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Leukaemia Section

Mini Review

Castleman's disease

Luis Miguel Juárez Salcedo, Samir Dalia

Principe de Asturias University Hospital, Madrid, Spain; Dr.luisjuarez@gmail.com (LMJS); Oncology and Hematology, Mercy Clinic Joplin, Joplin, MO, USA; sdalia@gmail.com (SD)

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Abstract

Castleman's disease are referred to a group of rare disorders that were discovered by Benjamin Castleman in 1954. The disease is more common in HIV positive patients and has been linked to human herpesvirus 8. The disease is diagnosed with excisional lymph node biopsy and carries a good prognosis. Treatment options including radiation, rituximab based therapy or monitoring.

KEYWORDS

Castleman disease

Clinics and pathology

Disease

This disease was reported by Benjamin Castleman in 1954 (Castleman B, Towne V). Castleman disease is a heterogeneous cluster of disorders, with distinct unicentric CD (UCD) and multicentric CD (MCD) subtypes. 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 and interleukin-6 (IL-6) in a significant proportion of cases.

Phenotype/cell stem origin

The disease appears to be polyclonal in origin in the majority of cases, however evidence for clonal expansion was documented in some cases, possibly representing transformation into non Hodgkin's lymphoma. In approximately 1/3 of the cases studied a monoclonal IgH rearrangement was documented. A minor T-cell clone, mostly in a polyclonal background, was also documented in some cases.

Etiology

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.

Epidemiology

The epidemiology of CD is difficult to characterize accurately due to its rarity and clinical heterogeneity. The incidence of CD is estimated at 21-25 cases per million person-years, with 23% of those cases potentially representing MCD (Munshi N et al.,2015).

The median age at presentation for UCD is 30-34 years. For HIV-negative MCD is 49-66 years and HIV-positive MCD between 36-40 years. The sex distribution is approximately equal, though some series have reported a male predominance, generally

in the HIV-positive population. UCD also has a slight female predominance (1.4:1) (Talat N, et al., 2011; Dispenzieri A et al., 2012).

Clinics

UCD may be asymptomatic at diagnosis and be incidentally discovered on chest or abdominal imaging performed for other reasons. Patients may present with painless lymphadenopathy or local anatomical symptoms varying by location. Common sites of presentation include the chest (30%), neck (23%), abdomen (20%), retroperitoneum (17%), and, rarely, the axilla (5%), groin (3%), or pelvis (2%). 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. Disease confined to the peripheral lymph node chains, including the neck, axilla, or groin, may present with nontender lymphadenopathy.

Systemic symptoms are a common feature of MCD; these include traditional "B" symptoms such as fever, night sweats, and weight loss, as well as lymphadenopathy and hepatosplenomegaly. More severe disease phenotypes include a severe, inflammatory vascular leak syndrome where patients may develop ascites, pericardial effusions, pleural effusions, and/or peripheral edema. Hematological sings include anemia driven by IL-6 or secondary to autoimmune hemolysis, immune thrombocytopenia, and acquired factor VIII deficiency (Marsh JH et al., 1990; Marietta M et al., 2003). Bronchiolitis obliterans, glomerulonephritis, and pemphigus have also been reported, with the presence of pemphigus associated with an unfavorable prognosis (Dong Y et al., 2015) MCD may be seen in association with the POEMS syndrome, which comprises polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (Dispenzieri A et al., 2003).

Diagnosis A high index of suspicion is required in patients presenting with a compatible clinical picture, such as unifocal or generalized lymphadenopathy, splenomegaly, and/or unexplained constitutional symptoms (Chan K et al., 2016). Common laboratory findings include anemia, thrombocytopenia, hypoalbuminemia, polyclonal hypergammaglobulinemia, and elevation of acute phase reactants, such as CRP. Elevations in circulating cytokines such as IL-6 and VEGF may also be detected although not essential for diagnosis, plasma VEGF levels can be useful in distinguishing and monitoring cases of CD associated with POEMS syndrome. Although not essential for diagnosis, plasma VEGF levels can be useful in distinguishing and monitoring cases of CD associated with POEMS syndrome.

Pathology

Castleman disease is a pathological diagnosis made by excisional biopsy of affected lymph node tissue. There are two variants: the hyaline-vascular and the plasma cell subtype. 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 (Soumerai J et al., 2014).

The hyaline-vascular type 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. Patients with "multicentric" Castleman disease show histologic features consistent with the plasma cell subtype.

Treatment

The optimal therapy for UCD is surgical excision if the mass is localized. 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 (Bower M, et al., 2011).

Available treatments for the MCD variant include glucocorticoids, single-agent and combination chemotherapy, antiviral strategies, and monoclonal antibody therapies targeting CD20 or IL-6.

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. For initial systemic therapy, rituximab monotherapy has been recommended based on encouraging efficacy and safety results. Novel agents targeting interleukin 6 (Siltuximab and tocilizumab) represent exciting new additions to the treatment armamenatrium (Casper C et al., 2013). Combination chemotherapy utilized for lymphoma must be reserved to relapsed or refractory disease (Bower M, 2012).

Prognosis

The prognosis of CD is variable and depends predominantly on disease subtype. As previously mentioned, patients with UCD enjoy excellent long-term outcomes if complete resection can be achieved, with 10-year overall survival rates greater than 95%.

Even in unresectable UCD cases, radiotherapy may offer good long-term response rates. %.

The HIV- and HHV-8-associated subtype of MCD has the worst prognosis, with the majority of patients

in early studies dying within 2 years of diagnosis. Those patients with multicentric disease who fail to respond to steroid treatment have a serious disease.

Cytogenetics

Cytogenetics morphological

Many of the cases so far studied showed a normal karyotype. Occasional abnormalities were found in a few patients, but none known to be a "driver" chromosome abnormality. There is growing evidence suggesting that the clonal proliferation involved dysplastic stromal cells (Chang et al., 2014).

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