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REVIEW

Current diagnosis and treatment of Castleman's disease☆

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Abstract Castleman's disease is not just a single disease but rather an uncommon, heterogeneous group of nonclonal lymphoproliferative disorders, which have a broad spectrum of clinical expression. Three histological types have been reported, along with several clinical forms according to clinical presentation, histological substrate and associated diseases. Interleukin-6, its receptor polymorphisms, the human immunodeficiency virus and the human herpes virus 8 are involved in the etiopathogenesis of Castleman's disease. The study of this disease has shed light on a syndrome whose incidence is unknown. Despite recent significant advances in our understanding of this disease and the increasing therapeutic experience with rituximab, tocilizumab and siltuximab, there are still difficult questions concerning its etiology, prognosis and optimal treatment.

PALABRAS CLAVE
Enfermedad de Castleman;
Enfermedad de Castleman multicéntrica;
Hiperplasia linfoide angiofolicular;
Virus de la inmunodeficiencia humana;

Diagnóstico y tratamiento actual de la enfermedad de Castleman

Resumen La enfermedad de Castleman no es una única enfermedad. Bajo este epónimo se reúne un heterogéneo grupo de trastornos linfoproliferativos no clonales, muy infrecuentes, con un amplio espectro de expresión clínica. Se han descrito 3 tipos histológicos, junto con varias formas clínicas, según la forma de presentación, el sustrato histológico y las enfermedades asociadas. La interleucina 6, los polimorfismos del receptor de esta interleucina, el virus de la inmunodeficiencia humana y el virus herpes humano tipo 8 están implicados en la etiopatogenia y su estudio ha aportado luz al conocimiento de un síndrome cuya incidencia es desconocida. A

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Virus del herpes humano tipo 8;
Rituximab;
Tocilizumab;
Siltuximab

pesar de avances recientes e importantes en su conocimiento y de la progresiva experiencia terapéutica con rituximab, tocilizumab y siltuximab, aún existen preguntas difíciles de contestar con los factores etiológicos, el abordaje terapéutico óptimo y el pronóstico.

Background

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia, was reported between 1954 and 1956 by Castleman, a pathologist from the renowned Massachusetts General Hospital, based on a series of 13 patients with mediastinal masses that mimicked thymomas.[1] Over the last 60 years, the term Castleman's disease has remained a general label for the heterogeneous collection of reactive lymphoproliferative processes that share well-defined histological traits but that differ in their patterns of location, clinical expression and etiopathogenesis. The term includes at least 4 diseases with different diagnoses and treatments: (1) unicentric CD (UCD); (2) multicenter CD (MCD) associated with infection by the human herpes virus 8 (HHV-8) and by the human immunodeficiency virus (HIV) (MCD-HHV-8+/HIV+); (3) MCD with infection by HHV-8 but not by HIV (MCD-HHV-8+/HIV-); and (4) MCD not associated with any of these viruses, which has recently been called idiopathic MCD (iMCD). CD as a whole is considered a rare or minority disease. Despite the considerable interest the disease has generated since its initial description and the significant developments in research (more than 2700 entries in PubMed in September 2015), there is still no consensus on its treatment. Therefore, one of the objectives of this review is to facilitate an understanding of the current therapeutic options.

Epidemiology

The incidence of CD is unknown. Based on patient cohort results extracted from databases, a number of authors have estimated an incidence of approximately 21 cases per million inhabitants in the United States.[2] The disease usually affects middle-aged people, although with a bimodal distribution with a peak in young patients (30–40 years) and another at approximately 60 years. The incidence is similar in both sexes. The incidence of MCD-HHV-8+/HIV+ has increased in recent years due to the AIDS epidemic.

Classification

CD is classically divided into 2 types based on the onset of isolated adenomegaly (UCD) or polyadenopathies (MCD). These 2 conditions have very different clinical and histological characteristics.

CD causes an architectural change in the structure of the lymph nodes, which affects all their compartments. Histologically, CD is classified into a hyaline-vascular (HV) form and a plasmocellular (PC) form, although mixed variants can occasionally be observed, especially in the MCD forms.[3] In the HV form, the follicles show atrophic germinal centers, invaded by dendritic follicular cells and hyalinized vessels, which form bridges and connections between them. These centers are surrounded by mantle lymphocytes arranged in concentric rings that mimic the typical ''onion layer'' presentation. Two subtypes have been reported in the HV form: the classical lymphoid subtype and the stroma-cell rich subtype. The latter subtype has been reported as a possible precursor of follicular dendritic cell sarcomas.[4] In the PC variant, the follicles show hyperplastic germinal centers, and the interfollicular regions characteristically contain polyclonal plasma cells; the characteristic vascular proliferation of the HV forms is not observed. A third histological variant, known as plasmablastic, has recently been reported,[5] which occurs in particularly aggressive cases of MCD associated with HHV-8[6] and in the forms associated with POEMS syndrome[7] (Crow-Fukase syndrome[8]).

This morphological complexity carries over to clinical practice, because there are patients who show an overlap between UCD and MCD. In the early years, there was certain controversy in the literature when describing the cases. The limitations in disease staging and the limited experience with the histological analysis of samples fostered confusion among the clinical and histological variants. Despite the improvements in diagnostic techniques and the experience acquired with CD, there are still a number of issues concerning its classification. Isolated unicentric masses, which used to be identified with plain radiographs, can now be accompanied by adenopathies in other regions or by reactive splenomegaly. In a small number of cases, the use of techniques such as computed tomography, magnetic resonance and positron emission tomography blurs the unequivocal separation between UCD and MCD. Despite these difficulties, however, the majority of patients can be classified into one of the 2 variants (Table 1).

Pathophysiology

There have been major advances in understanding the pathophysiology of CD. There are various theories based on the repeated antigenic stimulus of nodal B lymphocytes in response to some etiological agent. The most accepted model is the one derived from an abnormal overproduction