Case Report

Human Herpesvirus-8 Infection Associated with Kaposi Sarcoma, Multicentric Castleman’s Disease, and Plasmablastic Microlymphoma in a Man with AIDS: A Case Report with Review of Pathophysiologic Processes

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Kaposi sarcoma (KS), multicentric Castleman’s disease (MCD), and plasmablastic microlymphoma, are all linked to human herpesvirus-8 (HHV-8) infection and HIV-induced immunodeficiency. Herein, we describe the case of a Kenyan man diagnosed with HIV in 2000. He deferred highly active antiretroviral therapy (HAART) and remained in good health until his CD4+ count declined in 2006. He was hospitalized with bacterial pneumonia in 2008, after which he agreed to take HAART but did so sporadically. In 2010, he was hospitalized with fever, lymphadenopathy, pancytopenia, and an elevated HHV-8 viral load. A lymph node biopsy showed findings consistent with KS, MCD, and plasmablastic microlymphoma. Eight months after starting liposomal doxorubicin, Rituximab, and a new HAART regimen, he has improved clinically, and his HIV and HHV-8 viral loads are suppressed. These three conditions, found in the same lymph node, underscore the inflammatory and malignant potential of HHV-8, particularly in the milieu of HIV-induced immunodeficiency.

1. Introduction

In the current era of highly active antiretroviral therapy (HAART), people infected with HIV are not only less likely to develop AIDS-defining infections, they are also less likely to be diagnosed with an AIDS-defining neoplasm (i.e., Kaposi Sarcoma (KS) or non-Hodgkins lymphoma (NHL)) [1–3]. As these individuals live to their sixth decade of life and beyond, cancers associated with lifestyle choices and aging (i.e., lung, liver, and anal carcinomas) are increasingly important barriers to survival [4–6]. However, AIDS-defining malignancies remain a significant cause of morbidity and mortality for those individuals who are not on HAART because they are unaware of their HIV serostatus, they do not have access to HAART, or they are poorly adherent with prescribed therapies [7].

KS is etiologically linked to human herpesvirus-8 (HHV-8), also known as KS-associated herpesvirus (KSHV) [8]. The HHV-8 genome contains numerous genes that code for proteins with recognizable homology to human proteins, including an interleukin-6 (IL-6) homologue [9]. IL-6 has multiple systemic effects including the support of hematopoiesis and stimulation of B lymphocyte and plasma cell growth. When expressed in physiologic excess, IL-6 may contribute to dysregulation of immune responses [10].

IL-6 is also a major mediator of the systemic symptoms associated with Castleman’s disease (CD) [11, 12]. CD is a heterogeneous group of lymphoproliferative disorders of
unknown etiology. Unlike unicentric CD, multicentric CD (MCD) is strongly associated with immunosuppression and HHV-8 infection [13]. Patients with MCD frequently present with generalized lymphadenopathy, hepatosplenomegaly, fever, and night sweats. These debilitating systemic symptoms are in part due to the proinflammatory effects of IL-6 [14]. IL-6 also downregulates albumin production by the liver, leading to hypoalbuminemia, which may cause anasarca via decrease in oncotic pressure.

When comparing HIV-infected patients without MCD, those with MCD have a 15-fold increased risk of NHL, with the most common subtype of NHL being HHV-8-positive plasmablastic lymphoma. Among 60 patients with HIV and MCD, 14 were diagnosed with NHL of whom 6 (43%) had the plasmablastic variant [15]. In some cases, the precursor to HHV8+ plasmablastic lymphoma are the sheets of plasmablastic cells, termed microlymphomas, found in the lymph nodes of MCD patients [15, 16]. These microlymphomas typically express IgM with lambda light chain restriction, but are polyclonal whereas true HHV8+ plasmablastic lymphoma is monoclonal and follows an aggressive clinical course, responding poorly to multiagent chemotherapy [16].

Herein, we describe the case of an HIV-infected man with KS, MCD, and microlymphoma, all three of which were identified within a single resected lymph node. We also review the relevant literature with a focus on the common etiology of these various diseases.

2. Case Report

In 2000, a 42-year-old Kenyan man, who had sex with other men, was diagnosed with HIV infection and neurosyphilis while he was being evaluated for chronic sinusitis and headache. His initial CD4+ count was 595 cells/μl, and his HIV viral load was 5,490 copies/ml. Neurosyphilis was successfully treated, but the patient opted to defer HAART. In 2003, he had unilateral and painless right thigh enlargement and underwent surgical excision of a low-grade leiomyosarcoma. No adjuvant treatment was recommended, and he remained in good health for an additional two years, during which time his CD4+ count and his HIV viral load remained >550 cells/μl and <5,500 copies/ml, respectively.

In 2006, the patient had a precipitous and persistent fall in CD4+ count to <120 cells/μl and his HIV viral load increased to 35,000 copies/ml. However, he declined to begin HAART for fear of untoward medication-associated side effects. Over the next two years he lost 15 pounds, had waxing and waning adenopathy, and was hospitalized on one occasion with bacterial pneumonia. By June, 2008 he had greater than 15 discrete KS lesions on his legs, his CD4+ count was 30 cells/μl and his HIV viral load was 34,000 copies/ml (Figure 1).

In 2009, he was hospitalized for treatment of methacillin-susceptible staphylococcus aureus pneumonia and bacteremia. He subsequently agreed to begin HAART, but was poorly adherent with treatment, stopping and restarting his HIV medications on a number of occasions.
The patient, now age 52, began treatment consisting of liposomal doxorubicin (20 mg/m² every 14 days) in conjunction with Rituximab (375 mg/m² weekly times four) and concurrent HAART consisting of the same regimen listed above. More aggressive treatment with multiagent chemotherapy was not given since the patient had only premalignant plasmablastic microlymphoma, and not frank HHV8+ plasmablastic lymphoma, and MCD and KS have been shown to respond to this more conservative treatment.

At eight-months followup, anasarca had resolved and he had regained lost weight. Cutaneous KS was less prominent, and a CT scan showed diminished adenopathy. Laboratory studies are now notable for a gradual improvement in complete blood count, hepatic transaminases, and alkaline phosphatase. His serum albumin has returned to normal, his HIV viral load is nondetectable; although, his CD4+ count remains <50 cells/µL, and his HHV-8 viral load has decreased by greater than two orders of magnitude.
3. Discussion

The three separate conditions of KS, MCD, and plasmablastic microlymphoma, all identified within a single lymph node biopsy in a patient with AIDS, underscore the diverse malignant and inflammatory potential of HHV-8 infection, especially in the milieu of decreased cellular immunity due to HIV infection.

HHV-8 is a member of the gammaherpesvirus family and shows 40% sequence homology with the oncogenic Epstein-Barr virus [17]. Like other herpesviruses, HHV-8 is adept at evading the immune system through its ability to use viral immunomodulators that interfere with the host immune response, many of which are homologues of human genes [18]. One way HHV-8 evades the immune system is through the skewing of the host immune response from Th1 to Th2, in part accomplished by the action of viral-IL-6 (vIL-6). This homologue of human IL-6 acts through gp130 to promote Th2-cell development and responsiveness, while also inhibiting Th1-cell responses [19]. HHV-8 also encodes proteins that interact with the host immune system to inhibit complement and down regulate the adaptive immune response.

The oncogenic potential of HHV-8 is, in part, due to its ability to cause chromosomal instability, to alter gene expression, to increase telomerase activity, and, promote cell invasiveness, proliferation, and survival [20]. The latency-associated nuclear antigen (LANA) inhibits p53-induced apoptosis while also inactivating the retinoblastoma gene, which would otherwise inhibit progression through the G1/S cell cycle checkpoint [21, 22]. vIL-6 can activate multiple cellular pathways, including JAK/STAT, which in turn leads to vascular endothelial growth factor expression and signaling [23]. When vIL-6-expressing fibroblasts are injected into mice, highly vascular tumor formation, hematopoiesis, and plasmacytosis take place [24]. Other viral genes code for proteins that are also implicated in oncogenesis: viral interferon regulatory factor-1 (v-IRF-1) suppresses both type I and type II interferon responses; K13 (aka vFLIP) inhibits Fas-mediated apoptosis; viral g-protein-coupled receptor (vGPCR), a homologue of the IL-8 receptor, promotes tumors when vGPCR-expressing fibroblasts are injected into nude mice [25–28].

Since Chang and colleagues first identified HHV-8 in KS tissue from HIV seropositive patients, our understanding of the pathophysiology of various HHV-8-associated diseases has grown substantially [29]. HHV-8 is now etiologically linked to KS in HIV-infected patients, as well as KS in immunocompetent patients (classic KS) [30]. More recently, HHV-8 has been associated with MCD, HHV8+ plasmablastic lymphoma, primary effusion lymphoma, and germinotrophic lymphoproliferative disorders [31–33].

HIV-seropositive individuals with MCD have a significantly greater risk of NHL than their HIV-negative counterparts. In MCD, HHV-8 is specifically associated with monotypic (IgM λ) but polyclonal HHV-8+ plasmablasts which occur as isolated clusters of cells in the mantle zone of B-cell follicles, called microlymphomas [34, 35]. The expansion of these plasmablastic microlymphomas from MCD lesions to aggressive NHL is probably triggered by a second oncogenic event. This implies that MCD, microlymphoma and HHV8+ plasmablastic lymphoma represent three stages of a single disease in the backdrop of HIV-induced immunodeficiency.

The specific NHL implicated in this process, HHV-8+ plasmablastic lymphoma, is a rare, aggressive B-cell lymphoma with a poor prognosis [36]. In an abstract regarding 131 patients with AIDS-associated plasmablastic lymphoma, death occurred in 59% of patients with a median survival of only 14 months from diagnosis [37]. However, only 16% of those 131 cases were HHV-8+, and these were later excluded from the final, peer-reviewed publication [38], highlighting the fact that the HHV-8+ form of plasmablastic lymphoma is distinct from the more common plasmablastic lymphoma, which is more frequently associated with Epstein-Barr virus and often presents as skin or oropharyngeal nodules. The distinction between these different forms of plasmablastic lymphoma, and any possible differences in clinical course and response to treatment, is an area where further research is needed.

Coexistence of MCD and KS in the same tissue is a common phenomenon. Among 24 lymph nodes, 15 (63%) showed evidence of coexisting KS [39]. The association may be due to lytic HHV-8 infection of B-lymphoid cells exposing susceptible endothelial cells at vulnerable sites. Disregulation of IL-6 in HHV-8-infected cells is not only a major trigger for disease in the angiofollicular hyperplasia of MCD, and KS, it is also a major trigger for disease progression in HHV-8+plasmablastic and primary effusion lymphomas.

While the overall median survival of patients with AIDS and coexistent MCD and NHL is generally just a few months, there are exceptions [40, 41]. Horster and colleagues describe the case of a patient with AIDS, MCD and plasmablastic leukemia who was treated with multiagent chemotherapy, splenectomy, and maintenance thalidomide and who was still alive at a 28-month followup [42]. Another patient with AIDS and MCD had a plasmablastic lymphoma of the spermatic cord. He too was treated with multiagent chemotherapy, and despite a subsequent relapse of MCD he was alive at an 11-month followup [43]. Given recent successes associated with treating patients with HIV-associated MCD with antivirals, and the better outcome associated with treating AIDS-related lymphoma patients with modern supportive care in conjunction with HAART, rituximab, and when needed, chemotherapy, we are hopeful that the prospects of HIV-infected patients with HHV-8-associated plasmablastic lymphoma, KS, and MCD will also improve [44, 45].

References

[1] P. Appleby, V. Beral, R. Newton, G. Reeves, and L. Carpenter, “Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults,” Journal of the National Cancer Institute, vol. 92, no. 22, pp. 1823–1830, 2000.

[2] J. L. Long, E. A. Engels, R. D. Moore, and K. A. Gebo, “Incidence and outcomes of malignancy in the HAART era in
an urban cohort of HIV-infected individuals," AIDS, vol. 22, no. 4, pp. 489–496, 2008.

[3] P. Patel, D. L. Hanson, P. S. Sullivan et al., “Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003,” Annals of Internal Medicine, vol. 148, no. 10, pp. 728–736, 2008.

[4] T. Powles, D. Robinson, J. Stebbing et al., “Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection,” Journal of Clinical Oncology, vol. 27, no. 6, pp. 884–890, 2009.

[5] G. D. Kirk, C. Merlo, P. O’Driscoll et al., “HIV infection is associated with an increased risk for lung cancer, independent of smoking,” Clinical Infectious Diseases, vol. 45, no. 1, pp. 103–110, 2007.

[6] E. A. Engels, “Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities,” AIDS, vol. 23, no. 8, pp. 875–885, 2009.

[7] M. C. Uhlenkott, S. E. Buskin, E. M. Kahle, E. Barash, and D. M. Aboulafia, “Causes of death in the era of highly active antiretroviral therapy: a retrospective analysis of a hybrid hematology-oncology and HIV practice and the Seattle/King county adult/adolescent spectrum of HIV-related diseases project,” American Journal of the Medical Sciences, vol. 336, no. 3, pp. 217–223, 2008.

[8] P. S. Moore and Y. Chang, “Detection of herpesvirus-like DNA sequences in Kaposi’s sarcoma in patients with and those without HIV infection,” New England Journal of Medicine, vol. 332, no. 18, pp. 1181–1185, 1995.

[9] F. Neipel, J. C. Albrecht, A. Ensser et al., “Human herpesvirus 8 encodes a homolog of interleukin-6,” Journal of Virology, vol. 71, no. 1, pp. 839–842, 1997.

[10] D. S. Hong, L. S. Angelo, and R. Kurzrock, “Interleukin-6 and its receptor in cancer: implications for translational therapeutics,” Cancer, vol. 110, no. 9, pp. 1911–1928, 2007.

[11] S. M. Hsu, J. A. Waldron, S. S. Xie, and B. Barlogie, “Expression of interleukin-6 in Castleman’s disease,” Human Pathology, vol. 24, no. 8, pp. 833–839, 1993.

[12] T. S. Uldrick, V. Wang, D. O’Mahony et al., “An interleukin-6-related systemic inflammatory syndrome in patients co-infected with kaposi sarcoma-associated herpesvirus and HIV but without multicentric Castleman disease,” Clinical Infectious Diseases, vol. 51, no. 3, pp. 350–358, 2010.

[13] J. Soulier, L. Grollet, E. Oksenhendler et al., “Kaposi’s sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman’s disease,” Blood, vol. 86, no. 4, pp. 1276–1280, 1995.

[14] C. Casper, “The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care,” British Journal of Haematology, vol. 129, no. 1, pp. 3–17, 2005.

[15] E. Oksenhendler, E. Boulanger, L. Galicier et al., “High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease,” Blood, vol. 99, no. 7, pp. 2331–2336, 2002.

[16] P. Isaacson, E. Campo, and N. Harris, “Large B-cell lymphoma arising in HHV8-associated multicentric Castleman’s disease,” in WHO Classification: Tumours of Haematopoietic and Lymphoid Tissues, pp. 258–259, 2008.

[17] N. Raab-Traub, “Epstein-Barr virus in the pathogenesis of NPC,” Seminars in Cancer Biology, vol. 12, no. 6, pp. 431–441, 2002.

[18] L. Coscoy, “Immune evasion by Kaposi’s sarcoma-associated herpesvirus,” Nature Reviews Immunology, vol. 7, no. 5, pp. 391–401, 2007.

[19] S. Diehl and M. Rincón, “The two faces of IL-6 on Th1/Th2 differentiation,” Molecular Immunology, vol. 39, no. 9, pp. 531–536, 2002.

[20] K. W. Wen and B. Damania, “Kaposi sarcoma-associated herpesvirus (KSHV): molecular biology and oncogenesis,” Cancer Letters, vol. 289, no. 2, pp. 140–150, 2010.

[21] J. Friborg Jr., W. P. Kong, M. O. Hottinger, and G. J. Nabel, “p53 Inhibition by the LANA protein of KSHV protects against cell death,” Nature, vol. 402, no. 6764, pp. 889–894, 1999.

[22] S. A. Radkova, P. Kellam, and C. Boshoff, “The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells,” Nature Medicine, vol. 6, no. 10, pp. 1121–1127, 2000.

[23] C. Liu, Y. Okruzonov, H. Li, and J. Nicholas, “Human herpesvirus 8 (HHV-8)-encoded cytokines induce expression of an autocrine signaling by vascular endothelial growth factor (VEGF) in HHV-8-infected primary-effusion lymphoma cell lines and mediate VEGF-independent antiapoptotic effects,” Journal of Virology, vol. 75, no. 22, pp. 10933–10940, 2001.

[24] Y. Aoki, E. S. Jaffe, Y. Chang et al., “Angiogenesis and hematopoiesis induced by Kaposi’s sarcoma-associated herpesvirus-encoded interleukin-6,” Blood, vol. 93, no. 12, pp. 4034–4043, 1999.

[25] L. Burýšek, W. S. Yeow, B. Lubová et al., “Functional analysis of human herpesvirus 8-encoded viral interferon regulatory factor 1 and its association with cellular interferon regulatory factors and p300,” Journal of Virology, vol. 73, no. 9, pp. 7334–7342, 1999.

[26] S. J. Gao, C. Boshoff, S. Jayachandra, R. A. Weiss, Y. Chang, and P. S. Moore, “KSHV ORF K9 (vI RF) is an oncogene which inhibits the interferon signaling pathway,” Oncogene, vol. 15, no. 16, pp. 1979–1985, 1997.

[27] M. Djerbi, V. Scerpanti, A. I. Catrina, B. Bogen, P. Biberfeld, and A. Grandien, “The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors,” Journal of Experimental Medicine, vol. 190, no. 7, pp. 1025–1031, 1999.

[28] C. Bais, B. Santomasso, O. Coso et al., “G-protein-coupled receptor of Kaposi’s sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator,” Nature, vol. 391, no. 6662, pp. 86–89, 1998.

[29] Y. Chang, E. Cesaran, M. S. Pessin et al., “Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi’s sarcoma,” Science, vol. 266, no. 5192, pp. 1865–1869, 1994.

[30] F. Neipel and B. Fleckenstein, “The role of HHV-8 in Kaposi’s sarcoma,” Seminars in Cancer Biology, vol. 9, no. 3, pp. 151–164, 1999.

[31] J. Soulier, L. Grollet, E. Oksenhendler et al., “Kaposi’s sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman’s disease,” Blood, vol. 86, no. 4, pp. 1276–1280, 1995.

[32] E. Cesaran, Y. Chang, P. S. Moore, J. W. Said, and D. M. Knowles, “Kaposi’s sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas,” New England Journal of Medicine, vol. 332, no. 18, pp. 1186–1191, 1995.

[33] M. Sunil, E. Reid, and M. J. Lechowicz, “Update on HHV-8-associated malignancies,” Current Infectious Disease Reports, vol. 12, no. 2, pp. 147–154, 2010.
[34] J. L. Dargent, L. Lespagnard, N. Sirtaine, B. Cantinieaux, R. Li, and P. Hermans, “Plasmablastic microlymphoma occurring in human herpesvirus 8 (HHV-8)-positive multicentric Castleman’s disease and featuring a follicular growth pattern: case report,” *APMIS*, vol. 115, no. 7, pp. 869–874, 2007.

[35] M. Q. Du, H. Liu, T. C. Diss et al., “Kaposi sarcoma-associated herpesvirus infects monotypic (IgM  ) but polyclonal naïve B cells in Castleman disease and associated lymphoproliferative disorders,” *Blood*, vol. 97, no. 7, pp. 2130–2136, 2001.

[36] N. Dupin, T. L. Diss, P. Kellam et al., “HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma,” *Blood*, vol. 95, no. 4, pp. 1406–1412, 2000.

[37] J. Castillo, J. B. Dezube, and L. Pantanowitz, “Plasmablastic lymphoma in HIV: a review of 131 cases,” *Journal of Clinical Oncology*, vol. 26, abstract no. 19519, 2008.

[38] J. Castillo, J. B. Dezube, and L. Pantanowitz, “HIV-associated plasmablastic lymphoma in HIV: Lessons learned from 112 published cases,” *Journal of Clinical Oncology*, vol. 26, abstract no. 19519, 2008.

[39] K. N. Naresh, A. J. Rice, and M. Bower, “Lymph nodes involved by multicentric castleman disease among HIV-positive individuals are often involved by Kaposi sarcoma,” *American Journal of Surgical Pathology*, vol. 32, no. 7, pp. 1006–1012, 2008.

[40] R. M. Seliem, R. C. Griffith, N. L. Harris et al., “HHV-8+, EBV+ multicentric plasmablastic microlymphoma in an HIV+ man: the spectrum of HHV-8+ lymphoproliferative disorders expands,” *American Journal of Surgical Pathology*, vol. 31, no. 9, pp. 1439–1445, 2007.

[41] J. A. Yates, N. A. Zakai, R. C. Griffith, E. J. Wing, and F. J. Schiffman, “Multicentric Castleman disease, Kaposi sarcoma, hemophagocytic syndrome, and a novel HHV8-lymphoproliferative disorder,” *AIDS Reader*, vol. 17, no. 12, pp. 596–601, 2007.

[42] S. Horster, C. Jung, C. Zietz, C. D. Cohen, M. Siebeck, and F. D. Goebel, “AIDS, multicentric Castleman’s disease, and plasmablastic leukemia: report of a long-term survival,” *Infection*, vol. 32, no. 5, pp. 296–298, 2004.

[43] E. Boulanger, J. Brière, P. Gaulard, D. Droz, and E. Oksenhendler, “HHV8-related non-Hodgkin’s lymphoma of the spermatic cord in a patient with HIV-associated multicentric Castleman disease,” *American Journal of Hematology*, vol. 72, no. 1, pp. 70–71, 2003.

[44] M. Bower, “How I treat HIV-associated multicentric Castleman disease,” *Blood*, vol. 116, no. 22, pp. 4415–4421, 2010.

[45] J. A. Sparano, J. Y. Lee, L. D. Kaplan et al., “Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma,” *Blood*, vol. 115, no. 15, pp. 3008–3016, 2010.