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Treatment of Castleman Disease

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The Question What are your treatment approaches to Castleman disease with the advent of anti–interleukin-6 therapy?**Our Response**Castleman disease (CD) describes a group of heterogeneous lymphoproliferative disorders that share common histopathological lymph node changes. CD can present with localized (unicentric CD or UCD) or generalized lymphadenopathy (multicentric CD or MCD). MCD should be further divided into HHV-8–positive and HHV-8-negative MCD (Table 1). The latter is also referred to as idiopathic MCD (iMCD). MCD patients can exhibit a spectrum of clinical features from mild flu-like symptoms to sepsis-like multiple organ failure.[1] It is important to distinguish these three entities since they require entirely different therapeutic approaches.**UCD**UCD presents with lymphadenopathy confined to one lymph node region, and many patients are asymptomatic. Symptoms are usually due to compression of vital structures such as the trachea, blood vessels, or nerves. UCD occurs most frequently

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Castleman changes. Approximately 90 percent of UCD cases demonstrate the hyaline vascular (HV) subtype. The other 10 percent of patients with UCD demonstrate mixed cellularity or plasmacytic (PC) pathology and may have constitutional symptoms such as fever, fatigue, and weight loss. UCD is not associated with HHV-8 or HIV infection. There is an increased association with lymphoma, which may have been present all along, or the UCD may "transform" into lymphoma. The etiology of UCD is poorly understood, and there is usually no excess interleukin-6 (IL-6) secretion. Limited studies have demonstrated abnormal cytogenetics or evidence of monoclonality in stromal cells, but the significance of these findings is unknown.[2] Surgical extirpation is curative in 95 percent of UCD cases.[3] Unresectable cases can be treated with rituximab and steroids, which may induce complete responses or shrink the mass sufficiently to make it resectable. UCD lymphadenopathy is highly vascularized, and embolization is a further therapeutic option. Involution of lymphadenopathy after radiotherapy has also been reported. Difficult cases require a multimodal approach and are best managed at an experienced center.**HHV-8–Positive MCD**HHV-8–positive MCD presents with generalized lymphadenopathy and constitutional symptoms, and can progress to multi-organ failure leading to death. The disease is driven by the excessive release of viral IL-6, which is encoded by the HHV-8 virus and drives human IL-6, IL-10, and vascular endothelial growth factor (VEGF) secretion. HHV-8–positive MCD was first described during the AIDS epidemic and is classically thought to be due to lytic replication of HHV-8 in the setting of HIV infection.[4] However, there are also patients with HHV-8–positive MCD who are HIV negative. These patients may have another cause for immunosuppression that impairs their control of HHV-8.[5] Approximately 10 to 20 percent of individuals have been exposed to HHV-8, and the virus remains dormant in B lymphocytes. A diagnosis of HHV-8–positive MCD can be rendered if the patient has 1) a pathologic diagnosis of CD made on an excisional lymph node biopsy and 2) actively replicating HHV-8 virus detected in the peripheral blood by molecular testing (quantitative polymerase chain reaction [PCR]) or a positive stain of the lymph node for the HHV-8 latency associated nuclear antigen (LANA-1). HIV-positive, HHV-8–positive MCD patients may have coexistent Kaposi sarcoma and are prone to develop HIV-associated lymphomas. Lymph node pathology shows plasmacytic or plasmablastic changes, and the plasma cells may exhibit light chain restriction. Intranodal microlymphomas have also been reported. HHV-8–positive MCD is effectively treated with rituximab, which depletes the reservoir of HHV-8–positive cells and significantly reduces the risk of lymphoma.[6] More severely afflicted patients may require additional etoposide. Some experts recommend maintenance therapy with valganciclovir. HIV-positive patients should receive appropriate HAART therapy.[7] The value of tocilizumab, which blocks the human IL-6 receptor is the subject of ongoing studies. Siltuximab, which is a monoclonal antibody to IL-6, has not been studied in HHV-8–positive MCD because it did not bind to viral IL-6 in preclinical studies.**HHV-8–Negative (Idiopathic) MCD [iMCD]**HHV-8–negative MCD presents with generalized lymphadenopathy, constitutional symptoms, and can also develop multiorgan failure. The disease can wax and wane, be gradually progressive, or have severe

Competing Interests

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episodic flares resulting in death.[8] In a recent literature review, 22 percent of HHV-8–negative MCD patients had died by a median follow-up time of 29 months.[9] HHV-8–negative MCD is driven by pro-inflammatory hypercytokinemia, most notably of IL-6, which leads to: anemia; anasarca due to hypoalbuminemia from IL-6–mediated liver dysfunction and VEGF-mediated vascular permeability; and systemic inflammation with elevated ESR, CRP, and fibrinogen.[8] Some patients may develop kidney, liver, and bone marrow failure and succumb to their disease. Patients with HHV-8–negative MCD may also have one or more features of POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome, or a concurrent POEMS syndrome.[10] Patients with one or more features of POEMS often have less florid constitutional symptomatology. The etiology of the pro-inflammatory hypercytokinemia in iMCD has not yet been identified. The pathologic cell and the responsible intracellular inflammatory pathway responsible for producing the IL-6 in these patients has also not been elucidated. Hypothesized etiologies include an unknown virus, a small population of malignant cells, or germline genetic mutations in the immune system.[1] No single gene causing iMCD has been identified, but systematic sequencing has not been performed. The disease may be influenced by ethnicity and genetic factors such as a polymorphism of the IL-6 receptor.[11] Asian patients may demonstrate violaceous skin lesions or interstitial pneumonitis usually not seen in other populations. Currently, a diagnosis of iMCD can be made when patients have 1) histopathology typical of CD on excisional lymph node biopsy, 2) multiple regions of enlarged lymph nodes, 3) negative quantitative PCR for HHV-8 in the peripheral blood or negative LANA-1 staining of the lymph node biopsy, and 4) systematic exclusion of diseases known to demonstrate Castleman-like histopathology (e.g., systemic lupus erythematosus, Epstein-Barr virus, lymphoma, IgG4-associated lymphadenopathy). Hence, both HHV-8–positive and –negative MCD are not purely pathologic diagnoses. Efforts are currently underway to establish international consensus around clinical, pathologic, and exclusion criteria for the diagnosis of iMCD. Although the PC variant predominates in iMCD, HV and mixed pathology have also been reported.HHV-8-negative MCD has been historically managed with corticosteroids, rituximab, and/or chemotherapeutic agents derived from the CHOP regimen. Corticosteroids may temporarily control symptoms, but patients relapse on tapering. Rituximab has not been systematically evaluated in iMCD and a limited number of case reports suggest that patients often relapse. Monoclonal antibodies targeting IL-6 have been recently developed and more rigorously evaluated. A single-arm study of 28 Japanese patients on tocilizumab demonstrated a high response rate in terms of symptoms, laboratory parameters, and reduction in lymphadenopathy.[12] Siltuximab was evaluated in a double-blind, placebo-controlled, randomized study using a control arm of best supportive care including up to 60 mg of prednisone. The combined durable symptomatic and tumor response was 34 percent, and 50 percent of patients remained on drug for the duration of the study. This study provided the first placebo-controlled evidence for an iMCD therapy, and siltuximab is the first drug approved for iMCD

by the U.S. Food and Drug Administration and European Medicines Agency. Both siltuximab and tocilizumab are safe and well-tolerated.[13] For patients that do not respond to anti–IL-6 therapy, immunosuppressants, immunomodulators, biologics, and cytotoxic chemotherapies, including cyclosporine, sirolimus, bortezomib, thalidomide, anakinra, interferon-α, cyclophosphamide, and etoposide, have been reported to have some success in case reports or small series. **Choice of Therapy for iMCD**In the authors' opinion, patients with iMCD should first be treated with anti–IL-6 therapy approved in that region (siltuximab in North America and the European Union; tocilizumab in Japan). Patients with few symptoms or laboratory abnormalities suggestive of little excess IL-6 may not respond well to anti–IL-6 blockade and should be considered for rituximab and steroids. Severe hypercytokinemia and organ failure may not respond sufficiently to anti–IL-6 targeting monoclonal antibodies, and they require combination chemotherapy or consideration of experimental treatment. Dosing intervals can be spaced out in selected patients responding to anti-IL-6 therapy. Progressive motor polyneuropathy suggesting coexistent POEMS does not respond well to rituximab or to IL-6–targeted therapy, and these patients require autologous stem cell transplantation as part of their treatment plan.

Table. Features of the Different Types of Castleman Disease

Type of Castleman Disease	Type of Lymphadenopathy	Pathology	IL-6-Driven Inflammatory Syndrome*	Virologic Status	Treatment
Unicentric	Localized	90 percent hyaline vascular	Typically not	Negative for HHV-8 by QPCR or negative LANA-1 stain	Complete excision
Multicentric HHV-8-Positive	Generalized ± hepatosplenomegaly	Plasmacytic or plasmablastic	Yes	Positive for HHV-8 by QPCRMay be positive for HIV	Rituximab ± etoposideOptional valganciclo maintenance
Multicentric HHV-8-Negative (Idiopathic)	Generalized ± hepatosplenomegaly	Mostly plasmacytic, but can be hyaline vascular or mixed cellularity	Yes, but variable clinical presentation from mild to very severe	Negative for HHV-8 by QPCR or Negative LANA-1 stainNegative for HIV	SiltuximabTocilizimabRituximabChemother in severe cases

Abbreviations: QPCR, quantitative polymerase chain reaction; LANA-1, latency associated nuclear antigen.

*Symptoms: fevers, night sweats, anorexia, weight loss, fatigue. Laboratory abnormalities: anemia, thrombocytopenia or thrombocytosis, elevated C-reactive protein, Westergren erythrocyte sedimentation rate, fibrinogen, hypergammaglobulinemia, abnormal renal function, increased interleukin-6 (IL-6), vascular endothelial growth factor, interleukin-10.

The Future

The introduction of rituximab has been a major advance in HHV-8–positive MCD, whilst therapy with IL-6–targeting monoclonal antibodies are an important innovation in iMCD. However, anti–IL-6 therapy is not effective for all patients, and they are not curative, as cessation of treatment results in relapse. In 2012, we co-founded the Castleman Disease Collaborative Network (CDCN; www.castlemannetwork.org) to accelerate research and elucidate the pathogenesis of MCD. In 2.5 years, we have assembled a 23-member Scientific Advisory Board representing seven countries; built and facilitated collaboration among our community of more than 200 researchers and physicians worldwide; leveraged the community to establish and execute an international research agenda; and engaged patients throughout the entire process. We are currently finalizing plans to establish a registry/natural history study, which we believe will be crucial for establishing a diagnostic criteria and improving patient care. We also plan to launch viral discovery, serum proteomics, intracellular inflammatory pathway identification, and sequencing studies. We invite you to register on our website, attend our annual meeting at ASH, contribute samples for research, and encourage your patients to enroll in our registry.

Competing Interests

Dr. Van Rhee and Dr. Fajgenbaum indicated no relevant conflicts of interest.

References

1. Fajgenbaum DC, Van Rhee F, Nabel CS. HHV-8-negative, idiopathic multicentric Castleman disease: novel insights into biology, pathogenesis, and therapy. Blood. 2014;123:2924-2933. http://www.bloodjournal.org/content/123/19/2924

Google Scholar

2. Chang KC, Wang YC, Hung LY, et al. Monoclonality and cytogenetic abnormalities in hyaline vascular Castleman disease. Mod Pathol. 2014;27:823-831. http://www.ncbi.nlm.nih.gov/pubmed/24201121

Google Scholar

3. Talat N, Belgaumkar AP, Schulte KM. Surgery in Castleman's disease: a systematic review of 404 published cases. Ann Surg. 2012;255:677-684. http://www.ncbi.nlm.nih.gov/pubmed/22367441

Google Scholar

4. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. Blood. 2000;95:1406-1412. http://www.bloodjournal.org/content/95/4/1406

Google Scholar

5. Dossier A, Meignin V, Fieschi C, et al. Human herpesvirus 8-related Castleman disease in the absence of HIV infection. Clin Infect Dis. 2013;56:833-842. http://www.ncbi.nlm.nih.gov/pubmed/23223599

Google Scholar

6. Gerard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with hiv-associated multicentric Castleman disease. Blood. 2012;119:2228-2233. http://www.ncbi.nlm.nih.gov/pubmed/22223822

Google Scholar

7. Bower M. How I treat HIV-associated multicentric Castleman disease. Blood. 2010;116:4415-4421. http://www.ncbi.nlm.nih.gov/pubmed/20688959

Google Scholar

8. van Rhee F, Stone K, Szmania S, et al. Castleman disease in the 21st century: an update on diagnosis, assessment, and therapy. Clin Adv Hematol Oncol. 2010;8:486-498. http://www.ncbi.nlm.nih.gov/pubmed/20864917

Google Scholar

9. Fajgenbaum DC, Liu A, Ruth J, et al. HHV-8-negative, idiopathic multicentric Castleman disease (iMCD): a description of clinical features and therapeutic options through a systematic literature review [abstr.]. Blood. 2014;124:4861a. http://www.bloodjournal.org/content/124/21/4861

Google Scholar

10. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. Am J Hematol. 2012;87:997-1002. http://www.ncbi.nlm.nih.gov/pubmed/22791417

Google Scholar

11. Stone K, Woods E, Szmania SM, et al. Interleukin-6 receptor polymorphism is prevalent in HIV-negative Castleman diasease and is associated with increased soluble interleukin-6 receptor levels. PLoS One. 2013;8:e54610. http://www.ncbi.nlm.nih.gov/pubmed/23372742

Google Scholar

12. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood. 2005;106:2627-2632. http://www.ncbi.nlm.nih.gov/pubmed/15998837

Google Scholar

13. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014;15:966-974. http://www.ncbi.nlm.nih.gov/pubmed/25042199

Google Scholar

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