Official Case Reports Journal of the Asian Pacific Society of Respirology
Respirology Case Reports
OPEN ACCESS

Cryptococcal pleural infection in a recurrent pleural effusion: a case report

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Keywords
Acute myeloid leukaemia, cryptococcal pleural infection, cryptococcosis, pleural effusion.

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Received: 16 November 2017; Revised: 11 December 2017; Accepted: 11 December 2017; Associate Editor: Charles Feldman.

***Respirology Case Reports*, 6 (3), 2018, e00294**

doi: 10.1002/rcr2.294

Abstract

Cryptococcal pleural infection is rare with about 50 cases reported. It tends to occur in immunocompromised individuals. We describe a 38-year-old male who presented with a lymphocytic exudative right pleural effusion and a raised pleural fluid adenosine deaminase (ADA) level. He was initially treated for pleural tuberculosis, but presented again with worsening pleural effusion 6 weeks later. A thoracoscopic pleural biopsy revealed chronic nodular granulomatous pleuritis with cryptococcal organisms present. The repeat pleural fluid culture was positive for *Cryptococcus neoformans*. He was started on intravenous amphotericin B and oral flucytosine for 1 week, and then continued on oral fluconazole. He was subsequently diagnosed to have acute myeloid leukaemia. His peripheral blood film showed presence of blast cells (33%), with flow cytometry showing increased myeloblast population. Lymphocytic exudative pleural effusions with raised ADA levels in an immunocompromised patient can be due to opportunistic fungal infections.

Introduction

Pulmonary cryptococcosis is an opportunistic fungal infection often seen in patients with impaired cellular immune function, such as human immunodeficiency virus (HIV) infection, diabetes mellitus, hepatic cirrhosis, haematologic malignancies, solid organ and stem cell transplantation, corticosteroid therapy, sarcoidosis, connective tissue disorders and immunosuppressive medications [1]. Pleural presentation of cryptococcal infection is rarely seen in pulmonary cryptococcosis.

Here, we report a case of *Cryptococcus neoformans* pleural effusion in a patient who was also newly diagnosed with acute myeloid leukaemia (AML).

Case Report

A 38-year-old male was admitted for 1-day duration of right-sided chest pain. He was a smoker of 20pack-years and worked as a sales executive. He had no past medical history of note and did not keep any pets. Physical examination revealed decreased breath sounds over the right lung base. Chest radiography (CXR) showed a right pleural effusion (Fig. 1A).

The full blood count showed a normal white blood cell (WBC) count of 6.69×10^9/L with neutropenia (0.98×10^9/L) and lymphocytosis (4.51×10^9/L).

A right thoracocentesis was carried out, and pleural fluid studies revealed a lymphocytic exudative pleural effusion. Pleural fluid Ziehl–Neelsen stain was negative for acid fast bacilli; and tuberculosis (TB) culture was negative. TB polymerase chain reaction test was negative and adenosine deaminase (ADA) level was raised (Table 1).

He was started on empirical treatment for pleural TB with rifampicin 600 mg, isoniazid 300 mg, ethambutol 1400 mg, and pyrazinamide 1750 mg daily.

He was readmitted 6 weeks later for cough and breathlessness of 3-day duration. CXR showed a worsening and large right pleural effusion (Fig. 1B). He underwent repeat pleural drainage, and pleural fluid studies showed a similar lymphocytic effusion (Table 1).

A computed tomography (CT) of the thorax showed a moderate right pleural effusion with collapse consolidation

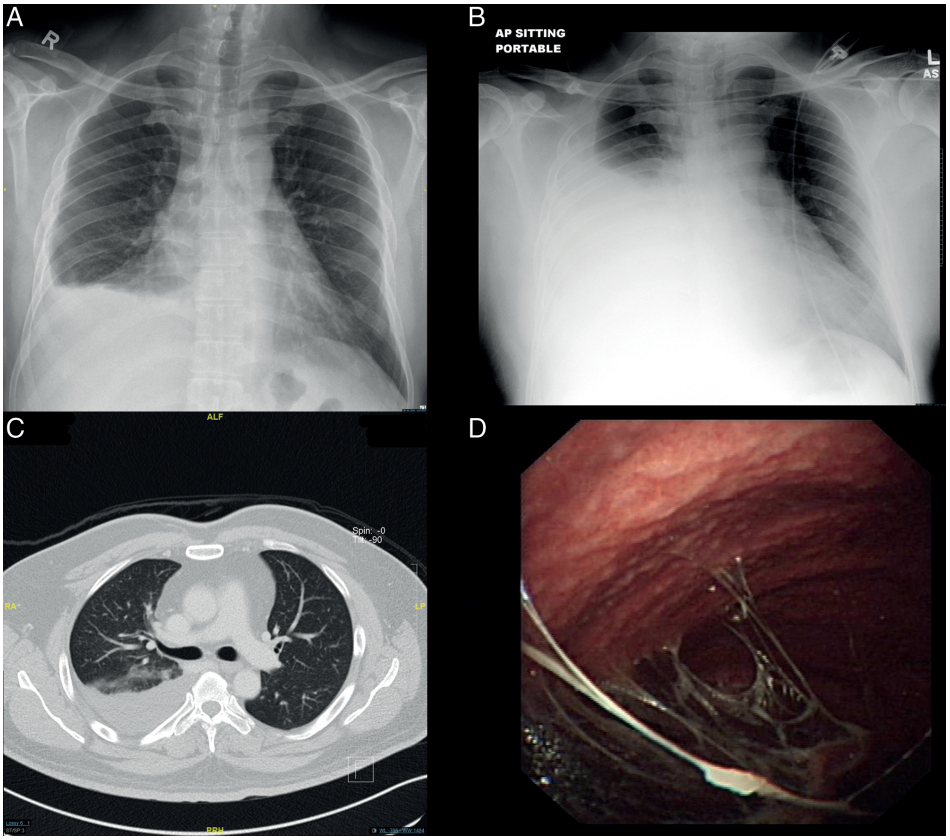

Figure 1. (A) Chest radiography (CXR) at first presentation showing right-sided pleural effusion. (B) CXR at second presentation showing worsening right-sided pleural effusion. (C) Computed tomography thorax (mediastinal window) showing right-sided pleural effusion. (D) Thoracoscopic view of pleural cavity showing multiple adhesions and nodules over parietal and diaphragmatic pleura.

of the right lower lobe. There were no suspicious masses seen in the lungs or the mediastinum (Fig. 1C).

The patient then underwent thoracoscopy which revealed multiple adhesions and nodules over the parietal and diaphragmatic pleura (Fig. 1D). Pleural biopsies were performed and the pleural fluid was sent for further investigations.

The pleural biopsy specimens showed chronic nodular granulomatous pleuritis with Cryptococcus organisms present. There was also associated reactive fibrinous/fibrous pleurisy (Fig. 2). Pleural biopsy TB culture was negative.

The culture of the pleural fluid was subsequently confirmed positive for *C. neoformans* (via mass spectrometry method).

His serum cryptococcal antigen (test performed using IMMY CrAg LFA; Immuno-Mycologics, Inc., USA) was negative and both his HIV test and diabetic screening were negative.

As cryptococcal infections tend to occur in those immunocompromised, he was started on intravenous amphotericin B 65 mg daily and oral flucytosine 2000 mg every 6-hourly whilst awaiting further investigations to rule out disseminated infection. Lumbar puncture was performed and his cerebrospinal fluid (CSF) studies did not reveal any evidence of cryptococcal meningitis. He was

Table 1. Pleural fluid studies.

	First pleural fluid studies	Second pleural fluid studies
pH	7.42	7.45
Protein	60.6	66.0
LDH	241	199
WBC	4150	1045
N	3.0%	3.0%
L	81.0%	95.0%
M	15.0%	2.0%
E	1.0%	0.0%
RBC	12,850	665
ADA	53	51
Aerobic culture	No growth	*Cryptococcus neoformans*
TB culture	No growth	No growth
Cytology	No malignant cells	No malignant cells
	Serum protein 82; Serum LDH 173	Serum protein 77; Serum LDH 133

ADA, adenosine deaminase; E, eosinophils; LDH, Lactate Dehydrogenase; L, lymphocytes; M, monocytes; N, neutrophils; RBC, red blood cells; TB, tuberculosis; WBC, white blood cells.

subsequently commenced on oral fluconazole 800 mg once daily.

A peripheral blood film showed atypical mononuclear-like cells with prominent nucleolus, probably lymphoid with scanty cytoplasm and some reactive lymphocytes; a manual differential count showed the presence of blast cells (33%). Peripheral blood flow cytometry revealed an increased myeloblast population indicative of AML.

He was referred to Haematology and transferred to a tertiary hospital for urgent chemotherapy and, subsequently, haemopoietic stem cell transplantation (HSCT). Fluconazole was switched to voriconazole (dose to achieve therapeutic target level of 2–5 mg/L) during the chemotherapy period and then back to fluconazole 400 mg once daily. Dose was decreased to 200 mg once daily after 5 months. He completed total 6 months of antifungal treatment.

Following HSCT, the patient was admitted once for diarrhoea and rash, possibly secondary to graft versus host disease (GVHD). Since then, the patient has remained well.

Discussion

Cryptococcosis is an invasive opportunistic fungal infection caused by the encapsulated *C. neoformans* or *Cryptococcus gattii; C. neoformans* is usually found in soil contaminated by pigeon droppings and can cause pulmonary cryptococcosis through the inhalation of these spores [1].

Pulmonary cryptococcosis may manifest as pulmonary nodules or infiltrates, mediastinal lymphadenopathy or pleural effusions. Amongst these presentations, cryptococcal infections of the pleura are rare, with only 50 cases reported so far in English literature.

In our patient, the pleural biopsies and pleural fluid cultures were diagnostic of cryptococcal pleural infection. However, in some cases, the pleural fluid cultures may be negative due to the small amount of organisms present in the pleural fluid. Another reason is that the effusion is an inflammatory response to the release of the antigen into the pleural fluid; hence in these cases, pleural fluid cryptococcal antigen may be useful in the diagnosis [2].

Because of the diagnostic difficulty of cryptococcal pleural infection, there have been similar case reports of these patients who were also initially treated for pleural TB because of raised ADA levels in exudative lymphocytic pleural effusions.

ADA is useful in the diagnosis of pleural TB due to its high sensitivity, where a negative result helps to exclude TB, and a high level lymphocytic effusion strongly favours TB [3].

Given that TB is endemic in Singapore with an incidence rate of 51 per 100,000 population in 2016, and the initial pleural fluid studies, the patient was started on anti-TB treatment for possible pleural TB. In addition, as the patient's immune status was not apparent at the initial presentation, pleural fluid fungal cultures were not sent.

Although the response to treatment for pleural TB is good, with resolution of fever within 2 weeks and resorption of pleural fluid within 6 weeks [4], up to 16% may have worsening pleural effusion after 2 weeks of anti-TB therapy due to a paradoxical response to TB treatment [5].

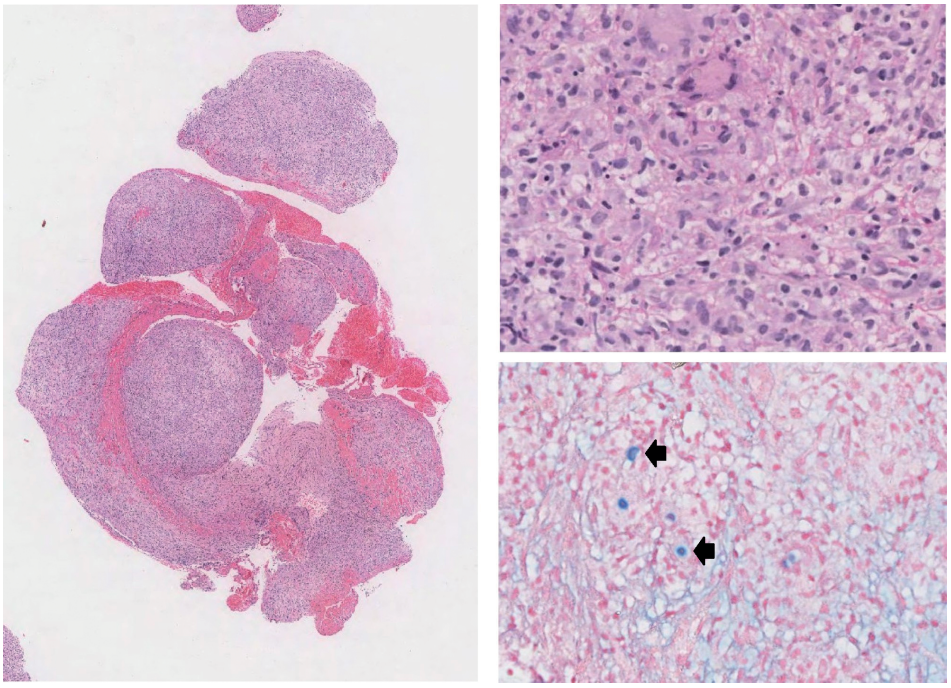

Figure 2. Left: Low power view of thoracoscopic biopsy showing nodular granulomatous pleuritis. Right: 40× magnification of nodule showing intracellular yeast organisms with mucoid capsules (upper: HE, lower: Alcian Blue). Alcian Blue stains the polysaccharide capsule of the Cryptococcus (arrows point to the cryptococcus organisms).

However, as other conditions such as malignancy, connective tissue disorders, chylothorax, and atypical infections can also cause lymphocytic effusions [3], one should maintain a high index of suspicion for alternative aetiologies and consider other investigations, such as a repeat pleural fluid testing with pleural biopsy for further evaluation of a worsening pleural effusion.

In conclusion, atypical infections like cryptococcal infection of the pleural should be considered as an alternative cause of a recurrent pleural effusion, especially in our patient who was also diagnosed with a haematological malignancy.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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