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HHV-8-Negative, Idiopathic Multicentric Castleman Disease (iMCD): A Description of Clinical Features and Therapeutic Options through a Systematic Literature Review

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Abstract

Background:

Multicentric Castleman disease (MCD) describes a heterogeneous group of poorly-understood diseases involving proinflammatory hypercytokinemia that ultimately results in systemic inflammatory symptoms, generalized lymphadenopathy, multiple organ system dysfunction, and even death. HHV-8 is responsible for driving MCD in immunosuppressed patients (HHV-8-associated MCD). There is also a cohort of HHV-8-negative MCD cases, referred to as idiopathic MCD (iMCD), in which the etiology remains unknown. No formal diagnostic criteria exist for iMCD, and knowledge is limited to small case series and case reports.

Objectives:

We conducted a systematic literature review to describe demographic, clinical, and laboratory features of iMCD as well as the treatments currently used in practice.

Methods:

PubMed was queried using a comprehensive list of terms to identify all published cases of HHV-8-negative MCD. Criteria for study inclusion were as follows: (1) Pathology-confirmed Castleman disease in multiple lymph nodes; (2) Exclusion of another cause of Castleman-like histopathology, such as SLE or POEMS syndrome; (3) Negative testing for HHV-8 via PCR of blood, PCR of lymph node tissue, serum serologies, and/or IHC for LANA-1; (4) Written in English and published from January 1995 to July 2013; and (5) Availability of specified minimum data elements. HIV-positive cases were excluded. Inclusion criteria were confirmed by three independent investigators, who also extracted data into a standardized database. Case report authors were contacted to gather additional data in a standardized case report form.

Results:

3,428 articles were identified on PubMed. Initial evaluation for exclusion criteria yielded 1,951 MCD cases; 629 patients were HIV-positive (32%). Of the 999 HIV-negative and 323 HIV-unknown MCD cases, 626 were HHV-8 negative (32% of total MCD), 517 were HHV-8-unknown (26%), and 179 were HHV-8-positive (9%).129 cases of HHV-8-negative MCD met all inclusion criteria and were included in the final analysis. 58% were male and median age was 50 years (range: 2-80). Frequently reported clinical features included: fever (51/64), enlarged liver and/or spleen (45/60), pleural effusion (29/38), edema (26/36), and weight loss (21/29). There were 43 plasmacytic, 26 mixed, and 23 hyaline vascular cases out of 108 cases that reported histopathological subtype. The most commonly reported laboratory abnormalities included elevated CRP (70/79), anemia (76/90), hypergammaglobulinemia (63/82), hypoalbuminemia (57/63), elevated IL-6 (57/63), and positive ANA (14/38). Of cases with abnormal platelet levels, 28 had thrombocytopenia and 14 had thrombocytosis. There were 19 reported cases with elevated soluble IL-2R levels and 15 with elevated VEGF. 27 patients were diagnosed with a malignancy before (5), concurrently with (12), or after (10) diagnosis. Most commonly employed first line therapies included corticosteroid monotherapy (36%), combinations of cytotoxic chemotherapies (36%) that included regimens with cytoxan (17%) and rituxan (12%), and anti-IL-6 therapies, such as siltuximab and tocilizumab, without a cytotoxic agent (10%). Thalidomide, bortezomib, anakinra, and IVIG were used less frequently. Patients experienced no response (21%), partial response (42%), and complete response (37%) to first-line therapies. Failure (relapse, death, additional treatment) of first line therapy occurred in 41% of patients, and median time to treatment failure was 6 months. Overall, 22% of patients died by the time of most recent follow up (median: 28 months) with median length of survival among fatal cases being 26 months (range: 1-120). The most common causes of death were septic shock, multi-organ failure, including renal and cardiac, pulmonary complications, and malignancy.

Conclusion:

This study identified a significant proportion of MCD patients who are HIV-negative and HHV-8-negative (iMCD). 45% of patients did not demonstrate the plasmacytic variant alone, which has been classically associated with MCD. It is striking that 22% of patients died by the time of most recent follow up, which had a median length of 26 months. Despite the many limitations of analyzing case reports, this study provides the most comprehensive data on HHV-8-negative MCD to date. A global natural history study and Castleman disease registry are urgently needed to gather more extensive data on MCD.

Disclosures

Fajgenbaum: *Janssen Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees. **Off Label Use:** Cyclophosphamide, rituximab, tocilizumab, thalidomide, bortezomib, anakinra, and intravenous immunoglobulin will be presented as drugs used in HHV-8-negative MCD. It is very important to inventory the treatments that a physician has available when conventional therapies do not work, which is frequent in MCD. At the time that this data set was assembled, there were no FDA approved therapies for this orphan disease. **van Rhee:** *Janssen:* Consultancy, Membership on an entity's Board of Directors or advisory committees.

Author notes

*Asterisk with author names denotes non-ASH members.