Treatment of Idiopathic Castleman Disease

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KEYWORDS

• Castleman disease • Treatment • Rituximab • Corticosteroids • Chemotherapy • Tocilizumab • Siltuximab

KEY POINTS

- Accurate diagnosis of the different varieties of multicentric Castleman disease is critical to guiding therapy.
- Monoclonal antibodies targeting the interleukin-6 signaling pathway are the best-studied agents in idiopathic multicentric Castleman disease and are front-line therapy for more severely ill patients.
- Rituximab has not been systematically studied, but is commonly used as initial therapy for more indolent idiopathic multicentric Castleman disease.
- Chemotherapy and immunomodulatory drugs are best reserved for the relapse setting.
- Autologous stem cell transplantation should be considered for patients with coexistent POEMS syndrome.

INTRODUCTION

Castleman disease (CD) is a rare, heterogeneous lymphoproliferative disorder first defined in 1954.[1] The variable manifestations of CD and infrequent presentation outside of academic centers of excellence result in difficulty of diagnosis and management of the disease. CD may be divided into 2 major forms. Unicentric CD (UCD) is typically a slow-growing solitary mass occurring at a single anatomic site; although the enlarging mass may compress vital structures, surgical excision is generally curative. In contrast, multicentric CD (MCD) affects multiple lymph node stations and often presents with lymphadenopathy, fever, weight loss, fatigue, edema, anemia, and hypoalbuminemia.[2–4] In severe cases, patients may develop hepatosplenomegaly, massive ascites, pleural effusions, or organ failure, and both UCD and MCD

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sometimes progress to non-Hodgkin lymphoma (NHL). MCD often concomitantly presents in the context of infection with the human immunodeficiency virus (HIV) and/or human herpesvirus 8 (HHV8). However, approximately 50% of patients with MCD who are negative for HIV and HHV8 comprise a subgroup that has recently been termed as idiopathic MCD (iMCD), as no causative etiology has been established. The rarity of CD has unfortunately limited the ability to perform systematic studies providing solid evidence of superiority of therapeutic strategies. In this article, we report on evidence for various treatments to synthesize a treatment algorithm for the practicing physician.

CLINICAL SYMPTOMATOLOGY OF MULTICENTRIC CASTLEMAN DISEASE AND ROLE OF INTERLEUKIN-6

Interleukin-6 (IL6) is a pleiotropic cytokine that plays a pivotal role in the pathogenesis and clinical symptomatology in many patients with iMCD. The notion that IL6 plays a causative role in iMCD is supported by several clinical and experimental observations. Clinically, MCD is characterized by a proinflammatory syndrome giving rise to the so-called B-symptoms comprising fevers, night sweats, malaise, and weight loss.[5] The C-reactive protein (CRP) is commonly elevated and is considered to be a surrogate marker for IL6 bioactivity.[6] Elevated fibrinogen levels in the setting of a systemic inflammatory response can cause deep venous thrombosis and other thrombo-embolic disorders. IL6 is an important growth, differentiation, and survival factor for both plasma cells and lymphocytes contributing to lymph node enlargement, plasmacytic infiltration, hepatosplenomegaly, and reactive bone marrow plasmacytosis with polyclonal hypergammaglobulenemia. IL6 also dysregulates the humoral immune response resulting in positive antinuclear antibody assays in approximately one-third of the patients, immune thrombocytopenia, hemolytic anemia, as well as a host of other autoimmune phenomena likely caused by expansion of $CD5^+$ B-lymphocytes.[7,8] Together with other cytokines, IL6 also induces polyclonal T-cell outgrowth reflected by the presence of activated $CD8^+$ T cells and increased soluble IL2 receptor levels. During the inflammatory response, IL6 increases the production of the peptide hormone regulator of iron homeostasis, hepcidin, by the liver. Hepcidin reduces intestinal iron absorption and impairs release of stored iron from macrophages, thus causing anemia.[9,10] Furthermore, IL6 inhibits albumin production by the liver, leading to hypoalbuminemia. IL6-induced vascular endothelial growth factor (VEGF) secretion promotes angiogenesis and vascular permeability; the latter combines with hypoalbuminemia to induce edema, ascites, pleural and pericardial effusions, and generalized anasarca due to vascular leak syndrome. In severe cases of iMCD, renal failure occurs, often due to thrombotic microangiopathy and multiorgan failure can ensue, resulting in death.

The role of IL6 is further underscored by the observation that surgical debulking with removal of lymph nodes can lead to rapid reductions in IL6 levels and clinical improvement.[11] Patients who have other malignancies that overproduce IL6 can have pathologic changes in enlarged lymph nodes that resemble CD and that resolve following surgical resection or with monoclonal antibody (mAb)-mediated IL6 blockade.[12,13] IL6 levels can also wax and wane in step with the severity of clinical symptoms.[5] Mice in which IL6 is overexpressed using retroviral transduced bone marrow cells develop a Castleman-like syndrome.[14,15] In IL6 transgenic mice, a similar MCD picture emerges, which is ameliorated by neutralization of IL6 with an antibody directed at the IL6 receptor (IL6R).[16,17] IL6 transcription is regulated by the transcription factor C/EBPβ and CCAAT/enhancer binding protein-β knockout transgenic mice develop lymphadenopathy, splenomegaly, and other Castleman features.[18] Interestingly viral IL6 expression in mice also yields an MCD-like phenotype. However, this phenotype