Primary Effusion Lymphoma in Two HIV-Negative Patients Successfully Treated with Pleurodesis as First-line Therapy

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Abstract. *Primary effusion lymphoma (PEL) is a rare non-Hodgkin's lymphoma (NHL) mostly occurring in HIV-positive patients. It is characterized by the development of effusion in one or more body cavities, with no tumor masses and a positive human herpes virus-8 (HHV8) status. It has a poor survival profile and no optimal treatment is yet defined. We report two HIV-negative, HHV8-positive patients with PEL of the pleural cavity who achieved a durable remission after pleurodesis with bleomycin and no systemic therapy. We also perform a review of the relevant literature regarding the clinical data, treatment, and survival of PEL in HIV-negative patients.*

Primary effusion lymphoma (PEL) is a rare non-Hodgkin's lymphoma (NHL) comprising approximately 0.3% of NHL in HIV-negative individuals and approximately 4% of NHL in HIV-positive patients (1). According to the World Health Organization classification of neoplastic diseases of haematopoietic and lymphoid tissue, it is characterized by the development of effusion in one or more body cavities, a lack of tumour mass and a positive human herpes virus-8 (HHV8) status (2, 3). Recently, it has been associated with other immunosuppressive conditions such as solid organ transplantation (4, 5). The diagnosis of PEL is mostly based on cytological examination of the fluid, which reveals a B-lymphoid population with immunoblastic or anaplastic features (6). As yet, the prognosis of the disease is poor, with a median survival time of 6 months and a one-year overall survival rate of 40% (7, 8). The appropriate treatment approach for PEL is not yet defined because of its rarity and therefore lack of sizable patient series. Combination chemotherapy with CHOP or similar regimens is considered as first-line therapy (9, 10). Another approach such as the use of intrapleural injections of cidofovir, an antiviral agent, was reported to induce remission of more than one year's duration in two HIV-negative patients (11, 12). Rituximab is not usually applicable as the neoplastic cells bear an aberrant immunophenotype and do not express the necessary CD20 antigen in the majority of cases (13).

In the present report, we describe the case of two HIV-negative patients with PEL of the pleural cavity who achieved relatively durable remission after pleurodesis by intrapleural injection of bleomycin without any systemic therapy.

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Key Words: Primary effusion lymphoma, lymphoma therapy, pleurodesis, body cavity lymphoma.

Case Report

Patient 1. A 73-year-old woman presented with worsening dypsnea of 2 months duration, anorexia and malaise. Her medical history was significant for type 2 diabetes mellitus, which was controlled with the appropriate diet. On admission, physical examination revealed an effusion occupying the entire left pleural cavity (Figure 1a). No peripheral lymphadenopathy, hepatosplenomegaly or other abnormal physical findings were noted. Laboratory data were as follows: Hb: 14.8 g/dl, white blood cell count (WBC): 8.68×10^9/l with normal differential, platelets (PLT): 239×10^9/l, erythrocyte sedimentation rate (ESR): 46 mm/h, glucose: 191 mg/dl, urea: 55 mg/dl, serum protein: 7.1 g/dl, lactate dehydrogenase (LDH): 353 IU/l. Her biochemical profile, including serum protein electrophoresis, was otherwise within normal limits.

The pleural fluid was an exudate with numerous red blood cells present, a cell count of 6.7×10^9/l, protein at 4.84 g/dl and LDH of 2086 U/l. Cytological examination of the mononuclear cells isolated from the pleural fluid disclosed a large-cell population with lymphoid appearance and anaplastic features, morphology consistent with PEL (Figure 2). The immunophenotypic study of these cells was as follows: $CD3^-$, $CD20^-$, $CD45^+$, $CD30^+$, EMA^+, $CD138^-$ and

CD79a$^-$, a profile more in keeping with a lymphoid malignancy. The patient's serum was negative for HIV antibody (ELISA) and positive for HHV8 DNA by PCR. Whole-body computed tomography (CT) scan did not reveal lymphadenopathy or other pathological findings, while bone marrow aspiration plus biopsy and pleural biopsy disclosed no evidence of lymphoma. Therefore, a diagnosis of an HHV8 positive PEL was established.

Pleurodesis was considered for the management of the disease due to the rapid fluid production. A Bulaw catheter was inserted and complete removal of the pleuritic fluid was performed. After drainage of the pleural fluid, 50 mg of bleomycin were diluted in 50 ml of normal saline and were infused intrapleurally *via* the catheter, which was then clamped. The patient was asked to move from supine, left lateral, right lateral and Trendelenburg position in 15 min intervals for 2 hours. The production of the fluid was suppressed, the effusion did not recur and the patient was asymptomatic (Figure 1b). A complete remission of the lymphoma was documented with imaging studies (CT scan). The patient was followed up clinically every three months and underwent a CT scan every 6 months, being completely asymptomatic and well for a total of 34 months. She then presented with massive ascites and pleural effusion of the other hemithorax. Disease relapse was documented after repeating the appropriate tests, as previously described. She received 6 cycles of cyclophosphamide, mitoxanthrone, and vincristine without prednisone, due to her history of diabetes mellitus, as well as pleurodesis of the right hemithorax with bleomycin and a partial remission was achieved, lasting for 4 months. Subsequently, she developed dysphagia and skin lesions. Upper gastrointestinal GI endoscopy revealed an extensive lesion of the gastrooesophageal junction; biopsy of the oesophageal and skin lesions disclosed lymphoma of similar morphology, infiltrating the skin and the oesophagus. The patient received palliative therapy and died a few weeks later.

Patient 2. A 43-year-old man presented with malaise and dyspnoea. During initial investigation, a large left pleural effusion was found. The patient's medical history was significant for Hodgkin's lymphoma, 25 years prior to his presentation, for which he had been treated with the ChlVPP combination chemotherapy and mantle field radiotherapy. Eighteen years previously, he was diagnosed with hepatitis C infection and was treated with interferon-α for a 12-month period. At presentation his laboratory data were as follows: Hb: 11.6 g/dl, WBC: 4.9×10^9/l (neutrophils: 30%, lymphocytes: 65%), PLT: 271×10^9/l, ESR: 43 mm/h, glucose: 91 mg/dl, urea: 33 mg/dl, serum protein: 8.0 g/dl, LDH: 384 IU/l. His biochemical profile was otherwise within normal limits. The pleuritic fluid disclosed 5.6×10^9 cells /l, 70% of which had a PEL lymphoid morphology, glucose: 10 mg/dl, protein: 7 g/dl and LDH: 10,000 U/l. The immunophenotype of these cells revealed a population positive for CD30 (ki-1), CD138, EMA and vimentin and negative for CD15, CD20, LCA, CD3, CD79a, CD45RO, S100, myeloperoxidase and CD68. All other investigations, including a whole-body CT scan, bone marrow aspiration plus biopsy, pleural biopsy and serology for HIV were negative, except for the confirmation of the pleural fluid in the left pleural cavity. Positivity for HHV8 infection with PCR both in the patient's serum and pleuritic fluid was found. Thus the diagnosis of an HHV8-positive PEL lymphoma was established.

Pleurodesis with bleomycin was performed as described for patient 1, which managed to suppress the production of the fluid. The patient was followed up as previously reported with clinical examination and CT scan and remained in complete remission without symptoms or other signs of lymphoma elsewhere for 22 months. He subsequently presented with cervical and inguinal lymphadenopathy, and a lymph node biopsy from the enlarged nodes revealed a diffuse infiltration by lymphoid cells (Figure 3). The cells exhibited a range in their appearance from large immunoblastic to plasmablastic with anaplastic morphology. The cell cytoplasm was abundant, denoting plasmacytoid differentiation, whilst occasional cells had basophilic vacuoles. Immunohistochemical analysis showed that these lymphoid cells were positive for CD138 and LMP1 and negative for CD3, LCA, CD79a; the histological findings were attributed to a nodal PEL relapse. He received three courses of CHOP without improvement and died three months later because of the disease.

Discussion

Body cavity-based lymphoma (BCBL) is diagnosed when a lymphoid population is found inside a body cavity without an identifiable contiguous mass. It is further classified as either extranodal large cell lymphoma or Burkitt's lymphoma according to cell morphology and c-MYC status when the patient is HHV8 negative; on the other hand, PEL is diagnosed when BCBL is accompanied by HHV8 infection, presents with anaplastic morphology and is c-MYC negative (14). PEL is a rare, aggressive lymphoma that is mainly seen in HIV-positive patients. Fewer than 30 PEL cases have been reported in HIV-negative patients and are usually encountered in elderly or immunosuppressed individuals (3, 13). The disease presents as a lymphomatous effusion in pleural, peritoneal and/or pericardial cavities, without concurrent tissue infiltration of these cavities, presence of tumour masses or lymph node involvement elsewhere (2, 3). It has a dismal median survival of 6 months (8) and optimal therapeutic strategies are not yet defined. In HIV-positive patients, the institution of highly-active antiretroviral therapy (HAART) is strongly recommended as useful adjunctive treatment of PEL

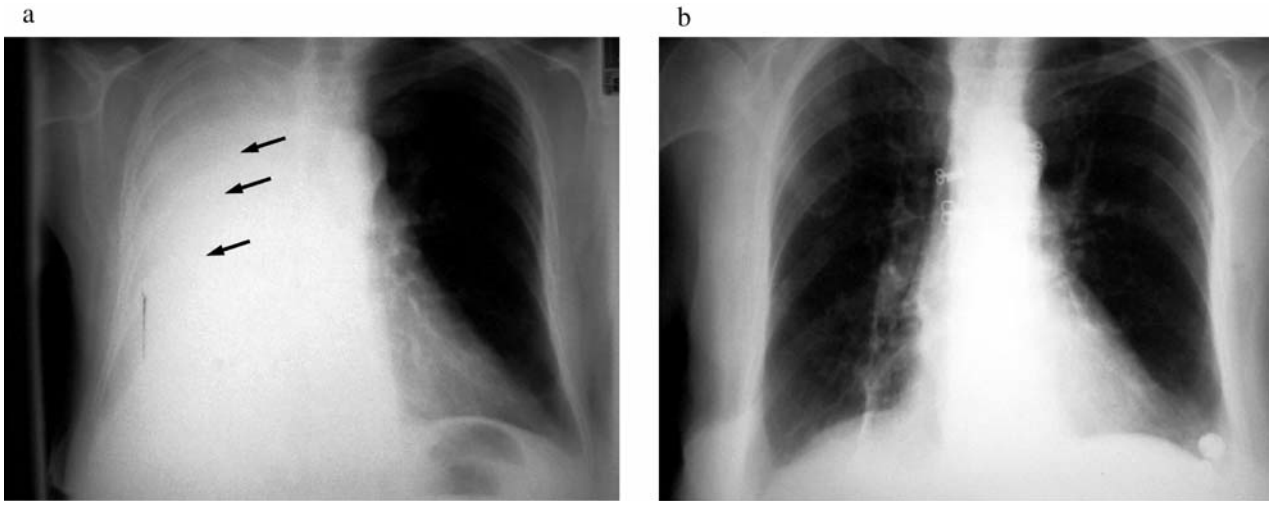

Figure 1. *a, Chest X-ray of patient 1 on admission. Pleural effusion occupying almost entirely the left pleural cavity can be seen. b, The same patient after pleurodesy. Complete resolution of the pleural fluid is clearly evident.*

(15). Rituximab has no role in PEL patients due to the nature of PEL lymphomatous cells, which usually do not express CD20 (13). Standard chemotherapy regimens used in aggressive NHL, such as CHOP, have been tried in PEL patients but their efficacy is hampered by the presence of effusions, where systemic chemotherapy might not reach therapeutic concentrations. As a result, many other approaches, such as systemic or intracavitary administration of antiviral agents, have been suggested but have not yet been sufficiently validated (11). Proteasome inhibitors and antiviral therapy targeting both HIV and HHV8 are yet to be clinically tested (16).

In a review of the literature on HIV-negative PEL cases, we were able to collect 20 reported PEL cases where the treatment and course of disease were recorded (4, 5, 17-33) (Table I). Eleven of the HIV-negative PEL patients received CHOP or modified CHOP, while in one, rituximab was also used due to positivity for CD20 of the lymphoid population. Four patients survived over a year and three were still alive at 15, 18 and 30 months after diagnosis, including the patient who received rituximab. One patient was alive at 12 months after diagnosis of PEL without any treatment apart from drainage of the fluid. Pleurodesis was used in one patient along with CHOP and was unsuccessful; the patient had bilateral pleural effusions and was on immunosuppressive treatment for 8 years due to heart transplantation.

Pleurodesis has been widely used in the treatment of recurrent pleural effusions, both benign and malignant, with satisfactory results (34). It is considered as palliative treatment in malignant disease, mainly of solid tumours and mesothelioma, and has also been used in lymphomatous effusions. Its mechanism of action involves the obliteration of the pleural space in order to prevent fluid accumulation. Bleomycin has been extensively studied as a sclerosing agent for pleurodesis and despite the fact that its exact effects on pleura remain unknown, it is considered to have a local antineoplastic and fibrinogenic action (35). Another advantage of chemical pleurodesis is that it is well tolerated and does not carry the adverse effects of systemic chemotherapy (36).

Both patients reported here were HIV negative and presented with pleural involvement alone, as shown by the whole-body CT scan, the bone marrow and pleura biopsy and the other laboratory tests, which were within normal limits. Both patients had a certain degree of immunosuppression: the first patient due to diabetes mellitus/advanced age and the second due to the preceding Hodgkin's lymphoma, chemo- and radiotherapy and to the presence of hepatitis C and use of interferon-α. In our Department, pleurodesis is used as adjunctive or palliative therapy in lymphomatous pleural effusions secondary to systemic lymphomas with satisfactory results (unpublished data). Thus a pleurodesis with bleomycin in these patients was considered, both for symptom alleviation and disease control. As a result, our patients remained symptom free and achieved a remission without systemic chemotherapy.

The discrete features of this entity, which only affects the body cavities and lacks a tumour mass, could provide an adequate explanation as to the complete and lasting remission achieved by an otherwise 'palliative' treatment modality in the presence of systemic disease. Thus, pleurodesis could be considered appropriate therapy for this type of lymphoma; it has been suggested that intrapleural bleomycin provokes a localized antineoplastic and fibrogenic reaction, which could account for the remission achieved when the disease is localized in the pleura. It must be noted that in our patients, the disease never relapsed at the site of

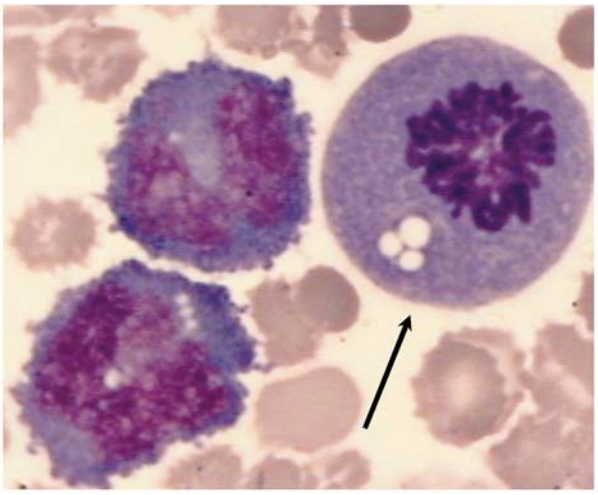

Figure 2. *Malignant cells of primary effusion lymphoma from the pleural cavity of patient 1. Cells are highly immature, very large with obscure nucleoli and a moderate amount of baseophilic cytoplasm. One mitosis (arrow) is present. Cytospin preparation, May-Grünwald-Giemsa stain, ×1,000.*

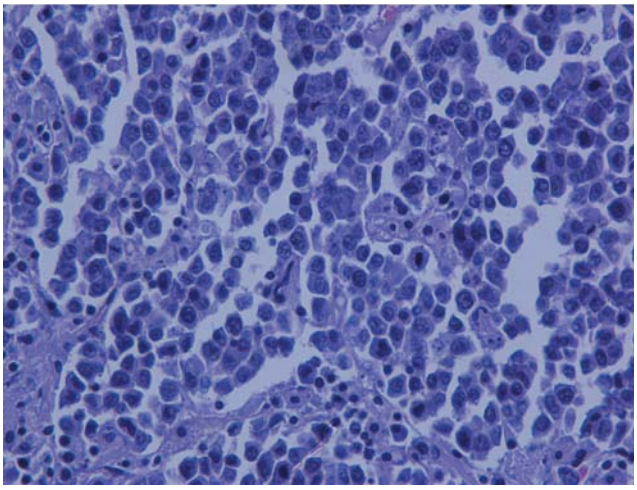

Figure 3. *Large pleiomorphic cells with eosinophilic macronucleoli and abundant cytoplasm, many of which have anaplastic or plasmacytoid appearance. Hematoxylin-eosin stain, ×200.*

Table I. *Treatment and outcome of HIV (–) HHV8 (+) PEL patients.*

Author	Age (years)	Gender	Initial sites	Treatment	Survival (months)	Survival status /remarks
Said *et al*., 1996 (17)	85	F	Pleura	Palliative (?)	4	
Strauchen *et al*., 1996(18)	94	M	Peritoneum	Drainage	72	
Carbone *et al*., 1996 (19)	69	F	Peritoneum	Chemotherapy	1	
Nador *et al*., 1996 (20)	85	M	Pleura	None	6	
Vu 1998 (21)	85	M	Pleura	CHOP	2	
Jones *et al*., 1998 (4)	67	M	Pleura	Pleurodesis bleomycin/CHOP1	6	Transplant patient
Okada *et al*., 1998 (22)	101	M	Pleura	Etoposide	8	
Cobo *et al*., 1999 (23)	58	M	Peritoneum	CHOP X2	3	
Ascoli *et al*., 1999 (24)	75	M	Pleura	None	12	Alive at the time of report
Dotti *et al*., 1999 (5)	56	M	Peritoneum	Chemotherapy	1	Transplant patient
San Miguel *et al*., 1999 (25)	83	M	Pleura	None	<1	
Codish *et al*., 2000 (26)	73	F	Peritoneum and lymph nodes	CHOP X4	4	
Ariad *et al*., 2000 (27)	68	M	Pleura, peritoneum	CHOP X4	9	
Polskj *et al*., 2000 (28)	80	M	Pleura	CHOP X4	8	Alive at the time of report
Perez *et al*., 2001(29)	72	M	Pleura, peritoneum	Rituximab	13	Alive at the time of report
Klepfish *et al*., 2001 (30)	78	M	Pleura	CHOP X8	18	
Boulanger *et al*., 2004 (31)	78	M	Peritoneum	C, P	1.5	
	86	F	Peritoneum	CHOP	2	
Halfdanarson *et al*., 2006 (32)	78	M	Pleura, lymph nodes	CHOP X2/cidofovir-radiotherapy	15	Alive at the time of report
Siddiqi *et al*., 2008 (33)	78	M	Pleura	Bortezomib, doxorubicin, rituximab	24	Alive at the time of report
Present study, 2009	73	F	Pleura	Pleurodesis	38	
	43	M	Pleura	Pleurodesis	24	

F=Female, M=Male.

pleurodesis and recurred in another site after a few years, while a second pleurodesis in patient 1 resulted again in local control of PEL in the contralateral pleural cavity. Novel diagnostic modalities, such as FDG-PET scan, could assist in excluding other localization of the disease and thus further facilitate patient selection for this treatment option.

The successful control of local disease by pleurodesis secured a durable complete remission in our patients. Therefore, we were later able to follow and document the pattern of relapse of the original disease (PEL) to nodal sites and to describe the histological picture at this site, a study for which limited information exists in the relevant literature. In spite of this fact, however, the precise histological classification of these nodal sites of involvement was not possible using the WHO criteria (2).

In conclusion, the use of pleurodesis in treating pleural PEL appears to be highly effective. This therapeutic approach may be useful as a therapeutic option in patients with PEL localized to the pleural cavity, considering the fact that the majority of patients present at an advanced age or with underlying conditions thus hampering the use of systemic chemotherapy. The addition of systemic chemotherapy, such as CHOP, after localized disease control in certain patients at risk of relapse should be further investigated. Eventually, pleurodesis may represent a useful supplement in the therapy of widespread PEL in order to rapidly control symptoms and improve quality of life, pending the development of novel, more effective treatments.

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Received July 26, 2009
Revised November 18, 2009
Accepted November 25, 2009