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Case Report

Beyond the obvious: unveiling primary effusion lymphoma in a 76-year-old female with multifaceted clinical presentation

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ABSTRACT

Primary effusion lymphoma (PEL) is an exceptionally rare and challenging entity to diagnose, characterized by the development of lymphomatous effusions in body cavities without a solid tumour mass. Here, we present a case of PEL in a 76-year-old retired professor with a complex medical history including diabetes, hypertension, and bilateral total knee replacement surgery. The patient initially presented with dry cough and breathlessness, which led to the discovery of a right pleural effusion exhibiting lymphocytic predominance with high ADA but lacking malignant cells. Prompt initiation of empiric anti-tubercular therapy (ATT) resulted in symptomatic improvement and resolution of the effusion. However, subsequent admission to the emergency room due to vomiting, weakness, and walking difficulties unveiled a positive rapid antigen test for COVID-19 and identified moderate right-sided pleural effusion. Additional investigations including positron emission tomography–computed tomography (PET-CT), magnetic resonance imaging (MRI) brain, and cell block analysis unveiled intriguing findings, prompting further evaluation and immunohistochemical (IHC) analysis. IHC markers revealed CD20+, Ki-67 proliferation index of 80%, CD79a+, CD 3 -, CD138-, CD30-, and CD10-, indicative of atypical B cell proliferation. Importantly, the presence of human herpes virus-8 (HHV-8) was confirmed through LANA1 staining, solidifying the diagnosis of primary effusion lymphoma. This case highlights the diagnostic challenges encountered and emphasizes the importance of comprehensive evaluation and IHC profiling confirmation in establishing an accurate diagnosis of PEL.

Keywords: Primary effusion lymphoma, Lymphomatous effusions, Immunohistochemical analysis, HHV-8

INTRODUCTION

Primary effusion lymphoma (PEL) is a large B cell neoplasm usually presenting as serous effusions without detectable tumour masses.[1] It predominantly affects immunocompromised individuals, particularly those with advanced HIV infection.[2] The disease also occurs in the absence of immunodeficiency, usually in elderly patients both men and women. However, PEL cases in HIV-negative patients remain exceptionally uncommon and pose diagnostic challenges. The most common sites are the pleural, pericardial and peritoneal cavities.[3] Extra-cavitary tumours are rare in PEL and may be histologically indistinguishable from PEL. We present a fascinating case of PEL in a 76-year-old female, HIV-negative, with multiple comorbidities.

CASE REPORT

A 76 years old retired professor, presented to the outpatient department with complaints of dry cough and breathlessness persisting for two weeks. Her physical examination revealed the following: blood pressure (BP) of 140/70 mmHg, heart rate of 97 beats/minute, respiratory

rate of 22 breaths/minute, and body temperature of 98°F. The patient was alert, afebrile, hydrated and without signs of respiratory distress. Symmetric thorax with diminished breath sounds in right lung base. Chest X-ray revealed right sided pleural effusion. Thoracocentesis was performed, which produced a straw-coloured fluid with a predominance of lymphocytes and the result of cytology was reported negative for malignancy. ADA level was 169 and no flow cytometry was performed.

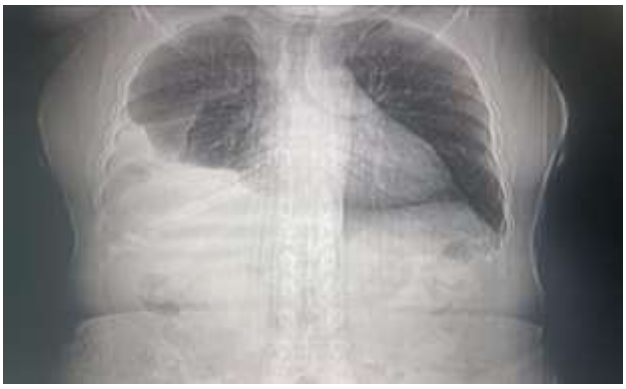

Figure 1: Chest radiography showing right sided pleural effusion.

Considering her clinical presentation and test results, she was started on anti-tubercular treatment (ATT). One month later, during follow-up, the patient showed symptomatic improvement and tolerated the ATT well, with a normal chest radiography.

Two months later, she presented to the emergency room with sudden-onset vomiting (4-5 episodes in one day), weakness, and difficulty walking. She had experienced a slip and fall at her residence a day prior but had not lost consciousness. Bilateral raccoon eyes were observed, she was vitally stable and her Glasgow Coma Scale (GCS) was recorded as E4V5M6. Chest X-ray was performed which revealed right sided homogenous opacification in the lower zone with blunting of costophrenic angle suggesting of right sided pleural effusion (Figure 1). A rapid antigen test for COVID-19 was positive, and an HRCT chest (Figures 2 and 3) revealed a moderate right-sided effusion along with small sub centimetric pretracheal, precarinal, and subcarinal lymph nodes. A subsequent ultrasound of the chest indicated a right-sided loculated pleural effusion, measuring approximately 600 ml. An MRI of the brain showed mild generalized age-related cerebral atrophy with small vessel ischemic changes. She was started on COVID treatment, oral corticosteroids, antiemetics, and other supportive medications, while we continued her Anti tubercular drug therapy.

A therapeutic thoracocentesis was planned and performed. During the thoracocentesis, AFB stain was negative, and gram stain showed no bacterial growth, but a few pus cells were observed. ADA level was 67, and cell block analysis revealed dense infiltrates of atypical lymphocytes. A whole body PET CT scan (Figure 4) was subsequently conducted to further evaluate the condition, which showed a sub centimetric pleural-based nodule in the middle lobe with no FDG uptake, along with mild right pleural effusion and sub centimetric mediastinal nodes, no organomegaly or any focal lesion and all negative for metabolically active disease.

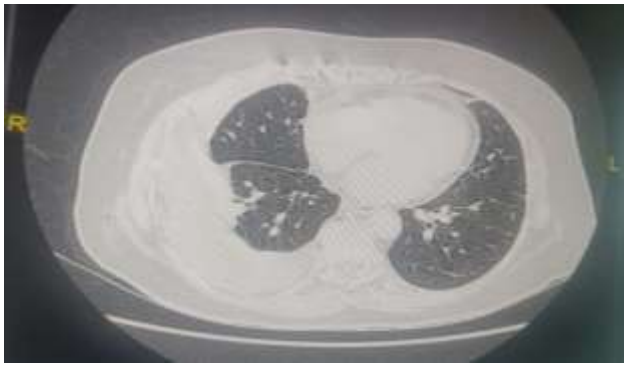

Figure 2: HRCT chest (lung window/axial view) showing moderate right sided pleural effusion with no parenchymal abnormalities noted.

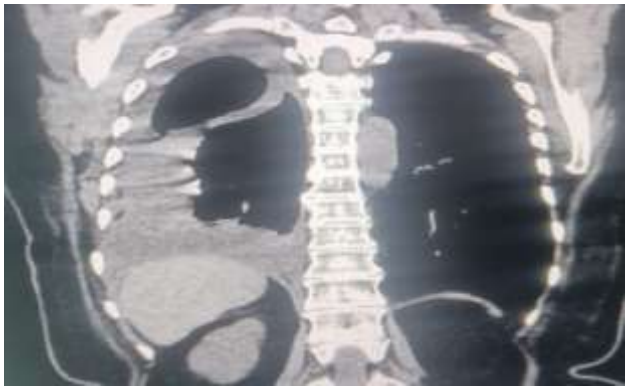

Figure 3: HRCT chest (mediastinal window/coronal view) showing moderate right sided pleural effusion with extension of the effusion into oblique fissure.

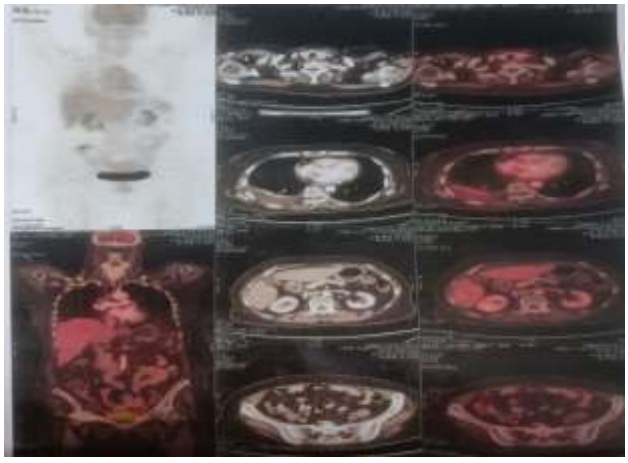

Figure 4: Whole body PET CT scan showing right sided pleural effusion with no metabolically active disease.

Results

In light of the PET CT findings, the possibility of PEL was considered. To confirm the diagnosis, immunohistochemical markers were analysed, which revealed positive CD20 (Figure 5), CD79a and Ki 67 proliferation index at 80% (Figure 6) with CD 3, CD138, CD30, and CD10 being negative. These findings suggested atypical B cell proliferation with a high proliferation index. Additionally, LANA1 staining (Figure 7) was performed, confirming an association with HHV-8. Thus, the diagnosis of PEL was established in this HIV-negative patient.

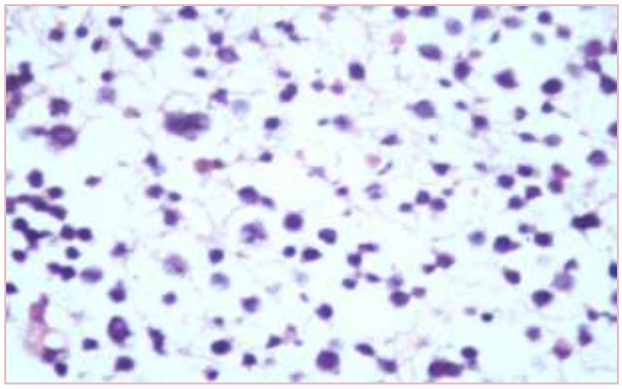

Figure 5: CD 20 positive.

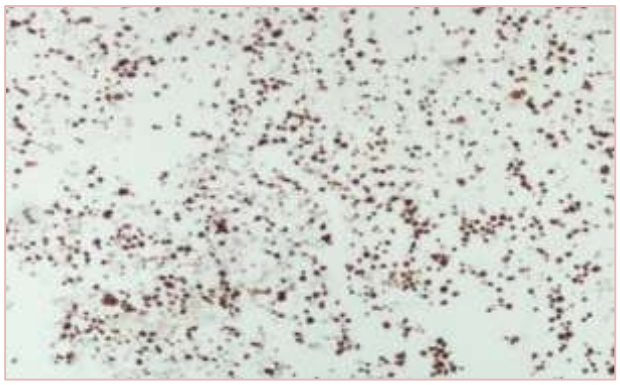

Figure 6: Ki 67 proliferative index 80%.

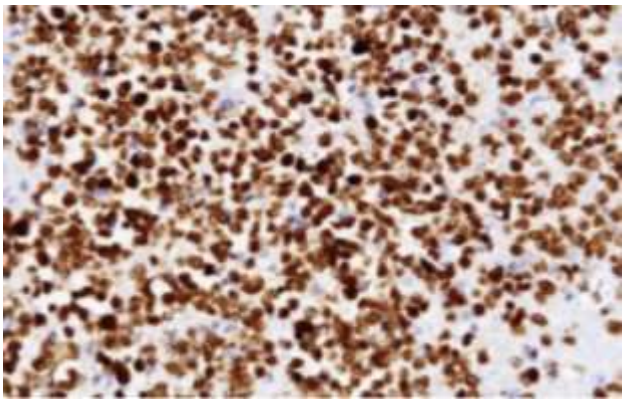

Figure 7: LANA-1 staining positive.


IMMUNOHISTOCHEMISTRY REPORT

IHC MARKER(S)	RESULT
HHV-8	Immunoreactive, score 3+ in neoplastic cells

Comment : All external controls show appropriate reactivity

SLIDE NO : BI 41634102

SPECIMEN : Block of pleural fluid cell block for IHC markers.

CLINICAL HISTORY : Pleural fluid cell block shows atypical b cell proliferation with high proliferation index.

GROSS : Received 1 formalin fixed paraffin embedded block labelled as 324122

INTERPRETATION

RESULT	SCORE
Non Immunoreactive	0
Immunoreactive in 1-25 % cells	1+
Immunoreactive in 26-50% cells	2+
Immunoreactive in 51-75% cells	3+
Immunoreactive in 76-100% cells	4+

HHV-8 (Clone - 13B10): Human Herpes Virus 8 is also known as Kaposi's Sarcoma-associated Herpes Virus. Human herpes virus type 8 (HHV-8) infection can lead to the development of lymphoproliferative diseases or other neoplasms, especially in the setting of HIV. These neoplasms include the plasma cell variant of Castleman disease, Kaposi sarcoma, and primary effusion lymphoma. Positive staining is observed in endothelial cells and spindle cells in HHV-8 associated Kaposi sarcoma (92% sensitive & highly specific).

Figure 8: HHV-8 report: immunoreactive, score 3+ in neoplastic cells.

DISCUSSION

Primary effusion lymphoma is a large B cell neoplasm usually presenting as serous effusions without detectable tumour masses. It is universally associated with human herpesvirus 8 (HHV8), also called as Kaposi sarcoma associated herpesvirus.[1] Usually occurs in young or middle aged men. There is frequent coinfection with monoclonal EBV.[4] PEL can also occurs in the absence of immunodeficiency, usually in elderly patients, both men and women. The neoplastic cells are positive for HHV-8 in all cases. Male homosexual contact is the most common risk factor followed by injection drug use.[5]

PEL is an exceedingly rare subtype of lymphoma, especially in HIV-negative individuals.[6] Its association with HHV-8 makes it a distinct entity, characterized by effusions in body cavities without any solid tumour masses or lymphadenopathy.[1] In this case, the patient's age and comorbidities, including diabetes, hypertension, and previous bilateral TKR surgery, were notable factors. HHV-8 encodes more than ten homologous cell proliferation and anti-apoptotic signalling genes and is the probable etiological agent of Kaposi's sarcoma.[7,8] DNA sequences of HHV-8 have been found in lesions of Kaposi's sarcoma, PEL, and multicentric Castleman's disease by polymerase chain reaction and in situ hybridization.[9,10] Latent nuclear antigen (LNA-1, LNA, LANA-1), also known as "ORF73," is a 222 or 234 kD protein that is consistently expressed in cells infected with HHV-8, which was positive by IHC in our patient's case.[11]

The management of PEL in HIV-negative patients can be challenging due to its rarity and lack of standardized treatment guidelines. Current therapeutic strategies often involve a combination of chemotherapy, targeted therapies, and antiviral agents targeting HHV-8.[12] Chemotherapy with dose-adjusted etoposide, prednisone,

vincristine, cyclophosphamide, and doxorubicin (EPOCH) has proven to increase survival rates in patients with this condition.[12,13,15] The clinical outlook is usually unfavourable with a median survival of less than 6 months.[14,16] The response to treatment and overall prognosis can vary widely, making early diagnosis is crucial.

CONCLUSION

We report a rare case of PEL that occurred in an immunocompetent patient who presented initially with latent manifestations leading to difficulty in diagnosing. Primary effusion lymphoma is a rare and aggressive disease. A high index of suspicion is important in the evaluation of patients with serosal involvement without clear or evident diagnosis.

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