Clinical Case Report

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Cryptococcal pleuritis with pleural effusion as the only clinical presentation in a patient with hepatic cirrhosis

A case report and literature review

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Abstract

Rationale: Cryptococcosis is a significant life-threatening fungal infection in worldwide, mainly reported in immunocompromised patients. Pleural effusion presentation of cryptococcal infection as the only clinical presentation is rarely seen in pulmonary cryptococcosis, which may lead to be misdiagnosed, and the study on this subject will provide further insights.

Patient concerns: A 64-year-old man was hospitalized in our department and diagnosed as hepatic B cirrhosis. A computed tomography (CT) of the thorax showed a massive right pleural effusion without pulmonary parenchymal abnormalities. He was started on empirical treatment for pleural tuberculosis (TB). However, during his hospitalization, a right pleural effusion developed and fever was not controlled.

Diagnoses: On day 14 admission, pleural fluid cultured positive for *Cryptococcus neoformans*. The *C neoformans* isolate belonged to ST5 and molecular type VNI (*var. grubii*).

Interventions: The patient was diagnosed with cryptococcal pleuritis, then amphotericin B and fluconazole were administrated.

Outcomes: Finally, the patient was improved and discharged from our hospital.

Lessons: Similar cases in cryptococcal pleuritis patients with pleural effusion as the only clinical presentation in the literature are also reviewed. Through literature review, we recommend that pleural effusion cryptococcal antigen test should be used to diagnose cryptococcal pleuritis to reduce misdiagnosis. The early administration of antifungal drug with activity to *Cryptococcus* seemed beneficial in preventing dissemination of cryptococcosis.

Abbreviations: CT = computed tomography, HIV = human immunodeficiency virus, HTLV-1 = human T-cell lymphotropic virus type 1, MIC = minimum inhibitory concentration, PCT = procalcitonin, TB = tuberculosis.

Keywords: cryptococcosis, *Cryptococcus neoformans*, hepatic cirrhosis, multilocus sequence typing (MLST), pleuritis

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1. Introduction

Cryptococcosis is a significant invasive fungal infection including cryptococcal meningitis, cryptococcemia, pulmonary cryptococcosis, disseminated cryptococcosis and so on, primarily caused by *Cryptococcus neoformans* and *Cryptococcus gattii*.[1,2] Cryptococcosis may occur in healthy hosts, the majority of infections occur in patients with impaired cellular immune function, such as immunodeficiency virus (HIV) infection, diabetes mellitus, hepatic cirrhosis, haematologic malignancies, solid organ and stem cell transplantation, corticosteroid therapy, and immunosuppressive medications.[2–7] However, pleural presentation of cryptococcal infection is rarely seen, especially as the only clinical manifestation without other lesions.

In this study, we reported a case of *C neoformans* pleural effusion as the only clinical presentation in a patient who was diagnosed with hepatitis B cirrhosis, and relevant literatures were reviewed and analyzed. Recognizing the clinical features of these patients may improve diagnosis and promote timely treatment.

2. Case report

A 64-year-old male was admitted for repeated fatigue and fever for 3 months and 1-week duration of right-sided chest pain in 2014. The patient was a farmer who was originated from a rural

area in Zhejiang Province, China. He had past medical history of hepatitis B for about 20 years but did not receive any antivirus therapy. He did not keep any pets. He had a 7-years history of smoking and drinking but had given up these habits for 20 years. Physical examination revealed decreased breath sounds over the right lung base, and his temperature was 38° to 39°C

During admission, the liver ultrasound finding suggested chronic liver disease. For further examination, liver biopsy was performed and the result showed a trend of chronic moderate hepatitis B with cirrhosis (G3S4), HBS(+), and HBC(+).

On admission, the patient's blood cultures were negative. HIV test was negative and the CD4+ count was normal. The full blood count showed a normal white blood cell (WBC) count of 4.2×10^9/L with neutropenia (2.4×10^9/L) and lymphocytosis (1.4×10^9/L). He had a moderately increased C-reactive protein (CRP) level of 30 (normal, <8) mg/L and a normal procalcitonin (PCT) level of 0.29 ng/mL (Table 1). A computed tomography (CT) of the thorax showed a moderate right pleural effusion. Biapenem, a kind of carbapenems, was empirically administrated for anti-infection. But the patient felt breathless and remained fever.

On day 7 admission, a CT of the thorax was repeated and it showed a worsening right pleural effusion without apparent pulmonary parenchymal abnormalities (Fig. 1). A right thoracocentesis was carried out, and pleural fluid studies revealed a lymphocytic exudative pleural effusion and raised protein level (Table 1). Pleural fluid acid-fast stain was negative for acid-fast bacilli, and no tumor cell was detected in pleural fluid. While the result of T-SPOT tuberculosis (TB) blood test was positive. He was started on empirical treatment for pleural TB with rifampicin 450 mg, isoniazid 300 mg, ethambutol 750 mg, and pyrazinamide 1500 mg daily. However, the temperature of the patient was still above 38°C and he remained breathlessness. He underwent repeat pleural drainage, and pleural fluid studies showed a lymphocytic effusion (Table 1).

On day 14 admission, the culture of the pleural fluid was confirmed positive for *C neoformans*. Subsequently, *C neoformans* had been isolated from the pleural fluid for 4 times. Lumbar puncture was performed and his cerebrospinal fluid (CSF) studies did not reveal any evidence of cryptococcal meningitis. As cryptococcal infections tend to occur in those immunocompromised, this patient was hepatic cirrhosis. So he was started on intravenous amphotericin B 40 mg daily and intravenous fluconazole 400 mg daily. Because the patient had liver disease, flucytosine was not used for its side effect of liver dysfunction.

On day 23 admission, the patient was improved and discharged from our hospital. The he admitted in the local hospital for continue treatment of cryptococcal infection. Culture for *Mycobacterium tuberculosis* in the pleural effusion was negative. Since then, the patient has remained well.

The *Cryptococcal* isolate from this patient was stored for further research. It was identified as *C neoformans* by internal transcribed spacer (ITS) sequencing and by 2 matrix-assisted laser desorptioneionization time-of-flight mass spectrometry (MALDI-TOF MS) systems. The isolate was susceptible to all of the 5 antifungal agents (amphotericin B minimum inhibitory concentration [MIC] 0.5 mg/L, fluconazole MIC 1 mg/L, flucytosine MIC 4 mg/L, itraconazole MIC 0.125 mg/L, and voriconazole MIC 0.06 mg/L). Multilocus sequence typing (MLST) was used to verify species/variety and to designate molecular types. It revealed that the *C neoformans* isolate belonged to ST5 and molecular type VNI (*var. grubii*).

We obtained an exempt status from the Institutional Review Board of the First Affiliated Hospital, College of Medicine, Zhejiang University to use these data.

3. Discussion

C neoformans infection usually presents as meningitis and is increasingly being recognized in immunocompromised patients. While, pleural diseases due to fungi are rare,[8] and more than half of the patients have moderate to severe underlying diseases such as HIV infection, leukemia and lymphoma, as previously reported.[9–11] Our patient was a 64-year-old man with hepatic B cirrhosis. The incidence of hepatic B cirrhosis has been high in

Table 1

Results of blood tests and pleural effusion.

Blood tests		Normal reference range	PCT, ng/mL	0.29	0.00–0.50
CRP, mg/L	30	0–8	ESR, mm/h	32	0–20
WBC, 10^9/L	4.2	4.0–10.0	Blood culture: bacteria	negative	
Neutrophil percentage, %	56.6	50.0–70.0	HBV DNA, IU/mL	1.56×10^9	
Lymphocyte percentage, %	32.2	20.0–40.0	Tspot	positive	
Eosinophil, 10^9/L	1.70	0.02–0.50	**Characteristics of pleural effusion**		
Hb, g/L	119	131–172	Color	red, turbid	
Platelet count, 10^9/L	149	83–303	Total protein, g/L	35.4	
BUN, mmol/L	6.0	2.9–8.2	Rivalta test	positive	
Creatinine, μmol/L	92	59–104	RBC (/uL)	40000	
Albumin, g/dL	26.8	35.0–55.0	WBC (/uL)	1000	
ALT, U/L	15	5–35	Neutrophil percentage, %	20	
AST, U/L	22	8–40	Lymphocyte percentage, %	76	
TB, μmol/L	26	0–21	mesothelial cells percentage, %	4	
Sodium, mmol/L	138	136–145	Ink stain	negative	
Potassium, mmol/L	4.12	3.50–5.20	Acid fast stain	negative	
INR	1.21	0.85–1.15	Culture: C. Neoformans	positive	
PT, s	14.0	10.0–13.5	Culture: M. tuberculosis	negative	
Fibrinogen level, g/L	2.9	2.0–4.0			
D-dimer, μg/L	1679	0–700			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Hb = haemoglobin concentration, INR = international normalized ratio, PCT = procalcitonin, PT = prothrombin time, RBC = red blood cell, TB = total bilrubin, WBC = white blood cell.

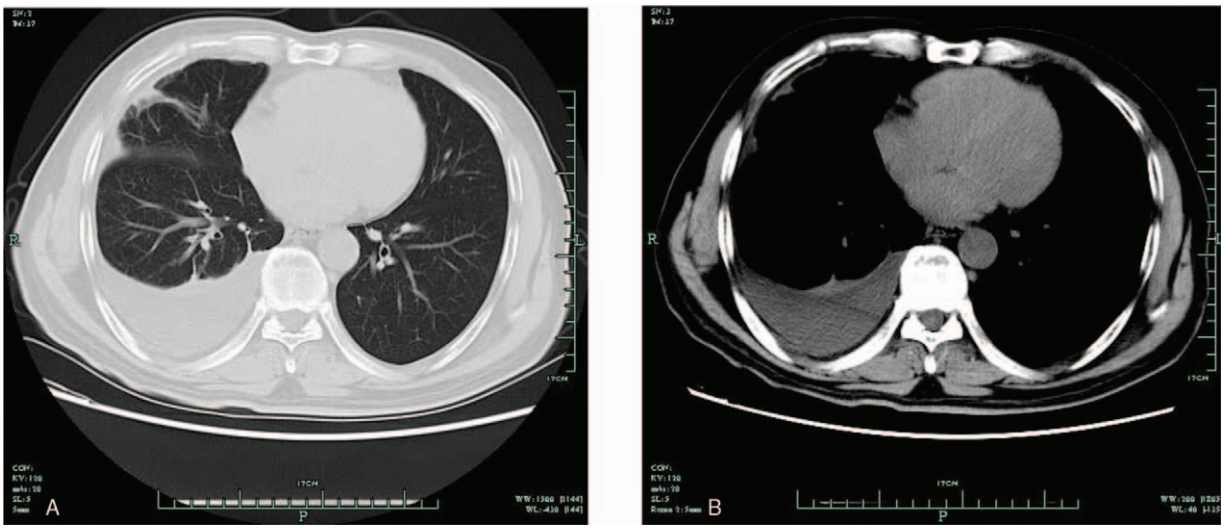

Figure 1. Computed tomography of the chest.

China.[12] However, cryptococcal pleuritis still remains uncommon. Hence, misdiagnosis and delay of therapy will lead to the cryptococcal dissemination and increase of mortality.

Cryptococcal pleuritis with pleural effusion as the only clinical presentation is rarely reported. We performed a literature search using the terms "cryptococcal pleural infection", "cryptococcal pleuritis", "empyema caused by cryptococcus", "Pleural cryptococcosis", and "cryptococcal empyema" on PubMed. Papers in English were included. Cryptococcal pleuritis cases with pleural effusion as the only clinical presentation were included. Several relevant reports in Spanish, French or Japanese were not included. Disseminated cryptococcosis cases with cryptococcal pleuritis were excluded. Cryptococcal pleuritis cases with apparent pulmonary parenchymal abnormalities were also excluded. Only reports on cryptococcal pleuritis with pleural effusion as the only clinical presentation including the main clinical and biological data and the survival status were taken into account. In total 11 studies (11 cases) met the inclusion criteria (Table 2).[9,10,13–21] Most of the studies (7/11) were from Asia including Japan (5 cases), Singapore (1case), and India (1 case), while no relevant report in English from China. All of the 11 patients were immunocompromised, with underlying diseases including HIV, human T-cell lymphotropic virus type 1 (HTLV-1) carriers, renal failure, transplantation, acute myeloid leukemia (AML), lymphoma, and rheumatoid arthritis (RA) with corticosteroids usage. Impaired cell-mediated immunity associated with HIV infection, blood disease, cancer and corticosteroid treatment are risk factors for cryptococcosis including cryptococcal pleuritis. Our patient had the underlying disease of hepatic B cirrhosis. Patients with hepatic cirrhosis were also immunocompromised, and decompensated liver cirrhosis was confirmed as 1 of the risk factors of invasive C. neoformans diseases.[22] Among patients with hepatic cirrhosis, cryptococcal meningitis was frequently reported, while several cases of cryptococcal peritonitis were reported, and cases of cryptococcal pleuritis were rarely reported especially as the only manifestation.[23–25]

Table 2

Reported cases of cryptococcal pleuritis with pleural effusion as the only clinical presentation.

				Pleural effusion						
Reference	Age (yr)/ gender	Country	Underlying disease	Percentage of lymphocyte (%)	ADA (IU/L)	Culture for cryptococcus	Cryptococcal antigen test	Serum Cryptococcal antigen test	Anti-fungal agents	Outcome
Taguchi H et al[13]	70/F	Japan	HTLV-1, macroglobulinemia	Lymphcyte predominant	ND	*C. neoformans*	+	–	5-FC, ITC	Survived
Fukuchi M et al[14]	52/F	Japan	RA, corticosteroid, chronic renal failure	Lymphcyte predominant	28	*C. neoformans*	+	+	AMPH, 5-FC, FCZ	Survived
Ramanathan V et al[10]	49/M	USA	Renal-pancreas transplantation, immunosuppresive agent	ND	ND	–	ND	+	5-FC, FCZ	Survived
Yoshino Y et al[15]	51/M	Japan	HIV	ND	86	*C. neoformans*	ND	+	AMPH, FCZ	Survived
Kushima Y et al[16]	80/M	Japan	RA, corticosteroid	100	101	*C. neoformans*	ND	+	FCZ	Died*
Mulanovich VE et al[17]	28/M	USA	HIV	37	ND	*C. neoformans*	+	+	AMPH, FCZ	Survived
Wee ACR et al[18]	38/M	Singapore	AML	81	53	*C. neoformans*	ND	–	AMPH, 5-FC, FCZ	Survived
Kinjo K et al[19]	64/M	Japan	HTLV-1, chronic renal failure, hemodialysis	94	33.2	*C. neoformans*	+	–	AMPH, 5-FC, FCZ	Survived
Swan CD et al[20]	79/M	Australia	Lymphoma, chemothrapy	normal	ND	*C. neoformans*	+	+	AMPH, FCZ	Survived
Cartwright E et al[9]	51/M	USA	HIV	Lymphcyte predominant	ND	*C. neoformans*	ND	+	FCZ	Survived
Shankar EM et al[21]	35/F	India	HIV, diabete	ND	ND	*C. laurentii*	ND	ND	FCZ	Survived

5-FC = flucytosine, ADA = adenosine deaminase, AML = acute myeloid leukemia, AMPH = amphotericin B, F = female, FCZ = fluconazole, HIV = human immunodeficiency virus, HTLV-1 = human T-cell lymphotropic virus type 1, ITC = itraconazole, M = male, ND = not described, RA = rheumatoid arthritis, VRC = voriconazole.

* died from aspiration pneumonia 5 months after the transfer.

Cryptococcal pleuritis with pleural effusion as the only clinical presentation had better prognosis than cryptococcal meningitis or disseminated cryptococcosis. After antifungal treatment, 10 of the 11 patients with cryptococcal pleuritis were survived, and the only 1 patient was died from aspiration pneumonia 5 months after discharge.

All of the 11 cryptococcal pleuritis cases without apparent pulmonary parenchymal abnormalities showed a right or left side of pleural effusion. Pleural effusion cultures for cryptococcus were positive in 10 of 11 patients including 9 patients infected with *C neoformans* and 1 patient with *Cryptococcus laurentii*. Pleural fluid examination results showed lymphocyte predominant in 6 cases, which was similar with our patient. Adenosine deaminase (ADA) was high in pleural fluid in previous reports of cryptococcal pleuritis, which was also similar with the pleural fluid characteristic of tuberculous pleuritis.[16] Hence, only according to the pleural fluid characteristic, cryptococcus and tuberculous pleuritis were difficult to be distinguished. Even rarely, cryptococcal pleuritis could be coincident with pulmonary tuberculosis.[16]

The sensitivity of cryptococcal antigen testing in disseminated disease was confirmed higher than that of blood culture, so serum and cerebrospinal fluid antigen tests were recommended to diagnose disseminated or cryptococcal meningitis by the European Conference on Infections in Leukemia.[26] In contrast, among non-HIV infected patients with pulmonary cryptococcosis, the sensitivity of serum cryptococcal antigen tests was only 56%,[27] and the sensitivity of serum cryptococcal antigen tests in the patients with only cryptococcal pleuritis was unclear. Although cryptococcal antigen test was not examined in our patient, serum or pleural effusion cryptococcal antigen test was examined in reviewed previous reports.[9,10,13–21] In the 11 patients, 3 patients were serum cryptococcal antigen test negative, but pleural effusion cryptococcal antigen test was done in 2 of the 3 patients showing positive. These findings suggest that pleural effusion cryptococcal antigen test had higher sensitivity than serum cryptococcal antigen test in cryptococcal pleuritis patients with pleural effusion as the only clinical presentation. Since pleural effusions cultures have low sensitivity for both cryptococcus and tuberculous pleuritis, pleural effusion cryptococcal antigen test should be recommended to be used in clinic for diagnosing cryptococcal pleuritis.

4. Conclusions

In conclusion, pleural presentation of cryptococcal infection as the only clinical presentation is rare, which may lead to be misdiagnosed, while delay in diagnosis may lead to treatment failure. Through study on clinical characteristics of our cryptococcal pleuritis case and previous relevant reports, it will helpful to be familiar with cryptococcal pleuritis and pleural effusion cryptococcal antigen test should be recommended to diagnose cryptococcal pleuritis. Reduction of misdiagnosis and the early administration of antifungal drug with activity to *Cryptococcus* seemed beneficial in preventing dissemination of cryptococcosis.

Author contributions

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References

[1] Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2016;30:179–206.
[2] El Fane M, Badaoui L, Ouladlahsen A, et al. Cryptococcosis during HIV infection. J Mycol Med 2015;25:257–62.
[3] Chau TT, Mai NH, Phu NH, et al. A prospective descriptive study of cryptococcal meningitis in HIV uninfected patients in Vietnam - high prevalence of Cryptococcus neoformans var grubii in the absence of underlying disease. BMC Infect Dis 2010;10:199–206.
[4] Ssekitoleko R, Kamya MR, Reingold AL. Primary prophylaxis for cryptococcal meningitis and impact on mortality in HIV: a systematic review and meta-analysis. Future Virol 2013;8:1–25.
[5] Fang W, Chen M, Liu J, et al. Cryptococcal meningitis in systemic lupus erythematosus patients: pooled analysis and systematic review. Emerg Microbes Infect 2016;5:e95–101.
[6] Li Y, Fang W, Jiang W, et al. Cryptococcosis in patients with diabetes mellitus II in mainland China: 1993–2015. Mycoses 2017;60:706–13.
[7] Sloan DJ, Parris V. Cryptococcal meningitis: epidemiology and therapeutic options. Clin Epidemiol 2014;6:169–82.
[8] O'Connor TM, O'Donnell A, Hurley M, et al. Allergic bronchopulmonary aspergillosis: a rare cause of pleural effusion. Respirology 2001; 6:361–3.
[9] Cartwright E, Rouphael N, Jain S, et al. Pleural effusion in a patient with AIDS. Clin Infect Dis 2008;46:1887–8.
[10] Ramanathan V, Kazancioglu R, Goral S, et al. Isolated pleural involvement by Cryptococcus in a kidney-pancreas transplant recipient. Nephrol Dial Transplant 2002;17:321–2.
[11] Chen M, Wang X, Yu X, et al. Pleural effusion as the initial clinical presentation in disseminated cryptococcosis and fungaemia: an unusual manifestation and a literature review. BMC Infect Dis 2015;15:385–92.
[12] Wang X, Lin SX, Tao J, et al. Study of liver cirrhosis over ten consecutive years in Southern China. World J Gastroenterol 2014;20:13546–55.
[13] Taguchi H, Kotani S, Sugito S, et al. Cryptococcal pleural effusion in an HTLV-I carrier with Waldenstroem's macroglobulinemia. Acta Med Okayama 1992;46:45–7.
[14] Fukuchi M, Mizushima Y, Hori T, et al. Cryptococcal pleural effusion in a patient with chronic renal failure receiving long-term corticosteroid therapy for rheumatoid arthritis. Intern Med 1998;37:534–7.
[15] Yoshino Y, Kitazawa T, Tatsuno K, et al. Cryptococcal pleuritis containing a high level of adenosine deaminase in a patient with AIDS: a case report. Respiration 2010;79:153–6.
[16] Kushima Y, Takizawa H, Machida Y, et al. Cryptococcal pleuritis presenting with lymphocyte-predominant and high levels of adenosine deaminase in pleural effusions coincident with pulmonary tuberculosis. Intern Med 2018;57:115–20.
[17] Mulanovich VE, Dismukes WE, Markowitz N. Cryptococcal empyema: case report and review. Clin Infect Dis 1995;20:1396–8.
[18] Wee ACR, Seet JE, Venkatalacham J, et al. Cryptococcal pleural infection in a recurrent pleural effusion: a case report. Respirol Case Rep 2018;6:e00294.
[19] Kinjo K, Satake S, Ohama T. Cryptococcal pleuritis developing in a patient on regular hemodialysis. Clin Nephrol 2009;72:229–33.
[20] Swan CD, Gottlieb T. Cryptococcus neoformans empyema in a patient receiving ibrutinib for diffuse large B-cell lymphoma and a review of the literature. BMJ Case Rep 2018;2018:bcr218-224786.
[21] Shankar EM, Kumarasamy N, Bella D, et al. Pneumonia and pleural effusion due to Cryptococcus laurentii in a clinically proven case of AIDS. Can Respir J 2006;13:275–8.
[22] Lin YY, Shiau S, Fang CT. Risk factors for invasive Cryptococcus neoformans diseases: a case-control study. PLoS One 2015;10: e0119090.
[23] Zhong YH, Tan F, Li M, et al. Comparisons of presentations and outcomes of cryptococcal meningitis between patients with and without hepatitis B virus infection. Int J Infect Dis 2014;20:31–6.
[24] Bal CK, Bhatia V, Khillan V, et al. Spontaneous cryptococcal peritonitis with fungemia in patients with decompensated cirrhosis: report of two cases. Indian J Crit Care Med 2014;18:536–9.

[25] Zamora I, Ferrer A, Buti M, et al. Isolation of Cryptococcus neoformans in the pleural fluid of a cirrhotic patient. Enferm Infecc Microbiol Clin 1992;10:377–8.
[26] Marchetti O, Lamoth F, Mikulska M, et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant 2012;47:846–54.
[27] Pappas PG, Perfect JR, Cloud GA, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis 2001;33:690–9.