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Extracavity primary effusion lymphoma presenting in a lymph node without lymphomatous effusions

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Abstract Primary effusion lymphoma (PEL) is a distinct clinicopathologic entity associated with human herpesvirus 8 (HHV8), which usually presents as a lymphomatous body cavity effusion. Rare cases of PEL are extracavitary and manifest as a solid tumor mass. Here we report an unusual case of extracavitary PEL (EPEL) involving lymph nodes with no evidence of a body cavity effusion. The neoplasm was comprised of large pleomorphic cells with prominent nucleoli and frequent mitotic figures that expressed HHV8, EBV, CD38 and CD30, but lacked all lineage-specific markers. The patient was found to be HIV positive after the diagnosis of EPEL. Antiretroviral therapy initially reduces tumor size, but the patient expired three months later due to multiple complications. PEL and EPEL are differing manifestations of a rare disease entity as defined by the World Health Organization 2008 classification. It is unknown why a small subset of these cases forms extracavitary masses with or without malignant effusions. Comparison with mouse xenograft models may provide unique insights into the pathogenesis of this disease for possible future studies.

1. Introduction

Primary effusion lymphoma (PEL) is an uncommon aggressive B-cell lymphoma that is universally associated with human herpesvirus-8 (HHV8) [1,2]. Typically, PEL presents with malignant effusions, without an associated tumor mass [3]. This lymphoma is most frequently diagnosed in HIV-positive patients, but may follow solid

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organ or stem cell transplantation. Most cases of PEL harbor the Epstein–Barr virus (EBV), which together with HHV8, is postulated to drive malignant transformation. Infrequently, PEL has been reported in the absence of immunosuppression in elderly patients in the Mediterranean where a high prevalence of HHV8 has been documented [4,5].

Extracavitary PEL (EPEL) is a rare manifestation of PEL that occurs as an isolated tumor mass. It may be synchronous or metachronous with cavitary effusions, but may also arise independently [6]. EPEL exhibits morphologic and immunophenotypic features as well as expression of specific genes that overlap with classical PEL [7]. The rarity of EPEL however, has hindered progress in understanding its pathogenesis.

We report an unusual case of EPEL involving lymph nodes in a patient with no known immunosuppression at the time of diagnosis. No body cavity effusions or other extranodal sites of disease were detected on staging studies. A workup triggered after the diagnosis confirmed HIV infection. This case raised the following important considerations: (1) the need for a high index of suspicion in the workup of nodal large cell lymphomas with atypical immunophenotypic features; (2) awareness of EPEL as a differential diagnostic consideration in unusual anatomic sites; (3) the need for thorough workup for immunodeficiency even in the absence of clinical history due to its strong association with cases of PEL and EPEL.

2. Case report

A 49-year old man presented with a rapidly enlarging and painful right neck mass, anorexia and an unintentional 80-pound weight loss over a period of 2–3 months. Apart from bipolar affective disorder, he had no past medical or family history. On physical examination, a 10 cm firm, non-tender, fixed mass without overlying skin changes was present in his right neck which extended from the angle of the jaw to the supraclavicular fossa vertically, to the midline of the neck anteriorly and to the lateral occiput posteriorly. A CT scan revealed a multilocular mass representing a collection of matted lymph nodes. An excisional biopsy was evaluated by histology, flow cytometry, and cytogenetic studies. Systemic workup revealed mild splenomegaly, but no effusions or other nodal or extranodal sites of disease. After an extensive immunohistochemical workup, a diagnosis of EPEL was made. A complex clonal karyotype was obtained by conventional cytogenetic analysis. The co-expression of HHV8 and EBV in neoplastic cells substantiated the diagnosis. Although there was no history of immunosuppression, HIV testing was warranted given the association of EPEL with HIV, which showed that the patient was seropositive for HIV with a high serum viral load and a low CD4 count. He also had marked anemia and neutropenia although a bone marrow biopsy showed no involvement by lymphoma.

Six weeks after the diagnosis of EPEL, the patient was hospitalized for Salmonella bacteremia, and started on highly active antiretroviral therapy (HAART). Two weeks later, the mass slightly diminished in size; he was given localized radiation to the right neck. He was hospitalized again shortly thereafter for worsening shortness of breath and developed bilateral subdural hematomas after sustaining a fall. His mental status continued to deteriorate and the clinical course was further complicated by Salmonella sepsis. The patient was transferred to hospice care and expired two weeks later.

3. Materials and methods

The case was sent in consultation to the Department of Pathology at Stanford University Medical Center. All investigations were carried out with the approval of the institutional review board of Stanford University.

Immunohistochemistry and in situ hybridization studies were carried out as part of the routine clinical workup of the case. An initial panel of immunohistochemistry was performed at the outside institution and was reviewed: these included CD20, CD3, CD5, CD43, CD10, BCL6, BCL1, BCL2, Ki67, cytokerin, HMB45, Melan A and S100. Additional immunohistochemical stains, including CD30, CD38, CD79a, OCT2, CD138, CKMIX, EMA, HHV8, MUM1, CD56, CD45RB and SALL4, and EBV/EBER in situ hybridization, were performed on an automated immunostainer (Ventana Benchmark, Roche/Ventana Medical Systems, Tucson, AZ). A 4-color Fluorescence-Activated Cell Sorter-Calibur instrument and Cell Quest software (Becton-Dickinson, San Jose, CA) was used. Specific cell populations were identified and gated based on antigen expression patterns compared by fluorescence intensity against standard isotype controls.

4. Results

Histologic examination revealed remnants of a lymph node capsule with complete architectural effacement by an abnormal infiltrate composed of sheets of large cells. Scant numbers of small lymphocytes and histiocytes were scattered in the background. The atypical large cells were dishesive and had highly pleomorphic nuclear outlines with one to several prominent nucleoli, vesicular chromatin and moderate amounts of cytoplasm. Atypical mitotic figures were frequent. The histologic differential