Cryptococcosis with Tuberculosis: Overlooked Coinfections

Christina S Suresh, Marilyn M Ninan, Anand Zachariah[1], Joy S Michael
Departments of Clinical Microbiology and [1]Medicine, CMC, Vellore, Tamil Nadu, India

Abstract

Tuberculosis and cryptococcosis are important opportunistic pathogens causing significant morbidity and mortality in immunocompromised individuals. Concurrent infections of these two agents are rarely reported. We report five cases of culture-proven coinfection of *Mycobacterium tuberculosis* and *Cryptococcus neoformans* during inpatient admission at a tertiary care hospital in southern India between 2007 and 2019. Four patients were persons living with HIV infection and one was on immune suppression for chronic renal disease. Maintaining a high degree of clinical suspicion will ensure early diagnosis and appropriate management of coinfections in the immunocompromised individual.

Keywords: Coinfections, cryptococcosis, tuberculosis

Introduction

India continues to have a high burden of tuberculosis[1] and affects 18% of people living with human immunodeficiency virus infection, resulting in mortality of up to 23.8%.[2] Cryptococcosis is the most common cause for meningitis in this population causing 15% of acquired immunodeficiency disease-related deaths.[3] Coinfections of cryptococcosis with tuberculosis in the same specimen are reported from different parts of the world, including India.[4] These organisms have the ability to evade the host immune system, remain inside the phagocytes inducing a Th2 response, and later result in clinical disease.[5] Similarities in modes of transmission, immune response, latency, and dissemination years later increase the likelihood of concurrent infections.

This was a retrospective series carried out at a tertiary center in South India, following ethics approval from the Institutional Review Board. The electronic patient records of 190 patients with culture-confirmed cryptococcal infection from 2007 to 2019 were reviewed to identify cases that were also culture positive for *Mycobacterium tuberculosis*, in the same sample. The diagnostic criteria were culture of *M. tuberculosis* and *Cryptococcus neoformans* from the same sample.

Case Series

We describe five patients with culture-positive cryptococcosis and tuberculosis from the same sample during a single period of inpatient admission [Table 1].

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Case 1

A 32-year-old male, newly diagnosed with HIV, from Jharkhand presented with features of chronic meningitis. CD4 counts were 12 cells/ml. Cerebrospinal fluid (CSF) examination showed white blood cells 1/cumm, glucose 40 mg/dl, and protein 42 mg/dl.

Direct microscopy on the CSF sample with India Ink was negative but cryptococcal antigen testing was positive. Sabouraud's dextrose agar (SDA) yielded *C. neoformans* with brown colonies on birdseed agar. Urease test was positive. The canavanine glycine bromothymol blue (CGB) media was negative. Culture and susceptibility testing on the CSF sample revealed a pansusceptible *M. tuberculosis*. The patient was started on highly active antiretroviral therapy (HAART) regimen along with fluconazole and cotrimoxazole prophylaxis. On review, he was started on antituberculous treatment and asked to follow-up at his hometown.

Case 2

A 48-year-old male from Tamil Nadu, known HIV positive on HAART for 1 year, was brought to casualty with features

Address for correspondence: Dr. Marilyn M Ninan, Department of Clinical Microbiology, CMC, Vellore, Tamil Nadu, India.
E-mail: marilyn@cmcvellore.ac.in

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Table 1: Summary of case presentations

	Case 1	Case 2	Case 3	Case 4	Case 5
Place	Jharkhand	Tamil Nadu	Andhra Pradesh	Assam	West Bengal
Age, gender	32, male	48, male	40, male	39, male	40, male
Co-morbid illness	HIV	HIV	HIV	HIV	Glomerulonephritis
Clinical presentation	Chronic meningitis	Chronic meningitis	Chronic meningitis	Fever of unknown origin	Fever of unknown origin
Sample	CSF	Brain tissue	Bone marrow	CSF	Bone marrow
Mycology smear	Negative	Positive	Positive	Positive	Negative
Acid-fast stain	Negative	Positive	Negative	Negative	Negative
Outcome	Discharged	Died	DAMA	Died	DAMA

CSF: Cerebrospinal fluid, DAMA: Discharged against medical advice, HIV: Human Immunodeficiency Virus

of chronic meningitis. CD4 count was 152 cells/ml. The preliminary diagnosis considered was cerebral tuberculosis, based on the computed tomography scan, which showed multiple thin-walled ring lesions with perilesional edema and hydrocephalus. Brain tissue biopsy sent to the microbiology laboratory showed Gram-positive budding spherical yeast and acid-fast bacilli by auramine O stain. The tissue was culture positive for both *C. neoformans* and *M. tuberculosis* which was susceptible to rifampicin, isoniazid, pyrazinamide, and ethambutol. While in the ward, the patient developed herniation of brain tissue and expired.

Case 3

A known HIV-positive 40-year-old male on HAART from Andhra Pradesh presented with features of chronic meningitis. CD4 count was 3 cells/ml. CSF examination showed 21 cells/cumm with 60% polymorphs and 40% lymphocytes. CSF glucose was 21 mg/dl and protein 71 mg/dl. Direct microscopy with India Ink showed capsulated budding yeasts. Fungal culture on SDA, brown colonies of birdseed agar, and a positive urease test confirmed *C. neoformans*, and the CGB was negative. The patient was started on amphotericin for cryptococcal infection. During therapy, fever did not subside and he continued to deteriorate clinically. Bone marrow examination yielded *C. neoformans* and *M. tuberculosis* though direct microscopy was negative. He was discharged against medical advice (DAMA) before cultures were reported so appropriate therapy could not be initiated.

Case 4

A 39-year-old male from Assam admitted with fever of unknown origin and weight loss was found to be HIV positive with a CD4 count of 68 cells/ml. India ink was positive for capsulated budding spherical yeasts. Fungal culture confirmed *C. neoformans* with brown colonies on birdseed agar that was urease positive. CGB was negative. Culture for mycobacteria was positive with drug susceptibility showing resistance to first-line antituberculous agents. He continued to deteriorate while in the ward and expired.

Case 5

A 40-year-old male from West Bengal on immune suppression with azathioprine and steroids for diffuse proliferative and segmental sclerosing glomerulonephritis presented with 1-month history of fever. He was HIV negative and had been advised renal transplant and was on renal replacement therapy with dialysis. On the evaluation of prolonged fever without a focus, bone marrow examination was performed which showed acid-fast bacilli on direct microscopy. India Ink preparation was negative for cryptococcal infection. Fungal culture yielded *C. neoformans* on SDA with brown colonies on birdseed agar and a positive urease test. CGB was negative. Mycobacterial culture on LJ medium grew *M. tuberculosis.* The patient was DAMA before culture reports were available. No further details were available regarding treatment and outcome.

Discussion

Cryptococcosis and tuberculosis are opportunistic infections in immunocompromised individuals. Treatment is prolonged in both cases with significant cost of therapy and adverse drug effects leading to poor compliance and increased antimicrobial resistance. A combination of both these infections delays diagnosis leading to increased mortality and morbidity in resource-poor settings.

All patients [Table 1] were male, between 30 and 50 years, from the southern and eastern parts of India. Four were persons living with HIV. Presenting features included chronic meningitis (60%) and fever of unknown origin. One patient was initiated on appropriate treatment and discharged to be followed up as outpatient, two died in the ward despite appropriate management while two others were DAMA after treatment was initiated.

The central nervous system has been described as the most common site of coinfection in China[6] whereas a pediatric study showed lungs as the most commonly infected organ.[7] The immunosuppressed host, such as in advanced HIV infection, is an exception to the clinical teaching that a patient is entitled to only one disease. Since TB meningitis and cryptococcosis are the most common CNS opportunistic infections, coinfection of these is known to occur. This case series demonstrates this association and the importance of sending a complete diagnostic workup. The availability of newer rapid diagnostic methods such as lateral flow assay (LFA) for screening of cryptococcosis and cartridge-based nucleic acid amplification tests for tuberculosis can prevent delay in diagnosis and associated mortality and morbidity.[8,9] Delays

in diagnosis, such as described from previous literature,[10] can be circumvented with the implementation of such tests.

In the context of wide availability of ART today, cryptococcal meningitis is infrequent and presentations less familiar. However, patients with undiagnosed HIV infection can present with cryptococcal meningitis and disseminated cryptococcosis as the indicator illness. This is the first case series of cryptococcal and tuberculosis coinfections described from India, with culture-confirmed disease of both organisms in all cases and provides valuable learning for clinicians and microbiologists for the diagnosis of combined infection with TB and cryptococcus. Sequence typing was not carried out as part of this study, remaining a limitation, and will be a part of future work.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient or legal guardian has given his consent for images and other clinical information to be reported in the journal. The patient or guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Research quality and ethics statement

The authors followed applicable EQUATOR Network ("http://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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