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Case Report

T-cell lymphoblastic lymphoma with elevated adenosine deaminase concentrations mimicking tuberculous pleural effusion: a case report

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Abstract: T-cell lymphoblastic lymphoma (T-LBL) is a rare non-Hodgkin lymphoma that requires rapid and accurate diagnosis and treatment. A quickly progressing mediastinal mass, body cavity effusions, and cervical lymphadenopathy are major manifestations of T-LBL. We report a 47-year-old male patient with a severe pleural effusion (PE), a small pericardial effusion, and a bulky mediastinal mass, but with a high level of adenosine deaminase (ADA) in the pleural fluid and a positive SPOT-Tuberculosis test (T-SPOT.TB test) and tuberculin skin test (TST). The possibility of tuberculous pleural effusion (TPE) was initially considered. However, the cell block (CB) method in combination with immunohistochemistry indicated that the pleural fluid was positive for CD1α, CD3, and CD99; weakly positive for terminal deoxynucleotidyl transferase (TdT); and negative for CD20. Ultrasound-guided biopsy of the mediastinal mass followed by immunohistochemistry was further performed, confirming the diagnosis of T-LBL. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy was initiated and led to progressive remission. This case highlights the notion that elevated ADA levels in PE should be cautiously considered as TPE in the absence of microbiological/histopathological confirmation, and that CB in combination with immunohistochemistry can enhance the diagnostic yield in cases of malignant PE.

Keywords: T-cell lymphoblastic lymphoma, pleural effusion, cell block method, adenosine deaminase

Introduction

Lymphoblastic lymphoma (LBL) is a rare malignant disorder accounting for 2% to 4% of adult non-Hodgkin lymphomas (NHLs). T-cell lymphoblastic lymphoma (T-LBL), which constitutes approximately 85-90% of all LBL, presents mainly with rapidly enlarging masses in the mediastinum, cervical lymphadenopathy, and body cavity effusions. The disease occurs most frequently in male adolescents, although it can appear in patients of any age [1]. T-LBL is well known for its low incidence, poor prognosis, and short survival time, as patients are usually diagnosed with advanced stage disease [2]. Thus, early diagnosis is essential both for treatment and for prolonging patients' lifespan. However, the accurate diagnosis of T-LBL is often very difficult because of the low positive rate of malignant cells, or the difficulty in differentiating malignant cells from other cell types by conventional cytological smears of pleural effusion (PE) [3]. The results can closely mimic tuberculous pleural effusion (TPE) when the levels of adenosine deaminase (ADA) in pleural fluid are elevated in the setting of an exudative PE with a predominance of lymphocytes by conventional cytological examination. The cell block (CB) method is an old and complementary technique that is used to assess body cavity fluids and can increase the sensitivity of detection of malignancy and reduce false positive results [4, 5]. Thus, the CB method combined with immunohistochemistry may have significant value in the diagnosis of T-LBL presenting with PE.

We report a male patient with a clinical picture resembling tuberculous pleuritis, who was finally diagnosed with T-LBL with the CB method of PE analysis and biopsy of the mediastinal mass combined with immunohistochemistry. To date,

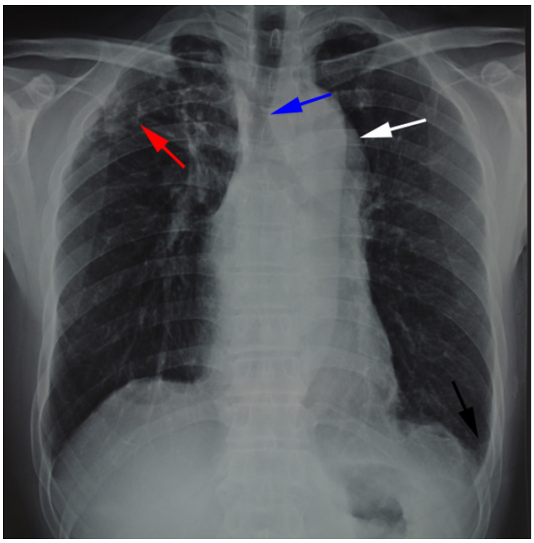

Figure 1. Chest radiography of the patient. Chest radiography revealed stripes and patchy shadows in the right-sided upper lung field (red arrow), left-sided costophrenic angle blunting (black arrow), and broadening of the left upper mediastinum (white arrow), resulting in contralateral shift and stricture of the trachea (blue arrow).

there have been few reports regarding diagnosis of T-LBL using the CB method combined with immunohistochemistry.

Case report

In 2016, a 47-year-old man presented to his doctor with a 20-day history of chest tightness and shortness of breath on exertion. The chest pain was located on the left posterior side and was felt during deep inspiration and rough coughing. The patient also experienced cough, palpitations, limb weakness, and 2-kg weight loss. He had no fever, expectoration, hemoptysis, night sweats, abdominal pain, or arthralgia. Prior to admission to our hospital; Chest X-ray had been performed at another hospital, showing stripes and patchy shadows in the right-sided upper lung field, left-sided costophrenic angle blunting, and broadening of the left upper mediastinum that resulted in contralateral shift and stricture of the trachea (**Figure 1**). The patient was treated with intravenous injection of cefotiam hydrochloride (4 g/day) for four days without any improvement of his symptoms. He reported progressive worsening of the chest tightness and shortness of breath on exertion. He was then referred to our hospital, where he was admitted. The patient had a history of pulmonary tuberculosis at age 22 and had been treated with anti-tuberculosis chemotherapy with 2HRZE/6HR. The patient had no history of smoking and heavy consumption of alcohol. His family history was unremarkable.

On general physical examination, the pulse rate was 112 beats per min, blood pressure (BP) was 134/86 mmHg, temperature was 36.3°C, and respiratory frequency was 20 breaths/min. No peripheral lymph node enlargement or venous prominences were observed. Physical examination of the chest revealed dullness to percussion and the absence of breath sounds on the left lower chest. No other remarkable findings were found on physical examination.

Routine laboratory blood tests showed some notable results, which are outlined in **Table 1**. D-dimer and renal function test results were normal. Urinalysis, routine stool examination, and human immunodeficiency virus (HIV) serology were negative. The serum cancer antigen 125 (CA125) level was 77.6 U/mL, and all other tumor markers were negative. Two hemoculture samples were negative for microorganisms. Rheumatic factor (RF), antinuclear antigen (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and antistreptolysin O (ASO) were also negative.

Blood gas analysis revealed oxygen saturation (SaO_2) of 93% and partial pressure of oxygen (PO_2) of 66 mmHg. Sputum cultures were negative for bacteria, *Mycobacterium tuberculosis,* and fungus. A sputum smear examination showed no bacteria, acid-fast bacilli, or fungi. A peripheral blood smear examination showed no abnormal lymphoid cells. Bone marrow examination revealed an increase in the percentage of bone marrow plasma cells to 3%. However, the SPOT-Tuberculosis (T-SPOT.TB) test and tuberculin skin test (TST) were positive.

Electrocardiogram (ECG) showed sinus tachycardia. No abnormalities were detected on abdominopelvic magnetic resonance imaging (MRI). Results of abdominal ultrasonography were unremarkable. The echocardiograph showed a light pericardial effusion and thickening of cardiac pericardium. Chest ultrasonography showed an opaque dark area of fluid with 9.3 cm in size in the left-sided thoracic cavity (**Figure 2A**) and no fluid in the right-sided thoracic cavity (**Figure 2B**).

Table 1. Routine laboratory blood test results of the patient

		Normal values
ESR (mm/h)	33.00	0-21
PCT (ng/mL)	0.052	<0.1
Hs-CRP (mg/L)	17.80	0-3
NT-proBNP (pg/mL)	41	0-125
hs-cTnI (ng/mL)	<0.006	0-0.78
Serum glucose (mmol/L)	4.88	3.5-6.1
Serum IgE (IU/mL)	83.20	0-378
WBC (cells/L)	7.79×10^9	$(3.5\text{-}9.5)\times10^9$
Hemoglobin (g/L)	149	130-175
PLT (cells/L)	274.00×10^9	$(125\text{-}350)\times10^9$
Neutrophils (%)	70.5	40-75
Lymphocytes (%)	17.8	20-50
AST (U/L)	15	9-50
ALT (U/L)	19.00	15-40
TP (g/L)	65.92	65-85

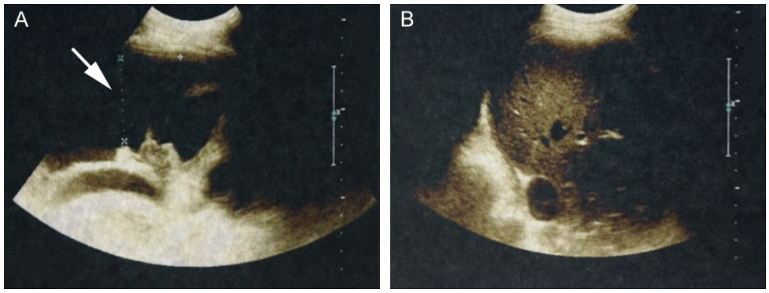

Figure 2. Chest ultrasonography of the patient. A. Chest ultrasonography showed an opaque dark area of fluid of 9.3 cm in the left-sided thoracic cavity (white arrow). B. Chest ultrasonography showed no fluid in the right-sided thoracic cavity.

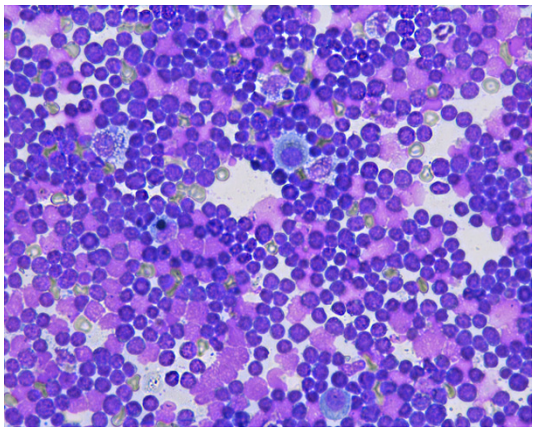

Figure 3. Conventional cytological smear of pleural effusion (PE) of the patient. Conventional cytological smear of PE showed a massive number of immature lymphocytes.

Subsequently, thoracentesis was performed in our department and showed an exudate with a total protein concentration of 44 g/L, lactate dehydrogenase (LDH) value of 792 U/L, glucose concentration of 0.2 mmol/L, and ADA level of 484.45U/L.Carcinoembryonic antigen (CEA) levels in the PE were normal. Pleural fluid cultures were negative for bacteria, fungi, and *M. tuberculosis*. Routine examination of the pleural fluid showed a total number of nucleated cells of 62.46×10^9 /L with a differential of 4% neutrophils, 85% lymphocytes, and 11% mesothelial cells. The pleural fluid was light yellow. In consideration of the positive T-SPOT.TB test and TST, the history of pulmonary tuberculosis, and the markedly elevated ADA level in the PE, the possibility of TPE was initially considered. However, the patient's symptoms of chest tightness and dyspnea on exertion had progressively worsened for a week and the PE expanded rapidly. Thoracentesis was again performed, and the PE was found to have changed to grossly bloody. Repeated biochemical examinations showed ADA 1121.1 U/L and LDH 1442.0 U/L. The other results were similar to those of previous examinations. A conventional cytological smear of the PE was performed, and this revealed immature lymphocytes (**Figure 3**). Following closed thoracic drainage, a chest computed tomography (CT) scan showed an anterior and middle mediastinal mass, stripes and patchy shadows and nodular calcifications in the right upper lung field, right-sided pleural thickening, left-sided PE, and a light pericardial effusion (**Figure 4A-D**).

Thus, the possibility of malignant PE was considered. The CB method of PE analysis was performed, and this revealed a massive number of immature lymphocytes. A combined immunohistochemistry examination showed CD1α (+),

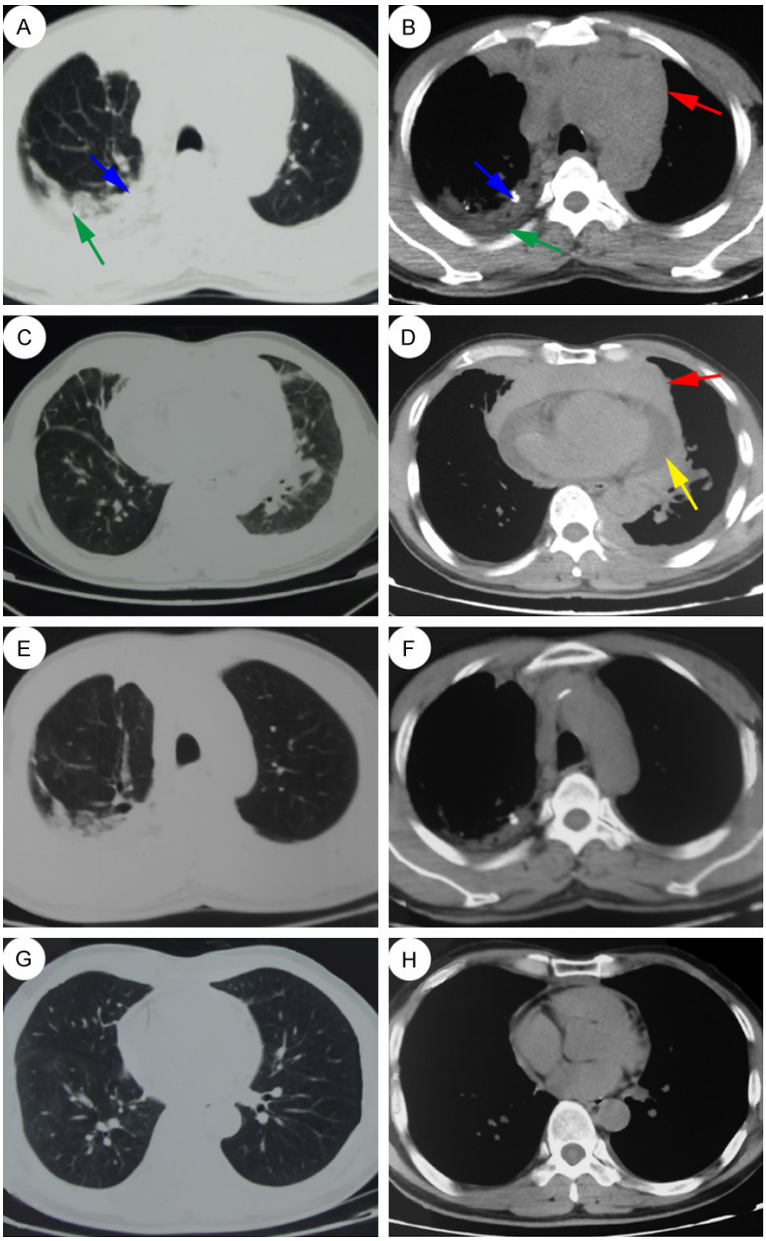

Figure 4. Chest computed tomography (CT) of the patient. Before cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, chest CT showed anterior and middle mediastinal masses (B, D, red arrow), stripes and patchy shadows (A, green arrow), and nodular calcifications (A, B, blue arrow) in the right upper lung field, right-sided *pleural thickening* (B, green arrow), and a light pericardial effusion (D, yellow arrow). Pleural effusion is not obvious in the left-sided thoracic cavity owing to closed thoracic drainage (A-D). After CHOP chemotherapy, chest CT showed marked reduction of the mediastinal mass and absence of pleural effusion in the left-sided thoracic cavity (E-H).

CD3 (+), terminal deoxynucleotidyl transferase (TdT) (weakly +), CD99 (+), CD20 (-), and Ki67% (80% LI), findings consistent with T-LBL (**Figure 5**). An ultrasound-guided biopsy of the mediastinal mass was subsequently performed, and immunohistochemistry of biopsy specimens showed CD1α (+), CD3 (+), CD99 (+), TDT (+), CD20 (-), and Ki67% (95% LI), which confirmed the diagnosis of T-LBL (**Figure 6**).

The patient was then treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy for T-LBL, and his symptoms improved markedly after five days. After the patient received a second round of CHOP chemotherapy, chest CT indicated that the mediastinal mass was markedly reduced and PE was absent (**Figure 4E-H**).

Discussion

T-LBL is an uncommon malignancy that originates from precursor T lymphocytes and is considered to have a rapid progression and poor prognosis. Mediastinal and body cavity involvement are common. Jin et al. [2] reported that 45.7% of cases of T-LBL presented with bulky mediastinal masses and 62.9% of cases presented with pleural and/or pericardial effusions, and patients are usually diagnosed with advanced stage cancer. Fortunately, the use of intensive chemotherapy can lead to high remission and better overall survival rates. Thus, early, accurate, and reliable diagnosis is of great significance for the prompt institution of therapy, which can be lifesaving.

The PE originating from T-LBL has a tendency to be misdiagnosed as tuberculosis (TB), especially on the basis of the exudate, predominant lymphocytes, and high ADA levels in the PE. To the best of our knowledge, two cases, in which the diagnostic methods are different from ours, howev-

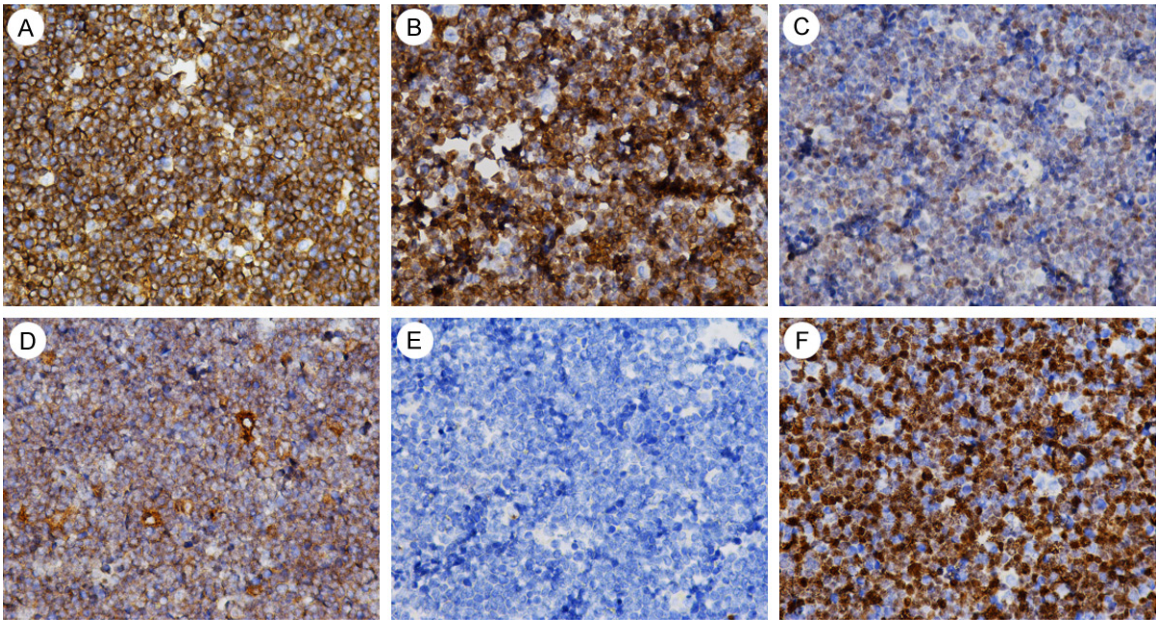

Figure 5. Cell block (CB) method combined with immunohistochemistry of pleural effusion (PE). A. CD1α immunoreactivity (original magnification ×400). B. CD3 immunoreactivity (original magnification ×400). C. Staining showed light positive reaction for TdT (original magnification ×400). D. CD99 immunoreactivity (original magnification ×400). E. Staining showed negative reaction for CD20 (original magnification ×400). F. Ki67 (original magnification ×400).

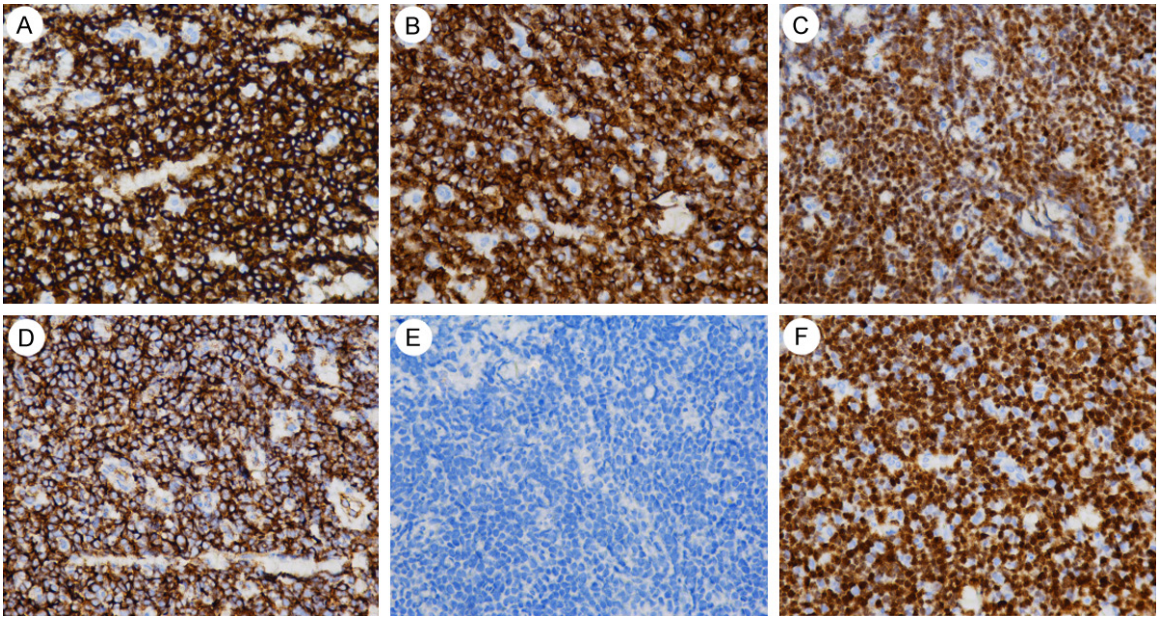

Figure 6. Histopathological examination of biopsy of the mediastinal mass (mediastinal mass infiltrates). A. CD1α immunoreactivity (original magnification ×400). B. CD3 immunoreactivity (original magnification ×400). C. TdT immunoreactivity (original magnification ×400). D. CD99 immunoreactivity (original magnification ×400). E. Staining showed negative reaction for CD20 in mediastinal mass infiltrates (original magnification ×400). F. Ki67 immunoreactivity (original magnification ×400).

er are found to be similar to ours on diagnosis process [6, 7] (**Table 2**). Tiwari et al. [6] reported a young male patient misdiagnosed with disseminated TB on the basis of exudative PE with

Table 2. The similar literatures of the manuscript

Title	Author	Journal-Name	Publication Date	Volume Number: page number
Pleuro-peritoneal lymphomatosis with concurrent tonsillar involvement in T-cell nonHodgkin's lymphoma: Clinical presentation mimicking disseminated tuberculosis	Tiwari P, Madan K, Jain D, Kumar R, Mohan A, Guleria R	Lung India	2014	31 (4): 380-382
A case of primary effusion lymphoma with elevation of ADA activity in pleural effusion	Kato F, Hirasawa Y, Iioka Y, Yoshida Y, Nabeta T, Kosugi N, Eguchi M	Nihon Kokyuki Gakkai Zasshi	2011	49 (10): 786-791

predominant lymphocytes and a high ADA level. The patient developed worsening symptoms within two weeks of initiation of antitubercular treatment. Then, biopsy of a tonsillar mass finally confirmed the diagnosis of T-LBL. Another case is that an old-age male, diagnosed with TPE first based on pleural effusion with exudative and lymphocytic with elevation of ADA, was discharged with lymphoma as final diagnosis by the cytology findings of the pleural effusion [7].

In the present study, we report a middle-aged man initially considered to have TPE because of an exudate with markedly elevated ADA levels in the PE and a positive T-SPOT.TB test and TST. However, due to the finding of immature lymphocytes in the pleural fluid, the final diagnosis of T-LBL was established with the CB method and biopsy of the mediastinal mass combined with immunohistochemistry. The patient received CHOP chemotherapy for T-LBL and experienced progressive remission. As such, elevated ADA levels in PE are not the gold standard for diagnosis of TPE. Zaric et al. [8] reported that the cutoff value of ADA in PE was 49 U/L, the sensitivity was 89.2%, and the specificity was 70.4% in the diagnosis of TPE; hence, the ADA assay should not be considered an alternative to biopsy or culture. Apart from TPE, high levels of ADA have also been reported in other conditions associated with a predominance of lymphocytes in PE, including lymphomas, pleural metastasis of malignancy, parapneumonic effusions (PPE), and rheumatoid effusions [6, 8, 9]. Lee et al. reported [10] that in PPE, particularly in complicated cases, ADA levels frequently exceeded the cutoff value for TPE. Choi et al. [11] reported a 30-year-old woman with an exudative, lymphocyte-predominant PE with high ADA levels, initially diagnosed as TB, and finally diagnosed as Behcet's disease. ADA is a polymorphic enzyme required for the conversion of adenosine to inosine and is found in many tissues including thymus, spleen, and other lymphoid tissues, and particularly in red blood cells and T-lymphocytes [8, 12]. In TPE, high ADA levels are related to the subset of T-lymphocytes activated in response to tuberculosis antigens. Lymphomas with a predominance of lymphocytes in PE can also be accompanied by high ADA levels. In the current report, the level of ADA in the PE was as high as 1121.1 U/L. Therefore, an elevated ADA level in PE shall be cautiously made for TPE diagnosis.

The CB method has been well established as an important and complementary technique for cytological diagnosis [13, 14]. The CB method provides an excellent milieu for morphologic translation with minor background staining and results that are similar to those reported in the surgical pathology literature [15]. In comparison with other methods, such as the conventional cytological smear, the main advantages of the CB method are preservation of tissue architecture and the ability to acquire multiple sections for special immunohistochemical studies and histochemical staining, which enhances diagnostic accuracy [16]. Although CB combined with immunocytochemistry/immunohistochemistry is comprehensively used in the differential diagnosis of malignant pleurisy [13, 17, 18], there are few reports regarding the diagnosis of T-LBL using the CB method. Bhaker et al. [19] reported that cell block immunocytochemistry (CB-ICC) of T-LBL demonstrated a uniform CD3 (+), TdT (+), CD20 (-) pattern, which was partly consistent with our findings. The pathological diagnosis of the mediastinal mass authenticated the final diagnosis in the present case, as well. Compared with other methods used in the diagnosis of PE, including medical thoracoscopy or surgery, the CB method is safe, less invasive, inexpensive, and reproducible [11]. Therefore, the CB method should be considered a useful adjuvant technique in combination with immunohistochemistry for specific biomarkers in evaluating the diagnosis of T-LBL.

Conclusion

In conclusion, we report a patient with markedly elevated ADA levels in PE mimicking tuberculous pleural effusion, which was finally diagnosed as T-LBL using the CB method of PE analysis and biopsy of the mediastinal mass combined with immunohistochemistry. This case emphasizes the notion that elevated ADA levels in PE should be cautiously considered as TPE in the absence of microbiological/histopathological confirmation, and early utilization of the CB method combined with immunohistochemistry is very important in cases of misdiagnosed PE.

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Disclosure of conflict of interest

None.

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