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HHV-8 and EBV-positive intravascular lymphoma: an unusual presentation of extracavitary primary effusion lymphoma

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Abstract

Intravascular lymphomas are rare and aggressive hematolymphoid tumors. Here we describe a human herpesvirus type-8/Kaposi sarcoma-associated herpesvirus (HHV-8/KSHV) and Epstein-Barr virus (EBV) positive intravascular lymphoma. The patient was a 59 year-old HIV-positive man who presented with diarrhea, abdominal pain, fevers, night sweats, and weight loss. Radiographic studies of the abdomen and pelvis revealed numerous subcentimeter nodules within the subcutaneous fat that lacked connection to the skin. An excisional biopsy demonstrated large atypical cells within vessels in the deep subcutaneous fat, and many of the vessels contained extensive organizing thrombi. The atypical cells lacked strong expression of most B-cell markers but were positive for MUM-1 and showed partial expression of several T-cell markers. An immunohistochemical stain for HHV-8 and an in situ hybridization for EBV were both positive in the neoplastic cells. The disease had a rapidly progressive and fatal course. This lymphoma appears to represent an entirely intravascular form of primary effusion lymphoma, and highlights the propensity for HHV-8 and EBV-positive lymphoid neoplasms to show aberrant expression of T-cell markers, illustrates the utility of skin biopsies for the diagnosis of intravascular lymphoma, and suggests that biopsies to evaluate for intravascular lymphoma should be relatively deep and include subcutaneous fat.

Keywords

intravascular lymphoma; human herpesvirus type-8; Kaposi sarcoma-associated herpesvirus; Epstein-Barr virus; primary effusion lymphoma

BACKGROUND

Several lymphoproliferative disorders (LPDs) are associated with coincident Epstein-Barr virus (EBV) and human herpesvirus-8/Kaposi sarcoma-associated herpesvirus (HHV-8/KSHV) infection, including primary effusion lymphoma (PEL)^{1–4}, extracavitary PEL^{5–9}, germinotropic lymphoproliferative disorder (GLD)¹⁰ and some cases of plasmablastic Castleman disease (PCD)^{11–13} (Table 1). These disorders can be diagnostically challenging because of their relative rarity, characteristic lack of expression of typical B-cell markers,

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and occasional aberrant expression of T-cell antigens^{1,4,6,14}. They are more common in immunocompromised patients, and usually occur in the setting of human immunodeficiency virus (HIV) infection, but have also been reported in transplant patients^{15,16} and the elderly^{8,14}. Additionally, there are rare reports of some of EBV and HHV-8 positive LPDs occurring in the absence of immunodeficiency^{10,17}.

Intravascular large B-cell lymphomas (IVLBCL) are also rare. IVLBCL is usually widely disseminated, but characteristically spares lymph nodes. The disease is aggressive, and the tumor cells occlude small vessels and capillaries causing end-organ ischemia. Different organs can be affected, leading to the protean presentation of IVLBCL; however, two major patterns of disease are recognized. A Western form presents with predominantly cutaneous or neurologic symptoms, often in conjunction with B symptoms including fever, weight loss and night sweats. An Asian variant of IVLBCL is associated with multi-organ failure, hepatosplenomegaly, pancytopenia, hemophagocytic syndrome and B symptoms^{1,18,19}.

Here we describe a case of intravascular lymphoma associated with EBV and HHV-8 co-infection, which to our knowledge has not been previously described. The clinical presentation and pathologic features of this unusual lymphoma highlight challenges in the diagnosis both of intravascular lymphomas and of neoplasms with HHV-8 and EBV co-infection.

MATERIALS AND METHODS

Formalin-fixed and paraffin-embedded tissue was subjected to hematoxylin and eosin (H&E) staining as well as immunohistochemical staining and in situ hybridization (ISH) using routine methods. HHV-8 latent nuclear antigen (LANA-1), the product of the viral gene open reading frame 73, was detected using the 13B10 monoclonal antibody (Leica Systems, NCL-HHV8) at a standard dilution of 1:50. EBV was detected using an ISH probe against EBER (Ventana, 760-1209 DNP Probe) and used pre-diluted, as received. Viral interleukin 6 (IL-6) staining was performed using a polyclonal rabbit antiserum raised against viral IL-6 peptides as previously described²⁰. All other immunohistochemical staining was performed using routine methods for clinical diagnosis.

Flow cytometric immunophenotyping was performed on fresh tissue. The material was dissociated by passing it through wire mesh, and the cell suspension was incubated with a combination of 4 monoclonal antibodies specific for CD19, CD3, kappa and lambda (Becton Dickinson, San Jose, CA) that were titrated for optimal staining according to standard protocol.

Analysis for B-cell clonality by immunoglobulin gene heavy chain (IgH) gene rearrangement and T cell clonality by T-cell receptor (TCR) gamma gene rearrangements were performed in the Johns Hopkins molecular pathology facility according to established protocols for clinical use. Slices of formalin-fixed, paraffin-embedded tissue were extracted with xylene and absolute ethanol. DNA was prepared using the QiaAMP DNA Mini kit (Quiagen, Valencia, CA, USA) according to the manufacturer's directions and subjected to PCR using degenerate consensus primers to amplify the hypervariable (VDJ) region of the IgH gene from the 3' end of the V region to the 3' end of the J region. The primers used were as follows: FR3A (directed at the 3' end of the V region) 5'-ACACGGCYSTGTATTACTGTG-3' and VLJH (directed at the 3' end of the J region) 5'-GTGACCAGGGTNCCTTGGCCCCAG-3' where Y=C or T, S=G or C and N=C, T, G, or A. In the presence of a monoclonal population, this amplification results in a distinct 50–150 base pair product. Amplification of the beta-globin gene was used as an internal control to ensure sufficient DNA quality and amplification. PCR amplified products were subjected to

gel electrophoresis for analysis of clonal bands. T-cell receptor-gamma gene rearrangement was evaluated using the TCRG Gene Clonality Assay (Invivoscribe Technologies, Inc.) according to the manufacturer's instructions.

CASE REPORT

A 59 year-old HIV-positive man presented with a three week history of diarrhea, abdominal pain, fevers, night sweats, dizziness, an unintentional 30 pound weight loss and recent cognitive decline. The patient had been diagnosed with HIV 27 years before, and was on highly active anti-retroviral therapy (HAART). The patient was not taking any medications requiring subcutaneous injection for administration and he denied intravenous drug use. Physical exam showed no evidence of skin lesions or lymphadenopathy.

Computed tomography scans of the chest, abdomen and pelvis demonstrated that the spleen was enlarged, but no significant lymphadenopathy or masses were seen. The CT scans were remarkable for numerous subcentimeter nodules scattered through the subcutaneous fat that did not show a connection to the overlying epidermis (Figure 1). These nodules showed mildly increased fluorodeoxyglucose uptake on a positron emission tomography scan.

Laboratory values on admission were notable for mild anemia (Hb 10.7 g/dL; normal range 13.9–16.3 g/dL) and thrombocytopenia (69 K/cu mm; normal 150–350 K/cu mm) with increased neutrophils (83%; normal 31–76%) and decreased lymphocytes (3%; normal 24–44%). The CD4 count was 526/cubic mm (normal 458–1344/cubic mm), and the HIV-1 viral load was 93 copies/mL. The patient also had an increased lactic dehydrogenase (1329 U/L; normal 118–273 U/L).

A bone marrow biopsy that was performed four days prior to admission at an outside hospital showed hypercellular marrow with trilineage hematopoiesis and increased polyclonal plasma cells with no evidence of lymphoma. Colon biopsies demonstrated severe acute colitis, but were negative for fungi, cytomegalovirus, and viral cytopathic effect. An initial fine needle biopsy of a subcutaneous nodule demonstrated large, atypical cells suggestive of malignancy but the material in the scant specimen was insufficient for a diagnosis.

A subsequent excisional biopsy of one of the subcutaneous nodules in the abdominal wall showed fibroadipose tissue with a patchy mixed inflammatory infiltrate and occasional hemosiderin-laden macrophages. Many of the vessels contained organizing thrombi, and some also contained large atypical cells. The atypical cells had a moderate amount of eosinophilic cytoplasm and round to oval nuclei with one or more prominent nucleoli (Figure 2). There were numerous apoptotic bodies and mitotic figures seen within the vessels.

A panel of immunohistochemical stains and in situ hybridization for EBV (EBER) demonstrated that the atypical cells were positive for MUM-1, CD43, HHV-8 (LANA-1), EBV and viral IL-6, with dim expression of CD79a and CD45 (Figure 3). A subset of the atypical cells expressed dim CD4, CD45-RO and cytoplasmic CD3. The atypical cells were restricted to the intravascular compartment, and had a high Ki-67 proliferation index. The B-cell markers CD20, CD19 and Pax-5 as well as the plasma cell markers CD138 and CD38 were negative in the neoplastic cells. Immunostains for IgG, IgM and IgA were difficult to interpret due to high background staining, but many of the atypical cells appeared to express IgG. Immunostains for kappa and lambda light chains were non-contributory due to high background staining. The tumor cells were also negative for CD5, CD7, CD8, TIA-1, CD25, CD30, CD56, CD68, CD163, myeloperoxidase, CD33, CD99, TdT, CD34, CD117, S100, and EMA.

Flow cytometry studies were performed on a portion of the excisional biopsy, but showed predominantly debris with no evidence of a monoclonal B-cell population. A PCR assay for immunoglobulin heavy chain (IgH) gene rearrangements showed an oligoclonal pattern, and a PCR assay for T-cell receptor gamma gene rearrangements was notable for poor amplification although there was a significant polyclonal component.

The patient's mental and respiratory status waxed and waned over the course of his hospital stay. Shortly after diagnostic tissue was obtained, the patient's condition abruptly declined and he was transitioned to comfort care. He died approximately 2 months from the reported onset of symptoms.

DISCUSSION

Here we report an intravascular lymphoma that is associated with both EBV and HHV-8 viral infection, which joins a small but growing family of LPDs driven by EBV and HHV-8 co-infection. EBV and HHV-8-positive lymphomas are often clinically aggressive in immunocompromised individuals, and include PEL presenting as an effusion²⁻⁴ or mass lesion^{5,6}, germinotrophic lymphoproliferative disorder¹⁰, rare cases of multicentric Castleman-associated plasmablastic lymphoma or microlymphoma^{12,13}, a cutaneous plasmablastic lymphoma arising in a transplant patient¹⁶, and rare large B-cell lymphomas¹⁷. Lymphomas in this family tend to have large, atypical cells with an unusual phenotype^{4,7,9}. The tumor cells typically lack pan B-cell markers such as CD20, CD19 and CD79a, but do show expression of one or more activation or plasma cell markers including MUM-1, CD138 or CD38^{1,10,12,17}. This case of EBV and HHV-8-positive intravascular lymphoma also demonstrated aberrant expression of T-cell markers, which can occasionally be seen in EBV/HHV-8-positive lymphomas^{6,8,14}. The expression of T-cell antigens on tumor cells initially raised the possibility that the biopsy findings represented a primary T-cell intravascular lymphoma.

While most intravascular lymphomas are large B-cell lymphomas, T-cell and NK/T-cell intravascular lymphomas have also been reported. NK/T-cell intravascular lymphomas are the most common of the intravascular T-cell lymphomas, and are characterized by frequent skin involvement and an aggressive clinical course. These express cytotoxic markers including CD8, TIA-1 and CD56, and most are EBV-positive²¹⁻²³. The lack of cytotoxic T-cell marker expression and clonal rearrangement of the TCR-gamma gene argues against a diagnosis of NK/T-cell intravascular T-cell lymphoma in this case. There have also been rare reports of intravascular anaplastic large cell lymphomas (ALCL)²⁴⁻²⁶. These lymphomas express CD4 and CD30 but are ALK and EBV-negative and typically form a discrete cutaneous mass with tumor cells localized to the lymphatics. Intravascular ALCLs are reported to have a relatively indolent clinical course. Finally, there are rare reports of skin lesions that contain a proliferation of atypical CD30-positive cells within small vessels, and these cases are thought to represent a reactive process²⁷. CD30, which is not a lineage-associated antigen, is not expressed in this case, making a diagnosis of intravascular ALCL or a reactive proliferation unlikely²⁸.

Although the immunophenotype of the tumor cells is consistent with PEL, we are unable to definitively assign a lineage to this intravascular lymphoma. The neoplastic cells are largely negative for B-cell specific antigens, there is no evidence of a B-cell clone on flow cytometric analysis, and IgH gene rearrangement studies did not reveal a clone. Additionally, while the tumor cells expressed dim CD3 and CD4, T-cell receptor (TCR) gene rearrangement studies showed no definitive evidence of a clonal T-cell population. Molecular studies were hampered by the sparse distribution of tumor cells and admixed inflammatory cells, which also precluded microdissection. Despite our inability to

demonstrate a B or T-cell clone the immunophenotype is typical of PEL, which is currently considered a mature B-cell lymphoma despite the fact that it characteristically lacks expression of B-cell antigens as well as surface and cytoplasmic immunoglobulin^{1,2,29}. Of note, PEL can also show aberrant expression of T-cell antigens, and may even demonstrate rearrangement of both TCR and immunoglobulin genes or TCR genes alone^{30,31,32}.

Another feature of the tumor in this patient was the finding of extensive organizing thrombi within the small vessels, which surrounded and obscured the neoplastic cells. While fibrin thrombi associated with hemorrhage and necrosis have occasionally been observed in both IVLBCL^{1,33} and intravascular cytotoxic T-cell lymphoma³⁴, the thrombi were particularly pronounced in this HHV-8 and EBV-positive lymphoma. Thrombosis in the setting of intravascular lymphoma could further accelerate end-organ ischemic damage, leading to a more rapid and aggressive disease course. The mechanism underlying the formation of thrombi in lymphoma is unclear but may relate to production of cytokines by the tumor cells, which could also be potentiated by viral infection. In particular, IL-6, an analogue of which is produced by HHV-8 viral infection, is known to promote coagulation without affecting fibrinolysis³⁵. In one study of the risk factors for developing thrombotic complications in HIV-infected individuals, malignancy in the form of Kaposi sarcoma was one of the most frequently identified risk factors³⁶. While the exact mechanism of thrombosis in this case is uncertain, it is intriguing to speculate that the production of viral cytokines by HHV-8 infected cells contributed to the formation of fibrin thrombi, and the fact that viral IL-6 is expressed by the tumor cells provides support for this hypothesis.

The diagnosis of intravascular lymphoma in this patient required sampling of deep subcutaneous adipose tissue. The excisional biopsy was prompted by the radiographic findings and insufficient sampling on fine needle aspiration. Even when no overt skin findings are present, blind skin biopsies have been shown to be a relatively sensitive way to diagnose intravascular lymphoma³⁷⁻⁴¹. In one case series, 10 of 12 consecutive patients with a known diagnosis of intravascular lymphoma had evidence of lymphoma on skin biopsies, both in lesions and in areas with healthy appearing skin³⁸. Several studies have shown that IVLBCL tends to involve the vessels of the subcutaneous fat but not the dermis^{37,39}. These studies and the findings in this case illustrate that a superficial shave or punch skin biopsy may not be sufficient to diagnose intravascular lymphoma.

The relative risk of developing a B-cell lymphoma is increased by a factor of at least 80-fold in patients with HIV as compared to the general population¹. The incidence of some types of viral-driven neoplasms in HIV-positive individuals has decreased dramatically with the introduction of HAART, including primary CNS lymphoma, which is nearly uniformly EBV-positive⁴²⁻⁴⁴. However, the incidence of other types of lymphoma has been relatively unaffected, including Hodgkin and Burkitt lymphoma^{11,42,44}. Reductions have also been seen in the frequency of neoplasms, such as Kaposi sarcoma, that arise in the presence of very low CD4 counts⁴⁴. Interestingly, lymphoproliferative disorders with HHV-8 and EBV co-infection may arise in patients with well controlled HIV viral loads and CD4 counts greater than 500, as occurred in this case³. Thus, as patients live longer with HIV infection and fewer deaths are attributable to opportunistic infections or other AIDS-defining illnesses, HHV-8 and EBV driven lymphomas may become increasingly prominent.

In summary, EBV and HHV-8 are recognized as important contributors toward lymphomagenesis, but only rare LPDs involving co-infection by these viruses have been described. The findings in this case suggest that inhibition of IL-6 signaling could provide a potential strategy for the amelioration of symptoms in some patients with HHV-8 lymphomas⁴⁵, and also demonstrate that HHV-8 and EBV-positive lymphomas can present not only as effusions or solid tumor masses but also as intravascular lymphomas.

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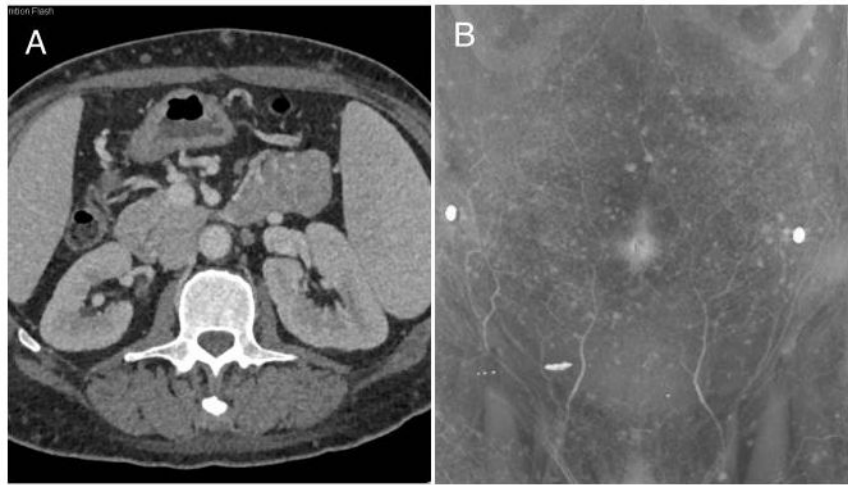


Figure 1. Radiographic studies of the abdomen and pelvis demonstrate numerous subcutaneous nodules

Axial computed tomography scans show multiple nodules in the subcutaneous fat without any enhancement (A). The 3D volume rendered images show the extent of lesion involvement over the abdominal wall (B). These nodules also demonstrated mild FDG uptake (not shown).

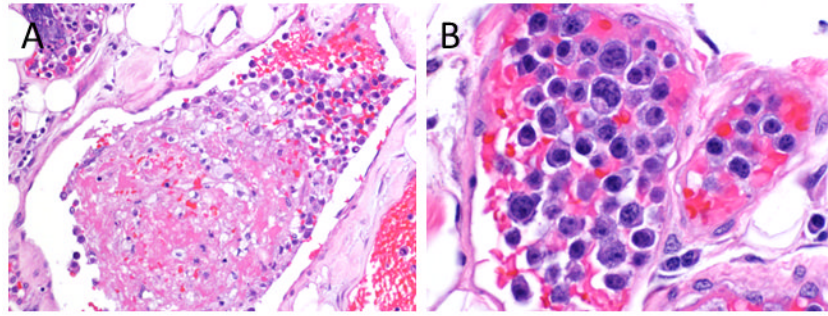


Figure 2. Thrombosed vessels with a mixed inflammatory infiltrate and prominent atypical intravascular cells

An excisional biopsy of the subcutaneous nodules revealed vessels that contained partially organizing thrombi and a mixed inflammatory infiltrate along with some atypical cells (A, H&E, original magnification 20X). The atypical cells had a moderate amount of eosinophilic cytoplasm and round to oval nuclei with one or more prominent nucleoli (B, H&E, original magnification 50X).

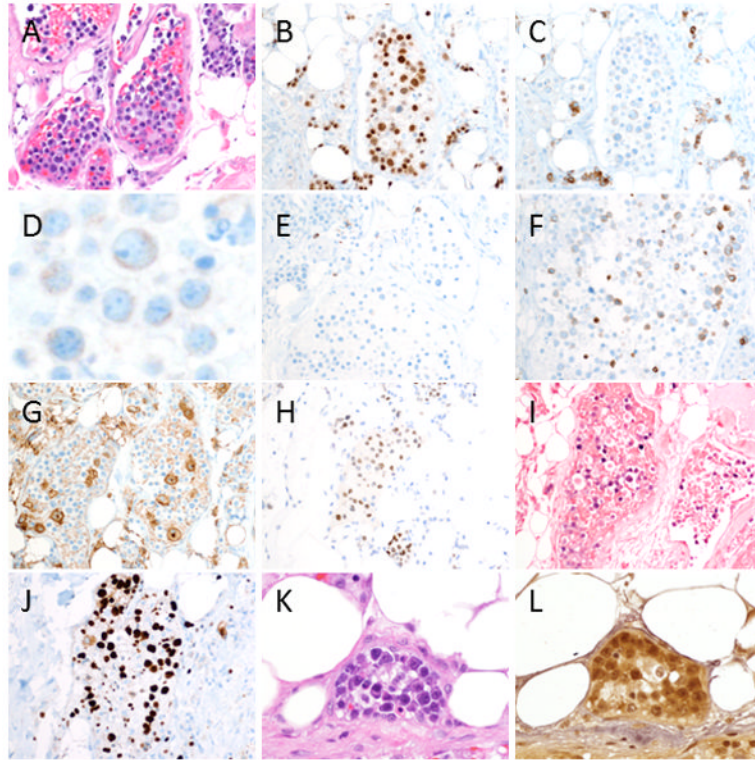


Figure 3. Immunostains and in situ hybridization reveal an HHV-8+, EBV+ B-cell lymphoma with aberrant T-cell marker expression

The atypical cells (A, H&E 20x) were positive for MUM-1 (B) and had dim expression of CD79a (C and D), but were negative for CD20 (E), CD19, Pax-5 and CD138 (not shown). The tumor cells also expressed dim cytoplasmic CD3 (F), dim CD4 (G), and CD45-RO (not shown), but were negative for CD5, CD7, CD8, CD56 and TIA-1 (not shown). An immunostain for HHV8 (LANA-1) (H) and an in situ hybridization for EBV (EBER) (I) were positive in the neoplastic cells, which were restricted to the intravascular compartment. The tumor cells had a high Ki-67 proliferation index (J). The neoplastic cells (K, H&E 50x) also showed expression of viral IL-6 (L).

Table 1

	Description	Presentation	Phenotype
Primary Effusion Lymphoma	<ul style="list-style-type: none"> • Large B cell neoplasm • Tumor cells can show immunoblastic, plasmablastic or anaplastic morphology 	<ul style="list-style-type: none"> • Serous effusions without detectable tumor masses • Can rarely present as solid masses (extracavitary PEL⁶) • Median survival <6 months • Often seen in patients with HIV or other immunodeficiency 	<ul style="list-style-type: none"> • Always HHV8+ • May lack EBV in the elderly • Lack pan B-cell markers, but usually MUM-1+ • Can show aberrant T cell antigen expression including CD3 • Thought to arise from post germinal center B- cells
Multicentric Castleman Disease and associated plasmablastic lymphoproliferative disorders	<p><u>MCD</u>: Angiofollicular hyperplasia and plasma cell infiltration</p> <p><u>Large B-cell lymphoma arising in HHV8-associated MCD</u>: monoclonal HHV-8-infected lymphoid cells that resemble plasmablasts, arising in the setting of MCD; as disease progresses the plasmablasts may become scattered in the interfollicular area and coalesce to form clusters or sheets termed microlymphomas</p>	<ul style="list-style-type: none"> • Systemic disease with peripheral or systemic lymphadenopathy, hepatomegaly and/or splenomegaly • Often preceded by Kaposi's sarcoma • Predominantly in HIV+ patients 	<ul style="list-style-type: none"> • Always HHV-8+ by the 2008 WHO classification⁴⁶ • Generally EBV negative, but EBV/HHV-8 co- infection has been reported with microlymphomas^{12,13} • Plasmablasts express IgM and lambda light chain • Lack clonal IgH gene rearrangements • Arise from naïve B-cells
Germinotrophic lymphoproliferative disorder	Germinotropic aggregates of plasmablasts	<ul style="list-style-type: none"> • Localized lymphadenopathy • Usually seen in HIV- negative patients • Indolent course 	<ul style="list-style-type: none"> • HHV-8 and EBV+ • Lack pan B-cell markers but MUM1+ • Polyclonal or oligoclonal IgH • Arise from post germinal center B-cells