Complete Remission in 4 Patients With Human Herpesvirus 8–Associated Multicentric Castleman Disease Using Rituximab and Liposomal Doxorubicin, a Novel Chemotherapy Combination

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Introduction

Plasmablastic-type multicentric Castleman disease (PMCD) is a rare, aggressive lymphoproliferative disorder first described by Frizzera and colleagues in 1983.[1] Today, the disease is most commonly diagnosed in individuals infected with human immunodeficiency virus (HIV) type 1. It has been shown that PMCD is associated with Kaposi sarcoma, and a majority of patients with both conditions are infected by human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma–associated herpesvirus.[2-4] The diagnosis is based on clinical, pathologic, and laboratory findings. The common clinical course is characterized by recurrent attacks of fever, generalized lymphadenopathy, fatigue, splenomegaly, hepatomegaly, and anemia. The pathologic examination of involved lymph nodes or spleen frequently shows an increased number of follicles, some of which have atrophic, hyalinized germinal centers, increased vascularity, and sheets of plasma cells within the interfollicular areas. A variable number of so-called plasmablasts, from scattered perifollicular cells to overt lymphoma, can be identified by immunohistochemical staining (IHC) with HHV-8. We have recently showed that in a significant proportion of these cases, the same cells are coinfected with Epstein-Barr virus (EBV).[5] Coexistent Kaposi sarcoma is often present in lymph nodes involved by PMCD or elsewhere. The initial disease can be self-limited; however, the prognosis is usually poor and most patients die with active PMCD or progress to HHV-8–associated non-Hodgkin lymphoma (NHL) within months.[6]

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A standard therapy for patients with PMCD has yet to be established. Studies have examined various single or combined chemotherapy regimens, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), etoposide, and vinblastine.[7-10] Although low-dose, single-agent therapies have been shown to be effective initially, there is a high recurrence rate with withdrawal of therapy.[11] The use of various antiviral therapies on PMCD in the HIV-positive population has been described; such treatments include highly active antiretroviral therapy (HAART),[12] ganciclovir,[13] cidofovir,[14] foscarnet,[15] and anti–IL-6 therapy.[16] The antiretroviral and antiherpesvirus therapies have led to regression of Kaposi sarcoma; however, the effectiveness of these treatments on PMCD is not clear.

Several studies and case reports have shown rituximab (Rituxan, Genentech; a monoclonal CD20+ B-cell antibody), which targets HHV-8 infected plasmablasts in the mantle zone, to be highly effective.[14,17-25] We report the successful treatment of 4 patients with HIV-related PMCD, using a combination of rituximab and liposomal doxorubicin.

Case 1

A 55-year-old man with a 10-year history of HIV infection presented to the emergency department with a several-week history of fatigue, generalized malaise, decreased appetite, weight loss of 15–20 pounds, and syncope. Physical examination showed fever (100°F), a distended abdomen with hepatosplenomegaly, and axillary lymphadenopathy. He had been on antiretroviral therapy until 2 weeks prior to onset of symptoms. Significant laboratory findings included anemia (hemoglobin, 8.2 g/dL), elevated white blood cell count (11.52 10^3/uL), thrombocytopenia (67 10^3/uL), low CD4+ T-cell count (95.50 T cells/uL) and CD4/CD8 ratio of 0.15. Imaging studies showed bilateral axillary adenopathy; mediastinal, perisplenic, peripancre-

atic, retroperitoneal, and inguinal adenopathy up to 4.1 cm; bilateral pleural effusion; and ascites.

An excised left axillary lymph node showed hyaline vascular changes in follicles associated with HHV-8–infected plasmablasts in the mantle zones, as demonstrated by IHC. The lymph node also showed capsular involvement by Kaposi sarcoma. Flow cytometric analysis failed to reveal any monoclonal B-cell or aberrant T-cell population.

The patient received combination chemotherapy with rituximab and liposomal doxorubicin and achieved a good clinical response. His treatment was also complemented with the use of valganciclovir, which had to be discontinued after a short period due to neutropenia that required the use of filgrastim. Complete recovery of the blood counts allowed chemotherapy to continue. The patient received a total of 6 cycles of treatment, with improvement in symptoms as well as improvement of adenopathy and hepatosplenomegaly. The patient has been off chemotherapy for more than 2 years and has been maintained on HAART only.

Case 2

A 40-year-old man with a history of advanced untreated AIDS presented with a 2-month history of progressive fever, lymphadenopathy, headache, weight loss, anemia, and diarrhea. The laboratory findings included high viral load (2,520 copies/mL), a decreased normal CD4 to CD8 ratio with decreased absolute CD4+ T cells (104 T cells/uL) and CD8+ T cells (117 cells/uL), and anemia. Computed Tomography (CT) scans demonstrated mediastinal and axillary lymphadenopathy. An excised left axillary lymph node showed the features of PMCD, including sheets of polyclonal plasma cells (by kappa and lambda IHC), reactive follicles with hyalinization, increased vascularity, and associated HHV-8 immunoreactive plasmablasts within the mantle zones. Cutaneous examination demonstrated Kaposi sarcoma of the extremities, which was biopsied and confirmed. The patient was treated with rituximab for 4 cycles, liposomal doxorubicin, and HAART therapy. He achieved complete resolution of his symptoms, lymphadenopathy, and skin lesions. Seven months later, he received a second course of doxorubicin for recurrent Kaposi sarcoma without evidence of PMCD. He remains in remission at 3 years of follow-up.

Case 3

A 32-year-old man with no medical history presented to the emergency department with complaints of intermittent cough, fever with chills, and night sweats over a 1-month period, plus a weight loss of 17 pounds. Physical examination revealed enlarged right neck lymph nodes and splenomegaly. Radiologic studies demonstrated multiple retroperitoneal, pelvic, and inguinal lymphadenopathies, and bilateral pleural effusions.

At the time of admission, significant laboratory findings included a CD4 T-cell count of 224 cells/uL, high viral load (2,210 copies/mL), and pancytopenia. Excision of a right neck lymph node showed hyperplastic follicles, increased large plasmablastic cells within the mantle zones, and sheets of plasma cells in the interfollicular areas consistent with PMCD. The large plasmablasts were reactive with HHV-8 by IHC. Capsular involvement of the lymph node by Kaposi sarcoma was also present.

A thoracentesis performed during the hospital course revealed atypical lymphoid cells immunoreactive with HHV-8 and CD138 diagnostic of primary effusion lymphoma. The patient was started on treatment with rituximab and liposomal doxorubicin, with a total of 8 cycles given, with a good response for 6 months. Thereafter, the effusions recurred without response to chemotherapy.

Case 4

A 26-year-old man with a 1-year history of HIV infection presented with a 1-week history of abdominal pain, fever, and weakness associated with a dry cough. The patient was on HAART therapy for HIV infection prior to the last admission. Physical examination showed multiple purpuric lesions in the skin compatible with Kaposi sarcoma and generalized lymphadenopathy. Radiologic studies demonstrated hepatomegaly and multiple enlarged mesenteric and axillary lymph nodes.

Laboratory studies showed significantly decreased CD4+ T-cell population (20 cells/uL), decreased CD4/CD8 ratio (0.07), a viral load of 532/mL, anemia, and thrombocytopenia.

An excisional lymph node biopsy from the left neck region was performed, showing features diagnostic of PMCD with associated Kaposi sarcoma. Treatment was initiated with rituximab and liposomal doxorubicin, as well as valganciclovir. It was complicated by neutropenic fever, which required the patient to be hospitalized and given intravenous antibiotics. The valganciclovir was discontinued, and the patient was started on filgrastim. Treatment was continued without complication for a total of 8 cycles. His HAART regimen was started, and the patient remains without lymphadenopathy or symptoms for more than 3 years since the time of diagnosis.

Results and Discussion

We describe 4 patients with HIV-associated PMCD. Three patients also had coexistent Kaposi sarcoma. We have observed complete remission of PMCD with no

clinical symptoms in all patients following rituximab plus doxorubicin chemotherapy, with a follow-up ranging from 6–38 months.

Previous studies showed that single-agent chemotherapies are initially effective, but most patients will relapse within a short period. Long-term survival has been reported as extremely poor, with most patients dying from the disease within a year after the diagnosis (reports range from 70–85% mortality at 8–14 months).

In our experience, the treatment was extremely well tolerated, with the patients able to begin new HAART regimens allowing for new virologic response with remission of the PMCD. Most of the patients, however, had persistently low CD4 counts. PMCD is a rare HHV-8– associated lymphoproliferative disorder that is usually seen in men with HIV infection.[1-3] It is an aggressive disorder, with diffuse lymphadenopathy, constitutional symptoms, and a usually fatal course. Since the discovery of HAART, survival has significantly increased in the HIV-infected population. On the other hand, as a result of viral effects and a suppressed immune system, this patient population is prone to aggressive diseases, including PMCD, Hodgkin lymphoma, and NHL. Multiorgan failure and progression to an overt aggressive HHV-8–associated NHL are the major causes of death in patients with PMCD.[6] Although HAART therapy has an effect of controlling HIV infection and progression to Kaposi sarcoma, its role in PMCD is not established. Aaron and coworkers[12] described 7 patients with HIV-associated PMCD who received HAART therapy. Chemotherapy was necessary for 6 patients in order to reduce lymphoplasmacytic proliferation and symptoms. Immune reconstitution was observed in 5 patients. However, patients in this study required long-term chemotherapy to prevent relapses of PMCD.

Coexistent Kaposi sarcoma is common due to frequent HHV-8 infection, as in 3 of our cases. With the well-established viral etiology, several studies sought to determine the effectiveness of anti–HHV-8 treatment of the disease.[13-16] However, there are reported cases of treatment failure with antiviral and anti-IL6 therapies in patients with PMCD.[14,26] Although the antiviral therapies are effective in controlling the viral load, systemic chemotherapy is frequently required to treat PMCD symptoms and avoid the possible progression to NHL.

Systemic chemotherapy is required for the treatment of PMCD. Several authors reported studies and cases of successful treatment of PMCD with combined or single-agent chemotherapies.[7-10] Although combined chemotherapies are effective, toxicity and poor tolerance remain an issue. On the other hand, single-agent therapy with rituximab has been shown to be effective in controlling the disease.[18-23] However, due to relapses of PMCD symptoms, life-long use is usually required. Marcelin and associates[17] described 5 patients treated with rituximab alone; 3 responded to therapy very well, but 2 died quickly while receiving therapy. Buchler and colleagues[27] also reported a failure with treatment consisting of rituximab only.

In the current report, we describe a novel combined chemotherapy consisting of rituximab and doxorubicin. All 4 patients received the chemotherapy infusion at the time of the diagnosis. The follow-up period ranges from 6–38 months. All 4 patients tolerated the chemotherapy well and remain free of PMCD to date, with complete resolution of lymphadenopathy. One patient has since relapsed with primary effusion lymphoma. On the basis of these results, a formal prospective study may be warranted in HIV-associated PMCD.

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Review

What Is the Best Treatment for HIV-Associated Multicentric Castleman Disease?

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Multicentric Castleman disease (MCD) is an infrequent lymphoproliferative disorder that presents with assorted symptoms that include pyrexia, anemia, and widespread lymphadenopathy. The diagnosis requires a distinctive histologic pattern with large abnormal plasmablasts within the mantle zones of involved lymph nodes.[1,2] These plasmablasts express high levels of cytoplasmic IgM immunoglobulin, which is Λ-light chain restricted immunoglobulin.[2,3] The diagnosis of plasmablastic MCD is nowadays most frequently made in association with human immunodeficiency virus (HIV) infection. Although a few cases of MCD were diagnosed during the first decade of the HIV pandemic,[4] it received little attention until the identification of Kaposi sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8). This is because KSHV infects the plasmablasts in MCD, which is detectable by immunohistochemical staining for KSHV-associated latent nuclear antigen-1 (LANA-1) in these cells.[2,5] Thus, the histopathologic identification of MCD has become more straight-forward in recent years, and awareness of the diagnosis has heightened amongst clinicians. Moreover, unlike Kaposi sarcoma, the incidence of MCD appears to be rising, although case identification bias may also play a role.[6]

The natural history of MCD is that of a relapsing and remitting illness, so it was necessary to devise a system to monitor the activity of the disease once a histologic diagnosis is established,[7] because without a measure of disease activity, it is impossible to determine the efficacy of therapeutic interventions. The French Agence Nationale de Recherche sur le SIDA 117 CastlemaB trial group have described criteria that define an attack of MCD, and these are being increasingly adopted in clinical practice.[8] Patients require a fever, raised serum C-reactive protein, and 3 of 12 additional clinical findings (Table 1). This scheme does not include detectable KSHV viremia, whether measured in the plasma or peripheral blood mononuclear cells; however, studies have shown that it is almost always detectable in the blood of patients with active MCD and that levels correlate with symptomatic disease.[9-15] In our recent series, quantitative measurement of plasma KSHV DNA was available at MCD diagnosis for 45 patients. All had detectable plasma KSHV DNA, and the median $\log_{10}$ plasma KSHV DNA load was 5.3 copies/mm^3 (range 2.3–8.7).[16] Thus, detectable plasma KSHV DNA may be considered as an additional parameter to add to the diagnostic criteria.

Similarly, a gold-standard approach to clinical management has yet to be formally established, although there is increasing support for the use of rituximab-based

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Table 1. Definition of an HIV MCD Attack[8]

Fever
At least 3 of the following symptoms:
Peripheral lymphadenopathy
Enlarged spleen
Edema
Pleural effusion
Ascites
Cough
Nasal obstruction
Xerostomia
Rash
Central neurologic symptoms
Jaundice
Autoimmune hemolytic anemia
Increased serum C-reactive protein level >20 mg/L in the absence of any other etiology

HIV=human immunodeficiency virus; MCD=multicentric Castleman disease.

approaches.[17] The introduction of rituximab into the algorithm of care for HIV-associated MCD has led to a dramatic improvement in survival. A systemic review of 70 published cases up to 2007 reported a fatality rate of 47%, with a median follow-up of 12 months.[18] This analysis includes the previously reported largest series from Paris of 20 patients, which recorded a median survival of just 14 months.[19] In contrast, in our series of 49 rituximab-treated patients, the 2-year and 5-year overall survival rates were 94% and 90%, respectively, compared to 42% and 33%, respectively, for 12 patients diagnosed prior to the adoption of rituximab-based protocols.[16] The case series published here of 4 patients treated with rituximab and liposomal doxorubicin adds to the growing literature supporting the use of rituximab-based therapy for this disease.[20]

Which patients may be treated with rituximab alone and which patients require chemotherapy and rituximab remains uncertain, but a risk stratification based on performance status and end organ involvement has been widely adopted.[17] This was based in part upon 2 series that described patients with aggressive HIV MCD and multi-organ failure who failed to respond to rituximab monotherapy.[21-23] Peker and colleagues treated all 4 patients with both rituximab and liposomal anthracycline chemotherapy.[20] Two patients had autoimmune cytopenias and pulmonary involvement, and all 4 had concomitant KSHV-related malignancies: 3 had Kaposi sarcoma and 1 had primary effusion lymphoma (PEL). The presence of Kaposi sarcoma may itself justify the addition of the liposomal anthracycline, since rituximab frequently induces a flare-up of Kaposi sarcoma.[8,16,24]

The coincidental diagnosis of MCD and PEL in 1 case is unsurprising, as there is a well-established association between MCD and lymphoma. Indeed, in a recently published series including 17 lymphomas arising in patients with MCD, PEL was the most frequent subtype of lymphoma diagnosed.[25] The very high risk of lymphoma was described in an early (pre-rituximab) prospective cohort series of 60 patients, with a median follow-up of 20 months. In this series, 14 patients developed lymphomas. The authors estimated an incidence of lymphoma in patients diagnosed with HIV-associated MCD of 101 per 1,000 patient-years.[26] However, since the era of rituximab-based treatment, this very high lymphoma incidence has declined.[16,25]

The improvements in diagnostic techniques, coupled with the clearer definition of disease activity, will enable clinicians to further study the optimal therapy for this relapsing and remitting disease. Whilst most clinicians are confident that rituximab should be included in the therapy for HIV-associated MCD, the role of chemotherapy and the optimal choice of agent should be investigated in a clinical trial.

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