Rapid Multiorgan Failure due to Large B-cell Lymphoma Arising in Human Herpesvirus-8-associated Multicentric Castleman’s Disease in a Patient with Human Immunodeficiency Virus Infection

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Abstract

A 46-year-old man presented with a high-grade fever, multiple lymphadenopathies, hepatosplenomegaly and human immunodeficiency virus (HIV) seropositivity, without severe immunosuppression. We suspected human herpesvirus-8 (HHV-8)-associated multicentric Castleman's disease (MCD) based on the results of a physical examination and laboratory investigations, including bone marrow aspiration. However, the patient died eight days after admission due to multiorgan failure. An autopsy revealed MCD and lymphoma cell infiltration in multiple organs. The final diagnosis was large B-cell lymphoma (LBCL) arising in HHV-8-associated MCD. This case illustrates the potential for LBCL in HHV-8 MCD in HIV-infected patients with hepatosplenomegaly and lymphadenopathy without severe immunosuppression and highlights the clinical significance of bone marrow aspiration.

Key words: MCD, LBCL, HHV-8 MCD, HIV, bone marrow aspiration


Introduction

Castleman’s disease is a benign lymphoproliferative disease, first described by Castleman et al. in 1956 (1). Human herpesvirus-8 (HHV-8)-associated multicentric Castleman’s disease (MCD) is fatal; such patients display HHV-8 infected lymphoid cells with an IgM-expressing plasmablast-like appearance and an increase in the number of plasma cells in the lymph nodes. In addition, MCD frequently progresses to lymphoma, most commonly large B-cell lymphoma (LBCL) (2). The occurrence of LBCL in the setting of HHV-8 MCD involves the monoclonal proliferation of HHV-8-infected lymphoid cells (3) and usually occurs in patients co-infected with HHV-8 and human immunodeficiency virus (HIV). Unlike other HIV- and HHV-8-related malignant diseases, such as primary effusion lymphomas and Kaposi’s sarcoma (KS), LBCL in HHV-8 MCD can arise in patients without severe immunosuppression. Furthermore, the incidence of KS in HIV patients has decreased due to the introduction of anti-retroviral therapy (ART), although ART cannot be used to combat MCD (4). Therefore, although MCD is rare, and the development of LBCL in HHV-8 MCD even more rare, making an early diagnosis of MCD is important. We herein report a case of multiorgan failure that rapidly progressed due to the onset of LBCL in an HIV patient with HHV-8 MCD.

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A 46-year-old man was transferred to our hospital due to a high fever, fatigue, diarrhea, anemia, thrombocytopenia and HIV seropositivity. The high fever and fatigue had persisted for six months prior to admission, while the diarrhea and severe fatigue developed a few days before admission. A physical examination revealed an increased respiratory rate and anemia without hemorrhage. The results of a peripheral blood test indicated HIV seropositivity, severe anemia, thrombocytopenia, hypoalbuminemia and an elevated level of C-reactive protein (CRP). With respect to the HIV status, the HIV-RNA copy number in the plasma was elevated at $2.2 \times 10^5$ copies/mL, whereas the CD4-positive T lymphocyte count (CD4) was suppressed at 254/μL. A computed tomography (CT) scan revealed hepatosplenomegaly and multiple lymphadenopathies throughout the patient’s body. Based on these findings, we suspected MCD. Therefore, additional blood examinations were performed, the results of which demonstrated elevated levels of interleukin (IL)-6 and soluble IL-2 (sIL-2) receptors in the serum. In addition, HHV-8 DNA was detected in the peripheral blood, at $4.2 \times 10^5$ copies/million cells [real-time polymerase chain reaction (PCR)]. Furthermore, the IgG and IgM levels were slightly elevated, and the M bow was not observed on immunoelectrophoresis, which suggested a pattern of chronic inflammation. An analysis of the bone marrow aspirate revealed 16% of the cells to be plasma cells with abnormal nuclei (Fig. 1). However, no signs of hemophagocytic syndrome were found in the specimen. The patient’s clinical course is summarized in Fig. 2. On day 4 of hospitalization, steroid therapy with prednisolone [1 mg/(kg/day)] was started as antitumor treatment and to suppress the severe inflammation (5). Nevertheless, after the introduction of prednisolone, acute renal failure developed, requiring hemodialysis, although there was no evidence of acute tumor lysis syndrome. The following day, VP-16 therapy was introduced as chemotherapy for MCD (5), as we were unable to wait for a definitive diagnosis. The patient’s condition continued to worsen, and he subsequently required respiratory management and continuous hemodialysis filtration due to severe acute renal failure, coma and low blood pressure. Despite these intensive interventions, he died eight days after admission. An analysis of the lymph node specimen of the neck (a lymph node biopsy of the patient’s neck was performed on day 4 of hospitalization) revealed the presence of numerous plasma cells and small lymphoid cells with an oniosiskin appearance, both of which are characteristic of Castleman’s disease. In addition, hyalinized blood vessels were prominent (Fig. 3). An analysis of another portion of the specimen revealed lymphoid cells with large abnormal nuclei gathered locally that were found to be CD3−/− and positive for KS-associated herpesvirus-related latent nuclear antigen-1 (LANA-1) and herpesvirus-related latent nuclear antigen-1 (LANA-1) and positive for KS-associated herpesvirus-related latent nuclear antigen-1 (LANA-1) and negative for Epstein Barr virus (EBV)-encoded RNA-1 (EBER) (Fig. 4). An autopsy revealed invading tumor cells at other sites in the lymph nodes and multiple organs, including the spleen, liver, kidneys and lungs. It was difficult to differentiate between MCD and LBCL in HHV-8 MCD.

**Discussion**

MCD is a very rare disease, with cases in which the condition is comorbid with LBCL being even more rare. In the present case, the diagnosis of MCD was made based on the findings of a clinical examination, laboratory tests and an analysis of the bone marrow aspirate. In 2007, Gerard et al. defined the diagnostic criteria for MCD (6). These criteria were met in the current case, as the patient had a high-grade fever, cough, nasal obstruction, elevated serum CRP level, multiple lymphadenopathies, splenomegaly, pleural effusion and jaundice, despite the absence of autoimmune anemia. However, little is known about the findings and clinical importance of bone marrow aspiration in cases of MCD (7). In
a recent study, Venkataraman et al. reported the predominance of plasmacytosis in bone marrow biopsy specimens in patients with MCD (8, 9). In the current case, we confirmed that bone marrow aspiration is an effective diagnostic approach, despite the absence of plasmablasts or atypical lymphocytes among peripheral blood cells, as the findings were similar to those associated with multiple myeloma. Moreover, no signs of bone marrow infiltration of lymphomas were found, and \( \lambda \)-chain restriction was present on flow cytometry in the lymph node biopsy specimen only, not in the peripheral blood. Based on these findings, we recommend performing bone marrow aspiration in cases in which MCD is suspected.

The potential for LBCL with HHV-8-associated MCD should be considered in HIV-infected patients with anemia, splenomegaly and a high fever who exhibit an elevated serum level of CRP without any evidence of bacterial infection (10). HHV-8 infection is common among men who have sex with men in Japan and can cause primary effusion lymphoma, KS and LBCL in HHV-8 MCD (11). Furthermore, the burden of HHV-8 infection, quantified using a PCR-based assay, together with the serum CRP and IL-6 levels, correlates with the MCD activity (2, 5, 12).

Unlike KS, the most common disease caused by HHV-8 infection in HIV-infected patients, the extent of MCD and LBCL in HHV-8 MCD cases is only weakly correlated with the CD4 count or administration of ART. Moreover, relapse is frequent. In the present case, however, the CD4 count in the peripheral blood was greater than 200/μL, and the patient was not severely immunocompromised. Therefore, regardless of the CD4 and ART status, the possibility of LBCL in HHV-8 MCD should be considered when an HIV-infected patient presents with clinical and laboratory findings similar to those described here. It is also noteworthy that our patient had elevated levels of CRP, IL-6 and sIL-2 receptor, suggesting that he experienced a cytokine storm due to the malignant lymphoma (Table). Hence, lymph node biopsies are also required in such cases.

LBCL in HHV-8 MCD is associated with the monoclonal proliferation of HHV-8-infected lymphoid cells, which express both IgM and viral IL-6 and exhibit a stippled nuclear staining pattern for LANA-1. The WHO classification describes these cells as being CD20\(^{-}\), CD79a, CD138, CD38\(^{-}\) and EBER, although an alternative classification has been proposed in which the presence of EBV, HIV and HHV-8 is considered to be a marker of this cell type (8). The immunophenotype observed in this case was slightly different from that specified in the WHO classification but

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**Figure 3.** Biopsy specimen of the patient’s right neck lymph node performed on day 4. A: Hematoxylin and Eosin (H&E) staining (×200). Plasma cells and small lymphoid cells arranged concentrically (onionskin appearance). B: H&E staining (×400). Numerous invading plasma cells, small lymphoid cells, and pronounced hyalinized blood vessels can be seen. C: LANA-1 staining (×400). Plasma cells stain positive in a circular fashion.
sufficiently similar to be considered LBCL in HHV-8 MCD.

Currently, the number of HIV-infected patients in Japan is increasing; therefore, the incidence of cases similar to the one described in this report may also increase. We hope that additional case studies will help to further refine the diagnosis and treatment of this rare but fatal disease.

The authors state that they have no Conflict of Interest (COI).

References
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