

[CASE REPORT]

Cryptococcal Pleuritis Presenting with Lymphocyte-predominant and High Levels of Adenosine Deaminase in Pleural Effusions Coincident with Pulmonary Tuberculosis

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Abstract:

Co-infection with cryptococcus and tuberculosis has rarely been reported. We herein report a case of an 80-year-old man with cryptococcal pleuritis concurrent with pulmonary tuberculosis. He was admitted for progression of left pleural effusion and consolidation in the left upper lobe. Culture for *Mycobacterium tuberculosis* was positive in sputum, and analyses of pleural effusion revealed lymphocyte-predominant high levels of adenosine deaminase (ADA). Medical thoracoscopy revealed massive infiltration of *Cryptococcus neoformans* in pleura without granuloma. This is the first case report of cryptococcal pleuritis coincident with pulmonary tuberculosis. Cryptococcal pleuritis should be ruled out when the adenosine deaminase levels are elevated in pleural effusion.

Key words: cryptococcal pleuritis, pulmonary tuberculosis, co-infection, adenosine deaminase, cryptococcal antigen test

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Introduction

Pulmonary cryptococcosis presents with a variety of lung parenchymal lesions, such as solitary or multiple subpleural nodules, masses and consolidation. Although cryptococcal pleuritis has rarely been reported, it occurs in association with subpleural parenchymal lesions (1). In contrast, tuberculous pleuritis is one of the most common features of extrapulmonary tuberculosis. The pathogenesis of cryptococcosis is associated with impaired cell-mediated immunity, similar to that in tuberculosis. However, co-infections with cryptococcosis and tuberculosis have rarely been reported.

We herein report a case of cryptococcal pleuritis exhibiting lymphocyte-predominant pleural effusion with high levels of adenosine deaminase (ADA) during treatment for pulmonary tuberculosis.

Case Report

An 80-year-old Japanese man with a history of pulmonary tuberculosis, chronic obstructive pulmonary disease and cerebral infarction presented to our hospital with a 1-month history of productive cough and worsening shortness of breath on exertion. His regular medications were daily aspirin, omeprazole and tiotropium inhaler. Chest radiography showed left-sided pleural effusion and right-sided pleural calcification (Fig. 1A). A chest computed tomography (CT) scan after left thoracentesis demonstrated consolidation in the left upper lobe and a nodule in the left lower lobe (Fig. 1B and C). Because the area of consolidation had not changed and a new nodule appeared in the left lower lobe compared with the CT findings obtained three years earlier, we suspected obsolete pulmonary tuberculosis in the upper

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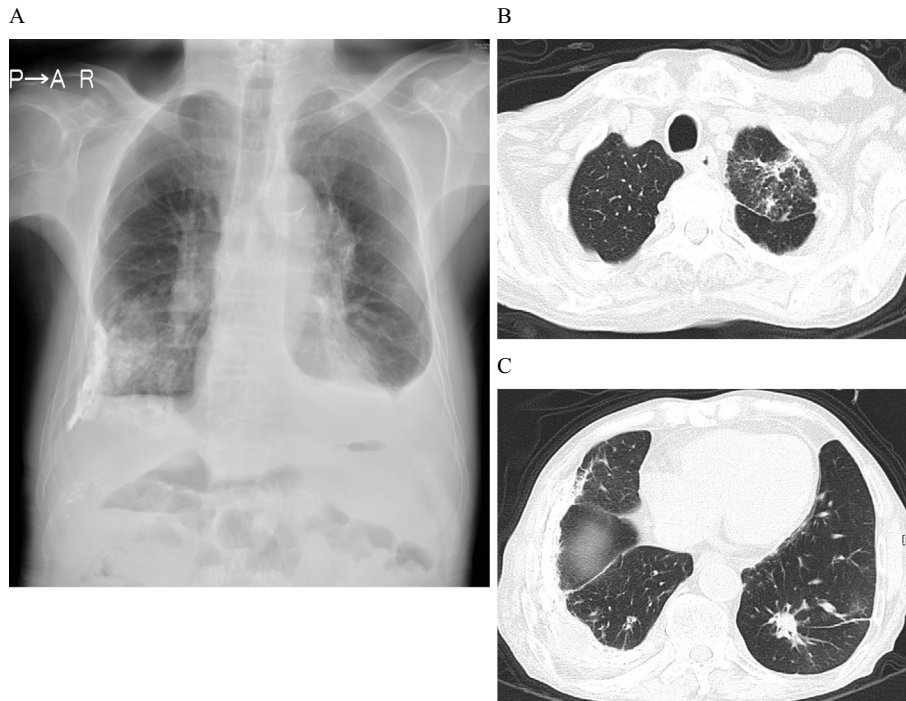


Figure 1. Chest radiograph from the first visit showing left-sided pleural effusion and right-sided pleural calcification (A). Chest CT after left thoracentesis on the first visit showing consolidation in the left upper lobe (B) and a nodule in the left lower lobe (C).

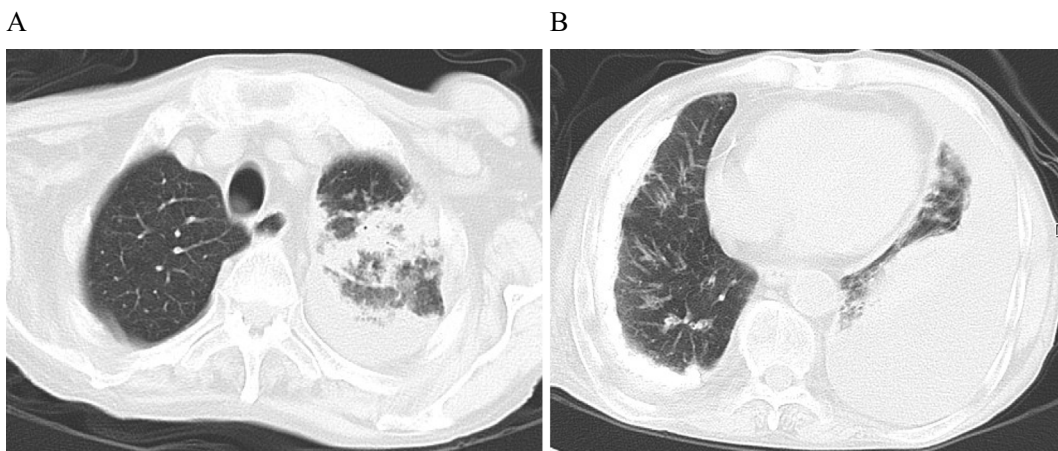


Figure 2. Chest CT on admission showing the development of consolidation in the left upper lobe (A) and left-sided pleural effusion (B).

lobe and primary lung cancer in the lower lobe. The pleural effusion was yellow and exudative with a white blood cell (WBC) count of $800/\text{mm}^3$ (lymphocyte 83%, neutrophil 2%), pH 7.33, glucose 126 mg/dL, protein 3.3 g/dL, lactate dehydrogenase 88 IU/L, ADA 25 IU/L and rheumatoid factor 119 IU/mL (serum rheumatoid factor 95 IU/mL). There were no malignant cells, and smear and cultures for mycobacteria or bacteria were negative. The patient refused more-invasive procedures, such as bronchoscopy or medical thoracoscopy. Although physical findings suggesting rheumatism were not present, he was treated with prednisolone at 25 mg/day based on a clinical diagnosis of pleuritis due to rheumatoid arthritis. The pleural effusion gradually de-

creased, and prednisolone was tapered to 17.5 mg/day.

After five months of prednisolone treatment, he presented with acute onset of dyspnea. On an examination, the patient was in distress, and his temperature was 36.1°C . His oxygen saturation was 90% on ambient air. A physical examination revealed left upper lobe crackles and a decrease in breath sounds of the left lung. The laboratory findings were as follows: WBC count $6,200/\text{mm}^3$, Hb 7.8 g/dL, platelet $13.8 \times 10^4/\text{mm}^3$, CRP 2.29 mg/dL, rheumatoid factor 67 IU/mL, anti-nuclear antibody titer $\times 20$ and positivity on interferon-gamma release assays (QuantiFERON[®]-TB gold in tube). A CT scan revealed the development of consolidation in the left upper lobe and left-sided pleural effusion (Fig. 2). A

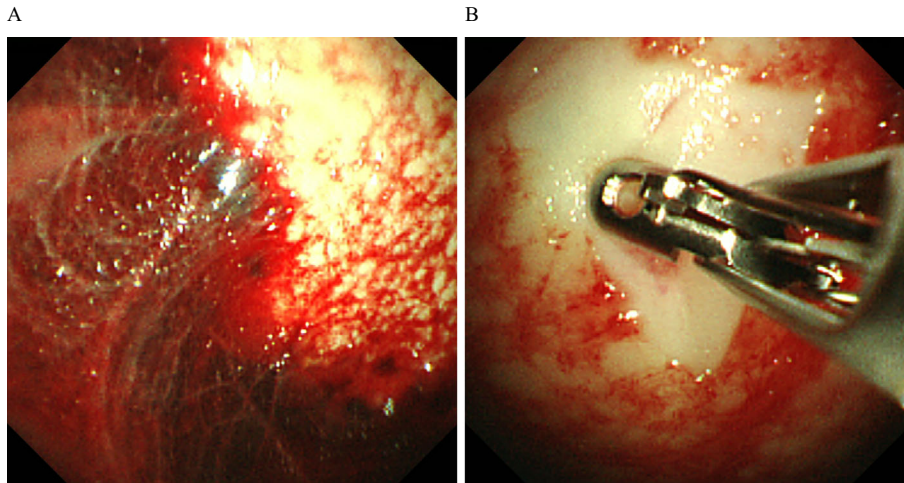


Figure 3. Thoracoscopic image showing pleural adhesion (A) and diffuse pleural thickening (B).

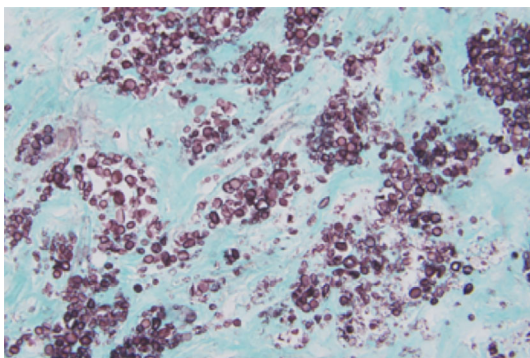


Figure 4. Histopathology of the parietal pleura showing massive infiltration of round, cryptococcal spores stained with Grocott's silver (200× magnification).

second thoracentesis was performed to evaluate the pleural effusion. The pleural effusion was exudative with a WBC count of 400 mm^3 , including 100% lymphocytes, and ADA was 101 IU/L. Although sputum culture on admission was positive for *M. tuberculosis*, acid-fast staining, polymerase chain reaction (PCR) and culture for *M. tuberculosis* in the pleural effusion were negative. Based on these findings, he was diagnosed with pulmonary tuberculosis and pleuritis and treated with an anti-tuberculosis regimen, including isoniazid (250 mg/day), rifampicin (450 mg/day) and ethambutol (750 mg/day).

Prednisolone was gradually tapered to 10 mg/day over 3 months because we could not rule out the possibility of pleuritis due to rheumatoid arthritis and were concerned that adrenal insufficiency due to corticosteroid withdrawal might develop. Nine days after admission, culture for *Cryptococcus neoformans* in the pleural effusion was positive, and serum cryptococcal antigen was positive at a titer of 1:8,192. He underwent additional treatment with intravenous fluconazole (400 mg/day). Because the pleural effusion increased despite three weeks of anti-tuberculosis treatment and two weeks of anti-cryptococcal treatment, medical thoracoscopy was performed to survey other infections or malignant dis-

eases. Severe pleural adhesion, fibrotic septa and diffuse thickening of parietal pleura without any nodules were observed, and 10 biopsy specimens were randomly obtained from the parietal pleura (Fig. 3). A histopathological examination of the pleura demonstrated massive infiltration of yeast-like fungi stained with Grocott's silver, and we were unable to detect any other etiologies of infection, malignant or granulomatous disease (Fig. 4). Therefore, because he was diagnosed with pulmonary tuberculosis and cryptococcal pleuritis, anti-tuberculosis and anti-fungal agents were continued.

Approximately one month after these treatments, the nodule in the left lower lobe disappeared, and the left-sided pleural effusion and consolidation in the left upper lobe were markedly resolved on CT. He was transferred to a rehabilitation hospital three months after admission. There was no recurrence of cryptococcosis or tuberculosis before his death from aspiration pneumonia five months after the transfer.

Discussion

We encountered a case of cryptococcal pleuritis concurrent with pulmonary tuberculosis. The differential diagnosis of tuberculous and cryptococcal pleuritis was difficult in this case for two reasons.

First, both diseases may present with lymphocyte predominance and elevated ADA levels in the pleural effusion. Among reported cases of cryptococcal pleuritis, including our present case, 10/13 (77%) patients had lymphocyte-predominant pleural effusion (Table) (1-15). Because host defense against cryptococcus is associated with cell-mediated immunity, similar to tuberculosis, cryptococcal pleuritis may present with lymphocyte-predominant pleural effusion. Furthermore, a significant correlation was demonstrated between ADA activity and numbers of CD4^+ cells in tuberculous pleural effusions (16, 17). Although the numbers of CD4^+ cells in pleural effusions in cryptococcal pleuritis have not been reported, ADA levels may be high in pleural

Table. Reported Cases of Cryptococcosis with Pleural Effusion.

Reference	Age	Sex	Underlying disease	Pleural effusion			Serum	
				Percentage of lymphocyte (%)	ADA (IU/L)	Cryptococcal antigen test	Culture for cryptococcus	Cryptococcal antigen test
(1)	42	M	Diabetes mellitus, chronic renal failure, hemodialysis	Lymphocyte-predominant	ND	+	+	-
(1)	66	F	Chronic heart failure, hemodialysis	Lymphocyte-predominant	ND	+	+	+
(2)	25	M	-	80	ND	ND	-	ND
(3)	21	M	Lymphoma, chemotherapy	ND	ND	ND	+	+
(4)	37	M	HIV	78	ND	ND	+	+
(5)	29	M	HIV	88	ND	ND	+	+
(6)	70	F	HTLV-1	Lymphocyte-predominant	ND	+	+	-
(7)	34	M	-	8 (neutrophil 92%)	ND	-	+	+
(8)	52	F	RA, corticosteroid, chronic renal failure	Lymphocyte-predominant	28	+	+	+
(9)	32	F	-	6 (neutrophil 94%)	ND	+	-	+
(10)	49	M	Renal-pancreas transplantation, immunosuppressive agent	ND	ND	ND	-	+
(11)	69	M	pneumoconiosis	83 (first thoracentesis) 53 (second thoracentesis)	25 (first thoracentesis) 46 (second thoracentesis)	+	-	+
(12)	24	M	-	ND	ND	+	-	+
(13)	51	M	HIV	ND	86	ND	+	+
(14)	57	M	Diabetes mellitus	9	68	+	-	+
(15)	63	M	Renal transplantation, immunosuppressive agent	70	24	ND	-	+
Present case	80	M	RA, corticosteroid (prednisolone 25mg)	100	101	ND	+	+

M: male, F: female, HIV: human immunodeficiency virus, HTLV-1: human T-cell lymphotropic virus type 1, RA: rheumatoid arthritis, ND: not described, ADA: adenosine deaminase

effusions in cryptococcal pleuritis because the capsular polysaccharide may induce the proliferation of CD4⁺ T lymphocytes (18). There is one case report of cryptococcal pleuritis presenting with a high ADA level in a lymphocyte-predominant pleural effusion (11). Pleural effusion associated with latent pulmonary cryptococcosis with a left lower lobe nodule was suspected in our patient; however, at the initial thoracentesis, the ADA levels in the pleural effusion were not elevated, and cultures for cryptococcus were negative. At the second thoracentesis, the ADA levels in the pleural effusion were elevated, and the cultures for cryptococcus were positive. Reactivated and increased cryptococcus levels induced by immune deficiency related to corticosteroid therapy may have been responsible for the elevated level of ADA in the pleural effusion.

Second, cultures of pleural effusions have low sensitivity for both cryptococcus and tuberculous pleuritis. The sensitivity was less than 40% in immunocompetent patients with tuberculous pleuritis (19). In cryptococcal pleuritis, pleural effusion cultures for cryptococcus were positive in 11 of 26 patients (42%) (1). The European Conference on Infections

in Leukemia recommends serum and cerebrospinal fluid antigen testing to diagnose disseminated or cryptococcal meningitis, as the sensitivity of cryptococcal antigen testing in disseminated disease is higher than that of blood culture (20). In contrast, the sensitivity of serum cryptococcal antigen tests in non-human immunodeficiency virus (HIV) infected patients with pulmonary cryptococcosis was only 56% (21), and there is no evidence supporting their usefulness in the diagnosis of cryptococcal pleuritis. When we reviewed previously reported cases of cryptococcal pleuritis, including our present case, the sensitivity of the cryptococcal antigen test was 88% (14/16) in serum and 89% (8/9) in pleural effusion. Furthermore, in six patients, pleural fluid culture was negative, and serum or pleural cryptococcal antigen test was positive (Table). These findings suggest that serum and pleural fluid cryptococcal antigen testing are useful for diagnosing cryptococcal pleuritis.

Co-infection with cryptococcus and *Mycobacterium tuberculosis* has rarely been reported. Impaired cell-mediated immunity associated with HIV infection, blood disease, cancer and corticosteroid treatment are risk factors for cryptococco-

sis and tuberculosis. In particular, the activation of Th1 lymphocytes and interferon- γ (IFN- γ) production is crucial for defending against intracellular pathogens, such as *Mycobacteria* and cryptococcus. However, both pathogens induce similar impairments of cell-mediated immunity involving the suppression of Th1 or activation of Th2 cells, according to disease severity. In an *in vitro* study, peripheral blood mononuclear cells from patients with severe tuberculosis produced higher interleukin (IL)-4 and transforming growth factor- β (TGF- β) levels with decreased IFN- γ synthesis than cells from mildly to moderately tuberculous patients in response to specific antigen stimulation (22). In an *in vivo* study, HIV-negative tuberculosis patients had lower serological markers of Th1 [soluble lymphocyte activation gene (LAG)-3] and higher serological markers of Th2 [IgE, soluble CD30 and macrophage-derived chemokine/C-C motif chemokine 22 (MDC/CCL22)] than healthy controls (23). Capsular polysaccharides expressed by cryptococcus have similar immunomodulatory effects. Capsular polysaccharide induces the proliferation of CD4⁺ T lymphocytes and differentiation into the dominant Th2 phenotype with the production of anti-inflammatory cytokines, such as IL-4 and IL-10, in the presence of viable splenic adherent cells (18). Although cryptococcosis and tuberculosis have been suggested to induce suppressive effects on the host immune system, co-infection is rarely reported. Indeed, of 151 patients with cryptococcosis, only 3 (1.99%) exhibited co-infection with tuberculosis (24). Another large, single-center study reported co-infection with tuberculosis and cryptococcosis in 23 patients (5.4% of cryptococcosis or 0.6% of tuberculosis) (25). Although the present case report is the first to describe cryptococcal pleuritis coincident with pulmonary tuberculosis, many cases of cryptococcal pleuritis may be mistaken for tuberculous pleuritis. Further investigation is required to determine the association between cryptococcal pleuritis and the ADA level or proportion of CD4⁺ lymphocytes in pleural effusion.

Our patient was treated with only fluconazole (400 mg/day) based on a diagnosis of non-severe pulmonary cryptococcosis; however, the pleural effusion initially increased. Rifampicin is an inducer of hepatic cytochrome P450 enzymes. The coadministration of rifampicin with fluconazole influences the pharmacokinetic parameters of fluconazole, inducing a 22% decrease in the area under the concentration-time curve and a 17% decrease in the maximum concentration (26). This pharmacokinetic interaction may have caused the aggravation in the pleural effusion. In addition, a positive serum cryptococcal antigen titer of 1:8,192 was found in our patient. A serum cryptococcal antigen titer $\geq 1:512$ is a poor prognostic factor (27), and the Infectious Diseases Society of America recommends that these patients be equally treated for central nervous system diseases (28). It may therefore have been better to treat this patient with other regimens, such as amphotericin B plus flucytosine for induction therapy.

In summary, we encountered a case of cryptococcal pleu-

ritis with elevated ADA levels in the pleural effusion during treatment for pulmonary tuberculosis. When pleural effusion develops during treatment for tuberculosis, cryptococcal pleuritis should be included in the differential diagnosis, and the determination of cryptococcal antigens in the serum or pleural effusion is recommended.

The authors state that they have no Conflict of Interest (COI).

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