- Case Report -

Diffuse Large B-cell Lymphoma Coexistent with Tuberculous Pleurisy Diagnosed by Diagnostic Thoracoscopy

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Abstract

An 80-year-old man was admitted with massive right pleural effusion and bilateral axillary lymph node enlargement. Because malignant lymphoma was suspected by cytological examination of the pleural effusion, axillary lymph node biopsy was performed. Histopathological examination revealed diffuse large B-cell lymphoma by immunostaining. However, the level of pleural adenosine deaminase (P-ADA) was elevated at 79.2 IU/L and the result of enzyme-linked immunospot assay was positive, although the results of acid-fast staining and polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* using a pleural effusion sample were both negative. Thus, because the coexistence of tuberculous pleurisy was strongly suspected, diagnostic thoracoscopy was performed under local anesthesia. The diagnostic thoracoscopy revealed multiple white lesions on the parietal pleura. Histopathologic examination showed granuloma including Langhans giant cells with necrosis. Then, because the *M. tuberculosis* culture of the pleural biopsy tissue was positive, tuberculous pleurisy was definitively diagnosed. When the level of P-ADA is elevated in cases of malignant lymphoma, the coexistence of tuberculous pleurisy should be suspected, even though acid-fast staining and PCR might be negative. In such cases, diagnostic thoracoscopy should then be considered to definitively diagnose tuberculous pleurisy.

Key words: diffuse large B-cell lymphoma , tuberculous pleurisy , adenosine deaminase, thoracoscopy

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1. Introduction

There have been several reports related to pleural effusion accompanied by malignant lymphoma.[1-4] In such cases, malignant lymphoma is usually diagnosed by cytopathologic examination of the pleural effusion sample. Several articles reported that the level of pleural adenosine deaminase (P-ADA) ranged widely from 11 to 98.9 IU/L in cases of malignant lymphoma with pleural effusion.[2,5,6] However, when pleural effusion is predominantly lymphocytic with a high level of P-ADA, tuberculous pleurisy is generally suspected. In the present report, we describe a case of diffuse large B-cell lymphoma (DLBCL) coexistent with tuberculous pleurisy diagnosed with the aid of diagnostic thoracoscopy.

2. Case Report

An 80-year-old man with a past medical history of hypertension was admitted to The Jikei University Daisan Hospital due to anorexia and general malaise in April 2014. Laboratory data on admission are shown in Table 1. Although his white blood cell count was within normal range at 4200/μL, his C-reactive protein level was elevated at 7.0 mg/dL. His soluble IL-2 receptor level was 2100 U/mL. Chest X-ray revealed a massive right pleural effusion (Fig. 1). Chest contrast-enhanced computed tomography also revealed right pleural effusion and swelling of the mediastinal and the bilateral axillary lymph nodes. The lung field was normal (Fig. 2).

Malignant disease was suspected because of hemorrhagic exudative pleural effusion. Cytological examination of the pleural effusion revealed large-sized atypical round cells with irregular karyotype that suggested malignant lymphoma (Fig. 3). Then, a biopsy of the right axillary lymph node was performed. Histopathological examination of the lymph node revealed diffuse medium-to-large-sized atypical round cells with moderate cytoplasm that were positive for CD20 and CD79α staining and negative for CD3, CD5, and CD30 staining (Fig. 4). As a result, DLBCL was definitively diagnosed.

Although the results of acid-fast staining and polymerase chain reaction (PCR) analysis of *Mycobacterium tuberculosis* using the pleural effusion sample, which was predominantly lymphocytic and exudative, were both negative, the P-ADA level was elevated at 79.2 IU/L. Moreover, the result of an enzyme-linked immunospot assay (T-SPOT.TB test; Oxford Immunotec Ltd., Summertown, UK) was positive. Because the coexistence of tuberculous pleurisy was suspected from these results, diagnostic thoracoscopy was performed under local anesthesia. Multiple white lesions were seen on the parietal pleura (Fig. 5). Unfortunately, the intrathoracic region could not be sufficiently observed because there were many severe adhesions. No tumors suspected of being malignant lymphoma were noted during the limited observation. Histopathological findings showed granuloma including Langhans giant cells with necrosis (Fig. 6). Because *M. tuberculosis* culture of the pleural tissue biopsied during the thoracoscopy and that of the pleural effusion were positive at 2 weeks and 4 weeks, respectively (Table 2), tuberculous pleurisy was definitively diagnosed. Ultimately, the patient was diagnosed as having both DLBCL and tuberculous pleurisy, although it was unclear whether the relation between the two diseases was as one being the complication of the other or just one of coexistence.

Anti-tuberculosis treatment was started with 3 standard drugs (isoniazid, rifampicin, and ethambutol) 6 days after performing the thoracoscopy because of the patient's advanced age. After the beginning of tuberculous treatment, we started combination chemotherapy with vincristine

and cyclophosphamide against DLBCL while paying attention to any worsening of the tuberculosis. These treatments were safely completed without severe adverse events or deterioration of the tuberculosis. After the tuberculosis treatment and chemotherapy, the patient's right pleural effusion had diminished, and swelling of the mediastinal and bilateral axillary lymph nodes was reduced.

3. Discussion

In the present case, the measurement of P-ADA and diagnostic thoracoscopy were useful examinations for diagnosing tuberculous pleurisy, which was suggested by the high P-ADA level. Moreover, granuloma with Langhans giant cells was identified from the pleural tissue biopsied during the thoracoscopy, and the culture of *M. tuberculosis* from the biopsy tissue was positive.

P-ADA is often measured in cases of pleural effusion and is elevated in various conditions such as malignant lymphoma, empyema, rheumatoid arthritis, and malignant mesothelioma in addition to tuberculous pleurisy. Some cases of malignant lymphoma were also reported that were difficult to distinguish from tuberculous pleurisy based on the level of P-ADA.[2,7] However, when the cut-off value for P-ADA level was set at 40 IU/L, the sensitivity and specificity of P-ADA for tuberculous pleurisy ranged from 68-91% and 72- 92%, respectively.[8-11] In contrast, Yao *et al.* reported that the median level of P-ADA was as low as 26 IU/L in cases of malignant lymphoma with exudative pleural effusion.[12] Because the level of P-ADA was markedly elevated at 79.2 IU/L in the present case, the result was compatible with tuberculous pleurisy.

Therefore, we believe that the measurement of P-ADA is useful for auxiliary diagnosis of tuberculous pleurisy to distinguish it from malignant lymphoma.

Tuberculosis sometimes develops alongside hematological malignancies such as malignant lymphoma and leukemia.[13,14] Hence, when chemotherapy for malignant lymphoma is administered, it is crucial to check for the coexistence of tuberculosis. In the present case, because the acid-fast bacillus smear and PCR analysis of the pleural effusion sample were negative, these examinations did not lead to the correct diagnosis. Indeed, in patients with tuberculous pleurisy, the positive rates of acid-fast bacillus smear and culture using pleural effusion samples are low at less than 10% and 40%, respectively.[15,16] However, because the elevated level of P-ADA suggested the coexistence of tuberculosis in the present case, diagnostic thoracoscopy was performed under local anesthesia that proved the coexistence of tuberculous pleurisy. Moreover, *M. tuberculosis* was more rapidly cultured from the pleural biopsy tissue than from the pleural effusion sample, and afterwards, anti- tuberculosis susceptibility testing could be performed. Hence, diagnostic thoracoscopy was useful for diagnosing tuberculous pleurisy.

In conclusion, the measurement of P-ADA and diagnostic thoracoscopy assisted in the accurate diagnosis of tuberculous pleurisy in a patient with malignant lymphoma. When the level of P-ADA is elevated in cases of malignant lymphoma, the coexistence of tuberculous pleurisy should be suspected, even though acid-fast staining and PCR results might be negative. In such cases, diagnostic thoracoscopy should be considered to definitively diagnose tuberculous pleurisy.

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Figure legends

Figure 1: Chest X-ray on admission revealed marked right pleural effusion.

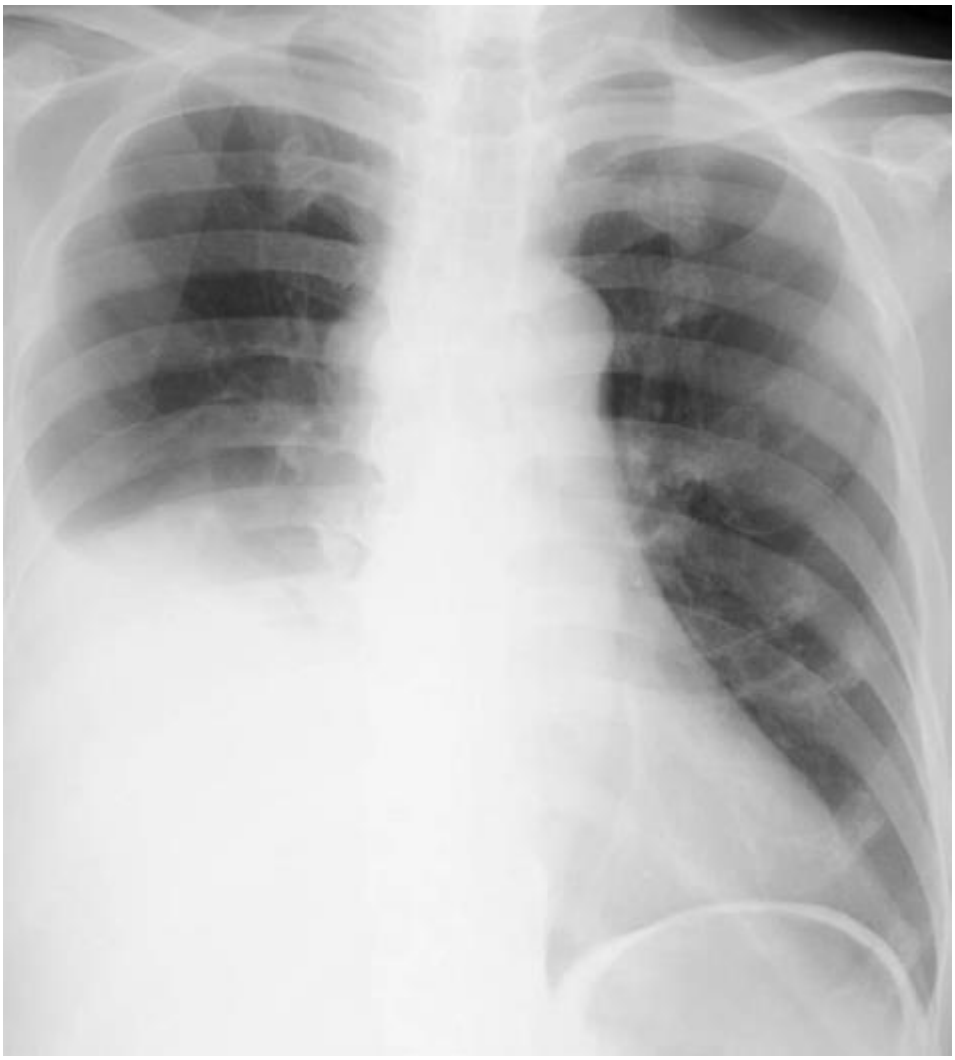

Figure 2: Chest contrast-enhanced computed tomography on admission. A-B: Swelling of the mediastinal and right axillary lymph nodes. C: Normal lung field. D: Marked right pleural effusion.

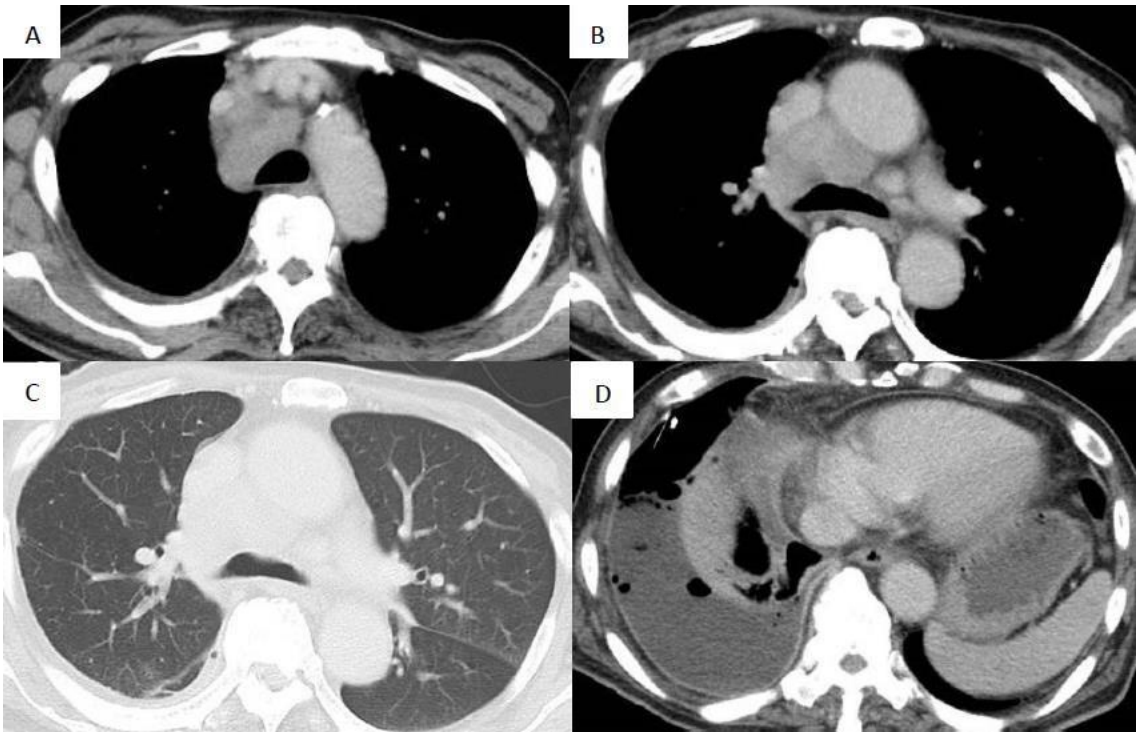

Figure 3: Large-sized atypical round cells showing karyotype irregularity were identified in the right pleural effusion (Papanicolaou staining, original magnification ×600).

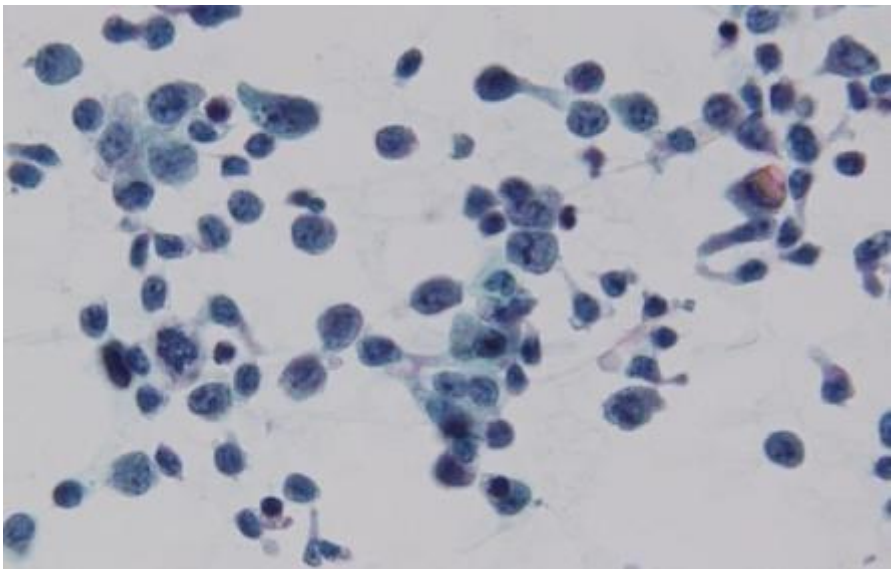

Figure 4: Diffuse medium-to-large-sized atypical round cells with moderate cytoplasm were identified in the right axillary lymph node (hematoxylin and eosin staining, original magnification ×400).

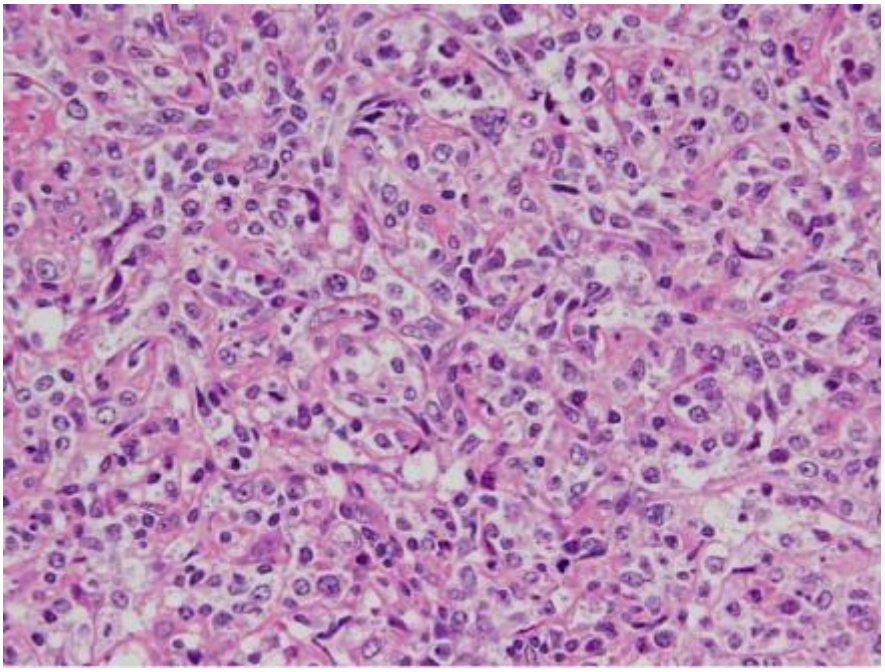

Figure 5: Thoracoscopy under local anesthesia showed severe adhesions and multiple white lesions on the parietal pleura.

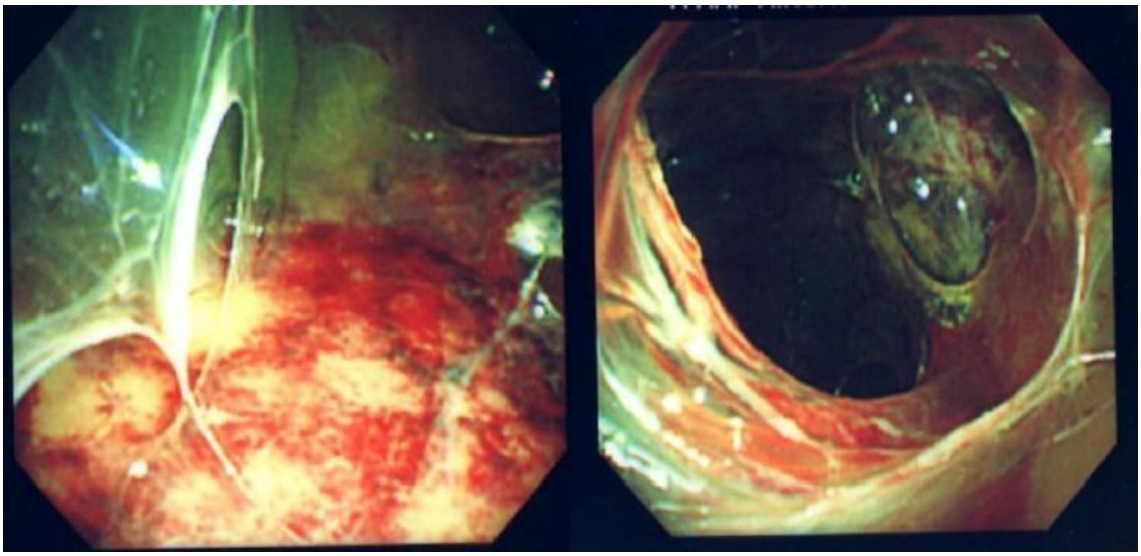

Figure 6: Pathological examination of the pleural tissue biopsy specimen revealed (A) Langhans giant cells and (B) granuloma (both, hematoxylin and eosin staining, original magnification ×200).

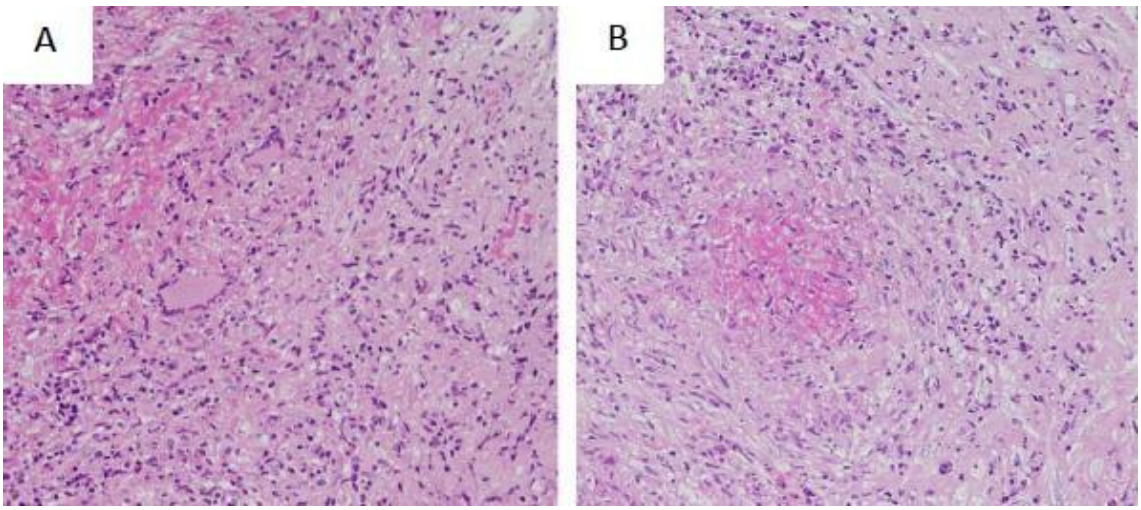

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Table 1. Laboratory Data on Admission

Peripheral Blood Data		**Biochemistry Data**	
White blood cells	4200/μL	Aspartate aminotransferase	38 IU/L
Red blood cells	$323\times10^4/\mu L$	Alanine aminotransferase	17 IU/L
Hemoglobin	8.7 g/dL	Lactate dehydrogenase	302 IU/L
Hematocrit	27.2%	Total protein	8.2 g/dL
Platelets	$7.7\times10^4/\mu L$	Albumin	2.5 g/dL
		Blood urea nitrogen	18 mg/dL
Serology		Creatinine	0.9 mg/dL
C-reactive protein	7 mg/dL		
Soluble IL-2 receptor	2100 U/mL		
Immunoglobulin G	3192 mg/dL		
Antinuclear antibody	40 times		
Rheumatoid factor	3.0 U/ml		
T-SPOT.TB test	Positive		

Table 2. Pleural Effusion and Pleural Tissue Biopsy Data

Pleural effusion		**Pleural tissue biopsy data**	
Total cell count	860/μL	Acid-fast bacillus smear	Negative
Neutrophil count	208/μL	TB PCR	Negative
Lymphocytes	652/μL	Mycobacterium culture	Positive at 2 weeks
Total protein	6.1 g/dL	Drug resistance	None
Lactate dehydrogenase	397 IU/L		
Glucose	51 mg/dL		
Adenosine deaminase	79.2 IU/L		
Cytology	Class V		
Acid-fast bacillus smear	Negative		
TB PCR	Negative		
Mycobacterium culture	Positive at 4 weeks		
Drug resistance	None		

TB: tuberculosis, PCR: polymerase chain reaction.

