Tuberculous peritonitis and pleurisy accompanied by pulmonary cryptococcosis: A case report

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Abstract
Although the infectious diseases tuberculosis (TB) and cryptococcosis both cause formation of single or multiple nodules in immunodeficient hosts, cases of co-infection of these diseases are rarely seen. We report a patient who was co-infected with TB and cryptococcosis. A male patient with no clinical evidence of immunodeficiency presented with a 3-week history of abdominal distension accompanied by oedema of recurring lower extremities. The patient was diagnosed with tuberculous peritonitis and tuberculous pleurisy by an abdominal puncture biopsy. Several months after being treated for TB, the patient was diagnosed with Cryptococcus infection and received antifungal treatment. Computed tomographic and magnetic resonance imaging findings suggested that treatment was effective. This case illustrates the challenges encountered during assessment of neoplasms associated with TB and cryptococcosis. Differential diagnosis requires an abdominal puncture biopsy. Diagnosis of Cryptococcus infection also requires a positive cryptococcal culture and positive India ink staining analysis. Notably, our patient also showed no obvious symptoms of cryptococcosis after receiving anti-TB treatment. Accordingly, in this report, we discuss the possible pathogenic mechanisms that underlie the coincidence of both types of inflammatory lesions. We emphasize the need for a greater awareness of atypical presentations of TB accompanied by Cryptococcus infection.

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Introduction
Mycobacterium tuberculosis and Cryptococcus neoformans/C. gattii complex are microbial pathogens that disproportionately affect immunocompromised human patients, such as those infected with human immunodeficiency virus (HIV). The classic symptoms of pulmonary tuberculosis (TB) include a dry or productive cough, fever, weight loss, and asthenia which, when associated with certain radiological patterns, can lead to a rapid clinical diagnosis. However, an atypical clinical and/or radiological presentation and/or a presentation associated with another chronic lung disease may complicate an aetiological diagnosis.

Despite the common epidemiologies of M. tuberculosis and Cryptococcus, only a few cases of co-infection have been reported in English journals during the past 2 decades. The first case of TB/cryptococcosis co-infection was reported in the United States in 1951. The English language literature also contains few reports of TB/cryptococcosis co-infection in the Chinese population. A single-centre study conducted at a university hospital in Taiwan from 1993 to 2006 reported only 23 cases of TB/cryptococcosis co-infection. Furthermore, a retrospective analysis of Chinese databases since 2000 only showed eight cases of cryptococcosis/TB co-infection in mainland China. Another investigation showed that 62.9% of all TB/cryptococcosis co-infection cases worldwide were reported in the Chinese population (n = 197) between 1965 and 2016, and 56.3% of these Chinese cases were reported after 2010.

In this case report, we describe our experience with an older, apparently immunocompetent male patient with an oligosymptomatic TB/cryptococcosis co-infection. Although the diagnosis was delayed by the initial refusal of the patient’s family members to consent to an abdominal puncture biopsy, a pathological examination ultimately showed TB. Cryptococcosis was diagnosed later after several months of anti-TB treatment.

Case report
On 9 December 2015, a 59-year-old Chinese man was admitted to The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China). He presented with a 3-week history of abdominal distension accompanied by oedema of the lower extremities. The patient had an occupational history of farming, no history of smoking or alcohol consumption, and no recent history of travel or contact with infectious diseases (no history of contact with patients with TB and pigeon’s excrement). According to a self-report, the patient had received corticosteroid therapy for intestinal TB many years earlier.

An examination of the patient showed a body temperature of 36.2°C, pulse rate of 76 beats/minute, and blood pressure of 146/110 mm Hg. A laboratory examination comprising routine blood and biochemical
tests showed normal urine and stool tests, and normal blood high-sensitivity C-reactive protein, albumin, and cancer antigen 125 (CA125) levels of 18.3 mg/L, 33.5 g/L, and 1083 U/mL, respectively. An axial computed tomography (CT) scan of the chest showed no obvious abnormalities (Figure 1). By contrast, CT of the abdomen showed a change in the initial segment of the descending colon, and thus neoplastic lesions could not be ruled out. An abdominal puncture drainage indicated exudate in the abdominal cavity. The adenylc deaminase level of abdominal distension was 48 U/L.

The clinical and laboratory findings, particularly the elevated blood CA125 level and CT data, suggested the possibility of colon cancer. However, the differential diagnosis also included a TB lesion. We next excluded ascites consequent to renal or cardiac causes or malnutrition, and distinguished between tumour and inflammatory diseases. We further investigated the nature of ascites, conducted a bacterial culture, and implemented a therapeutic strategy comprising blood pressure control and diuretic treatment.

A further blood evaluation on 19 December 2015 showed the following: antinuclear antibody titre of 1:100, lactate dehydrogenase level of 143 U/L, and CA724 level of 1 U/mL. Positron emission tomography CT indicated thickening and increased metabolic activity in the terminal ileum wall, suggestive of intestinal cancer. Additional thickening and increased metabolism in the mesentery, omentum, and liver capsule suggested diffuse implanted metastases. Increased metabolism was not observed in nodules in the middle left lung lobe and upper right lung lobe, suggestive

![Figure 1. Chest computed tomographic scans. The mediastinal window is shown at different times. The first computed tomographic scan of the chest shows no obvious abnormalities. The second scan shows multiple shadows, including some new lesions, in the upper lobe apex segment and posterior segment of the right lung, the middle lobe of the right lung, and the upper lobe apicoposterior segment of left lung. An increased number of peritoneal nodules can also be seen. The third scan shows an increase in the right lung shadow. The fourth scan shows an increase in the sizes of lesions in the apical right lung segment. The last scan shows that the right upper pulmonary nodules have decreased.](2978 Journal of International Medical Research 46(7))
of pulmonary metastatic neoplasms. The above-mentioned results led us to perform an ascites Thinprep cytological test as a dynamic tumour cell screen, as well as purified protein derivative and T-spot tests for TB.

The patient continued to experience abdominal distension. A laboratory examination conducted on 20 December 2015 showed negative T-spot and purified protein derivative test results and no obvious heterogenic tumour cells in an ascites Thinprep cytological test. Pathological analysis indicated that the ascites contained granulomatous nodules that comprised lymphocytes and epithelial cells, which suggested TB. Immunohistochemical analysis showed CD68 positivity and cytokeratin negativity. The patient’s family did not consent to an enhanced abdominal puncture biopsy, and the patient continued to receive albumin supplementation and diuretic therapy. The patient provided written informed consent for this report.

On 27 January 2016, the patient’s family agreed to a laparoscopic evaluation, which showed a few nodules in the abdominal wall, omentum, and mesentery, with no clear occupying lesions and a large quantity of abdominal ascites. No obvious hepatic, splenic, or gastric abnormalities were observed. The next day, a pathological examination of frozen omental sections showed a nodular hyperplastic granuloma (Figure 2). Two days later, a pathological examination of omental tissue showed *M. tuberculosis*, which led to the diagnosis of tuberculous peritonitis, tuberculous pleurisy, and intestinal TB. The patient began anti-TB treatment that comprised isoniazid (0.3 g/day, 1 time/day), rifampicin (0.45 g/day, 1 time/day, for 1 year), ethambutol (0.75 g/day, 1 time/day, for 1 year), pyrazinamide (1.5 g/day, 1 time/day, for 3 months), and prednisone (25 mg/day, 1 time/day, March 5 to April 4). In April 2016, the symptoms of cough and expectoration had disappeared. However, chest CT showed an increase in the right lung shadow to approximately 3.1 × 2.7 cm (Figure 1). In July 2016, a chest CT at the outpatient clinic revealed subpleural mass shadows in

Figure 2. Haematoxylin and eosin-stained omental tissue sample (magnification, ×100) shows a nodular hyperplastic granuloma.
the right upper lung, which showed heterogeneous enhancement with necrosis on an enhanced scan. Although anti-TB therapy gradually improved the abdominal lesions, the pulmonary lesions increased, and a tumour had not yet been ruled out. At another hospital, a pathological evaluation of a percutaneous lung biopsy identified foam cells, inflammatory cells, and double-capsuled thalli, which suggested fungal infection. The patient was readmitted to our hospital on 16 July 2016, where a laboratory examination and sputum fungal culture conducted in triplicate indicated the presence of \textit{C. neoformans}/\textit{C. gattii}. Two India ink staining tests also showed \textit{C. neoformans}/\textit{C. gattii}. An enzyme-linked immunosorbent assay for \textit{Cryptococcus} pathogen was positive, whereas the results of a G test, cerebrospinal fluid fungal culture, cerebrospinal fluid India ink stain, tumour marker (alpha-fetoprotein, carcinoembryonic antigen, CA199, and prostate-specific antigen) analyses, and HIV test were all negative. Accordingly, we made the diagnosis of pulmonary cryptococcosis and prescribed voriconazole (0.2 g twice daily) to treat the fungal infection.

On 25 July 2016, a chest CT showed increases in the sizes of lesions in the apical right lung segment to approximately $5.3 \times 4.2 \times 4.9$ cm (Figure 1). A cranial magnetic resonance imaging scan that was performed at another hospital showed abnormally enhanced nodules in the right frontal brain (Figure 3a). Taken together with the history of the case, these findings suggested a \textit{Cryptococcus} neoplasm. During the induction therapy stage (1 August to 5 October), the patient was treated with liposomal amphotericin B (50 mg/day, 1 time/day, 11 August to 12 September; 75 mg/day, 1 time/day, 13 to 21 September; 100 mg/day, 1 time/day, 22 September to 5 October) and flucytosine (7 g/day, 4 times/day, 1 to 18 August). On 29 August, a chest CT scan showed that the lung nodules had decreased to $3.3 \times 3.9 \times 3.8$ cm. During the consolidation stage, we administered voriconazole treatment (0.3 g twice daily, 6 October 2016 to 6 April 2017, for 6 months). On 24 October, a chest CT showed that the right upper pulmonary nodules had decreased to $2.7 \times 2.1 \times 2.6$ cm (Figure 1). On 25 October, the abnormal magnetic

![Figure 3](image.png)

**Figure 3.** Cranial magnetic resonance images obtained on (a) 25 July 2016, and (b) 25 October 2016. (a) Abnormally enhanced nodules in the right frontal brain can be seen. (b) The abnormal magnetic resonance imaging signal in the right frontal lobe is not visible.
resonance imaging signal in the right frontal lobe was no longer visible (Figure 3b). These findings led us to conclude that the current treatment was effective and the patient was discharged from the hospital. To date, the general condition of the patient is healthy and no further symptoms of cough and expectoration have been experienced.

Discussion

According to the World Health Organization estimates, the incidence of TB has been declining since 2004. However, the prevalence of TB remains high in tropical countries. Currently, *M. tuberculosis*, the aetiological agent of TB, is the second most deadly cause of communicable diseases among patients with HIV/acquired immunodeficiency syndrome (AIDS). The annual incidence of cryptococcosis, which is caused by members of the *C. neoformans/C. gattii* complex family, is almost 1,000,000 infections (with 625,000 mortalities) among patients with HIV/AIDS worldwide. In addition to HIV/AIDS, patients with underlying diseases, such as kidney diseases, blood diseases, diabetes mellitus, and cancer, are also susceptible to TB or cryptococcosis, as are those receiving treatment with corticosteroids or other immunosuppressive agents.

According to a Chinese database, the number of reported cryptococcosis cases has increased from 1985 to 2010. Furthermore, approximately 10% of global TB cases in 2014 occurred in mainland China. The patient in this study lived on a farm for many years, where he raised doves, cats, dogs, and other animals. Accordingly, he may have acquired *C. neoformans* and *M. tuberculosis* infections by inhaling aerosolized particles from the environment. Primary TB is considered a latent infection, and accordingly, tuberculous pleurisy and peritonitis in this patient may have resulted from reactivation of a latent pulmonary infection. The process of cryptococcosis onset includes primary progression, reactivation, and reinfection. Clinical studies have indicated development of cryptococcosis in patients after a latency infection period of months to years.

Although our patient was not otherwise immunosuppressed, his history of corticosteroid treatment for intestinal TB may have played a vital role in the development of a TB and cryptococcosis co-infection. T-cell-mediated immunity plays an important role in the host defence against *C. neoformans/C. gattii* complex and *M. tuberculosis*. *M. tuberculosis* can alter these cellular immune processes and is thus recognized as a potential factor in the development of cryptococcosis. Furthermore, cryptococcosis can inhibit tumour necrosis factor-α secretion and induce TB reactivation or promote infection. Corticosteroids are well-known suppressors of T-cell function and inflammatory cytokine (e.g., tumour necrosis factor-α, interleukin-6, interleukin-8) production. Such changes in immune function may explain why this patient developed cryptococcosis after corticosteroid treatment.

Conclusions

Most previous reports of TB/cryptococcosis co-infection in mainland China were published in Chinese journals, and no clinical guidelines have been proposed for treating these co-infection cases. Accordingly, this case of TB/cryptococcosis co-infection with atypical symptoms in a patient from mainland China should enhance our awareness and understanding of this condition. The lack of representative symptoms in our patient likely resulted in a delayed diagnosis and severe underestimation of the co-infection status. Therefore, we emphasize the importance of a positive *M. tuberculosis* culture for diagnosing TB, and a positive
Cryptococcus culture and positive India ink staining test for diagnosing cryptococcosis.

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Declaration of conflicting interest
The author(s) declare that there is no conflict of interest.

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