Castleman Disease in the 21st Century: An Update on Diagnosis, Assessment, and Therapy

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Abstract: Castleman disease (CD) is a nonclonal lymphoproliferative disorder that can affect single lymph node stations or, alternatively, can be generalized. Interleukin 6 (IL6) plays a pivotal role in the pathophysiology of CD. Human herpesvirus 8 (HHV8), which encodes a viral homolog of IL6, is the driving force in HIV-positive patients. The role of HHV8 in HIV-negative CD is controversial. Historically, the prognosis of patients with generalized or multicentric CD has been thought to be poor. However, CD responds extremely well to monoclonal antibodies directed at the IL6 receptor or IL6 itself, and in general, the long-term outcome of HIV-negative CD is excellent. Important strides forward have also been made in the management of HIV-positive CD.

Introduction

Dr. Benjamin Castleman described the typical pathology of mediastinal lymph node hyperplasia now carrying his name first in a case report in 1954 and later in a series of 13 patients in 1956.[1,2] Flendrig and Schillings noted that some patients with Castleman disease (CD) were enriched for plasma cells, and they distinguished plasma cell, intermediate, and hyalinized variants.[3] Keller, Hochholzer, and Castleman first used the terms *hyaline-vascular* (HV) and *plasma-cell* (PC) to describe types of CD in 1972.[4] Systemic symptoms in CD had already been recognized, but Gaba and colleagues reported the first case of multicentric CD in 1978.[5]

With the use of representational difference analysis, Chang and associates discovered in 1994 a novel gamma-herpes, later termed *human herpesvirus 8* (HHV8), in Kaposi sarcoma tissue derived from a patient with AIDS.[6] The simultaneous occurrence of Kaposi sarcoma and multicentric CD was described by Lachant and coworkers in 1985.[7] This finding spurred the discovery of HHV8 sequences by Soulier and coauthors in the lymph nodes of both HIV-positive and HIV-negative patients with multicentric CD.[8] Subsequently, anti-HHV8 therapy with foscarnet and, later, ganciclovir and valganciclovir was introduced in HIV-positive CD.[9,10]

Yoshizaki and associates first reported the elaboration of IL6 by B-lymphocytes in the germinal centers in CD lymph nodes in

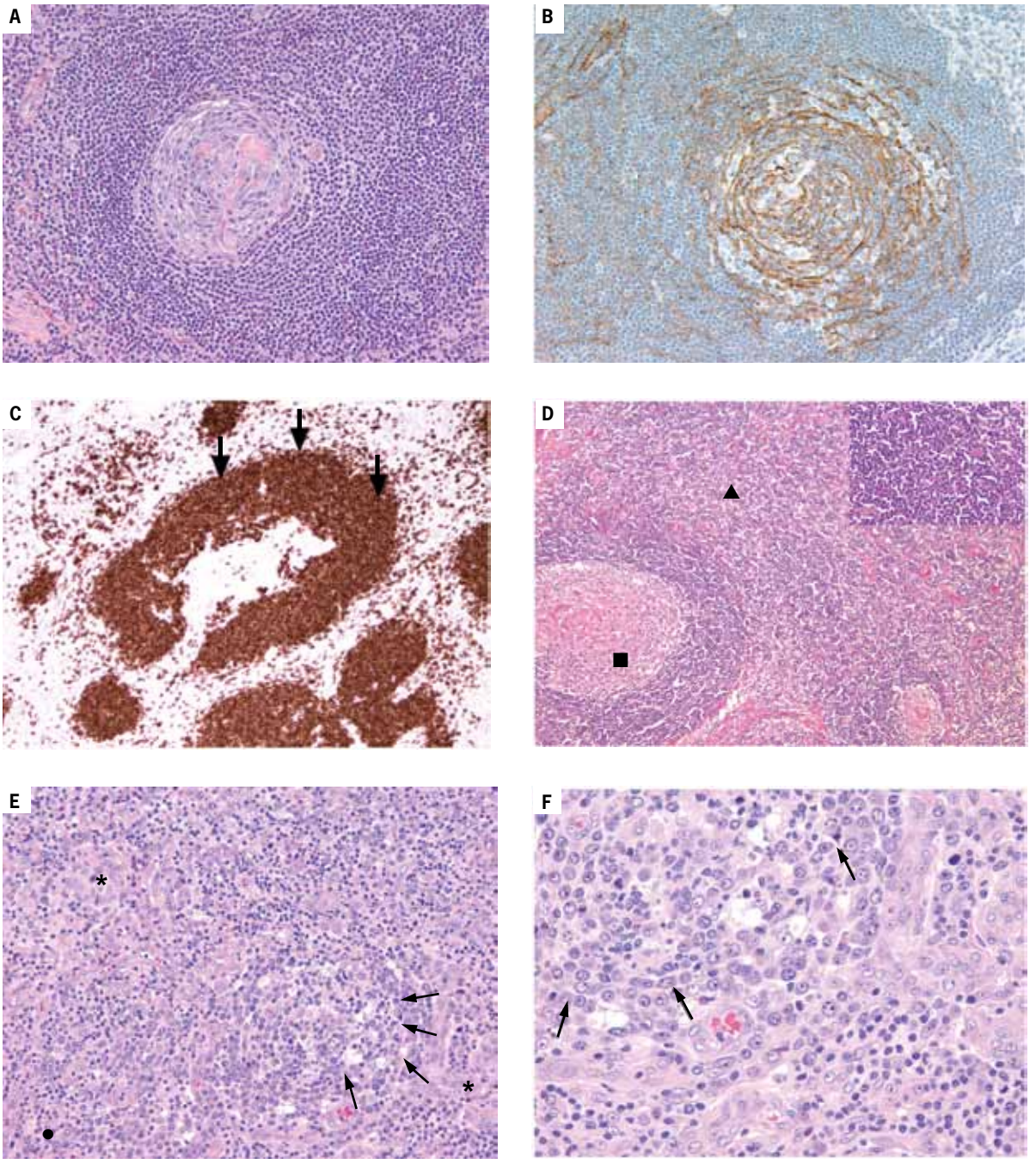

Figure 1. **(A)** Typical atretic follicle in hyaline-vascular Castleman disease (HV-CD) surrounded by concentric layers of mantle cells. Note the "lollipop-like" vessel, hematoxylin and eosin (H&E) ×200. **(B)** Expanded follicular dendritic cell network in HV-CD, anti-CD23 immunoperoxidase stain ×200. **(C)** CD20-positive mantle zone cells in HV-CD (arrows), anti-CD20 immunoperoxidase stain ×200. **(D)** Plasma-cell CD with hyperplastic follicles (■) and plasma cell–rich interfollicular region (▲), H&E ×100, inset H&E ×200. **(E)** human herpesvirus 8 (HHV8)-associated multicentric CD with numerous plasma cells (•) and increased vascularity (*) in the interfollicular region, and plasmablasts (arrows) in the germinal center, H&E ×200. **(F)** High-power (×400) view of plasmablasts (arrows) in the germinal center and mantle zone in HHV8–associated multicentric CD.

1989.[11] The cDNA sequences encoding interleukin 6 (IL6) and the IL6 receptor (IL6R) were cloned in 1986 and 1989, respectively, by Kishimoto and colleagues in Osaka.[12,13] This led to the treatment of CD with anti-IL6 and anti-IL6R monoclonal antibodies (mAbs).[14,15]

CD is rare, and its prevalence in the United States has not been well established. CD has been assigned orphan status by the National Cancer Institute. With the advent of the internet era, the Web site of the International Castleman's Disease Organization (www.castlemans.org) provides information for CD patients and is frequented approximately 5,000 times per year. The majority of CD patients are probably managed in the community setting, although there has been an increased tendency to refer patients to a small number of centers of excellence where experienced physicians can diagnose CD, provide advice regarding the management and prevention of complications, and outline a comprehensive treatment plan. This trend is likely to improve the prognosis of CD. Awareness of CD is important because the disease is not only rare, but also incompletely understood. Furthermore, this at times vexingly complex disease can be life threatening if suboptimally managed. This review will discuss the pathology, pathophysiology, clinical manifestations, and management of CD.

Pathology

Evaluation of a surgically excised lymph node is essential to render the diagnosis and to exclude malignancy and other disorders that may cause atypical lymph node hyperplasia. In the community setting, diagnosis is often delayed, and central review by an experienced pathologist is recommended in cases of suspected CD. Interpretation of the histopathology and subtype distinction in CD should be performed in concert with the clinical presentation and evaluation of laboratory tests for inflammatory cytokines, especially IL6, and serologic and molecular tests for HHV8, HIV, and other viruses, including Epstein-Barr virus and cytomegalovirus. Clinical and serologic exclusion of autoimmune disorders, connective tissue diseases, rheumatoid arthritis, and other similar entities is required prior to attributing the morphologic changes to CD, especially in cases of multicentric CD.

HV-CD is a lymphoid proliferation wherein the follicles are regressed, or depleted of germinal center cells, and have expanded mantle zones with small lymphocytes arranged concentrically in an "onion-skin" fashion (Figure 1A).[2,16,17] The interfollicular region is variably expanded with prominent hyalinized blood vessels; expanded, often dysplastic follicular dendritic cell (FDC) networks; myoid cells; dendritic reticulum cells; and small, mostly T-lymphocytes (Figure 1B).[18-21] Plasma cells and eosinophils are not abundant. The appearance of the hyalinized blood vessel penetrating the follicle together with the concentric rimming by mantle zone lymphocytes is often described as resembling a lollipop (Figure 1A). Focal aggregates of plasmacytoid dendritic cells are frequently noted in the interfollicular region.[22,23] Sinusoids are typically closed.[19] The vascular proliferation in HV-CD is believed to be driven by increased intrafollicular vascular endothelial growth factor (VEGF) expression. The vascular thickening and hyalinization observed in CD is most likely due to a VEGF-induced increase in vascular permeability and leakage of protein-rich plasma in the subendothelium.[24] Deficiency of BCL6–positive germinal center cells and follicular T-lymphocytes (BCL6–positive, CD57-positive) in the atretic follicles has been demonstrated immunohistochemically, and is suggested to result in abnormal follicle development.[25] The follicular mantle cells in HV-CD express CD5, in addition to CD20, and are reported by some to have an aberrant phenotype (Figure 1C).[26,27] By molecular analysis the lymphocytes are polyclonal.[28,29] FDC proliferations may range from nodular stromal overgrowths to neoplasms.[18-20] Isolated reports of clonal cytogenetic abnormalities in the FDC have been reported[29,30]; whether this implies that the FDC in CD are neoplastic, or if this is a secondary event, is currently unclear. Unlike the normal FDCs, and similar to FDC sarcomas, FDCs in CD demonstrate moderate to strong expression of epidermal growth factor receptor (EGFR),[31,32] a potential future therapeutic target. Increased VEGF expression is believed to contribute to development of vascular neoplasms in CD.

In PC-CD, the lymph nodes, in contrast, show preserved architecture with hyperplastic follicles (Figure 1D). The FDC network is neither expanded nor abnormal.[18,19,33] The most striking feature is increased interfollicular plasma cells. The plasma cells are usually polyclonal,[34,35] but may be monotypic and usually lambda light chain restricted (IgG or IgA),[36] especially in the PC-CD associated with osteosclerotic myeloma or polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and/or skin changes (POEMS) syndrome. Monoclonality[37,38] is rare and may herald development of a lymphoma. The histopathologic features described above are not specific and can be seen in reactive lymphadenopathies including but not limited to infections, autoimmune diseases, collagen vascular and mixed connective tissue disease, rheumatoid arthritis with certain toxins, and in HIV-related or other immunodeficiency-related lymphadenopathy.[33,39-44] Exclusion of these reactive states is necessary to render a diagnosis of PC-CD.

Cases of multicentric CD can be associated with presence of HHV8, and are considered a separate entity because of this distinct association, the presence of immu-

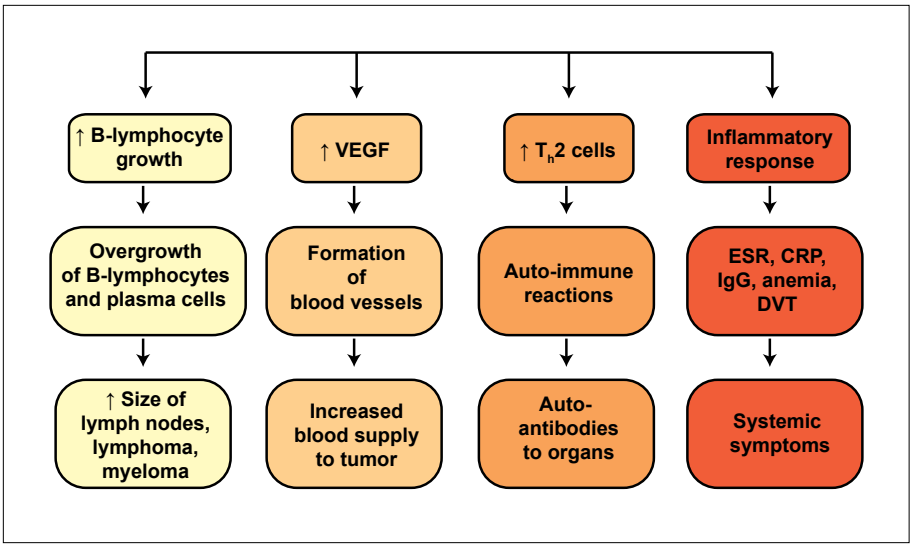

Figure 2. Pathophysiology of interleukin 6 (IL6) in Castleman disease. Excess IL6 in Castleman disease patients results in increased B-lymphocyte growth, lymph node vascularity, and inflammatory response. Autoimmune phenomena may also be present.

CRP=C-reactive protein; DVT=deep vein thrombosis; ESR=erythrocyte sedimentation rate; IgG=immunoglobulin G; T_h2=Type 2 helper T-lymphocytes; VEGF=vascular endothelial growth factor.

nodeficiency, and certain unique histologic features. The lymph nodes in HHV8-associated CD have increased numbers of immunoblasts (also called *plasmablasts*) present in the outer mantle zones of some follicles. These plasmablasts are lambda-light chain restricted, uniformly express cytoplasmic IgM, and may colonize the germinal centers (Figures 1E and 1F).[18,45-47] They are polyclonal and have heterogeneous, weak expression of CD20.[45,48-51] Localized collections of HHV8-positive plasmablasts may occur, referred to by some as *microlymphomas*.[52] Diffuse large B-cell lymphomas developing in a setting of HHV8-associated CD are a separate entity under the World Health Organization classification of hematolymphoid neoplasms.[53]

Pathophysiology

IL6 plays a central role in the pathophysiology of CD (Figure 2). IL6 can form a heterodimer with the soluble IL6R α, which subsequently binds to the gp130 signaling complex at the cell surface, resulting in activation of the JAK/STAT signaling pathway.[54] Alternatively, IL6 binds to the IL6R α that is already bound to gp130. Serum IL6 levels in CD can be much higher than in any other disorder, including Hodgkin lymphoma, non-Hodgkin lymphoma, rheumatoid syndromes, and multiple myeloma. Excess IL6 induces a pro-inflammatory syndrome that leads to severe constitutional symptoms, with elevation of acute phase reactants. IL6 also induces the secretion of VEGF, which can be found in the supernatant of cultured cells derived from CD lymph nodes.[55] Increased VEGF expression is present in the interfollicular areas of lymph nodes, and some patients have elevated systemic VEGF levels.[56] Excess VEGF explains the increased angiogenesis and vascularization that are present in CD lymph nodes. Autoimmune phenomena, such as cytopenias, are thought to arise due to IL6-induced immune dysregulation. IL6 is a potent growth and survival factor for B-lymphocytes and plasma cells, and it is at least partially responsible for lymph node hyperplasia in CD.

The crucial role of IL6 in CD is underscored by several observations. Symptoms wax and wane in accordance with IL6 levels. Surgical extirpation of all CD or the bulk of CD can lead to swift reductions in IL6 with rapid improvement in symptomatology.[11] Therapeutic interruption of the IL6 signaling cascade with anti-IL6 or -IL6R mAbs abrogates CD-related symptoms and, over time, leads to lymph node involution. Furthermore, human-IL6 transgenic mice develop a CD-like syndrome with plasmacytosis, splenomegaly, enlarged lymph nodes, fever, cachexia, and anemia, which can be ameliorated by administration of anti-IL6R mAbs.[57,58]

The lymph node histology in CD can have similarities to abnormalities found in chronic viral infections, and the discovery of HHV8 in HIV-positive CD has already been alluded to. The HHV8-genome encodes a number of homologs of human cellular genes, including viral IL6 (vIL6), which induces proliferation of HHV8-infected cells.[47] However, HHV8-infected cells secrete vIL6 at low levels,[59] and vIL6 has a low affinity for the human IL6R. Human IL6 secretion, perhaps stimulated in autocrine or paracrine fashion, is the most important mediator in CD.[60,61] Whereas most host mRNA is degraded via viral shutoff exonuclease in HHV8 lytic infection, IL6 mRNA escapes such degradation and is actually upregulated, resulting in increased transcription and secretion of human IL6 from HHV8-infected cells.[62]

The trigger of excess IL6 production in HIV-negative CD is not fully understood. HHV8-derived

DNA, mRNA, and proteins have been detected in the peripheral blood mononuclear cells and lymph nodes of a variable percentage of HIV-negative CD patients. The frequency is probably dependent on the type of material (eg, archival, paraffin-embedded tissue versus fresh-frozen specimens) and the sensitivity of the techniques used.[63-65] Certainly, there is no large reservoir of HHV8-infected cells in the lytic phase with active replication. HHV8 is lymphotropic and remains present in a dormant fashion in healthy individuals, further complicating the interpretation of HHV8 detection in HIV-negative CD.

Polymorphisms have been described in the *IL6* promoter, *IL6R*, and *gp130*, which increase IL6 levels and/or signaling. These polymorphisms influence the severity of a number of autoimmune disorders, such as rheumatoid arthritis and systemic sclerosis, promote development of metabolic syndrome, and may affect the outcome of prostate and breast cancer.[66-70] It is presently not known if such genetic variance influences the phenotype of CD.

Clinical Manifestations

CD displays a great variation in presenting symptoms and signs, which are determined by extent of the disease, type of pathology, HIV status, extent of IL6 secretion, associated autoimmune phenomena, and overlap with POEMS syndrome.

Unicentric disease typically affects 1 lymph node station, although occasionally small, regional, satellite nodes may be present. Patients are diagnosed incidentally or may have symptoms due to compression of neurovascular sites or other vital structures. The classic presentation is a mediastinal mass, but alternate sites include intra-abdominal masses or involvement of cervical, axillary, and inguinal nodes.[4,71,72] Rarely, unicentric CD presents in unusual sites, such as the lungs, orbits, mouth, or nasopharynx. Patients with unicentric CD are mostly HIV-negative, have HV pathology, and do not have systemic symptoms or laboratory abnormalities reflecting excess IL6 secretion. Approximately 10% of patients have the PC or mixed HV and PC type morphology, which can be associated with constitutional symptoms, anemia, elevated erythrocyte sedimentation rate (ESR), and other abnormal laboratory findings. Unicentric disease can occur at any age but is most common in the fourth decade.

Multicentric disease affects more than 1 lymph node station. Often, patients have generalized lymphadenopathy and enlargement of the liver or spleen, which occurs in 80% and 65% of patients, respectively.[5,73,74] Classically, the multicentric variety has been associated with PC histology,[5,73,74] but a review of cases treated at our institution shows that approximately 30% of patients have HV as the pathologic diagnosis. Multicentric CD has protean manifestations, including fever, drenching night sweats, weakness, severe fatigue, and anorexia accompanied by weight loss. The occurrence of night sweats may be reflective of exaggerated diurnal variations in IL6 secretion. IL6 reduces hepcidin production by the liver, thus reducing iron absorption and iron utilization and leading to anemia. IL6 also inhibits albumin production by the liver, causing lower intravascular oncotic pressures, which together with increased vascular permeability caused by VEGF, leads to edema, pleural effusions, and ascites. In severe cases, multi-organ failure and death can ensue. The onset of the disease is mostly gradual, although some patients relate the precise onset of symptoms to a presumed viral illness. The disease can follow 2 basic patterns: persistence with gradual worsening of symptoms or episodic exacerbations. The latter can be severe and accompanied by coma, seizures, and cerebrovascular accidents. The pro-inflammatory state is responsible for increases in platelets and fibrinogen, thus predisposing patients to venous thrombosis. Patients can have multiple cherry-red hemangiomata, which involute with effective therapy. Violaceous, large skin lesions resembling Kaposi sarcoma, caused by infiltrates of lymphocytes and plasma cells in the dermis, are mostly seen in HIV-negative Asian patients, indicating that race influences the phenotype of the disease. Other, more nonspecific skin rashes occur in 20% of patients. Lymphocytic interstitial pneumonia also seems to be more common in the Asian population.

CD patients often have some features of POEMS syndrome, and they should receive a careful work-up accordingly. Findings may include endocrine abnormalities, monoclonal gammopathy of undetermined significance (typically of the IgAλ variety or, rarely, due to myeloma), and sclerotic bone lesions. Neuropathy may occur in 20% of patients and is typically of the sensory, glove-and-stocking variety rather than the severe progressive, debilitating polyneuropathy seen in patients with POEMS syndrome.

Excess IL6 may cause immune dysregulation by impairing dendritic cell maturation and promoting a T_h2 immune profile. It has been suggested that IL6-induced expansion of auto-antibody–producing CD5-positive B-lymphocytes may be responsible for autoimmune phenomena.[36] Autoimmune hemolytic anemia and thrombocytopenia, Evan's syndrome, pure red cell aplasia, acquired factor VIII deficiency, systemic lupus erythematosus, and myasthenia gravis have all been described. Rarely, pemphigus, caused by antidesmoplakin, antienvoplakin, antidesmoglein, or antiplectin antibodies, is associated with CD. It is frequently accompanied by rapidly progressive respiratory failure due to bronchiolitis obliterans caused by an infiltrate of CD8-positive T-lymphocytes and has mostly been reported in children or young adults. It is

Table 1. Work-up of Castleman Disease

Excisional lymph node biopsy	Pathology, exclude clonal malignancy
Virology	HIV and HHV8 serology with quantitative PCR if positive
Cytokines	IL6, VEGF
Acute phase reactants	WESR, CRP, fibrinogen
General	CBC, renal and liver function
Immunology	ANA, others as indicated
Endocrine abnormalities	Thyroid function tests, others as indicated
Plasma cell dyscrasias	Immunoglobulins, urine and protein electrophoresis and immunofixation, light chains, bone marrow, 24-hour urine for protein quantification
Organ function	Echocardiogram, pulmonary function
Imaging	CT of neck, chest, abdomen, pelvis; CT-PET
Neurology	Nerve conduction as indicated

ANA=anti-nuclear antibody; CBC=complete blood count; CRP=C-reactive protein; CT=computed tomography; CT-PET=computed tomography–positron emission tomography; HHV8=human herpesvirus 8; PCR= polymerase chain reaction; VEGF=vascular endothelial growth factor; WESR=Westergren erythrocyte sedimentation rate.

fatal in 80% of cases, despite treatment with rituximab (Rituxan Genentech), steroids, and plasma exchanges. A variety of glomerulonephritides have been reported, for which the pathogenesis is less clear.[75-79]

Clonal hematologic disorders, such as multiple myeloma,[80] amyloidosis,[81-85] and lymphomas, have all been reported with increased frequency. Hodgkin lymphoma has been described both in multicentric and unicentric CD,[86,87] whereas non-Hodgkin lymphoma is more frequent in multicentric CD.[87] The exact frequency of these malignancies has been reported to be as high as 15%, but this rate may reflect reporting bias.

Laboratory findings at diagnosis include anemia, elevated ESR, C-reactive protein (CRP), IL6, fibrinogen, proteinuria, abnormal thyroid function tests, hypergammaglobulinemia, and thrombocytosis. A significant number of patients have elevated plasma VEGF levels (Table 1). A low titer of antinuclear antibodies is present in approximately one third of patients, mostly without any obvious autoimmune disturbances. Imaging by computed tomography scan is useful to distinguish unicentric from multicentric disease and to detect hepatosplenomegaly, pleural effusion, and ascites. Fluorodeoxyglucose-positron emission tomography scanning usually reveals low to moderate specific uptake values in affected lymph nodes. High specific uptake values should raise suspicion of lymphoma.

Management of Castleman Disease

There have been no published randomized clinical trials regarding the management of CD. Most of the literature is confined to small series or case reports, and it is difficult to make firm recommendations.

The preferred management of unicentric CD is complete surgical excision, which is curative in approximately 95% of patients and affords resolution of constitutional symptoms, if present.[4] Regional small "satellite" lymph nodes usually involute with surgical extirpation of the bulk of the disease. Surgery may prove impossible when the mass involves vital structures. In such cases, attempts can be made to render the mass amenable to surgery by neo-adjuvant therapy or embolization.[88] Long-term follow-up is recommended because recurrences as late as 11 years after incomplete resection have been reported (Figure 3).[4,89]

Local radiotherapy is an alternative therapeutic option for unresectable unicentric CD. One review identified 12 patients treated with radiotherapy, mostly with doses of approximately 4,000 cGy.[90] Seven patients achieved a complete response, and 3 had a decrease in the size of the lymph node mass or resolution of symptoms. One patient had a minimal response, and another patient initially responded, but subsequently relapsed after 10 months. Serious acute and late toxicities have been reported after radiotherapy.[91]

There are no established criteria defining response to therapy in multicentric CD, which hampers the interpretation of different treatment modalities. One recent study divided response into 2 components and established criteria for improvement in symptoms and laboratory values based on the Cheson criteria, modified to account for skin lesions, to measure reduction in lymphadenopathy.[92,93] The adoption of these criteria to standardize response will help to compare the results of future clinical studies (Table 2). Table 3 gives an overview of treatment modalities applied in multicentric CD.

Corticosteroids are often given to manage acute exacerbations of multicentric CD. High-dose steroids will improve symptoms and even improve lymphadenopathy. Complete remissions with steroid therapy alone have been reported.[94,95] However, most patients require

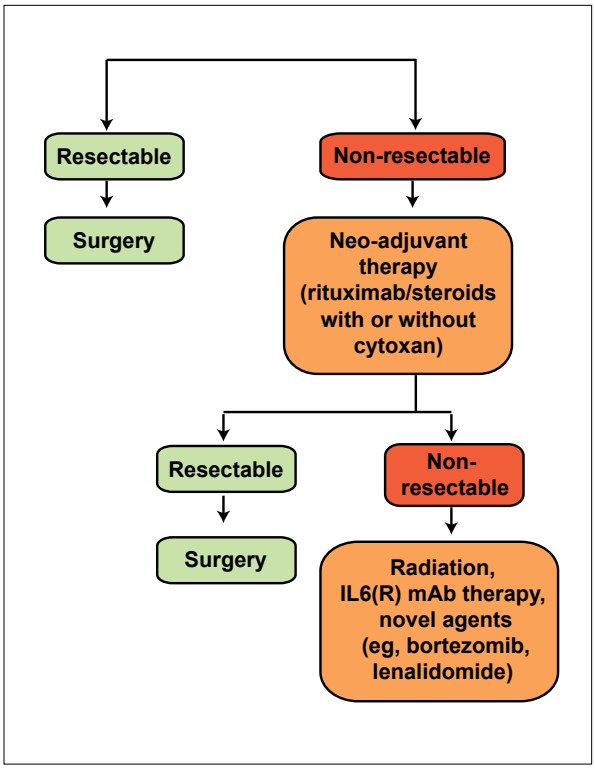

Figure 3. Treatment algorithm for unicentric Castleman disease. Surgical excision of the disease is curative in most cases. Nonresectable disease is debulked to render it amenable to surgery, if possible.

IL6(R) mAb=interleukin 6/interleukin 6 receptor monoclonal antibodies.

Table 2. Response Criteria for Castleman Disease*

Clinical Benefit Response
- ≥2 g/dL increase in hemoglobin without transfusions
- ≥1 CTC grade decrease in fatigue
- ≥1 CTC grade decrease in anorexia
- ≥2°C decrease or return to 37°C in fever/night sweats
- ≥5% increase in weight

Radiologic Response
- Complete response is defined as the complete disappearance of all measureable and evaluable disease
- Partial response is defined as ≥50% decrease in the sum of the product of the diameters of the indicator lesion(s) and at least stable disease in all other evaluable disease
- Progressive disease is defined as ≥50% increase in the sum of the product of the diameters of the indicator lesion(s) compared with nadir, at least 1 confirmed new lesion >1.5 cm in longest dimension, or a malignant transformation in a previously defined mass
- Stable disease is defined as none of the above

*Modified Cheson criteria define the parameters for clinical radiologic responses. The modification comprises the measurement of improvement in skin lesions. Clinical Benefit Response uses symptoms and laboratory parameters.[92]

CTC=National Cancer Institute Common Toxicology Criteria for Adverse Events Version 3.0

steroid doses that are too high to be tolerated long-term, and disease recrudescence is virtually inevitable during steroid tapering.[79] Steroids are therefore mostly used in conjunction with rituximab or alkylating agents, such as cyclophosphamide and chlorambucil.[72,96] Steroid therapy has also been noted to be associated with an increased risk of infection and death due to sepsis.[94,97]

A number of case reports or small series have reported on the management of multicentric CD, with rituximab used as the sole agent or in conjunction with steroids and chemotherapy. Of the 7 cases reported, 4 patients achieved a (near) complete response, and 3 of these patients had HV pathology.[49,98-101] In contrast, all patients with the PC variant of CD failed therapy. This finding can perhaps be explained by the predominance of CD20-positive B-lymphocytes in HV-CD, whereas the PC cases have ubiquitous plasma cells, which are CD20-negative.

Lymphoma-based chemotherapy (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [CVAD]) induces complete responses in approximately 50% of patients, but relapses are common, and the median survival is in the order of 19 months.[72,90] Durable responses occur in approximately 25% of cases, and remissions have been sustained in excess of 15 years.[72] However, other series have reported contradictory results and noted little success with combination chemotherapy.[74,94] 2-Chloro-2'-deoxyadenosine (2-CDA) induced response in 2 patients, both of whom subsequently developed lymphomas. This reaction suggests that 2-CDA increases the risk of transformation to lymphoma, perhaps due to its potent immunosuppressive properties.[102]

In case reports, a number of other agents have had activity in multicentric CD, including interferon-α, thalidomide, all-transretinoic acid, and bortezomib (Velcade, Millennium Pharmaceuticals).[103-105] These agents have not been systematically investigated and data may be affected by reporting bias, which makes it difficult to assess their exact efficacy. There have been several case reports of multicentric CD responding to interferon-α[106-109] The mechanism of action of interferon-α is speculative and might be due to downregulation of the IL6R.

Table 3. Castleman Disease: Treatment Modalities

Treatment Modality	Agents
Local	Surgery, irradiation
Corticosteroids	Prednisone, dexamethasone
Chemotherapy	Cyclophosphamide, etoposide, vinblastine, chlorambucil, liposomal doxorubicin, combination chemotherapy (CHOP, CVAD), 2-chloro-deoxyadenosine
Anti-CD20 mAb	Rituximab
Anti-IL6–based	Tocilizumab, siltuximab, anakinra, suramin
Immunomodulatory	Interferon-α, thalidomide, lenalidomide, all-transretinoic acid
Antiviral	Valganciclovir, foscarnet, cidofovir
Miscellaneous	Bortezomib, cimetidine
Autologous PBSCT	Melphalan, BEAM

BEAM=carmustine, etoposide, cytarabine, and melphalan; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CVAD=fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IL6=interleukin 6; mAb=monoclonal antibodies; PBSCT= peripheral blood stem cell transplant.

IL6 plays a central role in the pathophysiology of CD and has been targeted using a variety of treatment strategies. Suramin, a polysulfated naphthylurea, which was originally developed as an antitrypanosomal and antifilarial agent, induced complete remission in 2 patients with multicentric CD.[97,110] Suramin inhibits proliferation in myeloma and lymphoid cell lines by interfering with the binding of IL6 to its receptor and/or decreasing IL6R expression.[111,112] However, we observed little activity in a series of 5 patients treated with suramin at our institution. Anakinra (Kineret, Amgen), an IL1 receptor antagonist used for the treatment of Still's disease, has recently been reported to have activity in a pediatric case of multicentric CD.[113] Blocking of the IL1 receptor inhibits the nuclear factor kappa B pathway, thus reducing the transcription of pro-inflammatory cytokines, including IL6.

Beck and colleagues were the first to report administration of a murine anti-IL6 mAb to a patient with multicentric PC-CD, who had rapid improvement in symptomatology and laboratory abnormalities, including CRP, hematocrit, and albumin. However, the patient relapsed upon discontinuation of mAb therapy and was eventually managed with dexamethasone and surgical resection.[14] A humanized anti-IL6R mAb—tocilizumab (Actemra, Genentech)—was subsequently developed in Japan. In a phase II study, 35 patients were treated with twice-weekly infusion of tocilizumab for 16 weeks. Rapid normalization of CRP, ESR, fibrinogen, albumin, and hemoglobin was observed with concomitant resolution of constitutional symptoms, increase in body mass index, and reduction in lymphadenopathy.[114] Thirty patients continued to receive tocilizumab for 5 years, and the clinical improvements were sustained. Furthermore, 22 patients who began enrollment on corticosteroids were able to discontinue therapy.[115] A disadvantage is that continued therapy with tocilizumab appeared to be required because relapses were observed upon cessation. However, relapse did not occur in a patient treated with tocilizumab at our institution, and in another patient, dosing intervals could be extended. Tocilizumab is currently approved for the therapy of CD in Japan.

Recently, a chimeric, human-murine, immunoglobulin mAb—siltuximab (Ortho Biotech), formerly known as CNTO 328—that binds and neutralizes human IL6 with high affinity and specificity was evaluated in a phase I study enrolling 23 patients at dose levels of 6, 9, and 12 mg/kg. Overall, 18 of 23 patients achieved clinical benefit, and 12 demonstrated objective radiologic responses. There was a clear dose-dependent response; all 11 patients who were treated at the highest dose level achieved clinical benefit, with rapid improvement in laboratory parameters (CRP, ESR, fibrinogen, albumin, and hemoglobin) and resolution of symptoms. Eight patients had objective tumor responses using modified Cheson criteria. One patient with highly aggressive CD, who had failed multiple treatment modalities, including autologous peripheral blood stem cell transplantation, initially responded to siltuximab, but relapsed during the steroid taper. Clinical improvement occurred rapidly and preceded radiologic response, which typically took several months. The 2 remaining patients may still show radiologic improvement with further follow-up. Tocilizumab and siltuximab were well tolerated with few adverse events. Both agents can induce hyperlipidemia, and monitoring of cholesterol and triglycerides is recommended. Both mAbs clearly have major activity in CD and currently appear to be the best therapy for multicentric CD (Figure 4). The first randomized clinical trial in CD comparing siltuximab versus best supportive care and placebo has recently commenced.

POEMS and CD

Approximately 10–30% of patients with POEMS have associated CD.[116,117] In patients with CD, neuropathy is typically mild and sensory in nature, whereas patients with POEMS have a severe progressive polyneuropathy with a marked motor component resembling chronic

inflammatory demyelinating polyneuropathy, which is usually refractory to plasma exchange and intravenous immunoglobulins. The preferred therapy for CD patients with associated POEMS appears to be high-dose therapy supported by autologous peripheral blood stem cell transplantation, despite a substantial mortality of approximately 7% and increased rates of engraftment syndrome.[118,119] The polyneuropathy of POEMS improves substantially after autologous peripheral blood stem cell transplantation, whereas only modest neurologic improvements occur with anti-IL6R mAb therapy.[120,121] Emerging therapies such as immunomodulatory drugs (eg, thalidomide [Thalomid, Celgene] and lenalidomide [Revlimid, Celgene]) and proteasome inhibitors may have therapeutic efficacy in both CD and POEMS, but their exact role remains to be established.[105,122,123]

HIV-Positive CD

In HIV-positive patients, CD is typically multicentric and is likely driven by active replication of HHV8 in polyclonal B-lymphocytes, in which expression of the latency genes of HHV8 can be found to reflect induction of proliferation.[124] Detection of the HHV8 latency-associated nuclear antigen by immunohistochemistry clinches the diagnosis. vIL6, encoded by HHV8, can also be found in these cells, further explaining lymphoproliferation.[47] Typically, high copy numbers of HHV8 can be found by quantitative polymerase chain reaction in peripheral blood mononuclear cells and plasma, together with increased plasma IL6 levels—both of which correlate with disease exacerbations.[125-127] HHV8 appears to target IgMλ monotypic lymphocytes in the mantle zone of lymphoid follicles, which do not have somatic hypermutation of *IgH* chain genes, indicating that these cells are derived from naïve B-lymphocytes and have not undergone the germinal center reaction required for normal B-lymphocyte maturation.[45] The resulting plasmablasts may form microlymphomas or even frank plasmablastic lymphomas.[124,128] A prospective cohort study of 60 HIV-positive multicentric CD patients found that these patients have a 15-fold increased risk of developing HHV8-asssociated non-Hodgkin lymphoma as compared with the general HIV-positive population.[129] There is also a substantially increased frequency of Kaposi sarcoma in HIV-positive CD patients and, recently, Kaposi sarcoma foci have been described in the lymph nodes of nearly two thirds of patients.[7,50,130-132]

Besides the increased propensity towards developing tumors, multicentric CD in HIV-positive patients behaves more aggressively, with clinical features comprising severe constitutional symptoms, generalized lymphadenopathy, splenomegaly, (autoimmune) cytopenias, frequent bone marrow involvement, and severe interstitial pneumonitis causing acute respiratory distress syndrome and hemophagocytosis.[130,133,134] Historically, the prognosis has been poor, with a median survival not exceeding 25 months, although the prognosis may have improved with modern management.[129,130,134]

Multicentric CD typically occurs in HIV-positive patients who have low CD4-positive T-lymphocyte counts. Highly active anti-retroviral therapy (HAART) does not prevent the development of CD, and it is not effective as sole therapy. In fact, exacerbations have been reported after initiation of anti-retroviral therapy, perhaps as part of an immune reconstitution syndrome.[135]

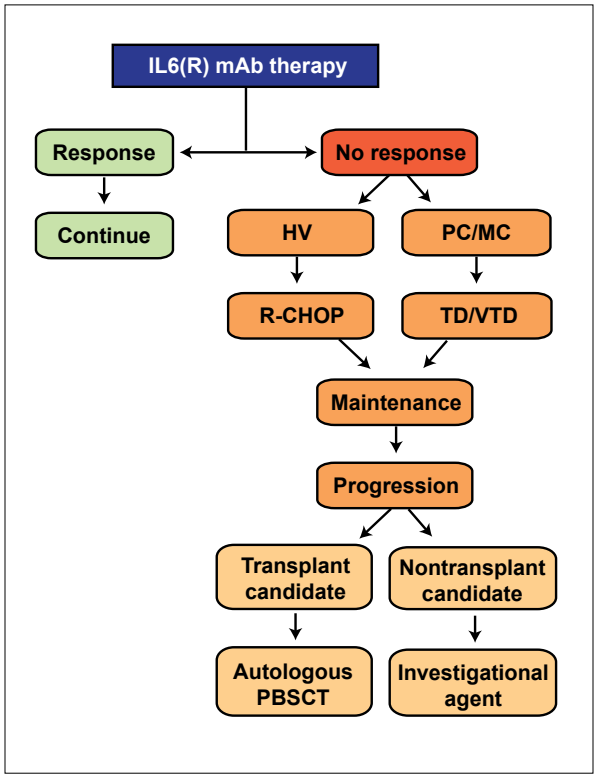

Figure 4. Treatment algorithm for multicentric Castleman disease. IL6/IL6R mAb therapy is the preferred treatment for multicentric Castleman disease. Combination chemotherapy for HV-CD can be lymphoma-based. It seems reasonable to try a myeloma-based regimen in PC-CD, where plasma cells predominate. Nonresponders to mAb therapy who progress after receiving combination chemotherapy may receive autologous PBSCT or an investigational agent.

HV=hyaline-vascular; HV-CD=hyaline-vascular Castleman disease; IL6(R)=interleukin 6/interleukin 6 receptor; mAb=monoclonal antibodies; MC=mixed cellularity; PBSCT=peripheral blood stem cell transplant; PC-CD=plasma-cell Castleman disease; PC=plasma-cell; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TD=thalidomide and dexamethasone; VTD=bortezomib, thalidomide, and dexamethasone.

However, a recent review of 84 CD cases suggests that HAART improves CD4-positive counts, reduces viral load, and prevents progression to lymphoma and development of Kaposi sarcoma, thus reducing the mortality rate and possibly improving overall outcome.[132,134]

The optimal therapy for HIV-positive CD relies on combining a) HAART, b) chemotherapy with agents such as etoposide to achieve acute disease control, c) rituximab to target CD20-positive B-lymphocytes and plasma cells, and d) antiviral therapy to inhibit HHV8 replication. Single-agent therapy with etoposide or vinblastine can be effective in controlling acute exacerbations of CD or rapidly improving the condition of patients who are severely ill.[134,136] In 2 open-label, nonrandomized trials enrolling a total of 43 patients, rituximab induced clinical and radiologic responses in more than 66% of patients.[137,138] However, other studies have linked rituximab to exacerbations of Kaposi sarcoma and increased risk of progression to lymphoma, suggesting that rituximab monotherapy may not be optimal.[139] Oral or intravenous ganciclovir reduced episodic flares and detectable HHV8 levels in 2 patients, and acute renal and respiratory failure was improved in a third patient.[10] Furthermore, valganciclovir can reduce oropharyngeal shedding of HHV8, suggesting a potential role for valganciclovir as maintenance therapy to suppress HHV8 replication.[140] Interestingly, in a separate study, 5 patients did not derive benefit from cidofovir.[141]

Recently, a therapeutic algorithm has been proposed for HIV-positive CD patients, using intravenous etoposide as induction therapy followed by therapy with rituximab, etoposide, and ganciclovir in patients with no active Kaposi sarcoma, in whom CD4-positive counts are higher than 50/mL and HIV-RNA copies are less than 50/mL. Patients with active Kaposi sarcoma or CD4-positive counts of less than 50/mL or HIV-RNA copies of more than 50/mL receive etoposide, valganciclovir, and HAART. Maintenance therapy with valganciclovir can be considered for both groups.[134]

Conclusion

Much progress has been made in our understanding and treatment of CD since its first description by Dr. Benjamin Castleman more than 50 years ago, but many questions remain. It is well established that unicentric CD can be cured in the vast majority of cases by simple surgical resection. Symptomatic, multicentric HIV-negative CD responds extremely well to mAb therapy directed at IL6 or the IL6R and, in general, the long-term prognosis of patients treated with these agents is excellent. It is anticipated that both mAbs—tocilizumab and siltuximab—will become widely available in the next few years. A disadvantage is that continued therapy with mAb is required, and oral JAK/STAT inhibitors may eventually replace mAb therapy. New drugs developed for myeloma, such as immunomodulatory drugs and proteasome inhibitors, may in due course find their place in the management of CD. HIV-positive CD still has a more guarded prognosis, although significant progress has been made by combining anti-retroviral and anti-HHV8 therapy with chemotherapy and rituximab. Anti-IL6(R) mAbs have not yet been applied in HIV-positive disease and may be an area for future research.

Although HHV8 is clearly central to the development of HIV-positive CD, its role, if any, in HIV-negative disease remains controversial. It is possible that HIV-negative CD is a chronic, nonspecific inflammatory process triggered by an as-yet unknown stimulus with perhaps the various pathologically recognized subtypes reflecting a differential host response. We also do not know whether unicentric CD and multicentric CD are different diseases or merely different manifestations of the same disease entity. It is likely that many of these questions will be answered in the next half-century of research into this enigmatic disorder.

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