Cryptococcal Pleuritis Containing a High Level of Adenosine Deaminase in a Patient with AIDS: A Case Report

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Established Facts

- In cryptococcal infection, pleural effusion alone is an unusual presentation.
- High levels of adenosine deaminase in the pleural fluid are used for clinical diagnosis of tuberculous pleuritis.

Novel Insights

- High levels of adenosine deaminase in the pleural fluid can be observed in cryptococcal pleuritis.
- Longer incubation of pleural fluid should be performed in cases of pleuritis with a high adenosine deaminase level as the only significant finding.

Key Words

Cryptococcus neoformans • Pleuritis • Adenosine deaminase • Pleural effusion

Abstract

Cryptococcal infection is the 4th most common opportunistic infection in patients with acquired immune deficiency syndrome (AIDS). Although pleural effusion alone is an unusual presentation, we present a case of cryptococcal pleu-

ritis in an AIDS patient which was initially difficult to discriminate from tuberculous pleuritis because of the high level of pleural adenosine deaminase (ADA). *Cryptococcus neoformans* was detected in the culture of the pleural effusion after the initiation of antituberculous treatment. High levels of ADA in the pleural fluid can be observed in patients with cryptococcal pleuritis, and longer incubation of pleural fluid should be performed in all patients who present with pleuritis associated with a high ADA level as the only significant finding.

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Introduction

Cryptococcus neoformans is an important fungal pathogen causing serious infections in patients with acquired immune deficiency syndrome (AIDS) [1]. It is thought that the lungs are the initial site of almost all infections due to *C. neoformans*, which primarily affects the respiratory tract and central nervous system. However, pleural effusion alone is an unusual presentation of cryptococcal infection in AIDS patients [2–4]. We present a case of an AIDS patient with cryptococcal pleuritis because of the high level of adenosine deaminase (ADA) in the pleural fluid. An elevated ADA level in pleural fluid is usually associated with tuberculosis, although it can occasionally be seen in nontuberculous pleuritis, including cryptococcosis.

Case Report

A 51-year-old Japanese man suffered from productive cough for 4 months without presenting to an internist. He had a history of chronic hepatitis B infection and contacted his primary care doctor for a follow-up examination. A left pleural effusion was observed by chance when an abdominal ultrasound was performed. He was admitted to the University of Tokyo Hospital, Japan, for examination and treatment. He had been assigned to Myanmar for 4 years, and 11 months prior to admission, he had unprotected sexual contact.

On admission, his physical exam revealed a temperature of 36.9°C, a pulse rate of 88 bpm and a blood pressure of 146/90 mm Hg. Breath sounds were attenuated on the left side of his chest, but neither rales nor murmurs were heard. There were no abnormalities on neurological examination such as neck stiffness or disori-

entation. Laboratory findings on admission showed a white blood cell count of 5,300/ μ l without a shift to the left and a C-reactive protein level of 7.33 mg/dl. His admission chest X-ray film revealed a pleural effusion occupying two thirds of the left lung (fig. 1a) which was confirmed on chest CT. The chest CT was otherwise negative. Sputum culture was also negative. Acid fast bacilli stain and polymerase chain reaction test of his sputum for *Mycobacterium tuberculosis* were also negative. Thoracentesis and pleural biopsy were performed. No granulomatous lesions were histopathologically detected, and acid fast smear and culture of the biopsy sample were both negative. Analysis of the pleural effusion revealed an exudative fluid with a white blood cell count of 2,600/ μ l and an ADA level of 85.9 IU/l. However, no microorganisms were detected in the culture of the pleural fluid after 1 week. Due to the high level of ADA in the effusion, a presumptive diagnosis of tuberculous pleuritis was made, and treatment with isoniazid, rifampicin, ethambutol and pyrazinamide, along with pleural drainage, was initiated.

After initiation of the antituberculous therapy, the pleural effusion gradually decreased, although the patient developed a fever. *C. neoformans* was detected in the culture of the pleural effusion by the 11th day of admission. A human immunodeficiency virus (HIV) antibody test was positive with 49/ μ l of CD4+ T cells. The serum cryptococcal antigen was detected, although a quantification assay of the antigen was not available. Lumbar puncture was also performed. No cells were detected in the cerebrospinal fluid and the total protein was 23 mg/dl, glucose was 52 mg/dl, and acid fast bacilli stain and culture were negative. India ink staining showed no causative agents and the cryptococcal antigen test was negative.

Antituberculosis treatment was discontinued and amphotericin B (0.7 mg/kg/day) was administered for 2 weeks, followed by fluconazole therapy (400 mg/day) for 8 weeks. Four weeks after initiation of antifungal treatment, the pleural effusion resolved (fig. 1b). Six weeks after initiation of antifungal treatment, highly active antiretroviral therapy was started. On the 8th week of admission, the acid fast bacilli culture of the pleural effusion was negative. This patient has been well for 3 years without relapse of his pleuritis.

Fig. 1. Chest X-ray on admission (a) and 4 weeks after initiation of antifungal treatment (b).

Discussion

Cryptococcal infection is the 4th most common opportunistic infection in patients with AIDS [1]. It is thought that the lungs are the initial site of almost all infections due to *C. neoformans*, and they are the second most clinically relevant site of infection after the central nervous system. However, pleural effusion is an unusual presentation of cryptococcal infection particularly in AIDS patients [2–4], and among 75 cases of HIV-infected patients with pleural effusion, only 4 cases were due to *C. neoformans* [5]. There have been few reports of AIDS patients presenting with cryptococcal pleuritis without other signs of infection [3, 6, 7].

Therefore, our patient was initially diagnosed with tuberculous pleuritis based on the analysis of the pleural effusion which showed a high level of ADA, even though the culture of the pleural fluid was negative. In patients with tuberculous pleuritis, pleural fluid cultures are negative in more than 70% of patients, although cultures obtained from pleural biopsies are positive in 40–80% of cases [8, 9]. Definitive diagnosis of tuberculosis pleural effusions depends on the demonstration of *Mycobacterium tuberculosis* in sputum, pleural fluid or pleural biopsy specimens. Most cases of pleural tuberculosis are diagnosed on the basis of cultures and histopathological findings [8, 10]. Some cases are clinically diagnosed by supportive evidence alone, including demonstration of classical tuberculosis granulomas in the lung and elevated ADA and interferon- γ levels in the pleural fluid. Previous studies have shown that levels of ADA in the pleural fluid >40 IU/l have a high sensitivity (81–100%) and a high specificity (83–100%) for tuberculosis pleuritis [8]. However, elevated levels of ADA in the pleural fluid can also be seen in empyema, lymphoma, other malignancies, parapneumonic effusions and pleural effusions associated with collagen vascular diseases [11, 12]. Because ADA is the enzyme that catalyzes the conversion of adenosine to inosine, and ADA is found in most cells,

particularly lymphocytes, it is conceivable that ADA would be elevated in lymphocyte-rich pleural effusions [13]. Cell fractionations of pleural fluid in previously reported cases of cryptococcal infection were lymphocyte rich [3, 14–17]. In our case, the lymphocyte percentage of the pleural fluid could not be determined because cell fractionation analysis of pleural fluid was not available in our hospital. However, other studies showed that an elevated level of ADA was seldom found in nontuberculous lymphocytic pleural effusions, and an ADA level <40 IU/l virtually excluded tuberculosis in lymphocytic pleural effusions, although cases of cryptococcosis were not included in these studies [18, 19]. In a study about tuberculous and nontuberculous pleuritis, evaluation of pleural ADA levels correlates with a CD4+ T lymphocyte population which is related to cellular immunity [20]. Other reported infectious diseases with high pleural ADA levels (other than tuberculosis) include legionellosis, brucellosis, coxiellosis and cryptococcosis [15, 21–23]. These are intracellular microbial agents, and their pathogenicity is related to cellular immunity [24–28]. There has been only 1 previous case of cryptococcosis where the ADA level in the pleural effusion was recorded as 27.8 IU/l [15]. More investigation is required to further determine the association between cryptococcal pleuritis and the ADA level in pleural effusions.

Although it took 11 days to detect *Cryptococcus* in the culture of our patient's pleural effusion, and *C. neoformans* is usually cultured within 3–7 days, the culture time of pleural effusion can vary up to 2 weeks [3]. We assumed that more than 7 days would be required to culture pleural effusion in order to diagnose cryptococcosis.

In conclusion, high levels of ADA in the pleural fluid can be observed in patients with cryptococcal pleuritis, and a longer incubation of pleural fluid should be performed in all patients who present with pleuritis as the only significant finding.

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