genomes are maintained as nonintegrated circular episomes, and very limited viral genes are expressed, including LANA (ORF73), v-cyclin (ORF72), v-FLIP (ORF71/K13) and Kaposin (K12). All of these latent gene products are transcribed from a single multicistronic locus. The other viral genes that encode components of the lytic cycle are kept silent through a bivalent epigenetic histone modification which maintains the chromatin in a poised quiescent state.\textsuperscript{35} Under specific conditions, the latently-infected cells can be induced to enter the lytic cycle through a not yet fully characterized process that involves the Replication and Transcriptional Activator (RTA), which serves as a major regulator that orchestrates the expression of viral lytic genes.\textsuperscript{36} However, it should be noted that the expression of KSHV/HHV8 genes may not be restricted by the paradigm of latent versus lytic cycles. Certain KSHV/HHV8 genes that are typically expressed during lytic cycles including vIL-6, vMIR1 and vMIR2 can be activated in the absence of full lytic activation, independent of viral RTA.\textsuperscript{37} Recently, the expression of vIL-6 was shown to be induced by the X-box binding protein-1 (XBP-1), which is commonly expressed in maturing B cells and plasma cells. In KSHV/HHV8-associated MCD, most of the vIL-6-producing cells were found to coexpress XBP-1.\textsuperscript{38} This extra layer of regulation may explain why it is not uncommon to see lytic gene expression in KSHV- HHV8-infected cells without full lytic replication.

One of the unique characteristics of KSHV/HHV8 is its ‘molecular piracy’ – the expression of several homologs of important human regulatory proteins involved in cell proliferation, survival and immune response.\textsuperscript{39, 40} The functions of those viral homologs as well as other major non-homologous KSHV/HHV8 gene products are summarized in Table 1. More detailed information can be found in several recent reviews.\textsuperscript{41, 42}

The viral gene expression profile appears to differ among KSHV/HHV8-infected disorders. In Kaposi sarcoma and PEL, the vast majority of KSHV/HHV8-infected cells express latent genes, while lytic proteins are expressed in only a small percentage of cells. In contrast, a substantial proportion of KSHV/HHV8-infected cells in MCD express lytic proteins including vIL-6 and vIRF1.\textsuperscript{82–84} The serum levels of antibodies against different KSHV/ HHV8 proteins can actually discriminate patients with Kaposi sarcoma from those with both MCD and Kaposi sarcoma.\textsuperscript{85}

The contribution of KSHV/HHV8-encoded proteins has been well established in the oncogenesis of Kaposi sarcoma and PEL.\textsuperscript{41} For KSHV/HHV8-associated MCD, the lytic activation, in particular the production of vIL-6, is thought to underlie its pathogenesis,\textsuperscript{86} although the latent proteins also appear to be involved. For instance, specific expression of the latent gene vFLIP in B cells has been shown to result in MCD-like abnormalities in mice.\textsuperscript{30}

MCD symptoms are thought to be caused by an excess of certain cytokines. The levels of several cytokines were noted to elevate during flares in MCD, including IL-6, IL-10, tumor necrosis factor-α (TNFα) and IL-1.\textsuperscript{87–89} In KSHV/HHV8-associated MCD, several KSHV/ HHV8 products are capable of upregulating cellular IL-6 expression- for example, vFLIP.
vGPCR and LANA-1, or activating its signaling pathways- for example, vIL-6 and kaposin 
B 43, 62, 72, 80, 81 Among them, vIL-6 is well known to play a pivotal role in the pathogenesis 
of MCD. KSHV/HHV8-encoded vIL-6 is different from its human counterpart in several 
aspects. Their sequence homology is approximately 25%. 40, 90 Unlike human IL-6 (hIL-6), 
whose signaling requires binding to both the classical IL-6 receptor gp80 (IL-6Rα) and 
gp130, vIL-6 is able to signal by forming complex with gp130 alone, and stimulate all of the 
known IL-6-induced signaling pathways.43, 91 Although the signaling potency of vIL-6 is 
lower than hIL-6, the ubiquitous expression of gp130 in human tissues allows vIL-6 to 
initiate signaling in a wider variety of cell types than hIL-6 does.43 In KSHV/HHV8-
associated MCD patients, vIL-6 can be detected in the circulation, and its levels correlate 
with disease activity.89, 93 When expressed constitutively in mice, both hIL-6 and vIL-6 can 
induce symptoms that resemble human MCD, while the symptoms can be ameliorated by 
bloklade of IL-6 signaling with anti-IL-6 receptor antibodies.94, 95 Of note, in the vIL-6 
transgenic mice, the production of endogenous IL-6 was also significantly upregulated; 
when the vIL-6 transgene was transferred onto an IL-6-deficient genetic background, the 
MCD-like phenotypes were abrogated, indicating that endogenous IL-6 is crucial in the 
pathogenesis of the disease.96 The collaboration of viral and endogenous IL-6 was also 
supported by clinical studies showing that clinical flares associated with elevations in both 
hIL-6 and vIL-6 tend to exhibit more severe laboratory abnormalities.89

**KSHV inflammatory cytokine syndrome**

Recently, another KSHV/HHV8-associated condition, the KSHV inflammatory cytokine 
syndrome (KICS) has been described in HIV-positive patients by Uldrick and colleagues.97 
The clinical manifestations of KICS resemble those of MCD, but lymphadenopathy is not 
prominent, and the pathological changes typically seen in MCD are absent, although 
abnormal KSHV/HHV8-infected mononuclear cells were sometimes detected in the biopsy 
specimens. All of the reported patients have had evidence of Kaposi sarcoma in skin, lymph 
nodes, or other sites. During follow-up, none of the patients developed MCD. A working 
case definition has been proposed that requires MCD-like clinical, laboratory, and 
radiographic manifestations together with evidence of KSHV lytic activity (> 100 viral 
copies / 10^6 peripheral blood mononuclear cells) and systemic inflammation (CRP > 3 g/ 
dL), and exclusion of MCD pathologically if the patients have enlarged accessible lymph 
nodes for biopsy.86

It was hypothesized that the symptoms of KICS also result from lytic activation of KSHV/ 
HHV8 and consequent cytokine production as in MCD.86 In the reported cohort of KICS, 
the patients all presented with markedly elevated KSHV loads in peripheral blood. The 
cytokine profiles including vIL-6, hIL-6 and IL-10 were similar to those seen in MCD flares. 
It was thought that patients with lytically active KSHV manifest systemic symptoms even in 
the absence of the pathological changes diagnostic MCD. However, the precise relationship 
between KICS and MCD is not clear. It is possible that KICS may represent a prodrome, or 
a limited presentation of MCD that may evolve to frank MCD. It is also possible that KICS 
may represent another entity with other cellular sources of KSHV lytic activation, such as 
KSHV infected monocytes or macrophages. Further studies are required to investigate those 
possibilities.
Large B-cell lymphoma arising in HHV8-associated MCD

Patients with KSHV/HHV8-associated MCD had been known to show a higher incidence of non-Hodgkin lymphoma. In HIV-associated MCD patients, the incidence was reported to be 15-fold higher than in the general HIV-positive population. In rare cases, the KSHV/HHV8-positive plasmablasts coalesce to form confluent clusters, which had been called ‘microlymphoma’ in the past to indicate the potential of transition to overt lymphoma, although the collections of plasmablastic cells did not show monoclonality in the reported cases. Although it is conceivable that some of the multiple clones in the so-called ‘microlymphoma’ might progress and give rise to an overt malignancy, a clear clonal relationship has not been demonstrated between the ‘microlymphoma’ and frank lymphoma in patients who concomitantly have both entities. Thus, to avoid confusion, the term ‘microlymphoma’ should not be used, and those cases are better considered as a variant of MCD.

On the other hand, there are rare cases of bona fide lymphoma that occur in the setting of MCD, which is recognized as large B-cell lymphoma arising in HHV8-associated MCD (LBCL-MCD) in the current World Health Organization classification. Histologically, LBCL-MCD usually present as sheets of plasmablastic cells outside the follicles. The phenotype of the atypical cells in LBCL-MCD is virtually identical to that of the KSHV/HHV8-infected plasmablasts in MCD. They both express OCT2, BLIMP1 and IRF4/MUM1, but lack PAX5, CD138 and EBV infection. LBCL-MCD also strongly expresses cytoplasmic IgM with λ light-chain restriction, but unlike the polyclonal nature of the plasmablastic cells in MCD, LBCL-MCD are monoclonal by definition. LBCL-MCD should be distinguished from other B cell lineage lymphomas with similar plasmablastic features, including plasmablastic lymphoma (PBL), ALK-positive large B-cell lymphoma (ALK-LBCL) and primary effusion lymphoma (PEL). The main features of these entities are summarized in Table 2. More information can be found in other recent reviews.

KSHV- and EBV-associated germinotropic lymphoproliferative disorder

Germinotropic lymphoproliferative disorder (GLPD) is a rare disease entity. It was first described by Du and colleagues, who reported 3 cases of a distinct KSHV/HHV8 and EBV-coinfected polyclonal lymphoproliferative disorder that preferentially involved the germinal centers. Since then, a few more cases have been published. The cases all presented as localized lymphadenopathy in HIV-negative patients without obvious systemic symptoms, and showed a favorable response to chemotherapy or radiotherapy. Histologically, it is characterized by plasmablasts forming large aggregates within the germinal centers (Figure 4A–B), while the uninvolved follicles show only reactive changes and the overall architecture of lymph node is preserved. The plasmablasts are negative for CD45, CD20, CD79a, CD10 and BCL6, but are positive for IRF4/MUM1, KSHV/HHV8 and EBV (Figure 4C–D). CD 138 is negative in most cases. The confluent plasmablastic cells show monotypic expression of immunoglobulins, but molecular analyses all showed polyclonal rearrangement pattern of the IG gene.

Morphologically and immunophenotypically, GLPD may mimic the previously-called ‘microlymphoma’ variant of MCD. Both entities show an atypical polyclonal plasmablastic...
proliferation that lacks B cell marker expression but exhibits early plasmacytic differentiation as suggested by the expression of IRF4/MUM1 and general lack of CD 138. They both show monotypic cytoplasmic Ig expression, but lack clonality at the molecular level. However, unlike the restricted IgM\(\lambda\) expression in MCD, the Ig subtype is not limited to IgM in GLPD, and there is no predilection for either \(\kappa\) or \(\lambda\) light chains. Additionally, somatic hypermutation of the Ig genes has been detected in GLPD,\(^{105}\) which is not present in MCD; this feature indicates a late or post-germinal center derivation of GLPD, which is different from the proposed origin from naïve B cells undergoing extrafollicular plasmacytic differentiation for MCD. Significantly, the KSHV/HHV8 infected cells in GLPD are confined to the involved germinal centers, and there is no background of MCD changes in the uninvolved portions. Moreover, the co-infection with EBV, the clinical presentation as localized disease without systemic symptoms and the favorable clinical outcome of GLPD are also distinct from MCD. However, the potential for GLPD to progress to a frank lymphoma is uncertain.\(^{101}\)

**KSHV/HHV8-negative Idiopathic Multicentric Castleman Disease**

Since the discovery of KSHV/HHV8 in MCD,\(^{12}\) intensive investigations have established the causative role of KSHV/HHV8 in the pathogenesis of MCD in all HIV-positive cases as well as in some HIV-negative patients. However, for the remaining cases of MCD that are negative for KSHV/HHV8, the etiology remains obscure. Those cases have been collectively denoted as idiopathic MCD (iMCD).\(^{13}\)

Like KSHV/HHV8-associated MCD, iMCD is also characterized by proinflammatory hypercytokinemia. Several cytokines and growth factors have been implicated, including IL-6, VEGF, IL-1 and TNF\(\alpha\).\(^{13}\) Among the cytokines that are dysregulated, IL-6 again plays a pivotal role. The pathophysiologic significance of IL-6 in iMCD has been confirmed by the efficacy of anti-IL-6 therapy in iMCD patients.\(^{110,112}\) A recent phase II randomized placebo-controlled clinical trial in iMCD showed a durable response to siltuximab, a chimeric monoclonal anti-hIL-6 antibody, in 34% of patients (versus 0% in the placebo group, \(p=0.0012\)) and which has led to the approval for this drug in the treatment of HIV-negative KSHV/HHV8-negative MCD by FDA.\(^{112,113}\)

However, the etiology that drives the cytokine hypersecretion has not been elucidated. Sporadic reports have shown cytogenetic abnormality or prevalent gene polymorphism that involves the IL-6 (presumed by the authors) or IL-6 receptor genes in iMCD patients,\(^{114,115}\) suggesting that germline aberration in genes involved in the regulation of innate immunity may play a role. Additional hypotheses have been proposed, including an autoimmune/autoinflammatory mechanism, paraneoplastic disorder or a unidentified non-KSHV/HHV8 viral etiology.\(^{13}\) Thus, iMCD likely represent a heterogeneous group of diseases with overlap in pathological features and clinical findings.

**Idiopathic MCD, plasma cell variant**

Like KSHV/HHV8-associated MCD, iMCD can also show features of both hyaline vascular and plasma cell variant CD. However, iMCD generally presents with marked plasmacytosis and a lesser degree of vascular proliferation and hyalination, in comparison to KSHV/HHV8-negative idiopathic MCD.
HHV8-associated MCD.\textsuperscript{116} In Japan, there have been cases referred to as idiopathic plasmacytic lymphadenopathy since 1980s,\textsuperscript{117, 118} which show similar features to those originally reported by Frizzera et al.\textsuperscript{5} The patients usually present with multicentric lymphadenopathy, prominent polyclonal hypergammaglobulinemia, anemia, elevated erythrocyte sedimentation rate, elevated serum IL-6, bone marrow plasmacytosis, etc. Histologically, it is characterized by sheet-like proliferation of polytypic mature plasma cells in the interfollicular area with relatively normal germinal centers (Figure 5A–B). Together these cases constitute what we refer to as the plasma cell variant of iMCD.

**TAFRO syndrome**

Recently, a distinct group of patients have been reported that present with lymphadenopathy showing MCD features and a constellation of symptoms including thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly, which was dubbed TAFRO syndrome.\textsuperscript{119} The TAFRO syndrome usually occurs in the middle-aged and elderly, with a median age of 56.\textsuperscript{120} It has a 4:1 predilection for female gender. It is not associated with viral infection including KSHV/HHV8, HIV or EBV. Patients with TAFRO syndrome generally have a prolonged clinical course, but with sporadic flares of the disease which can be severe.\textsuperscript{119} The disease appears to respond to corticosteroid and/or IL-6 targeting strategies, although with a reported lower rate of response than in plasma cell variant of iMCD.\textsuperscript{121}

The lymphadenopathy in TAFRO syndrome is usually mild, generally less than 1.5 cm in diameter. Histologically, the involved lymph nodes usually exhibit a lesser degree of plasmacytosis, and are characterized by marked vascular proliferation in the interfollicular areas. The germinal centers are often atrophic with increased vessels lined by plump endothelial cells with enlarged nuclei and less hyalinization than seen in classical unicentric CD. Bone marrow biopsies often show megakaryocyte hyperplasia with occasional megakaryocytic emperipolesis, associated with loose myelofibrosis. (Figure 5C–F).\textsuperscript{119–124} These distinct clinopathologic features suggest that the TAFRO syndrome may represent a distinct subtype of what has been considered iMCD.

**POEMS syndrome**

Of note, the morphologic features of the plasma cell variant of CD can be seen in association with the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes), which is a paraneoplastic syndrome due to an underlying monoclonal plasma cell neoplasm.\textsuperscript{125–127} Patients of POEMS syndrome usually present with sclerotic bone lesions, rather than the typical osteolytic lesions seen in multiple myeloma. In bone marrow biopsies, monoclonal plasma cells can be detected in two third of cases; the majority express \(\lambda\) light chain. Half of the patients show distinctive lymphoid aggregates rimmed by plasma cells. Megakaryocyte hyperplasia or clustering is also frequently seen.\textsuperscript{128} Between 11 and 30\% of POEMS patients were shown to have lymphadenopathy with Castleman-like histology.\textsuperscript{125} Some investigators believe this prevalence rate may be an underestimation, as only a small portion of POEMS patients with lymphadenopathy undergo lymph node biopsy.\textsuperscript{129} In fact, the presence of Castleman disease is one of the major criteria for the diagnosis of POEMS syndrome.\textsuperscript{125} Thus, all patients presenting with the plasma cell variant
of Castleman disease should be carefully surveyed to exclude the possibility of associated POEMS syndrome.

Conclusions

In this article, we reviewed the current knowledge of Castleman disease, with an emphasis on MCD, which is often diagnostically challenging. The challenges arise from several sources. First, the pathological findings are not specific, and can be seen in many conditions. Secondly, the presentation is heterogeneous. The heterogeneity may result from different disease stages or interplay between different etiologic cytokines. Thirdly, the associated viruses, including HIV, KSHV/HHV8 and even EBV can lead to various lymphoproliferative disorders either independent of or in association with MCD, which can greatly confound the differential diagnoses.

Since the first reports from Castleman and coworkers more than 60 years ago, our growing knowledge about the various conditions associated with name ‘Castleman disease’ has illustrated the paradigm of disease discovery. In this model a disease is initially recognized by distinctive pathological features; understanding of the disease further evolves through the integration of pathological findings with clinical observations. Ultimately, discoveries in the modern molecular era provide insights into pathogenesis, pathophysiology, and lead to advances in therapy and a resolution of multiple conditions that may share overlapping pathological features. Much is still unknown, not only about MCD, but also the related virus-associated lymphoproliferative disorders. We envision that diagnostic pathology will still play an integral part in defining new entities and driving the subsequent clinical and basic research in the future.

Reference

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Figure 1. Classification of Castleman disease
UCD: unicentric Castleman disease; MCD: multicentric Castleman disease; HV: hyaline vascular; PC: plasma cell; iMCD: idiopathic multicentric Castleman disease.
Figure 2. Hyaline vascular Castleman disease
A. H&E stain showing the hyaline vascular changes of the lymphoid follicles including the penetrating hyalinized vessels, layered mantle cells and twinning of the germinal centers. B. H&E stain showing occasional dysplastic follicular dendritic cells within the follicles.
Figure 3. Multicentric Castleman disease
A. Low magnification shows marked vascular proliferation in the paracortex, with increased vascularity within a reactive germinal center. B. High magnification H&E stain showing the plasmablastic cells in the mantle zone. C. Immunohistochemical stain for KSHV/HHV-8 encoded LANA-1 highlighting the infected plasmablasts in the mantle zone. D. Immunostain for vIL-6 showing that the plasmablasts express vIL-6. E-F. Immunohistochemical stains for immunoglobulin κ and λ light chains showing restricted
expression of \( \lambda \) light chain in the plasmablasts (arrow), while the plasma cells in the interfollicular areas are polyclonal.
Figure 4. Germinotropic lymphoproliferative disorder
A–B: H&E stains showing confluent aggregates of atypical plasmablasts within the involved germinal centers. C. Immunohistochemical stain for KSHV/HHV-8 encoded LANA-1 highlighting the atypical plasmablasts. D. In-situ hybridization for EBV-encoded RNAs (EBER) showing co-infection of EBV in the atypical plasmablasts.
Figure 5. Histologic features of the plasma cell variant of idiopathic multicentric Castleman disease (iMCD) and TAFRO syndrome

A–B: plasma cell variant of iMCD; C–F: TAFRO syndrome. A: H&E stain showing sheets of plasma cells in the interfollicular areas with relatively well formed germinal centers in plasma cell variant of iMCD. B. CD138 stain highlighting sheets of interfollicular plasma cells. C. H&E stain showing prominent vascular proliferation and atrophic germinal centers in TAFRO syndrome. D. CD138 demonstrating a lesser extent of plasmacytosis in the interfollicular areas. E. H&E stain highlighting marked vascular proliferation with plump...
endothelial cells. F. Bone marrow biopsy/aspirate showing megakaryocytic hyperplasia with occasional emperipolesis in megakaryocytes.
### Table 1

**Major KSHV/HHV8-encoded proteins and their cellular effects**

<table>
<thead>
<tr>
<th>Gene</th>
<th>ORF</th>
<th>Phase</th>
<th>Major cellular effects</th>
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<td>vIL-6</td>
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<td>K3</td>
<td>Lytic</td>
<td>Downregulates MHC-I</td>
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<td>Chemoattracts TH2-type lymphocytes by binding to CCR3</td>
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<tr>
<td>vCCL3</td>
<td>K4.1</td>
<td>Lytic</td>
<td>Chemoattracts TH2-type lymphocytes by binding to CCR4</td>
<td>47</td>
</tr>
<tr>
<td>vMIR2</td>
<td>K5</td>
<td>Lytic</td>
<td>Downregulates MHC-I</td>
<td>44, 45</td>
</tr>
<tr>
<td>vCCL1</td>
<td>K6</td>
<td>Lytic</td>
<td>Chemoattracts TH2-type lymphocytes by binding to CCR8</td>
<td>48</td>
</tr>
<tr>
<td>vIAP</td>
<td>K7</td>
<td>Lytic</td>
<td>Inhibits apoptosis by interacting with Bcl-2 and inhibiting caspase 3</td>
<td>49</td>
</tr>
<tr>
<td>vBCL-2</td>
<td>ORF16</td>
<td>Lytic</td>
<td>Inhibits apoptosis</td>
<td>50</td>
</tr>
<tr>
<td>vIRF1</td>
<td>K9</td>
<td>Lytic</td>
<td>Inhibits interferon-induced antiviral responses and apoptosis by blocking interferon signaling pathways and inactivating p53 and Bim</td>
<td>51–53</td>
</tr>
<tr>
<td>vIRF2</td>
<td>K11/K11.1</td>
<td>Lytic</td>
<td>Inhibits interferon-induced antiviral responses</td>
<td>54</td>
</tr>
<tr>
<td>vIRF3</td>
<td>K10.5/K10.6</td>
<td>Lytic</td>
<td>Inhibits interferon-induced antiviral responses, Promotes angiogenesis by stabilizing HIF-1 and inducing VEGF</td>
<td>55–57</td>
</tr>
<tr>
<td>vIRF4</td>
<td>K10/K10.1</td>
<td>Lytic</td>
<td>Inhibits apoptosis by stabilizing MDM2 to target p53, Activates lytic gene expression by cooperating with RTA</td>
<td>58, 59</td>
</tr>
<tr>
<td>vFLIP</td>
<td>ORF71/K13</td>
<td>Latent</td>
<td>Inhibits Fas/TNFR mediated cell death, Activates NF-κB pathway, Induces IL-6 expression by activating JNK/API1 signaling, Suppresses autophagy</td>
<td>60–63</td>
</tr>
<tr>
<td>vCyclin</td>
<td>ORF72</td>
<td>Latent</td>
<td>Promotes cell cycle progression by activating cdk6 to phosphorylate Rb and P27</td>
<td>64–66</td>
</tr>
<tr>
<td>vOX-2</td>
<td>K14</td>
<td>Latent</td>
<td>Modulates macrophage activity - increases basal cytokine production but downregulates response to IFNγ in macrophages</td>
<td>67, 68</td>
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<tr>
<td>vGPCR</td>
<td>ORF74</td>
<td>Lytic</td>
<td>Promotes angiogenesis by upregulating VEGF, VEGFR2 and angiopoietin-like 4, Activates Akt and mTOR pathways in endothelial cells, Upregulates cellular cytokine secretion</td>
<td>69–74</td>
</tr>
</tbody>
</table>
### II. Non-homologous viral gene products

<table>
<thead>
<tr>
<th>Gene</th>
<th>ORF</th>
<th>Phase</th>
<th>Major cellular effects</th>
<th>Selected references</th>
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<tbody>
<tr>
<td>RTA</td>
<td>ORF50</td>
<td>Lytic</td>
<td>* Master regulator of lytic gene expression</td>
<td>36</td>
</tr>
</tbody>
</table>
| LANA-1 | ORF73 | Latent | * Promotes cell cycle progression by targeting Rb  
* Inhibits apoptosis by repressing p53  
* Induces cellular IL-6 expression  
* Maintains latent status by stabilizing viral episomes and antagonizing RTA | 75–79                |
| Kaposins | K12  | Latent | * Stabilizes cytokine transcripts  
* Activates STAT3 pathways | 80, 81               |
### Table 2
Differential diagnoses of B cell lymphoproliferative disorders with plasmablastic features

<table>
<thead>
<tr>
<th></th>
<th>LBCL-MCD</th>
<th>GLPD</th>
<th>PEL</th>
<th>PBL</th>
<th>ALK-LBCL</th>
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</thead>
<tbody>
<tr>
<td>Immunophenotype</td>
<td>CD20+/−, IRF4/MUM1+, CD138−</td>
<td>CD20−, CD79a−, IRF4/MUM1+, CD138−/+</td>
<td>CD20−, CD79a−, IRF4/MUM1+, CD138+</td>
<td>CD20−, CD79a−, IRF4/MUM1+, CD138+, ALK+</td>
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<tr>
<td>Cytoplasmic Ig</td>
<td>+, monotypic IgM, λ</td>
<td>−</td>
<td>−</td>
<td>+, monotypic IgG, κ or λ</td>
<td>+, monotypic IgA &gt; IgG, κ or λ</td>
</tr>
<tr>
<td></td>
<td>+, monotypic variable IgH, κ or λ</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Ig rearrangement</td>
<td>Monoclonal</td>
<td>Polyclonal</td>
<td>Monoclonal</td>
<td>Monoclonal</td>
<td>Monoclonal</td>
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<tr>
<td>V\textsubscript{H} hypermutation</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>EBV</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>KSHV/HHV8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>HIV association</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

LBCL-MCD: Large B-cell lymphoma arising in HHV8-associated MCD; PEL: Primary effusion lymphoma; GLPD: Germinotropic lymphoproliferative disorder; PBL: Plasmablastic lymphoma; ALK-LBCL: ALK positive large B cell lymphoma.