Case Report

A rare primary pericardial DLBCL masquerading as an unexplained malignant pleural effusion in an elderly woman: A case report

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ABSTRACT

Introduction: Primary cardiac lymphoma (PCL) is an extremely rare and fatal heart neoplasm. Primary cardiac non-Hodgkin lymphoma (NHL) is uncommon, considering the rarity of pericardial diffuse large B-cell lymphoma (DLBCL) with advanced pleural metastasis.

Case presentation: We reported an 86-year-old female with primary pericardial DLBCL diagnosed initially by pleural effusion cytology. The chest imaging study revealed multiple pericardial lobulated infiltrative masses and epicardial invasion. Subsequently, she underwent an emergent pericardial window with a pericardial mass biopsy. The final histopathological and immunohistochemical (IHC) stain confirmed primary pericardial DLBCL, initially showing unexplained malignant pleural effusion.

Clinical discussion: The presence and extent of tumour invasion in the heart can be confirmed by echocardiography, computerised tomography (CT), or magnetic resonance imaging (MRI). However, the final histopathological diagnosis requires an examination of the endocardial, myocardial, pericardial window and biopsy or pericardial and pleural effusion cytology. This is the first case report of primary pericardial DLBCL diagnosed by metastatic malignant pleural effusion cytology per the literature review.

Conclusion: The definitive diagnosis for primary pericardial DLBCL is based on effusion cytology, histopathological and IHC evaluation, and clinical characteristics and image feature correlation.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common variant of non-Hodgkin lymphoma (NHL), accounting for approximately 40% of all lymphomas [1–6]. Primary cardiac and pericardial lymphoma involvement is an extremely rare NHL subset, accounting for 0.5% of cardiac involvement and 1% of extranodal NHL [6]. The most common diagnostic lymphoma subtype is DLBCL, but Burkitt lymphoma, T-cell lymphomas, small lymphocytic lymphoma, and plasmablastic lymphoma also occur [1,6].

Pericardial involvement with secondary pleural effusion is extremely rare [7]. Pericardial effusion is the most common presentation [2,3,5,6,8–12]. Pericardial lymphoma’s clinical presentation is nonspecific and depends on tumour size and location. Manifestations may include cardiac arrhythmia, syncope, dyspnea, superior vena cava syndrome, and restrictive cardiomyopathy [1]. Early diagnosis and treatment are critical, as this is a very lethal and rapidly progressive lymphoma characterised by an extremely poor prognosis and survival [6].

We reported an 86-year-old woman without an acquired immunodeficiency syndrome or a chronic immunosuppressive disease presenting with chest pain, shortness of breath (SOB), pleural effusion, and progressive dyspnea. This was an interesting and unique manifestation of aggressive primary pericardial DLBCL masquerading as a solitary unexplained malignant pleural effusion. The primary source of the disease was not apparent during diagnosis. It was also an extremely rare case of high-grade primary pericardial DLBCL detected initially in
secondary pleural effusion cytology. It highlighted cytopathology and CT scanning utility as valuable modalities for diagnosis and follow-up. This case highlighted the efficacy of routine effusion cytological examination in establishing an appropriate diagnosis. From this rare case report, we can understand and learn the importance of cytological diagnostic techniques in the diagnosis of advanced primary pericardial lymphoma, and also highlight the special techniques and diagnostic value of cytology. At the same time, the risk of invasive procedures can be reduced. In the process of diagnosis, medical insurance costs can be directly reduced, and the economic benefits of precision medicine can be achieved. This work was reported according to the SCARE 2020 criteria [13].

2. Case presentation

An 86-year-old woman was referred to the emergency department with chest pain, SOB, and progressive exertional dyspnea for one week. She underwent a series of tests, including a chest X-ray and an electrocardiogram. The chest X-ray revealed a massive left pleural effusion (Fig. 1). She was admitted for further evaluation and management.

In the emergent room, vital signs were BT: 36.4 °C, PR: 98/min, RR: 27/min, BP: 137/88 mmHg. Clinical physical examination was unremarkable, except for grade 2/6 systolic murmur on left sternal border (LSB). Others were non-significant abnormalities.

She was a hypertensive patient with poor medication adherence for years. She had gastric adenocarcinoma post-operation and has received a completely chemotherapeutic course for more than 20 years. She denied a history of socializing alcoholic beverages or using illegal drug. She was no any drug allergies and/or adverse reactions, or addiction. She did not report any B symptoms. There was no history of smoking, chewing betel nut, occupation, or travel in the past three months. In addition, there was no contributing family history included any relevant genetic information, and psychosocial history. Clinical laboratory abstracted analysis showed Hgb: 9.9 g/dl, Hct: 29.3%, MCV: 71.8 fl, MCH: 24.3 pg, MCHC: 33.8 g/dl, neutrophils: 81.4%, lymphocytes: 10.4%, monocyte: 7.7%, platelet count: 531 x 10³/mm. Biochemistry analysis was within the normal range. Microcytic anaemia was first suspected. The urine protein was trace. The tumour biomarker serum levels of CA19-9, CA125, AFP, CEA, SCC, and cardiac marker NT-proBNP (PBNP) were within normal limits. The serological evaluations were negative, including the HIV status evaluated by enzyme-linked immunosorbent assay (ELISA) or Western blot studies; detection of hepatitis C virus (HCV) by serologic studies or polymerase chain reaction (PCR); detection of EBV by PCR was negative.

She underwent left pleural effusion drainage, revealing inflammatory exudate and suspected empyema. Initial cytological examination revealed a mild inflammatory process with scant degenerative reactive mesothelial cells and large atypical lymphocytes (Fig. 2A and B). Subsequent echocardiography and chest CT-scan revealed multiple homogeneously dense, lobulated infiltrative masses, nodular pericardial thickening, epicardial invasion (Fig. 3A and B), and mild pericardial effusion. Secondary metastasis was highly suspected. They also presented massive left pleural effusion with atelectasis and annular mitral valve calcification, suggestive of valvular heart disease, tortuosity, and aorta atherosclerosis. Coronary arteries with cardiomegaly were also noticed.

However, the patient gradually developed dyspnea symptoms, and a chest X-ray revealed recurrent pleural effusions. Thoracocentesis by senior attending physician of Thoracic Surgery Division was repeated. An examination of the pleural fluid by cytological analysis using cyt centrifuge preparation was carried out. The pleural fluid’s cytological evaluation revealed a population of immature, intermediate-to-large atypical lymphoid cells with irregular nuclei, prominent nucleoli, and deeply basophilic cytoplasm with prominent vacuoles. Cytological morphology was as shown at the initial pleural cytology. The cells lacked cytological features of a primary effusion lymphoma, and the metastasis could not be excluded. The patient became symptomatic with dyspnea a week later, and a chest X-ray displayed recurrent pleural effusion. Repeat thoracentesis and pleural effusion were examined by cytology. Further immunocytochemical (ICC) analysis demonstrated many large atypical lymphocytes positive for CD45 and B-cell marker CD20 (Fig. 4A and B). In contrast, they were negative for pan-Ck, calretinin, mucin, and PAS histochemical staining. Few degenerative reactive mesothelial cells showed positive immunostaining for pan-Ck and calmodulin; negative for CD45. Further flow cytometry left pleural effusion analysis (data not shown) revealed 90% of the lymphocytes were positive for CD45, CD19, CD20, CD79a with aberrant expression of the T-cell antigen, CD3, and CD5. Surface light chains, CD3 and CD5, were negative. Terminal deoxynucleotidyl transferase (TdT) was positive. However, fluorescence in situ hybridisation (FISH) analysis for t(8, 14) MYC Oncogene translocation and the conventional cytogenetics were not performed.

The cytology and flow cytometry findings revealed evidence of malignant-appearing cells, and metastatic lymphoma was first suspected. Pleural fluid smear and bacterial culture were negative for acid-fast bacilli (AFB). In addition, there was no evidence of HIV and EBV infection. Cytogenetic analysis of HHV-8, bone marrow examination, and lymph node biopsy were not available.

Because the patient’s condition became progressively unstable, a chest ultrasonography with drainage of the left pleural effusion was immediately completed. The pathological report showed malignant pleural effusion; metastatic lymphoid neoplasm was suspected. We determined whether multiple pericardial tumors caused pleural effusion with distant metastases. Further, we consulted the doctors from the Cardiovascular Surgery (CVS) Division and Chest Surgery (CS) Divisions for surgical intervention. An emergent pericardial window with a pericardial tumour biopsy by a director operator of CVS was performed. A left thoracotomy with chest tube insertion by a senior attending physician operator in CS Division was performed, and a clear yellowish pleural fluid was collected.

3. Histopathological examination

The specimens submitted were two pericardial tissue fragments characterised as purple-brown, rubbery, and fibrous-connective, with the largest measuring up to 0.7 x 0.3 x 0.3 cm.

Microscopically, the pericardial tissue sections showed pericardial fibro-adipose tissue infiltration by large neoplastic cells (Fig. 5A). The
Fig. 2. Photographs of initial cytological analysis of left pleural effusion show a predominance of population of large atypical lymphoid cells (A, Papanicolaou stain, original magnification ×200) (B, Papanicolaou stain, original magnification ×400).

Fig. 3. Photographs of the ICC analysis of left pleural effusion demonstrate diffusely positive for B-cell marker CD20 (A, ICC, original magnification ×200; B, ICC original magnification ×400).

Fig. 4. CT scan photographs with contrast infusion of the chest exhibiting multiple homogeneous lobulated infiltrative masses and nodular pericardial thickness with epicardial invasion (A, axial view, arrow; B, coronal view, arrow).
multifocal marked reactive lymphoid hyperplasia revealed mild to moderate polymorphism, various cell types, focal vascular proliferation, and prominent lymphoid aggregation showing infiltrate in the pericardium. These tumour cells were characterised by a uniform and monotonous moderate-to-large lymphocytic proliferation with prominent nucleoli (Fig. 5B). The tentative diagnosis was malignant lymphoma.

Subsequent IHC staining results demonstrated that neoplastic cells were positive for CD45. Pan-B-cell antigens expression included diffusely positive immunoreactivity for CD20 (strongly diffuse membranous staining) (Fig. 5C), CD79a, and increased proliferative Ki-67 labelling index expression in approximately 90–95% of affected tumour cells (Fig. 5D). Tumour cells were also positive for Bcl-2 and MUM-1/IRF (multiple myeloma oncogene 1, post-germinatal centre or activated B-like) and focally positive for Bcl-6 (B-cell lymphoma 6, germinatal centre marker). In contrast, they were negative for CD3 (T-cell marker) with positive small background lymphocytes and negative for CD5, CD-10 (germinatal centre marker), pan-CK, TTF1, EMA (epithelial membrane antigen), calretinin (for mesothelial cell), CK7, CK20, NSE, CD4, CD30, and cyclin-D1 CD138 expression absence was indicative of a mature B-cell immunophenotype. IHC staining for HHV8 latency-associated nuclear antigen (LANA)-1 and in-situ hybridisation (ISH) for Epstein-Barr virus (EBV) analysis were negative. Taken together, histopathological findings confirmed the diagnosis of a high-grade DLBCL. Further staging to exclude a primary extra-cavity site of involvement was performed. CT scans of the chest, abdomen, or pelvis exhibited no mass, organomegaly, or lymphadenopathy. This case report illustrated the unique manifestations of primary pericardial DLBCL.

4. Discussion

DLBCL is the most common non-Hodgkin lymphomas (NHLs) subtype. It accounts for about 30–40% of NHL cases and >80% of aggressive lymphomas [1,14]. In PCL cases, the most common NHL type found histologically is DLBCL, as in our case. However, in the literature, Burkitt’s lymphoma, T-cell lymphomas, small lymphocytic lymphoma, and plasmablastic lymphoma could also occur [1,6]. Cardiac and pericardial lymphomas involvement is extremely rare, accounting for 0.5% of cardiac involvement and 1% of extranodal NHL. It is predominant in male patients in their 60s [6,15]. However, our patient was an elderly woman.

PCLs affect the right heart with a strong predilection for the right atrium, and only a few cases of lymphomas with the main bulk at the level of the left sections are described in the literature [15]. Some PCLs
are common in immunocompromised patients with acquired immunodeficiency syndrome and transplant recipients receiving immunosuppressive therapy [1,14,15]. Previously, investigators also described HIV-negative patients with a B-cell lineage primary effusion lymphoma involving the pleural cavity, whose tumour cells lack HHV8 infection [1,16], as in our case. Most PCLs are also seen in patients with normal functioning immune systems. However, our case occurred in the pericardium with characteristic cytological features and initial presentation as a pleural lymphomatous effusion in the absence of a palpable tumour mass.

Primary neoplasms of the pericardium are extremely rare, including primary and metastatic neoplasms. In the presence of pericardial effusion, especially with cardiac tamponade, the first malignancies that come to mind are lung (30%) and breast cancers (20%), Hodgkin lymphoma, and leukaemia [1]. The majority of patients are diagnosed by pericardial effusion sampling and biopsies. However, our patient was diagnosed by initial pleural effusion sampling and subsequent pericardial biopsy.

Primary effusion lymphoma (PEL) is a rare B-cell extranodal lymphoma with characteristic clinicopathological features, including an initial presentation of body cavity lymphoma with no detectable tumour mass. It occurs mainly in human immunodeficiency virus (HIV)-positive individuals. The antigen expression is associated with advanced B-cell differentiation stages, such as CD138 and MUM1/IRF4, without pan-B cell antigens expression [16].

The clinical manifestation of this reported case was SOB at the initial stage, which gradually developed into dyspnea. Heart failure and pericardial effusion are the two most commonly reported PCL clinical manifestations [1,16]. Patients present to the clinic most frequently with dyspnea [1]. It is mostly seen with cardiac symptoms (cardiac tamponade), such as in our case. However, it can also occur asymptptomatically. Generally, clinical manifestation occurs with right ventricular dysfunction and tamponade, which also carry important clues for central nervous system involvement [1,3,7].

In the present case, a chest X-ray showed left pleural effusion. Pleural effusion was considered in the elderly woman with current gastric cancer. Whether the gastric cancer recurrence or primary lung or breast cancer’s concurrent metastasis caused pleural effusion must be excluded. After a series of thoracotomy with pleural effusion collection for cytological evaluation, many large atypical lymphoid cells were found, and metastatic cancer was excluded. However, lymphoma was highly suspected in our case. After a follow-up chest CT scan, multiple pericardial tumors with obscure pericardial effusion were found. Finally, an emergent pericardial window with a pericardial tumour biopsy was performed. Primary pericardial lymphoma with pleural involvement was confirmed by histopathological and IHC examinations.

The presence and extent of an intracardiac mass can be evaluated by echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI). However, definitive diagnosis requires confirmation by endomyocardial biopsy or pericardial or pleural effusion cytology. A report showed a large mass centred in the right atrium and extending into the right ventricle, associated with pericardial effusion and bilateral pleural effusions. Subsequent cytological examination of the pleural fluid revealed large pleomorphic malignant cells. The report concluded that cytological flow cytometry and IHC findings established the de novo CD5-positive primary cardiac DLBCL diagnosis by effusion cytology [7].

Malignant effusion and supportive care remained significant in multimorbid analyses. The ancillary method described was used to confirm the morphological presence of lymphomatous effusions in some cases [2,3,7–10,12,17].

Multimodal imaging is essential for evaluating the nature of cardiac masses and can guide PCL diagnosis. Echocardiography is usually the first step in imaging; cardiac CT and MRI provide further tissue characterisation and anatomical information. In contrast, nuclear imaging is most useful in treatment management and assessing chemotherapy response [15]. Although there are no set criteria for PCL diagnosis, diagnostic evaluation usually includes transesophageal echocardiography, cardiac-directed imaging using MRI or CT, and biopsy [2,6,17]. The malignant effusions pathogenesis was defined as direct tumour cell infiltration or distant metastasis based on imaging assessments, including plain film, CT scan, and MRI [2,14,17].

We reported a case of primary pericardial DLBCL with pleural involvement, initially masquerading as malignant pleural effusion, diagnosed by initial malignant pleural effusion cytology. Subsequent histopathological examination of the pericardial tissue biopsy confirmed primary pericardial DLBCL. This is the first case report of primary pericardial DLBCL diagnosed by metastatic malignant pleural effusion cytology per the literature review.

The main factors affecting survival are nonspecific signs and symptoms, the rapid evolution of cardiac or pericardial involvement, and late diagnosis. Although the most common symptom is dyspnea, PCL’s clinical presentation is often vague, explaining the disease’s late diagnosis and poor prognosis. Symptoms of heart failure are present in almost half of the patients [7]. It can only be accomplished by incorporating PCL in the differential diagnosis of patients presenting with sudden decompensated CHF symptoms, arrhythmias, and heart blocks [1]. Cardiac lymphoma’s unique presentation was also illustrated in this case report.

However, the final definite diagnosis requires surgically obtained tissue based on histopathology and IHC. Tumour cells in DLBCL typically express pan-B cell antigens (CD19, CD20, CD22, CD79a, Pax-5) and CD45 using IHC [7,18].

The presence of lymphomatous effusions could provide useful prognostic information that may help guide therapeutic decisions. DLBCL type is difficult to determine because the clinical features and multiple findings are similar to those of pleural or pericardial effusion lymphoma. However, both were not diagnosed from the patient’s hematologic findings. The pleural effusion was exudative, empyemic, and appeared to cause the patient’s dyspnea.

This elderly patient has gastric cancer that had undergone resection in the past. Care was taken to exclude the possibility of gastric cancer recurrence and metastasis to the pericardium and pleura or pleural effusion caused by other cancers. Effusion analysis would be a useful addition to routine examination. Therefore, pericardial and pleural effusion cytology, combined with IHC analysis, could confirm the primary cardiac DLBCL or subtypes of other cancers diagnosis.

Treating these patients often requires individualised therapeutic strategies due to a lack of consistent evidence in the literature and based on tumour-specific features and localisation [15]. DLBCL patient treatment depends on the precise histological subtype, disease extent, localisation, and patient presentation. According to the Ann Arbor classification, the advanced disease is defined as stage III or IV and accounts for approximately 70% of DLBCL patients [1,18].

Pericardial DLBCL with pleural effusion has a poor prognosis. The overall prognosis is poor, with a median survival of <1 year after diagnosis [1,12,15]. Previously, a multicenter retrospective study demonstrated the prognostic significance of pleural or pericardial effusion and the implications for optimal primary mediastinal DLBCL management. This study has shown that the International Prognostic Index (IPI) score and simple pleural or pericardial effusion indicators can stratify patients with primary mediastinal large B-cell lymphoma and help guide treatment selection [1,12,17,19].

Our patient was diagnosed at an advanced stage, so her rapid decline made even a palliative care plan difficult. She also developed pleural effusion associated with increased mortality from PCL. One of the key adverse prognostic factors includes immunocompromised patients. Because of PCL’s high mortality rate, suspicion of this rare disorder may lead to early diagnosis in patients with advanced cardiac symptoms, including fluid accumulation, arrhythmias, and heart failure [6,12].

The present case was negative for HIV infection but had undergone an organ transplant, which presented with SOB secondary to progressive dyspnea, requiring an emergent pericardial window. She was then
diagnosed with primary pericardial DLBCL with pleural involvement. Subsequent pathology from the pericardial tissue and fluid cytology revealed that she had stage IV. Finally, she developed recurrent pleural effusions in both lungs with acute renal failure, rapid decompensation, and respiratory failure, leading to death before further evaluation or treatment. Our data may help classify patients with DLBCL into low- and high-risk groups and thus guide treatment planning.

Finally, the oncologist decided that the patient was unsuitable for R–CHOP therapy, considering her condition. The patient’s family refused chemotherapy. Unfortunately, the patient’s consciousness worsened, and the patient’s family signed the “do-not-resuscitate” (DNR) form after a detailed conversation. The family opted for (Palliative & Hospice Nursing) comfort care due to the patient’s overall poor prognosis and tenuous status. Patients typically have a median survival of one month after surgery.

5. Conclusion

Involvement of the pericardium is extremely rare in extranodal lymphomas. Effusion analysis after draining alone may help identify clinical or molecular histopathological features. IHC analysis of tumour cells would be a useful addition to highlight the efficacy of routine effusion cytological examination in establishing the correct diagnosis.

Ethical approval

Institutional Review Board Statement: This study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGH), National Defense Medical Center. The reference: IRB approval No. is TSGHIRB No: C202215027.

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Author contributions

Junn-Liang Chang: Manuscript review drafting, corresponding author, data interpretation and evaluation, information acquisition, and final approval; Yueh-Ching Chang & Yu-Gieh Lin: Responsible for operating pathological tissue sections, special chemical and IHC staining, information acquisition, critical review, and final approval. Kuang-Ting Liu: Responsible for operating pathological tissue/specimen processing, information acquisition, final approval, concept and design, critical review, and final approval.

Consent

Written informed consent was obtained from the patient’s family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

ICF/IC Waiver is granted by IRB approval (TSGHIRB No.: C202215027). A copy the IRB approval is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

This article is a case report; registration is not required. The datasets in this article are available in the repository upon request from the corresponding author.

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Provenance and peer review

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Declaration of competing interest

None.

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