CASE REPORT

Concurrent cryptococcal meningitis and disseminated tuberculosis occurring in an immunocompetent male

Marcellin Musabende,¹ Constance Mukabatsinda,¹ Elisabeth D Riviello,^{1,2} Onyema Ogbuagu^{1,3}

¹Department of Medicine, University Teaching Hospital of Kigali, Kigali, Rwanda

²Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA

³Section of Infectious Diseases, Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence to

Dr Onyema Ogbuagu, onyema.ogbuagu@yale.edu

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SUMMARY

A 61-year-old man living in rural Rwanda presented with a 2-month history of fevers, headaches, dry cough, weight loss and confusion. A cerebrospinal fluid analysis revealed neutrophilic pleocytosis, yeast and a positive cryptococcal antigen (CrAg). An HIV antibody test was negative. The patient's cough worsened while on antifungal induction therapy with intravenous conventional amphotericin B and high-dose oral fluconazole. Computerised tomography (CT) scan of the chest showed extensive miliary infiltrates.

Bronchoalveolar lavage revealed acid-fast bacilli on smear and a positive GeneXpert test without rifampicin resistance. The patient improved with the addition of antitubercular therapy. In this case report, we describe an unusual presentation of two opportunistic infections occurring together in an HIV-negative man with no other known immunocompromising conditions. The case highlights the fact that, in disease endemic areas, multiple disseminated infections can occur in individuals without obvious immunocompromise.

BACKGROUND

Opportunistic infections such as disseminated (or miliary) tuberculosis and cryptococcal meningitis are typically seen in individuals who are immunocompromised in the setting of certain conditions: HIV infection, receipt of immunosuppressive medications, uncontrolled diabetes mellitus, active malignancy, autoimmune disorders, severe malnutrition, or extremes of age.¹ However, in endemic countries, these disease conditions have also been reported in immunocompetent individuals. For cryptococcal disease in particular, certain species such as *Cryptococcus neoformans* var *gattii* cause infections in immunocompetent hosts.²

In this case report, we describe an unusual presentation of concurrent severe opportunistic infections in a presumed immunocompetent man. The presence of an opportunistic infection in an immunocompetent patient may itself signal a predisposition to other opportunistic infections; therefore, worsening symptoms in the setting of targeted treatment for a specific condition should prompt the clinician to look for additional aetiologies.

CASE PRESENTATION

A 61-year-old man, a farmer from a southern district of Rwanda, presented to a national referral

hospital after multiple previous contacts with healthcare facilities and traditional healers. One month prior to presenting to our hospital, he engaged the services of a traditional healer for treatment of a 1-month illness with symptoms of fever, sore throat and mild cough. A traditional uvulectomy was performed but was complicated by severe haemorrhage. He was placed on augmentin and ibuprofen for an unknown duration. Two weeks later, he presented to a private clinic for ongoing fever and cough, and was prescribed an unknown antibiotic. His symptoms did not improve, and he developed a headache and generalised malaise. He went to a district hospital from which he was immediately referred to our facility.

In our emergency department, he reported ongoing fever, generalised body weakness, headache and dry cough. A chest radiograph was performed; it was of very poor penetration, but was read as normal and not repeated. He received a 5-day course of intravenous ceftriaxone 1 g administered two times a day and was discharged. He was readmitted a week later with severe headache and vomiting. A review of systems was positive for night sweats and weight loss. He had no medical or surgical history. Other than treatments received during his current illness, he was not on any long-term medications. No drug or food allergies were reported. The patient, a heterosexual male, was married with eight children. He enjoyed traditional 'banana beer' three times a week (unknown quantity) and denied tobacco use in any form. He reported no illicit drug use. He had no travel history outside Rwanda. He reported a distant history of exposure to a neighbour with suspected pulmonary tuberculosis.

On admission, he was ill-appearing with a body mass index of 23. His vital signs were: blood pressure 115/46 mm Hg, heart rate 74 bpm, respiratory rate 18 breaths per minute, temperature 36°C and oxygen saturation 97% on room air. He was alert and interactive and Glasgow coma scale score was 15 (normal). Pupils were equal and reactive to light and he had no nystagmus. He had nuchal rigidity. His neurological examination was otherwise unrevealing including absent Kernig's and Brudzinski signs. He had no conjunctival pallor and no scleral jaundice. His lungs were clear to auscultation bilaterally. His heart examination revealed a regular rate and rhythm, with no murmurs. His abdomen was soft, with no organomegaly and normoactive

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bowel sounds. Genitourinary and musculoskeletal examinations were unremarkable. He had no lymphadenopathy and no skin rash.

INVESTIGATIONS

The patient's initial laboratory investigations revealed a white cell count of $15.6 \times 10^3/\mu\text{L}$ with 85.9% neutrophils and 5.1% lymphocytes. Haemoglobin was 7.4 g/dL with mean corpuscular volume-87.6 fL; platelet count was $390\,000/\mu\text{L}$. Blood sugar was 131 mg/dL, urea 2.4 mmol/L, creatinine $54\,\mu\text{mol/L}$, aspartate aminotransferase 11.6 units/L and alanine aminotransferase 11.1 units/L. A rapid HIV 1/2 antibody test was negative (negative predictive value: 99.8%). A CT scan of the head without contrast was unrevealing, with no ventriculomegaly and no space occupying lesion seen.

DIFFERENTIAL DIAGNOSIS

The initial working diagnosis was bacterial meningitis, and the patient received intravenous cefotaxime 2 g every 8 h, and oral paracetamol as needed for fevers. However, 3 days into his hospital stay, his fevers, nuchal rigidity and headache persisted, and a lumbar puncture was performed. An opening pressure was not documented. Cerebrospinal fluid (CSF) analysis showed 20 white cell count/mm³, with 80% neutrophils and 20% lymphocytes. Yeast was noted on wet mount, Gram stain and smear were negative for bacteria and acid-fast bacilli, respectively, and a qualitative cryptococcal antigen test was positive. CSF glucose was 0.11 mmol/L (normal range 2.25–4.17 mmol/L). Protein estimation could not be performed by the lab due to lack of reagents at the time. We considered the possibility of acute HIV infection or other reason for decreased CD4 count, so we requested an HIV viral load and CD4 count. Owing to resource considerations, the hospital policy prohibited checking the viral load in an HIV-antibody negative patient; however, the CD4 count was normal at 722 cells/mm³.

TREATMENT

The patient was initiated on intravenous amphotericin deoxycholate 0.7 mg/kg daily with oral fluconazole 800 mg daily. He received intravenous hydrocortisone 100 mg daily with oral paracetamol and normal saline as pretreatment for each amphotericin dose per local treatment guidelines, which has some support in the published literature, for the purpose of decreasing drug infusion reactions.³ Cefotaxime was discontinued. We performed two additional lumbar punctures in the first week of treatment due to subjective symptom of worsening headache with concern for raised intracranial pressure, but the patient was noted to have normal opening pressures (<20 cmH₂O) on both occasions. He completed a 15-day course of induction therapy with improvement of his central nervous system (CNS) symptoms; however, his fever persisted and his cough worsened.

Further investigations and treatment:

The worsening cough and ongoing fever prompted a chest radiograph 2 weeks into the patient's hospital stay, which revealed a miliary pattern of pulmonary infiltrates. A chest CT scan with contrast revealed a similar pattern of diffuse miliary infiltrates (figure 1). A bronchoalveolar lavage (BAL) was performed and studies revealed acid-fast bacilli on smear and a positive GeneXpert test with no rifampicin resistance gene detected. Cryptococcal antigen was also positive in the BAL fluid but fungal cultures were not performed. The patient was initiated on rifampin, isoniazid, ethambutol and pyrazinamide with vitamin B6 dosed according to WHO⁴ and national

Figure 1 CT scan of the chest without contrast (axial view) showing diffuse as well as coalescent pulmonary nodules in both lung fields.

guidelines; and after completion of a 2-month course, he will receive an additional 4 months of isoniazid and rifampin under directly observed therapy (DOT), if his BAL culture confirms susceptibility of his *Mycobacterium tuberculosis* strain to the drugs. He had completed induction therapy for cryptococcal meningitis and was started on a consolidation treatment regimen of fluconazole initially dosed at 400 mg/day, but subsequently increased to 600 mg to complete an 8-week course; with a plan for an additional 6–12 months of fluconazole dosed at 300 mg/day afterwards.⁵ The latter doses are a 50% increase from the standard doses in order to compensate for the anticipated decrease in levels of fluconazole associated with rifampin induction effect on the hepatic cytochrome-P450 enzyme system.

OUTCOME AND FOLLOW-UP

After addition of antitubercular medications, the patient defervesced, and his respiratory symptoms resolved. His appetite improved and he was able to ambulate. He was discharged home on antitubercular therapy under DOT and fluconazole, with planned follow-up in 1 month.

DISCUSSION

Concurrent cryptococcal and *Mycobacterium tuberculosis* infections have been reported in HIV-infected patients.^{6–8} A history of tuberculosis may be a risk factor for development of cryptococcal meningitis in HIV-infected patients.⁹ Cases of co-infection in non-HIV-infected patients are very rare. We were able to find very few cases of concurrent tuberculosis and cryptococcal disease occurring in immunocompetent individuals in the literature.^{8 10–17} In these individuals, it may be that the presence of one disseminated infection creates or reflects an

immunosuppressed state sufficient to allow for dissemination of another.^{17 18}

In our case, we suspect that the hydrocortisone given as pre-treatment with amphotericin doses contributed to the patient's susceptibility to disseminated tuberculosis infection as steroid use results in impaired T-cell mediated immunity.¹⁹ The patient showed no clinical evidence of malnutrition, which could also be a cause of impaired immunity. It is noteworthy that a recent study in Asia identified anti-interferon- γ autoantibodies in HIV-negative patients with opportunistic infections, the discovery of which highlights the fact that we have yet to elucidate many causes of immunocompromise.²⁰

While both cryptococcal meningitis and tuberculosis are more common in HIV-infected patients, both are also endemic in Rwanda and can affect HIV-negative hosts. While there are no published data on the burden of cryptococcal disease in immunocompetent individuals in Rwanda, a study performed in Gauteng province of South Africa, a similar setting, showed that, of 1235 cases of cryptococcosis whose HIV status was known, only 4 were HIV-negative.²¹ Unlike cryptococcal meningitis, in which few patients are HIV-negative and almost all have other identifiable risk factors, tuberculosis is much more common in immunocompetent individuals. In a report from Rwanda's Ministry of Health in 2013, of the 98% of patients with tuberculosis who were tested for HIV, only 25% were positive for the virus.²²

In our case, the patient's ongoing fever and worsening cough after 2 weeks of induction therapy for cryptococcal disease were concerning for a missed process. The chest CT study with diffuse small nodules would be an unusual presentation, though not unheard of, for pulmonary cryptococcosis, which manifests more frequently as a few large peripheral nodules rather than a diffuse miliary pattern.^{23 24} In addition, the cough had worsened in spite of effective antifungal therapy. These findings prompted a secondary evaluation for another underlying illness eventually leading to the diagnosis of disseminated tuberculosis.

It is worth highlighting that the clinical presentation of tuberculosis and cryptococcal disease may differ between immunocompetent and immunocompromised individuals. For example, compared to non-HIV infected controls with tuberculosis, individuals with HIV infection and tuberculosis are more likely to have extrapulmonary disease (60% vs 28%) as well as miliary pulmonary infiltrates (60% vs 32%).²⁵ One study showed that immunocompromised individuals with pulmonary tuberculosis are more likely to have symptoms of fever or dyspnoea,²⁶ but this finding is likely to be dependent on the population studied and degree or type of immunosuppressive condition. Another study found that the natural history of tuberculosis disease is altered with faster clinical progression in immunocompromised individuals.²⁷ For cryptococcosis, HIV-infected individuals are overwhelmingly more likely to have CNS disease while immunocompetent individuals typically present with pulmonary disease.²⁸

Some experts recommend longer courses of antifungal induction therapy for non-HIV, non-transplant individuals with cryptococcal meningitis, in the order of 4–6 weeks, probably driven by concern for infection with *C. neoformans var gattii*, a species that has a predilection to form CNS cryptococcomas and responds slower to antifungal therapy.²⁹ However, we opted to limit our patient's course of amphotericin to 2 weeks due to concerns for drug toxicity, absence of mass lesions on brain imaging and quick resolution of his CNS symptoms. Another therapeutic challenge during this patient's management was potential drug–drug interactions. As we had to administer

both rifampin and fluconazole concomitantly for his infections, the dose of fluconazole was increased, as rifampin causes an induction of hepatic microsomal enzymes, which metabolises and effectively reduces its concentration.³⁰

Patient's perspective

- ▶ Translated from Kinyarwanda language into English
- ▶ "I feel a bit improved, but still have some heaviness in my legs, which causes difficulty with walking. So, I use a cane to walk, but most of the time I stay at home and rest in bed. I am still taking my tuberculosis drugs; I was told the meningitis was cured. My illness was so mysterious. I want to complete the tuberculosis treatment and see the outcome. I like the way you have cared for me until now and I would like to visit you at your home or at the hospital. Where can I read what you write about my condition?"

Learning points

- ▶ In disease endemic areas, opportunistic (and disseminated) infections can occur in individuals without an obvious cause of immunocompromise.
- ▶ 'Ockham's razor', the law of parsimony, is not always the correct framing, particularly in cases of disseminated opportunistic infections (OIs). The presence of one OI may signal the patient's susceptibility to multiple infections.
- ▶ Cryptococcal disease and tuberculosis can present with miliary pulmonary infiltrates.
- ▶ Drug–drug interactions are a significant concern with the treatment of concurrent opportunistic infections and worthy of attention.

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