How I treat HIV-associated multicentric Castleman disease

Mark Bower[1]

[1]Department of Oncology, Chelsea & Westminster Hospital, London, United Kingdom

HIV-associated plasmablastic multicentric Castleman disease is an increasingly frequent diagnosis. Kaposi sarcoma herpesvirus is found in the monotypic polyclonal plasmablasts that characterize this disease. Unlike Kaposi sarcoma, the incidence does not correlate with CD4 cell count or use of highly active antiretroviral therapy. It is a relapsing and remitting illness, and diagnostic criteria are emerging that define disease activity based on the presence of a fever and raised C-reactive protein coupled with a list of clinical features. Treatment protocols increasingly stratify therapy according to performance status and organ involvement. I advocate rituximab monotherapy for good performance status patients without organ involvement and rituximab with chemotherapy for more aggressive disease. The success of antiherpesvirus agents in controlling active disease is limited, but valganciclovir may have a role as maintenance therapy in the future. (*Blood*. 2010;116(22):4415-4421)

Introduction

Benjamin Castleman originally described his eponymous disease in 1954.[1] Most of the patients he identified had asymptomatic localized mediastinal lymphadenopathy with follicular hyperplasia and capillary hyalinization.[2] During the 1960s, a new variant of Castleman disease was described that lacked hyalinization, had concentric sheets of plasma cells both surrounding the germinal centers and in the interfollicular space. It was associated with systemic manifestations[3] and became known as plasma cell variant of Castleman disease. More recently, a third subtype has been identified known as plasmablastic multicentric Castleman disease (MCD), which is multifocal, behaves more aggressively, and was first described in association with POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) or Crow-Fukase disease. In this variety, the mantle zones of involved nodes contain large abnormal plasma cells with prominent nucleoli and copious cytoplasm that have been named plasmablasts.[4,5] It is this form of plasmablastic MCD that is found with increased frequency in persons living with HIV infection,[6] and HIV-associated MCD (HIV MCD) is the focus of this review.

Although MCD occurs with a vastly increased incidence in people living with HIV infection, epidemiologic studies have demonstrated no correlation with CD4 cell count or the use of highly active antiretroviral therapy (HAART).[6] Indeed, a systematic review of all 72 cases of HIV MCD published up to 2007 found that 64% of the 48 patients diagnosed with MCD in the HAART era were already on HAART at the time of MCD diagnosis.[7] Moreover, there is also no correlation between the risk of relapse of HIV MCD and CD4 cell count.[8-12] In these respects, MCD resembles a number of non–AIDS-defining malignancies and, like them, the incidence of HIV MCD is not declining and has been reported to be rising, although case identification bias may also play a role.[6]

A link between MCD and Kaposi sarcoma (KS) was found in a number of early case reports, and the 2 diseases coexisted in 72% of HIV MCD patients in the systematic review[7] and 54% of 56 patients at Chelsea & Westminster Hospital, London (Table 1). In addition, biopsy specimens frequently demonstrate both diseases in the same lymph node.[13] After the identification of KS herpesvirus (KSHV), which is also known as human herpesvirus 8 (HHV8), this virus was found to be present in the plasmablasts in all cases of HIV MCD.[14,15] Furthermore, high levels of KSHV DNA may be quantified in peripheral blood mononuclear cells or plasma in patients with symptomatic active HIV MCD.[8,9,11,16-18]

Diagnosis and investigations

The diagnosis of HIV MCD is based on the presence of histopathologic features; however, because of the remitting and relapsing nature of MCD, clinical correlates should also be present to confirm a diagnosis of active disease.[19] The diagnosis can only be established with histologic confirmation, and this should be aggressively pursued in patients with clinical findings in keeping with HIV MCD. The histologic characteristics of plasmablastic MCD include the presence of plasmablasts within the mantle zone of B-cell follicles, and immunohistochemical staining reveals KSHV-associated latent nuclear antigen-1 in these cells[5,20] (Figures 1-2). The plasmablasts express high levels of cytoplasmic immunoglobulin, that is always IgMλ restricted.[5,21] Despite the expression of monotypic IgMλ, the plasmablasts have polyclonal immunoglobulin gene rearrangements[21] and the KSHV episomes are also polyclonal.[22]

The diagnosis of active HIV MCD requires not only the histopathologic findings described but also clinical features of active disease. Although there are no evidence-based "gold standard" criteria for establishing a diagnosis of active HIV MCD, the French Agence Nationale de Recherche sur le SIDA 117 CastlemaB trial group recognizing this deficiency have described criteria to define an attack of HIV MCD.[23] These are shown in Table 2. Patients require a fever, a raised serum C-reactive protein more than 20 mg/L in the absence of any other cause, and 3 of 12 additional clinical findings. Unfortunately, the incidence of each of these criteria is not described in the CastlemaB trial and have not

Submitted July 6, 2010; accepted July 29, 2010. Prepublished online as *Blood* First Edition paper, August 5, 2010; DOI 10.1182/blood-2010-07-290213.

all been prospectively collected in our cohort of patients. Interestingly, although both clinical and radiologic pulmonary manifestations appear to be common in HIV MCD,[24,25] localized central nervous system involvement by MCD, which may mimic meningioma,[26] has not been described in the context of HIV MCD. Similarly, the combination of peripheral neuropathy and monoclonal paraprotein with or without other features of POEMS is well recognized in plasma cell MCD but is only rarely seen in patients with HIV.[27] Nevertheless, the combination of pyrexia, lymphadenopathy, and splenomegaly with a raised C-reactive protein should alert clinicians to the possibility of this diagnosis and prompt investigations.

The only additional investigation that is of clinical value in aiding diagnosis is quantification of KSHV DNA levels in the plasma or peripheral blood mononuclear cells. Numerous published studies have shown that KSHV DNA is almost always detectable in the blood of patients with active HIV MCD and that levels of KSHV DNA correlate with symptomatic disease.[8,9,11,16-18,28] In contrast, KSHV DNA is only detectable in a minority of patients with KS, and the levels of KSHV DNA are significantly lower.[6,28] Marcelin et al went as far as to suggest that, in a patient with KS, a very high blood level of KSHV DNA may point to a diagnosis of HIV MCD,[28] and I agree with them. Although some groups have studied KSHV DNA levels in peripheral blood mononuclear cells and others have measured plasma levels, it appears that these correlate well,[29] so I use plasma levels that are cheaper to assay. Analysis of matched plasma KSHV DNA measurements and C-reactive protein estimations in patients with HIV MCD suggest that there is little difference between these 2 parameters in predicting disease activity (Figure 3).

Occasionally, patients present with clinical symptoms in keeping with HIV MCD, elevated blood KSHV DNA levels, and peripheral lymphadenopathy, but an initial lymph node biopsy fails

Table 1. Clinical features at HIV MCD diagnosis recorded in the systematic review of all published cases up to 2007 and in patients treated at Chelsea & Westminster Hospital, London

	Systematic review	CWH series
No. of patients	72	56
Median age, y (range)	40 (21-67)	42 (23-69)
Symptoms, no (%)		
Fever	72/72 (100)	55/56 (98)
Lymphadenopathy	69/72 (96)	56/56 (100)
Splenomegaly	62/72 (86)	51/55* (93)
Hepatomegaly	45/72 (63)	36/56 (64)
Pulmonary signs or symptoms	25/72 (35)	27/56 (48)
Edema	21/72 (29)	6/56 (11)
Ascites	4/72 (6)	2/56 (4)
Kaposi sarcoma	52/72 (72)	30/56 (54)
Median CD4 cells/mm^3 (range)	160 (1-1050)	234 (41-1429)

Data are from Mylona et al.[7]

*One patient had had a splenectomy for idiopathic thrombocytopenic purpura before HIV MCD diagnosis.

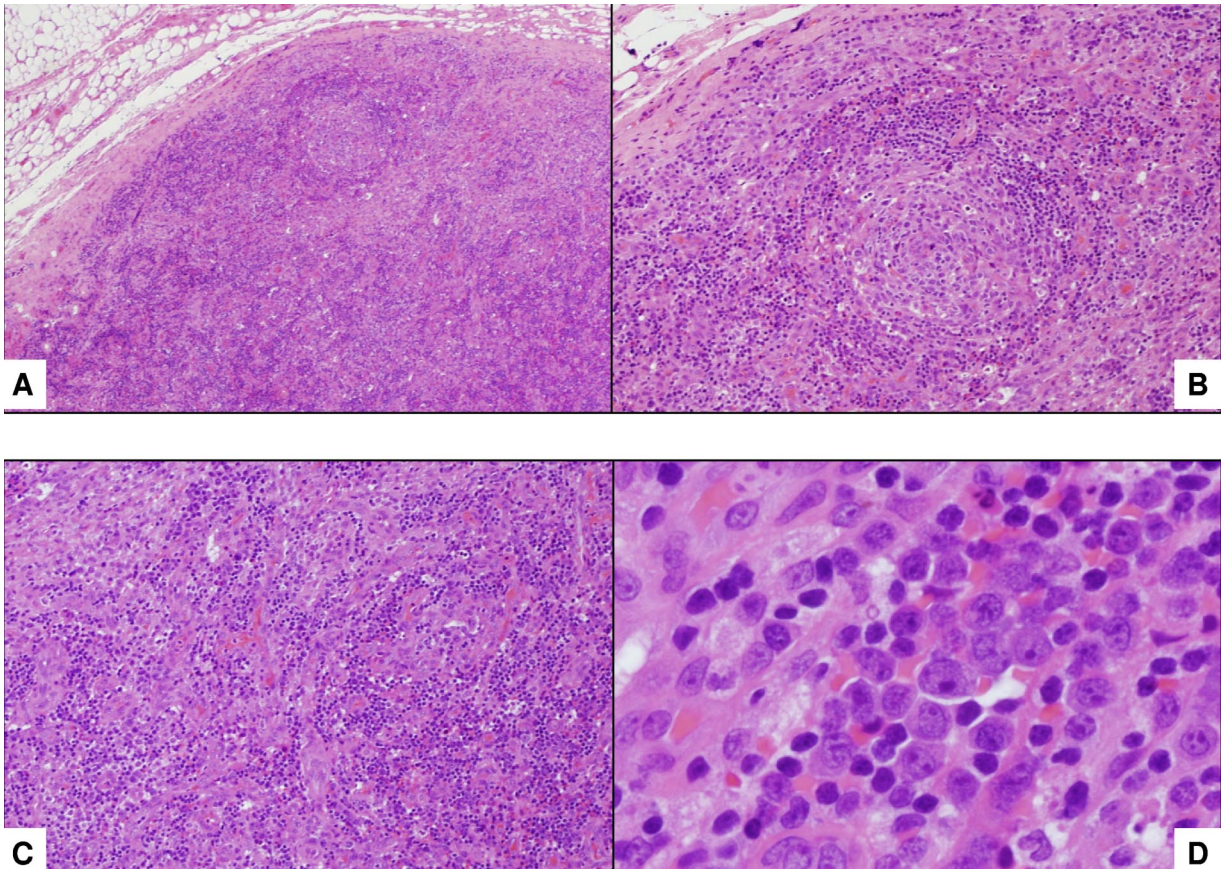

Figure 1. Histopathologic features of HIV MCD. (A) Lymph node shows a small follicle with relatively atrophic germinal center and mildly expanded mantle zone. The tissue outside the follicle (interfollicular area) is rich in vessels and plasma cells (hematoxylin and eosin; original magnification ×40). (B) Higher magnification of the follicle, including the mantle zone (hematoxylin and eosin; original magnification ×100). (C) Higher magnification of the interfollicular area (hematoxylin and eosin; original magnification ×100). (D) Within the mantle zone, there are several large cells with nucleoli, the so-called "plasmablasts" (hematoxylin and eosin; original magnification ×600).

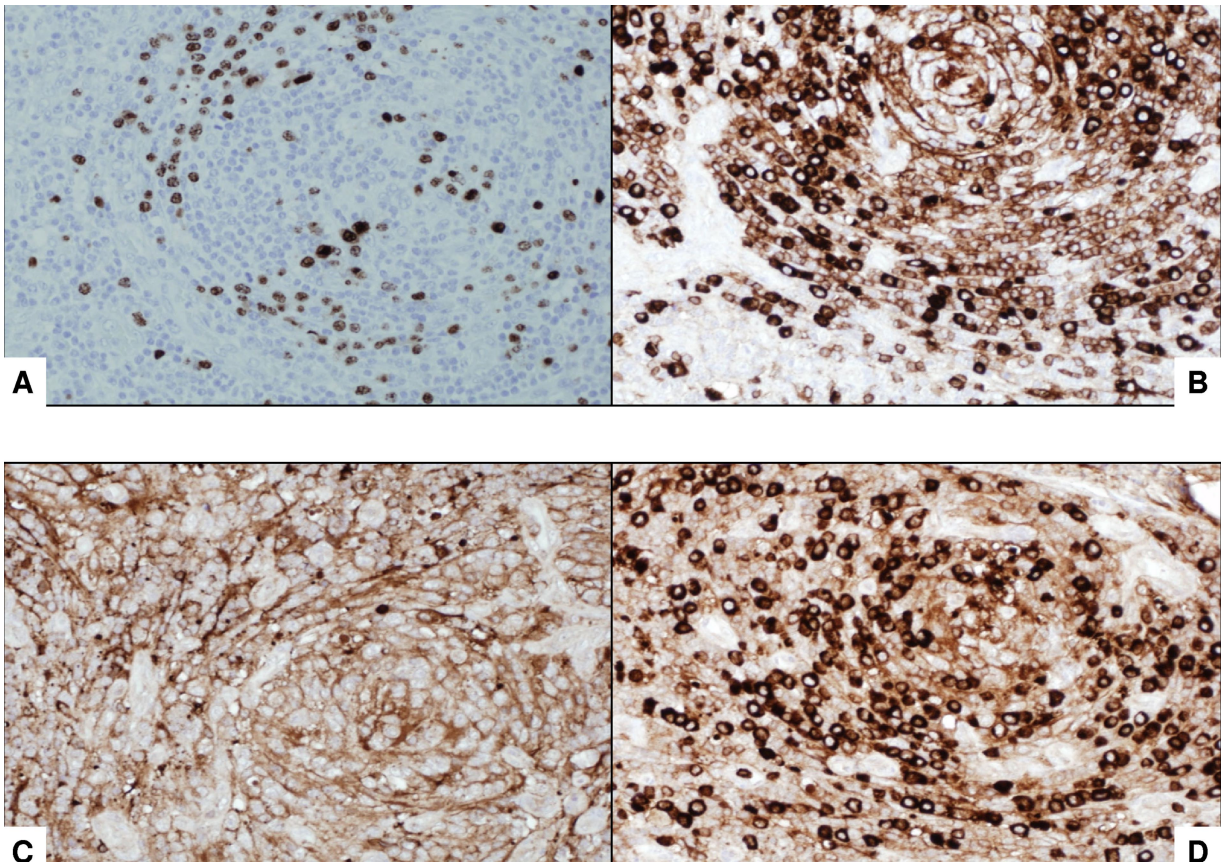

Figure 2. Immunocytochemical features of HIV MCD plasmablasts. (A) On immunohistochemistry, the large lymphoid cells with nucleoli, the so-called "plasmablasts," harbor HHV8 virus as demonstrated by the presence of HHV8–latent nuclear antigen-1. The cells express IgM (B) and lambda light chain (D) and are negative for kappa light chain (C). All original magnifications are ×600.

to confirm the diagnosis. In these circumstances, I advocate undertaking an ^{18}-fluorodeoxyglucose positron emission tomography scan. HIV MCD is fluorodeoxyglucose avid, and this may help in choosing which gland to biopsy next.[30]

Plasma cytokines, particularly interleukin-6 and interleukin-10, have been implicated in the pathogenesis of HIV MCD[31-33] and have been shown to rise and fall with disease activity.[9,34-37] However, their role in routine clinical care remains to be established.

Clinical management

As with many rare and relatively newly recognized illnesses, a standard approach to clinical management has yet to be formed, and the evidence for much of the treatment given is based on small case series, open-label trials, and personal experience. Numerous

Table 2. Definition of an HIV MCD attack

Feature
1. Fever
2. 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
3. Increased serum CRP level (> 20 mg/L) in the absence of any other etiology

Data are from Gerard et al.[23]
CRP indicates C-reactive protein.

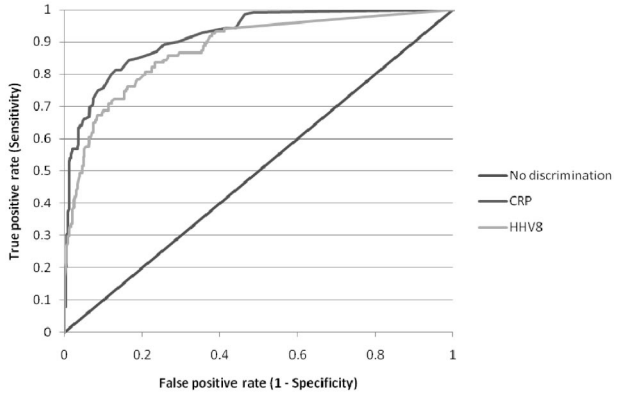

Figure 3. Receiver operating characteristic curve of serum C-reactive protein and plasma KSHV DNA in distinguishing active or remission of HIV MCD. A total of 471 matched C-reactive protein and KSHV DNA samples were available from 45 patients with HIV MCD either in clinical remission (332) or during an active episode (139) of HIV MCD.

approaches, including treatment with antiretrovirals, antiherpesvirus agents, single-agent and combination chemotherapy, and monoclonal antibody therapy, have all been advocated. There appears to be a consensus emerging that rituximab with or without etoposide chemotherapy is appropriate therapy for attacks of HIV MCD and that there may be a role for either rituximab or the antiherpes agent valganciclovir as maintenance therapy.[38]

Rituximab

Early series reported the use of cytotoxic chemotherapy for HIV MCD; and although remission rates were high, in the largest series treated before the introduction of HAART, 14 of 20 patients died and the median survival was only 14 months.[39] The introduction of HAART and the addition of rituximab to the therapeutic options have resulted in a change in approach and improved outcomes. Although KSHV-infected plasmablasts frequently do not express high levels of CD20,[40] numerous case series and 2 open-label studies have used rituximab. One study of 21 patients with newly diagnosed HIV MCD reported a radiologic response rate of 67%, and the overall and disease-free survival rates at 2 years were 95% and 79%, respectively.[41] The second prospective study enrolled 24 patients with HIV MCD who were classified as chemotherapy-dependent. Rituximab induced a sustained remission of 1-year duration in 17 of 24 (71%) patients and the 1-year overall survival was 92%.[23] Both trials reported an exacerbation of KS in patients who had KS at enrollment despite patients receiving HAART, and it is my policy to treat the KS with liposomal anthracyclines. However, 2 case series have described patients with aggressive HIV MCD and organ failure who failed to respond to rituximab monotherapy.[42-44] For this reason, I now follow a stratified approach to the management of HIV MCD, reserving rituximab monotherapy for patients without evidence of organ failure and using chemotherapy with rituximab for those with aggressive disease based on poor performance status (Eastern Cooperative Oncology Group Performance Status > 1) and evidence of organ damage, usually lung involvement, hemophagocytic syndrome, or severe hemolytic anemia.

Chemotherapy

Both single-agent and combination cytotoxic chemotherapy has been used in a number of patients with HIV MCD with various success.[10,12,39,43,45-55] Although rapid resolution of symptoms has been reported in patients with active disease, relapses occur frequently and the progression-free survival is often brief. A strategy using maintenance oral etoposide (100-200 mg/m^2, weekly) has been adopted in France.[23,39] However, the oncogenicity of etoposide, in particular the risk of secondary acute myeloid leukemia,[56] limits this approach. The encouraging results observed with rituximab monotherapy in patients with less aggressive HIV MCD have led to a combined immunochemotherapy approach in aggressive HIV MCD using rituximab with combination chemotherapy[27,57] or rituximab with single-agent etoposide.[38] The optimal chemotherapy has not been established; and although several case reports described successful treatment of HIV MCD with the cyclophosphamide, doxorubicin, vincristin, prednisone (CHOP) regimen without rituximab,[48,50,52,55] there is greater experience with rituximab and etoposide. I have used this approach combining weekly rituximab (375 mg/m^2) with intravenous etoposide (100 mg/m^2) for 4 weeks in 13 patients stratified as having aggressive HIV MCD with an overall survival at 2 years of 85%. In contrast, 23 patients with low-risk HIV MCD have been treated with rituximab monotherapy (375 mg/m^2 weekly for 4 weeks) and the overall survival at 2 years is 100%.

HAART

The algorithm of care for HIV MCD includes the use of HAART, although it is uncertain whether this contributes to control of the HIV MCD. First, epidemiologic evidence suggests that neither nadir CD4 cell count nor use of HAART influences the risk of HIV MCD.[6] Second, a significant number of patients develop HIV MCD, whereas their HIV is well suppressed on HAART. The systematic literature review included 48 patients diagnosed with HIV MCD in the HAART era, of whom 64% were on HAART at the time of MCD diagnosis.[7] Our series includes 55 patients diagnosed with HIV MCD in the HAART era of whom 24 (44%) were on HAART at the time of MCD diagnosis and of those patients 20 (83%) had plasma HIV viral loads less than 400 copies/mm^3. The failure of HAART to control HIV MCD is also supported by case reports, which include a description of acute deterioration of MCD symptoms on starting HAART.[58-60] Nevertheless, it is my practice to ensure all patients diagnosed with HIV MCD are treated with HAART as well as rituximab with or without etoposide. This approach may limit both the decline in CD4 cell counts attributable to the chemotherapy and the reactivation of KS related to the immunotherapy. As with the management of HIV-associated lymphomas with chemotherapy, it is my practice to initiate opportunistic infection prophylaxis in patients with low CD4 cell counts or whose CD4 cell counts are probable to decline with chemotherapy.[61]

Antiherpesvirus agents

Several antiherpesvirus agents, including cidofovir, foscarnet and ganciclovir, have been reported to show activity against KSHV in vitro.[62] These agents have been studied in HIV MCD with limited success: 0 of 7 patients responded to cidofovir,[16,18,63] 2 of 4 patients achieved remission with foscarnet,[60,63-65] whereas ganciclovir and its oral derivative valganciclovir induced remission in 1 patient and reduced the frequency of relapse in a further 2 patients.[11] None of these agents achieved the impressive remission rates documented with rituximab in much larger studies.

Tocilizumab

In addition to rituximab, there is experience with another monoclonal antibody in MCD in patients who are HIV-seronegative. The contribution of high plasma levels of interleukin-6 (IL-6) to the symptomatology of HIV MCD, whether the IL-6 is derived from the host (hIL6) or KSHV virus (vIL6), has led to attempts to block this pathway. Tocilizumab is a humanized monoclonal antibody that targets the IL-6 receptor. In Japan 28 HIV-negative adults with MCD were treated in an open-label study and symptoms, lymphadenopathy and inflammatory markers all improved.[66] However, not only were these patients all HIV-seronegative, only 2 of 28 patients were seropositive for KSHV. It is disappointing that no studies in

HIV MCD have been conducted or reported using this monoclonal antibody, which is now marketed for refractory rheumatoid arthritis.

Response evaluation

The definition of attacks and hence the criteria for evaluating disease response to therapy have not been established for HIV MCD. Although the criteria for disease activity have been clarified in the CastlemaB study,[23] I remain uncertain whether it is best to evaluate response clinically, radiologically, biochemically, or virologically. For example, in the open label study of rituximab, the clinical symptoms resolved in 95%, 67% achieved a radiologic response by Response Evaluation Criteria in Solid Tumors criteria, the improvement in biochemical parameters varied from 100% (for resolution of anaemia) to 31% (for normalization of C-reactive protein), whereas cytokine levels such as IL-6 normalized in 89%, and 80% achieved undetectable plasma KSHV DNA viral loads.[41]

Relapse

HIV MCD is a relapsing and remitting illness; and although there has been little emphasis on second or subsequent line therapy, it is clear that relapse flares may occur at any CD4 cell count and are not prevented by good HIV control by HAART.[8-12] In my experience, one-fourth of patients with HIV MCD will have relapsed by 3 years of follow-up, and retreatment with rituximab have achieved second remissions.[67]

Maintenance therapy

Because there is an appreciable risk of relapse in HIV MCD that is not diminished by HAART, groups have explored the role of both rituximab and antiherpesvirus agents as maintenance therapy. The CastlemaB trial enrolled 24 patients who were chemotherapy dependent into a prospective open-label study of 4 infusions of rituximab at weekly intervals and cessation of the chemotherapy.[23] One year later, 71% were alive in stable remission and the overall survival rate was 92%. This result may encourage clinicians to consider maintenance rituximab therapy; however, 1 patient died of acute respiratory failure of undetermined origin. Similarly, the AIDS malignancy consortium trial 010 randomized patients with HIV-associated lymphoma to receive CHOP or R-CHOP (with 3-monthly maintenance rituximab). An excess of respiratory infection related deaths was recorded among patients in remission who received maintenance rituximab.[68] An alternative approach to maintenance therapy is offered by the oral antiherpes agent valganciclovir, and this has been adopted in some algorithms of care,[38] although there are limited published data to support this. In a double-blind placebo-controlled crossover trial, valganciclovir has been shown to reduce oropharyngeal shedding of KSHV in both HIV-seronegative and -seropositive persons.[69] I do not currently offer patients in remission maintenance therapy, although I think that the approach with valganciclovir looks the most promising option.

Follow-up

There are no clear guidelines for the follow-up of patients treated for HIV MCD. It is my practice to monitor patients at 3 monthly intervals with clinical examination and quantitative estimation of the plasma KSHV DNA. However, although the plasma KSHV DNA level correlates with symptomatic disease,[8,9,11,16-18,28] it is not clear that a rising level predicts relapse. Another important issue in the follow-up of patients with HIV MCD is the very high risk of non-Hodgkin lymphoma recorded in 2 published series. In a French series of 60 patients over a median follow-up of 20 months, 14 developed NHL and 11 of these lymphomas were associated with KSHV (6 plasmablastic and 3 primary effusion lymphomas).[70] Similarly, in an Australian series of 11 patients with HIV MCD with a median follow-up of 48 months, 4 developed lymphoma.[12] Although Eric Oksenhendler, whose group at Hôpital Saint-Louis in Paris has one of the largest cohort of patients with HIV MCD, has suggested that this risk may be declining since the introduction of HAART.[38] The treatment and the clinical outcome of these KSHV-positive, CD20-negative lymphomas remain uncertain. It is my impression that they have a worse prognosis than diffuse large B-cell lymphomas in this population and may warrant a more aggressive approach.

Future directions

The future management of HIV MCD may incorporate screening with a combination of plasma KSHV DNA and cytokines as well as greater use of antiherpes virus agents in the chronic control of MCD as maintenance therapy and possibly in primary prevention strategies. However, both approaches are expensive and probably limited to nations with established market economies. The diagnosis of HIV MCD requires high levels of expertise and expensive specialist immunocytochemistry, and this may account for the very few reported cases described in African cohorts where the burdens of HIV and KSHV are greatest. Numerous initiatives, including the International Network for Cancer Treatment Research iPath telepathology and the Subsaharan Africa Lymphoma Consortium, aim to improve histopathology expertise in developing nations by collaborative mentoring and to expand access within these communities to limited panels of immunostains. Inevitably, much of this article is based on opinion along with the limited available evidence; and as a final personal view, I encourage clinicians to become involved with both International Network for Cancer Treatment Research and Subsaharan Africa Lymphoma Consortium.

Acknowledgments

The author thanks Professor Kikkeri Naresh (Department of Haematopathology, Imperial College, London) for kindly providing histopathologic images and Professor Justin Stebbing and Dr Adam Sanitt (Department of Oncology, Imperial College, London) for their assistance with the receiver operating characteristic analysis.

Authorship

Contribution: M.B. wrote the manuscript.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Mark Bower, Department of Oncology, Chelsea & Westminster Hospital, 369 Fulham Rd, London, United Kingdom, SW10 9NH; e-mail: m.bower@imperial.ac.uk.

References

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital: Case No. 40231. *N Engl J Med.* 1954;250(23):1001-1005.
2. Castleman B, Iverson L, Menendez V. Localized mediastinal lymph-node hyperplasia resembling thymoma. *Cancer.* 1956;9:822-830.
3. Festen C, Flendrig JA, Schillings PH. [Giant lymphomas]. *Ned Tijdschr Geneeskd.* 1969;113(43): 1918-1919.
4. Menke DM, Tiemann M, Camoriano JK, et al. Diagnosis of Castleman's disease by identification of an immunophenotypically aberrant population of mantle zone B lymphocytes in paraffin-embedded lymph node biopsies. *Am J Clin Pathol.* 1996;105(3):268-276.
5. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood.* 2000;95(4):1406-1412.
6. Powles T, Stebbing J, Bazeos A, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann Oncol.* 2009;20(4):775-779.
7. Mylona EE, Baraboutis IG, Lekakis LJ, Georgiou O, Papastamopoulos V, Skoutelis A. Multicentric Castleman's disease in HIV infection: a systematic review of the literature. *AIDS Rev.* 2008;10(1):25-35.
8. Grandadam M, Dupin N, Calvez V, et al. Exacerbations of clinical symptoms in human immunodeficiency virus type 1-infected patients with multicentric Castleman's disease are associated with a high increase in Kaposi's sarcoma herpesvirus DNA load in peripheral blood mononuclear cells. *J Infect Dis.* 1997;175(5):1198-1201.
9. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric Castleman disease in HIV-infected patients. *Blood.* 2000;96(6):2069-2073.
10. Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive Castleman disease in human immunodeficiency virus-infected patients: the impact of highly active antiretroviral therapy. *Clin Infect Dis.* 2002;35(7):880-882.
11. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood.* 2004;103(5):1632-1634.
12. Loi S, Goldstein D, Clezy K, Milliken ST, Hoy J, Chipman M. Castleman's disease and HIV infection in Australia. *HIV Med.* 2004;5(3):157-162.
13. Naresh KN, Rice AJ, Bower M. Lymph nodes involved by multicentric Castleman disease among HIV-positive individuals are often involved by Kaposi sarcoma. *Am J Surg Pathol.* 2008;32(7): 1006-1012.
14. Soulier J, Grollet L, Oskenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood.* 1995;86:1276-1280.
15. Suda T, Katano H, Delsol G, et al. HHV-8 infection status of AIDS-unrelated and AIDS-associated multicentric Castleman's disease. *Pathol Int.* 2001;51(9):671-679.
16. Corbellino M, Bestetti G, Scalamogna C, et al. Long-term remission of Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood.* 2001;98(12):3473-3475.
17. Boivin G, Cote S, Cloutier N, Abed Y, Maguigad M, Routy JP. Quantification of human herpesvirus 8 by real-time PCR in blood fractions of AIDS patients with Kaposi's sarcoma and multicentric Castleman's disease. *J Med Virol.* 2002;68(3): 399-403.
18. Berezne A, Agbalika F, Oksenhendler E. Failure of cidofovir in HIV-associated multicentric Castleman disease. *Blood.* 2004;103(11):4368-4369; author reply 4369.
19. Du MQ, Bacon CM, Isaacson PG. Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 and lymphoproliferative disorders. *J Clin Pathol.* 2007;60(12):1350-1357.
20. Dupin N, Fisher C, Kellam P, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. *Proc Natl Acad Sci U S A.* 1999;96(8):4546-4551.
21. Du MQ, Liu H, Diss TC, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. *Blood.* 2001;97(7):2130-2136.
22. Judde JG, Lacoste V, Briere J, et al. Monoclonality or oligoclonality of human herpesvirus 8 terminal repeat sequences in Kaposi's sarcoma and other diseases. *J Natl Cancer Inst.* 2000;92(9): 729-736.
23. Gerard L, Berezne A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. *J Clin Oncol.* 2007;25(22): 3350-3356.
24. Hillier JC, Shaw P, Miller RF, et al. Imaging features of multicentric Castleman's disease in HIV infection. *Clin Radiol.* 2004;59(7):596-601.
25. Guihot A, Couderc LJ, Agbalika F, et al. Pulmonary manifestations of multicentric Castleman's disease in HIV infection: a clinical, biological and radiological study. *Eur Respir J.* 2005;26(1): 118-125.
26. Coca S, Salas I, Martinez R, Saez MA, Vaquero J. Meningeal Castleman's disease with multifocal involvement: a case report and review of literature. *J Neurooncol.* 2008;88(1):37-41.
27. Schmidt SM, Raible A, Kortum F, et al. Successful treatment of multicentric Castleman's disease with combined immunochemotherapy in an AIDS patient with multiorgan failure. *Leukemia.* 2008; 22(9):1782-1785.
28. Marcelin AG, Motol J, Guihot A, et al. Relationship between the quantity of Kaposi sarcoma-associated herpesvirus (KSHV) in peripheral blood and effusion fluid samples and KSHV-associated disease. *J Infect Dis.* 2007;196(8): 1163-1166.
29. Tedeschi R, Marus A, Bidoli E, Simonelli C, De Paoli P. Human herpesvirus 8 DNA quantification in matched plasma and PBMCs samples of patients with HHV8-related lymphoproliferative diseases. *J Clin Virol.* 2008;43(3):255-259.
30. Barker R, Kazmi F, Stebbing J, et al. FDG-PET/CT imaging in the management of HIV-associated multicentric Castleman's disease. *Eur J Nucl Med Mol Imaging.* 2009;36(4):648-652.
31. Parravicini C, Corbellino M, Paulli M, et al. Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. *Am J Pathol.* 1997;151(6):1517-1522.
32. Abe Y, Matsubara D, Gatanaga H, et al. Distinct expression of Kaposi's sarcoma-associated herpesvirus-encoded proteins in Kaposi's sarcoma and multicentric Castleman's disease. *Pathol Int.* 2006;56(10):617-624.
33. Aoki Y, Tosato G, Fonville TW, Pittaluga S. Serum viral interleukin-6 in AIDS-related multicentric Castleman disease. *Blood.* 2001;97(8):2526-2527.
34. Beck JT, Hsu SM, Wijdenes J, et al. Brief report: alleviation of systemic manifestations of Castleman's disease by monoclonal anti-interleukin-6 antibody. *N Engl J Med.* 1994;330(9):602-605.
35. Nishimoto N, Sasai M, Nakagawa M, et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood.* 2000;95:56-61.
36. Newsom-Davis T, Bower M, Wildfire A, et al. Resolution of AIDS-related Castleman's disease with anti-CD20 monoclonal antibodies is associated with declining IL-6 and TNF-alpha levels. *Leuk Lymphoma.* 2004;45(9):1939-1941.
37. Bower M, Veraitch O, Szydlo R, et al. Cytokine changes during rituximab therapy in HIV-associated multicentric Castleman disease. *Blood.* 2009;113(19):4521-4524.
38. Oksenhendler E. HIV-associated multicentric Castleman disease. *Curr Opin HIV AIDS.* 2009; 4(1):16-21.
39. Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS.* 1996;10(1):61-67.
40. Naresh KN, Trivedi P, Horncastle D, Bower M. CD20 expression in the HHV-8-infected lymphoid cells in multicentric Castleman disease. *Histopathology.* 2009;55(3):358-359.
41. Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med.* 2007; 147(12):836-839.
42. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman disease: long-term remission of Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood.* 2003;102(8):2786-2788.
43. Neuville S, Agbalika F, Rabian C, Briere J, Molina JM. Failure of rituximab in human immunodeficiency virus-associated multicentric Castleman disease. *Am J Hematol.* 2005;79(4):337-339.
44. Buchler T, Dubash S, Lee V, et al. Rituximab failure in fulminant multicentric HIV/human herpesvirus 8-associated Castleman's disease with multi-organ failure: report of two cases. *AIDS.* 2008; 22(13):1685-1687.
45. Lachant NA, Sun NC, Leong LA, Oseas RS, Prince HE. Multicentric angiofollicular lymph node hyperplasia (Castleman's disease) followed by Kaposi's sarcoma in two homosexual males with the acquired immunodeficiency syndrome (AIDS). *Am J Clin Pathol.* 1985;83(1):27-33.
46. Wynia MK, Shapiro B, Kuvin JT, Skolnik PR. Fatal Castleman's disease and pulmonary Kaposi's sarcoma in an HIV-seropositive woman. *AIDS.* 1995;9(7):814-816.
47. Scott D, Cabral L, Harrington WJ Jr. Treatment of HIV-associated multicentric Castleman's disease with oral etoposide. *Am J Hematol.* 2001;66(2): 148-150.
48. Liberopoulos E, Tolis C, Bai M, Efremidis S, Pavlidis N, Elisaf M. Successful treatment of human immunodeficiency virus-related Castleman's disease: a case report and literature review. *Oncology.* 2003;65(2):182-186.
49. Jung CP, Emmerich B, Goebel FD, Bogner JR. Successful treatment of a patient with HIV-associated multicentric Castleman disease (MCD) with thalidomide. *Am J Hematol.* 2004; 75(3):176-177.
50. Bacon CM, Miller RF, Noursadeghi M, McNamara C, Du MQ, Dogan A. Pathology of bone marrow in human herpes virus-8 (HHV8)-associated multicentric Castleman disease. *Br J Haematol.* 2004; 127(5):585-591.
51. Kotb R, Vincent I, Dulioust A, et al. Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. *Eur J Haematol.* 2006;76(3): 269-271.

52. Fowler A, Collins L, de Ruiter A, Whittaker S, Kulasegaram R, Bradbeer C. Multicentric Castleman's disease in a patient with HIV. *Int J STD AIDS.* 2006;17(1):63-64.
53. Casquero A, Barroso A, Fernandez Guerrero ML, Gorgolas M. Use of rituximab as a salvage therapy for HIV-associated multicentric Castleman disease. *Ann Hematol.* 2006;85(3):185-187.
54. Bouvresse S, Marcelin AG, Franck N, et al. The first reported case and management of multicentric Castleman's disease associated with Kaposi's sarcoma in an HIV-2-infected patient. *AIDS.* 2007;21(11):1492-1494.
55. Izuchukwu IS, Tourbaf K, Mahoney MC. An unusual presentation of Castleman's disease: a case report. *BMC Infect Dis.* 2003;3(1):20.
56. Boshoff C, Begent RH, Oliver RT, et al. Secondary tumours following etoposide containing therapy for germ cell cancer. *Ann Oncol.* 1995; 6(1):35-40.
57. Bestawros A, Michel R, Seguin C, Routy JP. Multicentric Castleman's disease treated with combination chemotherapy and rituximab in four HIV-positive men: a case series. *Am J Hematol.* 2008; 83(6):508-511.
58. Dupin N, Krivine A, Calvez V, Gorin I, Franck N, Escande JP. No effect of protease inhibitor on clinical and virological evolution of Castleman's disease in an HIV-1-infected patient. *AIDS.* 1997; 11(11):1400-1401.
59. Zietz C, Bogner JR, Goebel FD, Lohrs U. An unusual cluster of cases of Castleman's disease during highly active antiretroviral therapy for AIDS. *N Engl J Med.* 1999;340(24):1923-1924.
60. Bottieau E, Colebunders R, Schroyens W, et al. Multicentric Castleman's disease in 2 patients with HIV infection, unresponsive to antiviral therapy. *Acta Clin Belg.* 2000;55(2):97-101.
61. Bower M, Collins S, Cottrill C, et al. British HIV Association guidelines for HIV-associated malignancies 2008. *HIV Med.* 2008;9(6):336-388.
62. Klass CM, Offermann MK. Targeting human herpesvirus-8 for treatment of Kaposi's sarcoma and primary effusion lymphoma. *Curr Opin Oncol.* 2005;17(5):447-455.
63. Senanayake S, Kelly J, Lloyd A, Waliuzzaman Z, Goldstein D, Rawlinson W. Multicentric Castleman's disease treated with antivirals and immunosuppressants. *J Med Virol.* 2003;71(3):399-403.
64. Revuelta MP, Nord JA. Successful treatment of multicentric Castleman's disease in a patient with human immunodeficiency virus infection. *Clin Infect Dis.* 1998;26(2):527.
65. Nord JA, Karter D. Low dose interferon-alpha therapy for HIV-associated multicentric Castleman's disease. *Int J STD AIDS.* 2003;14(1):61-62.
66. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood.* 2005;106(8):2627-2632.
67. Powles T, Stebbing J, Montoto S, et al. Rituximab as retreatment for rituximab pretreated HIV-associated multicentric Castleman disease. *Blood.* 2007;110(12):4132-4133.
68. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase III trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin's lymphoma: AIDS-malignancies consortium trial 010. *Blood.* 2005;24:1538-1543.
69. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis.* 2008; 198(1):23-30.
70. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood.* 2002;99(7): 2331-2336.