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Human Herpesvirus Type 8 (HHV8)

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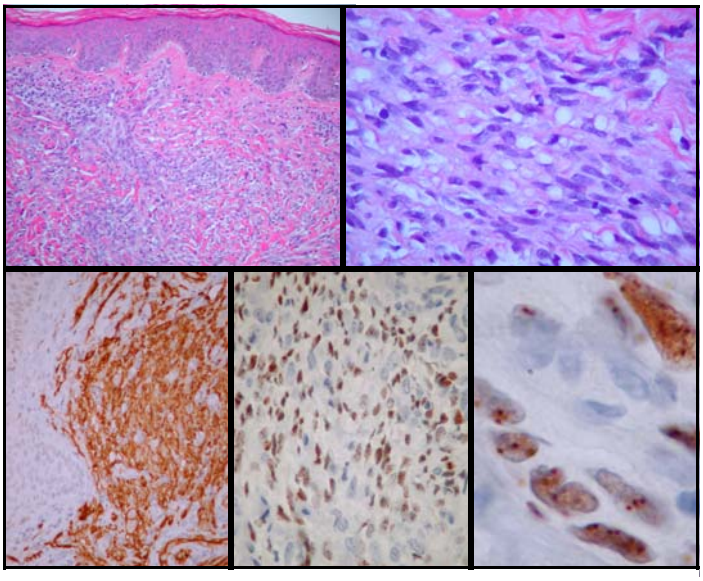
HHV8 is a recently discovered human herpesvirus that has been found to be intimately associated with **Kaposi's sarcoma**. ProPath recently acquired an antibody to HHV8 (latent nuclear antigen) that is applicable to paraffin section material, so this month we briefly review the conditions where HHV8 is found and discuss potential diagnostic uses of HHV8 immunostaining.

Before the emergence of AIDS in humans, Kaposi's sarcoma was most commonly found in elderly males of Eastern European or Mediterranean descent. However, as the number of HIV-infected people has risen, the prevalence of the disease has increased substantially. Multiple investigators have determined that HHV8 is associated with essentially all cases of Kaposi's sarcoma, regardless of whether the disease occurs in HIV-positive or HIV-negative patients. It has been found that HIV-positive patients have a higher frequency of Kaposi's sarcoma in extracutaneous sites, and many of us have struggled with the interpretation of small areas of atypical spindle cell proliferation in tiny (non-cutaneous) biopsy specimens taken from HIV-positive patients, where Kaposi's sarcoma enters into the differential diagnosis. Because of the universal association of HHV8 with Kaposi's sarcoma, identification of HHV8 in a suspicious spindle cell lesion can provide strong evidence in support of the diagnosis. This can be of great assistance, particularly if the atypical focus of interest is quite small or distorted by biopsy artifact.

Distinction of Kaposi's sarcoma from other vascular lesions can also be a challenging task, particularly when the biopsies in question are taken from HIV-positive patients. For example, the distinction of an angiomatoid/hemosiderotic variant of dermatofibroma from Kaposi's sarcoma is reportedly difficult in some small skin biopsies taken from HIV-positive patients. The obvious question that arises in this situation is whether or not HHV8 can assist in a distinction of Kaposi's sarcoma from its histological mimics. Although there have been some older publications of molecular studies that have reported HHV8 DNA sequences in non-Kaposi's vascular proliferations, a number of these studies have not been reproducible, and more recent studies have been unable to document the presence of HHV8 in vascular or other lesions that may mimic Kaposi's sarcoma. Therefore, these authors have concluded that identification of HHV8 is a very useful tool for distinguishing Kaposi's sarcoma from its mimics.

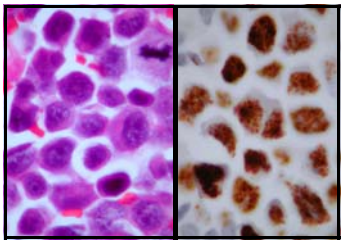


H&E sections (top left and top right) of a punch biopsy of skin from the upper back of a 46 year-old HIV-positive male, showing an atypical spindle cell proliferation suspicious for Kaposi's sarcoma. The CD31 immunostain (bottom left) was strongly positive, and immunostains for HHV8 (bottom center and bottom right) were also positive in the nuclei of the spindle cells, confirming the diagnosis of Kaposi's sarcoma. Many of the positive nuclei in this case showed prominent nuclear dots on high power.

Multicentric Castleman's disease is another disease that has been found to have an association with HHV8. The association is very high in multicentric Castleman's disease occurring in AIDS patients, although it has also been found in about half of non-HIV-associated multicentric

Castleman's disease. In multicentric Castleman's disease, HHV8 has been described in endothelial cells and in a population of large B-cells found in the mantle zone. It has also been found to be useful in highlighting early areas of involvement by Kaposi's sarcoma in lymph nodes demonstrating features of multicentric Castleman's disease.

Body cavity based lymphoma (BCBL) (also known as primary effusion lymphoma, or PEL) is another AIDS-associated neoplasm that has been found to have a very high association with HHV8 (and also an association with EBV in many cases). These are unusual lymphomas that present as effusions in a body cavity, that often are not associated with an identifiable mass, although in some cases an adjacent soft tissue mass or lymphadenopathy is noted. These tumors are typically composed of large anaplastic cells that generally do not express surface markers of B-cells or T-cells, although they frequently express CD45, EMA, CD30, and plasma cell-related markers such as VS38 or CD138. Because of the high degree of association with HHV8, immunostaining for HHV8 (or EBER in situ hybridization) can be useful in recognition of these unusual lymphomas. (Parenthetically, it is worth mentioning that since the original reports on this entity, there have been some reported cases of this lymphoma that have not been associated with either HIV or HHV8). There is also a report of HHV8-associated lymphomas occurring in the colon that have developed in HIV-positive patients, that were only secondarily associated with effusions. However, to our knowledge, HHV8 has not been identified in other lymphohematopoetic malignancies, with the exception of some reports of a possible association with multiple myeloma.



H&E (left) and HHV-8 (right) on an AIDS-associated lymphoma

HHV8 latent nuclear antigen immunoreactivity is localized to the nucleus of the infected cells, where it may appear as diffuse nuclear reactivity or as a series of dots within the nucleus. This antibody is currently available in the ProPath immunohistochemistry lab. Although it is not yet listed on the client requisition form, simply write it in if you would like this stain on a case.

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