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A Case of Fluid Overload-associated Large B-cell Lymphoma in a Human T-cell Leukemia Virus-1 Carrier

Shinsuke Inoue[1], Keiji Sato[1], Shou Maruono[1], Haruto Nishida[2,3]* and Tsutomu Daa[3]

[1]Division of Laboratory Medicine, Oita San-ai Medical Center, Oita, Japan
[2]Department of Diagnostic Pathology, Oita San-ai Medical Center, Oita, Japan
[3]Department of Diagnostic Pathology, Oita University, Oita, Japan

Abstract

Fluid Overload-Associated Large B-Cell Lymphoma (FO-LBCL) is a rare B-cell malignancy primarily found in body fluids without obvious mass formation or Human Herpes Virus type 8 (HHV-8) involvements. We report a case in which cell block specimens were useful for the diagnosis of FO-LBCL in the primary pericardial effusion of a human T-lymphotropic virus type 1 carrier patient. A 75-year-old man presented at our hospital complaining of fatigue and anorexia. Computed tomography revealed a massive pericardial effusion, but no mass lesions or enlarged lymph nodes. Analysis of the drained pericardial fluid revealed numerous solitary atypical cells with a high nuclear/cytoplasmic ratio and irregularly shaped nuclei of various sizes on Papanicolaou staining and blast-like and large atypical cells with multiple lobulated, clover-shaped and floating nuclei on Giemsa staining. Immunohistological staining of cell block specimens showed CD20 positivity and CD3 and HHV-8 negativity. The lesion was confined to the pericardial effusion and there was no obvious mass formation; hence, the patient was diagnosed with FO-LBCL. We observed the characteristic cytological features of FO-LBCL, such as clover-like or floating nuclei, in this case.

Keywords: B-cell lymphoma • Cytology • Giemsa stain • HHV-8 • Pericardial infusion

Abbreviations: ATL: Adult T-Cell Lymphoma; EBV: Epstein-Barr Virus; FO-LBCL: Fluid Overload-associated Large B-Cell Lymphoma; HHV-8: Human Herpes Virus type 8; HIV: Human Immunodeficiency Virus; HTLV-1: Human T-Lymphotropic Virus type 1; PEL: Primary Effusion Lymphoma; PEL-LL: Primary Effusion Lymphoma-Like Lymphoma; WHO: World Health Organization

Introduction

Fluid Overload-associated Large B-Cell Lymphoma (FO-LBCL) was newly classified by the World Health Organization (WHO) in 2022 (fifth edition) [1]. It is a rare B-cell malignancy characterized by fluid overload conditions such as chronic heart failure, renal failure, protein-leakage gastroenteropathy and cirrhosis [1-3]. It has a predilection for body cavities, particularly the thoracic cavity, without obvious mass formation or Human Herpes Virus 8 (HHV-8) infection [1]. It is most common in the elderly and has a good prognosis [2]. We report a case in which cell block specimens were useful for the diagnosis of FO-LBCL in the primary pericardial effusion of a human T-Lymphotropic Virus type 1 (HTLV-1) carrier patient.

Case Presentation

A 75-year-old man with type 2 diabetes mellitus had been regularly followed up at our hospital since 2012. He had a history of renal cancer, carotid artery stenosis and paroxysmal atrial fibrillation and was an HTLV-1 carrier. His family history was unremarkable. After a routine visit in August 2023, he experienced breathing difficulties on exertion that persisted for approximately 2 weeks, as well as fatigue, anorexia and vomiting. On admission to our hospital, computed tomography revealed a massive pericardial effusion and mild bilateral pleural effusion. Echocardiography revealed collapse of the right ventricle and right atrium, suggesting cardiac tamponade. No neoplastic lesions or lymphadenopathy was noted. Blood tests showed normal tumor marker levels, mildly elevated lactate dehydrogenase (575 U/L) and interleukin-2 receptor (1457 U/mL) levels and a highly elevated HTLV-1 antibody level (1024 times above normal).

Papanicolaou staining of the pericardial fluid revealed numerous isolated, scattered atypical cells in a hematogenous background (Figure 1a). The cells had a high nuclear/cytoplasmic ratio and chromatin content, irregular size, irregularly shaped nuclei and enlarged nucleoli; numerous mitoses and lymphoglandular bodies were also seen (Figure 1b). Giemsa staining revealed a mixture of mononuclear round atypical cells and large atypical cells with multilobed nuclei, both with basophilic cytoplasm and numerous vacuoles in the cytoplasm and nucleus (Figure 1c). The large atypical cells had markedly irregular, clover-shaped nuclei with rough granular chromatin (Figure 1d). Strongly slitted lobulated nuclei appeared to float in the cytoplasm (Figure 1).

Cell surface antigen analysis using flow cytometry revealed atypical cells in the pericardial fluid that were highly positive for CD20 and CD19. Immunoglobulin light chains were heavily biased toward lambda chains. On immunohistochemistry, pericardial fluid cell block specimens prepared *via* residual sedimentation of cytology specimens were positive for CD20, PAX5, BCL2 and BCL6; partially positive for c-Myc; and negative for CD3, CD4, CD8, CD25, CD10, CD30, CD56, CD138, AE1/AE3, EMA, ALK and HHV-8 (Figures 2a-c). The percentage of Ki-67-positive cells was 55% and the results of Epstein-Barr Virus (EBV)-encoded small RNA *in situ* hybridization were negative (Figure 2d). Blood HTLV-1 antibody was positive; however, Southern blotting of pericardial fluid samples showed no HTLV-1 proviral DNA monoclonality. Human Immunodeficiency Virus (HIV) antibody was negative. Based on these findings, the patient was diagnosed with diffuse large B-cell lymphoma. Because no mass lesions or lymphadenopathy in any part of the body was noted, the final diagnosis was FO-LBCL (Figure 2).

***Address for Correspondence:** Haruto Nishida, Department of Diagnostic Pathology, Oita University, Oita, Japan; Tel: +81-97-586-5683, Fax: +81-97-586-5686; E-mail: nharuto@oita-u.ac.jp*

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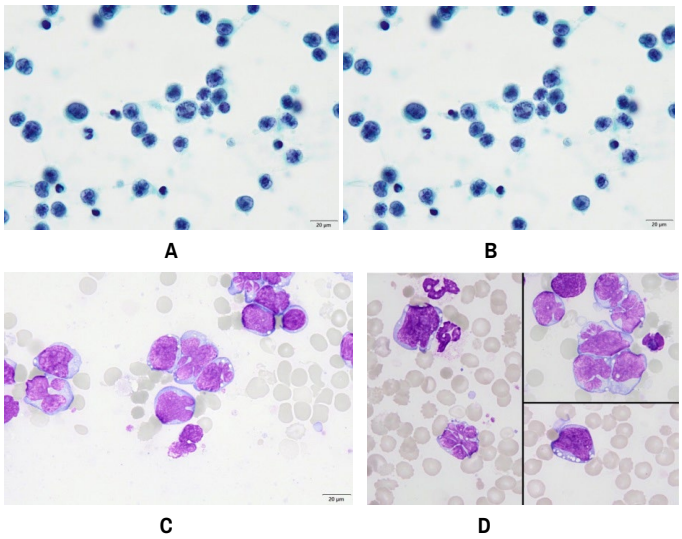

Figure 1. Cytological analysis of the pericardial fluid. **A)** Numerous isolated, scattered atypical cells in a hematogenous background are observed (Papanicolaou, X20). **B)** Each cell has a high nuclear/cytoplasmic ratio and chromatin content, irregular size, irregularly shaped nucleus, and enlarged nucleolus. There are many mitoses and lymphoglandular bodies. (Papanicolaou, X100). **C)** The pericardial fluid contains a mixture of mononuclear round atypical cells and large atypical cells with multilobed nuclei, both with basophilic cytoplasm and numerous vacuoles in the cytoplasm and nucleus (Giemsa, X100) and **D)** The large atypical cells have markedly irregular, clover-shaped nuclei with rough with granular nuclear chromatin, and strongly slitted lobulated nuclei appear to be floating in the cytoplasm (Giemsa, X100).

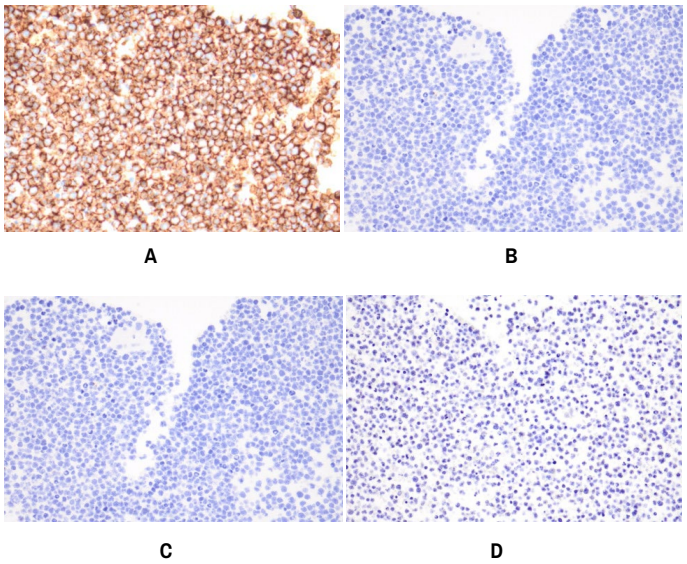

Figure 2. Immunohistochemical staining of pericardial fluid cell block specimens. **A)** Atypical cells in the pericardial fluid are highly positive for CD20. **B)** Negative for CD3. **C)** Human herpes virus type 8 and **D)** The results of Epstein-Barr virus-encoded small RNA *in situ* hybridization are negative.

Pericardial drainage was performed for 2 days from the time of arrival; a total of 700 ml of pericardial fluid was drained. The patient was discharged 8 days after admission. He was referred to a more specialized hospital, where chemotherapy was proposed in consideration of possible recurrence; however, the patient refused and was followed up at our hospital. On the last report, 3 months after the first visit, the patient was doing well with no signs of recurrence.

Discussion

A Primary Effusion Lymphoma (PEL) is a rare large B-cell lymphoma that grows without mass formation in ascites fluid or pleural, pericardial, or other effusions; it is defined as an independent disease in the WHO classification of HHV-8 infectious diseases [4]. It often occurs in immunocompromised patients, mainly those with underlying HIV infection and is most common in young to mature men [4]. PEL cells often express CD30 and CD138, but do not express CD20, CD19, or pan-B cell markers such as CD79a [4].

Cases resembling PEL but without HHV-8 infection were initially classified as PEL-Like Lymphoma (PEL-LL), but were reclassified as FO-LBCL by the WHO in 2022 [1]. The essential criteria for the diagnosis of FO-LBCL are as follows: (1) large-cell lymphoma restricted to body cavity effusions, (2) no secondary involvement of systemic lymphoma, (3) B-cell phenotype and (4) Kaposi's sarcoma-associated herpesvirus/HHV-8 negativity [1]. Approximately 60% of FO-LBCL cases are reported in Japan, where the disease is most common in the elderly and slightly more common in men than women [1,2].

PEL are mature B cells rather than plasmablastic and the positivity rate of EBV infection is 13-30%; some patients are HHV-8 negative without any background immunodeficiency complications [1,2]. Our patient was an elderly man who was HTLV-1 positive but negative for both HHV-8 and HIV antibodies. The presence of large atypical CD19- and CD20-positive cells localized in the pericardial fluid met the essential criteria for the diagnosis of FO-LBCL. Quantitative DNA analysis of the pericardial fluid for HHV-8 is desirable, but was not possible in our case because all specimens were used for cytology. However, HHV-8 (and also EBV) can also be detected *via* immunocytological analysis of cell blocks, as was done here and is useful for diagnosis. In our case, the suspicion of malignancy was reported to the clinician approximately 15 min after the Giemsa stain was collected; thus, cell surface antigen analysis using flow cytometry and an extra pericardial fluid sample was immediately performed. The possibility of malignancy was also addressed *via* immunocytochemical analysis of a cell block with the pericardial fluid, which led to an early diagnosis.

In many institutions, it is often speculated whether Papanicolaou staining should be implemented along with May-Giemsa staining. For tumors that originate in body cavity fluids, preparing a tissue specimen is sometimes difficult. Rapid cytological examination can be useful in these cases and other appropriate examinations can be performed if needed. Preparing cell blocks while the specimens are still fresh may facilitate diagnosis. In our case, the presence of HTLV-1 antibodies in the blood and large atypical cells with segmented lobed nuclei in the cytological specimen made it difficult to distinguish FO-LBCL from Adult T-cell Lymphoma (ATL) [5,6]. However, the absence of CD4, CD25 and HTLV-1 proviral DNA in the pericardial fluid excluded ATL.

In some reports of PEL/PEL-LL, the nuclei are multilobed on cytological examination [7-9]. PEL/PEL-LL cells can range in size from small to large and show marked nuclear irregularities such as multiple nucleoli, binucleation, multinucleation and large nuclear slits; centroblast-like cells with narrow nuclei may also be apparent [1-3,7-9]. T-cell lymphoma cells are also multilobed; therefore, differential diagnosis is required [10-14]. Peripheral Ki-1-positive large-cell, anaplastic T-cell lymphomas have a low incidence of nuclei with three or more lobes or a three-dimensional slit-like appearance; instead, most nuclei are round, kidney-shaped, reniform, or doughnut-shaped [13,14]. Some have deeply slitted nuclei, cells resembling Reed-Hodgkin cells and multinucleated giant cells with a deeply lobed flower crown-like arrangement and three-dimensional structure [11]. Two stamp cytology reports describe the nucleus of multilobed B-cell lymphomas as having a "chrysanthemum petal shape" and being neutrophil-like and centered on a single point [10,14].

In the present case, more than 40% of the atypical cells had lobed nuclei; however, the lobed nucleus did not originate from a single point; instead, each lobe was separate from the others. The lobed nuclei floated in the cytoplasm. Despite having intricate lobes, the nuclei were flat and could not be described as three-dimensional "gyrus-like" structures. Unlike T-cell lymphomas, the lymphoma in our case lacked Reed-Sternberg- and Hodgkin-like cells. These cytological features and HHV-8 negativity allowed us to exclude PEL. Although more cases need to be studied in the future, based on our own experience, clover-shaped and floating nuclei may be characteristic features of FO-LBCL. ATL and PEL have a poor prognosis, whereas PEL-LL has a good prognosis, with reports of remission after body fluid drainage alone [1,12]. Chemotherapy is one of the factors accounting for a better prognosis in Japan than in other countries.

Conclusion

We report a case of FO-LBCL with primary pericardial effusion in which a cell block was very useful for diagnosis, despite similarities between FO-LBCL and other lymphomas the cytomorphology. Because tumors in body cavity fluids lack mass formation, their diagnosis is often left to cytology. In this case, we observed cytological features characteristic of FO-LBCL such as clover-shaped and floating nuclei. We expect to accumulate more FO-LBCL cases in the future, which will further define their characteristics.

Limitations and Recommendations for Future Studies

This is a case report and that is a limitation. For future studies and prospects, more cases should be collected and analyzed.

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Conflict of Interest

The authors declare no conflict of interest.

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