



Case report

A case of *Cryptococcus gattii* infection in South Carolina: A possible challenge to known endemicity



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ABSTRACT

In the United States, *C. gattii* is considered to be endemic to the Pacific Northwest and although uncommon, additional cases have been documented in other regions including the Southeastern United States. While it has been hypothesized in the past that *C. gattii* may be endemic to the Southeastern United States, there remains a paucity of evidence. Here, we present a patient with no history of HIV/AIDS and no organ transplant and document the course of his disease and presentation. There were no adverse long-term neurological outcomes in this patient and the combination of steroid use, antifungal agents, and cerebrospinal fluid drainage resulted in his discharge from the hospital after 12 days. This patient's subacute presentation with vague neurological symptoms highlights the importance of understanding the treatment of rare causes of meningitis.

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Background

Cryptococcosis in the United States is usually attributed to *Cryptococcus neoformans* in immunocompromised patients, such as patients with HIV/AIDS, patients receiving immunosuppressive drugs like chemotherapy, or patients who have received solid organ transplant [1]. However, in recent years, there have been cases where species of the recently revised Cryptococcal species complexes, such as *C. gattii* and *C. deuterogattii*, have been attributed to illness in immunocompetent patients [1].

C. neoformans is a largely opportunistic pathogen that is particularly devastating in the demographic encompassing patients with AIDS and conditions leading to immunocompromise [2]. A number of virulence factors have been identified in *C. neoformans* including *rim101* which has a role in inducing inflammation as well as inducing adaptations to pH changes [3]. *C. neoformans* has been shown to have a higher susceptibility to antifungal azole agents than *C. gattii* and *C. neoformans*.⁴ *C.*

deuterogattii has been isolated in Australia, as well as Denmark, Germany, and Japan, with an increase in the number of cases reported after international travel [5]. Across the species complex, *C. deuterogattii* possesses the largest cell size and the greatest tolerance to high-heat conditions [6]. Additionally, *C. deuterogattii* has been shown to be the least susceptible of cryptococcus species to antifungal azoles [4].

C. gattii, is considered to be endemic to a number of regions throughout the world including the Pacific Northwest of the United States, parts of South America, Oceania, and possibly the Southeastern United States [7]. It shares many virulence factors with *C. neoformans*, including the same polysaccharide capsule structure and superoxide dismutase [1]. Most cases have involved immunocompetent patients with a history of travel to an endemic region [1].

Infection with Cryptococcal spores occurs by inhalation [8]. Symptoms can vary with the severity of infection from asymptomatic to pneumonia, as well as infection of the eyes, the skin, and the CNS causing meningitis and meningoencephalitis [8]. A protease produced by *C. gattii* allows for the formation of large inflammatory Cryptococcomas that could potentially require long-term treatment with antifungal therapy and even neurosurgical intervention [9].

Treatment options vary depending on the patient and are divided into three subgroups: HIV patients, organ transplant patients, and non-HIV/non-transplant patients [10]. Various

Abbreviations: HIV/AIDS, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome; U.S., United States; CDC, Centers for Disease Control; COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastroesophageal Reflux Disease; RPR, Rapid Plasma Reagin; Mg, milligrams; Kg, kilogram; IV, Intravenous.

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combinations and formulations of amphotericin B, flucytosine, and fluconazole are the most commonly used medications based on these subgroups in order to achieve appropriate therapy during induction, consolidation, and maintenance [10,11].

C. gattii infections have been documented throughout the world in diverse locations including Thailand, Australia, Papua New Guinea, the U.S. (United States), Columbia, Brazil, and other Latin American nations [12–16]. Within the United States specifically, cases have been documented in Alabama, California, Florida, Georgia, Hawaii, Idaho, Michigan, Montana, New Mexico, North Carolina, Oregon, Rhode Island, South Carolina, Utah, Washington [7,17–20]. A map depicted in Fig. 2 displays these states.

While a previous case was accounted for in the state of South Carolina by Lockhart et. al. in a CDC (Centers for Disease Control) report, this is the first case report documenting *C. gattii* infection in South Carolina to date. We present a case of *Cryptococcus gattii* meningitis in a non-HIV/AIDS and non-transplant patient in the state of South Carolina [7].

Case report

A 43-year-old male patient with a recent history of multiple recurrent pneumonias initially presented to the emergency department with a chief complaint of persistent headache and blurry vision. His past medical history included COPD, GERD, hemochromatosis, and lupus. The headache was described as being frontal initially and then becoming retroorbital bilaterally while gradually spreading throughout his head. He reported intermittent photophobia, but denied fever, chills, nausea, and vomiting. No focal neurological deficits were present and no signs of meningismus were detected. However, he was found to have a subacute case of cryptococcal meningitis at that time. Following this finding, treatment with 800 mg fluconazole daily was initiated and he was deemed safe to return home. He was discharged with a combination of hydrocodone-acetaminophen, promethazine, and dexamethasone to manage his nausea and headaches after treatments with 100 % oxygen and sumatriptan failed to yield improvement.

After multiple repeat visits to the emergency department for chronic headache and intractable nausea/vomiting as well as reported confusion and word-finding difficulty, neurology was

consulted, and imaging of the head was ordered. CT revealed asymmetric effacement of occipital sulci, while MRI revealed multiple non-specific lesions, and diffuse leptomeningeal enhancement (Fig. 1).

Initial vitals revealed that the patient was afebrile and tachycardic, with no electrolyte abnormalities on initial labs. Lumbar puncture performed on the day of admission revealed opening pressure 32 cm, closing pressure 17 cm, white blood cell count of 12, red blood cell count of 427, glucose 4, and protein 137. Cryptococcal antigen was also positive, and titers were >1:2560. On CBC, his white blood cell count was 5.3, with 44.8 % neutrophils and 40.8 % lymphocytes. CD4 count from previous hospitalization was 559. Immunological workup revealed normal levels of Immunoglobulin A, Immunoglobulin E, Immunoglobulin G, and Immunoglobulin M. Further, the patient was HIV negative and had a negative RPR (Rapid Plasma Reagin). Imaging of the chest taken revealed multiple opacities consistent with pneumonia.

Given his high intracranial pressure, neurosurgery was consulted on initial admission and serial lumbar punctures were recommended to prevent further elevation of pressure.

On Day 2 of admission, fluconazole was discontinued and therapy with 5 mg/kg of amphotericin B QD and 2 g flucytosine q6hours was initiated. A lumbar drain was also placed by interventional radiology.

On Day 4 of admission, follow-up revealed opening pressure 22 cm (initial was 32 cm) and repeat cerebrospinal fluid cell count drawn from the lumbar drain revealed white blood cell count 107, red blood cell count 5, glucose 82, and protein 104.9. The lumbar drain was removed on hospital day 8 and the patient was monitored for 4 days before discharge on hospital day 12.

On discharge, amphotericin B and fluconazole were prescribed for 42 days pending further evaluation on follow-up [21]. At 2-week follow-up, the Infectious Disease physician recommended readmission to the hospital, which the patient refused. In lieu of admission, outpatient treatment was initiated with amphotericin B 5 mg/kg (milligrams/kilogram) daily, and fluconazole 800 mg daily. On 1-month follow-up, the patient's therapy was de-escalated to fluconazole 800 mg daily and his symptoms had not progressed further.

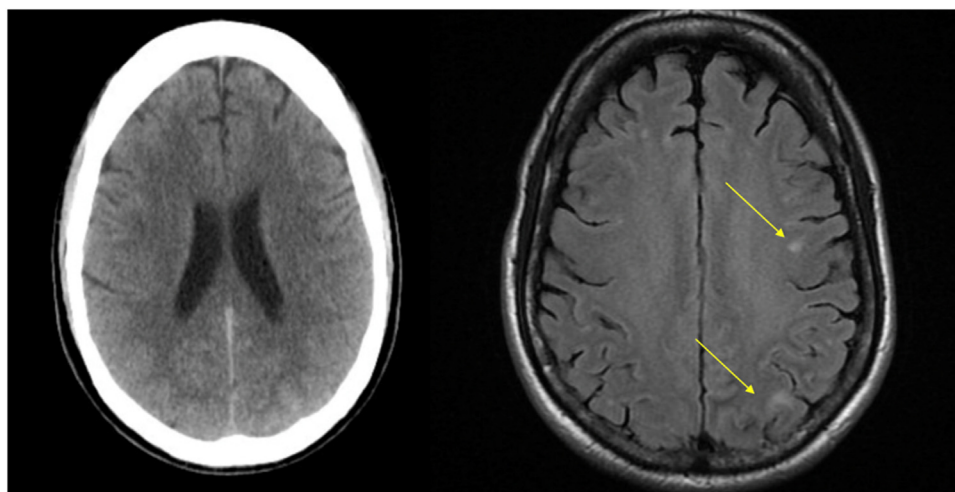


Image 1: CT Head with Contrast

Image 2: MRI Brain T2 Flair

Fig. 1. This figure contains CT and MRI imaging of the patient's head, showing leptomeningeal enhancement consistent with meningitis and nonspecific lesions.

Possible new development in endemicity

Of interest is the patient's denial of recent travel outside the southeastern United States, since previously, most documented cases in the region entailed a connection with California or the Pacific Northwest [20]. Given that the Pacific Northwest has seen the paramount of cases in the U.S., the mode of transmission to this patient raises questions about the communicability of this disease, particularly given the other states in which *C. gattii* infection has been documented. There has been documentation of multiple cases in which other patients with *C. gattii* in the southeastern United States have had no contact with regions considered to be endemic such as the Pacific Northwest or Oceania [24]. This case combined with previous cases lends further support to the hypothesis that *C. gattii* is endemic the southeastern United States (Fig. 2) [24].

Evidence for steroid use as treatment

One randomized, double-blind, control study on the treatment of patients with HIV/AIDS associated cryptococcal meningitis demonstrated that treatment with steroids in these patients was harmful [25]. Of note is the immunocompromised status of these patients and the lack of generalizability to an immunocompetent population. Given the inflammation that follows central nervous system infections, it has been suggested that the use of steroids, particularly after clearance of infection has occurred, may be beneficial [26]. Currently, the ongoing study "Cryptococcus Infection Network in Non-Human Immunodeficiency Virus Cohort (CINCH)" has released preliminary results that indicate positive outcomes in immunocompetent patients treated with steroids relative to those treated without [26,27]. Another study reviewed the outcomes of 4 immunocompetent patients treated with dexamethasone and determined that 3 of 4 had positive outcomes [28]. Although some evidence for steroid use in non-HIV/AIDS and populations exists, the current paucity of conclusive studies on patients without and the contraindication in patients with HIV/AIDS guided the clinical decision to avoid steroids. This patient's initial subacute course and subsequent chronic infection treated with long term fluconazole provide an example of successful chronic treatment without the long-term use of steroids.

Conclusion

With over 1,000,000 cases and 600,000 deaths estimated due to cryptococcosis worldwide, the global burden of *Cryptococcus* is significant [2]. Thus, understanding this pathogen is critical from both a worldwide standpoint and from the standpoint of public health in the United States, where it is *C. gattii* is considered to be endemic to at least the Pacific Northwest [20]. Given that this is the first case report to describe infection with this pathogen in the state of South Carolina, it is important for the infectious disease community within the state and the region to consider *C. gattii* as an emerging pathogen that may now be endemic to the southeastern United States. The patient described in this case report remained positive for the antigen for at least 4 months after his initial diagnosis. Although neurological cryptococcosis can result in rapid increases in intracranial pressure, the patient continued to only complain of headaches in the outpatient setting that did not increase in severity. With regard to the use of steroids in cryptococcal meningitis, there is a paucity of published data on the use of steroids in the treatment in patients without HIV/AIDS or organ transplant and thus steroids were avoided. This case gives anecdotal evidence for the use of treatments currently supported by literature and for avoidance of dexamethasone until evidence

for its use in non-HIV/AIDS and non-transplant populations is put forward.

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Author contribution

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Declaration of Competing Interest

The authors report no declarations of interest.

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