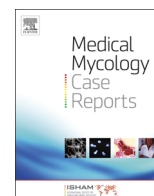




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Miliary pulmonary cryptococcosis

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ABSTRACT

A 32-year-old HIV positive male presents with fevers and a non-productive cough. Initial X-ray and subsequent computerised tomography of the chest shows a bilateral miliary pattern of pulmonary infiltration highly suggestive of disseminated tuberculosis. However subsequent results were consistent with disseminated cryptococcosis, including pulmonary involvement, with cryptococcus identified on transbronchial tissue biopsy, and on blood and cerebrospinal fluid cultures.

Imaging features of pulmonary cryptococcosis are generally of well-defined pleural-based nodules and less commonly alveolar infiltrates, lymphadenopathy, pleural effusions or cavitating lesions. Miliary pulmonary infiltrates are an exceptionally rare presentation.

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1. Introduction

Most cases of pulmonary cryptococcosis in the immunocompromised patient are due to reactivation of latent infection, although primary infection is also postulated. Clinical manifestations are broad and can range from asymptomatic pneumonia to respiratory failure [1]. Those who are immunocompromised are more likely to present with coexisting extrapulmonary disease [2].

The most common finding on CT imaging from two case series for pulmonary cryptococcosis in the immunocompetent host is that of solitary or scanty well-defined pleural based nodules, but can also include alveolar infiltrates, hilar or mediastinal lymphadenopathy, pleural effusions or cavitating lesions [3,4]. However, those with advanced HIV tend to present with more fulminant imaging findings; interstitial infiltrates found in the majority of multiple published case series, with alveolar opacities, adenopathies, cavitary lesions, and pleural effusions being less common [1,5,6].

2. Case

A 32 year old previously well male presented initially to his general practitioner with a 3-month history of cough and 3 weeks of low-grade fevers and headache. While the cough was initially productive of green sputum it was non-productive on

presentation. There was no accompanying chest pain or dyspnoea. Oral antibiotics were prescribed without improvement. Subsequent Human Immunodeficiency Virus (HIV) serology was positive with a mature Western blot, CD4 count of $12 \times 10^6/L$ [500–1650] and serum HIV viral load of 331,000 copies/ml, at which stage he was referred to hospital.

In the emergency department (Day 0) the patient looked reasonably well but was tachycardic at 120 beats per minute with a low-grade temperature of 37.5 °C and mildly decreased oxygen saturations of 97% on room air. Blood pressure was normal. Auscultation of his chest revealed generalised decreased air entry and audible adventitious sounds. Perianal ulcers, suggestive of herpes simplex infection, were noted in addition to one small skin lesion of the left leg with an appearance consistent with Kaposi's sarcoma. The rest of the physical examination was non-contributory.

The patient was born in Ireland but lived in New Zealand for approximately 2 years, before moving to Australia 3 years prior to this presentation. He was residing in Sydney and had travelled only to urban centres in eastern Australia. In the 4 months preceding this presentation he also travelled to both the eastern and western seaboard of the USA, visiting San Francisco, Los Angeles and New York, but of note there was no travel outside major urban areas. He alleged that he had a negative HIV test for immigration purposes 3 years prior to presentation but confirmation of this was not available. There was no other medical history of note, including no history of tuberculosis exposure, viral hepatitis or sexually transmitted infections. The patient was a single homosexual male with no history of intravenous drug use.

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Initial investigations revealed a lymphopenia of $0.3 \times 10^9/L$ [1.0–4.0], consistent with the diagnosis of advanced HIV infection, and a mildly elevated C-reactive protein of 18 mg/L [0–5]. Initial blood cultures were negative. Chest X-ray (CXR) (Fig. 1) showed a miliary pattern of infiltration throughout both lung fields and a possible left hilar lesion, but no focal consolidation or pleural effusions. Subsequent (Day +1) computerised topography (CT) (Fig. 2) identified a focal cavitating lesion at the left hilum. An induced sputum procedure (Day +2) was unsuccessful so it was decided that the patient undergo bronchoscopy with bronchoalveolar lavage (BAL) (Day +5). In the interim serum cryptococcal antigen (Cryptococcal Antigen Latex Agglutination System (CALAS), Median Bioscience, USA) was reported as strongly positive at a titre of 1/8192, and the patient was commenced on oral fluconazole (400 mg twice daily).

Transbronchial tissue biopsy taken during bronchoscopy demonstrated cryptococcus on India ink staining. The Giemsa stain on the BAL revealed large numbers of encapsulated yeast-like bodies and the mucicarmine stain was highly suggestive of

cryptococcus. *Cryptococcus neoformans* was subsequently isolated from blood cultures, but not from the BAL or tissue culture, although the patient had received 3 days of fluconazole treatment prior to bronchoscopy. Despite the classic miliary pattern on imaging of the chest no acid-fast bacilli were identified on the tissue specimen or the BAL and Polymerase Chain Reaction (PCR) for *Mycobacterium tuberculosis* on the latter was negative. An interferon gamma release assay (Quantiferon gold, Qiagen, Australia) for *M. tuberculosis* was also negative, with a normal mitogen response. *Pneumocystis jirovecii* was not detected on the lavage sample. Serology for syphilis and toxoplasma was also negative.

By this stage (Day+5) the patient was also reporting intermittent diplopia. Fundoscopic examination revealed cryptococcal-related multifocal choroiditis. Magnetic Resonance Imaging (MRI) of the brain demonstrated maxillary sinusitis but no features of meningo-encephalitis or any intra-cerebral lesions. Subsequent lumbar puncture (Day+6) showed a mildly elevated opening pressure of 19 cm H₂O [9–18]. Cryptococcus was seen on India ink staining of the cerebrospinal fluid (CSF) with a cryptococcal antigen titre of 1/128 and was subsequently cultured. Other CSF findings were a mildly raised white cell count of 12 cells/ μ L [< 5], lymphocyte-predominant, normal glucose of 2.6 mmol/L [2.0–4.0] and an elevated protein of 771 mg/L [200–400]. PCR for herpes simplex, varicella zoster and cytomegalovirus was negative.

Given the presence of cryptococcal meningitis the patient was commenced on 2 weeks of induction therapy with liposomal amphotericin (265 mg daily) and flucytosine (1.5 g six-hourly) changing to consolidation therapy (Day+20) with oral fluconazole (400 mg twice daily). Repeat CT imaging of the chest at that stage (Day+21) demonstrated persisting miliary features, albeit with improvement. Prolonged mycobacterial cultures on both blood and BAL fluid remained negative. Over the following months our patient made a full recovery and was subsequently commenced on antiretroviral therapy with good immune reconstitution and no further opportunistic infections.

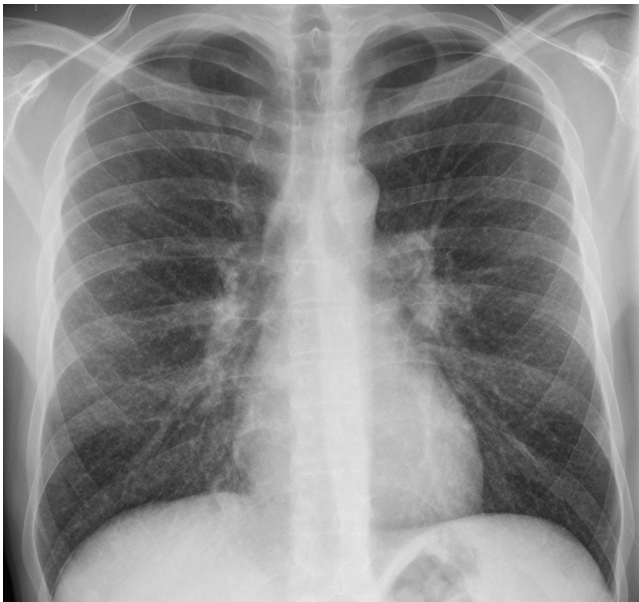


Fig. 1. CXR reveals bilateral miliary pulmonary infiltrates.



Fig. 2. CT confirms presence of miliary infiltrates.

3. Discussion

A miliary pattern of infiltration is a highly unusual presentation of pulmonary cryptococcosis and none of the patients in the previously mentioned case series [1,3–6] were reported as presenting in this manner, even those who were immunocompromised. Indeed, we are aware of only two previous reports of pulmonary cryptococcosis presenting in such a miliary pattern.

The first was that of a 71-year-old male with advanced non-Hodgkin's lymphoma, undergoing treatment with chemotherapy and corticosteroids [7]. He developed fever and dyspnoea, with miliary features on CXR and was empirically treated with antituberculous agents. He subsequently died of cardiorespiratory failure with post-mortem findings of disseminated cryptococcosis. The second case involved a 33-year-old male, with an 8 year history of HIV infection, a CD4 count of 40 and previous pneumocystis pneumonia [8]. He presented with fever, cough and dyspnoea and, again, miliary pattern infiltration on CXR. *C. neoformans* was isolated from bronchoalveolar lavage, and blood cultures and CSF. He was treated with 3 weeks of amphotericin B, with subsequent clinical improvement.

Our case illustrates the importance of considering a broad range of differential diagnoses of respiratory infections in immunocompromised patients, even when faced with imaging findings that are classically associated with other pathogens commonly found in this cohort and, additionally, the value of pursuing a microbiological diagnosis in the management of such patients.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

Nothing to declare.

References

- [1] Meyohas MC, Roux P, Bollens D, et al. Pulmonary cryptococcosis: localized and disseminated infections in 27 patients with AIDS. *Clin Infect Dis* 1995 Sep;21(3):628–33.
- [2] Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. *Ann Intern Med* 1981;94(5):611–6(May).
- [3] Lindell RM, Hartman TE, Nadrous HF, et al. Pulmonary cryptococcosis: CT findings in immunocompetent patients. *Radiology* 2005;236(1):326.
- [4] Fox DL, Müller NL. Pulmonary cryptococcosis in immunocompetent patients: CT findings in 12 patients. *AJR Am J Roentgenol* 2005;185(3):622.
- [5] Cameron ML, Bartlett JA, Gallis HA, et al. Manifestations of pulmonary cryptococcosis in patients with acquired immunodeficiency syndrome. *Rev Infect Dis* 1991;13(1):64.
- [6] Clark RA, Greer DL, Valainis GT, et al. *Cryptococcus neoformans* pulmonary infection in HIV-1-infected patients. *J Acquir Immune Defic Syndr* 1990;3(5):480.
- [7] Amthor M, Arents B, Bartelheimer E. Cryptococcal sepsis simulating miliary tuberculosis in malignant lymphoma. *Pneumologie* 1991 Mar;45(3):110–3.
- [8] Douketis JD, Kesten S. Miliary pulmonary cryptococcosis in a patient with the acquired immunodeficiency syndrome. *Thorax* 1993 Apr;48(4):402–3.