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Castleman disease is an uncommon and heterogeneous lymphoproliferative disorder for which management is rapidly evolving.

Diagnosis and Management of Castleman Disease

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Background: *Castleman disease is an uncommon lymphoproliferative disorder characterized as either unicentric or multicentric. Unicentric Castleman disease (UCD) is localized and carries an excellent prognosis, whereas multicentric Castleman disease (MCD) is a systemic disease occurring most commonly in the setting of HIV infection and is associated with human herpesvirus 8. MCD has been associated with considerable morbidity and mortality, and the therapeutic landscape for its management continues to evolve.*

Methods: *The available medical literature on UCD and MCD was reviewed. The clinical presentation and pathological diagnosis of Castleman disease was reviewed, along with associated disorders such as certain malignancies and autoimmune complications.*

Results: *Surgical resection remains the standard therapy for UCD, while systemic therapies are required for the management of MCD. Rituximab monotherapy is the mainstay of therapy; however, novel therapies targeting interleukin 6 may represent a treatment option in the near future. Antiviral strategies as well as single-agent and combination chemotherapy with glucocorticoids are established systemic therapies. The management of Castleman disease also requires careful attention to potential concomitant infections, malignancies, and associated syndromes.*

Conclusions: *UCD and MCD constitute uncommon but well-defined clinicopathologic entities. Although UCD is typically well controlled with local therapy, MCD continues to pose formidable challenges in management. We address historical chemotherapy-based approaches to this disease as well as recently developed targeted therapies, including rituximab and siltuximab, that have improved the outcome for newly diagnosed patients. Ongoing research into the management of MCD is needed.*

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Submitted March 31, 2014; accepted June 18, 2014.

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The authors have disclosed that this article discusses unlabeled/unapproved uses of the drug tocilizumab for the treatment of Castleman disease.

Introduction

Castleman disease, also known as angiofollicular lymph node hyperplasia, is an uncommon lymphoproliferative disorder originally described in a case published in 1954.[1] The patient from that case was a man aged 42 years who presented with high fevers, sweats, fatigue, and a nonproductive cough. He was found to have an anterior mediastinal mass with anemia and an elevated sedimentation rate. The treating physician suspected tuberculosis and empirical streptomycin was administered prior to complete surgical resection. The discussants favored a diagnosis of teratoma or dermoid cyst, also considering

mediastinal tuberculoma, thymoma, and Hodgkin disease. Castleman presented the surgical pathology and described a new syndrome characterized by hyperplasia of mediastinal lymph nodes with regressed germinal centers.[1] The disease did not recur in this patient following surgical resection. This case, followed 2 years later by a case series,[2] described what is now known as unicentric Castleman disease (UCD), which is distinct from multicentric Castleman disease (MCD), a condition with unique clinical and pathological features.

Histologically, Castleman disease may be classified as either the hyaline-vascular or plasma cell variant, with occasional cases demonstrating mixed features.[3] The hyaline-vascular histology accounts for most UCD cases and the plasma cell type characterizes most cases of MCD. UCD is typically localized, associated with minimal symptoms, and treated with local therapy alone. However, MCD is a systemic disease that commonly occurs in the setting of HIV infection and is clinically characterized by diffuse lymphadenopathy, splenomegaly, anemia, and systemic inflammatory symptoms.[4] Accordingly, MCD is primarily treated with systemic therapies.

Although Castleman disease is not a malignant condition, the condition has been associated with an increased risk of developing certain malignancies and other diseases, most notably large B-cell lymphomas, along with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormality (POEMS) syndrome, follicular dendritic cell sarcomas, and paraneoplastic pemphigus.[5-7] Kaposi sarcoma is also commonly diagnosed concurrently or sequentially with MCD because the 2 entities share a common viral pathogenesis.

Pathogenesis

The pathogenesis of Castleman disease is not fully understood; however, the central roles of interleukin (IL) 6 in UCD and both IL-6 and human herpesvirus (HHV) 8 in MCD have been well described.[8-12] Dysregulated and overproduced IL-6, particularly in patients with MCD, stimulates the production of acute phase reactants in the liver, resulting in constitutional symptoms, including fever, sweats, and fatigue, and laboratory abnormalities, such as anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia. IL-6 also stimulates B-cell proliferation and induces the expression of vascular endothelial growth factor and increased angiogenesis. The activation of the IL-6 receptor further results in the activation of the Janus kinase–mediated activation of the signal transducers and the activation of transcription pathway and the mitogen-activated protein kinase cascade, which enhances B-cell proliferation and survival. IL-6 has emerged as a therapeutic target in Castleman disease based on its critical role in pathogenesis and driving of symptomatology.

HIV-associated MCD is uniformly associated with HHV-8 infection, although its prevalence in HIV-negative MCD varies by the local prevalence rate of HHV-8. Plasma levels of HHV-8 DNA correlate with clinical symptoms and predict relapse rates in HIV-associated MCD.[13] In patients with HHV-8-positive MCD, HHV-8-infected vascular and lymphoid cells express a viral analog of IL-6 (vIL-6), which likely contributes to the pathogenesis of this significant subset of Castleman disease. Both human IL-6 and vIL-6 are sufficient to induce disease flares in HIV-associated MCD and promote the expression of proinflammatory cytokines during disease flares.[12,14-16]

Pathological Diagnosis

Castleman disease is a pathological diagnosis made by excisional biopsy of affected lymph node tissue. In cases of deeper or less accessible disease, core needle biopsy is preferred to fine needle aspiration, because fine needle aspirations are insensitive for both UCD and MCD.

Most cases of UCD are histologically classified as the hyaline-vascular variant, which is characterized by increased numbers of small, hyalinized blood vessels within and between follicles with obliteration of the medullary sinuses.[3] Lymphoid follicles are increased in number and exhibit features of "regression," a term referring to a predominance of dendritic cells within germinal centers with a relative paucity of lymphocytes and a consequent broadening of mantle zones. The small lymphocytes of the mantle zones are frequently arranged in concentric rings around the germinal center ("onion-skinning"), and follicles may be radially penetrated by a blood vessel ("lollipop" follicle; Fig 1). Plasma cells may be found in the interfollicular region, but they are typically few and present in small clusters. Cases with abundant plasma cells likely reflect examples of UCD with "mixed" or "transitional" features between the hyaline-vascular and plasma cell histological variants.[17]

By contrast to hyaline-vascular Castleman disease, cases of plasma cell variant Castleman disease typically show greater retention of the nodal architecture with hyperplastic follicles of varying sizes and focally patent medullary sinuses. The interfollicular region may be mildly hypervascular and characteristically contains sheets of mature-appearing plasma cells, which show monotypic immunoglobulin (Ig) G or IgA λ restriction in up to 50% of cases (Fig 2).[17] Cases positive for HHV-8 show distinctive histological features with greater interfollicular vascularity, blurring of the germinal center-mantle zone boundary, and scattered plasmacytoid immunoblasts, or plasmablasts present within the mantle zones (Fig 3), giving rise

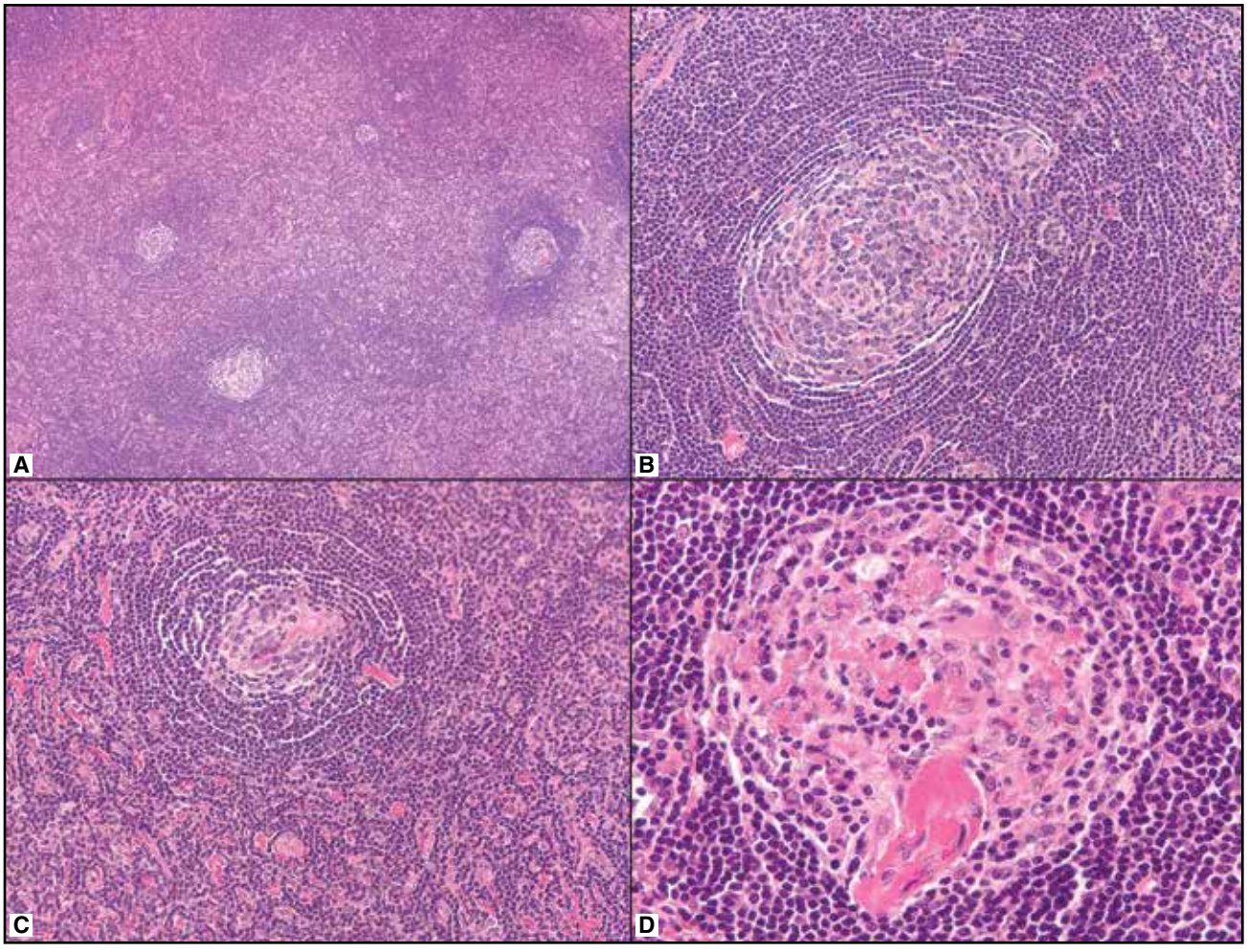

Fig 1. — Hyaline-vascular Castleman disease. (A) Low power view of an involved lymph node shows increased numbers of lymphoid follicles with small, regressed germinal centers and broad mantle zones. The interfollicular areas demonstrate increased vascularity with obliteration of medullary sinuses (H & E, × 40). (B–D) Higher magnification reveals typical features of the follicles, including an increased proportion of follicular dendritic cells relative to lymphocytes within germinal centers, known as follicle regression; concentric arrangement of mantle zone lymphocytes in an "onion skin" pattern; and hypervascularity of follicles, some of which are radially penetrated by a hyalinized blood vessel, resembling a lollipop (B–C: H & E, × 200; D: H & E, × 400). Note the sharp demarcation between the germinal center and mantle zone in images B to D, a feature unlike that seen in HIV-associated multicentric Castleman disease. H & E = hematoxylin and eosin.

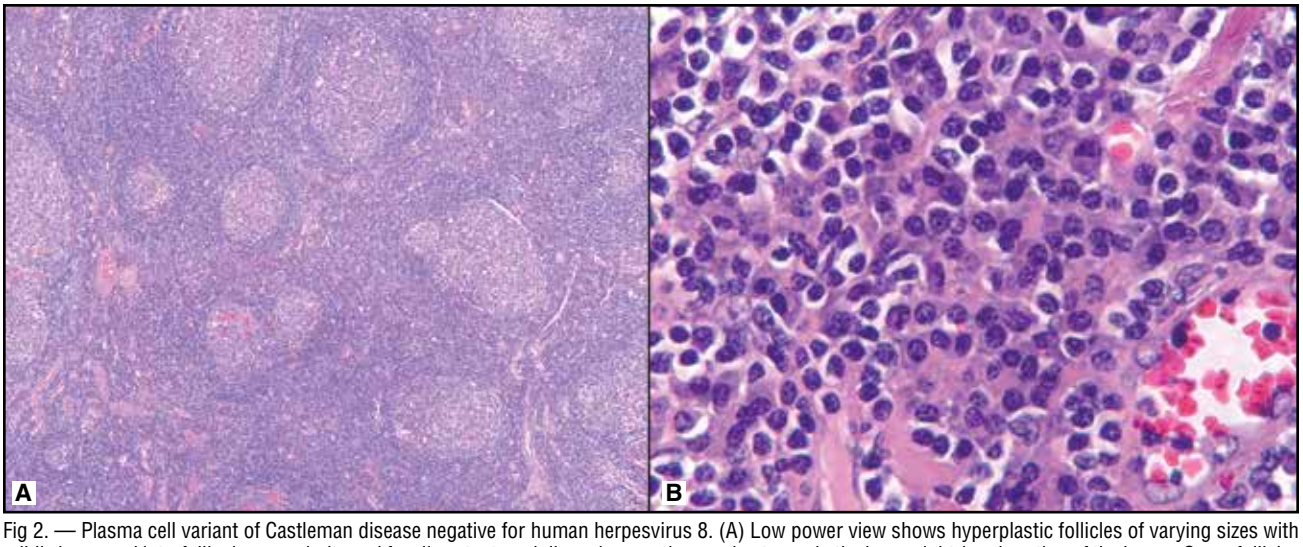

Fig 2. — Plasma cell variant of Castleman disease negative for human herpesvirus 8. (A) Low power view shows hyperplastic follicles of varying sizes with mildly increased interfollicular vascularity and focally patent medullary sinuses; they are best seen in the lower right-hand portion of the image. Some follicles contain more than 1 germinal center, a feature that may also be seen in the hyaline-vascular variant (H & E, × 25). (B) Higher magnification of the interfollicular areas shows sheets of mature plasma cells with eccentric nuclei and clumped chromatin (H & E, × 400). H & E = hematoxylin and eosin.

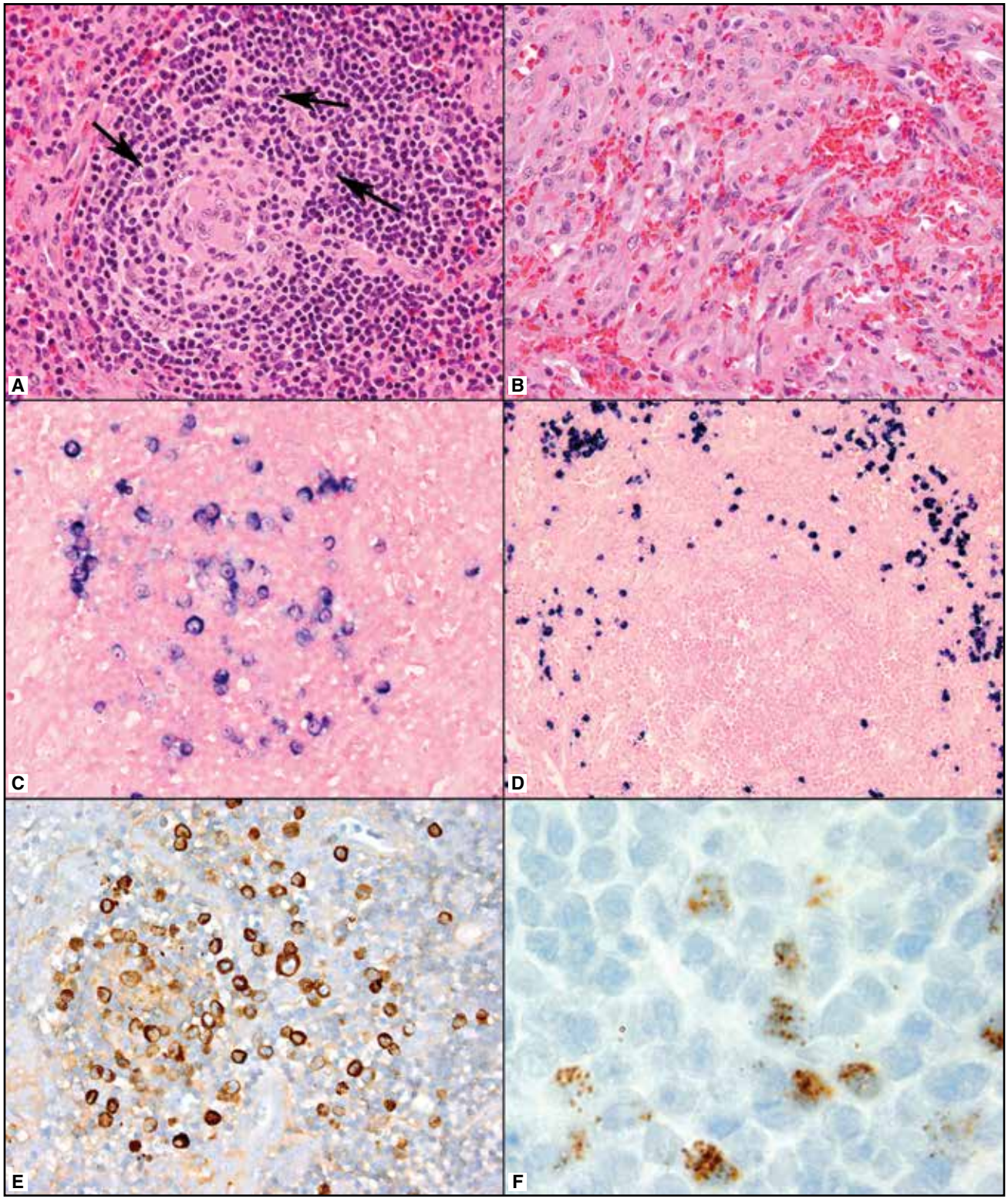

Fig 3. — HIV-associated plasmablastic Castleman disease with concurrent nodal involvement by Kaposi sarcoma. (A) Follicles are regressed with a paucity of lymphocytes, hypervascularity, and an indistinct border between the germinal center and surrounding mantle zone, which contains scattered, large, atypical plasmablasts (arrows) with vesicular chromatin, prominent nucleoli, and scant to moderate pink cytoplasm (H & E, × 400). (B) In this case, further examination revealed an atypical spindled cell proliferation consisting of plump endothelial cells with small nucleoli and prominent red blood cell extravasation extending from the lymph node capsule to the subcapsular region, consistent with nodal involvement by Kaposi sarcoma (H & E, × 400). (C) Plasmablasts within the mantle zones showed λ light-chain restriction (Λ-mRNA in situ hybridization, × 400). (D) K-mRNA in situ hybridization showed staining of mature polytypic plasma cells outside of follicles (× 200). (E) Plasmablasts were also positive for immunoglobulin M heavy chain (anti-μ immunohistochemical stain, × 400). (F) Immunohistochemistry with an antibody specific for human herpesvirus 8 latency-associated nuclear antigen 1 showed finely stippled nuclear staining of the plasmablasts (× 1000); a similar staining pattern with this antibody was seen in the endothelial cells of the vascular proliferation (not shown), confirming the concurrent diagnoses of Castleman disease and Kaposi sarcoma involving the same lymph node. H & E = hematoxylin and eosin.

to the term "plasmablastic variant" of Castleman disease.[18] Immunohistochemistry demonstrates positivity of plasmablasts for HHV-8 latency-associated nuclear antigen 1; these cells express monotypic IgM λ, but they have been shown to be polyclonal. In some cases, the atypical plasmablasts coalesce to form microscopic nodules adjacent to or replacing some follicles, an early stage of large B-cell lymphoma arising in HHV-8-associated MCD; cases of frank lymphoma are characterized by complete effacement of the lymph node architecture by sheets of atypical plasmablasts expressing HHV-8 latency-associated nuclear antigen 1.[19] Foci of Kaposi sarcoma may be present in some cases, and a diagnosis of Kaposi sarcoma must also be excluded in cases positive for HHV-8; in such cases, the atypical endothelial cells also show staining for HHV-8 latency-associated nuclear antigen 1 (see Fig 3).

From a pathological standpoint, Castleman disease is a diagnosis of exclusion and its varied histological features give rise to a broad differential diagnosis that includes both benign and neoplastic entities, most of which can be excluded on the basis of careful histological examination, immunohistochemical, or other ancillary studies (eg, flow cytometry, molecular genetics) and correlation with clinical, laboratory, and radiological findings. Angioimmunoblastic T-cell lymphoma and rare cases of early interfollicular Hodgkin lymphoma may be associated with Castleman disease–like changes, including the regression of residual germinal centers and hypervascularity. However, Castleman disease lacks an atypical interfollicular population of neoplastic T cells or Reed–Sternberg cells. The appearance of the follicles in hyaline-vascular Castleman disease may raise the possibility of early nodal involvement by follicular lymphoma in which atypical follicles can show variable degrees of hyalinization. The prominence of the mantle zones in hyaline-vascular Castleman disease may also raise the possibility of early mantle cell lymphoma. Finally, the plasma cell variant of Castleman disease may mimic lymphoplasmacytic lymphoma (Waldenström macroglobulinemia) due to the large number of interfollicular plasma cells; this distinction may be particularly challenging in cases showing λ light chain restriction. In all of these scenarios, the diagnosis of Castleman disease can be made based on the lack of additional histological features supporting a diagnosis of lymphoma and the absence of a clonal B-cell population with a characteristic immunophenotype. In addition, lymphoplasmacytic lymphoma commonly expresses IgM heavy chain and may not show λ light chain restriction, unlike IgG or IgA λ-restricted plasma cell variant Castleman disease.[17]

Among non-neoplastic conditions, the plasma cell variant of Castleman disease may mimic lymph nodes biopsied in the setting of rheumatoid arthritis or syphilitic (luetic) lymphadenitis due to overlapping features of follicular hyperplasia and increased interfollicular plasma cells. In addition, lymphadenopathy associated with IgG4-related disease may show features that overlap with Castleman disease. The diagnosis of rheumatoid arthritis, syphilis, or IgG4-related disease can be readily established based on clinical and laboratory features. In addition, Castleman disease lacks the histiocytic inflammation and inflamed vasculature seen in syphilis in which spirochetes can be identified using special histochemical stains or antitreponemal immunohistochemistry.[17,20-22] Perhaps the most challenging histological distinction in the pathological diagnosis of MCD is with that of HIV-related generalized lymphadenopathy, which is characterized by plasmacytosis, vascular prominence, and hyperplastic or regressive changes in the follicles of involved lymph nodes depending on their stage of evolution. However, HIV-related lymphadenopathy should not contain plasmablasts positive for HHV-8 that characterize HIV-associated MCD. For the diagnosis of other subtypes of Castleman disease in the setting of HIV infection, one should adhere to strict morphological criteria given the known histological overlap between these entities.[17]

Staging

Once Castleman disease is confirmed and the histological subtype has been identified, clinical staging guides treatment decisions and prognosis. The goals of the staging and pretreatment evaluation in Castleman disease are to (1) determine whether the patient has unicentric or multicentric disease, (2) identify patients with systemic inflammatory manifestations of Castleman disease, and (3) assess for the presence of HIV, as well as associated conditions and malignancies.

The initial laboratory evaluation of patients with Castleman disease includes a complete blood count, inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), complete metabolic panel, and albumin. HIV testing should be performed in all patients. Plasma HHV-8 DNA levels should be obtained, because these levels correlate with symptomatic disease and may serve as a helpful biomarker, both to support the diagnosis of MCD and to monitor disease activity and response to therapy. Although levels of cytokines, most notably IL-6 and IL-10, are important in the pathogenesis of Castleman disease and have been used as surrogate markers of disease activity in clinical studies, we do not recommend routinely measuring them. Serum protein electrophoresis with immunofixation should be obtained when POEMS syndrome is suspected. In patients with HIV-associated MCD, a thorough skin examination should be performed to assess for previously undiagnosed Kaposi sarcoma given the common concurrent presentation of these entities.

Computed tomography of the chest, abdomen, and pelvis should be obtained at the time of diagnosis to assess for adenopathy and splenomegaly. This imaging modality also helps inform the question of resectability in patients with UCD. A role for routine positron emission tomography has not been established in the setting of Castleman disease, although involved nodes in MCD are quite fludeoxyglucose-avid.

Unicentric Castleman Disease

Epidemiology

UCD most commonly presents in the third and fourth decade of life, with the mean age of diagnosis being 34 years (range, 2–84 years); UCD also has a slight female predominance (1.4:1).[23] No association with HIV or HHV-8 infection exists and epidemiological risk factors have not been established.

Clinical Presentation

UCD may be asymptomatic at diagnosis and be incidentally discovered on chest or abdominal imaging performed for other reasons. Other patients may present with painless lymphadenopathy or local anatomical symptoms varying by location. Common sites of presentation in UCD include the chest (30%), neck (23%), abdomen (20%), retroperitoneum (17%), and, rarely, the axilla (5%), groin (3%), or pelvis (2%).[23] Intrathoracic disease is frequently found along the tracheobronchial tree or lung hila. Thoracic disease may present with cough, hemoptysis, dyspnea, or chest discomfort. Abdominal, retroperitoneal, and pelvic disease may present with abdominal or back discomfort.[2] Bowel and ureteral obstruction have been described as presenting symptoms, but they are rare.[24] Disease confined to the peripheral lymph node chains, including the neck, axilla, or groin, may present with nontender lymphadenopathy. Systemic manifestations, including B symptoms (fevers, drenching night sweats, and weight loss) and laboratory abnormalities (anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia) are uncommon in unicentric disease, but such symptoms are observed frequently among patients with the plasma cell variant.

Management

The optimal therapy for UCD is surgical resection, which is usually curative if the disease is amenable to complete resection.[3,23] For disease that cannot be completely excised, radiation therapy is an option due to its high rates of objective response, including complete responses in nearly one-half of reported cases.[25-31]

For select patients who are not candidates for surgical excision, but who are also not candidates for radiation therapy based on the location of the disease, partial resection followed by clinical observation alone may result in lengthy remissions; however, such treatment warrants careful attention to local progression. Select patients who are asymptomatic with a low disease burden who cannot be treated with either surgery or radiation may be closely followed, given the often indolent nature of the disease. Systemic options for MCD, as necessary, should be considered for patients with symptomatic local disease who cannot be treated with surgery or radiation or for those whose disease fails to respond to such treatment.

Multicentric Castleman Disease

Epidemiology

MCD commonly presents in the sixth decade of life, although patients with HIV infection tend to present at a younger age.[4,25,32] A slight male predominance is seen in MCD. HIV infection is an important risk factor for MCD, and all patients with HIV-associated MCD are coinfected with HHV-8. HHV-8 infection is present in approximately 50% of HIV-negative cases of MCD and varies with the HHV-8 seroprevalence of the population.

Large population studies have revealed an increased incidence of HIV-associated MCD since the introduction of antiretroviral therapy, which is in contrast to the marked decline in incidence of HIV-associated Kaposi sarcoma.[33] The mechanism of this increase is unclear, but such an increase may reflect improved survival rates, longstanding immune dysregulation associated with long-term HIV infection, or an increased awareness of the disease among health care professionals.

Clinical Presentation

Systemic inflammatory manifestations characterize the vast majority of patients with MCD who present with fevers, night sweats, weight loss, and fatigue.[4,25,32] Physical examination is typically notable for generalized lymphadenopathy and hepatosplenomegaly, and many patients have evidence of fluid retention with lower extremity edema, pleural and pericardial effusions, and abdominal ascites. Common hematological abnormalities include anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia. Systemic symptoms and hematological abnormalities have been shown to correspond to elevated inflammatory markers and cytokine levels, particularly IL-6 and IL-10.

The natural history of MCD is variable. Some patients may present with indolent disease and very slow progression over months to years, while others will experience a relapsing-remitting course or an acute and fulminant disease that can be fatal within weeks; the latter courses are more common in patients with HIV-associated MCD.[34,35] HIV-associated

MCD may also concurrently or sequentially present with other concomitant malignancies, including Kaposi sarcoma or primary effusion lymphoma, each of which share an HHV-8–mediated pathogenesis. Kaposi sarcoma may be identified in 72% of HIV-related MCD cases at diagnosis and may be seen in HIV-negative MCD, although at a far lower rate.[33] Patients are also at significant risk for diffuse large B-cell lymphoma, which may arise directly out of HHV-8–positive MCD; therefore, one must consider the possibility of a second malignancy at the time of diagnosis and perform a thorough skin examination for cutaneous Kaposi sarcoma, as well as consider biopsying bulky or visceral locations seen on imaging studies for staging that may constitute a distinct histology from Castleman disease. Repeat biopsy should also be considered at progression or relapse to evaluate for lymphomatous transformation. Patients with HIV-associated MCD will often present with a low CD4 count, so concomitant opportunistic infections must also be considered at diagnosis and during the course of illness, including *Pneumocystis jiroveci*, *Toxoplasma gondii*, cytomegalovirus, and mycobacterial infections, among others.

Treatment

Treatment options for MCD are based on few nonrandomized prospective studies, small case series, and expert opinion; therefore, the body of evidence must be interpreted with caution. Available treatments include glucocorticoids, single-agent and combination chemotherapy, antiviral strategies, and monoclonal antibody therapies targeting CD20 or IL-6.

Antiretroviral Therapy: All patients with HIV infection and MCD should be initiated on combination antiretroviral therapy if they are not already taking it, although antiretroviral therapy alone is unlikely to independently result in a Castleman disease response. The risk of developing MCD is not influenced by the use of combination antiretroviral therapy or by the CD4 count at the time of diagnosis.[33] However, independent of MCD, the initiation of combination antiretroviral therapy can prevent further consequences of poorly controlled HIV, including opportunistic infections and malignancies, and allows for the safe administration of chemotherapy due to immune reconstitution. Patients should be monitored for immune reconstitution inflammatory syndrome, including an exacerbation of MCD and concurrent Kaposi sarcoma.[36]

Glucocorticoids: Glucocorticoids have activity as monotherapy in MCD and may offer short-term control of symptoms, but complete remissions are rare and are generally short-lived. Twenty-one cases of MCD treated with glucocorticoids alone have been described in case reports and small case series, and responses were observed in approximately 80% of patients.[4,32,37-42] None of these reported cases were known to be positive for HIV. Given the delayed response to rituximab monotherapy, glucocorticoid pulses may be helpful as an initial adjunct for acutely symptomatic disease. In these patients, prednisone 1 mg/kg daily or its equivalent may be added to rituximab until systemic inflammatory symptoms are adequately controlled and then tapered off.

Cytotoxic Chemotherapy: Various agents have been used as single-agent chemotherapy in the treatment of MCD, although data are limited to few case reports and small case series. These include oral etoposide,[5] vinblastine,[43] cyclophosphamide,[32] cladribine,[44,45] chlorambucil,[32] and liposomal doxorubicin.[46,47] Responses following these agents are often short-lived and symptoms may rapidly recur following the completion of therapy. Single-agent chemotherapies are often administered at doses and schedules routinely used to treat patients with lymphoma. Etoposide may be administered at a dose of 50 or 100 mg by mouth daily on days 1 through 7 of a 14-day cycle until maximal response, or 100 mg/m^2 intravenously once weekly for 4 weeks, and can be used with a maintenance schedule to prolong remission duration. Vinblastine may be administered at a dose of 4 to 6 mg/m^2 every 2 weeks until maximal response, and it can be used with a maintenance schedule in the absence of significant toxicity.

Combination chemotherapy with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or cyclophosphamide/vincristine/prednisone (CVP) without rituximab have produced durable remissions in small case series of patients with MCD,[4,25,32,46,48,49] although many patients will progress or experience infectious toxicities. These data are primarily from before the introduction of rituximab, and the impact of rituximab in combination with chemotherapy in these patients is unknown. Our practice is to include rituximab for most patients and to administer chemotherapy at doses and schedules typical for patients with lymphoma, but infectious risk is increased; therefore, caution and attention to supportive care are required, particularly in patients with low CD4 counts.

Dose reductions may be necessary on the basis of interactions with antiretroviral therapy, because protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the CYP450 system, which is either induced or inhibited by many chemotherapeutic agents, including cyclophosphamide, doxorubicin, etoposide, vinblastine, and vincristine.

Rituximab: Rituximab is highly active as monotherapy in MCD. Its role in HIV-associated MCD is supported by prospective and retrospective trials demonstrating sustained remissions.[34,50-55] Small case series have also demonstrated activity in patients with MCD who are HIV negative.[56-59]

A prospective study enrolled 24 patients with chemotherapy-dependent, HIV-associated MCD.[50] Patients had received single-agent chemotherapy (etoposide, vinblastine, or liposomal doxorubicin) for a median of 13 months and all patients had failed at least 1 attempt to discontinue chemotherapy. All patients received concurrent combination antiretroviral therapy. After 4 weekly infusions of rituximab at a dose of 375 mg/m^2, 22 of 24 patients (92%) achieved the primary endpoint of sustained remission at 60 days off treatment, and 17 patients (71%) were alive and in remission at 1 year.[51] A second prospective trial enrolled 21 patients with previously untreated HIV-associated MCD and treated with 4 weekly rituximab infusions.[51] Clinical and radiological responses occurred in 20 (95%) and 14 (67%) patients, respectively, and the 2-year progression-free survival rate was 79%.[51]

These small prospective studies are also supported by a retrospective analysis of 49 patients naive to treatment with HIV-associated MCD who were given rituximab with or without etoposide.[34] Combination therapy with rituximab/etoposide was reserved for patients with a poor performance status or evidence of end-organ involvement. For the entire cohort, 5-year progression-free and overall survival rates were 61% and 90%, respectively.[34] No difference was seen in outcomes between the 2 treatment arms; however, the 2 arms included distinct patient populations by design, and it is unknown whether patients treated with combination therapy would have performed as well if treated with rituximab alone. This does add to a body of literature demonstrating favorable progression-free and overall survival rates in patients treated with rituximab therapy.[34]

Patients with concomitant MCD and Kaposi sarcoma require vigilance for Kaposi sarcoma flareups during rituximab therapy. Exacerbations of Kaposi sarcoma during rituximab treatment was observed in all trials of rituximab in HIV-associated MCD, occurring in 36% to 67% of reported patients.[34,50,51]

Anti-Interleukin 6 Therapy: Siltuximab and tocilizumab are monoclonal antibodies targeting IL-6 and its receptor (IL-6R), respectively. The US Food and Drug Administration (FDA) has approved siltuximab for the treatment of patients with HIV negative, HHV-8 negative MCD, where it shows significant clinical activity, resulting in control of IL-6–dependent systemic symptoms and laboratory abnormalities.[60,61] A phase 2 study that included 19 patients with HIV negative and HHV-8 negative MCD reported 8 radiological responses, including 1 complete response.[61] At a median follow-up of 5.1 years (range, 3.4–7.2 years), all 19 patients taking siltuximab therapy were still alive.[61]

The data from those studies prompted a multicenter, randomized, double-blind, placebo-controlled trial of siltuximab in patients with HIV negative, HHV-8 negative MCD.[62] Patients were randomized 2:1 to siltuximab or placebo administered once every 3 weeks. Patients receiving placebo were permitted to cross over to open-label siltuximab at progression. Of the 79 randomized patients, 53 received siltuximab and 26 received placebo. The median age was 48 years and a 2:1 male predominance was seen.[62] Hyaline-vascular, plasma cell, and mixed pathologies were observed in 33%, 23%, and 44% of patients, respectively.[62] A total of 58% had received prior therapy and 30% were on corticosteroids at enrollment.[62] The primary endpoint was durable radiological and symptomatic responses (improvement or stabilization of symptoms) lasting at least 18 weeks. Treatment with siltuximab was associated with a higher rate of achieving the primary endpoint (34% vs 0%).[62] Radiographic tumor response rates were seen in 38% and 4% of patients, favoring the siltuximab arm, and symptomatic response rates were 57% and 19%.[62] Complete symptom resolution was observed in those receiving siltuximab (25% vs 0%).[62] Patients receiving siltuximab also had improvements in anemia and hypoalbuminemia, and a decrease in inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and fibrinogen) relative to patients receiving placebo. These data demonstrate that siltuximab is highly active in MCD with durable disease control and improvement in clinically relevant outcomes. However, an important caveat is that patients with HIV and HHV-8-associated MCD were excluded from this study. Siltuximab was also compared against a placebo rather than rituximab.

The anti-IL-6R humanized monoclonal antibody tocilizumab is also active in MCD. Twenty-eight patients with symptomatic MCD were enrolled in a phase 2 trial,[63] all of whom were HIV negative and only 2 of whom were positive for HHV-8. All patients had pathological findings consistent with the plasma cell variant. Patients received tocilizumab every 2 weeks for 16 weeks and the study drug was continued thereafter at the discretion of the treating investigator. The alleviation of systemic inflammatory symptoms was universal and weight gain occurred in all patients. Laboratory abnormalities, including anemia, hypoalbuminemia, and elevated C-reactive protein, all improved with therapy, as did lymphadenopathy. Eleven of the 15 (73%) patients receiving corticosteroids at enrollment were able to decrease or discontinue concomitant corticosteroid therapy.[63] It is worth noting, however, that tocilizumab is currently FDA approved only for rheumatoid arthritis and systemic or polyarticular juvenile idiopathic arthritis.

Monoclonal antibodies targeting IL-6 remain largely unevaluated in patients with HIV and HHV-8-associated MCD. It is not known whether targeting IL-6 is similarly effective in this population, yet several

features make these patients appealing candidates for therapies targeting IL-6. Although vIL-6 is implicated in the pathogenesis of HHV-8-associated MCD and is not targeted by the current monoclonal antibodies, human IL-6 is also elevated in the majority of patients with HIV-associated MCD and likely remains a significant contributor to disease activity and symptomatology.[12] Three cases in the literature have demonstrated activity of IL-6 targeted therapy in HIV and HHV-8-associated MCD,[64,65] speaking to the need for prospective clinical trials in these patients.

Antiherpesvirus Therapy: Antiherpesvirus agents have been explored as therapy for HIV-associated MCD given the pathogenetic link with HHV-8.[66-68] Lytic replication of HHV-8 is common in MCD and may be important in its pathogenesis, as opposed to Kaposi sarcoma in which HHV-8 infection most often remains latent. Many HHV-8–derived gene products, including vIL-6, are expressed during the lytic cycle of HHV-8 replication.[69] Therefore, MCD is potentially targetable with antiviral therapy, particularly in patients with detectable HHV-8 viral loads. An early report of 3 patients with MCD treated with intravenous or oral ganciclovir was promising.[70] Two patients experienced flares of symptomatic disease less frequently and a third patient had prolonged remission.[70] This report prompted a prospective study evaluating the use of high-dose zidovudine (600 mg orally every 6 hours) and valganciclovir (900 mg orally every 12 hours) given for 1 out of every 3 weeks.[67,68] Fourteen patients with symptomatic HIV-associated, HHV-8 positive MCD were enrolled and demonstrated overall clinical and complete response rates of 86% and 50%, respectively. The overall radiographic response rate was lower at 36%, with 29% of patients experiencing a complete radiographic response. Three patients who achieved a complete clinical and radiographic response remained in sustained remission at a median of 29 months after the completion of therapy.[68] Antiherpesvirus agents have not been studied in patients who were HIV negative in whom HHV-8 is often present but whose role in pathogenesis is less clearly defined. Among small reports, success has not been observed with cidofovir.[71]

Bortezomib: Bortezomib is a proteasome inhibitor active in plasma cell neoplasms by multiple mechanisms; it also decreases the production of IL-6 via the NFκB blockade.[72] Anecdotal reports of durable clinical and radiographic responses in MCD warrant further study in the context of clinical trials.[73-76]

Summary of Treatment Approaches: For initial systemic therapy, rituximab monotherapy has been recommended based on encouraging efficacy and safety results, with a high likelihood of initial response and associated long-term, progression-free survival rates reported to be between 60% and 79%.[34,50-57,59,77,78] Treatment involves 4 weekly doses at 375 mg/m^2 that can be repeated as necessary for subsequent flareups in patients who previously responded favorably to therapy.[55,77]

In patients who are negative for HIV but who have failed to respond to, or relapse rapidly following rituximab monotherapy, siltuximab monotherapy is recommended. For patients who progress following treatment with siltuximab, single-agent chemotherapy can be utilized with etoposide,[5] vinblastine,[43] or liposomal doxorubicin[47] with or without rituximab. Combination chemotherapy regimens such as rituximab plus CHOP (R-CHOP) and rituximab plus CVP (R-CVP) are options for patients with resistant or rapidly progressive disease. In patients with HIV-associated MCD who fail to respond to or relapse rapidly following rituximab monotherapy, the use of either single-agent chemotherapy with or without rituximab or antiherpesvirus therapy with high-dose zidovudine and valganciclovir is recommended.[67] Given the increased toxicity in patients with HIV infection and MCD, combination therapy with R-CHOP or R-CVP should be reserved for select patients with treatment-resistant, rapidly progressive, or fulminant disease.

In cases of progression following second-line therapy, the use of alternative single-agent or combination chemotherapies with or without rituximab, bortezomib, antiherpesvirus therapies, or IL-6-directed therapy with siltuximab or tocilizumab should be considered. Siltuximab or tocilizumab should be considered for use in patients positive for HIV in the context of a clinical trial. Corticosteroid pulses may be helpful for acutely symptomatic disease; however, steroids alone are unlikely to induce lengthy remissions, so they should be reserved for short-term symptomatic control.[3,32,37-42] The emerging IL-6 and its receptor antibodies appear highly active in clinical trials, although they have not been studied in HIV-associated MCD.[60-62,65,79,80] A recommended treatment algorithm is provided in Fig 4.

Associated Conditions and Malignancy Risk

Kaposi Sarcoma

HHV-8 plays a critical role in the pathogenesis of both MCD and Kaposi sarcoma, and the clinical association of these diseases was noted prior to the identification of HHV-8 as a common underlying viral pathogen. Patients with HIV-associated MCD have a 72% risk of being diagnosed with Kaposi sarcoma, either concurrently or sequentially, and the 2 diseases may coexist in the same pathological specimen (see Fig 3).[33] The association is lower with Kaposi sarcoma negative for HIV, where the dual incidence is reported at 0% to 13%.[33,81] Exacerbations of Kaposi sarcoma have been observed with rituximab therapy[34,50,51]; therefore, vigilance for flareups of Kaposi sarcoma is necessary

when using treatments containing rituximab in a patient with both diseases.

Lymphoma

Patients with Castleman disease are at increased risk for lymphoma. Non-Hodgkin lymphoma has been reported in approximately 20% of patients with MCD, as well as in patients with UCD.[18,32,38,82,83] Among these, large B-cell lymphoma arising in HHV-8-associated MCD is the most common lymphoma subtype. Patients with MCD are also at increased risk for primary effusion lymphoma, which shares a common HHV-8-mediated pathogenesis. Patients infected with HIV may also develop other HIV-associated lymphomas not directly related to MCD, including plasmablastic lymphoma, Hodgkin lymphoma, and primary lymphoma of the central nervous system. Amyloidosis has also been reported in association with both UCD and MCD.[84-88]

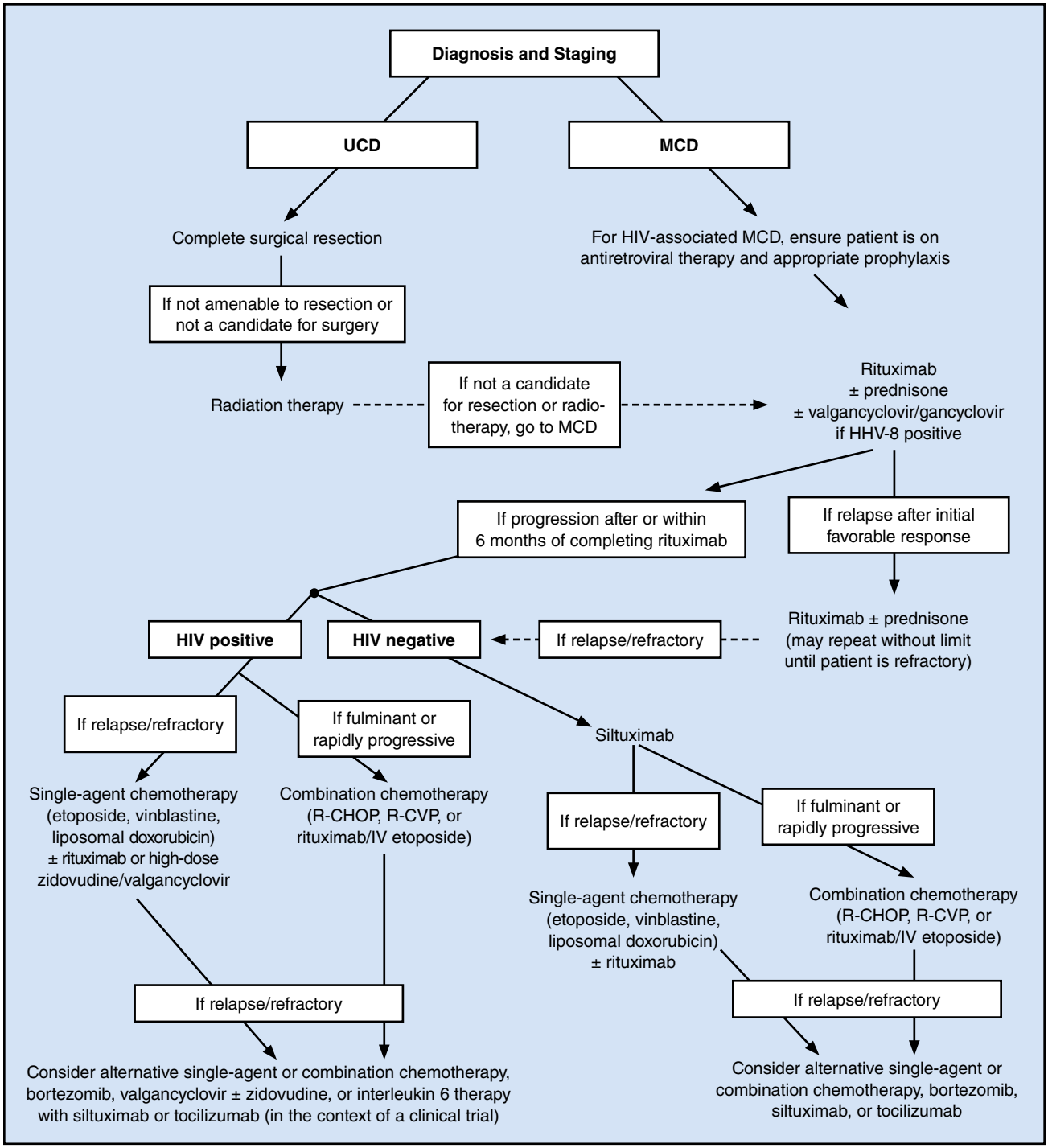

Fig 4. — Recommended treatment algorithm for Castleman disease. IV = intravenous, MCD = multicentric Castleman disease, R-CHOP = rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, R-CVP = rituximab/cyclophosphamide/vincristine/prednisone, UCD = unicentric Castleman disease.

Although most cases of lymphoma arising in MCD occur in patients with HIV or HHV-8 infection, patients with MCD in the absence of HIV or HHV-8 infection are also at increased risk of lymphoma to a lesser degree.[82,89]

POEMS Syndrome

POEMS syndrome is characterized by a λ light chain restricted monoclonal gammopathy and a progressive polyneuropathy with early sensory symptoms and later more severe motor symptoms, resembling a chronic inflammatory demyelinating polyneuropathy.[90,91] MCD is present in 15% to 25% of patients with POEMS syndrome and is included as a major criterion for the diagnosis of POEMS syndrome.[7,92] Other common features include osteosclerotic bone lesions, elevated levels of vascular endothelial growth factor, hepatosplenomegaly, lymphadenopathy, endocrinopathy, skin changes, and elevated protein in the cerebrospinal fluid. Treatment is directed at the plasma cell clone and includes dexamethasone, lenalidomide, and alkylator-based therapy, with high-dose chemotherapy and autologous stem cell transplantation reserved for select cases.

Follicular Dendritic Cell Sarcoma

Follicular dendritic cell sarcoma is a rare malignancy that frequently occurs in lymph nodes, although it may also involve extranodal sites. Follicular dendritic cell sarcoma has been associated with UCD; in such cases, follicular dendritic cell sarcoma is diagnosed either concurrently with or following the diagnosis of UCD.[93-100] Optimal therapy is surgical resection, with or without adjuvant radiation therapy or chemotherapy, although data to guide chemotherapy in this population are scant given the rarity of the disease.

Paraneoplastic Pemphigus

Paraneoplastic pemphigus is an autoimmune mucocutaneous blistering disease associated with localized Castleman disease in 18% of cases and can be a devastating disease with a high mortality rate.[101] Approximately two-thirds of patients with paraneoplastic pemphigus have either UCD or an associated malignancy (eg, B-cell lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia) at the time of diagnosis.[102] The disease precedes the diagnosis of UCD or cancer in the remaining cases. UCD should be suspected in any young patient with paraneoplastic pemphigus. Complete resection of UCD results in clinical improvement or complete remission in most patients.

Conclusions

Castleman disease is an uncommon lymphoproliferative disorder that continues to pose clinical challenges. Although surgical resection remains the standard therapy for unicentric disease, the landscape for the management of multicentric disease continues to evolve. Rituximab monotherapy is the current mainstay of therapy, and novel agents targeting interleukin 6 represent exciting new additions to the treatment armamentarium. Single-agent and combination chemotherapies as well as antiviral therapy provide adjunctive support, particularly in the setting of relapsed or refractory disease. The ongoing exploration of antiviral and novel strategies, such as proteasome inhibition, is warranted. The management of Castleman disease also requires careful attention to potential concomitant infections, malignancies, and associated syndromes.

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