Case Report

Pulmonary cryptococcosis misdiagnosed as smear-negative pulmonary tuberculosis with fatal consequences

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Abstract

HIV-associated pulmonary cryptococcosis is under diagnosed, and may progress to fatal meningoencephalitis. We present a case of HIV-associated pulmonary Cryptococcus neoformans infection, initially mis-diagnosed as smear-negative pulmonary TB, which progressed to fatal cryptococcal meningitis. Autopsy series suggest that pulmonary cryptococcosis is common in African AIDS patients, and, due to limited diagnostic capacity, often mis-diagnosed as smear negative TB. Serum cryptococcal antigen testing may facilitate diagnosis in such cases.

1. Introduction

HIV-associated pulmonary disease due to Cryptococcus neoformans is less frequently reported than cryptococcal meningitis, but is likely underdiagnosed. Without appropriate treatment severe pulmonary manifestations and progression to meningoencephalitis may occur, both with high mortality. We present the case of a patient with pulmonary cryptococcosis, initially misdiagnosed as smear-negative pulmonary tuberculosis, who later developed extensive lung disease and fatal cryptococcal meningoencephalitis.

2. Case report

A 27-year-old African female was admitted to the medical ward with a 3-week history of cough, dyspnea, pleuritic chest pain, fever, and night sweats. She was not complaining of headache, and a neurological assessment was unremarkable. She had developed a standard 6-month course of anti-tuberculous therapy for culture-proven pulmonary tuberculosis 8 days previously. A chest X-ray (CXR) showed bilateral diffuse nodular infiltrates with multiple cavities (Figure 1A). Sputum microscopy was negative for acid-fast bacilli and HIV testing was positive. Her CD4 count was 27 cells/µL. There was no response to amoxicillin prescribed to cover community-acquired pneumonia, and a diagnosis of smear-negative pulmonary tuberculosis was made using the World Health Organization (WHO) algorithm for the diagnosis of TB in resource-constrained, HIV-prevalent settings. The patient was commenced on standard anti-TB therapy, and discharged with a plan to commence antiretroviral therapy following 4 weeks of treatment. Sputum was sent for TB culture and drug susceptibility testing in view of concerns about drug-resistant TB; however cultures were negative.

Nineteen days later the patient presented again following three grand mal seizures. She had a 3-day history of headache and confusion, and a productive cough since discharge. There was marked neck stiffness and two molluscum-like lesions typical of cutaneous cryptococcosis on her face. A repeat CXR showed more extensive infiltrates (Figure 1B). India ink staining of the cerebrospinal fluid revealed numerous encapsulated yeasts and C. neoformans was subsequently cultured. Amphotericin B-based therapy for cryptococcal meningitis was started along with...
phenytoin, but the patient’s neurological condition worsened and she died on the second day of admission.

Post-mortem studies revealed basal meningitis and cryptococcomas in the right caudate lobe and cerebellum, with numerous cryptococci within the meninges. A cut section of the right lung showed an apical cavity and multiple foci of consolidation with a mucoid appearance (Figure 1C). Histologically these lesions consisted of massively distended alveoli filled with cryptococci (Figure 1D), with numerous cryptococcal organisms also seen in the dilated lymphatics, submucosa, and peri-bronchial tissue. There was no inflammatory response to the cryptococci, and no evidence of pulmonary tuberculosis.

3. Discussion

Pulmonary involvement in patients with HIV-associated cryptococcal meningitis is reported in up to 55% of cases, and symptoms may precede the onset of meningoencephalitis, suggesting diagnosis prior to neurological involvement may be possible. In many areas of high HIV prevalence, diagnostic capacity is limited, meaning pulmonary cryptococcosis is rarely diagnosed. In the few studies that have used bronchoscopy or induced sputum investigation in AIDS patients with respiratory symptoms, pulmonary cryptococcosis is relatively common, and is a frequent finding in autopsy series of AIDS deaths in Africa. An autopsy series of 8421 South African miners, with an estimated HIV prevalence of 24%, identified 589 cases of pulmonary cryptococcosis (overall prevalence of 7%). Ante-mortem 46.9% of these cases had a diagnosis of cryptococcal meningitis, and 1.2% had been diagnosed with pulmonary cryptococcosis. The remaining 51.9% of cases had frequently been misdiagnosed as pulmonary tuberculosis. Further evidence that suggests pulmonary cryptococcosis is often empirically treated as pulmonary tuberculosis is the finding that the commonest cause of late mortality at autopsy in a large African cohort on treatment for TB was cryptococcosism, and that cryptococcal infection has been shown to be a common cause for clinical deterioration in those taking anti-tuberculous therapy in our setting.

Our experience in a public sector referral hospital in South Africa, where 37% of patients presenting with cryptococcal meningitis have pulmonary symptoms and 15% have been diagnosed with smear-negative TB in the 3 months preceding admission with cryptococcal meningitis, suggests the diagnosis of pulmonary cryptococcosis is frequently overlooked or attributed to tuberculosis, leading in many cases to the development of cryptococcal meningoencephalitis (unpublished data). While bronchoscopy, induced sputum examination, or fungal sputum cultures are not readily accessible in resource-limited settings, existing highly sensitive and specific cryptococcal antigen detection (CRAG) tests for use on serum could easily be made available. We advocate serum CRAG screening as part of the diagnostic work-up of patients with suspected smear-negative pulmonary TB. The WHO smear-negative algorithm facilitates earlier diagnosis of TB in HIV-infected patients. However, this case
highlights the potential shortcomings of making an empiric diagnosis of TB, particularly in situations where guidelines may not be so readily applied, such as following recent completion of anti-tuberculous therapy. It is important to exclude alternative diagnoses such as pulmonary cryptococcosis.

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References