

Primary Effusion Lymphoma: An Untrivial Differential Diagnosis for Ascites

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A primary effusion lymphoma is a rare type of non-Hodgkin's lymphoma where serous cavities are involved. That cause peritoneal, pleural and pericardial effusions without any lymphadenopathy. They affect immunosuppressive patients with human herpes virus-8 being the suspected etiological agent. The prognosis is usually poor despite treatment. Herein, the case of an immunocompetent patient with ascites and pleural effusion diagnosed as primary effusion lymphoma is presented and discuss the case in the light of the current literature.

Key Words: Primary effusion lymphoma, human herpes virus-8, ascites

Received: May 3, 2003

Revised: April 23, 2004

Accepted: April 23, 2004

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· The authors have no financial conflicts of
interest.

INTRODUCTION

A primary effusion lymphoma (PEL) is a fairly rare clinical variant of a non-Hodgkin's lymphoma (NHL) which usually occur in immunocompromised patients-predominantly in human immunodeficiency virus (HIV)-positive individuals. That are characterized by malignant effusions of serous body cavities where no primary lymphoid tumor mass exists.¹⁻⁵ Human herpes virus (HHV)-8 is the most common etiological factor found in association with this clinical entity. In this case report, a patient with ascites and pleural effusion diagnosed as PEL is presented, along with some extraordinary clinical features.

CASE REPORT

A 63 year old man with the complaints of progressive abdominal swelling, weight loss and malaise was admitted. He had been taking oral anti-diabetic drugs for the last 5 years but his previous history was otherwise noncontributory. The general condition of the patient was moderate and his vital signs were as follows; temperature: 36.8°C, heart rate: 120/min and blood pressure: 100/60 mmHg, respiration: 16/min. A physical examination revealed bilateral rales, tachycardia, deeper heart sounds and ascites without splenomegaly. No peripheric lymphadenopathy (LAP) was detected. A complete blood count yielded hemoglobin: 10.5 g/dL, hematocrit: 31-%, leukocytes: 9,600/mm³, platelets: 210,000/mm³ and erythrocyte sedimentation rate (ESR): 86 mm/h. A peripheric smear disclosed 60% polymorphonuclear leukocytes, 30% lymphocytes, 8% monocytes, normochrome and normocytic red blood cells. The other laboratory tests were as follows: blood glucose: 229 mg/dL, total protein: 5.3 g/dL and albumin: 3.2 g/dL, with normal liver and renal function tests. Hepatitis markers and anti-HIV were

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negative, but he was Epstein-Barr virus (EBV) immunoglobulin (Ig) G positive. Serum protein electrophoresis was normal but with low albumin level. Tumor markers were negative but the cancer antigen-125 (Ca-125) was > 500 U/mL. Posterior-anterior chest radiography depicted left pleural effusion. The echocardiography was normal but with minimal pericardial effusion. Abdominal ultrasonography demonstrated massive ascites and upper gastrointestinal tract endoscopy detected an active gastric ulcer in the cardia. A biopsy specimen from the lesion was relevant with regenerative hyperplasia. The onward computerized tomography of the thorax and abdomen demonstrated bilateral pleural effusions and pronounced ascites but neither organomegaly nor LAP. The aspirated material

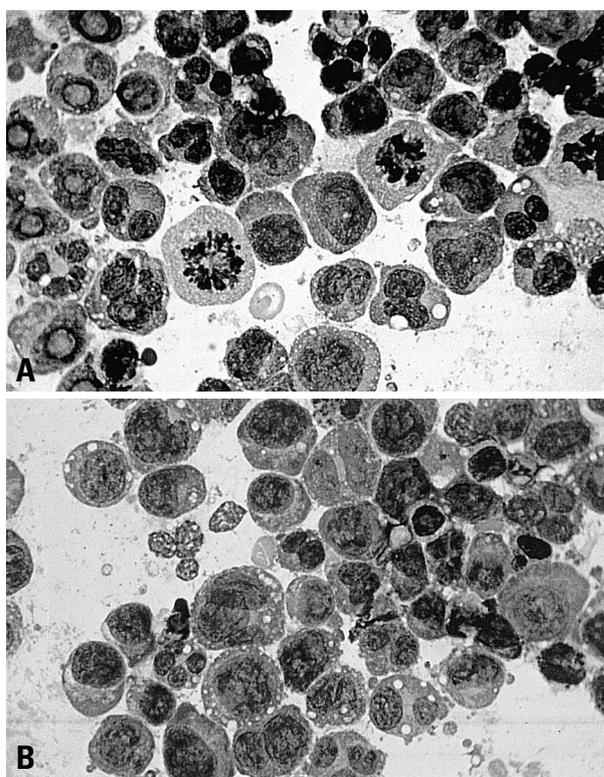


Fig. 1. Atypical lymphoid cells with (A) features of abundant mitotic figures, pleomorphism, basophilic cytoplasm with clear vacuoles and prominent nucleoli (MGG \times 40) and (B) features of pleomorphism and multinucleation (MGG \times 40).

Table 1. Flow Cytometry from the Peritoneal Fluid

Antigen	%	Antigen	%
CD 45	99	CD 20	97
CD 14	9	CD 103	11
HLA-DR	98	CD 11c	28
CD 22	95	CD 44	83
CD 5	10	CD 54	91
CD 19	95	Kappa	90
CD 25	11	Lambda	8
CD 23	26	cBCL 2	46

CD, cluster of differentiation; BCL, Burkitt cell line (Bcl-2).

from the ascites was exudative and direct microscopy uncovered atypical lymphomononuclear cells without any tuberculous bacilli (Fig. 1). The adenine deaminase level was < 200 U/L. A bone marrow biopsy was normal but hypocellular. During the follow up, thoracentesis and paracentesis were performed as the patient had progressive dyspnea and a cytological analysis of both fluid materials displayed a high grade malignant lymphoma. The immune phenotype analysis by flow cytometry was consistent with B-cell predominant NHL with kappa monoclonality (Table 1). The levels of interleukin (IL)-6, IL-10 and HHV-8 were not studied due to laboratory insufficiency.

Overall, the patient was diagnosed as PEL and a further laparoscopic peritoneal biopsy was planned. This however could not be accomplished due to the worsening general conditioning of the patient. A CHOP chemotherapy protocol (cyclophosphamide 750 mg/m², adriamycin 50 mg/m², oncovine 14 mg/m² on day 1 and prednisolone 100 mg on days 1-5, repeated every 21 days) was applied. The patient's general condition improved, both the pleural effusion and ascites regressed in a one week period. The ESR declined to 24 mm/h and the patient was discharged with an appointment for the second cycle of chemotherapy. The second cycle was given on an outpatient basis thereafter the remaining protocol could not be sustained due to the patient's untoward hematological status. The patient died in the fifth month following diagnosis of progressive ascites and dyspnea.

DISCUSSION

Due to its distinct biological and clinicopathological features, PEL has been recognized as an independent lymphoproliferative malignancy -with a large cell morphology, B cell genotype and tendency to infiltrate serous mucosa causing effusions without any tumoral mass or LAP.^{1,4,6-8} More specifically, it is defined as a lymphoma of the post-germinal center, pre-terminally differentiated B-cells.² PEL became salient around 1995, after which there has been much effort to clarify its -yet uncertain- obscure pathogenesis. By and large, HHV-8 and EBV are the leading suspect etiological factors.¹⁻⁵ HHV-8, also termed as Kaposi's sarcoma (KS)-associated herpes virus,^{4,9} is a gamma herpes virus which encodes genes highly homologous to cytokine genes and genes closely related to cell cycle control.^{4,9,10} According to experimental studies, HHV-8 is also found to induce acceleration of the cell cycle and cell transformation or promote the proliferation of infected cells.^{11,12} HHV-8 DNA is rarely found in various tumor and non-tumor tissues from patient groups not at risk of KS whereas it has been shown to be in

exclusive association with KS, multicentric Castleman's disease and PEL but less so with multiple myeloma and sarcoidosis.^{3,5,13,14}

Despite the skepticism of its role in the pathogenesis of PEL, a concurrent EBV infection takes place in approximately 70% of patients.⁴ It is also speculated that a pathological synergy exists between EBV and HHV-8 in the pathogenesis of PEL. In contrast to HIV-positive patients who are usually also EBV-positive, almost all HIV-negative cases with PEL are EBV-negative.⁵ Interestingly, EBV IgG was positive in our patient.

PEL is usually observed in patients with acquired immune deficiency syndrome (AIDS) or other forms immunocompromisation.¹⁵ Although very rare, the clinical scenario of PEL, when it occurs in immunocompetent patients, is different comprising old age, normal immunity, less EBV co-infection and apparently a less aggressive disease course.⁸ The precise mechanism of PEL occurring in healthy individuals with normal immunity can not be elucidated whereas aging, decreased T cell immunity with normal or increased humoral response are few of the proposed mechanisms.^{4,8} Extraordinarily, our patient was relatively younger than the HIV-negative males hitherto mentioned in the literature,^{5,8} with EBV IgG positivity and an aggressive clinical course.

The diagnosis of PEL is usually established with relevant clinical evidence-effusions with tropism for the serous cavities and inconclusive attempts of demonstrating any primary lymphoid tumoral mass and with further analysis of the fluid material by either immunohistochemistry or flow cytometry. Moreover, genetic analysis for the presence of HHV-8 and EBV DNAs can additionally strengthen the diagnosis. Similarly to our patient, the serum Ca-125 level can anecdotally be high in some cases due to an inflammatory serosal reaction.¹⁶

The prognosis of PEL is usually poor and the majority of the patients die within one year of diagnosis.^{3,7} The effusions can temporarily be kept under control despite various chemotherapy protocols such as CHOP.^{3,9,17}

Our HIV-negative male patient relatively younger than the aforementioned patients in the literature with normal immunity but EBV IgG positivity and an aggressive clinical course exemplifies a somewhat extraordinary clinical scenario, per se, of such a rare pathology. Herein, we also orient the clinicians towards being vigilant about PEL -vis-a-vis the differential diagnosis of ascites.

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