

## Case Series

# Cryptoccal meningitis in non-HIV, non-organ transplant diabetic patients

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### ABSTRACT

Cryptococcosis is an important opportunistic fungal infection and also cause of death due to central nervous system disease among patients with human immunodeficiency virus worldwide. Most of the cases occur in immunocompromised patients like HIV infected people, people with organ transplants and on immunosuppressants. Nowadays there is increase in cases of cryptoccal meningitis among diabetic patients. Current case series includes cryptococcal meningitis among diabetic patients after ruling out of other immunocompromised states.

**Keywords:** Cryptoccal meningitis, Diabetic patients, HIV, Organ transplant

### INTRODUCTION

Cryptococcosis is an important opportunistic fungal infection causing an estimated 1 million cases and 625,000 deaths per year due to central nervous system (CNS) disease among patients with human immunodeficiency virus worldwide.<sup>1</sup>

The vast majority of cases globally were caused by *Cryptococcus neoformans*, compared to the more geographically restricted *Cryptococcus gattii*. Although cryptococcosis is most often associated with HIV infection, in many centers, especially in more developed countries, the majority of cases occur among non-HIV infected individuals including transplant recipients; patients who are receiving immunosuppressive agents such as glucocorticosteroids, cytotoxic chemotherapy, TNF-alpha inhibitors, and other disease modifying agents; and a heterogeneous group of patients with underlying disorders such as organ failure syndromes, innate immunologic problems, common variable immunodeficiency and hematologic disorders. Moreover, in many centres, up to 20% of cases of cryptococcosis

occur in phenotypically “normal” or otherwise clinically non-immunocompromised patients.<sup>2</sup> Individuals with uncontrolled diabetics are prone to infections due to numerous factors as the glucose rich blood serves as an excellent media for growth.

### CASE SERIES

#### Case 1

An 87 years old male patient presented to the emergency room with history of fever, mild degree, intermittent since 8 days and altered sensorium since 3 days. History of type 2 diabetes and hypertension since 8 years on regular medications.

On examination GRBS was 361 mg/dl, patient was in altered sensorium. CNS examination revealed positive signs of meningeal, neuroinfection. CT brain showed no significant abnormality. Planned lumbar puncture and CSF analysis showed cells-8 all were lymphocytes, protien-24, glucose-43 and cryptococcal antigen and India ink preparation for cryptococci were positive. HIV was negative, RFT, LFT were within normal limit.

HBA1C was 12.8, immunodeficiency was thus ruled out. Patient was started on amphotericin B injection (0.7 mg/kg) and flucanazole 1200 mg/day. In between patient developed renal impairment and amphotericin B was stopped. Patient expired on day 7 of admission due to sepsis and septic shock.

### Case 2

A 77 years old male patient presented to the emergency room with history of fever and headache since 10 days, history of altered sensorium since 2 days, history of vomiting was present. History of hypertension was reported since 4 years and patient was on regular medication, Patient was also newly detected to have type 2 diabetes mellitus 3 days back, not on treatment.

On examination GRBS was 423mg/dl. CNS examination revealed positive signs of meningeal neuroinfection. CT brain was normal and CSF analysis showed cells-6 predominantly lymphocytes, protein-42, glucose-48, cryptococcal antigen and India ink preparation for cryptococci were positive. HIV was negative. HBA1C was 12.2, immunodeficiency was thus ruled out. Patient was started on amphotericin B injection (0.7 mg/kg) and flucanazole 1200 mg/day. Repeat CSF analysis was done after 2 weeks, CSF culture showed no growth. Patient was discharged with oral flucanazole.

### Case 3

A 64 years old male patient presented to the emergency room with history of fever and headache since 4 days and altered sensorium since 1 day. History of one episode of GTCS was present. History of type 2 diabetes and hypertension was noted and patient since 12 years was on regular medications.

On examination GRBS was 383 mg/dl. CNS examination revealed positive signs of meningeal neuroinfection. CT brain was normal and CSF analysis showed 42 cells, predominantly lymphocytes, protein-42, glucose-34, cryptococcal antigen and India ink preparation were positive. HIV was negative, HBA1C was 13, immunodeficiency was thus ruled out. Patient was given amphotericin B injection (0.7 mg/kg) and flucanazole 1200 mg/day. Repeat CSF analysis done after 2 weeks CSF culture showed no growth. Patient was discharged with oral flucanazole.

### Case 4

A 60 years old female patient presented to the emergency room with history of fever and headache since 8 days. History of 4 episodes of GTCS was present. History of type 2 diabetes and hypertension was noted and patient since 8 years was on regular medications.

On examination GRBS was 413 mg/dl. CNS examination revealed positive signs of meningeal neuroinfection. CT

brain was normal and CSF analysis showed 64 cells, predominantly lymphocytes, protein-52, glucose-30, cryptococcal antigen and india ink preparation were positive. HIV was negative, HBA1C was 12.8, immunodeficiency was thus ruled out. Patient was started on amphotericin B injection (0.7 mg/kg) and flucanazole 1200 mg/day. Repeat CSF analysis done after 2 weeks CSF culture showed no growth. Patient was discharged with oral flucanazole.

## DISCUSSION

*C. neoformans* meningitis is relatively uncommon among non-HIV infected person. Kiertiburanakul *et al* showed that conditions associated with *Cryptococcal* infection in non-HIV individual included immunosuppressive drug treatment (41%), systemic lupus erythematosus (16%), malignancies (16%), and diabetes mellitus (14%).<sup>3</sup>

Although relatively uncommon, current case series has shown that diabetes mellitus remains an important cause for *C. neoformans* meningitis. In diabetic patients, persistent hyperglycemic environment favors immune dysfunction, leading to dysfunction of neutrophil activity (chemotaxis and phagocytosis), reduced T lymphocyte response and humoral immunity and depression of antioxidant system.<sup>4</sup> Fungal infection in diabetes mainly occurs due to neutrophil dysfunction. Studies have revealed that a deficiency of the complement C4 component in diabetes mellitus is associated with polymorphonuclear dysfunction and reduced cytokine response.<sup>5,6</sup>

*C. neoformans* is the most common cause of fungal meningitis in HIV and non-HIV individuals.<sup>7</sup> It is thought to be acquired through inhaling soil contaminated with bird droppings. Two species, transmitted by inhalation, are the principal human pathogens: *C. neoformans* and *Cryptococcus gattii*.<sup>8</sup> *C. neoformans* causes cryptococcal meningitis in immunocompromised patients, whereas *C. gattii* is associated with illness in immunocompetent individuals.<sup>9</sup> Studies have demonstrated lymphocyte dysfunction and proliferative function of CD4, T lymphocytes and their response to antigens are impaired when the hba1c is  $\geq 8\%$ .<sup>10,11</sup> In current case series HBA1C was higher that might have caused lymphocyte dysfunction and impaired proliferation of CD4 lymphocyte and finally low CD4 count.

## CONCLUSION

Cryptococcal meningitis should be considered in the differential diagnosis for all individuals, including non-HIV patients, presenting with chronic headache, altered sensorium in the presence of fever. Non-HIV, non-transplant recipient requires a longer duration of combination therapy than HIV infected individuals. Diabetic patients are at increased risk of opportunistic infection similar to HIV patients. Strict hyperglycemic

control and longer parenteral antifungal should be a goal to prevent mortality.

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