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Case Report

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Primary Effusion Lymphoma with Extracavitary Presentation and A T-Cell Immunophenotype: A Potential Diagnostic Pitfall

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Abstract

Primary Effusion Lymphoma (PEL) is a unique immunodeficiency-associated malignancy that requires infection with Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8). Although thought to arise from mature B-lymphocytes, PEL typically has a null Immunophenotype but can very rarely show lineage specific aberrancies, including aberrant T-cell markers. Here we present one such case of PEL where aberrant T-cell markers led to a misdiagnosis of peripheral T-cell lymphoma. We performed a review of the literature to identify similar cases of PEL with strong T-cell antigen expression. Most cases occurred in men who were HIV positive or otherwise immunodeficient. Many were EBV positive. Rare cases demonstrated T-cell receptor gene rearrangements. Postulated theories for the cause of disordered differentiation include immunodeficiency and/or EBV infection. The expression of T-cell antigens on PELs may be a source for error in diagnosis and awareness of this correlation is of practical diagnostic relevance.

Keywords: Body Cavity Lymphoma; Effusion Lymphoma; Extracavitary Primary Effusion Lymphoma; KSHV/HHV8; PEL; Primary Effusion Lymphoma; T-Cell Primary Effusion Lymphoma

Introduction

Primary Effusion Lymphoma (PEL) is a distinct diagnostic entity defined by the World Health Organization (WHO) as a large B-cell neoplasm usually presenting with serous effusions. Requisite for this classification is an association with Human Herpesvirus 8 (HHV8) also known as Kaposi Sarcoma Herpesvirus (KSHV). This association was initially noted in cases of lymphomatous effusions in Human Immunodeficiency Virus (HIV) infected males who had severe immunodeficiency and frequently had a concomitant co-infection with Epstein-Barr Virus (EBV) [1]. However, over time, documented cases have shown PEL arising in the setting of solid organ transplants, elderly patients, and HHV8 endemic geographical regions. Not uncommonly, a solid variant termed extracavitary PEL is present with approximately half of patients having a concurrent Kaposi sarcoma [2]. Cases of PEL-like lymphomas unrelated to HHV8 have also been described [3,4]. Most cases of PEL's are null Immunophenotype or express some B-cell markers [2]. Herein we discuss a case of PEL with T-cell Immunophenotype and review the literature of other reported cases.

Methods and Materials

A literature review was performed to identify reports of PEL with strong immunohistochemical staining for aberrant T-cell marker expression. Cases were selected through a retrospective analysis of Pub med indexed reports using MeSH and non-MeSH queries for the following search terms: primary effusion lymphoma; Primary effusion lymphoma review; and body cavity lymphoma.

Cases with documented HHV8 and T-cell antigen positivity were reviewed. Specific features of each case including patient demographics, clinical presentation, cell morphology, aberrant immunophenotypic markers, and presence of lineage specific gene rearrangement. Reports without sufficient information or documented T-cell antigen positivity were excluded.

Case Report

The patient was a 53-year-old HIV positive male who was diagnosed in 2005, and treated with HAART regimen, but was noncompliant in the past 2 to 3 years. He also had history of treated syphilis, brucellosis, and shingles. In November 2016, he presented to ER with fever, tachycardia and abdominal pain. He reported night sweats, mild dysphagia and approximately 10 lb weight loss in the last two months. Lab work up showed CD4 count 108, HIV viral load 1,050,579 and elevated liver enzymes, Complete blood count showed severe pancytopenia. CT demonstrated a soft tissue mass to the left of the suprarenal aorta, which extended above the diaphragm and lifted the aorta off the spine. Retrocrural, retroperitoneal lymphadenopathy, and hepatosplenomegaly was noted. Chest x-ray revealed a small left pleural effusion. Blood culture was positive for Candida sp. and enterococcus. He underwent para-aortic lymph node biopsy, thoracentesis of the pleural effusion, and bone marrow biopsy.

The lymph node biopsy showed a diffuse pattern of large atypical lymphoid cells and was initially diagnosed as Peripheral T-cell lymphoma, NOS, at an outside hospital due to strong CD3 and CD4 expression by immunohistochemistry (Figure 1; panels A and C). The pleural fluid cytology showed clusters of highly atypical lymphoid cells with high nuclear/cytoplasmic ratios, basophilic cytoplasm, and bizarre appearing nuclei with multiple prominent nucleoli (Figure 1; panel B). The bone marrow biopsy was negative for lymphomatous involvement. Additional immunohistochemical stains performed at UCLA showed strong HHV8 positivity in the atypical cells (Figure 1; panel D). An in-situ hybridization for EBV-EBER was also positive.

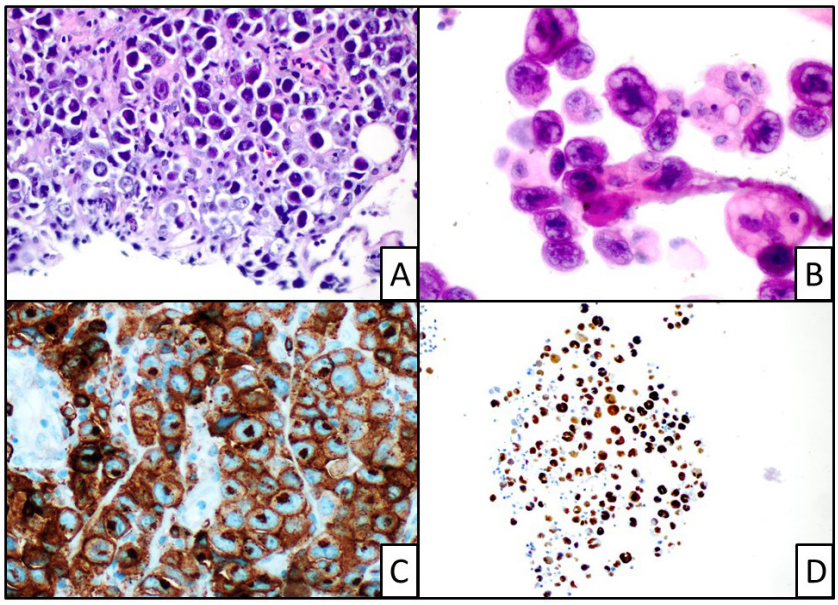

Figure 1: [A: Para-aortic lymph node biopsy; H&E 20x] Highly atypical infiltrative lymphoid cells with high N:C ratios. [B: Pleural effusion cytology; H&E 100x] Bizarre cytology with multiple prominent nucleoli. [C: Para-aortic lymph node biopsy; CD4 immunohistochemistry 40x] Strong and diffuse cytoplasmic and nucleolar CD4 staining patterns. [D: Pleural effusion cytology: HHV8 immunohistochemistry 10x] Strong and diffuse nuclear staining for HHV8.

Results

Based on the morphologic features, HHV8 positivity and the clinical findings a diagnosis of extracavitary Primary Effusion Lymphoma (PEL) was rendered. Immunohistochemistry demonstrated lymphoma cells positive for CD3 and CD4, HHV8 and EBER with a Ki-67 proliferation index of >90%. The lymphoma cells were negative for CD20, PAX5, CD8, CD30, CD5, CD7, BF1, TCR gamma and ALK-1. Molecular genetic studies demonstrated a clonal immunoglobulin heavy chain rearrangement. The patient was started on chemotherapy with EPOCH: Etoposide, prednisone, Vincristine, Cyclophosphamide, and Doxorubicin. He was restarted on HAART medication. Unfortunately, he subsequently developed septic shock followed by hypoxic respiratory failure then multiorgan failure. His condition continued to decline, was placed on comfort care in accordance with the family's wishes and passed away peacefully.

The demographics, clinical characteristics, and pathologic features for similar reported cases have been summarized in (Table 1). Overall, patients were all males with ages ranging from 27 to 88 (median 49). While 62% (8/13) were HIV positive, the remaining patients had other causes for immunodeficiency including four patients with advanced age and one patient with a history of a renal

transplant. The most common presentation was a pleural effusion (62%, 8/13) while three cases showed extracavitary masses (23%). In cases with available follow up data, two patients survived following treatment (29%, 2/7). Histopathologic morphology varied and included immunoblastic (38%), anaplastic (38%), large cell, (16%), and plasmablastic (8%) cytology. The most common aberrant T-cell markers were CD3 (54%), CD7 (38%), and CD4 (31%). EBV detected by EBER in-situ hybridization was positive in 55% (6/11) cases. Four (36%) cases had T-cell gene rearrangements with two (18%) cases being bigenotypic.

#	Reference	Demographics	Outcome	History/effusion	Morphology	Immunophenotype (T-cell markers)	Viral status	B/T gene rearrangments
1	Stelling et al (2017 Current Case)	53M, HIV+	Deceased, <1 year survival	Pleural, extracavitary para-aortic LN	Immunoblastic	CD3, CD4	HHV8+, EBER+	Monoclonal IGH
2	Wang et al (2015) [5]	80M, HIV-, history of heart disease	NA	Pleural	Plasmablastic	CD4	HHV8+, EBER+	Monoclonal TRG and IGH
3	Kalogeraki et al (2014) [6]	49M, HIV-, Renal transplant	Alive at 10 month follow up	Peritoneal	Anaplastic	CD3	HHV8+, EBER-	Monoclonal IGH
4	Goto et al (2013) [7]	39M, HIV+	Deceased, <1 month survival	Pleural	Immunoblastic	CD4	HHV8+, EBER-	Monoclonal IGH
5	Pan et al (2012) [8]	37M, HIV+, history of anal squamous cell carcinoma	Deceased, <1 month survival	Extracavitary, mesenteric LN	Anaplastic	CD3	HHV8+, EBER+	Monoclonal IGH
6	Nepka et al (2012) [9]	88M, HIV-, HBV Cirrhosis, Mediterranean descent	NA	Peritoneal	Anaplastic	CD4, CD5 (weak), CD8 (weak)	HHV8+ EBER-	NA
7	Brimo et al (2007) [10]	27M, HIV+, history of KS	Deceased, <1 year survival	Pleural	Immunoblastic	CD3, CD43	HHV8+ EBER NA	NA
8	Coupland et al (2005) [11]	41M, HIV+	NA	Extracavitary, axillary LN	Large cell	CD7, CD43	HHV8+, EBER+	Monoclonal TRG
9	Munichor et al (2004) [12]	74M, HIV-, Ashkenazi Jewish descent	NA	Pleural	Immunoblastic	CD3, CD7	HHV8+, EBER-	Monoclonal IGH, Kappa
10	Lechapt-Zalcman et al (2001) [13]	87M, HIV-	NA	Pleural	Large cell	CD3	HHV8+, EBER-	Monoclonal TRG
11	Vince et al (2001) [14]	39M, HIV+	Deceased, 5 month survival	Pleural	Immunoblastic	CD7	HHV8+, EBER+	NA
12	Polskj et al (2000) [15]	80M, HIV+, history of heart disease	Alive at 8 month follow up	Pleural	Anaplastic	CD7, CD56	HHV8+ EBER NA	Monoclonal IGH
13	Said et al (1999) [16]	33M, HIV+, HBV+, history of pericarditis	NA	Pericardial, Peritoneal	Anaplastic	CD2, CD3, CD5, CD7	HHV8+, EBER+	Monoclonal IGH, TCR-beta and gamma rearrangement

Table 1: Demographics, clinical characteristics, and pathologic features for similar reported cases.

Discussion

Prior to the discovery of HHV8, proposed criteria for body cavity lymphoma included a clinical presentation of isolated effusion, characteristic cytomorphology, absence of B-cell or immunoglobulin immunohistochemical markers, clonal immunoglobulin gene rearrangements, and Epstein-Barr virus infection [17,18]. Many patients had a concurrent Kaposi's sarcoma diagnosis, which led to the association of KSHV/HHV8 becoming the essential diagnostic factor in PEL. There is strong support for PEL being a B-cell lymphoma. First, the pathogenesis may rely on viral transformation. Hensler et al studied the in vitro virology of KSHV/HHV8 and identified a glycoprotein interaction with cells through the receptor DC-SIGN (CD209), normally mediating the interactions between antigen presenting cells and helper T-cells and is found primarily on dendritic cells, macrophages, and B-cells [19]. Infection is only possible in lymphocytes with B-cell lineage as CD209 receptor is associated with B-cells. In an additional example: Epstein-Barr virus, a frequent co-infectious agent, binds to complement receptor CD21, which also appears on B-cells. Fais et al performed in vitro sequencing studies of immunoglobulin genes and demonstrated clonal rearrangement and statistical evidence for antigen selection. The variable regions in both heavy chains and light chains showed point mutations that differ from the germline, which is associated with and suggests a mature antigen experienced B-cell counterpart [20]. In fact, it is notable that many markers of activation and plasma cell differentiation including CD30, CD38, CD138, and EMA are often present. Gene expression profiles examined by Klein et al suggest plasmablastic differentiation similar to other AIDS associated non-Hodgkin lymphomas [21].

Despite these observations, rare cases show aberrant expression of lymphoid markers including those of T-cells. In addition, cases may show abnormal genotypic features including T-cell receptor rearrangements and even bigenotypic rearrangements [22]. Our literature review suggests that TCR gene rearrangements are not infrequently seen in cases of aberrant T-cell immuno phenotype. The findings of bigenotypic lineage and EBV are associated with immunodeficiency and may be a factor in abnormal differentiation [22]. To our knowledge, the mechanism of immunodeficiency in the genetic evolution of lymphoid neoplasms is poorly understood and practical considerations during the diagnosis of PEL and other immunodeficiency-associated lymphomas include an awareness of possible disordered gene expression. In summary, PEL should be included in the differential diagnosis of large cell lymphoid neoplasms even in cases that have an extracavitary mass, HIV negative history, or aberrant lymphoid markers. Although a rare circumstance, an awareness of these scenarios can prevent a possible missed diagnosis.

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