



Case Report

Herpesvirus-8 Negative Primary Effusion Lymphoma Presenting as Pericardial Tamponade

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Abstract

Abstract: Isolated lymphomatous body cavity effusion is usually related to profound immunosuppression and herpesvirus-8 infection and is recognized as primary effusion lymphoma. A rare subtype of herpesvirus-8 negative primary effusion lymphoma has been described with substantial clinical and prognostic differences. We report the case of a patient diagnosed of herpesvirus-8 negative primary effusion lymphoma with pericardial effusion causing pericardial tamponade. Corticosteroids and rituximab therapy was started achieving complete response without signs of recurrence 6 months after treatment.

Keywords: Herpesvirus 8, Primary effusion lymphoma, Herpesvirus 8 negative primary effusion lymphoma, Pericardial effusion

Introduction

Presence of lymphomatous cells in body cavity effusions is usually related to the presence of a systemic disease involving near lymphatic nodes; in most cases diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma. Primary effusion lymphoma (PEL) is a rare entity recognized by the WHO classification of hematolymphoid neoplasms [1], characterized by lymphomatous body effusions without concomitant tumoral masses or systemic disease. It is universally related to Herpesvirus-8 (HHV8) infection and affects heavily immunocompromised patients, in most cases due to human immunodeficiency virus (HIV) infection. A rare entity, described only by case reports and small case series, and named PEL-like lymphoma or HHV8

negative PEL (HHV8 negative PEL) has been recognized. HHV8 negative PEL is also characterized by an isolated body effusion without tumoral masses or systemic dissemination, but displays relevant epidemiological, phenotypical, and prognostic differences in comparison to classical PEL. Herein, we report the case of a 77-years-old woman presenting with pericardial tamponade of unknown etiology and subsequent diagnosis of HHV8 negative PEL.

Clinical Case

A 77-year-old woman was admitted due to progressive shortness of breath and deterioration of her functional class in the last few days. The patient's medical history included limited systemic sclerosis diagnosed two years before, which was under treatment with mycophenolate mofetil (discontinued one month before beginning of symptoms) and associated pulmonary hypertension treated with double vasodilatory therapy (tadalafil and ambrisentan). The patient also had a history of ischemic cardiopathy

and acute pulmonary thromboembolism secondary to deep venous thrombosis four years ago. She was also diagnosed with IgG kappa monoclonal gammopathy of unknown significance (MGUS), with last control two months prior to the current episode without signs of progression to multiple myeloma. Anamnesis and physical exploration were performed. No thoracic pain or orthopnea was associated to progressive dyspnea. Constitutional symptoms were absent and physical examination did not reveal lymphadenopathy or hepatosplenomegaly. Transthoracic echocardiography (TTE) showed severe pericardial effusion to which clinical symptoms were attributed. Pericardial fibrin deposits were also noted, related to the presence of chronic pericardial effusion. Due to recent discontinuation of immunosuppressive therapy, the pericardial effusion was linked to worsening of her autoimmune disease and treatment with systemic corticosteroids and colchicine was started. She had an adequate clinical and echocardiographic response and steroids were tapered and the patient was discharged. Due to the quick improvement no invasive procedures were performed. Ten days later, the patient was admitted again with a second episode of progressive dyspnea. Echocardiography showed recurrence of pericardial effusion and, in this case, signs of pericardial tamponade (Figure 1). Due to high risk of progressing to clinical tamponade, at this time pericardiocentesis was performed and the pericardial fluid was analyzed. Laboratory analysis of the effusion showed glucose levels below 2 mg/dL, high protein levels (5.1 mg/dl), a lactate dehydrogenase (LDH) of 13,338 U/L and 11,517 leucocytes/ μ L, composed of 95% mononucleated cells and 5% polymorphonuclear cells. Concomitant blood parameters showed hemoglobin of 11.1 g/dL, platelets 133x1000/uL, neutrophils 7.0x1000/uL and lymphocytes 1.0x1000/uL. Blood LDH level was of 355 U/L (normal limit 135-214 U/L) without other relevant biochemical alterations. A reevaluation of the previously diagnosed MGUS was made, without significant changes since last follow up. A cytocentrifuge preparation of the effusion (Figure 2) revealed large abnormal mononucleated cells, with a high nuclear-to-cytoplasmic ratio, large irregular nucleus with loose chromatin and prominent nucleoli, and a deep blue cytoplasm, compatible with atypical anaplastic lymphocytes, some of them exhibiting plasmacytoid features. Subsequent flow cytometry analysis of the effusion confirmed large (high FSC) and complex (high SSC) lymphocytes exhibiting strong expression of B-cell markers

cluster of differentiation (CD)19 and CD20. These lymphocytes did not express CD5 or CD10 and lacked plasmatic cell markers like CD138 (negative) and CD38 (weak expression). No surface light chain restriction was exhibited.

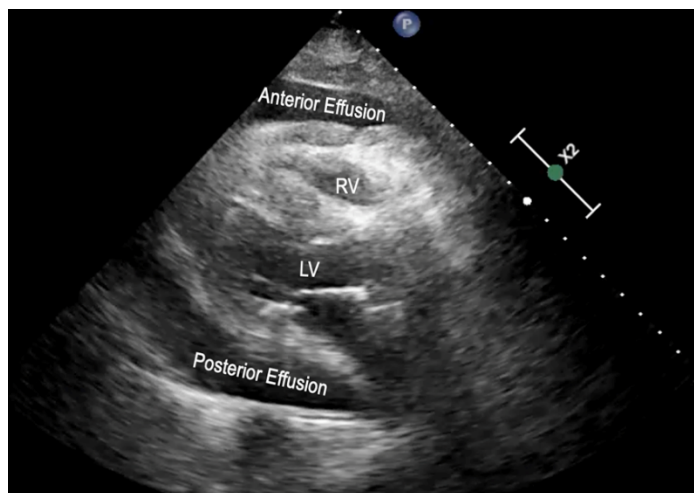


Figure 1: TTE was performed exhibiting severe pericardial effusion. Parasternal long axis view. RV: right ventricle, LV: left ventricle.

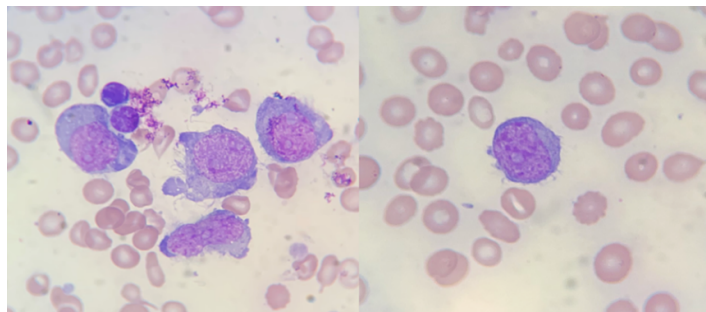


Figure 2: Cytocentrifuge preparation, hematoxylin eosin (HE) staining. Effusion was composed of large, atypical lymphocytes, with irregular nuclei and prominent nucleoli. A high nuclear-to-cytoplasmic ratio can be seen with basophilic cytoplasm. Some of the large cells showed signs of plasmacytoid differentiation.

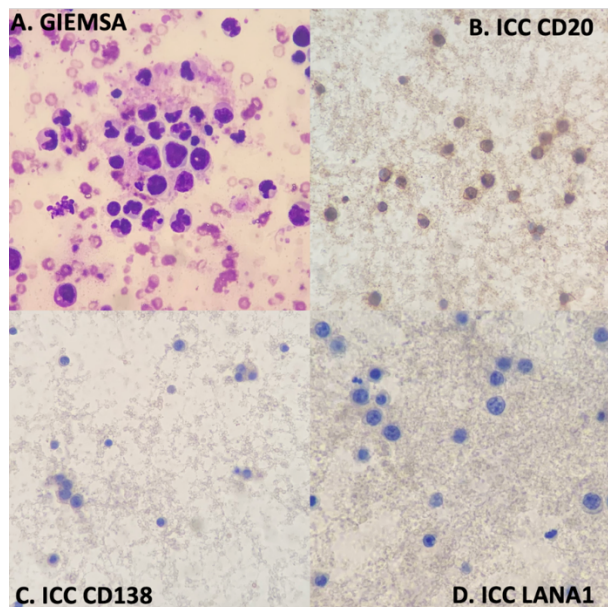


Figure 3: ICC preparation of the effusion. A. Giemsa staining: large, polymorphic lymphoid cells with deep blue cytoplasm and large nuclei are observed. B. ICC for CD20 resulted positive in the atypical cells. C. and D. ICC for CD138 and HHV8's LANA1 resulted negative.

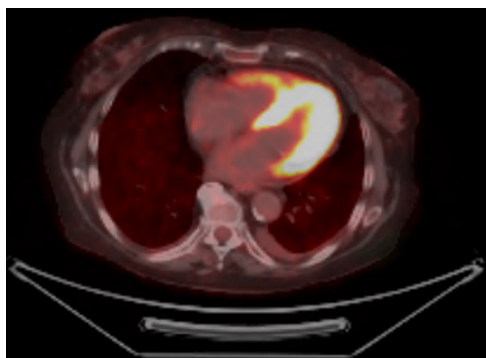


Figure 4: PET/CT (performed after aspiration of the effusion) imaging showing physiological myocardial uptake. No signs of pericardial uptake or pericardial effusion are detected. There were no other relevant sites of pathological uptake suggestive of lymphoproliferative disorder.

Immunocytochemical (ICC) analysis (Figure 3) revealed strong expression of CD45, CD20 and PAX-5, and confirmed lack of CD138 expression. Latency-associated nuclear antigen 1 (LANA1), a nuclear protein linked to the presence of HHV8 infection, was negative. On the contrary, latent membrane protein 1 (LMP1), a protein linked to cellular infection by Epstein Barr virus (EBV), was present on the aberrant lymphocytes EBV

infection, although it could not be confirmed by EBV—encoded small RNA in situ hybridization (EBER). Strong expression of Ki-67 was detected, suggesting high cellular proliferation. No cytogenetic or molecular analysis was able to be performed due to the lack of sample. Based on the previous data, an aggressive B cell lymphoproliferative disorder was suspected. A whole-body positron emission tomography/computerized tomography (PET/CT) (Figure 4), which did not reveal pathological glucose uptake suggestive of tumoral masses. Serology of HIV and hepatitis C virus (HCV), as well as other usual pathogens resulted negative. EBV serology for IgG was positive. A bone marrow biopsy was performed, not showing lymphoma infiltration by flow cytometry analysis and pathological review. In conclusion, the presence of an isolated lymphomatous effusion with negativity for HHV8 in an elderly, immunosuppressed patient with cardiological comorbidity and chronic fluid retention led to the diagnosis of HHV8 negative PEL or PEL-like lymphoma, a rare subtype of B cell large lymphoma characterized by its indolent behavior and overall good prognosis. Due to significant comorbidities and the indolent/non-aggressive nature of the disease the decision was made not to administer chemotherapy. Instead, complete aspiration of pericardial effusion was performed, and high dose prednisone was started (mg per kilogram of body weight), again with quick resolution of symptoms. Corticosteroids were subsequently tapered with 4 weekly doses of 375mg/m² rituximab single agent. An CR was achieved (disappearance of effusion by imaging). Six months after starting treatment patient is well and alive, and there are no signs of clinical or echocardiographic lymphomatous recurrence.

Discussion

PEL is a rare subtype of aggressive lymphoma characterized by the presence of neoplastic effusions without detectable tumor masses. It is necessarily linked to HHV8 infection [1], while EBV coinfection is frequent. PEL is diagnosed at a median age of 40-50 years and has been classically related to profound immunosuppression, such as HIV-patients or recipients of solid organs and other forms of immunodeficiency. It exhibits some characteristic pathological features like the lack of pan-B markers CD19, CD20 and CD79a. PEL derives from post germinal center lymphocytes, exhibiting morphological and immunophenotypical (CD138) characteristics of plasmacytoid differentiation. It is an aggressive disease with overall survival (OS) inferior to 6 months and treatment is based on polychemotherapy with cyclophosphamide, vincristine, adriamycin and prednisolone (CHOP)-like regimens without rituximab and strategies focused on restoring immunity, such as antiretroviral therapy or reducing doses of immunosuppressive agents [2,3]. During the last decades several reports and case series have reported a clinical entity defined as PEL-like lymphoma or HHV8 negative PEL. HHV8

negative PEL is characterized, like the HHV8 positive entity, by the presence of neoplastic effusions composed by large, atypical lymphocytes without evidence of tumoral masses or systemic dissemination. However, significant epidemiological, pathological, and prognostic differences have been noted, being the most relevant the lack of HHV8 infection on neoplastic cells. HHV8 negative PEL is mostly diagnosed in elderly people above 70 years of age [4,5] with a variable male-to-female predominance depending on the series. Similarly to our case, in up to 40% of cases comorbidities leading to chronic fluid overload are detected, like cirrhosis, chronic kidney disease, cardiac diseases or malnutrition leading to hypoalbuminemia [6]. Effusion is mostly detected within the pleural space (up to two thirds of the cases) [6] but in up to 30% of cases it may appear in the peritoneum, pericardium or at multiple locations [4-6]. While most patients do not exhibit an immunosuppressive state, this entity has also been described in HIV-infected patients and solid organ recipients [7]. The pathogenesis of HHV8 negative PEL is not well understood. While aberrations in PAX5 and MYC genes have been linked to the lymphomagenesis [6], other theories involve the presence of chronic effusion as one of the main pathogenic events, leading to proliferation of EBV infected B cells within the effusion, where immune surveillance is not able to recognize and eliminate these aberrant cells, similar to fibrin associated diffuse large B cell lymphoma and diffuse large B cell lymphoma associated with chronic inflammation [6,8] This would explain the possibility of attaining a complete response merely through aspiration of the effusion. However, questions remain since the prevalence of EBV infection ranges from only 6% to 30% in HHV8 negative PEL [4,5]. HCV infection, particularly in patients with peritoneum affection has also been hypothesized as a possible pathogenic cause, suggesting that chronic antigenic exposure could lead to lymphoid proliferation [7,9].

Morphologically, neoplastic cells are similar in HHV8+ and HHV8- entities, both being characterized by the presence of large lymphoid cells with basophilic cytoplasm, large irregular nucleus, and prominent nucleoli. Pleomorphic and anaplastic morphology are frequent, and plasmablastic/plasmacytoid morphology might also be detected, mostly on HHV8+ PEL (10%) [6]. Immunophenotypical analysis might be useful to distinguish both entities since HHV8- PEL is characterized by the expression of pan-B markers (as opposed to HHV8+ PEL) like CD19, CD79a and CD20 [4] in most patients (73-90%) [5,7], and light chain restriction is detected in up to 70% of cases. Ki67 proliferation index is variable, ranging from 3% to 93% [4]. When cytogenetic study is performed, a complex karyotype is frequently detected and single translocations of MYC, BCL2 and BCL6 genes may be detected in a small proportion of cases (approximately 15%). Recently, a xenograft mouse model for HHV8- PEL has been proposed [10]. However, a comprehensive characterization of

the underlying biology is still lacking [4]. In terms of prognosis, striking differences arise between both entities, with OS at two years higher than 80% in HHV8 negative PEL [4,6]. In some cases, good prognosis might be hampered by the presence of significant cardiac, hepatic or kidney comorbidities. But important heterogeneity in clinical behavior has been described, with survival reports ranging from weeks to more than eight years [5,9]. Treatment modalities include CHOP-like polychemotherapy schemes used for other aggressive B cell lymphomas, including rituximab therapy due to the high prevalence of CD20 expression. Other modalities of treatment include rituximab single agent and aspiration-only of the effusion. In general, it is admitted that chemotherapy containing regimens offer better survival advantages. However, but this may be at least partially based on selection bias with older and more comorbid patients being less likely to receive aggressive treatment options. Any of these modalities is able to lead to CR with to long term disease control and in many cases death is related to other causes. However, relapses have been described, both as recurrence of the effusion but also as mass lesions outside of body cavities [9].

In conclusion, although not recognized by the WHO classification of hematolymphoid neoplasms, HHV8 negative PEL seems to represent a clinical entity with distinct epidemiological, clinical, phenotypical, and prognostic features. Further studies with higher number of patients are required to delimit risk factors and the possible role of viral infections in its pathogenesis. Finally, collaborative efforts are needed to establish ideally within prospective trials the best treatment options and delimit prognostic factors.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, et al. (2017) WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours, revised 4th edition, IARC, 2.
2. Shimada K, Hayakawa F, Kiyoi H. (2018) Biology and management of primary effusion lymphoma. *Blood*. 132: 1879H. Bi
3. Narkhede M, Arora S, Ujjani C. (2018) Primary effusion lymphoma: current perspectives. *OncoTargets Ther*. 11: 3747ffusi
4. Kaji D, Ota Y, Sato Y, Nagafuji K, Ueda Y, et al. Primary human herpesvirus 8 infection, Ueda Y, Okamoto M, et al. rent perspectives. s. . O classification of tumours of haematopoietic and lymphoid tissue.
5. Usmani A, Walts AE, Patel S, Alkan S, Kitahara S. (2015) HHV8-negative effusion based lymphoma: a series of 17 cases at a single institution. *J Am Soc Cytopathol*. 4: 37-43.
6. Alexanian S, Said J, Lones M, Pullarkat ST. (2013) KSHV/HHV8-negative Effusion-based Lymphoma, a Distinct Entity Associated With Fluid Overload States. *Am J Surg Pathol*. 37: 241-249.
7. Wu W, Youm W, Rezk SA, Zhao X. Human Herpesvirus 8s 8-negative Effusion-based Lymphoma, a Distinct Entity Associated With Fluid Overload States. A

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8. Kim M, An J, Yoon S, Yong S, Kim J, et al. (2020) Human herpesvirus 8-negative effusion-based lymphoma with indolent clinical behavior in an elderly patient: A case report and literature review. *Oncol Lett.* 20: 1-1.
9. Saini N, Hochberg EP, Linden EA, Jha S, Grohs HK, et al. (2013) HHV8-Negative Primary Effusion Lymphoma of B-Cell Lineage: Two Cases and a Comprehensive Review of the Literature. *Case Rep Oncol Med.* 2013: 1-12.
10. Nishimori T, Higuchi T, Hashida Y, Ujihara T, Taniguchi A, et al. (2021) Development of a novel cell linelineage: xenograft model of primary herpesvirus 8-unrelated effusion large B-cell lymphoma and antitumor activity of birabresib in vitro and in vivo. *Cancer Med.* 10: 8976.