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# Unicentric Castleman disease

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## INTRODUCTION

Castleman disease (CD, angiofollicular lymph node hyperplasia) describes a heterogeneous group of lymphoproliferative disorders that share common histopathologic features.

CD is classified into at least three distinct disorders based on the number of regions of enlarged lymph nodes with characteristic histopathologic features and the presence/absence of human herpesvirus 8 (HHV-8, also called Kaposi sarcoma associated herpesvirus [KSHV]) infection:

- Unicentric CD (UCD) involves one or more enlarged lymph node(s) in a single region of the body that demonstrates CD histopathologic features that lie along a spectrum with hyaline vascular histopathologic subtype on one end and plasma cell histopathologic subtype on the other. A subset of patients have systemic symptoms.

- Multicentric CD (MCD) involves multiple regions of lymphadenopathy that demonstrate CD histopathologic features that lie along a spectrum with hypervascular histopathologic subtype on one end and plasma cell histopathologic subtype on the other. These patients also have systemic inflammatory symptoms with generalized lymphadenopathy, hepatosplenomegaly, cytopenias, and organ dysfunction due to excessive pro-inflammatory hypercytokinemia, often including interleukin (IL)-6. MCD is further subclassified according to the presence of HHV-8:

    - HHV-8-associated MCD: Approximately half of MCD cases are caused by HHV-8 infection in human immunodeficiency virus (HIV)-positive or otherwise immunocompromised individuals, and these cases are referred to as HHV-8-associated MCD.

- HHV-8-negative/idiopathic MCD (iMCD): Approximately half of patients with MCD are HHV-8 negative. These cases have nearly identical clinical and histopathologic features as HHV-8-associated MCD, but the etiology is unknown. These cases are referred to as HHV-8-negative MCD, idiopathic MCD, or iMCD.

It is essential that all cases of CD are subdivided into UCD, HHV-8-associated MCD, or iMCD at the time of diagnosis as all three subtypes have varying clinical features, treatments, and outcomes. CD is also associated with a number of malignancies, including non-Hodgkin lymphoma, Hodgkin lymphoma, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

This topic review will discuss the epidemiology, pathogenesis, clinical and pathologic features, diagnosis, and treatment of UCD. HHV-8-negative/idiopathic MCD, HHV-8-associated MCD, a review of diseases associated with HHV-8 infection, and the virology of HHV-8 are presented separately.

- (See "HHV-8-negative/idiopathic multicentric Castleman disease".)
- (See "HHV-8-associated multicentric Castleman disease".)
- (See "Disease associations of human herpesvirus 8 infection".)
- (See "Virology, epidemiology, and transmission of human herpesvirus 8 infection".)

## PATHOGENESIS

The pathogenesis of UCD is poorly understood. The characteristic histopathologic features of lymph nodes from patients with Castleman disease (CD) are believed to either be exaggerations of the types of reactive changes that can be seen in response to normal antigenic stimuli or representative of a low-grade neoplastic process. These features include atrophic and hyperplastic germinal centers, follicular dendritic cell (FDC) prominence, the accumulation of immunoblasts and plasma cells, and increased vascularity. Similar histologic changes are seen in other disorders associated with chronic immune activation, including autoimmune diseases, lymphomas, various congenital immunodeficiency states, and viral infections. (See 'Pathology' below.)

**Etiology** — Viral, autoimmune, and neoplastic processes have all been proposed as possible etiologies underlying UCD. Unlike human herpesvirus 8 (HHV-8)-associated multicentric CD, UCD is **not** associated with HHV-8 infection or HIV infection.

A subset of UCD cases may be the result of somatic mutations in monoclonal cell populations that act through neoplastic mechanisms. The following findings suggest a neoplastic mechanism driving UCD pathogenesis:

- Monoclonality was identified in lymph node tissue from 19 of 25 UCD cases using conventional and methylation-specific polymerase chain reaction (PCR) methods, but in 0 of 20 cases of lymphoid hyperplasia [1]. Since the T cells and B cells were polyclonal, the monoclonal cell populations were likely stromal cells.

- In another study, UCD lymph nodes were found to have increased numbers of small follicles with abnormally low proliferation by Ki67 staining, which is also observed in follicular lymphoma [2].

- Cytogenetic abnormalities have been identified in several cases of UCD, many of which are believed to occur in stromal cell populations. These include modifications in chromosome segment 12q13–15, which is commonly found in mesenchymal tumors and a clonal cytogenetic anomaly (t(1;22)(p22;q13)) hypothesized to affect megakaryoblastic leukemia 1 (MKL1) gene, which is implicated in acute megakaryocytic leukemia, and endothelial cell growth factor 1 (ECGF1) gene, which promotes angiogenesis and prevents cellular apoptosis [3-6].

Familial cases of UCD have been rarely reported, though genomic sequencing has not been performed to identify inherited mutations [7,8].

While studies evaluating the role of Epstein-Barr virus (EBV) infection on UCD have had mixed results, EBV is unlikely to be the primary driver of UCD given the high prevalence of EBV infection and rarity of UCD. A potential role for EBV in the pathogenesis of UCD was suggested when lymph nodes from one cohort of 18 patients with UCD were all found to be EBV-positive by PCR [9]; however, there were no control samples and this was not reproduced in a separate cohort [10]. In a separate study, the lack of T-bet expression by UCD lymph node T and B cells suggested that UCD is not virally driven, as T-bet is expressed by cells in the context of high interferon gamma during intracellular pathogen infection [11].

**Cell type** — The precise cell type within the lymph node responsible for driving UCD pathogenesis and producing cytokines has also not been identified [12]. Candidate cells include FDCs, germinal center B cells, and interfollicular plasma cells [13,14].

Several findings suggest that stromal cells, specifically FDCs, play a key role in the pathogenesis of UCD. Stromal cell overgrowth, FDC prominence, and FDC dysplasia are common in UCD [15], and several studies have identified monoclonal stromal cells in UCD [1,3,5,6]. FDCs are essential for normal germinal center formation, directing lymphocytes into appropriate regions within the lymph node, and promoting B cell survival. The dysmorphic germinal centers in UCD may reflect FDC dysfunction [16]. Further support comes from case studies that have described patients who developed FDC sarcoma concurrently with UCD and in the same region of lymph nodes where a UCD lymph node was resected [17].

**Signaling pathways/effector cytokines** — Though the etiology of the hypercytokinemia is unknown, a portion

of UCD, HHV-8-associated multicentric CD (MCD), and HHV-8-negative MCD are linked to excessive release of interleukin (IL)-6 or related polypeptides [18]. Early studies correlated local production of IL-6 to the systemic manifestations seen in a minority of patients with UCD [13,14], since lymph node excision resulted in relief of symptoms along with a decrease in serum IL-6 levels [13,19]. However, levels of IL-6 and other inflammatory mediators have not been systematically studied in a large number of UCD cases.

An increased prevalence of an IL-6 receptor single nucleotide polymorphism (SNP), which is associated with increased soluble IL-6 receptor levels, was identified in a cohort of UCD and HHV-8-negative MCD compared with healthy controls [20]. The significance of this SNP is unclear since it is present in 33 percent of healthy individuals.

Studies in UCD have also reported increased vascular endothelial growth factor (VEGF) expression in interfollicular areas of lymph nodes and increased serum VEGF levels [21,22]. Increased VEGF expression is believed to be induced by IL-6 and may be responsible for the increased angiogenesis seen in UCD tissue. Overexpression of epidermal growth factor receptor (EGFR) has also been reported in UCD [17].

The pathogenesis of HHV-8-associated MCD and HHV-8-negative MCD is discussed in more detail separately. (See "HHV-8-associated multicentric Castleman disease", section on 'Etiology and pathogenesis' and "HHV-8-negative/idiopathic multicentric Castleman disease", section on 'Etiology and pathogenesis'.)

## EPIDEMIOLOGY

It is estimated that approximately 6500 to 7700 new cases of Castleman disease (CD) are diagnosed each year in the United States, of which approximately 4900 to 5900 cases are estimated to be UCD [23]. No epidemiologic studies have explored UCD incidence outside of the United States, but communication among the international community of CD physicians suggests no clear associations with particular ethnicities. Now that there is a unique ICD-10 code being used internationally for CD (D47.Z2), more accurate estimations of epidemiology are expected.

While UCD can occur at any age, it is generally a disease of younger adults. The median age at presentation is approximately 35 years [24,25]. There is a slightly increased incidence of UCD in women than men [26].

Life expectancy is usually not changed following the diagnosis of UCD. However, patients with UCD are at increased risk of developing paraneoplastic pemphigus and lymphomas, which can both be fatal. CD is also associated with autoimmune diseases including autoimmune hemolytic anemia, immune thrombocytopenia, and acquired factor VIII deficiency. Unlike HHV-8-associated multicentric CD, UCD is **not** associated with HHV-8 infection or HIV infection.

## CLINICAL FEATURES

**Signs and symptoms** — Patients with UCD are commonly asymptomatic and come to clinical attention when an enlarged lymph node is noted on physical examination or imaging studies [24,25]. UCD usually affects just one lymph node. If more than one lymph node is enlarged, those lymph nodes, by definition, must be confined to a single lymph node region (eg, left cervical chain) to be considered to represent UCD. If the lymphadenopathy occurs in multiple regions of the body, then diagnostic criteria for human herpesvirus 8 (HHV-8)-negative multicentric Castleman disease (MCD) should be evaluated [27]. (See "HHV-8-associated multicentric Castleman disease" and "HHV-8-negative/idiopathic multicentric Castleman disease".)

Rarely, patients with UCD experience one or more systemic symptoms described in the international consensus diagnostic criteria for HHV-8-negative MCD, including [27,28]:

- Constitutional symptoms (night sweats, fever >38°C, weight loss, fatigue)
- Enlarged spleen and/or liver
- Fluid accumulation (peripheral edema, pleural effusion, ascites)
- Skin findings (violaceous papules and eruptive cherry hemangiomata)
- Lymphocytic interstitial pneumonitis

While these systemic symptoms may be experienced by any patient with unresected UCD regardless of histopathologic subtype, they are more commonly seen in patients with the plasma cell histopathologic subtype of UCD. In contrast, signs and symptoms related to the hyaline vascular histopathologic subtype are typically due to impingement and compression of neighboring structures (eg, airway, vessels) by the enlarging mass.

UCD can present in any lymph node in the body, and the size of the enlarged lymph node is typically greater than the enlarged lymph nodes seen in HHV-8-associated MCD or HHV-8-negative/idiopathic MCD. The distribution of disease differs between case series. In one review of 278 cases, the median lymph node size was 5.5 cm, with the most common sites of disease being the chest (24 percent), neck (20 percent), abdomen (18 percent), and retroperitoneum (14 percent) [25]. Less common sites included the axilla, groin, and pelvis. A separate large series found that the most common sites for UCD were abdomen (40 percent), neck (23 percent), mediastinum (16 percent), inguinal (9 percent), lung hilum (7 percent), and axilla (7 percent) [28]. UCD lesions are typically confined to lymph node tissue, however, there are rare reported cases of UCD lesions in solid organs. These are most frequently seen in the parotid gland, where the disease may originate in intraparotid lymph nodes.

**Laboratory studies** — Laboratory studies are usually normal in patients with UCD. Patients with UCD can sometimes demonstrate laboratory abnormalities described in the international consensus diagnostic criteria for HHV-8-negative MCD, including [27,28]:

- Elevated C-reactive protein (CRP; >10 mg/L) or erythrocyte sedimentation rate (ESR; >15 mm/h)
- Anemia (hemoglobin <12.5 g/dL for males, >11.5 g/dL for females)
- Thrombocytopenia (platelet count <150,000/microL) or thrombocytosis (platelet count >450,000/microL)
- Hypoalbuminemia (albumin <3.5 g/dL)
- Renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m$^2$) or proteinuria (total protein 150 mg/24 hours or 10 mg/100 mL)
- Polyclonal hypergammaglobulinemia (total gammaglobulin or immunoglobulin G >1700 mg/dL)

While these laboratory abnormalities may be present in any patient with unresected UCD regardless of histopathologic subtype, they are more commonly seen in patients with the plasma cell histopathologic subtype of UCD. Conversely, lactate dehydrogenase (LDH) can be elevated in a subset of cases of the hyaline vascular histopathologic subtype of UCD.

Immunofixation should be performed to exclude a clonal plasma cell disorder. (See "Laboratory methods for analyzing monoclonal proteins", section on 'Serum immunofixation'.)

**Imaging** — UCD may present in any lymph node in the body, often as an asymptomatic finding on imaging. The most common radiologic presentation is that of an enhancing hypervascular mediastinal or hilar mass [29]. While the following features are suggestive of UCD, biopsy is necessary to confirm the diagnosis [29]:

- **Computed tomography (CT)** – CT usually demonstrates a well-circumscribed mass of soft tissue attenuation (image 1). Smaller masses typically have homogeneous enhancement following contrast, while larger masses have heterogeneous enhancement. Calcification is infrequent and, when present, the pattern of calcification is variable (punctate, coarse, peripheral, arborizing).
- **Magnetic resonance imaging (MRI)** – MRI usually demonstrates a solid mass that is slightly increased on T1 compared with muscle and hyperintense on T2. There may be intralesional flow voids on T1 and T2 images (reflecting the vascularity of the lesion) and central linear hypointense septae.
- **Positron emission tomography (PET)** – Lesions are usually fluorodeoxyglucose (FDG) PET avid with a standardized uptake value (SUV) lower than that typical of lymphoma. PET may identify involvement of nodes that are not increased in size. In one study of PET in 11 cases of UCD, the median SUV max in the involved lymph node was 3.91 (SD: 1.33) [28].

## PATHOLOGY

UCD is characterized by expansions of morphologically benign lymphocytes that usually leave the structure of the underlying lymph node at least partially intact. B cells and plasma cells are polyclonal and T cells show no evidence of an aberrant immunophenotype. Three histopathologic subtypes are recognized for UCD:

- **The hyaline vascular histopathologic subtype of UCD** is characterized by the following features (picture 1) [12,24,30]:
  - Small, regressed or atrophic germinal centers – The regressed germinal centers, which are often hyalinized, are depleted of lymphocytes.
  - "Onion-skin appearance" of the mantle zone around the germinal centers – The follicles are surrounded by prominent mantle zones containing small lymphocytes arranged in a concentric fashion.
  - Germinal center "twinning" or "budding" – Frequently, two or more closely adjacent atrophic germinal centers are encircled by a single mantle zone.
  - Follicular dendritic cell (FDC) prominence – The population of FDCs are prominent within the regressed germinal centers. These FDCs express CD21, CD23, CD35, and epidermal growth factor receptor. The FDCs occasionally demonstrate dysplasia or morphological atypia.
  - "Lollipop appearance" – Sclerotic blood vessels radially penetrate atrophic germinal centers.
  - High endothelial venules in interfollicular zones – The interfollicular lymphoid tissue contains numerous small blood vessels known as high endothelial venules that are lined by plump, activated endothelial cells.
  - Tight aggregates of plasmacytoid dendritic cells – These cells may also be appreciated in interfollicular regions, particularly with immunohistochemical stains for CD123, but they are not sufficiently specific to be of diagnostic utility.
  - Obliterated sinuses and architectural disruption.
- **The plasma cell histopathologic subtype of UCD** is characterized by the following features (picture 2):
  - Interfollicular plasmacytosis – The interfollicular region contains sheets of plasma cells.
  - High endothelial venules in interfollicular zones – The interfollicular lymphoid tissue contains numerous small blood vessels known as high endothelial venules that are lined by plump, activated endothelial cells.

- Large hyperplastic reactive germinal centers – The germinal centers are often hyperplastic (unlike the regressed germinal centers in hyaline vascular histopathologic subtype). They can also have typical reactive features including polarization into light and dark zones, frequent mitotic figures, and numerous macrophages containing apoptotic debris (tingible body macrophages).

- Follicle variability – Abnormally enlarged or hyperplastic germinal centers are often present along with some regressed or "hyaline vascular"-like follicles in the same lymph node.

- Patent sinuses with no architectural disruption.

- **Mixed histopathologic subtype of UCD** is characterized by a mix of hyaline vascular (predominantly regressed germinal centers) and plasma cell (interfollicular plasmacytosis) features in the same lymph node.

More than 50 percent of UCD cases demonstrate the hyaline vascular histopathologic subtype. Approximately 10 to 25 percent of UCD cases are of the plasma cell histopathologic subtype [24,25], while the remaining have a mixed histologic appearance with features of both the hyaline vascular and plasma cell subtypes [15,31-34].

A case series evaluated the morphologic features and cell populations found in lymph node and bone marrow samples from 43 UCD cases and 31 human herpesvirus 8 (HHV-8)-negative multicentric Castleman disease (MCD) cases [28]. When compared with the HHV-8-negative MCD cases, flow cytometry of UCD lymph node tissue revealed fewer CD3+ T cells (median 43 versus 59 percent) and more CD19+/CD5+ B cells (median 17 versus 6 percent). Abnormal bone marrow features were present in 10 of 22 UCD cases and included hypercellularity (n = 6), plasma cell infiltration (n = 3), hypocellularity (n = 2), and lymphohistiocytic aggregation (n = 1).

## DIAGNOSIS

Patients with UCD are commonly asymptomatic and are brought to clinical attention when an enlarged lymph node is noted on physical examination or imaging studies. UCD should be suspected in the setting of a single persistently enlarged lymph node associated with moderate to intense post-contrast enhancement on computed tomography (CT). In such cases, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) should be considered to establish that the disease is limited to a single site with a relatively lower standardized uptake value (SUV) in other nodes. An excisional biopsy of the enlarged lymph node is necessary to diagnose UCD by histopathologic review.

The biopsy should demonstrate the histopathologic features described above. Immunohistochemistry for

LANA-1 of lymph node tissue to detect HHV-8 should be performed on all patients believed to have any form of Castleman disease (CD). UCD can be diagnosed if all of the following requirements are met:

- Imaging demonstrates that the lymph node or lymph nodes are confined to a single lymph node region
- Histopathologic review of lymph node tissue is consistent with UCD and LANA-1 is negative
- Other disorders that can demonstrate CD-like histopathologic features, such as atrophic and hyperplastic germinal centers as well as increased numbers of plasma cells are excluded (see 'Differential diagnosis' below)

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of UCD includes other disorders that can present with an enlarged lymph node and/or systemic symptoms. As a general rule, it is unusual for other causes of reactive lymphadenopathy to present with enlargement of a solitary lymph node, or to result in lymph node enlargement to sizes greater than 2 to 3 cm, clues that can be helpful when the histologic appearance raises the possibility of UCD.

Diseases that can demonstrate Castleman disease (CD)-like histopathologic features and may mimic UCD include infectious diseases, malignancies, autoimmune conditions, and other conditions.

- Infectious diseases:
  - ***Toxoplasma* lymphadenitis** – In *Toxoplasma* lymphadenitis, the lymph nodes have large reactive follicles with well-developed germinal centers that are infiltrated by clusters of epithelioid histiocytes, as well as interfollicular collections of monocytoid B cells. Atrophic follicles are usually absent. Peripheral lymph nodes (cervical, axillary, inguinal) are most commonly affected. Serologic studies can usually confirm the diagnosis of *Toxoplasma*. (See "Toxoplasmosis in immunocompetent hosts".)
  - **HIV lymphadenitis** – Generalized lymphadenopathy is common in primary HIV. A localized, solitary enlarged lymph node is rare in HIV. The nodes decrease in size following the acute presentation, but a modest degree of adenopathy often persists. These lymph nodes may demonstrate involuted follicles with hyalinized germinal centers and interfollicular vascular proliferation that mimics hyaline vascular histopathologic subtype of UCD. Unlike in UCD, clusters of plasmacytoid dendritic cells are not prominent. Serologic studies would confirm HIV infection. (See "Acute and early HIV infection: Clinical manifestations and diagnosis".)
- Neoplasia:

  **Lymphoma** – Non-Hodgkin lymphoma (NHL) subtypes that may mimic the hyaline vascular

- histopathologic subtype of UCD include follicular lymphoma, mantle cell lymphoma, and nodal marginal zone B cell lymphoma. All of these lymphoma variants have immunophenotypic features that differ from UCD and express monoclonal immunoglobulin, whereas UCD is typically polyclonal. (See "Clinical manifestations, pathologic features, diagnosis, and prognosis of follicular lymphoma" and "Clinical manifestations, pathologic features, and diagnosis of mantle cell lymphoma" and "Nodal marginal zone lymphoma".)

  NHL subtypes that may mimic the plasma cell histopathologic subtype of UCD include lymphoplasmacytic lymphoma, marginal zone B cell lymphomas, and angioimmunoblastic T cell lymphoma. Unlike in UCD, these neoplasms typically efface the normal lymphoid structure and demonstrate clonality. (See "Clinical manifestations, pathologic features, and diagnosis of lymphoplasmacytic lymphoma" and "Clinical manifestations, pathologic features, and diagnosis of angioimmunoblastic T cell lymphoma".)

- **Follicular dendritic cell (FDC) sarcoma** – FDC sarcoma can demonstrate histopathologic features mimicking the hyaline vascular histopathologic subtype of UCD. It can also occur in lymph nodes adjacent to a previously diagnosed UCD lymph node. (See "Follicular dendritic cell sarcoma", section on 'Pathologic features'.)

- **Plasmacytoma** – Both plasmacytoma and the plasma cell histopathologic subtype of UCD can demonstrate sheets of plasma cells. In plasmacytoma, these sheets are comprised of atypical monoclonal plasma cells that efface the normal lymph node architecture. In contrast, in the plasma cell histopathologic subtype of UCD the plasma cells are typically polyclonal and are found in a richly vascular interfollicular region, and lymph node follicles are retained. (See "Diagnosis and management of solitary extramedullary plasmacytoma".)

- Autoimmunity:

  - **Rheumatoid arthritis** – The lymph nodes of patients with untreated rheumatoid arthritis may have marked interfollicular plasmacytosis and reactive follicular hyperplasia that can mimic the plasma cell histopathologic subtype of UCD. UCD is suggested by the presence of a subset of follicles with hyaline vascular changes. Also, a localized, solitary enlarged lymph node is rare in rheumatoid arthritis. A positive serum rheumatoid factor supports a diagnosis of rheumatoid arthritis. (See "Diagnosis and differential diagnosis of rheumatoid arthritis", section on 'Diagnosis'.)

- Other:

  - **Follicular hyperplasia** – In reactive follicular hyperplasia, histology shows discrete follicles of varying sizes and shapes that are separated from one another by interfollicular regions rich in T cells within

the lymph node cortex. The follicles are polarized with well-formed light and dark zones and contain tingible body macrophages and mitotic figures. Sinuses are intact and may be distended. In contrast, the sinuses in the hyaline vascular histopathologic subtype of UCD are usually absent.

- **Autoimmune lymphoproliferative syndrome (ALPS)** – Patients with ALPS may demonstrate solitary or multicentric lymphadenopathy with CD-like features. Investigations for FAS mutations, double-negative T cells, and other features of ALPS are necessary in suspected cases. (See "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis", section on 'Diagnosis'.)

- **HHV-8-associated MCD** – The histopathologic features for the plasmablastic histopathologic subtype of human herpesvirus 8 (HHV-8)-associated multicentric CD (MCD) are nearly identical to the plasma cell histopathologic subtype of UCD. However, LANA-1 staining of lymph node tissue for HHV-8 will be positive in HHV-8-associated MCD. Polymerase chain reaction (PCR) for HHV-8 will be positive in the peripheral blood of HHV-8-associated MCD patients during active disease flares. Furthermore, imaging will show involvement of multiple lymph nodes. (See "HHV-8-associated multicentric Castleman disease".)

- **HHV-8-negative/idiopathic MCD (iMCD)** – The histopathologic features of UCD will be nearly identical to the histopathology of iMCD. However, imaging will show involvement of multiple lymph nodes rather than a solitary enlarged lymph node of UCD. (See "HHV-8-negative/idiopathic multicentric Castleman disease".)

## PRETREATMENT EVALUATION

Once the diagnosis of UCD has been confirmed by pathologic evaluation of the involved lymph node, a pretreatment evaluation provides a baseline of disease activity and assessment of comorbidities that may impact treatment options (table 1).

In addition to a history and physical examination, it is our practice to perform the following pretreatment studies in patients with UCD:

- Laboratory studies include a complete blood count with differential; liver and renal function chemistries, electrolytes, lactate dehydrogenase (LDH), and albumin; serum protein electrophoresis with immunofixation and quantitative immunoglobulins; and testing for acute phase reactants, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and fibrinogen. We also measure serum interleukin (IL)-6 and vascular endothelial growth factor (VEGF) in cases with suspicion for multicentric Castleman disease (MCD).

- Serologies for hepatitis B and HIV, with quantitative assays if positive. Polymerase chain reaction (PCR) for human herpesvirus 8 (HHV-8) in peripheral blood during active disease is performed if there is suspicion for HHV-8-associated MCD.
- Serologic investigations for autoimmune disorders are performed only if suspected clinically.
- Imaging with a combined positron emission tomography (PET) and contrast-enhanced computed tomography (CT) scan is performed to detect all areas of lymph node involvement and to document the standardized uptake value (SUV) of involved areas.

## TREATMENT

Data regarding the treatment of UCD come from systematic reviews of the literature, case series, and case reports. Given the rarity of the condition, there have been no randomized trials.

**Resectable disease** — Complete surgical resection of the involved lymph node(s) is almost always curative and is considered the gold standard approach for the treatment of UCD (algorithm 1) [25,35]. Systemic symptoms and laboratory abnormalities, if present, tend to resolve with complete resection of the enlarged lymph node(s) [24,36-40]. In one series, complete remission was obtained following surgical resection in 30 out of 33 patients with UCD [28]. Two of the three remaining cases achieved complete remission after a subsequent resection.

Recurrences of UCD have been rarely reported and are usually related to incomplete initial resection or missed lymph nodes at the initial evaluation, though not all UCD recurrences are in the same anatomical location [26]. We are also aware of rare patients with UCD who have persistent inflammatory symptoms even after complete surgical resection.

A systematic review of the literature identified 278 patients with UCD who had undergone complete resection (94 percent) or diagnostic biopsy [25]. Disease-free survival rates at three and five years were 90 and 81 percent, respectively. Outcomes were significantly better for those who had undergone complete resection. Complete resection was the only significant predictor of mortality (4 percent for those who had undergone complete resection versus 18 percent for those who had undergone diagnostic biopsy without complete surgical resection). Deaths in this population are typically related to the development of paraneoplastic pemphigus, lymphoma, or follicular dendritic cell (FDC) sarcoma.

**Unresectable disease** — Occasionally, a large UCD mass may be unresectable due to size or, more often, location. This is frequently encountered in the setting of a mediastinal mass that is very close to a main bronchus or major blood vessels. In these patients, we proceed with initial debulking of the mass with

embolization or rituximab, with the goal of converting the mass to a resectable lesion.

Cases that are refractory to this initial treatment may respond to immunomodulators/immunosuppressants, such as cyclosporine and sirolimus, which are more commonly used for human herpesvirus 8 (HHV-8)-negative/idiopathic multicentric Castleman disease (MCD). (See "HHV-8-negative/idiopathic multicentric Castleman disease", section on 'Chemotherapy and immunomodulators/immunosuppressants'.)

Anti-IL-6 therapy with siltuximab is reserved for patients with laboratory abnormalities consistent with systemic inflammation (eg, elevated CRP/ESR, anemia) and constitutional symptoms. (See "HHV-8-negative/idiopathic multicentric Castleman disease", section on 'IL-6 inhibitors'.)

If possible, each of these treatments may be followed by safer surgical intervention, and the systemic treatments may be discontinued.

As an example, a case report described the successful use of rituximab in a single patient with recurrent chest pain due to an unresectable UCD lymph node encompassing the right main pulmonary artery and main bronchus [41].

The role of systemic glucocorticoids and radiation therapy (RT) is limited. Systemic glucocorticoids can provide symptomatic relief but do not predictably reduce UCD lymph node size. RT has been utilized, but with limited response. RT with approximately 30 to 45 Gy can result in complete and partial remission rates of 40 and 10 percent, respectively [38,39]. Importantly, radiation-induced fibrosis may make subsequent surgical intervention more difficult, limiting its use in general practice. RT is also associated with potential long-term sequelae, especially when used in pediatric and younger adult populations.

Other interventions used for HHV-8-negative/idiopathic MCD (eg, cytotoxic immunodepletion) can also be considered for treatment of unresectable UCD or UCD with systemic symptoms. (See "HHV-8-negative/idiopathic multicentric Castleman disease", section on 'Classes of therapies'.)

In patients whose lesions cannot be completely resected, it is unclear what outcomes should be expected. Partially resected masses may remain stable and asymptomatic for many years [24,38,39]. However, greater investigation of how to manage unresectable cases and their risk of developing comorbidities due to remaining UCD lymph node tissue is needed.

## FOLLOW-UP

**Evaluation for relapse** — After completion of the initially planned treatment (usually complete surgical resection), patients should be evaluated to determine the disease response to treatment and should be followed longitudinally for relapse and complications.

One month following the completion of planned therapy, the response to treatment should be documented by history, physical examination, and laboratory studies (complete blood count [CBC], lactate dehydrogenase [LDH], biochemical profile, albumin, interleukin [IL]-6, C-reactive protein [CRP], serum free light chain assay, and quantitative immunoglobulins). Post-treatment imaging should be performed between one and three months following the completion of planned therapy. The post-treatment imaging study of choice is the positron emission tomography with computed tomography (PET/CT) scan, which provides information on the size and activity of residual masses. CT of the chest, abdomen, and pelvis with contrast is an acceptable alternative. If a PET/CT is performed, the scan should be done at least two months after surgery to ensure that there is no FDG update due to post-operative changes.

Following excision, patients are followed annually with PET/CT and laboratory studies, which include CBC, LDH, chemistries with liver and renal function and electrolytes, albumin, IL-6, CRP, serum free light chain assay, and quantitative immunoglobulins. Annual imaging may be discontinued after five years if the patient remains disease free.

**Complications** — Most patients with UCD will experience long-term disease-free survival following complete resection. Death due to UCD is rare, with a systematic review of 278 cases of UCD reporting a 4 percent mortality over 10 years of follow-up [25]. Complete resection of the UCD lymph node, rather than diagnostic/incomplete resection, was the only significant predictor of survival. Among cases with complete resection, cases with visceral lymph node resection had a significantly worse overall survival than peripheral lymph node resection.

UCD may be associated with an increased risk of lymphoma. Of 48 reported cases of UCD in one series, three developed B cell non-Hodgkin lymphoma (NHL), one developed Hodgkin lymphoma (HL), and two others amyloidosis, despite complete resection [36-40,42]. Another series of eight cases of UCD associated with NHL has been reported [43]. The two diagnoses were concurrent in three, with a mean interval of 46 months between the diagnosis of UCD and the subsequent NHL. Also in this series was a case of HL with UCD-like histologic changes in the same lymph node. It is unclear whether these cases represent a true malignant transformation or presence of lymphoma at the initial diagnosis of Castleman disease that was not detected. Initial evaluation of the lymph node biopsy with molecular studies for IgH gene rearrangement is recommended to rule out the latter.

Paraneoplastic pemphigus (PNP) is an often fatal paraneoplastic mucocutaneous blistering disease that is most commonly induced by lymphoproliferative disorders. Approximately 15 percent of instances of paraneoplastic pemphigus are associated with UCD [44]. Resection of the UCD lymph node may result in improvement of the paraneoplastic pemphigus, but that is not always the case. Aggressive treatment of the paraneoplastic pemphigus and possible development of cryptogenic organizing pneumonia (formerly called bronchiolitis obliterans organizing pneumonia [BOOP]) is necessary. (See "Paraneoplastic pemphigus" and

"Cryptogenic organizing pneumonia".)

There are no reported cases of UCD transforming into either form of multicentric Castleman disease (MCD).

## ADDITIONAL RESOURCES

The Castleman Disease Collaborative Network (CDCN) connects an international community of physicians, researchers, patients, and loved ones to advance research and treatments for all subtypes of Castleman disease (CD).

Patients can visit the CDCN website to learn about and directly enroll themselves onto an international natural history registry of CD (www.CDCN.org/ACCELERATE). The CDCN also provides patient information and opportunities to engage others interested in CD through virtual communities and in-person meetings.

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Castleman disease".)

## SUMMARY AND RECOMMENDATIONS

- Castleman disease (CD) describes a heterogeneous group of lymphoproliferative disorders that share common histopathologic features and abnormal proliferation of morphologically benign lymphocytes. CD is classified based on the number of lymph node regions with enlarged lymph nodes. Unicentric CD (UCD) involves one or more lymph node(s) in a single region, while multicentric CD (MCD) involves multiple lymph node sites and is subclassified into human herpesvirus 8 (HHV-8)-associated MCD and HHV-8-negative/idiopathic MCD.

- UCD is most often an isolated lymphoproliferative disorder of young adults. Patients are commonly asymptomatic and are brought to clinical attention when an enlarged lymph node is noted on physical examination or imaging studies. Most lesions are in the mediastinum, but UCD can present in any lymph node location. Laboratory and clinical abnormalities are seen in less than 25 percent of cases. (See 'Signs and symptoms' above.)

- UCD should be suspected in the setting of a single persistently enlarged lymph node associated with moderate to intense post-contrast enhancement on computed tomography (CT). 18F-fluorodeoxyglucose positron emission tomography (FDG PET) should establish that the disease is limited to a single site. (See

'Imaging' above.)

- The diagnosis is made upon pathologic review of a biopsy of involved tissue, typically an excisional biopsy of a lymph node. Biopsy should demonstrate histopathologic features consistent with the hyaline vascular, plasma cell, or mixed histopathologic subtypes, though the clinical utility of these histopathologic subtypes is unclear. HHV-8 testing via LANA-1 should be performed and be negative in all cases of UCD. (See 'Pathology' above.)

- The evaluation should exclude other disorders that can present with a solitary enlarged lymph node that displays CD-like histopathologic features. (See 'Differential diagnosis' above.)

- For most patients, we recommend complete excisional resection of the involved lymph node rather than core biopsy or incomplete resection (algorithm 1) (**Grade 1C**). Complete resection is curative in the majority of patients. If the involved lymph node cannot be completely removed because of its anatomic location, we proceed with systemic therapy to reduce mass size followed by surgical resection. Options for systemic therapy include treatments utilized for HHV-8-negative/idiopathic MCD. Localized radiation therapy has a relatively limited role. (See 'Treatment' above and "HHV-8-negative/idiopathic multicentric Castleman disease", section on 'Classes of therapies'.)

- After resection, patients should be evaluated to determine the disease response to treatment and should be followed longitudinally for relapse and complications. Follow-up generally includes annual imaging and laboratory studies. (See 'Follow-up' above.)

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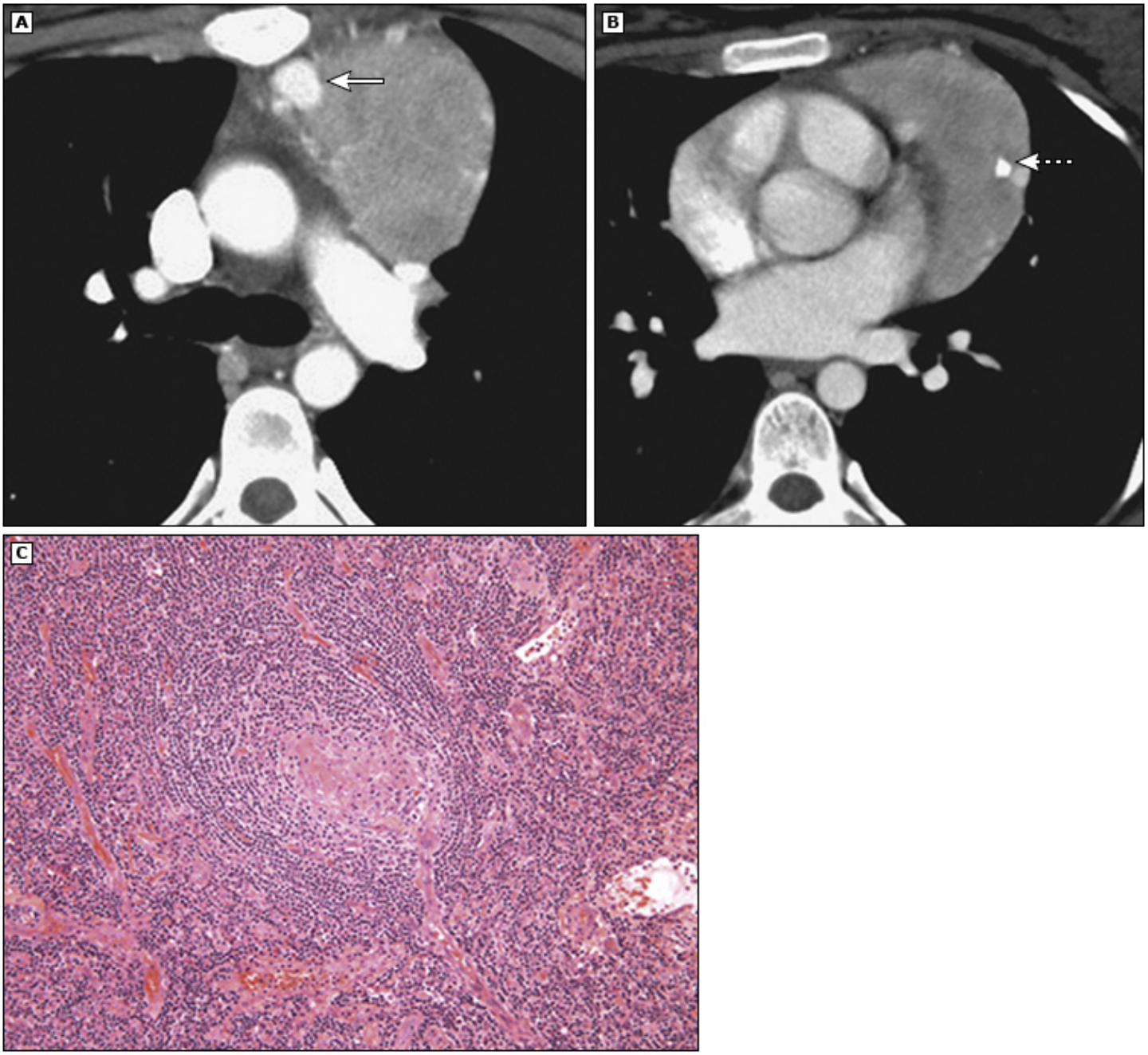
## GRAPHICS

### Computed tomography of unicentric Castleman disease




A 29-year-old woman with asthma and recently diagnosed anterior mediastinal mass. (A) and (B) contrast enhanced computed tomography shows an intensely enhancing mass anterior to great vessels. Large vessels anterior to the mass correspond to large veins draining into the innominate vein (arrow) and are not usually seen in thymic epithelial neoplasms. Dense calcific focus in the left lateral aspect of mass (dashed arrow) would be unusual in an untreated lymphoma. (C) Photomicrograph (H&E, 200×) shows regressed germinal center with vascular proliferation, concentric layers of small mantle zone lymphocytes, penetrating vessel imparting the characteristic "lollipop on a stick" appearance, and interfollicular hypervascularity consistent with hyaline-vascular Castleman disease.

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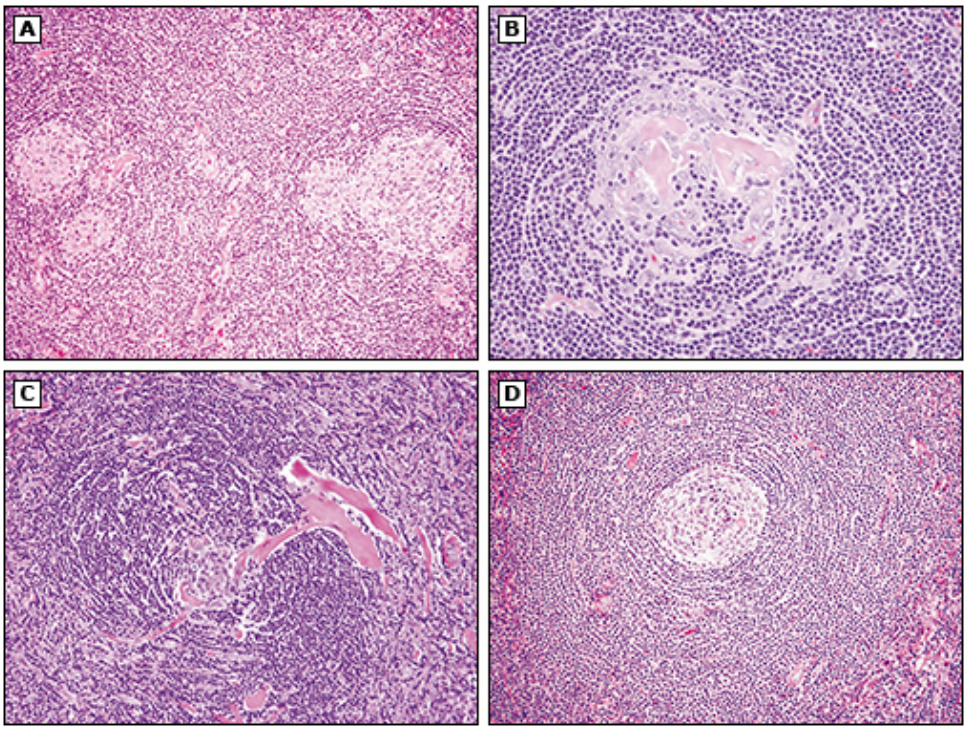
Graphic 115626 Version 1.0

**Pathologic features of hyaline vascular histopathologic subtype of unicentric Castleman disease**




(A) Two follicles are present in this field. The follicles contain small, regressed germinal centers. The follicle to the left of the field contains more than one germinal center ("twinning"). Hematoxylin and eosin stain.
(B) Hyaline deposits are present within the germinal center. Hematoxylin and eosin stain.
(C) Hyaline vascular ("lollipop") lesion in which a follicle is radially penetrated by a sclerotic blood vessel. Hematoxylin and eosin stain.
(D) The follicle is surrounded by a broad mantle zone composed of concentric rings of small lymphocytes (so-called "onion skin"). Hematoxylin and eosin stain.

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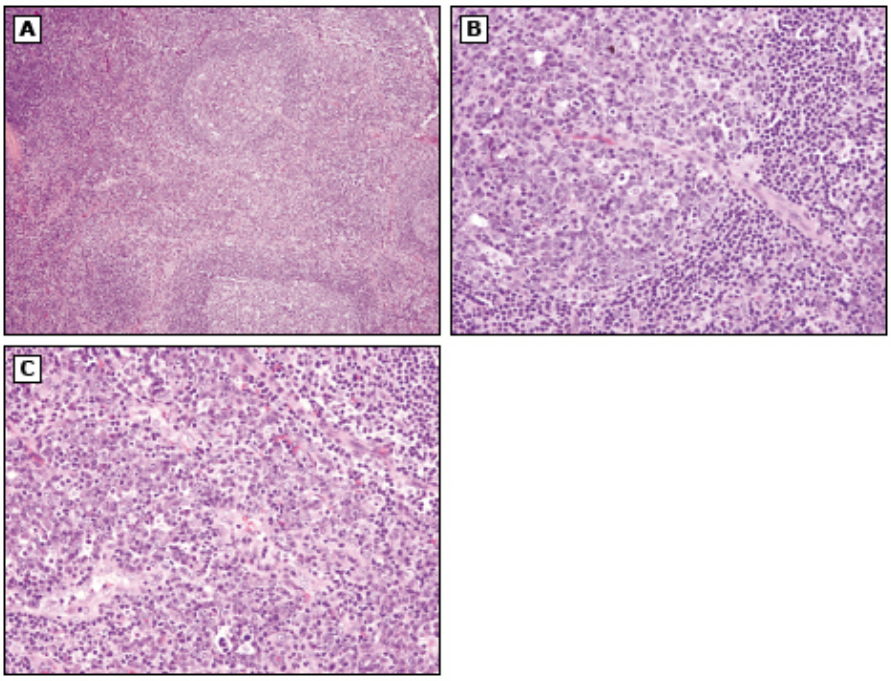
Graphic 90402 Version 7.0

**Pathologic features of plasma cell histopathologic subtype of unicentric Castleman disease**




(A) Reactive lymphoid follicles and interfollicular plasmacytosis are present.
(B) In this field, the reactive germinal center is radially penetrated by a prominent blood vessel.
(C) Sheets of cytologically mature plasma cells are present within the interfollicular region. Hematoxylin and eosin stain.

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Graphic 90404 Version 6.0

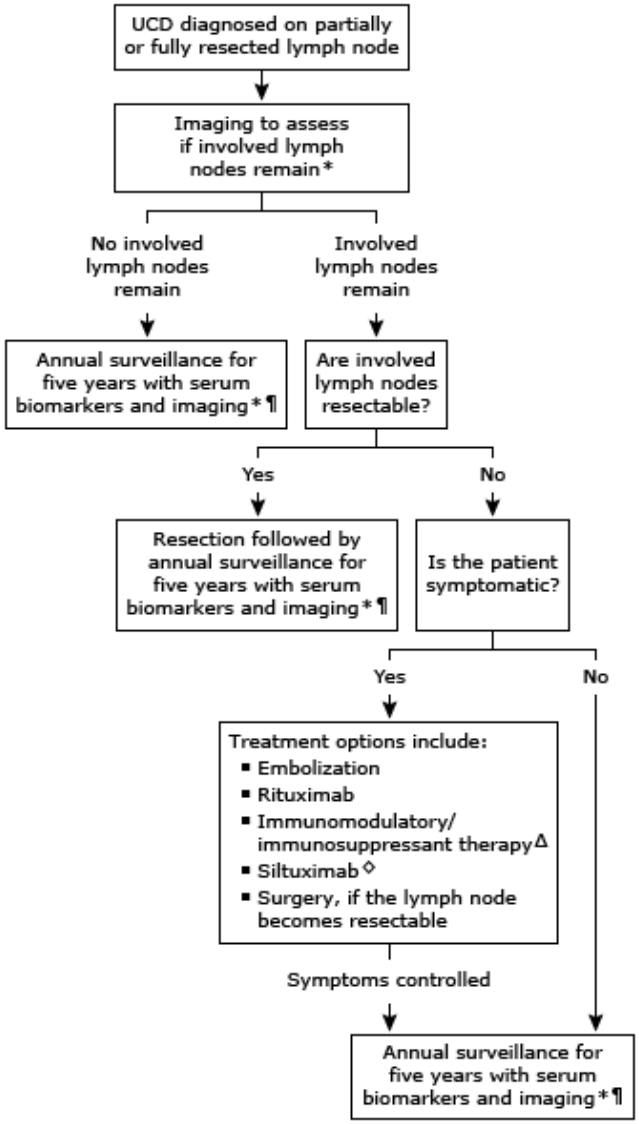
**Pretreatment evaluation in patients with unicentric Castleman disease**

| Investigation | Common findings |
|---|---|
| Complete blood count (CBC) | Normal CBC, but anemia, thrombocytopenia, and thrombocytosis can be seen |
| Serum chemistry | Normal serum chemistry panel, but hypoalbuminemia and elevated lactate dehydrogenase can be seen |
| Acute phase reactants | Normal acute phase reactants, but elevated ESR, CRP, ferritin, and fibrinogen can be seen |
| SPEP, quantitative immunoglobulin, immunofixation | Normal with no M spike, IFE negative, but elevation in one or more immunoglobulin class (IgG, IgA, IgM) can be seen |
| Serum cytokine levels: IL-6 and VEGF (in select cases) | Normal cytokine levels, but elevated IL-6 and VEGF can be seen |
| Serological investigations for autoimmune disorders: only if clinically suspected | Normal serological tests for autoimmune disorders, but positive tests can be seen |
| Viral testing for HHV-8, HIV; if positive, quantitative assay. Staining of lymph node biopsy for HHV-8. | Negative viral testing for HHV-8 and HIV and negative staining for HHV-8 in all cases. If PCR for HHV-8 of serum is positive or HHV-8 staining is positive, then HHV-8-associated MCD should be highly suspected and thoroughly investigated. |
| Imaging: PET/CT | Should only demonstrate enlarged/active lymph node(s) in one region of the body. The SUV should be 2.5 to 7. If there is more than one region of lymph node involvement, then iMCD should be investigated as an alternate diagnosis. If SUV uptake is >10, lymphoma should be investigated as an alternative diagnosis. |
| IgH gene rearrangement study on lymph node specimen | Should be negative, which rules out clonal disorder, mainly occult lymphoma |

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SPEP: serum protein electrophoresis; IFE: immunofixation; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; UCD: unicentric Castleman disease; HHV-8: human herpes virus 8; PET/CT: positron emission tomography/computed tomography; MCD: multicentric Castleman disease; iMCD: idiopathic MCD; PCR: polymerase chain reaction; SUV: standardized uptake value.

Graphic 93417 Version 2.0

## Management of unicentric Castleman disease




UCD: unicentric Castleman disease; FDG PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography; CT: computed tomography.
* Imaging with whole body FDG PET/CT is preferred. CT of the chest, abdomen, and pelvis with contrast is an acceptable alternative.
¶ Serum biomarkers include complete blood count, blood chemistries, and C-reactive protein.
Δ Potential immunomodulatory/immunosuppressant therapies include cyclosporine and sirolimus.
◇ Siltuximab should be used only if the patient has laboratory abnormalities consistent with systemic inflammation (eg, elevated C-reactive protein and erythrocyte sedimentation rate, anemia) and constitutional symptoms.

Graphic 117393 Version 3.0

## Contributor Disclosures

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