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CASE REPORT
Cardiovascular imaging

Where has the lymphoma gone? Pericardial effusion adenosine deaminase may play a key role in diagnosing primary effusion lymphoma-like lymphoma: a case report

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Background Primary effusion lymphoma (PEL) is a non-Hodgkin lymphoma that is exclusively generated by body cavity effusion. Primary effusion lymphoma develops in patients infected with human immunodeficiency virus (HIV) and is associated with the human herpes virus (HHV)-8 infection. However, there are sporadic cases without HHV-8 infections or any history of immunodeficiency, called 'PEL-like lymphoma'.

Case summary An 83-year-old man was admitted to our institution because of shortness of breath, fatigue, and facial oedema. Laboratory findings were unremarkable, including negative results for HIV antibodies. Transthoracic echocardiography revealed massive pericardial effusion surrounding the entire heart, which resulted in the early diastolic collapse of the right ventricular free wall, indicating elevated intra-pericardial pressure. He underwent pericardial centesis and 700 mL of pericardial fluid was drained. Adenosine deaminase (ADA) in the pericardial effusion showed an abnormally high value of 221 U/L. Cytological examination revealed a cellular population compatible with diffuse large B-cell lymphoma with prominent blastic characteristics and negative for HHV-8 latent nuclear antigens. Thus, the patient was diagnosed with HHV-8 unrelated HIV-negative PEL-like lymphoma. He was followed for more than 10 months in complete remission after a single pericardial drainage without any chemotherapy.

Discussion Exhaustive drainage of the lymphomatous effusion may induce complete remission in some patients with PEL-like lymphoma. Furthermore, the ADA value in the pericardial effusion may serve as a valuable guide to facilitate the accurate diagnosis of PEL-like lymphoma.

Keywords Primary effusion lymphoma-like lymphoma • Adenosine deaminase • Cardiac tamponade • Case report

ESC curriculum 2.1 Imaging modalities • 2.2 Echocardiography • 6.6 Pericardial disease • 6.8 Cardiac tumours

Learning points

- Primary effusion lymphoma (PEL) is a rare and aggressive type of non-Hodgkin's lymphoma, which is related to human herpes virus (HHV)-8, and has a characteristic feature of exclusively generating in the body cavity without obvious mass lesion.
- In cases without HHV-8 infections or a history of immune deficiency, this disease condition is referred to as PEL-like lymphoma.
- Exhaustive drainage of the lymphomatous effusion might induce complete remission in some patients with PEL-like lymphoma.
- The adenosine deaminase value in the body cavity effusion may be a valuable guide to facilitate the accurate diagnosis of PEL-like lymphoma.

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Introduction

Primary effusion lymphoma (PEL), a rare and aggressive type of non-Hodgkin lymphoma (NHL), presents with a characteristic exclusive generation of pleural, peritoneal, or pericardial effusion without obvious mass lesions, and it accounts for ~4% of NHL.[1] Patients with PEL present with dyspnoea from pleural or pericardial effusion, or abdominal distension from ascites, resulting from mass effects of malignant effusions. In general, PEL develops in immunocompromised patients infected with human immunodeficiency virus (HIV)[2] and is always associated with the human herpes virus (HHV)-8 infection.[3–5] Although traditional chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is the most common regimen for treating PEL, lymphomatous effusion progresses, and as a result, involves other sites and forms tumour lesions during its clinical course. However, the accumulation of cases has revealed that there are sporadic cases without HHV-8 infection or a history of immunodeficiency.[6] These cases, called 'PEL-like lymphoma', are significantly different from the typical PEL in terms of clinical background, prognosis, and responsiveness to treatment, and have recently gained significant prominence.[7]

Herein, we report a unique case of PEL-like lymphoma with cardiac tamponade as the initial presentation in a patient who remained in complete and prolonged remission, with treatment by pericardial drainage alone.

Summary figure

1 year ago	Shortness of breath, easy fatiguability, and facial oedema developed
On admission	Internal jugular vein was extremely distended without any *y* descent. Cardiac auscultation revealed Grade 2/6 systolic ejection murmur at the fourth left intercostal space with muffled heart sounds
	Chest radiography exhibited a globular heart silhouette with water-bottle configuration
	Transthoracic echocardiography exhibited massive pericardial effusion surrounding the entire heart, which resulted in early diastolic collapse of the right ventricular free wall
Pericardial centesis	The patient underwent pericardial centesis and 700 mL of pericardial fluid was completely drained, and his symptoms significantly improved soon after the drainage
	The pericardial effusion was bloody and exudative, and adenosine deaminase level was abnormally high at 221 U/L
	Cytology revealed cellular population compatible with diffuse large B-cell lymphoma with prominent blastic characteristics
	The patient was finally diagnosed with HHV-8 unrelated HIV negative PEL-like lymphoma
10 months later	He has remained in complete remission without any chemotherapy. Moreover, after only a single pericardial drainage, no re-accumulation of pericardial effusion was observed until now

Case presentation

An 83-year-old man was admitted to our institution owing to shortness of breath, fatigue, and facial oedema for ~1 year. His medical history was unremarkable, except for hypertension and benign prostate hyperplasia. On admission, his blood pressure was 120/73 mmHg, heart rate was 62 b.p.m., and oxygen saturation was 94%. On physical examination, leg oedema, hepatosplenomegaly, and general lymphadenopathy were not observed; however, the internal jugular vein was extremely distended without any *y* descent. Cardiac auscultation revealed a Grade 2/6 systolic ejection murmur in the fourth left intercostal space with muffled heart sounds. Laboratory findings were unremarkable, including negative results for HIV antibodies; however, the soluble interleukin-2 receptor was mildly elevated to 932 U/mL. Electrocardiography showed normal sinus rhythm with a complete right bundle branch block. Chest radiography revealed a globular heart silhouette with a water bottle configuration (*Figure 1A*). Computed tomography revealed massive pericardial effusion without pericardial thickening, lymphadenopathy, or an obvious mass lesion (*Figure 1B*). Transthoracic echocardiography revealed massive pericardial effusion surrounding the entire heart, resulting in early diastolic collapse of the right ventricular free wall (see Supplementary material online, *Videos S1–S3*), indicating elevated pericardial pressure (*Figure 2A* and *D*). Doppler echocardiography showed a significant inspiratory reduction in cardiac output in the left ventricular outflow tract and expiratory augmentation of forward flow (*Figure 2B*). Conversely, the opposite response was observed at the right ventricular outflow tract under spontaneous respiration, suggesting 'pulsus paradoxus' and exacerbated ventricular interdependence (*Figure 2C*). Transmitral flow showed an impaired relaxation pattern (*Figure 2F*), and superior vena cava flow exhibited a remarkable systolic component dominant pattern (*Figure 2E*), in accordance with the inspection findings of the jugular venous waveform, all indicating the presence of cardiac tamponade. The patient underwent pericardiocentesis, and 700 mL of pericardial fluid was drained. His symptoms significantly improved soon after the drainage.

The pericardial fluid was bloody and exudative, and most importantly, its adenosine deaminase (ADA) level showed an abnormally high value of 221 U/L. Microbiological studies found no bacteria, fungi, or acid-fast organisms. However, cytological examination revealed a cellular population compatible with diffuse large B-cell lymphoma with prominent blastic characteristics (*Figure 3*). Immunocytochemistry showed that the tumour cells were positive for CD20 and Epstein–Barr virus-encoded small RNA *in situ* hybridization but negative for HHV-8 latent nuclear antigen (*Figure 3*). Thus, the patient was diagnosed with HHV-8-unrelated HIV-negative PEL-like lymphoma. Based on oncological consultation, chemotherapy was withheld, considering the age and poor physical status of the patient. Although initial ^{18}F-fluorodeoxyglucose-positron emission computed tomography (^{18}F-FDG-PET CT) showed mild accumulation of ^{18}F-FDG in the mediastinum and left supraclavicular lymph nodes (*Figure 4A*), the accumulation improved 3 months after pericardial drainage alone (*Figure 4B*). The patient is closely followed up by an oncologist every 3 months using echocardiography and ^{18}F-FDG-PET CT, and he has been in complete remission without any chemotherapy for more than 15 months.

Discussion

Primary effusion lymphoma is a rare malignant lymphoma originating exclusively in body cavities, such as the pericardial, peritoneal, and pleural spaces, without generating obvious mass lesions. In 1989, PEL was first reported as a peculiar lymphoma with an extranodal primary site and proliferation within a body cavity.[2] In 1995, Green *et al.*[8] reported a case series of primary lymphomatous effusions in 18 patients with acquired immunodeficiency syndrome, offering a novel insight into

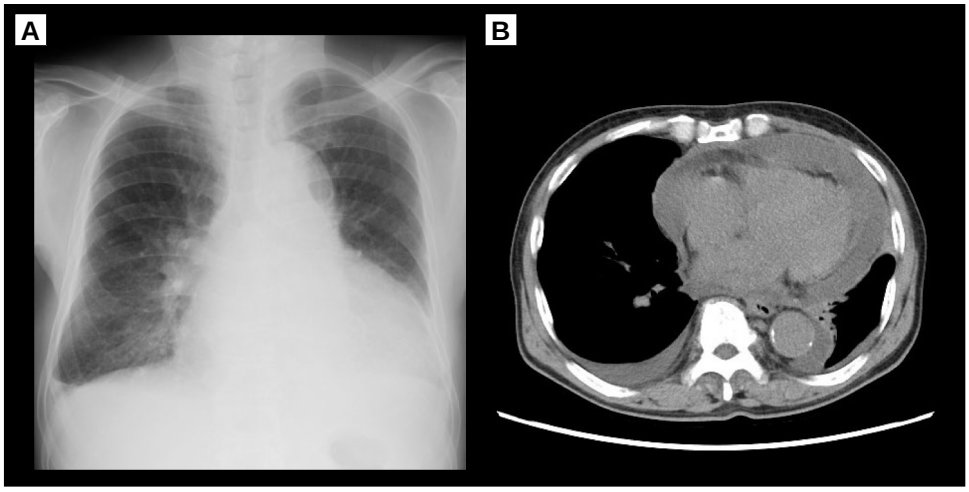


Figure 1 Chest radiography and computed tomography of an 83-year-old man. (*A*) Chest radiography reveals a globular heart silhouette with a water-bottle configuration. (*B*) Computed tomography reveals a massive pericardial effusion.

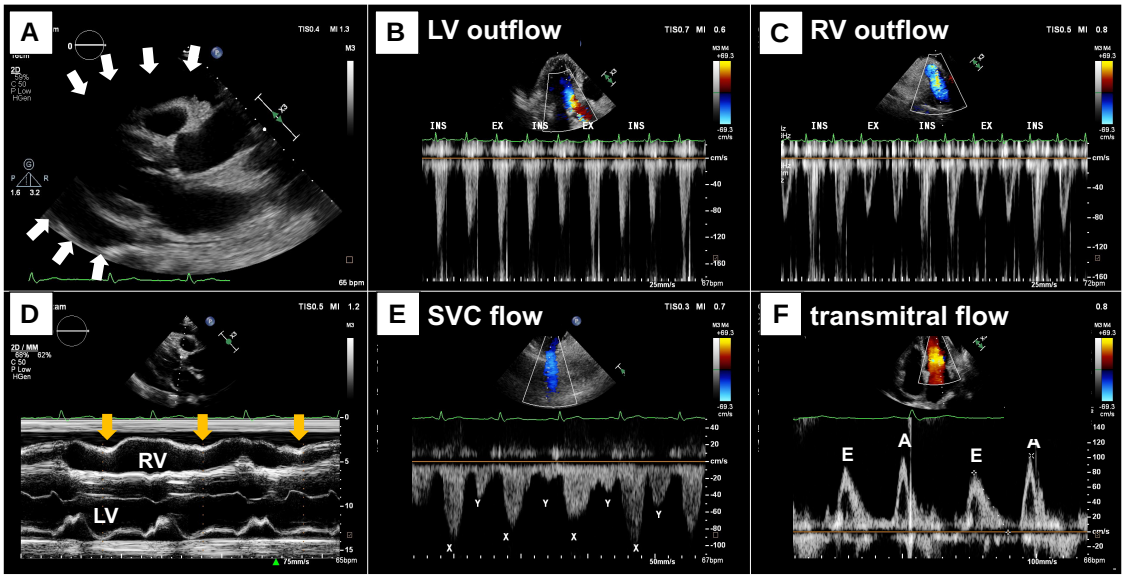


Figure 2 Transthoracic echocardiogram of an 83-year-old man. (*A*) Parasternal long-axis view shows massive pericardial effusion (arrows). (*B*) Pulsed-wave Doppler echocardiography shows a significant inspiratory reduction in cardiac output and expiratory augmentation at the left ventricular outflow tract. (*C*) Conversely, significant inspiratory augmentation and expiratory reduction in cardiac output are observed at the right ventricular outflow tract. (*D*) Early-diastolic right ventricular free wall collapse is shown (arrows). (*E*) Superior vena cava flow shows a systolic component dominant pattern. (*F*) Transmitral flow shows an impaired relaxation pattern. LV, left ventricle; RV, right ventricle; SVC, superior vena cava; Ins, inspiration; Ex, expiration.

the pathogenesis and significant association of body cavity-based lymphoma and HIV infection. This observation was expanded upon by Cesarman *et al.*,[4] who further proposed the relationship between primary lymphomatous effusion and HHV-8 infection, and a novel disease concept designated PEL was established in 1996.[5] Upon accumulating further cases, unique cases of HHV-8-unrelated HIV-negative PEL have emerged. The clinical course of these special cases is quite different from that of PEL; thus, a separate disease concept for PEL-like lymphoma has been established and has received considerable attention.[7]

The prognosis of PEL is extremely poor, with a 1-year survival rate of 17.3%, while it has been reported that PEL-like lymphoma has a better prognosis, with a 1-year survival rate of 35.5%.[7] From a therapeutic point of view, since most patients with PEL-like lymphoma are

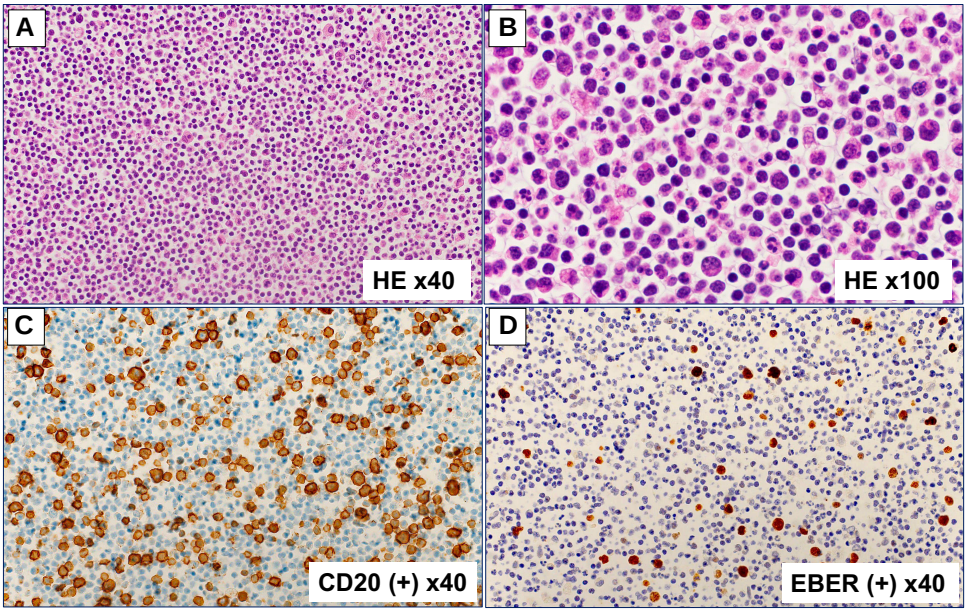


Figure 3 Histopathological specimen of pericardial effusion of an 83-year-old man. Haematoxylin and eosin staining reveals a cellular population compatible with diffuse large B-cell lymphoma with prominent blastic characteristics (*A* and *B*). Immunostaining for CD20 and Epstein–Barr virus-encoded small ribonucleic acid (EBER) are positive (*C* and *D*). CD, cluster of differentiation; RNA, ribonucleic acid.

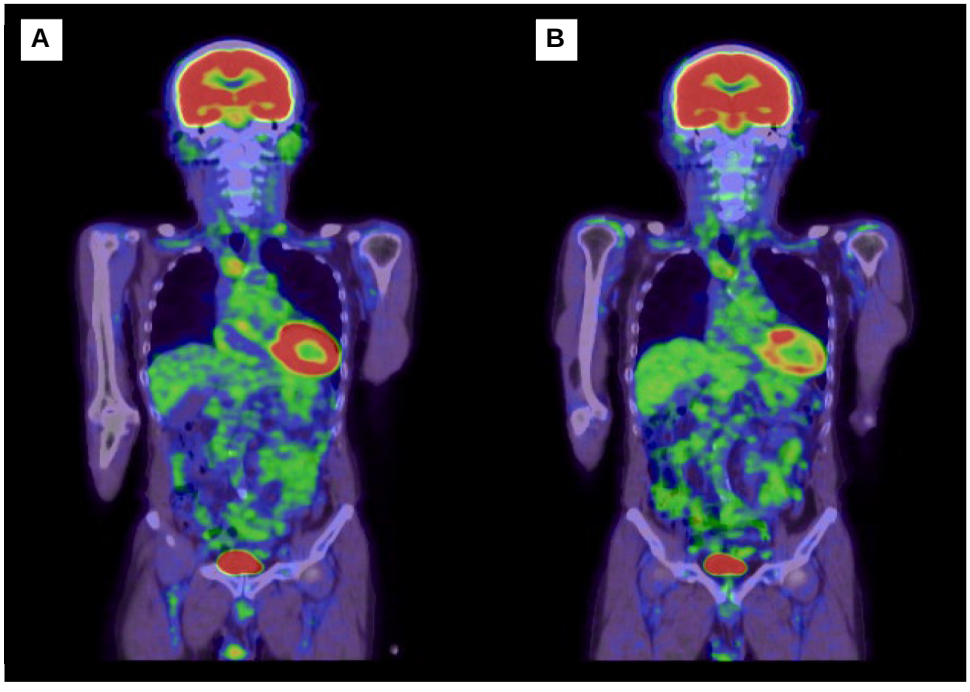


Figure 4 Comparison of ^{18}F-FDG-PET CT at initial presentation and 4 months after drainage. ^{18}F-fluorodeoxyglucose-positron emission computed tomography (^{18}F-FDG-PET CT) images at initial presentation (*A*) and 4 months after pericardial drainage (*B*) are shown. The accumulation of ^{18}F-FDG in the lymph nodes and mediastinum also improved 3 months after pericardial drainage. FDG, fluorodeoxyglucose.

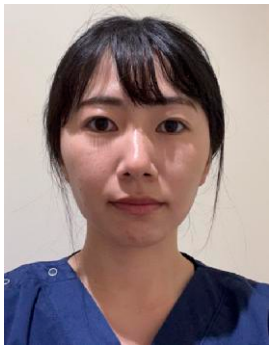
CD-20 positive, rituximab is expected to be effective, and many cases with complete response have been reported when rituximab is used. In extreme cases of PEL-like lymphoma, as in our patient, clinical remission with effusion drainage alone has been reported.[9,10] This clinical characteristic is highly unusual in terms of malignant neoplasms; therefore, it is critical to differentiate between PEL and PEL-like lymphoma from a therapeutic standpoint. Primary effusion lymphoma-like lymphoma occurs in older patients who are often intolerant of anticancer chemotherapy; therefore, simply draining as much pleural fluid as possible can be an important treatment option for these patients.

Owing to the various aetiologies of pericardial diseases, definitive diagnoses of some pericardial effusions are difficult by routine examination. Therefore, in addition to routine biochemical and microbiological testing, it may be important to create additional cell blocks for flow cytometry and immunohistochemical staining to characterize pericardial effusion. Moreover, a literature review suggests that ADA levels in pleural effusion may be significantly elevated in patients with PEL-like lymphomas. Although ADA in body cavity fluid has typically been used as a marker for tuberculosis, Nakako *et al.*[11] recently reported in a literature review that ADA levels in pleural fluid were markedly elevated to an average value of 225 (101–477) IU/L in patients with PEL-like lymphoma, as was observed in our patient. From a previous study, median ADA levels in the pleural fluid were 73 and 84 IU/L in patients with lymphoma-associated malignant effusion and tuberculosis, respectively.[11] Therefore, substantially high ADA levels in the body cavity fluid can be a key marker of PEL-like lymphoma.

Conclusion

We encountered a unique patient with PEL-like lymphoma initially manifesting as cardiac tamponade who maintained complete and prolonged remission after pericardial drainage alone. This pathophysiological condition should be considered in cases of unexplained pericardial effusion. Moreover, the ADA value in the pericardial fluid may facilitate the accurate diagnosis of similar cases with PEL-like lymphoma.

Lead author biography



After graduating from Kobe University in 2019, the author traversed the path of General Internal Medicine at Kasumi Hospital and Prefectural Tamba Medical Centre after 2 years of residency at Steel Memorial Hirohata Hospital.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case is available online as Supplementary data.

Consent: The authors confirm that written consent for the publication of this case report, including images and associated text, has been obtained from the patient in line with the COPE guidance.

Conflict of interest: The authors declare no conflicts of interest.

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Data availability

Unidentified data is available on request.

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