A Rare Genital Concomitant Presentation of Extracavitary Primary Effusion Lymphoma and Squamous Cell Carcinoma

KINDA RAJAB, MD; YAEL TSENTER, MD; ADAM J. OLSZEWSKI, MD; LIU LIU, PhD, CYNTHIA JACKSON, PhD; LIANG CHENG, MD; DIANA O. TREABA, MD

ABSTRACT

Primary Effusion Lymphoma (PEL) is a rare subtype of large B-cell lymphoma characterized by malignant effusions in body cavities, typically without solid masses. Commonly affected areas include pleural, pericardial, and peritoneal spaces. However, PEL can present as Extracavitary Primary Effusion Lymphoma (EC-PEL) with solid tumor masses in different organs. We encountered a unique case of EC-PEL in an HIV-infected patient presenting concomitant with a squamous cell carcinoma as a penile mass. This case highlights the diverse presentations of PEL and the importance of considering lymphomatous involvement in uncommon sites, particularly in immunocompromised individuals. To our knowledge, this is the first EC-PEL case presenting as a penile mass, in association with an invasive squamous cell carcinoma.

KEYWORDS: Primary Effusion Lymphoma; Extracavitary PEL, HIV; penile mass; immunocompromised

INTRODUCTION

Human Herpesvirus 8 (HHV8), also known as Kaposi sarcoma-associated herpesvirus, is an oncogenic lymphotropic virus prevalent in sub-Saharan Africa and the Mediterranean. It is associated with various malignancies, including PEL, a rare and aggressive form of large B-cell non-Hodgkin lymphoma. PEL presents as malignant effusions without solid masses, often within pleural, pericardial, and peritoneal spaces. While predominantly diagnosed in HIV-infected individuals and universally associated with HHV8, co-infection with EBV occurs in approximately 80% of cases.[1] PEL also affects the elderly and transplant recipients. Beyond its classic presentation, PEL may manifest as solid tumor masses, known as extracavitary PEL (EC-PEL).[2] EC-PEL has been documented in various sites, including lymph nodes, gastrointestinal tract, lungs, skin, liver, and spleen, with lymph nodes being most frequently affected,[3,4] while CNS,[5] bone marrow, heart[4,6] or intravascular[7] presentations being rarely reported.

CASE PRESENTATION

A 77-year-old man, with a long history of HIV (>20 years) on antiretroviral therapy (most recently on bictegravir-emtricitabine-tenofovir alafenam and rilpivirine), resected brain tuberculoma, squamous cell carcinoma of the esophagus treated with chemoradiation therapy, and well-to-moderately differentiated, keratinizing invasive squamous cell carcinoma of the oral cavity treated with surgery and radiation therapy, presented with a persistent ulcerating mass located on the head of his penis, initially noted seven years before. The patient's CBC was notable only for a mild thrombocytopenia (118 x 10^9/L, reference range 168–382 x 10^9/L). Flow cytometry studies detected a CD4:CD8 cell ratio of 0.228 (reference range 0.9–5) with a significantly decreased CD4 positive absolute lymphocyte count of 0.182 x 10^9/L (reference range 0.5–1.9 x 10^9/L).

A biopsy of the penile lesion identified an invasive keratinizing squamous cell carcinoma invading the corpus spongiosum and lymphovascular structures and the patient underwent a partial penectomy with resection of a 2.5 x 1.5 cm fungating mass with focal invasion in the corpora spongiosa.

Microscopic examination was notable for invasive keratinizing squamous cell carcinoma and also for adjacent dense aggregates of highly atypical large lymphoid cells [**Figure 1**], primarily with immunoblast-like morphology [**Figure 2**].

Figure 1. Hematoxylin and eosin stain. Ob. 4x. Extracavitary Primary Effusion Lymphoma and Squamous Cell Carcinoma.

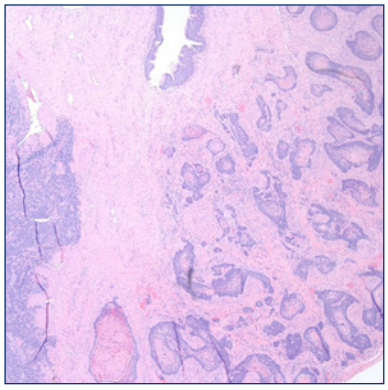


Figure 2. Hematoxylin and eosin stain. Ob. 50x, immersion oil. Extracavitary Primary Effusion Lymphoma cells with a predominant immunoblast-like morphology.

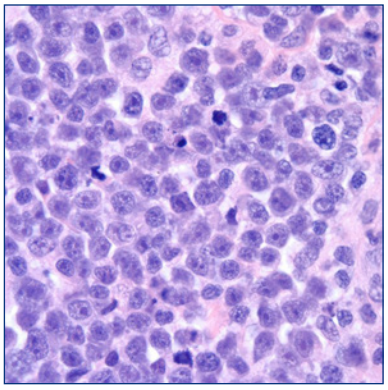


Figure 3. MUM1 immunostain. Ob. 50x, immersion oil. Lymphoma cells have uniform nuclear MUM1 positivity.

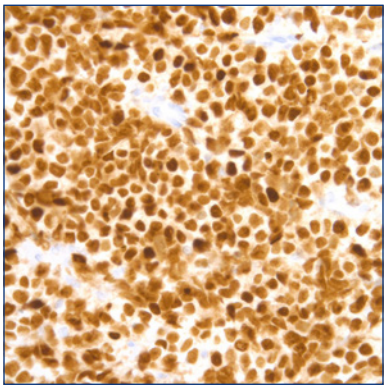


Figure 4. HHV8 immunostain. Ob. 50x, immersion oil. Lymphoma cells have uniformly nuclear HHV8 positivity.

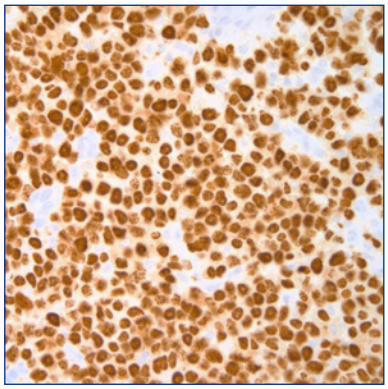


Figure 5. Ob. 50x, immersion oil. Lymphoma cells have uniformly nuclear EBER positivity.

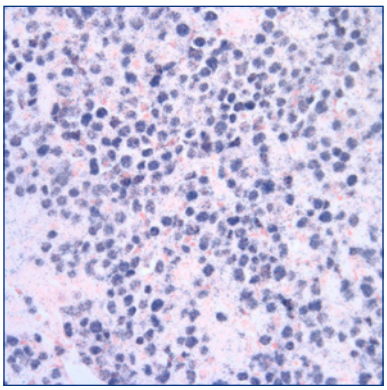
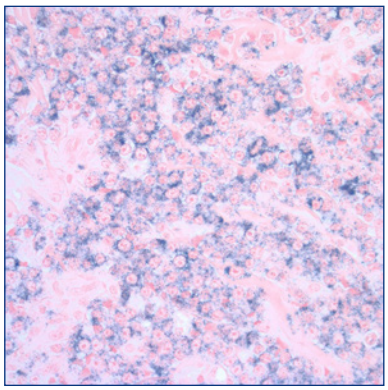


Figure 6. Kappa in-situ hybridization stain. Ob. 50x, immersion oil. Lymphoma cells have weak uniform kappa immunoglobulin cytoplasmic staining.



There were admixed plasmablast and centroblast-like cells, and an increased number of mitoses.

The neoplastic lymphoid cells were positive for MUM-1 [**Figure 3**], HHV-8 [**Figure 4**], c-myc, and CD30, with uniform, moderate-to-strong CD3 cytoplasmic staining. They had variable CD45, OCT2, CD7 and EMA expression and in a small subset (25–30%) were p53 positive. Their proliferation rate was high (~100% with MIB1 antibody to Ki-67 antigen). The neoplastic large lymphoid cells were negative for CD15, CD138, CD4, CD8, granzyme B, CD56, ALK1, GATA3, BCL2, BCL6, BCL1, CD10, CD21, CD20, PAX5, CD79a, BOB1, CD19, IgM, and TdT. EBER in-situ hybridization was positive, indicating EBV infection [**Figure 5**], and the neoplastic population was kappa restricted (weak staining) by in-situ hybridization stains [**Figure 6**]. PCR studies detected the presence of immunoglobulin heavy chain gene rearrangements and identified a minor clonal T-cell receptor beta gene rearrangement. FISH analysis was reported negative for MYC rearrangement. Molecular next generation sequencing analysis of a selected area of lymphoma identified two variants with variant allele frequency (VAF) close to 50%, likely arising from germline origin: MPL c.1653+1del likely pathogenic variant with a variant allele frequency (VAF) of 43.5% and UBA1 p.P25S variant of unknown significance (VUS) with 49.3% VAF. In addition, three low level somatic pathogenic variants were also detected with VAFs between 1–3%: TET2 p.Y1598Hfs*14, ATM p.Q2414* and DNMT3A p.R320*. A diagnosis of extracavitary primary effusion lymphoma was rendered.

Clinical evaluation revealed a well-healed penectomy stump and an additional presence of 2.5 cm ulcerated squamous cell cutaneous carcinoma on the scalp. A positron emission tomography combined with computerized tomography (PET-CT) demonstrated the cutaneous carcinoma, two sites of metabolic uptake (SUVmax of 7.4) in the site of penectomy, suggestive of residual tumor, but no other sites suspicious for lymphoma. After consideration of treatment options, the patient declined to consider further radiation therapy or cytotoxic chemotherapy, and elected to receive off-label therapy with the anti-CD30 antibody-drug conjugate brentuximab vedotin in combination with a PD-1 inhibitor nivolumab, as the combination has shown safety in other settings[8] for older individuals and was expected to have activity against residual PEL or penile squamous carcinoma. After three courses of this therapy the patient attained a complete metabolic response and discontinued further therapy. His cutaneous carcinoma has markedly decreased on therapy as well and allowed for subsequent resection. He remains free of the lymphoma at 16 months from diagnosis.

DISCUSSION

HIV-infected individuals are at higher risk for hematological malignancies, particularly aggressive B-cell non-Hodgkin lymphomas.[9] PEL is linked to HHV-8 and is most commonly diagnosed in HIV-positive patients, and less commonly in elderly and transplant recipients. PEL primarily affects males.[10] Though it constitutes 2–4% of all AIDS-related NHLs, the lack of comprehensive epidemiologic data complicates precise quantification.[11]

PEL/EC-PEL lymphoma cells, originating from B-cells, may lack CD45, risking misdiagnosis. They also typically lack B-cell markers such as CD19, CD20, CD22, PAX5, OCT2, BOB1, and CD79a and often lack surface/cytoplasmic immunoglobulin light chain expression. They do not express germinal center markers (CD10, BCL6) being characterized of markers of terminal B-cell differentiation: HLA-DR, CD30, EMA, CD38, VS38c, CD138, and MUM1.[12]

EC-PELs may more frequently than PELs express B-cell–associated antigens and/or immunoglobulin light chains.[13]

Notable is also the expression of T-cell markers, especially CD3, which occurs in up to 33% of the cases,[4] with less frequent CD4, CD2 and CD5 expression. This immunophenotypic signature when corroborated with CD30 expression may incorrectly suggest an ALK negative anaplastic large cell lymphoma or other T-cell lymphomas.[10] The cause of T-cell marker expression remains unclear; however, EBV infection may play a role, as it has been associated with T-cell marker expression in B-cell lymphomas.[14]

The diagnosis of PEL and EC-PEL requires the demonstration of KSHV/HHV8, often performed using an antibody to KSHV/HHV8 LANA. MYC protein overexpression is usually identified in PEL cases,[15] probably due to the activity of HHV8-encoded latent protein.

Gene expression profiling indicate that PEL cell of origin seems to be of post-germinal center, plasmablastic derivation[16] while typical NHL-related rearrangements or mutations of BCL2, MYC, and TP53 are not identified. In their paper, Calvani et al using a 36-gene lymphopanel identified in 5/10 PELs, either a single or two mutations per sample across four different pathways: epigenetic modifiers (EP300, ARID1A), BCR-NF-κB (TNFAIP3), apoptosis (TP53), and T-cell immunity (CD58 and B2M).[10]

Genes involved in inflammation, cell adhesion and evasion such as Aquaporin-3, P-selectin glycoprotein ligand 1/SELPLG, and mucin1 were identified overexpressed in PEL, findings which may explain the presentation in body cavities. In addition, a frequent occurrence of complete or partial trisomy 12, trisomy 7, and abnormalities of bands 1q21–25 have been reported in PEL.[16]

In our case it remains unclear if the pathogenic MPL c.1653+1del and the variant of unknown significance UBA1 c.73C>T detected are playing a role in the development of this lymphoma. Of interest is the patient's mild but chronic thrombocytopenia that has been reported for more than 20 years, and may have been clinically attributed to chronic anti-retroviral therapy. Since MPL mutations have been reported in congenital amegakaryocytic thrombocytopenia,[17] and the low VAF somatic mutations identified in TET2, ATM and DNMT3A, raise the concern of a possible idiopathic cytopenia of undetermined significance (ICUS); a bone marrow examination remains under consideration as part of the ongoing clinical work-up.

PEL is an aggressive lymphoma, associated with poor prognosis, despite advances in HIV-related lymphoma treatment.[13] Chemotherapy and antiretroviral therapy (ART) have shown promise in achieving remission and prolonging survival.[18] EBV-positive PEL cases may experience more favorable outcomes.[19] Extracavitary forms may have a somewhat better prognosis than classic PEL, with lower relapse rates among patients in remission.[12,13]

There is no standardized treatment for PEL or EC-PEL. Management includes ART for HIV and cytotoxic chemotherapy, most commonly cyclophosphamide, doxorubicin, vincristine, and prednisolone, and for eligible patients using the infusional dose-adjusted regimen with etoposide (DA-EPOCH). Alternatives include dexamethasone, high-dose cytarabine, cisplatin, methotrexate, and brentuximab vedotin.

Due to high CD30 expression, Brentuximab vedotin, a CD30-targeted therapy, has been used in PEL. It has shown efficacy in vitro in PEL cell lines and in vivo in animal models.[20,21] Case reports have also documented prolonged remission with this regimen.[22] Our case was particularly challenging because of the patient's extensive prior oncologic history with chemotherapy and radiation exposure, advanced age and persistent AIDS, his personal refusal to consider any further cytotoxic chemotherapy, and concurrent presence of two squamous cell carcinomas of the penis and of the skin, in itself associated with guarded prognosis. The application of brentuximab vedotin and nivolumab has allowed for control of all malignancies with minimal toxicity and excellent oncologic outcome so far, demonstrating the utility of novel immunotherapy approaches even with patients who are compromised by immunosuppression and geriatric comorbidities.

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Authors

Kinda Rajab, MD, Department of Pathology and Laboratory Medicine, Rhode Island Hospital, Providence, RI.

Yael Tsenter, MD, Department of Pathology and Laboratory Medicine, Rhode Island Hospital, Providence, RI.

Adam J. Olszewski, MD, Associate Professor of Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

Liu Liu, PhD, Assistant Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

Cynthia Jackson, PhD, Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

Liang Cheng, MD, Professor of Surgery, Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

Diana O. Treaba, MD, Professor of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University, Providence, RI.

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Correspondence

Diana O. Treaba, MD
Rhode Island Hospital
APC 11th floor, #1147
593 Eddy Street Providence, RI 02903
401-444-8897
Fax 401-606-1233
DTreaba@BrownHealth.org