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ID TEACHING CASES

A Fatal Fungal Infection: *Cryptococcus gattii* (VGI) Meningitis in Texas

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Cryptococcus gattii is an underrecognized cause of meningitis, especially in nonendemic regions. This report details *C gattii* disease progression from admission to autopsy in an otherwise healthy 40-year-old male in Texas. It brings awareness to an often unsuspected organism that can cause severe infection requiring early recognition and treatment in immunocompetent individuals.

Keywords. cryptococcoma; *Cryptococcus gattii*; meningitis; VGI.

CASE PRESENTATION

A 40-year-old male presented to the hospital with new-onset uncontrolled seizures. He was unresponsive when emergency medical services arrived and was consequently intubated, sedated, and brought to our institution's emergency department (ED). He was initially diagnosed with status epilepticus, treated with anticonvulsants, and admitted to the neurological critical care unit.

The patient had no significant past medical history. He lived and worked in swimming pool maintenance in Hardin County, Texas, and had not traveled outside of the state. Five months before admission, he experienced progressively worsening migraines refractory to pharmacologic therapy. These were accompanied by nausea, vomiting, intermittent neck stiffness, and decreased appetite with a 30-pound unintentional weight loss. Eight days before admission, he presented to an outside hospital complaining of severe headaches, photophobia, and neck and back pain. He sustained a 10-minute episode of slurred speech, tremors, drooling, and left facial droop. After imaging returned negative, the symptoms were attributed to migraine headache and he was discharged home.

During the workup in our ED, noncontrast computed tomography (CT) imaging of his head and spine was unremarkable. Laboratory evaluation revealed an elevated white blood cell (WBC) count (12.9×10^9/L; range, 4.5 to 11.0×10^9/L). An electroencephalogram showed moderate to severe diffuse slowing only partially explained by sedative medication. Lumbar puncture (LP) demonstrated mildly elevated opening pressure at 30 cmH_2O (range, 6–25 cmH_2O), low glucose (<20 mg/dL; range, 50–80 mg/dL), elevated protein (230 mg/dL; range, 15–60 mg/dL), and 39 WBCs/dL with the following differential: 63% segmented neutrophils (range, 0%–7%), 26% lymphocytes (range, 28%–96%), 10% macrophages (range, 16%–56%), 1% eosinophils (range, 0%–1%). Vancomycin and piperacillin-tazobactam were administered empirically.

Gram stain (Figure 1A) and India Ink stain (for educational and capsule visualization purposes only) (Figure 1B) of the cerebrospinal fluid (CSF) demonstrated encapsulated, variably sized yeast cells suggestive of *Cryptococcus* species. The BioFire FilmArray Meningitis/Encephalitis Panel (Salt Lake City, UT) performed on the CSF specimen was positive for *Cryptococcus neoformans/Cryptococcus gattii*. CrAg LFA (IMMY, Norman, OK) cryptococcal antigen (Ag) tests were positive on both CSF and serum, and titers were determined by Enzyme Immuno Assays with 1:122 and 1:95, respectively (ARUP Laboratories, Salt Lake City, UT). Empiric antibiotics were promptly exchanged with intravenous amphotericin B (4 mg/kg per day) and flucytosine (100 mg//kg per day) on hospital day (HD) 1. Cerebrospinal fluid cultures grew *C gattii* (Figure 1C), which was identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry with 99% confidence (bioMérieux, Inc., Hazelwood, MO). The isolate produced the characteristic blue color on L-canavanine, glycine, 2-bromothymol blue (CGB) agar, which corroborated *C gattii* identification (Figure 1D). Multilocus sequence typing at 8 unlinked genomic loci (*ITS*, *CAP59*, *GEF1*, *LAC1*, *PLB1*, *RPB2*, *SOD1*, *TEF1*) revealed that the genotype was VGI (Supplementary Figure 1).

The patient remained unresponsive after withdrawal of sedatives and was noted to have worsening fevers, shivering, and neck stiffness. Thoracic CT identified a focus of left lung consolidation and bronchoalveolar lavage was performed. Infectious diseases consultants recommended the continuation

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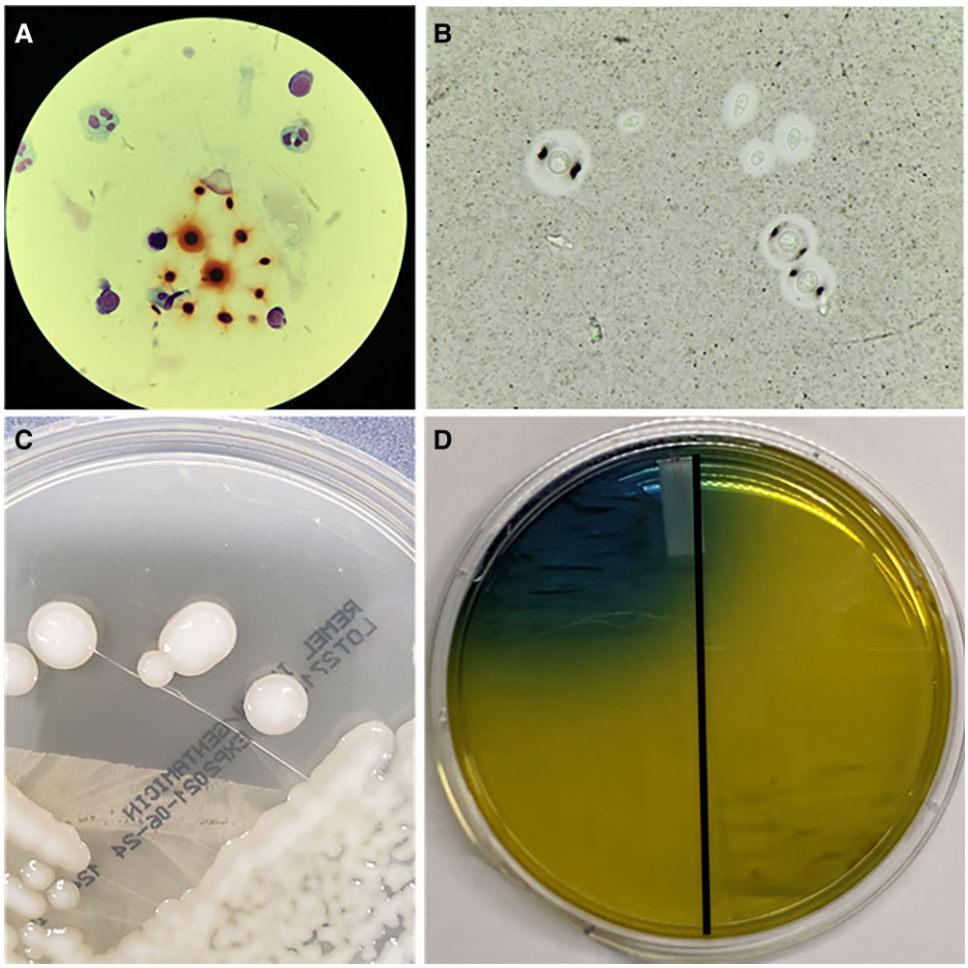

Figure 1. Microscopic and macroscopic pictures of *Cryptococcus gattii*. (A) Gram stain of cerebrospinal fluid (CSF). (B) India Ink stain of CSF. (C) Creamy, white colonies growing on IMA agar. (D) The characteristic diffuse blue pigment seen with *C gattii* on CGB agar (left) in contrast with nonpigmented *Cryptococcus neoformans* (right).

of antifungal therapy, serial LP, and a thorough evaluation of the patient's immune status. The LP was repeated 4 more times, each with opening pressures of >55 cmH_2O with persistently elevated protein, decreased glucose, and elevated leukocyte counts. Despite an extensive workup, there was no evidence of immunocompromised state demonstrated by the following: (1) the negative human immunodeficiency virus (HIV) 1/2 Ag-antibody (Ab), hepatitis A/B/C panel, QuantiFERON-TB Gold, alpha-1-antitrypsin, antimitochondrial Ab, and antinuclear Ab assays; (2) immunoglobulin (Ig) panel with normal IgA and only mildly decreased IgG and IgM; (3) normal CD4/CD8 ratio with mildly decreased absolute lymphocyte count and absence of lymphoproliferation or leukemia; and (4) normal CSF angiotensin-converting enzyme. Although reduced absolute CD4 (164 cells/μL [range, 410–1590 cells/μL] %CD4 [52, range 31–60]) and absolute CD8 (65 cells/μL [range, 190–1140 cells/μL], %CD8 [20; range, 12–41]) counts and reduced IgG (550 mg/dL; range, 636–1600 mg/dL) and IgM (21 mg/dL; range, 56–352 mg/dL) were measured on HD 2 and HD 3, respectively, it is well known that lymphopenia develops in settings of severe infection and sepsis [1]. Chromosomal analysis of his bone marrow revealed a normal male chromosomal complement with no abnormal clones detected (ARUP Laboratories).

Serial magnetic resonance imaging (MRI) revealed symmetric cortical and subcortical diffusion restriction of the bilateral cerebral hemispheres, leptomeningeal enhancement, hemorrhagic transformation of the left posterior parietal lobe, and focal areas of restricted diffusion in the right upper cervical spinal cord (Figure 2). Throughout the 14-day hospital course, the patient remained unable to follow commands. His neurological status decompensated from eye-opening to purposeful withdrawal from pain and thereafter to abnormal decerebrate posturing and compromise of brainstem reflexes. After discussing the prognosis with his family, he was discharged to inpatient hospice and died on HD 14.

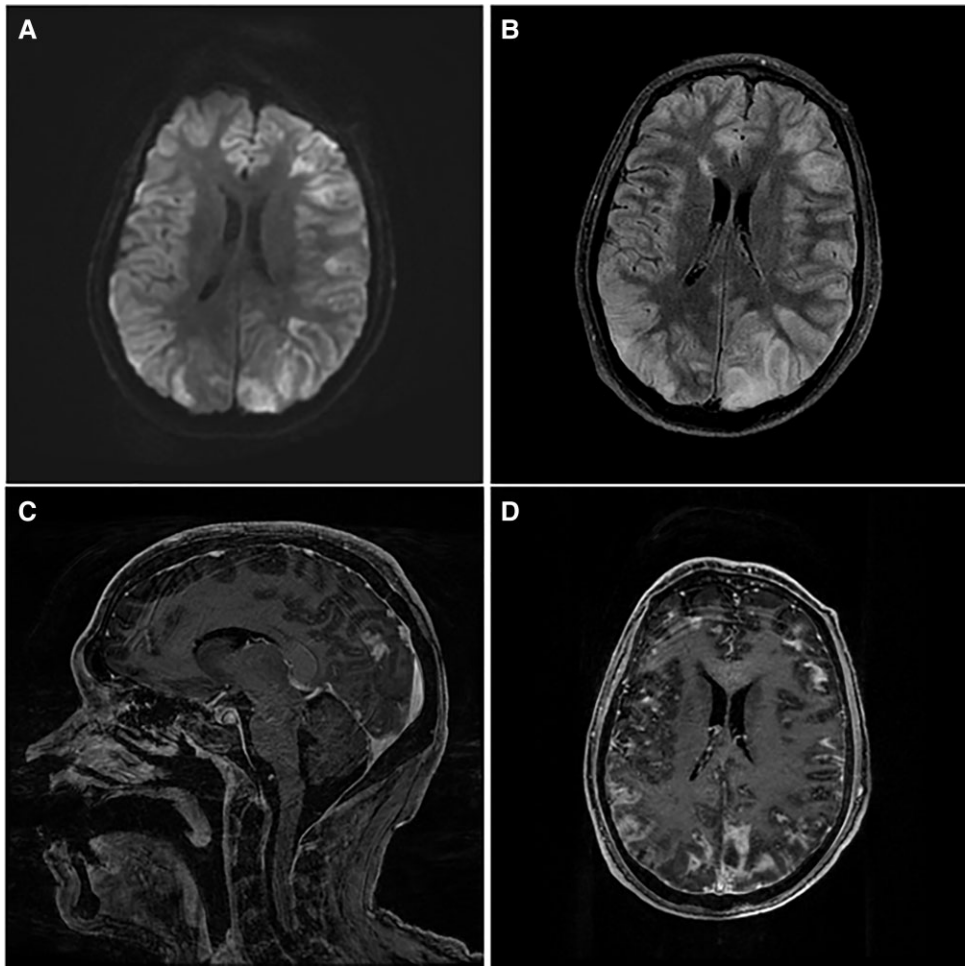

Figure 2. Magnetic resonance imaging (MRI) brain imaging revealed extensive parenchymal involvement with both vasogenic and cytotoxic edema in both cortex and white matter. (A) Diffusion-weighted imaging shows extensive changes secondary to cytotoxic edema in gray matter extending into the white matter in cerebral hemispheres. (B) T2-weighted-fluid-attenuated inversion recovery shows extensive gray and white matter inflammatory vasogenic edema in bilateral cerebral hemispheres. (C and D) MRI T1-weighted postcontrast sequences show the white signal of the contrast enhancement of leptomeningeal lining, indicating active inflammation (C, sagittal; D, axial).

A complete autopsy was performed under infectious precautions. Significant findings at autopsy included extensive granulomatous meningitis involving the brain, spinal cord, and posterior pituitary, with numerous cryptococcal organisms (Figure 3A and B). No intraparenchymal microorganisms were identified in the brain, but there were diffuse bilateral cerebral cortical infarcts with hemorrhage in the left posterior parieto-occipital region. A small infarct was identified in the cervical spinal cord, correlating with MRI findings. In addition, there was a large cryptococcoma in the upper lobe of the left lung (5 cm) comprising a partially encapsulated area of necrosis admixed with pools of mucin containing numerous cryptococcal organisms (Figure 3C and D). In addition, rare cryptococcal organisms were diffusely present throughout bilateral lungs. The cause of death was determined to be from complications of disseminated cryptococcosis with cryptococcal meningitis.

PATIENT CONSENT

Written consent was obtained from the family and the study design conforms to all standards.

EPIDEMIOLOGY AND GENOTYPES

Cryptococcus neoformans and *C gattii* independently evolved an estimated 30–40 million years ago [2]. Believed to be a primary pathogen and not limited to opportunistic infections in immunocompromised hosts [2], *C gattii* was reported to be endemic only in tropical and subtropical climatic zones such as Australia, Brazil, Southern and Southeast Asia, Mexico, Southern California, and countries in central Africa, until the outbreak in British Columbia, Canada in 1996 [3, 4]. Since then, *C gattii* has emerged in other areas of North America, with the majority of cases reported in Washington state, Oregon, and Northern California [5, 6].

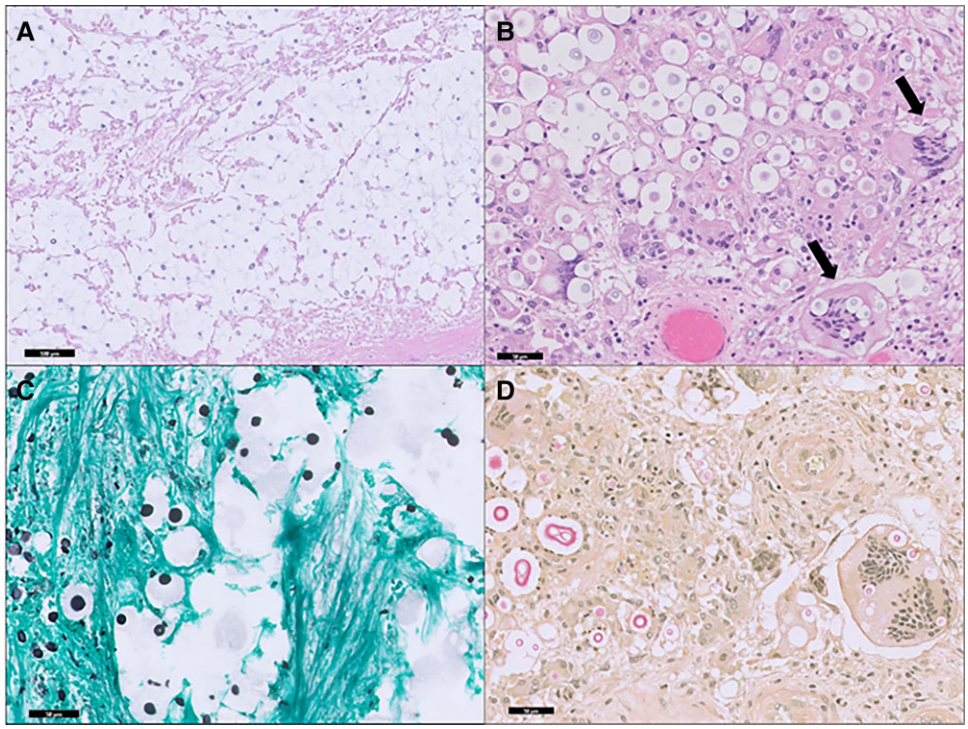

Figure 3. Histopathological features of *Cryptococcus gattii*. (A) Hematoxylin and eosin (H&E)-stained histologic section of cryptococcoma in the lung (H&E, 100×; scale bar = 100 μ). (B) Granulomatous meningitis with giant cells (arrows) engulfing cryptococcal organisms (H&E, 200×; scale bar = 50 μ). (C) Grocott methenamine silver (GMS) stain shows cryptococcal organisms in the lung (GMS, 200×; scale bar = 50 μ). (D) Mucicarmine stain highlights the capsule of the yeast forms in the meninges (mucicarmine, 200×; scale bar = 50 μ).

Cryptococcus gattii is divided into 4 lineages—VGI, VGII, VGIII, and VGIV—according to the International Society for Human and Animal Mycology (ISHAM) [2]. In 2019, a new lineage, named VGV was discovered in environmental samples from the Central Miombo Woodlands of Zambia, Africa [7]. The predominant genotype of the isolates from the environment and infected humans and animals in the Pacific Northwest of the United States (US PNW) is VGII, whereas VGIII is more often found in Southern California [5, 8]. The distribution of the molecular subtypes in the US PNW is as follows: VGIIa (50%), VGIIc (32%), VGIIb (10%), VGI (5%), and VGIII (3%) [9]. Outside of the US PNW, the molecular subtypes in the United States have been identified as VGIII (43%), VGI (42%), and VGII (15%) [6]. We now report a VGI case in Texas.

Cryptococcal infections are believed to be acquired by the inhalation of fungal cells from the environment, and *C gattii* has been isolated from several types of trees, soil, air, and water [3, 9, 10]. Upon inhalation, the yeasts travel through the respiratory system to the terminal alveoli where they reproduce, enter the lymph nodes and bloodstream, and disseminate to other organs, predominantly to the central nervous system [5, 11, 12]. Many *C gattii* cases have been reported in the US PNW area since 1996, but there are only 14 reported cases in the southern United States: 8 in Georgia (VGI, 6; VGIII, 2), 2 in Florida (VGI, 1; VGII, 1), 1 in Alabama (VGI), and 3 in New Mexico (VGI, 1; VGIII, 2) [6, 13]. Similar to our patient, there was no known relevant travel history in many of these cases, and the isolates were genetically different from those found in the endemic region of the US PNW, indicating that they were likely locally acquired. Genotype-dependent differences within the *C gattii* species complex help characterize pathogenesis and virulence. For example, VGI, VGII, and VGIII affect immunocompetent hosts more commonly than VGIV [5]. Data have shown that VGII causes severe lung disease and death, usually without dissemination and central nervous system (CNS) involvement, whereas VGI usually causes CNS disease with concurrent lung involvement [5].

In addition, antifungal susceptibility varies among genotypes. In a study assessing the antifungal susceptibility profiles of 350 *C gattii* isolates from clinical, environmental, and veterinary sources, VGII isolates had significantly higher geometric mean minimum inhibitory concentrations (MICs) than VGI isolates for the following antifungal drugs: amphotericin B, fluconazole, itraconazole, voriconazole, and isavuconazole [14]. In addition, clinical VGII isolates had a significantly higher geometric mean MIC than clinical VGI isolates for flucytosine [14]. Fluconazole and flucytosine had the lowest levels of activities against the *C gattii* strains, while isavuconazole,

posaconazole, and voriconazole maintained in vitro activity regardless of genotype [14].

CLINICAL MANIFESTATIONS

Cryptococcus gatti infections present primarily in individuals with no known immune deficiencies, whereas *C neoformans* preferentially infects immunocompromised individuals with most infections occurring in patients with HIV/acquired immune deficiency syndrome [15, 16]. Although HIV is a predisposing risk factor for *C gattii* infection, steroid use, chronic lung, liver and kidney diseases, malignancy, and solid organ transplant have also been shown to increase risk [10, 17]. Although pathophysiology is similar in both *C gattii* and *C neoformans* infections, patients infected with *C gattii* tend to form cryptococcomas in the lungs and brain, have increased neurological morbidity, and respond more slowly to antifungal drugs than those infected with *C neoformans* [15, 18].

Furthermore, a study by Hu et al [19] reported that immunocompetent patients diagnosed with pulmonary cryptococcosis were at a younger age than infected immunocompromised patients. However, cavitation was less likely to occur in immunocompetent pulmonary cryptococcosis patients [20]. Similar to pulmonary cryptococcosis, cryptococcal meningitis presents in a younger population in the immunocompetent group as well [12]. Headache, fever, vomiting, and meningeal irritation were the common clinical manifestations reported for both immunocompromised and immunocompetent patients with cryptococcal meningitis. However, immunocompetent patients presented with more visual and auditory symptoms than immunocompromised patients, suggesting an increased inflammatory response and intracranial pressure in the brain of immunocompetent patients [12]. These features were consistent with the clinical presentations of our patient.

DIAGNOSIS AND TREATMENT

Because *C gattii* primarily infects otherwise healthy patients with no known predisposing risk factors, and symptoms evolve slowly along an indolent course, these patients tend to wait longer to seek medical treatment and often present with advanced neurological symptoms [15]. This impedes early recognition and treatment initiation, making rapid diagnosis of utmost importance.

Current guidelines recommend antigen testing as the initial diagnostic tests in the setting of cryptococcosis [21]. However, not all cryptococcal antigen tests are reliable. It is important to utilize tests with a broad range of reactivity to reduce genotype bias and increase sensitivity [22]. Even so, cryptococcal antigen tests can be accurate and rapid diagnostic tools [23]. Several studies have shown excellent sensitivity (93%–100%) and specificity (94%–100%) with serum and CSF, especially in patients with disseminated cryptococcosis [21, 24]. Multiplex PCR syndromic panels are currently available for the rapid detection of *C neoformans/C gattii* in CSF, but they do not differentiate between the 2 species [25]. Gram stain and culture remain diagnostic gold standards [21] and are required to isolate the organism for subsequent susceptibility testing.

For the initial management of invasive cryptococcal disease, including disseminated, severe pulmonary, and/or CNS infections, an amphotericin-based treatment strategy remains the therapeutic mainstay, with flucytosine as an adjunct [26]. Serial lumbar punctures are critically important to alleviate elevated intracranial pressure when present. Fluconazole is typically reserved for continued "consolidative" and long-term "maintenance" phase treatment or for milder forms of isolated pulmonary cryptococcosis. These recommended antifungal regimens are the same for *C gattii* and *C neoformans*. Clinical practice guidelines have also suggested more intensive radiological follow-up for intracerebral cryptococcomas due to the propensity for *C gattii* to cause more numerous lesions [26]. Such extensive intracerebral disease may necessitate surgical amelioration, prolonged antifungal therapy, or both. In addition, *C gattii* clinical isolates may display reduced triazole susceptibility, hindering consolidative and maintenance-phase treatment [27, 28]. Posaconazole, voriconazole, and isavuconazole have been used as alternatives in this situation, with varying degrees of reported success [29–31]. As such, the cryptococcal antifungal armamentarium is currently quite limited.

CONCLUSIONS

This case further characterizes *C gattii* VGI disease progression, which may help define genotype-specific factors that impact the infectious process. Although fatal *C gattii* meningitis cases have been described, the majority have either not been due to VGI or have not specified the genotype [23]. Because clinical presentations can vary and disease progression, treatment regimens, and outcomes are species and genotype-dependent, this case highlights the importance of identifying *C neoformans/C gattii* complex genotypes. Increasing awareness and recognition of this pathogen and its lethal potential in immunocompetent patients is important for ensuring appropriate specimen collection, timely diagnosis, early treatment, and continued vigilance.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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We thank the patient's family. Written consent to publish the details of the case was obtained from the patient's mother. She hopes her son's case

will bring awareness to this disease and help improve outcomes for other patients in the future.

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Potential conflict of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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