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Case Report

Concurrent Pulmonary and Cerebellar *Cryptococcus Gattii* Cryptococcoma in an Apparently Immunocompetent Patient in Florida

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Cryptococcus infection is caused by one of the two species, *Cryptococcus neoformans,* or the less common *Cryptococcus gattii.* While *Cryptococcus neoformans* commonly infects the immunocompromised population, *Cryptococcus gattii* has been seen more frequently in immunocompetent patients. Many seemingly immunocompetent patients, however, may have unidentified underlying immunodeficiencies. Recently, antigranulocyte-macrophage colony-stimulating (GM-CSF) antibodies have been identified as a risk factor for cryptococcosis. We describe a case of disseminated *Cryptococcus gattii* infection in a seemingly immunocompetent young man, who is found to have anti-GM-CSF antibodies.

1. Introduction

Cryptococcus is a genus of opportunistic pathogenic yeasts consisting of two primary species, *Cryptococcus neoformans (C. neoformans)* and *Cryptococcus gattii (C. gattii)*. In the worldwide immunocompromised population, there are upwards of one million cases of cryptococcal infections per year, largely affecting AIDS patients with significant associated mortality due to meningitis as well as pulmonary, bone, skin, and brain infection [1, 2]. Of the two primary species, *C. neoformans* is estimated to cause 95% of infections with up to 5% caused by *C. gattii* [1]. Additionally, while *C. neoformans* infects both immunocompromised and immunocompetent hosts, *C. gattii* has been shown to mostly infect apparently immunocompetent hosts, who may have undetected immunodeficiencies or immunocompromised states [3]. In apparently immunocompetent hosts, *C. gattii* infections commonly present as cryptococcomas, progressing from the lungs to the central nervous system through hematogenous spread.

C. neoformans is a widely distributed, global pathogen, whereas *C. gattii* has historically been documented in tropical and subtropical regions including California, Hawaii, Brazil, Australia, Southeast Asia, and Central Africa, as well as relatively recent outbreaks in British Columbia of Canada and the Pacific Northwest of United States [1, 3–5]. Several scattered cases have also been reported in North Carolina, Rhode Island, New Mexico, Michigan, Georgia, Southern California, and Montana as well as 2 cases in Florida [4, 6–8].

We present the case of 20-year-old male in Florida with worsening headache, found to have *C. gattii* pulmonary and cerebellar cryptococcomas.

2. Clinical Presentation and Case History

A 20-year-old African American male with a past medical history of asthma presented to the emergency department with a one-month history of progressively worsening occipital headaches, nausea, and vomiting. The patient had no recent travel outside of Florida. Social history was significant

for employment as a construction worker, ½ pack per day tobacco use, and occasional marijuana use. Vitals showed temperature of 36.8 °C, blood pressure of 128/78 mm Hg, heart rate of 54 beats per minute, and respiratory rate of 17 breaths per minute. Physical exam was remarkable only for slight right end point dysmetria on finger-nose-finger testing and slower rapid finger tapping on the right side. Laboratory evaluation was notable for a white blood cell count of 17,100 cells/mm^3.

CT imaging of the brain revealed a 3.7 cm × 3.6 cm peripherally enhancing right cerebellar mass and smaller 2.0 cm × 1.6 cm peripherally enhancing right middle cerebellar peduncle mass. MRI with and without contrast was performed for further evaluation which showed multifocal posterior fossa masses with additional findings of early hydrocephalus and compression of the cerebral aqueduct (Figure 1 and Figure 2). Neurosurgical consultation was obtained, with leading differential diagnosis of glial tissue neoplasm.

Stereotactic-guided suboccipital craniotomy with microsurgical resection was completed, with frozen tissue sectioning revealing cryptococcoma (Figure 3). Fungal culture grew *Cryptococcus gattii*.

Further investigation revealed no history of residency or travel outside of Florida, no history of incarceration, and no intravenous drug use. Sexual history was significant for five prior female sexual partners without any genitourinary symptoms. Prior HIV testing was reportedly negative.

The patient was started on IV amphotericin B and flucytosine. Further workup with chest X-ray was completed revealing a left hilar mass with follow-up Chest CT revealing a 7.0 cm × 5.0 cm cavitary mass of the left upper lobe lingula consistent with a mycetoma (Figure 4). Bronchoscopy with bronchoalveolar lavage and biopsy was performed, confirming cryptococcus infection of the left lingula. After monitoring for response to antifungal therapy, the patient underwent video-assisted thoracoscopic surgery with minithoracotomy resulting in left upper lobectomy. Both CT and biopsy showed no evidence of pulmonary alveolar proteinosis.

Evaluation of immunocompetence revealed negative HIV antibody and PCR testing, mildly depressed C3 and C4, and normal IgA, IgG, and IgM levels. White blood cell count was normal with lymphopenia, including a CD4 count of 120 cells/mm^3 and a CD4/CD8 ratio of 0.4. Further workup to ascertain a cause of the CD4 T cell lymphopenia was performed showing negative respiratory viral panel, acute hepatitis panel, CMV, EBV, HHV 6, and HTLV I/II. Repeat CD4 testing showed values of 520 cells/mm^3 and 674 cells/mm^3, consistent with returning to normal range. The patient's plasma was tested through the National Institute of Allergy and Infectious Diseases (NIAID) for anti-granulocyte-macrophage colony-stimulating antibodies (anti-GM-CSF antibodies). Specifically, our patient's plasma at 1 : 100 dilution exhibited GM-CSF binding activity measured as fluorescence intensity in an assay developed at NIH (patient's fluorescent intensity: 12,428; normal range: less than 718). In a separate assay, healthy donor peripheral blood monocytes were cultured with the patient's plasma.

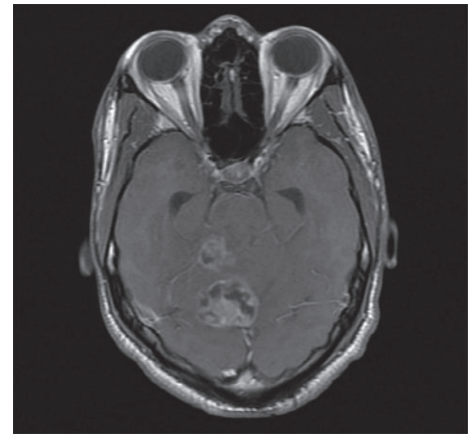

Figure 1: Magnetic resonance imaging of the brain revealing cryptococcal lesions in the cerebellum.

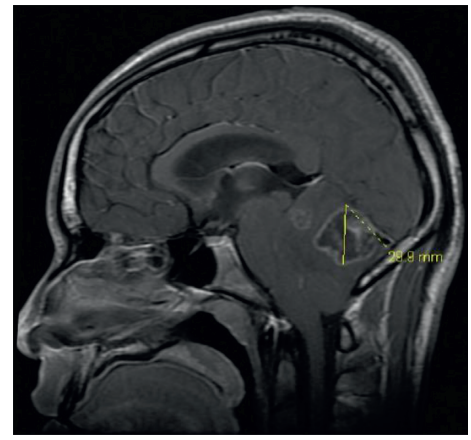

Figure 2: Magnetic resonance imaging revealing cryptococcal lesion in the cerebellum.

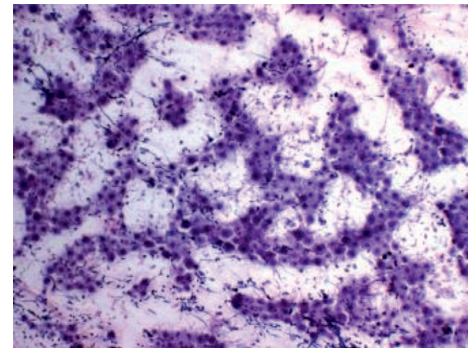

Figure 3: Frozen section of the brain mass revealing cryptococcoma.

Following stimulation with 10 ng/ml GM-CSF, monocytes were stained intracellularly for phosphorylated signal transducer and activation of transcription 5 (pSTAT5). Data were acquired by flow cytometry. The patient's plasma prevented GM-CSF-induced STAT5 phosphorylation, when compared to normal plasma. Detailed protocol has been published by Rosen et al. [9].

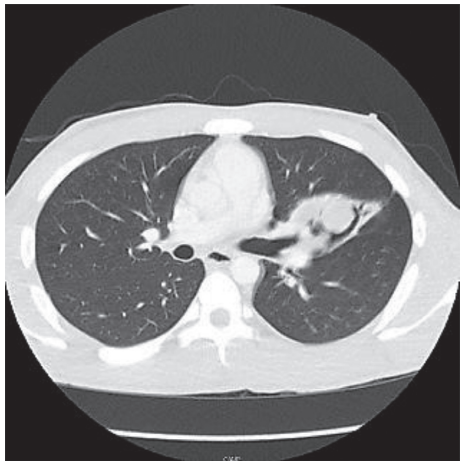

Figure 4: Computed tomography scan of the chest showing cavitary cystic mass of the lingula.

The patient was treated with liposomal amphotericin B with the addition of flucytosine for 4 weeks of induction therapy. Fluconazole was initiated at discharge as a consolidation and maintenance therapy with plan to continue for at least one year. The patient was ultimately transferred to a hospital closer to his home for rehabilitation and completion of IV antifungal medications and was lost to follow-up after giving permission to document his case.

3. Discussion

Cryptococcus gattii accounts for under 5% of *Cryptococcus* infections, although true incidence might be higher since some medical centers do not differentiate between *C. neoformance* vs. *C. gattii*. *C. gattii* has historically been associated with endemicity in tropical and subtropical regions in Southeast Asia, Australia, Brazil, and central Africa, with recent outbreaks in the Pacific Northwest of the United States and British Columbia of Canada [1, 3–5]. Of importance to the case presented, at least 2 previous cases of *C. gattii* infection in apparently immunocompetent patients in Florida have been reported in 2011 and 2015 [4, 6]. In these cases, travel to the Pacific Northwest had been ruled out implying a locally acquired infection, similar to our case which also occurred in 2015, indicating potential endemicity in the Southeastern United States.

In cases of *C. gattii* infection, the most common route of infection is respiratory inhalation of organisms, establishing a primary infection in the lungs [1]. The initial infection is typically asymptomatic and contained alveolar macrophages which recruit T cells to form granulomatous inflammation. It is hypothesized that if the immune system becomes suppressed, the infection can disseminate throughout the body, particularly to the central nervous system (CNS) [1]. Though CNS involvement has been documented more frequently in *C. neoformans*, *C. gattii* has more predilection to form cryptococcomas as opposed to meningitis and meningoencephalitis seen with *C. neoformans* infection [1, 3].

Although cases of *C. gattii* infection have been reported in HIV patients with low CD4 T-cell counts in Southern California and Southwestern Georgia [7, 8], most *C. gattii* infection occur in apparently immunocompetent host. In non-HIV patients, several conditions including corticosteroid use, idiopathic CD4 T-cell leukopenia, certain malignancies, diabetes mellitus, renal disease, organ transplant, and immunoglobulin deficiencies have been implicated as risk factors for *Cryptococcus gattii* infection [3]. More recently, IgG anti-GM-CSF antibodies have been associated with *C. gattii* infection in otherwise immunocompetent individuals [10].

In the presented case, the patient had a history of asthma and tobacco use and was employed as a construction worker. He endorsed the presence of eucalyptus trees in his backyard, which may account for his exposure risk to *C. gattii.* Positive testing for anti-GM-CSF antibodies in the patient's serum demonstrates consistency with previous reviews detailing the connection of *C. gattii* infection with increased anti-GM-CSF titers and is the likely origin of susceptibility to this pathogen. Specifically, anti-GM-CSF antibodies have been shown to inhibit macrophages, neutrophils, dendritic cells, and Th1-type mediated cellular immunity, possibly allowing increased susceptibility to primary infection and more likely permitting reactivation of previously contained infection when anti-GM-CSF antibodies are produced [10]. This is a more probable etiology than idiopathic CD4 leukopenia for our patient, as his CD4 count recovered to normal levels during the course of treatment, indicating a transient leukopenia.

Cryptococcus gatii infection is often seen in apparently immunocompetent patients. Newly identified immunodeficiencies, such as anti-GM-CSF antibodies as found in our case, have been identified that may predispose seemingly immunocompetent patients to these infections. In these patients, HIV testing, CD4 enumeration, and anti-GM-CSF testing should be obtained to evaluate for these less-known underlying risk factors.

Data Availability

All significant clinical and laboratory findings are included within the article.

Consent

Consent to document and distribute this case report was obtained from the patient directly.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

All authors had a role in writing the manuscript.

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References

[1] E. K. Maziarz and J. R. Perfect, "Cryptococcosis," *Infectious Disease Clinics of North America*, vol. 30, no. 1, pp. 179–206, 2016.

[2] B. J. Park, K. A. Wannemuehler, B. J. Marston, N. Govender, P. G. Pappas, and T. M. Chiller, "Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS," *AIDS*, vol. 23, no. 4, pp. 525–530, 2009.

[3] L. MacDougall, M. Fyfe, M. Romney, M. Starr, and E. Galanis, "Risk factors forCryptococcus gattiiInfection, British Columbia, Canada," *Emerging Infectious Diseases*, vol. 17, no. 2, pp. 193–199, 2011.

[4] R. Kunadharaju, U. Choe, J. R. Harris, S. R. Lockhart, and J. N. Greene, "Cryptococcus gattii, Florida, USA, 2011," *Emerging Infectious Diseases*, vol. 19, no. 3, pp. 519–521, 2013.

[5] P. G. Pappas, "Cryptococcal infections in non-HIV-infected patients," *Transactions of the American Clinical and Climatological Association*, vol. 124, pp. 61–79, 2013.

[6] A. V. Tiro, D. J. Springer, R. Irby et al., "A case of cryptococcus gattii in Western Florida," *Infectious Diseases in Clinical Practice*, vol. 23, no. 2, pp. 105–108, 2015.

[7] S. Chaturvedi, M. Dyavaiah, R. A. Larsen, and V. Chaturvedi, "Cryptococcus gattiiin AIDS patients, Southern California," *Emerging Infectious Diseases*, vol. 11, no. 11, pp. 1686–1692, 2005.

[8] K. T. Bruner, C. Franco-Paredes, A. F. Henao-Martínez, G. M. Steele, and D. B. Chastain, "Cryptococcus gattii complex infections in HIV-infected patients, Southeastern United States," *Emerging Infectious Diseases*, vol. 24, no. 11, pp. 1998–2002, 2018.

[9] L. B. Rosen, A. F. Freeman, L. M. Yang et al., "Anti-GM-CSF autoantibodies in patients with cryptococcal meningitis," *The Journal of Immunology*, vol. 190, no. 8, pp. 3959–3966, 2013.

[10] T. Saijo, J. Chen, S. C.-A. Chen et al., "Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by Cryptococcus gattii in otherwise immunocompetent patients," *mBio*, vol. 5, no. 2, pp. e00912–14, 2014.