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Primary Effusion Lymphoma in a HIV-1/2-Infected Patient

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Abstract

Background: Primary effusion lymphoma (PEL) is a lymphoid proliferation related to Kaposi sarcoma herpesvirus 8/human herpesvirus 8 (KSHV/HHV8) that affects mainly human immunodeficiency virus (HIV) infected individuals but can also occur in other immunodeficiency settings. It is characterized by lymphomatous effusions in different serous body cavities without the presence of a detectable tumor mass. The diagnosis is challenging and the clinical outcomes are poor. **Aim:** The aim of this paper is to report a rare case of PEL in a man who have sex with women (MSW) with HIV-1/2 infection, history of visceral Kaposi sarcoma (KS) and the development of a seronegative arthritis previous to the lymphoproliferative disease diagnosis. PEL presented with ascites, was treated with high-dose chemotherapy and autologous stem cell transplantation, with a good clinical outcome. **Case Presentation:** We describe a case of a 48-year-old HIV-1/2-infected patient from a high HHV8 seroprevalent country, hospitalized following a three-month history of increased abdominal volume and general constitutional symptoms. Laboratory data revealed normocytic normochromic anemia and a high level of lactate dehydrogenase. A diagnostic paracentesis was performed with cytology compatible with high-grade B-cell lymphoma. Peritoneal fluid cytology showed large lymphoid cells expressing leucocyte-common antigen CD45 without expression of the CD20 antigen (B-lymphocytes) and positivity for HHV8 by immunocytochemical staining, compatible with the diagnosis of PEL.

Keywords

Primary Effusion Lymphoma, Acquired Immunodeficiency Syndrome,

HIV-1, HIV-2, Kaposi Sarcoma Herpesvirus 8/Human Herpesvirus 8, People Living with HIV

1. Introduction

According to the World Health Organization, PEL (primary effusion lymphoma) is a B-cell lymphoid proliferation related to Kaposi sarcoma herpesvirus 8/human herpesvirus 8 (KSHV/HHV8) that affects mainly human immunodeficiency virus (HIV) infected individuals [1]. PEL accounts for approximately 4% of all HIV-related non-Hodgkin's lymphomas (NHL) [2] [3] and up to half of the patients with PEL have a previous history of Kaposi sarcoma (KS) [4]. It is also associated with other immunodeficiency settings and may less frequently occur in the elderly due to decreased immune function [5].

Seroprevalence of HHV8 is high in risk groups [6] (such as people living with HIV (PLHIV)) and countries where HHV8 infection is ubiquitous, like African countries, have a high risk of development of KS [7] [8]. HIV and HHV8 coinfection and low access to combined antiretroviral therapy (cART) may increase the risk of their associated neoplasms but in the cART era it has been observed an improvement of Acquired Immunodeficiency Syndrome (AIDS) related lymphomas prognosis, including PEL [5].

Concerning previous works related to PEL, an institutional study by Simonelli *et al.* showed that PEL occurs as a late manifestation of HIV disease and was more significant in men who have sex with men (MSM). The primary site of the lymphoma presentation was predominantly pleural effusions and only 3 patients had peritoneal effusions [3]. A large series prospective cohort study concerning HIV-associated PEL described by Guillet *et al.* observed that a majority of patients had HHV8-associated diseases and PEL was manifested by serous lymphomatous proliferation with peritoneal effusions as the second most common presentation [9].

In this article we describe a rare case of PEL in a man who have sex with women (MSW) from a high HHV8 seroprevalent country with HIV-1/2 infection and history of visceral Kaposi sarcoma (KS). PEL presented uncommonly with ascites and after high-dose chemotherapy and autologous stem cell transplantation the patient had a good clinical outcome.

2. Case Report

A 48-year-old male HIV-infected patient, born in Guiné-Bissau and living in Portugal since 2007 was hospitalized in 2021 following a three-month history of increased abdominal volume, weight loss (18% of total body weight) and fever. He had been diagnosed with dual HIV-1/2 infection (initial CD4 T-cell count of 41 cells/mL) concurrently with chronic Hepatitis B Virus (HBV) infection, in 2010. The transmission was through past sexual contact (man who have sex with

women (MSW)) and the patient was under cART with tenofovir disoproxil fumarate 300 mg QD, emtricitabine 200 mg QD, darunavir 600 mg BID boosted with ritonavir 100 mg BID, with undetectable viral load and CD4 T-cell count of 119 cells/mL at the time of the admission. Concerning past HIV-associated opportunistic diseases the patient had history of gastrointestinal KS treated with 12 cycles of doxorubicin, disseminated tuberculosis diagnosed by hepatic biopsy and treated for 12 months with antituberculous agents, with the development of immune reconstitution inflammatory syndrome (IRIS), *Pneumocystitis jirovecii* pneumonia and Citomegalovirus colitis. One year before the actual complaints the patient had a seronegative arthritis in the right ankle that was treated with prednisolone.

On admission the patient was febrile (auricular temperature of 38.9˚C) and on physical examination ascites was noted together with multiple peripheral adenopathies. No other abnormalities were found.

Blood tests revealed normocytic normochromic anemia (Hb 11.2 g/dL, HGM 28.2 pg, VGM 84.6 fL), C-reactive protein of 18 mg/dL (≤0.8 mg/dL) and lactate dehydrogenase of 963 UI/L (reference range 80 - 225 UI/L).

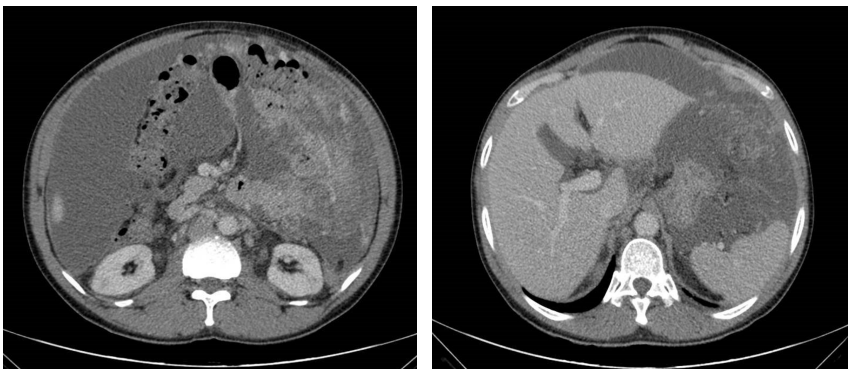
For evaluation of the new onset ascites an abdominal ultrasound was performed and confirmed marked ascites without hepatosplenomegaly. A diagnostic abdominal paracentesis was performed, with drainage of turbid ascitic fluid with serum ascites albumin gradient of 0.9 g/dL, cell count with 21,600/μL leukocytes and 60% of lymphocytes, total proteins of 7.6 g/dL and glucose < 5 mg/dL. Cytological ascitic fluid evaluation revealed infiltration by high grade B-cell lymphoma, despite ascitic immunophenotyping being inconclusive. Full body computed tomography (CT) scan revealed multiple peripheral adenopathies and ascites (**Figure 1(a)** and **Figure 1(b)**) and an excisional biopsy of an inguinal node was obtained with histology showing an unspecific inflammatory process.

A diagnostic laparoscopy was subsequently performed and observed a turbid milky ascites combined with multiple peritoneal implants. Peritoneal fluid was sent for cytological examination, which reveled large lymphoid cells with multiple figures of apoptosis expressing leucocyte-common antigen CD45 without expression of the CD20 antigen (B-lymphocytes) (**Figure 2(a)** and **Figure 2(b)**), and intense positivity for HHV8 by immunocytochemical staining (**Figure 2(c)**), compatible with the diagnosis of PEL.

For simplification the cART was changed to a single tablet regimen (STR) daily containing tenofovir alafenamide 25 mg, emtricitabine 200 mg and bictegravir 50 mg, with the maintenance of virological suppression.

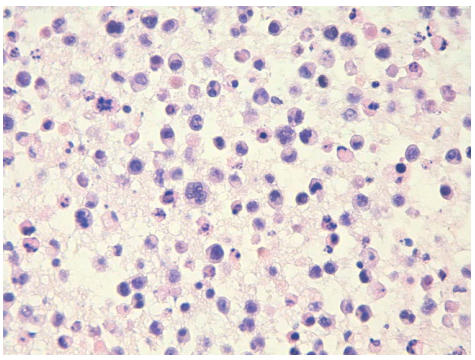
The patient was referred to the Hemato-Oncological department for further investigation. To complete staging, a bone marrow aspirate and biopsy were performed that reveled neoplastic infiltration and confirmed PEL diagnosis. A lumbar puncture was also performed which excluded central nervous system involvement. According to Lugano classification for NHL it was considered stage IV. Infusion chemotherapy with etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin (EPOCH) was started after the initiation of

prophylaxis for chemotherapy related immunosuppression. The patient maintained antiviral therapy for HIV and chronic HBV infection and started trimethoprim-sulfamethoxazole because of high risk for pneumonia from *Pneumocystitis jirovecii*, acyclovir due to herpes simplex virus-1 seropositive state and treatment for latent tuberculosis with isoniazide and pyridoxine. The patient was also vaccinated against Pneumococcal disease, Coronavirus disease-19 and seasonal Influenza.

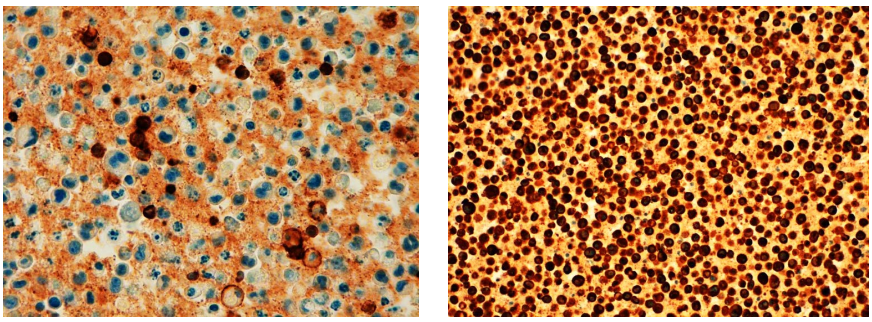


(a) (b)

Figure 1. Computed tomography scan of the abdomen findings. (a) retoperitoneal adenopathies; (b) ascites.



(a)



(b) (c)

Figure 2. Peritoneal fluid biopsy findings. (a) large lymphoid cells with multiple figures of apoptosis (hematoxylin-eosin, 400×); (b) lymphoid cells expressing CD45 (immunocytochemical staining, 400×); (c) intense positivity for HHV8 (immunocytochemical staining, 200×).

During chemotherapy several complications occurred, namely mucositis with Extended-Spectrum β-Lactamase producing *Escherichia coli* bacteremia treated with piperacillin-tazobactam, perianal abscess and bilateral pneumonia, without microbiological etiological identification, which were successfully managed. After 6 cycles of EPOCH, he was submitted to mobilization therapy with granulocyte colony stimulation factors, including plerixafor, followed by intensification therapy with autologous hematopoietic stem cell transplant support, with a favorable clinical outcome. The patient performed a Positron Emission Tomography scan 4 months after the transplant confirming complete remission with absence of ascites and no further radiological changes.

After 7 months of autologous stem cell transplantation the patient continues without disease relapse and maintenance of virological suppression in follow up consultations of Hemato-Oncology and Infectious Diseases.

3. Discussion

PEL was first described in the late 1980s and was associated with AIDS related KS [10] [11]. It occurs in patients usually in an advanced stage of immune depletion [3] and is considered an AIDS-defining disease. In HIV individuals the median age of PEL diagnosis is 44 - 45 years old and it commonly occurs in MSM [9] [12] [13].

HHV8 is transmitted by saliva and replicates in oropharyngeal cells [13]. It can also be transmitted by blood transfusions or transplants [14]. Immune evasion mechanisms result in a complex interaction between the virus and the host immune system, with persistent latent infection in lymphoid cells, like other gamma herpesviruses, and the development of lymphoproliferative disorders [15]. Coinfection with Epstein-Barr virus (EBV) is found in approximately 80% of general PEL cases [16] suggesting its synergistic pathogenic role [5] and EBV positivity is associated with increased survival [12].

Classical PEL is characterized by lymphomatous effusions in different serous body cavities (pleura, peritoneum and pericardium [5]) without the presence of a detectable tumor mass [15]. PEL occurs in serous body cavities but there are also cases reported of extraserous PEL involvement [3]. Extracavitary PEL presents with extranodal tumors and is very similar in morphology and immunophenotype as the classical variant. It occurs in HIV-infected patients and the HHV8 viral status is also positive [13].

The clinical presentation depends on the location of the effusion and systemic symptoms may occur (weight loss, fever and night sweats) [17] together with adenopathy and splenomegaly [12].

Diagnosis is challenging and based on cytological examination of the body fluid effusion. Morphologically, PEL cells may show features of immunoblastic and anaplastic lymphomas [5] and the immunophenotype is usually indeterminate (lacking lineage markers of both T and B lymphocytes [4]) but it is represented by a monoclonal B-cell population by immunogenotypic studies [18]. In more than 90% of the cases PEL cells have expression of the CD45 anti-

gen [5]. Determination of KSHV/HHV8 is also important for the diagnosis by immunocytochemical staining or by detection of KSHV/HHV8 deoxyribonucleic acid (DNA) sequences in the tumor cells by molecular methods [5] [19].

In order to estimate the disease burden, staging of PEL is based on full body CT scan, bone marrow biopsy and endoscopic investigation, if needed. Ann Arbor staging is not considered important in PEL staging and generally all cases are considered stage IV [5].

Further investigation methods must be provided to exclude other clinical entities and establish a differential diagnosis. Other lymphomas associated with HIV must be considered because of their clinical and cytomorphological overlap with PEL. Burkitt lymphoma (BL) and extranodal diffuse large B-cell lymphoma are not associated with KSHV/HHV8 infection but can occur as primary lymphomatous effusions. In the case of BL it is associated with translocation of the MYC proto-oncogene [5]. HIV associated multicentric Castleman disease (MCD) is a rare lymphoproliferative disease related to KSHV/HHV8 infection that must also be taken into consideration. The main presenting symptoms of MCD are fever, weight loss, peripheral adenopathy [20] and because of increased vascular permeability, caused by high levels of vascular endothelial growth factor (VEGF), pleural effusions and ascites may occur [21] [22]. For this reason, a lymph node biopsy is necessary to establish a differential diagnosis [23].

There are no specific guidelines for PEL treatment but it is generally based on dose-adjusted EPOCH [15] or cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP-like) chemotherapy regimens [3] [24] (with or without methotrexate [25]) even though CHOP didn't increase the median survival for PEL patients [24]. Rituximab can also be used in PEL cases that express CD20, but this rarely occurs [15]. Autologous stem cell transplantation (ASCT) can be provided in cases of chemotherapy-responsive relapsed disease in patients with good performance status [26] but there is no evidence of its use as consolidation therapy in the first remission episode [5]. Initiation or continuation of cART is recommended in HIV individuals together with granulocyte colony-stimulating factors [5] to avoid cytopenias. The cART itself has a favorable effect in reversing the immunosuppression and has a benefit in the treatment of PEL [3]. There are rare cases of tumor regression when HIV individuals with PEL are treated with antiretroviral therapy alone [27].

PEL has a poor clinical outcome. The published survival time of patients with PEL depends whether data was collected before or after cART era. According to Simonelli *et al.*, in pre/early cART era, the median survival of PEL in those who achieved complete remission was 6 months, despite treatment [3]. A suggested predictor of clinical outcome in KSHV/HHV8 lymphoproliferative disorders in HIV individuals is the patients' performance status together with KSHV/HHV8 viral load [28]. Boulanger *et al.* also described that a predictor of poor outcome in HIV individuals is the poor performance status and the absence of cART before PEL diagnosis [24] and these were associated with the impaired outcome of

PEL. The International Prognostic index has never been validated in patients with PEL [5].

4. Conclusions

In this article we report a rare case of PEL in a MSW with HIV-1/2 infection, history of visceral KS and the development of a seronegative arthritis, eventually paraneoplastic, previous to the lymphoproliferative disease diagnosis. PEL was treated with high dose chemotherapy and autologous stem cell transplantation with complete remission. To the present date the patient continues without disease relapse but longer follow up is necessary.

As far as we know, there are several case studies published about PEL in HIV-infected patients and all conclude the poor clinical outcomes defined by this condition. A delay in the diagnosis can influence the clinical outcomes in PEL patients. PEL can manifest with nonspecific constitutional symptoms, that overlap with other HIV-associated conditions, as in this case, with the uncommon presentation of the effusion as ascites. Another consideration is that HIV patients are poor candidates for aggressive chemotherapy [29] but despite that, the HIV status alone shouldn't influence the decision of the choice of treatment of PEL, and other options of treatment may be considered together with prophylaxis for iatrogenic immunosuppression. PEL may have a favorable outcome by introduction of cART, which is also recommended.

To conclude, PEL is associated with advanced AIDS and its immune depletion. The diagnosis is challenging especially if the effusion is the primary manifestation of the disease. It is important to consider PEL in HIV-infected patients if previous KS infection is documented and not delay the diagnosis and treatment options in order to obtain better clinical outcomes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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