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KSHV/HHV8-associated lymphomas

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It was only after the discovery of KSHV/HHV8, that primary effusion lymphoma (PEL) could be recognized as a distinct entity, thanks to its consistent association with HHV-8 infection. As a consequence, PEL has been included in the recent WHO lymphoma classification, within the group of lymphomas occurring more specifically in HIV positive patients.

PEL is a rare subset of AIDS non-Hodgkin's lymphoma predominantly growing in the pleural, pericardial, and peritoneal cavities as neoplastic effusions, usually without a contiguous tumor mass. Morphologically, PEL shows features bridging immunoblastic and anaplastic large-cell lymphomas, and frequently displays a certain degree of plasma cell differentiation.

Phenotypically, expression of CD45 antigen confirms the hematolymphoid derivation of PEL cells, which exhibit an indeterminate immunophenotype since they lack expression of B- and T-cell associate antigens. Conversely, PEL cells generally express various markers associated with activation, including CD30, CD38, CD71, and epithelial membrane antigen (EMA). Moreover, PEL cells usually express several plasma cell markers (including CD138, VS38c and MUM-1/IRF4). Despite its indeterminate phenotype, PEL is consistenjtly represented by a monoclonal B-cell population, as documented by immunogenotypic studies. Taken together, the immunophenotypic and immunogenotypic characteristics of PEL suggest that this lymphoma represents the malignant counterpart of a B-cell that has reached a mature stage of development and is shifting toward terminal plasma cell differentiation.

Recently, KSHV/HHV8 has been detected by immunohistochemistry and/or polymerase chain reaction even in lymphoma cases presenting as tissue masses. However, all these KSHV/HHV8-associated lymphomas, also called "solid PEL", have been reported prior the development of an effusion lymphoma and/or following resolution of PEL. These cases primarily involved extranodal tissue locations and curiously demonstrated morphology, immunophenotype, KSHV/HHV8 viral status, and immunoglobulin light chain gene rearrangement identical to their PEL counterpart. According to the HIV viral status of the patient, these KSHV/HHV8-associated lymphomas are commonly found in HIV setting. However, cases of KSHV/HHV8-associated solid lymphomas have also been discovered in HIV-seronegative patients with serous effusions.

More recently, the spectrum of KSHV/HHV8-associated lymphoproliferative diseases in HIV setting has been expanded to include KSHV/HHV8-associated solid lymphomas without serous effusions. In fact, KSHV/HHV8 has been detected by immunohistochemistry and/or polymerase chain reaction in lymphoma cases presenting as tissue masses or lymph node-based disease (in individuals with MCD or AIDS-associated KS). These lymphomas were generally composed of a proliferation of immunoblastic-like cells, but in some cases the neoplastic cells showed greater pleomorphism, anaplastic or plasmablastic features. Irrespective of morphologic type, tumor cells usually express a plasma cell-related phenotypic profile.

In a recent work we reported four cases of KSHV/HHV8 bearing solid lymphomas without serous effusions. These lymphomas occurred in AIDS patients and in a seronegative person. This is the first work which provides evidence for the existence of a new, previously undescribed, KSHV/HHV8-associated lymphoma in HIV-seronegative patients without serous effusions.

These lymphoma cases were extracavitary, with a predilection for the lymph nodes, and displayed immunoblastic or anaplastic large cell morphology. Paraffin immunohistochemical studies showed that the tumor cells were strongly positive for the plasma cell reactive antibody MUM1/IRF4. Summing up, despite the diversification in the clinical presentation of KSHV/HHV8-associated lymphomas, the cases reported shared an identical

biopathologic base with similar morphology (immunoblastic-like or anaplastic features), and immunophenotype (consistent expression of plasma cell markers in the absence of common lymphoid markers). These lymphomas probably represent different variants of the same disease.

Table 1: Clinical presentation of KSHV/HHV8-associated lymphomas.

Primary Effusion Lymphomas (PEL) – in the absence of tumor masses*
"Solid" lymphomas associated with serous effusions**
- prior to the development of PEL
- following resolution of PEL
"Solid" lymphomas without serous effusions***
- extranodal tissue based
- lymph node based

** mainly found in the HIV setting and usually related to marked disruption of the immune function; ** commonly found in the HIV setting; *** irrespective of the HIV status*

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