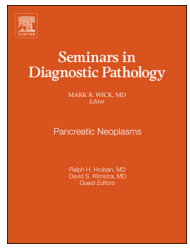
Seminars in Diagnostic Pathology 33 (2016) 294–306

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/semdp



Multicentric Castleman disease: Where are we now?

*Hao-Wei Wang, MD, PhD, Stefania Pittaluga, MD, PhD, Elaine S. Jaffe, MD**

Hematopathology Section, Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

ARTICLE INFO

Keywords:
Castleman disease
Kaposi sarcoma-associated herpesvirus
Human herpesvirus type-8
Interleukin-6
TAFRO syndrome
Acquired immune deficiency syndrome

ABSTRACT

Multicentric Castleman disease (MCD) encompasses a spectrum of conditions that give rise to overlapping clinicopathological manifestations. The fundamental pathogenetic mechanism involves dysregulated cytokine activity that causes systemic inflammatory symptoms as well as lymphadenopathy. The histological changes in lymph nodes resemble in part the findings originally described in the unicentric forms Castleman disease, both hyaline vascular and plasma cell variants. In MCD caused by Kaposi sarcoma-associated herpesvirus/human herpesvirus-8 (KSHV/HHV8), the cytokine over activity is caused by viral products, which can also lead to atypical lymphoproliferations and potential progression to lymphoma. In cases negative for KSHV/HHV8, so-called idiopathic MCD, the hypercytokinemia can result from various mechanisms, which ultimately lead to different constellations of clinical presentations and varied pathology in lymphoid tissues. In this article, we review the evolving concepts and definitions of the various conditions under the eponym of Castleman disease, and summarize current knowledge regarding the histopathology and pathogenesis of lesions within the MCD spectrum.

Published by Elsevier Inc.

Historical background

In 1954, Castleman and Towne[1] reported the first case of Castleman disease presenting as a large mediastinal mass in a 40-year-old male patient. Histological examination revealed hyperplastic lymphoid tissue with hyalinized germinal centers that mimic Hassall corpuscles. In a subsequent report of 12 more cases, Castleman et al.[2] further characterized the clinicopathologic findings. The patients all presented with enlarged mediastinal masses with none or only mild nonspecific systemic symptoms. Two major histologic features were recognized: hyalinization of lymphoid follicles and marked capillary proliferation, affecting both the follicles and interfollicular regions. These features later gave rise to the denotation of hyaline vascular type to this entity.

In addition to the prototypic Castleman disease,[1,2] Flendrig described a different type, which exhibited prominent interfollicular fields of mature plasma cells, and was invariably associated with clinical presentations including fever, lymphadenopathy, splenomegaly, and anema.[3] In 1972, Keller et al. reviewed 81 cases, and established two histological types of Castleman disease: the originally reported hyaline vascular type and the plasma cell type seen more rarely (9 cases).[4] Both types presented as solitary masses, with the plasma cell type more often associated with systemic symptoms.

* *Correspondence to*: Hematopathology Section, Laboratory of Pathology, NCI, National Institutes of Health, Building 10, Room 3S 235, MSC-1500, Bethesda, MD 20892.
E-mail address: ejaffe@mail.nih.gov (E.S. Jaffe).

http://dx.doi.org/10.1053/j.semdp.2016.05.006
0740-2570/Published by Elsevier Inc.

Subsequently, cases with similar histologic features but involving multiple sites were described. In 1983, Frizzera et al. reported 15 patients of multicentric Castleman disease (MCD),[5] and comprehensively analyzed the morphological, clinical, and immunophenotypic features.[5–7] Clinically, all patients presented with constitutional symptoms such as fever, night sweats, or weight loss. Morphologically, the involved lymph nodes were characterized by a histologic triad—(1) diffuse marked plasmacytosis, (2) prominent germinal centers often showing hyaline vascular changes, and (3) preserved nodal architecture. In other words, there were features of both hyaline vascular and plasma cell types.

Soon after the acquired immunodeficiency syndrome (AIDS) was described, lymphadenopathy with Castleman-like features was reported to be associated with AIDS.[8,9] After the human immunodeficiency virus (HIV) was identified as the etiologic agent of AIDS, the association between MCD and HIV infection was further established.[10,11] However, the *bona fide* etiologic agent of HIV-associated MCD had been elusive until Soulier et al.[12] identified KSHV/HHV8 sequences in all of the HIV-positive MCD cases and 40% of HIV-negative cases in 1995.

Nonetheless, there remained cases with clinical and histological features resembling MCD cases in HIV-negative patients that were negative for KSHV/HHV8; these cases have been referred to as idiopathic MCD (iMCD).[13] The diagnosis of iMCD is made when clinical and histological manifestations of MCD are observed, but all infectious (including KSHV/HHV8), autoimmune and neoplastic disease known to demonstrate these features have been excluded.

In the end, a spectrum of various conditions has come to be associated with the eponym of Castleman disease (Fig. 1). It is clear that these represent several different disease entities, which share some overlapping histological features, but have different etiologies and very different clinical outcomes. Unicentric CD is usually self-limited, contains dysplastic dendritic and stromal elements, and carries a small risk for subsequent follicular dendritic cell sarcoma, whereas MCD associated with KSHV/HHV8 is primarily a lymphoproliferative disorder with risk of progression to lymphoma. The greatest questions remain regarding iMCD, which probably constitutes more than one entity. However, recent data have delineated at least one distinctive syndrome, "thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly" or TAFRO, that had been included in iMCD. In this review, we will summarize the current knowledge regarding the clinical presentation, histopathology and pathogenesis of Castleman disease, focusing on MCD.

Unicentric Castleman disease

Hyaline vascular Castleman disease

Hyaline vascular type comprises more than 90% of unicentric Castleman disease. It has a broad range of age distribution from pediatric to elderly patients. There is no predilection for either gender. Most patients present with a localized mass without constitutional symptoms or laboratory abnormalities. The mediastinum is the most common location, although the disease can also occur in extrathoracic sites such as the abdomen or neck.[4,14] Surgical excision is the treatment of choice, and recurrence is uncommon.[14,15]

The involved lymph nodes are characterized by prominent vascular proliferation and hyalinization. The follicular centers are often atretic, and traversed by radially penetrating vessels that are usually ensheathed by collagenous hyalinization. The germinal centers are surrounded by mantle lymphocytes arranged in layers, imparting an onion-skin appearance. Some of the follicles may group together by fusion of the mantle zones, giving a "twinning" appearance with large irregular follicles containing more than one germinal center (Fig. 2A). Between the follicles, there is usually extensive vascular proliferation with perivascular hyalinization. Of note, the follicular dendritic cells sometimes show dysplastic features (Fig. 2B), and instances of follicular dendritic cell sarcoma have been described.[16,17] In fact, recent molecular studies demonstrated clonality in the stromal cells in hyaline vascular Castleman disease, and suggested that genetic alteration in stromal cells including FDCs may be the underlying cause of the disease.[18–20]

Unicentric Castleman disease, plasma cell type

The plasma cell type comprises around 10% of cases of unicentric Castleman disease.[3,4] The demographic features resemble those of the hyaline vascular type.[4,14] However, in contrast to the hyaline vascular type, the plasma cell variant is almost always associated with systemic symptoms and abnormal laboratory findings. The common clinical presentations include fever, night sweats, fatigue, weight loss, splenomegaly, anemia, and hypergammaglobulinemia. The

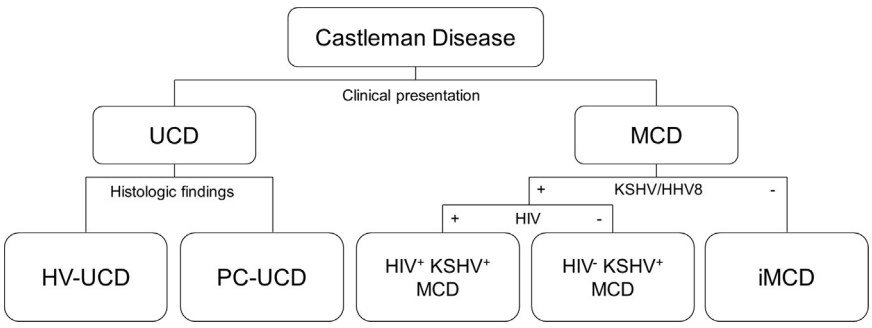


Fig. 1 – Classification of Castleman disease. UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; HV, hyaline vascular; PC, plasma cell; iMCD, idiopathic multicentric Castleman disease.