Human Pathology: Case Reports (2015) 2, 49–54

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Human PATHOLOGY Case Reports

http://www.humanpathologycasereports.com

Unusual immunophenotypic variant of large B-cell lymphoma associated with HHV-8 and EBV in an HIV positive patient

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Received 7 December 2014; revised 5 February 2015; accepted 6 February 2015

Keywords:
Primary effusion lymphoma;
Epstein–Barr virus;
Kaposi sarcoma-associated herpesvirus;
Human herpesvirus type 8

Abstract Human herpesvirus type 8, also known as Kaposi's sarcoma-associated herpesvirus (HHV-8/KSHV) has been associated with several lymphoproliferative disorders including Kaposi's sarcoma, primary effusion lymphoma (PEL), cases of multicentric Castleman's disease (MCD) including plasmablastic lymphoma associated with MCD, and germinotropic lymphoproliferative disorder. These lymphoproliferative disorders, with the exception of the latter, usually arise in HIV-positive or profoundly immunosuppressed patients. Herein, we describe an unusual large B-cell lymphoma in a 43 year-old male infected with HIV who presented with multiple lymphadenopathies. The tumor cells were positive for EBV, HHV-8/KSHV, CD20 (small subset), PAX5, and IgM and negative for CD138, and IgG. This lymphoma is difficult to classify following the 2008 WHO criteria and expands the current spectrum of viral-associated lymphomas.

1. Introduction

HHV-8/KSHV positive lymphomas include primary effusion lymphoma (PEL), plasmablastic lymphoma associated with multicentric Castleman's disease (MCD), and germinotropic lymphoproliferative disorder. PEL is a distinct clinicopathologic entity that accounts for approximately 4% of all AIDS-related lymphomas [1]. It usually

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http://dx.doi.org/10.1016/j.ehpc.2015.02.002

involves one specific body cavity (pleural, peritoneal or pericardial) in the form of an effusion without the presence of a tumor mass [2]. This type of lymphoma occurs most commonly in HIV and HHV-8/KSHV positive middle-aged males, is frequently associated with EBV, and has a dismal survival [2,3]. Less commonly, HIV positive patients may present with HHV-8/KSHV positive lymphomas that involve solid organs, lack a concurrent effusion, and exhibit morphologic, genotypic, and immunophenotypic features of classic PEL [4]. This distinct presentation, also known as the extracavitary/solid form, may involve lymph nodes, gastrointestinal tract, skin, lungs, and the central nervous system as the only site of involvement; however, it may also precede or follow the development of a malignant effusion of typical PEL [4].

Solid PEL can be difficult to diagnose. The tumor cells have variable cytomorphology ranging from plasmablastic or immunoblastic to frankly anaplastic and usually lack expression of pan-B-cell markers as well as surface and cytoplasmic immunoglobulins; nevertheless B-cell lineage can be demonstrated by the presence of monoclonal *IgH* gene rearrangements [4,5]. Detection of HHV-8/KSHV in tumor cells is required to establish the diagnosis [6].

Herein, we report the clinicopathologic features of a very unusual case of HIV-associated large B cell lymphoma, which is difficult to classify following the 2008 WHO criteria and discuss the divergence in the clinicopathologic features of this unusual case between the most important differential diagnoses (solid PEL, plasmablastic lymphoma associated with MCD, and germinotropic lymphoproliferative disorder).

2. Case report

The patient is a 43-year-old homosexual male with a remote history of syphilis who initially presented to an outside hospital in August of 2013 complaining of a four-month history of fevers, chills, and night sweats. He was admitted and found to be HIV positive for which he was started on highly active antiretroviral therapy. At presentation his absolute CD4 count was 99 cells/mL and HIV viral load was 243 copies (log 2.39). A CT scan revealed diffuse lymphadenopathy (axillary, mesenteric root, and retroperitoneum) and mild hepatosplenomegaly. An excisional biopsy of two right axillary lymph nodes was performed. A bone marrow biopsy near the time of diagnosis was negative for involvement by lymphoma. Chemotherapy with R-EPOCH (rituximab, etopoxide, vincristine, doxorubicin cyclophosphamide, prednisone) protocol was initiated three months after his initial presentation, for a total of six cycles. To assess response to therapy, a CT scan of the neck, chest, abdomen, and pelvis was performed after the fourth cycle and showed an increase in the number and size of chest and abdominal lymph nodes, indicating progressive disease. The patient underwent salvage chemotherapy but unfortunately passed away seven months after initial presentation.

Two blocks of formalin fixed paraffin embedded (FFPE) tissue containing two excisional lymph node biopsies, measuring 2 and 1.2 cm in greatest dimension were sent in consultation to the Division of Hematopathology at the University of Miami/Sylvester Comprehensive Cancer Center. Multiple 4-μm-thick tissue sections were prepared and stained with hematoxylin and eosin, and specific immunohistochemical stains. Molecular studies were performed on FFPE to determine *IgVH*, *IgH*, and T-cell receptor (TCR) gamma genes rearrangements by gene sequencing and fragment analyses.

Histologic sections revealed lymph nodes involved by lymphoma. The neoplasm had vaguely nodular pattern in one of the lymph nodes (Fig. 1A and B) and a diffuse pattern in the other lymph node (Fig. 1C). The lymph node sinuses were open and free of tumor cells. The tumor cells were large, mostly immunoblastic with occasional plasmablastic appearance. Mitotic figures and apoptotic bodies were common (Fig. 1D–F). A "starry sky" pattern was focally noted. Kaposi sarcoma or morphologic changes reminiscent of Castleman's disease were not identified.

Immunohistochemical stains showed that the tumor cells were positive for CD45/LCA, CD20 (weak, small subset) (Fig. 2A), PAX-5 (subset), MUM-1 (Fig. 2B), IgM (strong) (Fig. 2C), and CD30 (subset) (Fig. 2D); and were negative for CD3, CD4, CD5, CD7, CD34, CD56, CD138 (Fig. 2E), EMA, and IgG (Fig. 2F). They were also positive for HHV-8/KSHV (nuclear granular pattern) (Fig. 3A and insert), which highlighted the nodular pattern of the malignant cells. *In situ* hybridization analysis for EBV-encoded RNA (EBER) was positive (Fig. 3B and insert). The tumor cells were also moderately to strongly positive for nuclear expression of c-MYC (90%) (Fig. 3C) and BCL-6 (subset) (Fig. 3D). Additionally, immunohistochemistry for kappa and lambda light chains showed lambda light chain restriction (Fig. 3E and F) in the tumor cells and polytypic scattered plasma cells in the background. CD21 was performed to assess the status of the follicular dendritic cell network; nevertheless residual tissue was not present for adequate interpretation. However, staining for BCL-6 did not demonstrate remaining germinal centers.

Molecular studies revealed monoclonal *IgH* gene rearrangement and were negative for monoclonal *TCR* gamma gene rearrangement. Despite the strong expression of c-MYC detected by immunohistochemistry, rearrangements of the *MYC* gene were not detected by fluorescence *in situ* hybridization. An attempt to determine the mutational status of *IgVH* gene to support the presence of somatic