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HIV-Associated Multicentric Castleman Disease with Human Herpes Virus-8 Coinfection: A Case Report

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Abstract

Castleman Disease (CD) is a rare lymphoproliferative disorder classified into unicentric or multicentric variants. The Multicentric CD (MCD) involves diffuse lympadenopathy and the presence of type B symptoms (fevers, night sweats and weight loss), and relates to HIV/Human Herpes Virus (HHV)-8 infection. We report an MCD case of an HIV-infected 57 year old male patient. Histopathological examination showed Epstein-Barr Virus-Encoded small RNAs (EBERs) in addition to HHV-8 positivity with prednisolone and rituximab treatment, fever and pancytopenia were regressed. Multicentric CD should be considered in the differential diagnosis of patients presenting with lymphadenopathy and systemic symptoms. Patients with HIV-associated MCD should be followed routinely because of the relapsing and remitting nature of the disease.

Keywords: Castleman disease; Multicentric castleman disease; HIV; Human Herpes Virus-8 (HHV)

Introduction

Castleman Disease (CD), also known as lymphoid angiofollicular non-neoplastic hyperplasia or giant lymph node hyperplasia, is an uncommon lymphoproliferative disorder which was first described in 1954 by Benjamin castleman. It is classified into two main forms. The unicentric form is the most frequent type with an incidence of 16 cases per million person-years and the multicentric form has an estimated incidence of 5 cases per million person-years. Unicentric CD (UCD) presents as localized lymphadenopathy with mild or no symptoms and good prognosis. It can be treated by surgical excision with full recovery and without relapse in almost all cases. In contrast, Multicentric CD (MCD) is characterized by diffuse lymphadenopathy with systemic manifestations and poor prognosis. Management of MCD varies according to the specifications of the case, but it is usually difficult to be treated. Histopathologically, CD can be classified as either hyaline-vascular or plasma cell variant, with occasional cases demonstrating mixed features. The hyaline-vascular histology is seen in 90% of UCD cases and the plasma cell type accounts for 80%-90% of MCD. Approximately 50% of MCD is linked to Human Herpes Virus (HHV) 8 coinfection. In MCD that is linked to HHV-8, pathogenesis relates to production of specific proteins that lead to increase of hypoxia-inducible factor and to the expression of the vascular endothelial growth factor, resulting in proangiogenic signals. HHV-8 also has a role in the dysregulation and overproduction of IL-6, which promotes the growth of B-cell tumors and lymphoproliferative syndrome, as well as triggering the acute-phase inflammatory reaction that results in clinical features and laboratory changes of MCD. HIV infection is an important risk factor for MCD that is associated with HHV-8.

All cases that have HIV-related MCD are coinfected with HHV-8. The incidence of MCD in HIV positive persons has shown an increase with widespread use of antiretroviral treatment, suggesting that immune dysregulation rather than immunosuppression is a key pathophysiological mechanism of HIV-related MCD. In this article, we report a case with HIV infection and has a HHV-8 associated MCD, presented with a palpable mass in the neck area [1-6].

Case Report

A 57-year-old male patient presented to an external clinic with a palpable mass in his neck. He had no known chronic disease. He was having night sweats and fatigue in the past one month. Laboratory tests showed: White Blood Cells (WBC): $3.58^{*}103/mm^3$, neutrophil: $2^{*}103/mm^3$, lymphocyte: $1.46^{*}103/mm^3$, hemoglobin: 9.7g/dL, platelets: $128^{*}103/mm^3$, Lactate Dehydrogenase (LDH): 164 U/L, creatinine: 0.6 mg/dL. Computerized Tomography (CT) of the neck, thorax and abdomen revealed bilateral pathological size lymph nodes around cervical chain, parotid, mediastinum, right paratracheal, bilateral axillar, paraaortic, pericaval and bilateral inguinal areas. Hepatosplenomegaly was also detected as shown in Table 1 [7-9].

Body fluids	Range
White blood cells	$58^{*}103/mm^3$
Neutrophil	$2^{*}103/mm^3$
Lymphocyte	$1.46^{*}103/ mm^3$
Heamoglobin	9.7g/dL
Platelets	$128^{*}103/mm^3$
Lactate dehydrogenase	164 U/L
Creatinine	0.6 mg/dL

Table 1: Patient data on body fluids and range.

The patient was referred to our clinic. Further examinations showed: WBC: $3.36^{*}103/mm^3$, neutrophil: $1.59^{*}103/mm^3$, lymphocyte: $1.38^{*}103/mm^3$, hemoglobin: 8.9 g/dL, platelets: $100^{*}103/mm^3$, C-Reactive Protein (CRP): 32 mg/dL, Sedimentation: 75 nm/h. In blood smear, anisocytosis and microcytic erythrocytes were observed. Additional tests revealed: HbsAg (-), Anti-Hbc IgG (-), Anti-HCV (-), Brucella serology (-), Coombs Wright (-), Cytomegalovirus (CMV) DNA (-), Parvovirus PCR (-), Anti-HIV (+), Epstein-Barr Virus (EBV) DNA: 348,662 copies/mL, PPD: 7 mm as shown in Table 2 [10].

Body fluids	Range
White blood cells	3.36*103/mm^3
Neutrophil	1.59*103/mm^3
Lymphocyte	1.38*103/mm^3
Heamoglobin	8.9 g/dL
Platelets	100*103/mm^3
C-reactive protein	32 mg/dL
Sedimentation	75 nm/h

Table 2: Report of clinical examination.

Supra- and infra-diaphragmatic multiple numbers of hypermetabolic lymph nodes observed in PET CT were deemed as lympho proliferative disease or malignancy. Bone marrow biopsy and excisional lymph node biopsy were performed. Due to EBV viremia, intravenous acyclovir was initiated until the pathology results are confirmed. HIV confirmation test was positive with HIV RNA: 697,324 copies/mL. During follow-ups, the patient had fever and pancytopenia deepened [11].

Lymph node biopsy results showed hyaline vascular changes and atypical lymphoid proliferation with EBV-Encoded small RNA (EBERs) positivity. No significant increase in plasma cell ratio and rare presence of positive reaction with HHV-8 made the exact interpretation difficult. HHV-8 was examined in serum and 17,826 copies/ml were detected. Foscarnet was considered for the treatment of HHV-8. Meanwhile, bone marrow biopsy was normal with mild to moderate reticulin fiber increase, T cell lymphocytosis and interstitial mild plasmacytosis. The case was diagnosed as HHV-8 associated MCD. Prednisolone and Rituximab treatments were initiated. In the follow-ups, the patient had no fever and pancytopenia was improved [12].

Results and Discussion

We presented a case of HHV-8 associated MCD in a male patient with HIV. Multicentric CD commonly presents in people aged 50 years-60 years, although patients with HIV infection tend to present at a younger age. It is seen slightly more in men than women.

Individuals with MCD present with symptoms consistent with an inflammatory process. Main symptoms include fever, weight loss, night sweats, and fatigue. Physical exam shows generalized lymphadenopathy, hepatosplenomegaly, edema, abdominal ascites, pleural and pericardial effusion. Laboratory signs are related to chronic and inflammation-related diseases such as anemia, thrombocytopenia, elevation of inflammatory markers and electrolyte disturbances. In our case, most of these symptoms and signs were present. In addition to the existence of all laboratory markers related to inflammation, our patient was tested positive for EBV as well as HIV and HHV-8. At imaging, multiple lymphadenopathies are commonly found in MCD as also seen in our case [13,14].

However, the exact diagnosis of CD is usually confirmed with histopathological examination of affected lymph node tissue. In our case, lymph node biopsy showed as a hyalinize-vascular type, although this type is mostly seen in UCD, while plasma cell type characterizes most cases of MCD. Additionally, there were EBER and HHV-8 positivity in lymphoid cells. The coexistence of HHV-8 and EBV in a lymph node was reported to be associated with a rare entity called germinotropic lymphoproliferative disorder usually present in HIV-negative patients. In a series of 19 MCD in HIV infected patients, 4 (21%) were also found to have both viruses in lymph node samples. Treatment of MCD includes corticosteroids, chemotherapy, monoclonal antibodies and radiotherapy or a combination of these specifically, MCD in HIV-infected patients is treated with a combination of antiretroviral therapy, chemotherapy, and rituximab. Rituximab depletes the viral reservoir and reduces the risk of lymphoma. Studies using rituximab reported an overall survival of up to 95% with disease-free survival of up to 79% in MCD in HIV infected patients [15-17].

Multicentric CD may progress very slowly in some patients, while others may have a relapsing and remitting path or an acute disease that can lead to death rapidly. Severe progress is more common in patients with HIV-associated MCD. Relapse flares may occur at any CD4 count and not thought to be prevented by antiretroviral treatment and control of the HIV. HIV-associated MCD may also exist with related malignancies, including Kaposi sarcoma or primary effusion lymphoma, each of which share an HHV-8-mediated pathogenesis. Kaposi sarcoma could be identified in 72% of HIV-associated MCD cases at diagnosis. Patients infected with HIV may also develop other HIV-related lymphomas not directly related to MCD, such as plasmablastic lymphoma, Hodgkin lymphoma, and primary lymphoma of the central nervous system [18,19].

Conclusion

This case demonstrates that clinicians should be aware of and consider MCD in the differential diagnosis of patients presenting with lymphadenopathy and systemic symptoms. In HIV positive patients, as in our case, EBV and HHV-8 viremia can be seen together in MCD. Obtaining definitive histological diagnosis is important for right treatment. Patients with HIV-associated MCD should be followed routinely because of the relapsing and remitting nature of the disease.

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