Published in final edited form as:

Semin Diagn Pathol. 2016 September ; 33(5): 294–306. doi:10.1053/j.semdp.2016.05.006.

Multicentric Castleman Disease: Where are we now?

Hao-Wei Wang, M.D., Ph.D., Stefania Pittaluga, M.D., Ph.D., and Elaine S. Jaffe, M.D.

Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health

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.¹ In a subsequent report of twelve more cases, Castleman and colleagues further characterized the clinicopathologic findings.² The patients all presented with enlarged mediastinal masses with none or only mild nonspecific systemic symptoms. Two major

Address for correspondence: Elaine S. Jaffe, M.D., Head, Hematopathology Section, Laboratory of Pathology, NCI, Building 10, Room 3S 235, MSC-1500, National Institutes of Health, Bethesda, MD 20892, ejaffe@mail.nih.gov, Phone: 301-480-8461, FAX: 301-480-8089.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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,^{1, 2} 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.³ 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).⁴ 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),⁵ and comprehensively analyzed the morphological, clinical and immunophenotypic features.⁵⁻⁷ 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,^{8, 9} After the human immunodeficiency virus (HIV) was identified as the etiologic agent of AIDS, the association between MCD and HIV infection was further established.^{10, 11} 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 1995.¹²

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).¹³ 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.^{4, 14} Surgical excision is the treatment of choice, and recurrence is uncommon.^{14, 15}

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.^{16, 17} 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.^{18–20}

Unicentric Castleman disease, plasma cell type

The plasma cell type comprises around 10% of cases of unicentric Castleman disease.^{3, 4} The demographic features resemble those of the hyaline vascular type.^{4, 14} 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.^{4, 14}

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,¹⁴ although rare cases that exhibit monotypic immunoglobulins, predominantly of λ light chain, have also been reported.^{21–23}

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.²⁴ 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.²⁵ They express high levels of cytoplasmic IgM with monotypic λ 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.^{25, 26}

The monotypic but polyclonal nature of the λ -restricted KSHV/HHV8-infected cells has been enigmatic. Two hypotheses have been proposed, including preferential targeting of λ light chain-expressing B cells by KSHV/HHV8 viruses or selective expansion of λ light chain-expressing B cells in response to viral infection.²⁶ The detection of κ light chain or its transcript in other KSHV/HHV8-associated lymphoproliferative disorders, such as primary effusion lymphoma (PEL),²⁷ appears to argue against the first hypothesis. However, a study using *ex vivo* KSHV/HHV8 infection of tonsillar cells showed that latent KSHV/HHV8-infected cells were overwhelmingly enriched in the λ than the κ subset, suggesting that KSHV/HHV8 preferentially targets λ light chain-expressing B cells for stable latent infection.²⁸ In addition, recent studies demonstrated that the generation of λ light chain-positive B cells is dependent on the NF- κ B signals during normal B cell development.²⁹ Interestingly, in a transgenic mouse model, targeted expression of KSHV/HHV8 gene vFLIP, which acts as a NF- κ B activator, in B cells resulted in an increase in λ light chain-expressing cells in addition to other MCD features.³⁰ The data suggest that the intrinsic viral effects (eg. vFLIP) may also be implicated in this enigmatic predilection for λ 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,³¹ and was subsequently established to also be the etiologic agent of primary effusion lymphoma (PEL) and MCD.^{12, 32, 33} It is a gamma herpesvirus that has a large double-stranded DNA genome encoding 87 open reading frames (ORFs) and an array of

microRNAs.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.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.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.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-1.³⁸ 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.^{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.^{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.^{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.⁸⁵

The contribution of KSHV/HHV8-encoded proteins has been well established in the oncogenesis of Kaposi sarcoma and PEL.⁴¹ For KSHV/HHV8-associated MCD, the lytic activation, in particular the production of vIL-6, is thought to underlie its pathogenesis⁸⁶, 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.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 (TNF α) and IL-1.^{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-6R α) 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-6⁹², 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 blockade 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.^{98–100} In HIV-associated MCD patients, the incidence was reported to be 15-fold higher than in the general HIV-positive population.⁹⁸ 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.^{26, 100–102} 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.²⁶ 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.¹⁰³ 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.^{23, 104}

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.¹⁰⁵ Since then, a few more cases have been published.^{101, 106–109} 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 λ expression in MCD, the Ig subtype is not limited to IgM in GLPD, and there is no predilection for either κ or λ 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 α .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-associated MCD.¹¹⁶ In Japan, there have been cases referred to as idiopathic plasmacytic lymphadenopathy since 1980s,^{117, 118} which show similar features to those originally reported by Frizzera et al.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.¹¹⁹ The TAFRO syndrome usually occurs in the middle-aged and elderly, with a median age of 56.¹²⁰ 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.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.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 emperipoiesis, associated with loose myelofibrosis. (Figure 5C–F).^{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.^{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 λ light chain. Half of the patients show distinctive lymphoid aggregates rimmed by plasma cells. Megakaryocyte hyperplasia or clustering is also frequently seen.¹²⁸ Between 11 and 30% of POEMS patients were shown to have lymphadenopathy with Castleman-like histology.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.¹²⁹ In fact, the presence of Castleman disease is one of the major criteria for the diagnosis of POEMS syndrome.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

1. Castleman B, Towne VW. CASE records of the Massachusetts General Hospital Weekly Clinicopathological Exercises: Case 40011. *N Engl J Med*. 1954; 250:26–30. [PubMed: 13111435]
2. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymphnode hyperplasia resembling thymoma. *Cancer*. 1956; 9:822–830. [PubMed: 13356266]
3. Flendrig JA. Benign giant lymphoma: clinicopathologic correlation study. *The Year Book of Cancer*. 1970:296–299.
4. Keller AR, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer*. 1972; 29:670–683. [PubMed: 4551306]
5. Frizzera G, Banks PM, Massarelli G, Rosai J. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease. Pathological findings in 15 patients. *Am J Surg Pathol*. 1983; 7:211–231. [PubMed: 6837832]
6. Miller RT, Mukai K, Banks PM, Frizzera G. Systemic lymphoproliferative disorder with morphologic features of Castleman's disease Immunoperoxidase study of cytoplasmic immunoglobulins. *Archives of pathology & laboratory medicine*. 1984; 108:626–630. [PubMed: 6204622]
7. Frizzera G, Peterson BA, Bayrd ED, Goldman A. A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: clinical findings and clinicopathologic correlations in 15 patients. *J Clin Oncol*. 1985; 3:1202–1216. [PubMed: 4031967]
8. Harris NL. Hypervascular follicular hyperplasia and Kaposi's sarcoma in patients at risk for AIDS. *N Engl J Med*. 1984; 310:462–463. [PubMed: 6694687]
9. Lachant NA, Sun NC, Leong LA, Oseas RS, Prince HE. Multicentric angiofollicular lymph node hyperplasia (Castleman's disease) followed by Kaposi's sarcoma in two homosexual males with the

acquired immunodeficiency syndrome (AIDS). *Am J Clin Pathol.* 1985; 83:27–33. [PubMed: 3871303]

10. Lowenthal DA, Filippa DA, Richardson ME, Berton M, Straus DJ. Generalized lymphadenopathy with morphologic features of Castleman's disease in an HIV-positive man. *Cancer.* 1987; 60:2454–2458. [PubMed: 3478119]
11. Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *Aids.* 1996; 10:61–67. [PubMed: 8924253]
12. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood.* 1995; 86:1276–1280. [PubMed: 7632932]
13. Fajgenbaum DC, van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. *Blood.* 2014; 123:2924–2933. [PubMed: 24622327]
14. Frizzera G. Castleman's disease and related disorders. *Semin Diagn Pathol.* 1988; 5:346–364. [PubMed: 2464187]
15. Talat N, Belgaumkar AP, Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. *Annals of surgery.* 2012; 255:677–684. [PubMed: 22367441]
16. Chan JK, Fletcher CD, Nayler SJ, Cooper K. Follicular dendritic cell sarcoma Clinicopathologic analysis of 17 cases suggesting a malignant potential higher than currently recognized. *Cancer.* 1997; 79:294–313. [PubMed: 9010103]
17. Chan AC, Chan KW, Chan JK, Au WY, Ho WK, Ng WM. Development of follicular dendritic cell sarcoma in hyaline-vascular Castleman's disease of the nasopharynx: tracing its evolution by sequential biopsies. *Histopathology.* 2001; 38:510–518. [PubMed: 11422494]
18. Pauwels P, Dal Cin P, Vlasveld LT, Aleva RM, van Erp WF, Jones D. A chromosomal abnormality in hyaline vascular Castleman's disease: evidence for clonal proliferation of dysplastic stromal cells. *Am J Surg Pathol.* 2000; 24:882–888. [PubMed: 10843293]
19. Cokelaere K, Debiec-Rychter M, De Wolf-Peeters C, Hagemeijer A, Sciort R. Hyaline vascular Castleman's disease with HMGIC rearrangement in follicular dendritic cells: molecular evidence of mesenchymal tumorigenesis. *Am J Surg Pathol.* 2002; 26:662–669. [PubMed: 11979097]
20. Chang KC, Wang YC, Hung LY, et al. Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. *Mod Pathol.* 2014; 27:823–831. [PubMed: 24201121]
21. Radaszkiewicz T, Hansmann ML, Lennert K. Monoclonality and polyclonality of plasma cells in Castleman's disease of the plasma cell variant. *Histopathology.* 1989; 14:11–24. [PubMed: 2925176]
22. Hall PA, Donaghy M, Cotter FE, Stansfeld AG, Levison DA. An immunohistological and genotypic study of the plasma cell form of Castleman's disease. *Histopathology.* 1989; 14:333–346. discussion 429–332. [PubMed: 2737612]
23. Hsi ED, Lersbach RB, Fend F, Dogan A. Plasmablastic lymphoma and related disorders. *Am J Clin Pathol.* 2011; 136:183–194. [PubMed: 21757592]
24. Uldrick TS, Polizzotto MN, Yarchoan R. Recent advances in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Curr Opin Oncol.* 2012; 24:495–505. [PubMed: 22729151]
25. Chadburn A, Hyjek EM, Tam W, et al. Immunophenotypic analysis of the Kaposi sarcoma herpesvirus (KSHV; HHV-8)-infected B cells in HIV+ multicentric Castleman disease (MCD). *Histopathology.* 2008; 53:513–524. [PubMed: 18983461]
26. Du MQ, Liu H, Diss TC, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. *Blood.* 2001; 97:2130–2136. [PubMed: 11264181]
27. Wakely PE Jr, Menezes G, Nuovo GJ. Primary effusion lymphoma: cytopathologic diagnosis using in situ molecular genetic analysis for human herpesvirus 8. *Mod Pathol.* 2002; 15:944–950. [PubMed: 12218212]
28. Hassman LM, Ellison TJ, Kedes DH. KSHV infects a subset of human tonsillar B cells, driving proliferation and plasmablast differentiation. *The Journal of clinical investigation.* 2011; 121:752–768. [PubMed: 21245574]

29. Derudder E, Cadera EJ, Vahl JC, et al. Development of immunoglobulin lambda-chain-positive B cells, but not editing of immunoglobulin kappa-chain, depends on NF-kappaB signals. *Nature immunology*. 2009; 10:647–654. [PubMed: 19412180]
30. Ballon G, Chen K, Perez R, Tam W, Cesarman E. Kaposi sarcoma herpesvirus (KSHV) vFLIP oncoprotein induces B cell transdifferentiation and tumorigenesis in mice. *The Journal of clinical investigation*. 2011; 121:1141–1153. [PubMed: 21339646]
31. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994; 266:1865–1869. [PubMed: 7997879]
32. Bhutani M, Polizzotto MN, Uldrick TS, Yarchoan R. Kaposi sarcoma-associated herpesvirus-associated malignancies: epidemiology, pathogenesis, and advances in treatment. *Semin Oncol*. 2015; 42:223–246. [PubMed: 25843728]
33. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med*. 1995; 332:1186–1191. [PubMed: 7700311]
34. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. *Nature reviews. Cancer*. 2010; 10:707–719. [PubMed: 20865011]
35. Gunther T, Grundhoff A. The epigenetic landscape of latent Kaposi sarcoma-associated herpesvirus genomes. *PLoS pathogens*. 2010; 6:e1000935. [PubMed: 20532208]
36. Sun R, Lin SF, Gradoville L, Yuan Y, Zhu F, Miller G. A viral gene that activates lytic cycle expression of Kaposi's sarcoma-associated herpesvirus. *Proceedings of the National Academy of Sciences of the United States of America*. 1998; 95:10866–10871. [PubMed: 9724796]
37. Chang H, Dittmer DP, Shin YC, Hong Y, Jung JU. Role of Notch signal transduction in Kaposi's sarcoma-associated herpesvirus gene expression. *J Virol*. 2005; 79:14371–14382. [PubMed: 16254371]
38. Hu D, Wang V, Yang M, et al. Induction of Kaposi Sarcoma Herpesvirus-encoded Viral Interleukin-6 by X-Box Binding Protein-1. *J Virol*. 2015
39. Coscoy L. Immune evasion by Kaposi's sarcoma-associated herpesvirus. *Nature reviews. Immunology*. 2007; 7:391–401.
40. Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science*. 1996; 274:1739–1744. [PubMed: 8939871]
41. Schulz TF, Cesarman E. Kaposi Sarcoma-associated Herpesvirus: mechanisms of oncogenesis. *Curr Opin Virol*. 2015; 14:116–128. [PubMed: 26431609]
42. Cesarman E. Gammaherpesviruses and lymphoproliferative disorders. *Annu Rev Pathol*. 2014; 9:349–372. [PubMed: 24111911]
43. Osborne J, Moore PS, Chang Y. KSHV-encoded viral IL-6 activates multiple human IL-6 signaling pathways. *Hum Immunol*. 1999; 60:921–927. [PubMed: 10566591]
44. Ishido S, Wang C, Lee BS, Cohen GB, Jung JU. Downregulation of major histocompatibility complex class I molecules by Kaposi's sarcoma-associated herpesvirus K3 and K5 proteins. *J Virol*. 2000; 74:5300–5309. [PubMed: 10799607]
45. Coscoy L, Ganem D. Kaposi's sarcoma-associated herpesvirus encodes two proteins that block cell surface display of MHC class I chains by enhancing their endocytosis. *Proceedings of the National Academy of Sciences of the United States of America*. 2000; 97:8051–8056. [PubMed: 10859362]
46. Weber KS, Grone HJ, Rocken M, et al. Selective recruitment of Th2-type cells and evasion from a cytotoxic immune response mediated by viral macrophage inhibitory protein-II. *European journal of immunology*. 2001; 31:2458–2466. [PubMed: 11500830]
47. Stine JT, Wood C, Hill M, et al. KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells. *Blood*. 2000; 95:1151–1157. [PubMed: 10666184]
48. Endres MJ, Garlisi CG, Xiao H, Shan L, Hedrick JA. The Kaposi's sarcoma-related herpesvirus (KSHV)-encoded chemokine vMIP-I is a specific agonist for the CC chemokine receptor (CCR)8. *The Journal of experimental medicine*. 1999; 189:1993–1998. [PubMed: 10377196]
49. Wang HW, Sharp TV, Koumi A, Koentges G, Boshoff C. Characterization of an anti-apoptotic glycoprotein encoded by Kaposi's sarcoma-associated herpesvirus which resembles a spliced variant of human survivin. *EMBO J*. 2002; 21:2602–2615. [PubMed: 12032073]

50. Cheng EH, Nicholas J, Bellows DS, et al. A Bcl-2 homolog encoded by Kaposi sarcoma-associated virus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. *Proceedings of the National Academy of Sciences of the United States of America*. 1997; 94:690–694. [PubMed: 9012846]
51. Lin R, Genin P, Mamane Y, et al. HHV-8 encoded vIRF-1 represses the interferon antiviral response by blocking IRF-3 recruitment of the CBP/p300 coactivators. *Oncogene*. 2001; 20:800–811. [PubMed: 11314014]
52. Seo T, Park J, Lee D, Hwang SG, Choe J. Viral interferon regulatory factor 1 of Kaposi's sarcoma-associated herpesvirus binds to p53 and represses p53-dependent transcription and apoptosis. *J Virol*. 2001; 75:6193–6198. [PubMed: 11390621]
53. Choi YB, Nicholas J. Bim nuclear translocation and inactivation by viral interferon regulatory factor. *PLoS pathogens*. 2010; 6:e1001031. [PubMed: 20700448]
54. Fuld S, Cunningham C, Klucher K, Davison AJ, Blackbourn DJ. Inhibition of interferon signaling by the Kaposi's sarcoma-associated herpesvirus full-length viral interferon regulatory factor 2 protein. *J Virol*. 2006; 80:3092–3097. [PubMed: 16501120]
55. Joo CH, Shin YC, Gack M, Wu L, Levy D, Jung JU. Inhibition of interferon regulatory factor 7 (IRF7)-mediated interferon signal transduction by the Kaposi's sarcoma-associated herpesvirus viral IRF homolog vIRF3. *J Virol*. 2007; 81:8282–8292. [PubMed: 17522209]
56. Shin YC, Joo CH, Gack MU, Lee HR, Jung JU. Kaposi's sarcoma-associated herpesvirus viral IFN regulatory factor 3 stabilizes hypoxia-inducible factor-1 alpha to induce vascular endothelial growth factor expression. *Cancer research*. 2008; 68:1751–1759. [PubMed: 18339855]
57. Wies E, Hahn AS, Schmidt K, et al. The Kaposi's Sarcoma-associated Herpesvirus-encoded vIRF-3 Inhibits Cellular IRF-5. *The Journal of biological chemistry*. 2009; 284:8525–8538. [PubMed: 19129183]
58. Lee HR, Toth Z, Shin YC, et al. Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor 4 targets MDM2 to deregulate the p53 tumor suppressor pathway. *J Virol*. 2009; 83:6739–6747. [PubMed: 19369353]
59. Xi X, Persson LM, O'Brien MW, Mohr I, Wilson AC. Cooperation between viral interferon regulatory factor 4 and RTA to activate a subset of Kaposi's sarcoma-associated herpesvirus lytic promoters. *J Virol*. 2012; 86:1021–1033. [PubMed: 22090118]
60. Thome M, Schneider P, Hofmann K, et al. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. *Nature*. 1997; 386:517–521. [PubMed: 9087414]
61. Liu L, Eby MT, Rathore N, Sinha SK, Kumar A, Chaudhary PM. The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and persistently activates the Ikkappa B kinase complex. *The Journal of biological chemistry*. 2002; 277:13745–13751. [PubMed: 11830587]
62. An J, Sun Y, Sun R, Rettig MB. Kaposi's sarcoma-associated herpesvirus encoded vFLIP induces cellular IL-6 expression: the role of the NF-kappaB and JNK/AP1 pathways. *Oncogene*. 2003; 22:3371–3385. [PubMed: 12776188]
63. Lee JS, Li Q, Lee JY, et al. FLIP-mediated autophagy regulation in cell death control. *Nat Cell Biol*. 2009; 11:1355–1362. [PubMed: 19838173]
64. Godden-Kent D, Talbot SJ, Boshoff C, et al. The cyclin encoded by Kaposi's sarcoma-associated herpesvirus stimulates cdk6 to phosphorylate the retinoblastoma protein and histone H1. *J Virol*. 1997; 71:4193–4198. [PubMed: 9151805]
65. Ellis M, Chew YP, Fallis L, et al. Degradation of p27(Kip) cdk inhibitor triggered by Kaposi's sarcoma virus cyclin-cdk6 complex. *EMBO J*. 1999; 18:644–653. [PubMed: 9927424]
66. Mann DJ, Child ES, Swanton C, Laman H, Jones N. Modulation of p27(Kip1) levels by the cyclin encoded by Kaposi's sarcoma-associated herpesvirus. *EMBO J*. 1999; 18:654–663. [PubMed: 9927425]
67. Chung YH, Means RE, Choi JK, Lee BS, Jung JU. Kaposi's sarcoma-associated herpesvirus OX2 glycoprotein activates myeloid-lineage cells to induce inflammatory cytokine production. *J Virol*. 2002; 76:4688–4698. [PubMed: 11967286]

68. Salata C, Curtarello M, Calistri A, et al. vOX2 glycoprotein of human herpesvirus 8 modulates human primary macrophages activity. *Journal of cellular physiology*. 2009; 219:698–706. [PubMed: 19229882]
69. Sodhi A, Montaner S, Patel V, et al. The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1 alpha. *Cancer research*. 2000; 60:4873–4880. [PubMed: 10987301]
70. Montaner S, Sodhi A, Pece S, Mesri EA, Gutkind JS. The Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor promotes endothelial cell survival through the activation of Akt/protein kinase B. *Cancer research*. 2001; 61:2641–2648. [PubMed: 11289142]
71. Bais C, Van Geelen A, Eroles P, et al. Kaposi's sarcoma associated herpesvirus G protein-coupled receptor immortalizes human endothelial cells by activation of the VEGF receptor-2/ KDR. *Cancer cell*. 2003; 3:131–143. [PubMed: 12620408]
72. Montaner S, Sodhi A, Servitja JM, et al. The small GTPase Rac1 links the Kaposi sarcoma-associated herpesvirus vGPCR to cytokine secretion and paracrine neoplasia. *Blood*. 2004; 104:2903–2911. [PubMed: 15231571]
73. Sodhi A, Chaisuparat R, Hu J, et al. The TSC2/mTOR pathway drives endothelial cell transformation induced by the Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor. *Cancer cell*. 2006; 10:133–143. [PubMed: 16904612]
74. Ma T, Jham BC, Hu J, et al. Viral G protein-coupled receptor up-regulates Angiopoietin-like 4 promoting angiogenesis and vascular permeability in Kaposi's sarcoma. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:14363–14368. [PubMed: 20660728]
75. Friborg J Jr, Kong W, Hottiger MO, Nabel GJ. p53 inhibition by the LANA protein of KSHV protects against cell death. *Nature*. 1999; 402:889–894. [PubMed: 10622254]
76. Ballestar ME, Chatis PA, Kaye KM. Efficient persistence of extrachromosomal KSHV DNA mediated by latency-associated nuclear antigen. *Science*. 1999; 284:641–644. [PubMed: 10213686]
77. Radkov SA, Kellam P, Boshoff C. The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. *Nat Med*. 2000; 6:1121–1127. [PubMed: 11017143]
78. An J, Lichtenstein AK, Brent G, Rettig MB. The Kaposi sarcoma-associated herpesvirus (KSHV) induces cellular interleukin 6 expression: role of the KSHV latency-associated nuclear antigen and the AP1 response element. *Blood*. 2002; 99:649–654. [PubMed: 11781250]
79. Lan K, Kuppers DA, Verma SC, Robertson ES. Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen inhibits lytic replication by targeting Rta: a potential mechanism for virus-mediated control of latency. *J Virol*. 2004; 78:6585–6594. [PubMed: 15163750]
80. McCormick C, Ganem D. The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. *Science*. 2005; 307:739–741. [PubMed: 15692053]
81. King CA. Kaposi's sarcoma-associated herpesvirus kaposin B induces unique monophosphorylation of STAT3 at serine 727 and MK2-mediated inactivation of the STAT3 transcriptional repressor TRIM28. *J Virol*. 2013; 87:8779–8791. [PubMed: 23740979]
82. Staskus KA, Sun R, Miller G, et al. Cellular tropism and viral interleukin-6 expression distinguish human herpesvirus 8 involvement in Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castlemans disease. *J Virol*. 1999; 73:4181–4187. [PubMed: 10196314]
83. Katano H, Sato Y, Kurata T, Mori S, Sata T. Expression and localization of human herpesvirus 8-encoded proteins in primary effusion lymphoma, Kaposi's sarcoma, and multicentric Castlemans disease. *Virology*. 2000; 269:335–344. [PubMed: 10753712]
84. Parravicini C, Chandran B, Corbellino M, et al. Differential viral protein expression in Kaposi's sarcoma-associated herpesvirus-infected diseases: Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castlemans disease. *Am J Pathol*. 2000; 156:743–749. [PubMed: 10702388]

85. Burbelo PD, Issa AT, Ching KH, et al. Distinct profiles of antibodies to Kaposi sarcoma-associated herpesvirus antigens in patients with Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. *J Infect Dis*. 2010; 201:1919–1922. [PubMed: 20443737]
86. Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical Manifestations of Kaposi Sarcoma Herpesvirus Lytic Activation: Multicentric Castleman Disease (KSHV-MCD) and the KSHV Inflammatory Cytokine Syndrome. *Front Microbiol*. 2012; 3:73. [PubMed: 22403576]
87. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood*. 2000; 96:2069–2073. [PubMed: 10979949]
88. Bower M, Veraitch O, Szydlo R, et al. Cytokine changes during rituximab therapy in HIV-associated multicentric Castleman disease. *Blood*. 2009; 113:4521–4524. [PubMed: 19224759]
89. Polizzotto MN, Uldrick TS, Wang V, et al. Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Blood*. 2013; 122:4189–4198. [PubMed: 24174627]
90. Neipel F, Albrecht JC, Ensser A, et al. Human herpesvirus 8 encodes a homolog of interleukin-6. *J Virol*. 1997; 71:839–842. [PubMed: 8985427]
91. Boulanger MJ, Chow DC, Brevnova E, et al. Molecular mechanisms for viral mimicry of a human cytokine: activation of gp130 by HHV-8 interleukin-6. *J Mol Biol*. 2004; 335:641–654. [PubMed: 14672670]
92. Aoki Y, Jones KD, Tosato G. Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. *J Hematother Stem Cell Res*. 2000; 9:137–145. [PubMed: 10813527]
93. Aoki Y, Tosato G, Fonville TW, Pittaluga S. Serum viral interleukin-6 in AIDS-related multicentric Castleman disease. *Blood*. 2001; 97:2526–2527. [PubMed: 11307774]
94. Aoki Y, Jaffe ES, Chang Y, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. *Blood*. 1999; 93:4034–4043. [PubMed: 10361100]
95. Katsume A, Saito H, Yamada Y, et al. Anti-interleukin 6 (IL-6) receptor antibody suppresses Castleman's disease like symptoms emerged in IL-6 transgenic mice. *Cytokine*. 2002; 20:304–311. [PubMed: 12633573]
96. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, et al. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice. *Blood*. 2012; 119:5173–5181. [PubMed: 22490805]
97. Uldrick TS, Wang V, O'Mahony D, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. *Clin Infect Dis*. 2010; 51:350–358. [PubMed: 20583924]
98. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood*. 2002; 99:2331–2336. [PubMed: 11895764]
99. Weisenburger DD, Nathwani BN, Winberg CD, Rappaport H. Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. *Hum Pathol*. 1985; 16:162–172. [PubMed: 2579015]
100. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000; 95:1406–1412. [PubMed: 10666218]
101. Courville EL, Sohani AR, Hasserjian RP, Zukerberg LR, Harris NL, Ferry JA. Diverse clinicopathologic features in human herpesvirus 8-associated lymphomas lead to diagnostic problems. *Am J Clin Pathol*. 2014; 142:816–829. [PubMed: 25389336]
102. Li CF, Ye H, Liu H, Du MQ, Chuang SS. Fatal HHV-8-associated hemophagocytic syndrome in an HIV-negative immunocompetent patient with plasmablastic variant of multicentric Castleman disease (plasmablastic microlymphoma). *Am J Surg Pathol*. 2006; 30:123–127. [PubMed: 16330952]
103. Isaacson, PG.; Campo, E.; Harris, NL. Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. 4th. Lyon, France: IARC Press; 2008.

104. Montes-Moreno S, Montalban C, Piris MA. Large B-cell lymphomas with plasmablastic differentiation: a biological and therapeutic challenge. *Leuk Lymphoma*. 2012; 53:185–194. [PubMed: 21812534]
105. Du MQ, Diss TC, Liu H, et al. KSHV- and EBV-associated germinotropic lymphoproliferative disorder. *Blood*. 2002; 100:3415–3418. [PubMed: 12384445]
106. Oh J, Yoon H, Shin DK, et al. A case of successful management of HHV-8(+), EBV(+) germinotropic lymphoproliferative disorder (GLD). *Int J Hematol*. 2012; 95:107–111. [PubMed: 22167655]
107. D'Antonio A, Addesso M, Memoli D, et al. Lymph node-based disease and HHV-8/KSHV infection in HIV seronegative patients: report of three new cases of a heterogeneous group of diseases. *Int J Hematol*. 2011; 93:795–801. [PubMed: 21509436]
108. D'Antonio A, Boscaino A, Addesso M, Piris MA, Nappi O. KSHV- and EBV-associated germinotropic lymphoproliferative disorder: a rare lymphoproliferative disease of HIV patient with plasmablastic morphology, indolent course and favourable response to therapy. *Leuk Lymphoma*. 2007; 48:1444–1447. [PubMed: 17613780]
109. Papoudou-Bai A, Hatzimichael E, Kyriazopoulou L, Briasoulis E, Kanavaros P. Rare variants in the spectrum of human herpesvirus 8/Epstein-Barr virus-copositive lymphoproliferations. *Hum Pathol*. 2015; 46:1566–1571. [PubMed: 26299509]
110. Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood*. 2000; 95:56–61. [PubMed: 10607684]
111. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood*. 2005; 106:2627–2632. [PubMed: 15998837]
112. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2014; 15:966–974. [PubMed: 25042199]
113. Deisseroth A, Ko CW, Nie L, et al. FDA approval: siltuximab for the treatment of patients with multicentric Castleman disease. *Clin Cancer Res*. 2015; 21:950–954. [PubMed: 25601959]
114. Nakamura H, Nakaseko C, Ishii A, et al. [Chromosomal abnormalities in Castleman's disease with high levels of serum interleukin-6]. [Rinsho ketsueki] *The Japanese journal of clinical hematology*. 1993; 34:212–217. [PubMed: 8492420]
115. Stone K, Woods E, Szmania SM, et al. Interleukin-6 receptor polymorphism is prevalent in HIV-negative Castleman Disease and is associated with increased soluble interleukin-6 receptor levels. *PLoS One*. 2013; 8:e54610. [PubMed: 23372742]
116. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. *Pathology international*. 2001; 51:671–679. [PubMed: 11696169]
117. Kojima M, Nakamura N, Tsukamoto N, et al. Clinical implications of idiopathic multicentric castleman disease among Japanese: a report of 28 cases. *Int J Surg Pathol*. 2008; 16:391–398. [PubMed: 18499694]
118. Kojima M, Nakamura S, Shimizu K, et al. Clinical implication of idiopathic plasmacytic lymphadenopathy with polyclonal hypergammaglobulinemia: a report of 16 cases. *Int J Surg Pathol*. 2004; 12:25–30. [PubMed: 14765269]
119. Kawabata H, Takai K, Kojima M, et al. Castleman-Kojima disease (TAFRO syndrome) : a novel systemic inflammatory disease characterized by a constellation of symptoms, namely, thrombocytopenia, ascites (anasarca), microcytic anemia, myelofibrosis, renal dysfunction, and organomegaly : a status report and summary of Fukushima (6 June, 2012) and Nagoya meetings (22 September, 2012). *J Clin Exp Hematop*. 2013; 53:57–61. [PubMed: 23801135]
120. Kubokawa I, Yachie A, Hayakawa A, et al. The first report of adolescent TAFRO syndrome, a unique clinicopathologic variant of multicentric Castleman's disease. *BMC pediatrics*. 2014; 14:139. [PubMed: 24890946]
121. Kawabata H, Kotani S, Matsumura Y, et al. Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. *Internal medicine*. 2013; 52:1503–1507. [PubMed: 23812199]

122. Konishi Y, Takahashi S, Nishi K, et al. Successful Treatment of TAFRO Syndrome, a Variant of Multicentric Castleman's Disease, with Cyclosporine A: Possible Pathogenetic Contribution of Interleukin-2. *The Tohoku journal of experimental medicine*. 2015; 236:289–295. [PubMed: 26250536]
123. Inoue M, Ankou M, Hua J, Iwaki Y, Hagihara M, Ota Y. Complete resolution of TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) after immunosuppressive therapies using corticosteroids and cyclosporin A : a case report. *J Clin Exp Hematop*. 2013; 53:95–99. [PubMed: 23801140]
124. Iwaki N, Fajgenbaum DC, Nabel CS, et al. Clinicopathologic analysis of TAFRO syndrome demonstrates a distinct subtype of HHV-8-negative multicentric Castleman disease. *Am J Hematol*. 2016; 91:220–226. [PubMed: 26805758]
125. Dispenzieri A. POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2014; 89:214–223. [PubMed: 24532337]
126. Dispenzieri A. POEMS syndrome. *Blood Rev*. 2007; 21:285–299. [PubMed: 17850941]
127. Takatsuki K, Sanada I. Plasma cell dyscrasia with polyneuropathy and endocrine disorder: clinical and laboratory features of 109 reported cases. *Jpn J Clin Oncol*. 1983; 13:543–555. [PubMed: 6315993]
128. Dao LN, Hanson CA, Dispenzieri A, Morice WG, Kurtin PJ, Hoyer JD. Bone marrow histopathology in POEMS syndrome: a distinctive combination of plasma cell, lymphoid, and myeloid findings in 87 patients. *Blood*. 2011; 117:6438–6444. [PubMed: 21385854]
129. Li J, Zhou DB. New advances in the diagnosis and treatment of POEMS syndrome. *Br J Haematol*. 2013; 161:303–315. [PubMed: 23398538]

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 λ light chain in the plasmablasts (arrow), while the plasma cells in the interfollicular areas are polyclonal.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Major KSHV/HHV8-encoded proteins and their cellular effects

I. Homologs of human gene products					
Gene	ORF	Phase	Major cellular effects		Selected references
vIL-6	K2	Lytic	•	Activates IL-6 signaling pathways	43
vMIR1	K3	Lytic	•	Downregulates MHC-I	44, 45
vCCL2 (vMIP-II)	K4	Lytic	•	Chemoattracts TH2-type lymphocytes by binding to CCR3	46
vCCL3 (vMIP-III)	K4.1	Lytic	•	Chemoattracts TH2-type lymphocytes by binding to CCR4	47
vMIR2	K5	Lytic	•	Downregulates MHC-I	44, 45
vCCL1 (vMIP-I)	K6	Lytic	•	Chemoattracts TH2-type lymphocytes by binding to CCR8	48
vIAP	K7	Lytic	•	Inhibits apoptosis by interacting with Bcl-2 and inhibiting caspase 3	49
vBCL-2	ORF16	Lytic	•	Inhibits apoptosis	50
vIRF1	K9	Lytic	•	Inhibits interferon-induced antiviral responses and apoptosis by blocking interferon signaling pathways and inactivating p53 and Bim	51–53
vIRF2	K11/K11.1	Lytic	•	Inhibits interferon-induced antiviral responses	54
vIRF3 (LANA-2)	K10.5/K10. 6	Lytic	• •	Inhibits interferon-induced antiviral responses Promotes angiogenesis by stabilizing HIF-1 and inducing VEGF	55–57
vIRF4	K10/K10.1	Lytic	• •	Inhibits apoptosis by stabilizing MDM2 to target p53 Activates lytic gene expression by cooperating with RTA	58, 59
vFLIP	ORF71/K13	Latent	• • • •	Inhibits Fas/TNFR mediated cell death Activates NF-κB pathway Induces IL-6 expression by activating JNK/AP1 signaling Suppresses autophagy	60–63
vCyclin	ORF72	Latent	•	Promotes cell cycle progression by activating cdk6 to phosphorylate Rb and P27	64–66
vOX-2	K14	Latent	•	Modulates macrophage activity - increases basal cytokine production but downregulates response to IFNγ in macrophages	67, 68
vGPCR	ORF74	Lytic	• • •	Promotes angiogenesis by upregulating VEGF, VEGFR2 and angiopoietin-like 4 Activates Akt and mTOR pathways in endothelial cells Upregulates cellular cytokine secretion	69–74

II. Non-homologous viral gene products

Gene	ORF	Phase	Major cellular effects		Selected references
RTA	ORF50	Lytic	•	Master regulator of lytic gene expression	36
LANA-1	ORF73	Latent	•	Promotes cell cycle progression by targeting Rb	75–79
			•	Inhibits apoptosis by repressing p53	
			•	Induces cellular IL-6 expression	
			•	Maintains latent status by stabilizing viral episomes and antagonizing RTA	
Kaposins	K12	Latent	•	Stabilizes cytokine transcripts	80, 81
			•	Activates STAT3 pathways	

Table 2

Differential diagnoses of B cell lymphoproliferative disorders with plasmablastic features

	LBCL-MCD	GLPD	PEL	PBL	ALK-LBCL
Immunophenotype	CD20+/-, IRF4/MUM1+, CD138-	CD20-, CD79a- IRF4/MUM1+, CD138-/+	CD20-, CD79a- IRF4/MUM1+, CD138+	CD20-/+, CD79a+/- IRF4/MUM1+, CD138+	CD20-, CD79a- IRF4/MUM1+, CD138+, ALK+
Cytoplasmic Ig	+, monotypic IgM, λ	+, monotypic variable IgH, κ or λ	-	+, monotypic IgG, κ or λ	+, monotypic IgA > IgG, κ or λ
Ig rearrangement	Monoclonal	Polyclonal	Monoclonal	Monoclonal	Monoclonal
V _H hypermutation	-	+	+	+/-	?
EBV	-	+	+	+/-	-
KSHV/HHV8	+	+	+	-	-
HIV association	+	-	+	+	-

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