Pathology of Castleman Disease

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KEYWORDS

• Pathology • Castleman disease • Hyaline-vascular • Hypervascular
• Plasmacytic features • HHV8/KSHV • TAFRO

KEY POINTS

- The term Castleman disease encompasses several distinct lymphoproliferative disorders, with different underlying disease pathogenesis and clinical outcomes.
- There are three general histologic patterns encountered in Castleman disease: (1) hyaline-vascular occurring in unicentric disease, and (2) hypervascular and (3) plasma cell rich, mainly encountered in patients with multicentric disease; admixed hypervascular and plasmacytic features may be seen.
- HHV8-positive Castleman disease nearly always presents with multicentric disease; HHV8-infected plasmablasts are most often found in the mantle or marginal zones of lymph nodes, and exhibit lambda light chain restriction.
- Thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/reticulin fibrosis, and organomegaly (TAFRO) represents a distinct clinicopathologic form of idiopathic HHV8/KSHV-negative Castleman disease with mixed hypervascular and plasmacytic histologic features within involved lymph nodes, but additionally has loose bone marrow fibrosis, megakaryocytic hyperplasia, and other syndromic features.

INTRODUCTION

The term Castleman disease has been applied to several different lymphoproliferatiive disorders comprising of several distinct clinicopathologic entities.[1–4] Its prevalence has been estimated recently based on medical insurance claims to be ~21 to 25 cases per million person-years,[5] and thus qualifying it as an orphan disease. The disease presents clinically as unicentric or multicentric in nature[2,3,6,7] (**Table 1**). In the unicentric variant of Castleman, patients have localized disease affecting only a single, enlarged lymph node, or at most a group of adjacent nodes in a single region, with

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Table 1
Clinical variants of Castleman disease and key features

Clinical Variant	Histologic Variant	Key Microscopic Changes	Laboratory Abnormalities	Disease Aggressiveness
Unicentric	Hyaline-vascular (~90%) and plasma cell (10%)	Atretic follicles with hyalinization, and lymphodepletion; concentric "onion-skin" appearance of circumferential mantle zone cells; penetrating vessels imparting "lollipop" appearance; proliferation of vasculature; unapparent sinuses	Limited	Surgical resection is typically curative with excellent outcome
Multicentric	Hypervascular or plasmacytic variant, or commonly mixed	Similar histologic features as hyaline-vascular unicentric Castleman, but typically without dysplastic follicular dendritic cells Diffuse proliferation of plasma cells and hyperplastic germinal centers, preserved sinuses	Dysregulation of IL-6 (increased) or other cytokines, such as VEGF, IL-1, TNF-α	Can be life-threatening with end-organ damage and failure
HHV8-positive Castleman disease	Plasma cell rich	Evidence of HHV8 infection of plasmablasts present in mantle zones with lambda light chain restriction polyclonal plasmacytosis present		Can be aggressive with disease progression to HHV8-positive large B-cell lymphoma
TAFRO	Mixed hypervascular and plasmacytic change	Hypervascular lymph nodal changes and bone marrow reticulin fibrosis with megakaryocytic hyperplasia and emperipolesis	Thrombocytopenia, no hypergammoglobulinemia as frequently seen in idiopathic multicentric Castleman disease	Prolonged course, with occasional flares that can be aggressive and fatal

Abbreviations: HHV8, human herpes virus 8; IL, interleukin; TAFRO, thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/reticulin fibrosis, and organomegaly; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

the mediastinum and other thoracic lymph nodes being commonly involved. Patients typically lack significant systemic symptoms and their clinical outcomes are generally favorable with limited morbidity and surgical resection being essentially curative.[8] By contrast, in multicentric Castleman disease, there is diffuse lymphadenopathy affecting multiple groups of lymph nodes in association with marked systemic inflammatory symptoms.[1] The cause of multicentric disease is multifactorial[3] and may in many patients be idiopathic. In patients in whom infection by human herpes virus 8 (HHV8; also known as Kaposi sarcoma herpes virus [KSHV]), is established, a viral cause is clear. However, in cases in which HHV8 infection is absent, the underlying cause is currently unknown with the possible etiologies hypothesized to occur at an intersection of rheumatology, infectious disease, and oncology (**Box 1**).[3] Irrespective of the pathogenesis, multicentric Castleman disease is commonly associated with constitutional symptoms (eg, night sweats, fever, weight loss) and systemic cytokine dysregulation,[9] resulting in prominent abnormal blood count and chemistry, hepatosplenomegaly, and complex organ dysfunction. In some patients, the disease may be particularly aggressive and progress to multiorgan dysfunction and in some individuals, death.[2]

The term Castleman disease has its origins in a case report published in 1954 by the pathologist by Dr. Benjamin Castleman.[10] This initial case report was soon followed by more detailed analysis of patients having isolated mediastinal lymphadenopathy.[10,11] In these initial publications, Castleman and colleagues[11] described what is currently appreciated as unicentric disease with hyaline-vascular histopathologic features. Further work by Keller and coworkers[12] subsequently demonstrated that the

Box 1
Potential clinical and histopathologic mimics of Castleman disease

Autoimmune diseases

Rheumatoid arthritis/juvenile idiopathic arthritis

IgG4-related disease

Systemic lupus erythematosus

Hemophagocytic lymphohistiocytosis/macrophage activation syndrome

Adult-onset Still disease

Autoimmune lymphoproliferative syndrome

Infections

Acute Epstein-Barr virus infection

Acute human immunodeficiency virus infection

HHV8/KSHV infection

Other (cytomegalovirus, toxoplasmosis, tuberculosis)

Malignancies

Lymphoma including Hodgkin and non-Hodgkin

Follicular dendritic cell sarcoma

Plasma cell neoplasm, including POEMS

Adapted from Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129(12):1652; with permission.

histologic features of unicentric disease could also include plasmacytosis. The uncommon plasma cell form of unicentric Castleman disease was more often associated with systemic symptoms.[12] In subsequent reports published in the late 1970s and early 1980s, the multicentric variant of Castleman was described, demonstrating the propensity of this disease variant to include severe clinical symptomatology with diffuse lymphadenopathy.[12–15] That these patients could be quite sick was a key clinical feature of this multicentric variant of Castleman disease.

In the 1980s, significant insights regarding the pathogenesis of Castleman disease were gained, when Yoshizaki and colleagues[16] identified elevation of the key cytokine interleukin-6 (IL-6) in patients with Castleman disease. This observation along with discoveries by others collectively paved the way for preclinical experimental investigation into the biology and pathogenesis of Castleman disease. With the establishment of IL-6 dysregulation (abnormally increased) in some patients with Castleman disease, the role of this key cytokine in the pathogenesis of some cases of Castleman disease was highlighted. Exogenous expression of IL-6 in murine models led to a lymphoproliferative disorder that mimicked the typical histologic features seen in resected lymph nodes of patients with Castleman disease.[17] In the 1990s, identification of Kaposi sarcoma–associated herpesvirus-like DNA in patients with Castleman disease further led to confirmation of the hypothesis that some aspects of Castleman changes were driven by IL-6, because it was soon appreciated that a viral homologue of IL-6 was produced by KSHV/HHV8-infected cells.[18–21] These insights together led to evaluation of the clinical efficacy of targeting of IL-6 through the use of monoclonal antibodies. Clinical trials were soon performed, resulting in subsequent approval of anti-IL-6 therapies.[22–26] Since then, insight into Castleman disease pathogenesis has steadily increased in time as evidenced by the ever increasing number of publications on this topic.

The term “Castleman disease” has come to be associated with several distinct clinical syndromes and disease entities, which broadly speaking are referred to as unicentric versus multicentric Castleman (**Fig. 1**). The histologic features of unicentric hyaline-vascular disease remain largely unchanged since the original descriptions by Castleman and colleagues in the 1950s, and as a disease entity, is distinct from the more complex clinical syndromes referred to as multicentric Castleman disease. Although historical approaches for subclassifying multicentric

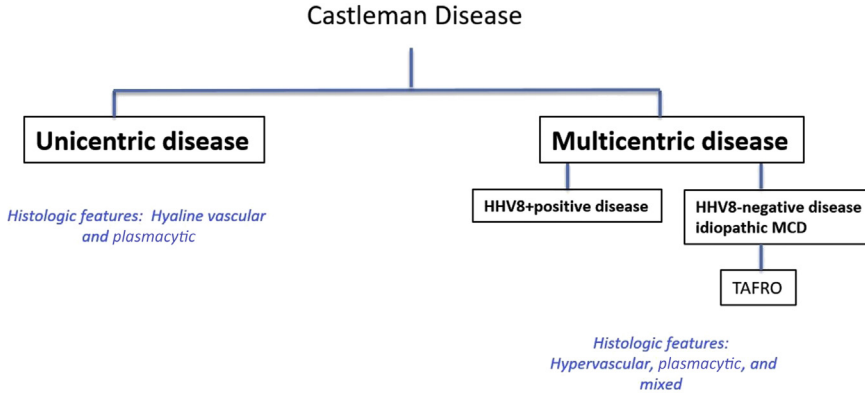

Fig. 1. Clinical variants (*bold*) of Castleman disease and correlated histopathologic patterns (*italicized*). TAFRO, thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/reticulin fibrosis, and organomegaly. MCD, multicentric castleman disease.

Castleman disease had previously segregated cases based on association with infection by human immunodeficiency virus (HIV), this approach was revised when research showed the critical role of KSHV/HHV8 in this disease, irrespective of HIV infection.[18,27] Accordingly the current diagnostic pathologic paradigm considers multicentric Castleman disease to be subdivided based on whether there is HHV8 infection, either as HHV8-positive Castleman disease versus HHV8-negative, idiopathic Castleman disease[3] (see **Fig. 1**). Although each of these clinicopathologic variants has some distinctive histopathologic features, it should be noted that there is significant pathologic overlap between these different variants in the resected lymph node samples, and that histopathologic findings are not specific when interpreted in isolation.

HISTOPATHOLOGIC FEATURES

Unicentric Castleman Disease

In most cases of unicentric Castleman disease, lymph nodes are significantly enlarged (median diameter of ~6 cm) and have histopathologic features of hyaline-vascular variant[6,12] (**Fig. 2**). Less commonly, in about one-tenth of unicentric cases, lymph nodes in unicentric disease may have marked plasmacytosis[6] that is more commonly seen in multicentric disease. The lymph nodes involved by the hyaline-vascular histologic variant of Castleman disease exhibit follicular and interfollicular changes with the degree of such changes being variable from case to case. In cases in which follicular changes in the lymph node predominate, the lymphoid follicles are highly abnormal in appearance. The follicles may be increased in density and they may be disorganized, but notably appear atretic in nature, being depleted of lymphoid cells, but with notable retention of follicular dendritic cells (see **Fig. 2**A). The mantle zone lymphocytes surrounding the follicles are concentrically arranged, exhibiting a target-like pattern with a broad zone of small, mature lymphocytes with condensed chromatin and minimal cytoplasm, imparting an onion-skin-like appearance (see **Fig. 2**B). Frequently, there may be radially penetrating sclerotic blood vessels that together with the atretic follicles and concentric mantle zones impart a so-called "lollipop" appearance (see **Fig. 2**C). In some cases, there may be two more adjacent, atretic follicles enveloped by a concentric mantle zone and dendritic meshwork, resulting in a histopathology feature commonly referred to by pathologists as "twinning" (see **Fig. 2**D). Within the interfollicular zones of the excised lymph nodes in hyaline-vascular variant, there often is often a marked proliferation of vasculature, resulting from an increase in density of vasculature with prominent endothelial cells, lining these proliferative vascular walls (see **Fig. 2**E). In unicentric hyaline-vascular variant, lymph node sinuses are typically absent or unapparent, which is a distinction from the hypervascular histopathologic variant seen in multicentric Castleman disease (discussed later) in which nodal sinuses are preserved. Peripherally, the lymph node capsule may be slightly thickened and sclerotic. Other pathologic features of the hyaline-vascular variant of Castleman disease include the presence of intermediate-to-large-sized follicular dendritic cells that may show cytologic atypia.[28,29] Although there has not been consistent evidence in the hyaline-vascular variant of unicentric Castleman to show evidence of clonality of B cells or plasma cells by analysis of immunoglobulin (*IGH*) gene rearrangement,[30,31] some groups using special methods have demonstrated genomic evidence to suggest that hyaline vascular Castleman disease may represent the end result of clonal aberrations occurring in nonlymphoid cells, in particular follicular dendritic cells.[32–34] The stromal/dendritic cell elements in hyaline vascular Castleman disease frequently show dysplastic features. In exceptionally rare cases, follicular dendritic cells may

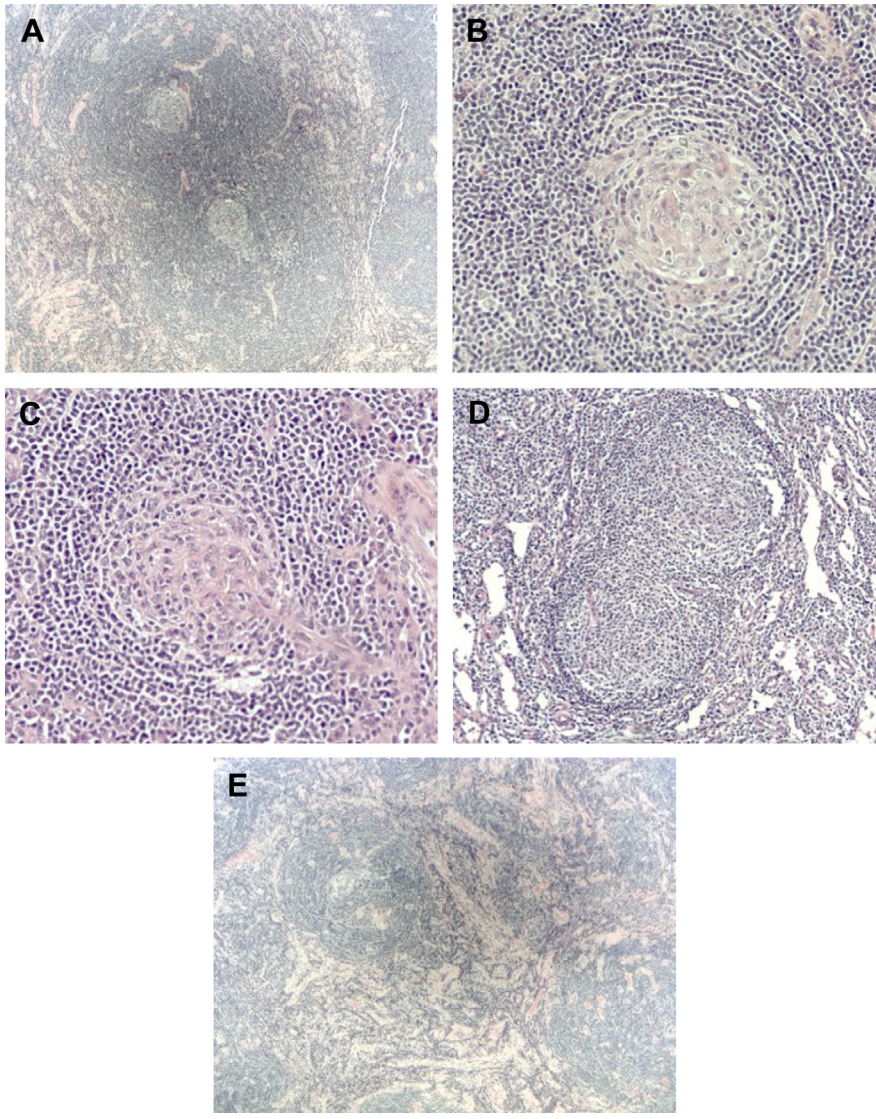

Fig. 2. Example of hematoxylin and eosin (H&E) histologic changes seen in unicentric hyaline vascular and multicentric hypervascular variants. (*A*) Altered follicles with expanded mantle zones (original magnification ×5). (*B*) Atretic follicles with mantle zone B cells exhibiting target-like features surrounding residual follicular dendritic cells (original magnification ×20). (*C*) Radially penetrating sclerotic vasculature (original magnification ×20). (*D*) Twinning (original magnification ×10). (*E*) Interfollicular vascular proliferation (original magnification ×5).

be increased in density and proportion, raising concern for a follicular dendritic cell neoplasm. Rarely, such lesions may indeed develop frank morphologic and cytologic atypia of dendritic cells, and be regarded as a follicular dendritic sarcoma.[35,36] Confluent sheets of plasma cells are only rarely seen in unicentric Castleman disease.

By immunohistochemistry, the lymphoid follicles in unicentric hyaline-vascular Castleman disease exhibit significant depletion of follicle centers imparting an atretic appearance. B cells, however, remain present within the expanded mantle zones as evidenced by expression of typical B-cell antigens, such as CD20. These mantle zone cells can further be confirmed by expression of IgD, and using sensitive immunohistochemical techniques may express CD5, an antigen expressed on mantle zone cells in early ontogeny.[37] Although there may be scattered polyclonal plasma cells through the lymph node, large clusters or sheets of plasma cells are not a prominent feature of the hyaline-vascular variant of unicentric Castleman disease. Lastly, atypical dendritic cells within atretic follicles are highlighted by follicular dendritic cell antigens, such as CD21 or CD23.

Rare cases of unicentric Castleman disease (~10%) exhibit prominent plasmacytosis akin to that seen in multicentric Castleman disease, more typically affecting a group of adjacent lymph nodes rather than a single node.[1,12] Indeed, similar to multicentric Castleman disease, these patients with unicentric disease, but plasma cell-rich histopathology may have significant systemic symptomatology. However, unlike multicentric Castleman, these patients with unicentric disease usually benefit from disease resection with resolution of clinical symptoms.[4,8] Interestingly, such cases may show light chain restriction, with preferential expression of lambda.[37]

Multicentric Castleman Disease

In multicentric Castleman disease, patients typically present with diffuse lymphadenopathy or at a minimum, lymphadenopathy that involves more than one lymph node region. On microscopic examination of excisional lymph node biopsies, there are two common histologic patterns identified: hypervascular and plasmacytic variants. These histologic patterns are not specific or mutually exclusive, because features of either histologic variant may be seen in multicentric Castleman irrespective of cause. These various histologic patterns may also commonly be seen admixed together, and most patients with multicentric Castleman disease show some degree of plasmacytosis.[7]

The hypervascular variant of multicentric Castleman disease[7] is reminiscent in name and histologic features to that of the hyaline-vascular variant of unicentric Castleman disease. A key distinction is that this histopathologic variant is used to describe multicentric Castleman disease in the context of idiopathic multicentric disease with TAFRO syndrome (thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/reticulin fibrosis, and organomegaly), because of the marked proliferation of the vasculature in this entity. Furthermore, a distinction of the hypervascular variant of multicentric Castleman disease from that of hyaline-vascular variant of unicentric disease is that in the former, lymph node sinuses generally remain patent, whereas lymph node sinuses are absent or not apparent in unicentric Castle disease.[7] The other predominant histologic variant of multicentric Castleman disease is the plasmacytic variant, characterized by the presence of typically large collections or sheets of plasma cells, usually in the absence of regressive changes of follicles and increased vascularity.

Hypervascular variant of multicentric disease

The hypervascular variant of multicentric Castleman disease shares some histopathologic features in common with the unicentric, hyaline-vascular variant of Castleman disease, and was named similarly given the overlap of many histopathologic features commonly observed in the unicentric variant of this disease.[7] The follicles in

hypervascular variant of multicentric Castleman disease appear similarly abnormal, principally appearing lymphodepleted with atretic and sclerotic changes being most apparent. Follicle center B cells are diminished in proportion with only residual follicular dendritic cells remaining. Mantle zone B cells may be concentric arranged around the follicles imparting an onion-skin appearance. There is often a marked vascular proliferation in the interfollicular zones with an abundance of high-endothelial venules, and vessels that radially penetrate these atretic follicles, imparting the so-called "lollipop" appearance. One difference between this hypervascular variant and the hyaline-vascular disease of unicentric Castleman disease is the retention of nodal sinuses in multicentric disease versus absence in unicentric disease. In the context of multicentric Castleman disease, particularly the TAFRO variant, some of the distinctive features of hyaline-vascular unicentric disease features, such as the presence of dysplastic follicular dendritic cells, are not observed.[7]

Plasmacytic variant of multicentric disease

This histologic variant is most commonly seen in multicentric Castleman disease and is characterized by the prominence of interfollicular plasma cells within the lymph node (**Fig. 3**). The lymph node architecture is typically preserved with numerous lymphoid follicles showing features of reactive follicular hyperplasia (not shown). The plasma cells are present as large aggregates, or often as confluent sheets, located between the lymphoid follicles (see **Fig. 3**A). The plasma cells are cytologically mature in appearance, without prominent immunoblastic or plasmablastic cytologic features (see **Fig. 3**B). By contrast, plasmablastic cells with prominent nucleoli are not observed unless in the context of KSHV/HHV8 infection, as seen in HHV8-positive Castleman disease. Compared with the hypervascular variant there is less vascular proliferation and hyalination. Although the lymphoid follicles usually appear hyperplastic in nature, typically, in a subset of patients with multicentric disease, there may be some admixed follicles appearing depleted of follicle-center B cells and regressed in nature (see **Fig. 3**A).

By immunohistochemistry, the plasma cells in multicentric Castleman disease are typically polytypic with respect to immunoglobulin light chain expression. By contrast, in HHV8-positive Castleman disease, immunostaining or *in situ*

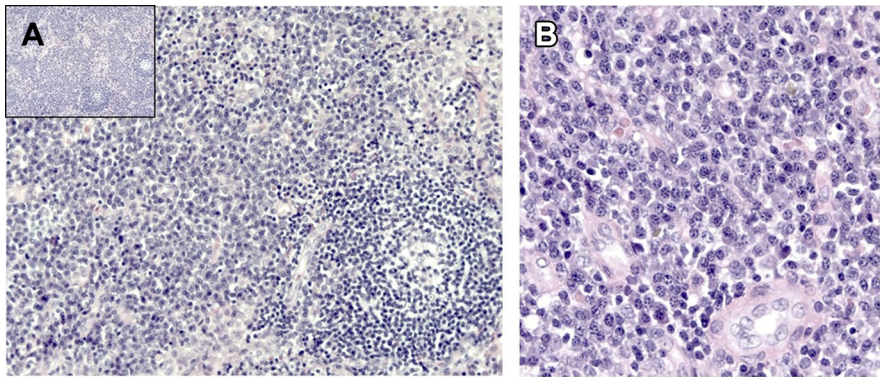

Fig. 3. Example H&E histologic change seen in multicentric plasmacytic variant. (*A*) Diffuse plasmacytosis (original magnification ×10; inset magnification at ×5). (*B*) Mature plasma cells without plasmablasts/immunoblasts. Note the paracoritcal plasmacytosis and in addition, two atretic follicles with slightly expanded mantle zones (original magnification ×40).

hybridization can frequently identify lambda light chain–restricted plasmablasts present within mantle zones with evidence of concurrent infection by HHV8/KSHV.

In patients with idiopathic multicentric Castleman disease the lymph nodes may show variation in the histologic features, so that in any given lymph node biopsy, there may be plasmacytic histology, whereas in other biopsies there may be hypervascular histology.[6,38] Indeed, in some cases of multicentric Castleman disease, there may be histologic features of both the hypervascular variant and the plasmacytic variant, so-called "mixed variant." The significance of the proportion of these different histologic patterns within a given biopsy from a patient with Castleman disease is not clear. Some studies have noted that patients with plasmacytic histology, as compared with the hypervascular histology, have an overall more clinically aggressive course[4] and are less responsiveness to anti-IL-6 therapy.[23] However, these different histologic patterns may be variably seen in the same patient at different times.[7,23] It is likely that these different patterns reflect differences in pathogenesis, because for most cases of idiopathic multicentric Castleman disease, the pathogenesis is unknown.

Thrombocytopenia, ascites/anasarca, myelofibrosis/fever, renal dysfunction/ reticulin fibrosis, and organomegaly syndrome

The syndrome of TAFRO is a recently described variant of idiopathic HHV8-negative multicentric Castleman disease,[39–42] occurring in adults (median age ~ 50 years). Although first described in Japan, this variant has since been described in patients of other ethnicities, including white persons.[42] In this variant, there are similar clinicopathologic features to that of idiopathic multicentric Castleman disease, including involvement of multiple lymph nodes with typical mixed (plasmacytic and hypervascular) histologic features[39] and systemic disease symptomatology. The lymph nodes typically show marked vascular proliferation in the interfollicular areas, and exhibit more a more modest increase in plasma cells. Most follicles often appear atretic and regressed and depleted of germinal center B cells with only remnant dendritic cells. In contrast to that observed in unicentric hyaline-vascular variant, dysplasia of follicular dendritic cells is not seen. Immunostaining for viral markers for HHV8 infection is definitionally negative. Bone marrow core biopsies of patients with TAFRO typically performed to evaluate thrombocytopenia show megakaryocytic hyperplasia with clustering in a background diffuse reticulin fibrosis.[40,42,43] A novel feature is emperipolesis exhibited by megakaryocytes, not encountered in other forms of Castleman disease.

Human Herpes Virus 8-Positive, Castleman Disease

In some patients, many of whom may be immunosuppressed because of HIV infection, HHV-8/KSHV-positive infection can result in a systemic cytokine dysregulation that results in a clinicopathologic picture of multicentric Castleman disease. Although historical classification of multicentric Castleman had initially considered the importance of HIV infection, recognition of the critical role of the HHV-8 virus in these and other patients without HIV infection[18] led to reconsideration of Castleman disease classification on the basis of HHV-8 infection, and not HIV.[3] The histopathologic features of excised lymph nodes are similar to that seen in idiopathic, HHV8-negative multicentric disease with the presence of atretic lymphoid follicles with prominent interfollicular polytypic plasmacytosis.[44] Overall the lymph node architecture is generally preserved. There may be concurrent follicle hyalinization and lymphodepletion with prominent interfollicular vasculature. HHV8-positive/KSHV infected plasmablasts, which are medium-to-large-sized mononuclear cells with amphophilic cytoplasm, may be readily identified within the mantle cell zones surrounding these nodal follicles (**Fig. 4**). In some cases, these plasmablasts may coalesce together,

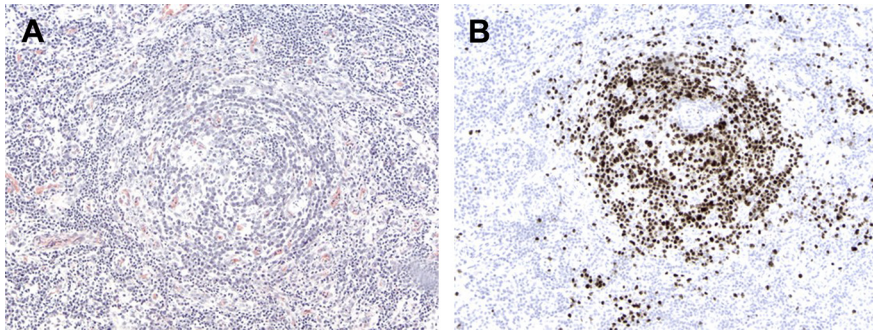

Fig. 4. Example of infection by HHV8 in HHV8-positive multicentric Castleman disease. (*A*) Prominent increase in plasmablasts (H&E, original magnification ×10). (*B*) Immunostaining for HHV8 (latent nuclear antigen-1) (original magnification ×10).

forming prominent aggregates. Immunohistochemical studies show evidence of infection by HHV8/KHSV based on expression of viral proteins, including latent nuclear antigen-1 (see **Fig. 4**B). These cells express B cell and plasma cell markers, including CD20, CD79a, and IRF4/MUM1, but typically lack expression of CD10, PAX5, and BCL6.[44] The plasmablastic cells are typically polyclonal with respect to analysis of immunoglobulin gene rearrangement, but may show IgM lambda light chain restriction. The cause of the preferential expression of lambda light chain in these plasmablastic cells is under current investigation. Some recent studies, summarized by Wang and colleagues,[45] suggest that HHV8 viral transcriptional programming may result in preferential enrichment and/or selection of lambda-expressing plasma cells. In some cases, plasmablasts may aggregate in a manner histologically concerning for malignancy on microscopic examination because of the increased clustering and density. However, the main differential diagnosis in this context is HHV8-positive diffuse large B-cell lymphoma. In contrast, in multicentric Castleman disease, plasmablastic cells are not present in a diffuse sheet-like pattern.[44] In the 2008 World Health Organization classification approach, aggregates of plasmablasts were previously termed so-called "microlymphomas." However, this designation has since been updated in the 2016 World Health Organization revision because of the recognition that not all plasmablastic aggregates are definitively clonal in nature, and that not all plasmablastic proliferations uniformly transform or progress into lymphoma. Nevertheless, in a minor subset of cases, these plasmablasts may acquire additional genomic aberrations, expand in proportion to further more extensively involve the lymph node, and progress to histologically recognizable lymphoma, currently termed HHV8-positive diffuse large B-cell lymphoma.[44]

HISTOLOGIC DIFFERENTIAL DIAGNOSES

Castleman-like histopathologic change may occur in a variety of reactive and neoplastic contexts (see **Box 1**). Accordingly, careful clinicopathologic and laboratory correlation is always required to make a formal diagnosis of Castleman disease. This is true for all histopathologic forms, including the unicentric hyaline-vascular variant, but is typically more critical for the patient with possible multicentric Castleman disease. Hyaline-vascular-like and plasmacytic-like Castleman changes may also be observed in the context of reactive settings (eg, autoimmune disorders, infection), and in some non-Hodgkin lymphomas[46,47] and Hodgkin lymphomas.[48–52] In cases in which there

may be concern for lymphoma versus Castleman disease, typically the Castleman-like features are usually limited in nature, not fully involving the lymph node as would happen in true Castleman disease. Importantly, the patient lacks the typical clinical and laboratory picture of Castleman disease. Evidence for the presence of a clonal or light chain–restricted B-cell population by either concurrent molecular analyses of immunoglobulin gene rearrangement or flow cytometry, respectively, provides additional support for the presence of a non-Hodgkin lymphoma. Careful interpretation of histologic features and immunohistochemistry studies is nevertheless required to distinguish nodal involvement by non-Hodgkin or Hodgkin lymphomas from Castleman disease.[53,54] Indeed, according to the recent consensus diagnostic approach, all potential reactive and malignant mimics of Castleman must be excluded before making a diagnosis of idiopathic multicentric Castleman disease.[7] Any diagnosis of Castleman disease should be made using a full excisional lymph node biopsy, because use of only needle-core biopsies is wholly inadequate.

CONSENSUS DIAGNOSTIC CRITERIA FOR HUMAN HERPES VIRUS 8-NEGATIVE, IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE

In 2015 to 2016, a group of pathologists and clinicians, led by Drs David Fajgenbaum of University of Pennsylvania and Frits van Rhee of University of Arkansas, converged to formulate a systematic review of the criteria for the diagnosis of Castleman disease resulting in the first international consensus diagnostic criteria for idiopathic (HHV8/KSHV-negative) multicentric Castleman disease based on review of 288 clinical cases and 88 tissue samples.[7] This group met to define the diagnostic histopathologic and clinical features of Castleman disease first through informal meetings held concurrently with the annual American Society of Hematology meetings, and second through multiple organized teleconferences and subsequently in-person meetings. During this process, a group of hematopathologists concurrently reviewed numerous Castleman disease cases together with a multiheaded microscope. These cases were derived principally from the cohort of patients with idiopathic HHV8-negative Castleman disease enrolled in the study that resulted in the approval of an anti-IL6 drug,[23] but included numerous, additional cases derived from personal consultative files of participating expert hematopathologists.

Through iterative meetings conducted in person and subsequently virtually, diagnostic histologic and clinical criteria were formulated and agreed on with subsequent submission for external review.[7] The culmination of this extraordinary effort was the development of the first international consensus diagnostic criteria focused on the diagnostic clinicopathologic features of idiopathic (HHV8-negative) multicentric Castleman diseases nearly 70 years after Castleman's original report.[7]

To make a diagnosis of idiopathic multicentric Castleman disease, identification of major and minor clinical and histopathologic criteria is required with exclusion of all reactive, and/or secondary mimics including autoimmune disease and infection.[7] The major criteria require characteristic lymph node histopathology, and evidence of multicentric lymphadenopathy (greater than 1 cm in more than two nodal groups). (**Table 2**). Additionally, 2 of 11 minor criteria must be identified from either laboratory or clinical criteria, with at least one representing a clinical laboratory abnormality. Lastly, exclusion of confounders that may mimic multicentric Castleman disease (see **Box 1**) must be performed. The development of a consensus diagnostic clinicopathologic approach will lead to standardized diagnoses and improvements in understanding of the clinical behavior and response to therapies and disease treatment algorithms.

Table 2
Pathologic diagnostic criteria for HHV8/KSHV-negative idiopathic multicentric Castleman disease

Histologic Features	Spectrum of Changes	Diagnostic Criteria Required
Regressed germinal centers	None > few > many > most	Few or many regressed germinal centers to satisfy major criterion 1 (grade 2–3)
Prominent follicular dendritic cells	None > mild > moderate > very prominent	
Vascularity	Normal > mildly increased > moderately increased > very prominent	
Hyperplastic germinal centers	None > few > many > most	
Plasmacytosis	Normal > mildly > moderately > very increased (sheet-like)	Mildly or moderately increased plasmacytosis to satisfy major criterion 1 (grade 2–3)

For a diagnosis of idiopathic HHV8-negative Castleman disease, cases must satisfy both major criteria and must have at least 2 of 11 potential minor criteria (including at least one laboratory criterion). Major criterion 1 are histopathologic in nature and are detailed above. Major criterion 2 is the presence of enlarged lymph nodes ($\geq$1 cm short axis diameter) in $\geq$2 lymph node stations. Minor criteria include laboratory alterations (elevated C-reactive protein, anemia, thrombocytopenia, hypoalbuminemia, renal dysfunction, polyclonal hypergammaglobulinemia) and clinical findings (constitutional symptoms, hepatosplenomegaly, fluid accumulation, eruptive cherry hemangiomatosis or violaceous papules, lymphocytic interstitial pneumonitis). See Fajgenbaum and coworkers[7] for further details.

Adapted from Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017;129(12):1652; with permission.

SUMMARY AND DISCUSSION

The term Castleman disease has been used to encompass a spectrum of diverse lymphoproliferative disorders with immune perturbations and variable clinical features; disease pathogenesis (although many cases are frequently idiopathic); and as described herein, histopathologic features. The clinicopathologic syndromes may have overlapping histopathologic features, but even these are generally not specific in nature. The most histologically distinctive changes are seen in unicentric Castleman disease of the hyaline-vascular variant. The disease is limited in scope without significant systemic dysfunction or patient morbidity. In multicentric Castleman disease, patients typically exhibit diffuse lymphadenopathy and significant constitutional symptoms, laboratory abnormalities, and hepatosplenomegaly that may result in significant morbidity and mortality. The histologic findings in idiopathic multicentric Castleman disease include hypervascularity (particularly in TAFRO) or marked plasmacytosis, with these two features together bookending the spectrum of histologic changes that may be seen. Frequent admixture of these two histologic patterns along a continuum is observed. The hypervascular variant of multicentric Castleman shares some features with the hyaline-vascular variant of unicentric Castleman, but is distinguished principally by the clinical context (multicentric vs unicentric disease), the presence of patent sinuses in the former and absence in the latter, and absence of

dysplastic dendritic cells in hypervascular variant. Additionally, perhaps paradoxically, hyaline vascular Castleman disease usually presents with markedly enlarged lymph nodes resulting in localized mass lesions, whereas the lymph nodes in TAFRO are only moderately enlarged. Additionally, TAFRO presents with thrombocytopenia and loose marrow fibrosis along with nodal Castleman-like changes, in particular hypervascularity. Lymph node changes in TAFRO are characterized by markedly increased vascularity, which extends to the residual follicles, and modest plasmacytosis. In HHV8/KSHV-positive Castleman disease, in addition to marked plasmacytosis, resembling the plasma cell variant, there is notable evidence of HHV8-positive infected plasmablasts within nodal mantle/marginal zones. Lastly, it is important to emphasize that Castleman-like histopathologic changes may be observed in reactive (infectious and autoimmune) disorders, and in malignant lymphomas (non-Hodgkin and Hodgkin lymphoma). Accordingly, careful clinicopathologic correlation is always required to ensure correct diagnoses are made. In this regard, the recent development and publication of international consensus criteria for diagnosing idiopathic, HHV8-negative multicentric variant of Castleman disease should be most helpful.[7]

The increased interest and research into delineating the diagnostic clinicopathologic features of Castleman disease will enable further insight into the disease pathogenesis of the clinicopathologic variants currently grouped together under the eponym of Castleman disease. With further insight into pathogenesis, improved clinical diagnoses may be possible with an expectation that better disease classification and prognostication should contribute to improved patient care.

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