Treatment of Kaposi Sarcoma Herpesvirus–Associated Multicentric Castleman Disease

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KEYWORDS

- Kaposi sarcoma herpesvirus • Human herpesvirus-8
- Multicentric Castleman disease • Human interleukin-6 • Viral interleukin 6
- Rituximab • Liposomal doxorubicin

KEY POINTS

- Kaposi sarcoma herpesvirus (KSHV)-associated multicentric Castleman disease is a B-cell lymphoproliferative disorder caused by KSHV that is characterized by waxing and waning inflammatory symptoms, laboratory abnormalities, edema, adenopathy, and splenomegaly. It is most common in patients with HIV.
- Four weekly doses of rituximab, 375 mg/m^2, lead to remission in a majority of mildly symptomatic patients but may lead to exacerbation of concurrent Kaposi sarcoma (KS).
- Rituximab, 375 mg/m^2, plus liposomal doxorubicin, 20 mg/m^2, administered every 3 weeks effectively treats patients with aggressive disease or concurrent KS.
- Rituximab-based treatment has increased 5-year overall survival to more than 90%.
- Current studies are evaluating targeted rituximab-sparing approaches that may decrease toxicity and/or be appropriate for patients with concurrent KS.

INTRODUCTION

Castleman disease is a term used to describe a variety of pathologic entities ranging from indolent localized angiofollicular hyperplasia (unicentric Castleman disease), as first described by Benjamin Castleman in the 1950s, to multicentric lymphoproliferations associated with inflammatory symptoms (multicentric Castleman disease [MCD]). One epidemiologically distinct plasmablastic form of MCD described in

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patients with HIV and associated with high mortality[1] was found caused by a newly discovered virus, called Kaposi sarcoma–associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8). KSHV was first identified as the etiologic agent for Kaposi sarcoma (KS) and is now recognized as the cause of almost all MCD in HIV-positive patients and rare cases of MCD in HIV-negative patients.[2]

KSHV-MCD is clinically characterized by intermittent inflammatory symptoms, cytopenias, edema lymphadenopathy, and splenomegaly, which often wax and wane. The diagnosis is confirmed pathologically, generally through a lymph node biopsy. Disease manifestations are associated with elevated levels of cytokines, especially interleukin (IL)-6 and IL-10.[3–5] Untreated, KSHV-MCD is generally lethal within 2 years.[5] Its rarity, intermittent manifestations, association with HIV, and nonspecific symptoms make diagnosing KSHV-MCD a challenge. The past decade, however, has seen the development of several effective therapies and substantial improvement in overall survival; therefore, increased recognition and timely diagnosis are important.

EPIDEMIOLOGY

KSHV-MCD incidence is unknown and the disease is almost certainly underdiagnosed. Powles and colleagues[6] estimated the incidence of KSHV-MCD in HIV-positive individuals to be 4.3 cases per 10,000 person-years and noted increasing incidence despite availability of effective antiretroviral therapy (ART) for HIV. KSHV-MCD often occurs in the setting of suppressed HIV, relatively preserved $CD4^+$ T-cell counts, and evidence of KSHV-specific $CD8^+$ T-cell response.[7,8] An improved understanding of the timing of KSHV-MCD diagnosis in relation to initiation of ART is required. It is possible that like KS and lymphoma, incidence is highest in the first year after ART initiation.[9]

KSHV-MCD is especially likely to be underdiagnosed in areas of sub-Saharan Africa with a high seroprevalence of both KSHV and HIV.[10–12] Unlike developed countries where KSHV prevalence in the general population is 2% to 5%, KSHV is endemic in large parts of sub-Saharan African, with 40% to greater than 80% of adults seropositive in much of the region.[10,11] The lack of reported KSHV-MCD cases almost certainly represents underdiagnosis, because KSHV-MCD has been described among African immigrants.[13,14] Due to lack of pathology services in many parts of sub-Saharan Africa, KS is sometimes treated empirically and without evaluation for concurrent KSHV-MCD in suspected cases. Additionally, fevers and lymphadenopathy, when present, are often empirically treated as tuberculosis.[13,15] Increased diagnostic capacity for Kaposi sarcoma herpesvirus-associated diseases, including KSHV-MCD, is needed in this setting.

PATHOGENESIS

KSHV is a gammaherpesvirus, most closely related to Epstein-Barr virus, with latent and lytic phases characteristic of all herpesviruses. In addition to KSHV-MCD, it is the etiologic agent of KS, primary effusion lymphoma (PEL), and Kaposi sarcoma herpesvirus-associated diffuse large B-cell lymphoma. Also, it is the cause of a newly identified condition called KSHV inflammatory cytokine syndrome, in which patients have severe inflammatory symptoms that mimic KSHV-MCD but lack the requisite pathologic findings of KSHV-MCD.[16,17]

KSHV encodes several proteins that allow for immune evasion via down-regulation of surface proteins required for immune surveillance.[18,19] The development of KSHV-MCD in HIV-positive patients may be related to reduction or functional impairment of invariant natural killer T (iNKT) cells.[20] iNKT cells play a major role in innate immunity and control of EBV infected B cells through activation of glycolipid antigens presented