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Successful Treatment of Aggressive HIV-associated Multicentric Castleman's Disease: A Case Report

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ABSTRACT

Background: Multicentric Castleman's disease (MCD) in human immunodeficiency virus (HIV)-infected patients is an aggressive form of lymphoproliferative disorder that usually has a rapidly fatal outcome. Overall mortality is 70%-85%, and median survival is only 8-14 months. No standard or optimal therapy for MCD has been established.

Case: A 49-year-old man with HIV infection presented with 1-week duration of low-grade fever, night sweats, left sided abdominal pain, and generalized weakness. Physical examination revealed a supraclavicular, anterior cervical and axillary lymphadenopathy, and splenomegaly. Excisional biopsy of the left axillary lymph node confirmed the diagnosis of an angiofollicular hyperplasia, or MCD, hyaline vascular type with CD20 positivity. Treatment included a combination of the chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with the monoclonal anti-CD20 antibody rituximab. The chemotherapy was administered in parallel with highly active antiretroviral therapy (HAART). At a 3-year follow-up, the patient remains in complete remission and his HIV parameters have normalized with continued HAART.

Conclusion: This is the second publication describing the use of an aggressive combination of chemotherapy with rituximab in HIV-associated MCD. For an HIV patient with MCD, an aggressive treatment with full CHOP regimen combined with monoclonal anti-CD20 antibody rituximab should be considered, and the use of HAART does not need to be discontinued.

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INTRODUCTION

Castleman's disease (CD) is a rare, lymphoproliferative disease that was first described in 1956 by Benjamin Castleman and his colleagues about a group of patients with localized hyperplastic mediastinal lymphadenopathy.[1] Three histopathologic subtypes of Castleman's disease were identified: the hyaline vascular variant, the plasma cell variant, and the mixed subtype.[2] Hyaline vascular type is the most common variant. Clinically, patients with CD are classified according to either of 2 presentations: unicentric (UCD), which is a localized, or multicentric (MCD), which is a systemic disease manifested with generalized lymphadenopathy, organomegaly, and constitutional symptoms. Patients with UCD usually have a benign course and are highly curable through surgical resection. Those who are not surgical candidates can get a similar positive result from radiation therapy.[3] Patients with MCD can have variable clinical courses that can range from rapidly progressive to chronic persistent.[4]

MCD in human immunodeficiency virus (HIV)-infected patients is an aggressive form of lymphoproliferative disorder that usually has a rapidly fatal outcome. Overall mortality is 70%-85%, and median survival is 8-14 months.[5] Patients tend to be young and present with multiple systemic signs and symptoms. Symptoms include fever, hepatosplenomegaly, lymphadenopathy, weight loss, respiratory symptoms, and peripheral edema, while laboratory findings include anemia, pancytopenia, polyclonal hypergammagobulinemia, and elevated levels of C-reactive protein. Causes of death are usually fulminant infection, multi-organ failure, and associated malignancies such as Kaposi's sarcoma and lymphoma. The pathogenesis of CD is unclear, however; HIV-associated MCD is strongly linked with HHV-8 (Human Herpesvirus 8).[6] It is believed that

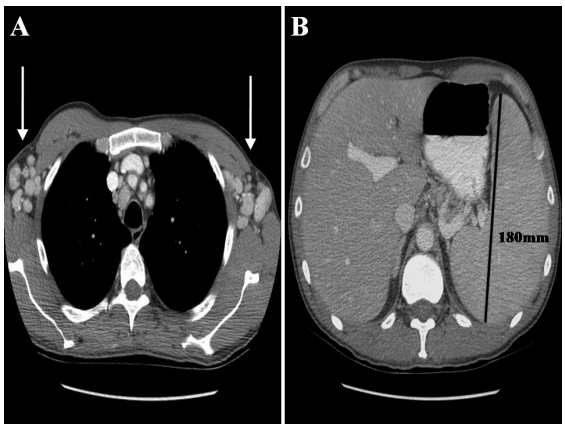

Figure 1. Computed tomographic (CT) scan of the chest and abdomen showing multiple bilateral axillary Lymphadenopathy (A) (white arrows) and splenomegaly (B) at presentation of Multicentric Castleman's disease (MCD).

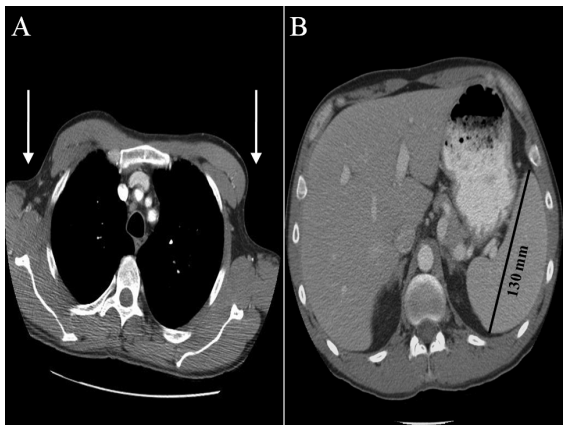

Figure 2. Computed tomographic (CT) scan of the body done 2 weeks after the last cycle of chemotherapy revealed a complete resolution of splenomegaly and lymphadenopathy in the neck, axilla, mediastinum, and retroperitoneum. The figure shows the complete resolution of bilateral axillary lymphadenopathy (white arrows) (A) and regression of splenomegaly (B).

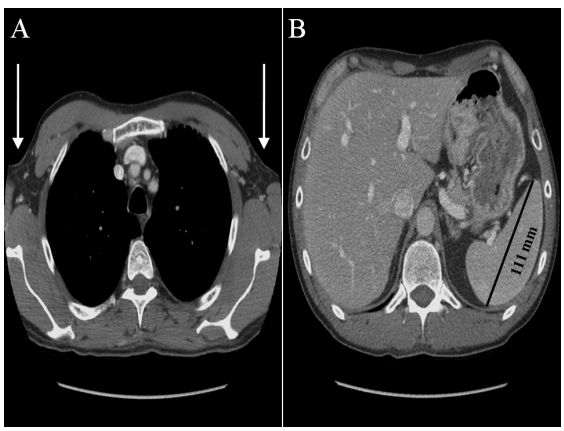

Figure 3. Computed tomographic (CT) scan at 3-year follow up showing normal findings in the chest (A) and further resolution of splenomegaly (B).

HHV-8 induces vascular endothelial growth factors, which subsequently stimulates the production of several cytokines. The cytokines, particularly IL-6, have been shown to be responsible for the histopathologic changes of the involved lymph nodes and the systemic inflammatory symptoms.[7-8] No standard or optimal therapy for HIV-associated MCD has been established. The role of concomitant use of highly active antiretroviral therapy (HAART) during active chemotherapy treatment is also not clearly defined. In this report, the authors share the treatment of a patient with HIV-associated MCD.

CASE REPORT

A 49-year-old man with HIV infection presented with low-grade fever, night sweats, left sided abdominal pain, and generalized weakness with a 1-week duration. The patient was diagnosed with HIV approximately 7 years before the onset of MCD symptoms. A community physician treated him with HAART. (The specific combination was unknown to the researchers in this study.) Apparently, the patient became less responsive to his regimen of antiviral agents and subsequently transferred his care to our hospital. He was started on a new HAART regimen consisting of viread, epivir, videx, visodex, and fuzeon. The CD4+ counts from his blood test were 244 and quantitative polymerase chain reaction (PCR) for HIV was >400,000 copies per ml at the diagnosis of MCD. Physical examination revealed a multiple bilateral anterior cervical, supraclavicular, and axillary lymphadenopathy, the largest measuring 3 cm. The liver was not enlarged but the spleen was palpable at the left subcostal margin. There was no evidence of Kaposi sarcoma lesions.

Laboratory tests showed normocytic anemia and normal white blood counts with differential. Liver function test and electrolytes were within normal limits. Qualitative study of the patient sera showed the presence of anti-human herpes virus-8 (HHV-8) antibodies and HHV-8 DNA. Computed tomographic (CT) scan of the chest, abdomen, and pelvis revealed multiple enlarged lymph nodes in the neck, axilla, mediastinum, retroperitoneum, as well as the presence of markedly enlarged spleen (Figure 1). An excisional biopsy of the left axillary lymph node confirmed the diagnosis of an angiofollicular hyperplasia or MCD, hyaline vascular type with CD20 positivity. The patient then received a combination chemotherapy (CHOP) composed of cyclophosphamide, doxorubicin, vincristine, and prednisone together with the monoclonal anti-CD20 antibody rituximab (CHOP-R). The dose of CHOP-R

regimen was cyclophosphamide at 750 mg/m^2, doxorubicin at 50 mg/m2, vincristine at 1.4 mg/m^2 (maximum 2 mg), and prednisone at 100 mg daily for 5 days. Rituximab was given at 375 mg/m^2 on the same day prior to the CHOP-R regimen. Treatment was repeated every 21 days for a total of 6 cycles. The chemotherapy was administered in parallel with HAART; the patient experienced no major adverse events except for the development of 1 episode of neutropenic fever, which was resolved with intravenous antibiotics. Repeat CT scan of the body 2 weeks after the last cycle of chemotherapy revealed a complete resolution of splenomegaly and lymphadenopathy in the neck, axilla, mediastinum, and retroperitoneum (Figure 2). At a 3-year follow-up, the patient remains in complete remission (CR) (Figure 3), and his HIV parameters have normalized with continued HAART.

DISCUSSION

Over the past few years, a newly diagnosed HIV-associated MCD has been recognized as an aggressive form of disease in which most of the patients develop progressive lymphadenopathy and B-symptoms, usually with a rapidly fatal course. The treatment outcomes of MCD in HIV patients are generally unfavorable.

Management of MCD involves mainly systemic chemotherapy; the only exception is splenectomy for temporary symptomatic relief.[3] Steroids have been used with about a 60% response rate, but no durable remission is reported.[9] Use of neutralizing antibodies against interleukin-6 (IL-6) or monoclonal antibody blocking the IL-6 receptor has demonstrated some clinical efficacy but again with no durable response.[10] Single agent chemotherapy with cladribine induced durable CR, but it was found to accelerate its transformation to highly aggressive non-Hodgkin's lymphoma (NHL).[11] Intensive treatment with full CHOP regimen has been tested in the past, but only a few cases of long-term remission have been reported.[12] Monoclonal anti-CD20 antibody rituximab alone was shown to induce durable CR in some MCD patients.[13]

Optimal therapy for HIV-associated MCD is not well defined; no double-blind, randomized prospective studies have been conducted to compare different therapies. Because CD20 is expressed by HIV-associated MCD lymphoma cells, anti-CD20 monoclonal antibody may be of interest for the management of HIV-associated MCD. Recently, CHOP-R has become the standard treatment for aggressive NHL. This combination of chemotherapy with monoclonal antibody regimen has shown a better remission rate and event-free survival than CHOP regimen alone in NHL.[14] More recently, 4 patients with HIV-associated MCD were successfully treated with CHOP-R.[15] Since HIV-associated MCD is a form of systemic aggressive lymphoproliferative disease that also demonstrates typical B cell markers, including CD20, this study suggests CHOP-R would be effective in this poor-risk patient population. In this case report, our patient was given an intensive chemotherapy regimen, CHOP-R, which resulted in rapid resolution of clinical symptoms, generalized lymphadenopathy, and splenomegaly. The treatment was also demonstrated to be safe and well tolerated with only 1 significant side effect (neutropenic fever). Although a previous report suggested that initiation of HAART could lead to a worse outcome in MCD, this remains to be confirmed.[16] The patient in this study was able to continue HAART throughout the intensive chemotherapy treatment without any major complications. This is the second publication about the use of the aggressive combination of chemotherapy with rituximab in HIV-associated MCD.

In conclusion, for HIV patients who present with MCD, an aggressive treatment with full CHOP regimen combined with monoclonal anti-CD20 antibody rituximab should be considered, while the use of HAART does not need to be discontinued. This case report provides some useful observation on the successful application of intensive chemotherapy in addition to HAART in HIV-associated MCD.

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