Primary Effusion Lymphoma
Sanjay Patel, MS, MPH; Philip Xiao, MD

Primary effusion lymphoma is a large cell non-Hodgkin lymphoma localized predominantly in body cavities and occasionally in extracavitary regions. It presents with characteristic lymphomatous effusions in the absence of solid tumor masses, and pleural, peritoneal, and pericardial spaces are most often involved. It is typically associated with human herpesvirus 8 infection in immunocompromised individuals, in the setting of human immunodeficiency virus infection, organ transplantation, or in rare cases advanced age. Histologically, primary effusion lymphoma is characterized by atypical lymphoid cells of B-cell lineage with large nuclei and prominent nucleoli. Demonstration of human herpesvirus 8 latent antigens is required for diagnosis, and treatment modalities are limited at this time. In this review, we aim to summarize clinicopathologic features of this rare and unique entity.


Primary effusion lymphoma (PEL) was first recognized as a distinct entity in the World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues in 2001. It is characteristically associated with human herpesvirus 8 (HHV8) infection; coinfection with Epstein-Barr virus (EBV) is commonly found. It presents as a large cell non-Hodgkin lymphomatous effusion within body cavities (pleural, peritoneal, or pericardial) and usually involves only one body site.

EPIDEMIOLOGY

The majority of cases occur in young to middle-aged males, either homosexual or bisexual, with human immunodeficiency virus (HIV) infection and severely immunocompromised. However, it can also occur in HIV-negative individuals who are immunocompromised as a result of solid-organ transplantation or cirrhosis. In rare instances, PEL can affect elderly individuals who are otherwise immunocompetent but live in geographic areas with high HHV8 prevalence, such as the Mediterranean region; these cases may be EBV negative.

ETIOLOGY AND PATHOGENESIS

HHV has been implicated in the pathogenesis of PEL; it encodes numerous genes involved in inducing cell proliferation and inhibiting apoptosis. Epstein-Barr virus, although integrated clonally in lymphoma cells, may not be pathogenic because it has a restricted latency pattern with only EBNA1 and EBER gene expression. Comparative genomic hybridization studies have identified deletions of the fragile site tumor suppressors WWOX and FHIT. coinfection with EBV was associated with significantly fewer gross genomic aberrations.

CLINICAL PRESENTATION

Primary effusion lymphoma is clinically unique in that it arises predominantly as a lymphomatous effusion within body cavities such as the pleural, pericardial, and peritoneal spaces, typically without any associated extracavitary masses. Symptoms result from the accumulation of malignant effusion, which often produces mass effects. Patients with pleural or pericardial disease may present with dyspnea, and those with peritoneal disease can present with ascites. A subset of cases develop solid tumors in structures adjacent to the body cavity (eg, the pleura). Cases involving solid masses exhibiting morphology, immunophenotype, and gene expression profiles similar to classical PEL have also been described and subsequently labeled “extracavitary PEL.” Such extracavitary presentations more commonly involve the gastrointestinal tract. The most frequent causes of death in PEL patients, aside from progression of the lymphoma, are opportunistic infections and other HIV-related complications.

MORPHOLOGIC FEATURES

Cytologic (cytospin) preparations of the involved effusion fluid are typically used for pathologic examination and diagnosis. The neoplastic cells of PEL are usually large, with round to irregular nuclei, prominent nucleoli, and varying amounts of deeply basophilic cytoplasm with occasional cells vacuolated (Figure 1). Characteristically, the cells range in appearance from immunoblastic to plasmablastic to anaplastic (Figure 1). Anaplastic cells may occasionally resemble the Reed-Sternberg cells found in classical Hodgkin lymphoma. Lymphoma cells appear less pleomorphic in histologic sections than in cytospin preparations. Proliferation rate is high; numerous mitotic figures are appreciated, with some cases showing a “starry-sky” pattern.

ANCILLARY STUDIES

Primary effusion lymphoma cells typically display a “null” lymphocyte phenotype: CD45 is expressed, but common

Accepted for publication September 19, 2012.
From the Department of Pathology and Laboratory Medicine, The Brooklyn Hospital Center, Brooklyn, New York.
The authors have no relevant financial interest in the products or companies described in this article.
Reprints: Philip Xiao, MD, Department of Pathology and Laboratory Medicine, The Brooklyn Hospital Center, Brooklyn, NY 11201 (e-mail: px9001@nyp.org).
pan-B-cell (CD19, CD20, CD79a, surface immunoglobulins) and T-cell (CD3, CD4, CD8) markers are absent. Instead, however, markers of lymphocyte activation (CD30, CD38, CD71, epithelial membrane antigen, human leukocyte antigen–DR) and plasma cell differentiation (CD138) are often present.\(^{1,12}\) Bcl-6 is usually absent.

Definitive diagnosis hinges on detection of viral infection by HHV8 in the neoplastic cells. Immunohistochemical studies to detect expression of latency-associated nuclear antigen, LANA-1 (Figure 2), are currently the standard assay to demonstrate evidence of infection; typically, positive results are characterized by a nuclear dotlike pattern. Epstein-Barr virus infection can be demonstrated by in situ hybridization for EBV-encoded small RNA (EBER); immunohistochemical studies for EBV latent membrane protein 1 are negative. Viral interleukin 6 is expressed by a variable subset of lymphoma cells, and immunohistochemical studies for this protein may be helpful for confirmation. Molecular studies demonstrate clonal immunoglobulin gene rearrangements and somatic hypermutation, indicating that the cell of origin is a postgerminatal center B cell.\(^{1-4,13}\) Polymerase chain reaction can demonstrate presence of the viral genome.\(^{4,13-16}\) Cytogenetic studies have not demonstrated any recurrent chromosomal abnormalities.

**DIFFERENTIAL DIAGNOSIS**

Initial assessment of a malignant effusion is performed by a cytopathology laboratory. A lymphoma may not be suspected initially when malignant cells in the smear or cell block are reviewed. A high index of suspicion in the proper demographic setting may be helpful in the case of a malignant lymphoid effusion within a body cavity; PEL has to be differentiated from other types of non-Hodgkin lymphoma by its morphologic features and unique immunophenotype. Human immunodeficiency virus–positive individuals, for example, may have a Burkitt lymphoma with plasmacytoid differentiation, which can in rare cases present as a lymphomatous effusion. However, such cases will be negative for HHV8 but will demonstrate C-MYC gene rearrangement.

Pyothorax-associated lymphoma may mimic PEL clinically.\(^{17}\) However, it typically arises in elderly men who are HIV negative. It is related to the past treatment of pulmonary or pleural tuberculosis by inducing artificial pneumothorax. Although more cases have been reported from Japan, the entity exists in the Western hemisphere. Morphologically, lymphoma cells in pyothorax-associated lymphoma are large in size, express B-cell markers, are EBV positive, and are HHV8 negative. These features differentiate it from PEL.

Plasmablastic lymphoma is an HIV-associated variant of diffuse large B-cell lymphoma demonstrating plasmablastic morphology that can mimic PEL. Neoplastic cells show prominent central nucleoli and abundant basophilic cytoplasm and are typically CD20 negative/CD138 positive, indicative of terminal B-cell differentiation, much like those found in PEL. Nearly all cases of plasmablastic lymphoma have been found in HIV-positive patients, and most involve the oral cavity or jaw.\(^{18}\) In addition, nearly all cases of plasmablastic lymphoma are EBV positive. Like PEL, plasmablastic lymphoma is associated with an unfavorable outcome.

Anaplastic large cell lymphoma is a rare form of non-Hodgkin lymphoma presenting commonly in young patients (median, 33 years), albeit carrying the best overall 5-year survival rate (77%) among all high-grade lymphomas.\(^{19}\) Anaplastic large cell lymphoma cells are characterized by strong CD30 positivity and frequent epithelial membrane antigen positivity as well. Leukocyte common antigen (CD45) is often expressed along with various T-cell–specific markers, although null-cell immunophenotype forms also exist in spite of having T-cell genotypes.\(^{20}\) Many cases demonstrate an anaplastic lymphoma kinase–nucleophosmin t(2;5) gene translocation.\(^{21}\) Anaplastic large cell lymphoma may be either predominantly systemic or primarily cutaneous in its presentation. Very rarely, as shown by Chan et al,\(^{22}\) the presenting feature of anaplastic...
large cell lymphoma can be a pleural effusion mimicking PEL. Such forms demonstrate pleural fluid containing large, lymphoid cells with marked nuclear atypia. However, these rare cases of anaplastic large cell lymphoma, in spite of having cytologic features that resemble PEL, are differentiated immunologically by their absence of HHV8 and EBV expression and clinically by a younger and HIV-seronegative patient population.

A diagnosis of plasma cell myeloma should also be entertained in patients with suspected PEL. Whereas the neoplastic cells of PEL are typically CD45 positive, and fail to produce immunoglobulin, plasma cell myeloma is marked by a neoplastic proliferation of clonal immunoglobulin-producing plasma cells in the bone marrow; these are typically CD56, CD38, and CD138 positive and CD45 negative. Plasma cell myeloma is characterized by plasma cells that range in morphology from mature forms with condensed “clock face” chromatin and no nucleoli appreciated to immature forms with higher nuclear to cytoplasmic ratio and distinct to prominent nucleoli; some cases may have plasmablastic morphology. The characteristic clear area adjacent to the nucleus (hof) represents the Golgi apparatus and is indicative of ongoing immunoglobulin production.

Although each of these differential diagnoses shares morphologic features with PEL, each can also be distinguished from PEL by the absence of demonstrable HHV8 antigen within neoplastic cells.

**TREATMENT**

There is no standard treatment available for PEL at present. Attempts have been made at using standard chemotherapy regimens (eg, cyclophosphamide, doxorubicin, vincristine, and prednisolone) but the prognosis for patients with PEL remains extremely poor. Median survival is less than 6 months. For those with HIV-associated PEL, treatment with highly active antiretroviral therapy is often used, if not already implemented. A few cases have demonstrated prolonged remissions with bortezomib-containing regimens.

**CONCLUSION**

Primary effusion lymphoma is a HHV8-related lymphoma. It can present as an intracavitary malignant serous effusion in the absence of solid mass(es) or rarely as solid lesions in areas such as the gastrointestinal tract. Diagnosis hinges on demonstrating HHV8 latent antigen expression in lymphoma cells, which serves to differentiate it from other lymphomas having similar clinical presentations and morphologic profiles.

**References**