Disseminated Fungal Disease Caused by Magnusiomyces clavatus in a Pediatric Cancer Patient: First Case Report in North America and Review of the Literature

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Abbreviations:

CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
MIC	Minimum Inhibitory Concentration
MRI	Magnetic Resonance Imaging

We present a 6-year-old female with B-cell acute lymphoblastic leukemia admitted for medullary relapse five years after initial diagnosis. Her re-induction chemotherapy included vincristine, dexamethasone, pegylated asparaginase, doxorubicin, and intrathecal methotrexate and cytarabine. While severely neutropenic on prophylactic micafungin, she developed headache, dizziness, fever, and seizures. Brain magnetic resonance

imaging (MRI) revealed left superior parietal lobule leptomeningeal enhancement, concerning for infection or leukemic infiltration (Figure 1A). Within 48 hours, blood and CSF cultures demonstrated growth of a fungal pathogen, identified morphologically as *Magnusiomyces clavatus* . Her antifungal coverage was changed to voriconazole and liposomal amphotericin B. A whole body CT revealed disseminated fungal disease with innumerable small lesions in her liver, spleen, kidneys, pancreas, and lungs (Figure 1B). Blood cultures cleared after four days of combination antifungal treatment. A repeat CSF sample was sterile two weeks later. She had no history of foreign travel or high-risk environmental exposures.

Despite blood culture clearance, she continued to experience unrelenting spiking fevers (Figure 2A). After neutrophil count recovery, a repeat brain MRI showed development of a left parietal abscess and numerous punctate foci throughout the brain, representing disseminated central nervous system (CNS) fungal disease unveiled by immune reconstitution (Figure 1C). Flucytosine was added for additional antifungal action and CNS penetration. She underwent a left parietal craniotomy and drainage of the dominant abscess. Fungal culture of the contents of this abscess were sterile. Her fevers resolved after this procedure and shortly thereafter, she restarted cancer therapy with two cycles of blinatumomab.

She continued on combination antifungal therapy for seven months until CT imaging revealed gradual improvement in size and number of her disseminated lesions, allowing her to wean to only voriconazole (Figure 1D). With her fungal disease well-controlled and her malignancy in second complete remission (negative flow cytometry and high throughput sequencing), she successfully underwent a mismatched unrelated cord blood transplantation 10 months ago with no complications related to her fungal infection or antifungal toxicity. We intend to continue antifungal therapy through immune reconstitution and resolution of her imaging findings.

We report, to our knowledge, the first occurrence of a*Magnusiomyces clavatus* infection in North America and only the 11th reported case in a pediatric patient. Further, our patient underwent a successful cord blood transplant without further fungal infection complications. *M. clavatus* , formerly phylogenetically classified as *Geotrichum clavatum* and*Saprochaete clavata* , is an arthroconidial, filamentous, yeast-like opportunistic fungus increasingly recognized as an emerging pathogen in immunocompromised patients[1,2]. Closely related to, and potentially misidentified as, *Magnusiomyces capitatus* , its incidence has likely been underestimated prior to use of advanced identification techniques[3,4]. Detailed ecological studies are scarce but other *Magnusiomyces* spp are ubiquitous in environmental sources like water, soil, and plants[5]. In one study of hospitalized adults, asymptomatic colonization with *Magnusiomyces* spp was relatively common, especially in the respiratory tract, and associated with invasive infection in immunocompromised individuals[6]. Hospital device and food contamination have been reported including nine cases of *M. clavatus* fungemia in France linked to a dishwasher and four cases of disseminated *M. capitatus* in Spain spread through milk flasks[7,8]. Because isolates from multiple*M. clavatus* nosocomial outbreaks were from the same clade, human-to-human transmission is potentially possible in the setting of device contamination[9]. Invasive disease has been reported mostly in patients with hematologic malignancies and rarely with lymphoma, polycystic kidney disease, Crohn's disease, hemophagocytic lymphohistiocytosis, aplastic anemia, and multiple myeloma. Most cases have occurred in France and Italy with occasional reports elsewhere in Eastern Europe, the Middle East, China, and South America (Figure 2B)[10-12]. Case series have identified hematologic malignancy, chemotherapy, neutropenia, broad-spectrum antimicrobials, and central venous catheters as risk factors for infection[9,10]. Chemotherapeutics that alter gut mucosa may lead to increased gut translocation associated with *M. clavatus* infection[9]. Reported cases frequently include significant dissemination[2]. Isolates appear to be intrinsically resistant to echinocandins and fluconazole, but other azoles, amphotericin-B, and flucytosine have all demonstrated *in vitro* antifungal activity and low minimum inhibitory concentrations (MIC), though no clinical breakpoints have been defined for any*Magnusiomyces* spp[2,13]. The most commonly utilized antifungals have been combinations of voriconazole, posaconazole, amphotericin-B, and flucytosine[10]. Despite these therapies, *M. clavatus* mortality rates are 60-85% in some case series[2].

Pediatric cases of *M. clavatus* are much less common. Our literature search yielded 10 cases from 2007-2022 (Table 1)[6, 14-23]. Acute leukemias were the most common underlying diagnoses and all patients were im-

munocompromised during infection. Disseminated spread occurred in all but two cases. Fungal isolates were identified almost exclusively from blood cultures with CSF and skin biopsy samples also documented[18,22]. As with our case, the most commonly used antifungal regimen was voriconazole, amphotericin-B, and flucytosine. Mortality rates, when noted, are more favorable with survival in 80% of cases.

We present the first case of a *M. clavatus* infection in North America and the 11th documented pediatric case.*M. clavatus* should be recognized as a rare, but emerging pathogen in pediatric oncology patients, particularly in the setting of hematologic malignancy and/or echinocandin-based antifungal prophylaxis[23]. In this case, early identification, neurosurgical abscess drainage, and aggressive combination antifungal therapy led to successful management of disseminated disease, which allowed for an effective allogeneic hematopoietic stem cell transplant.

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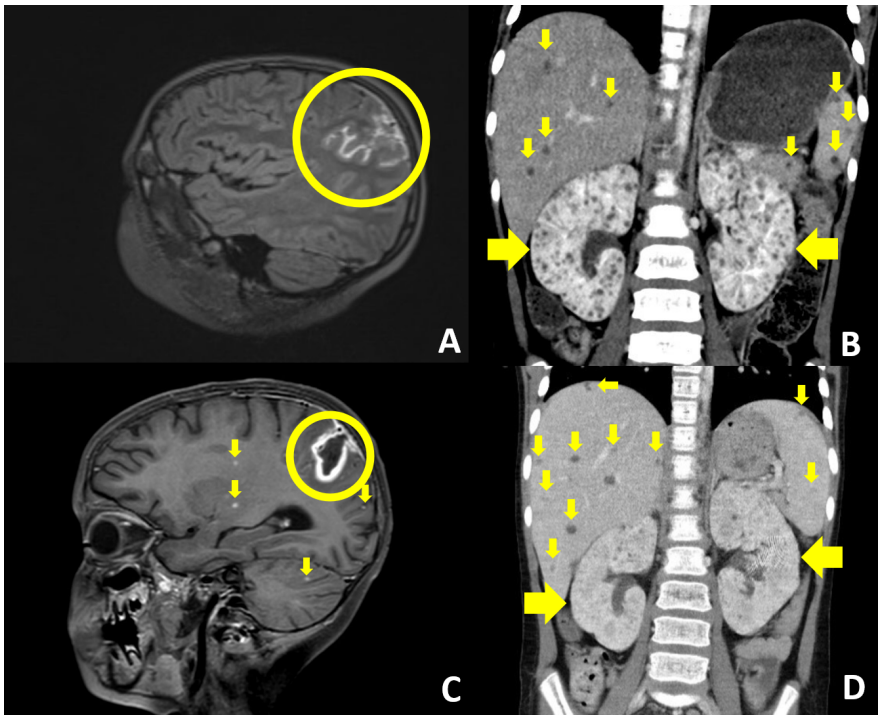
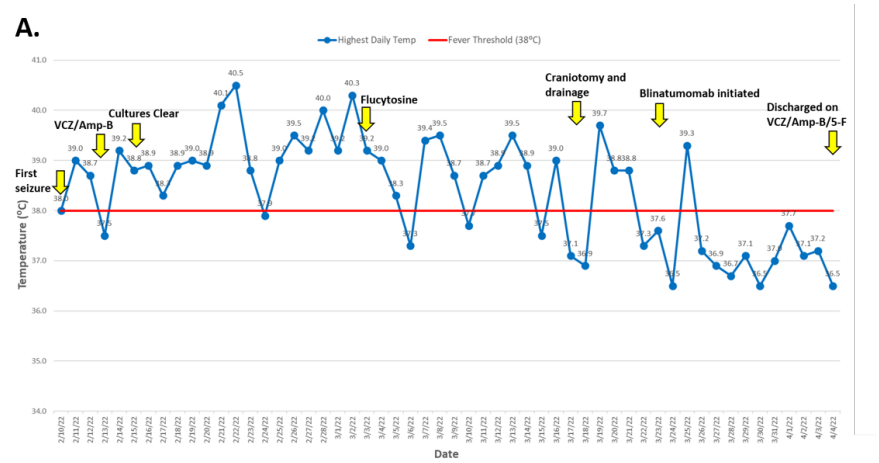
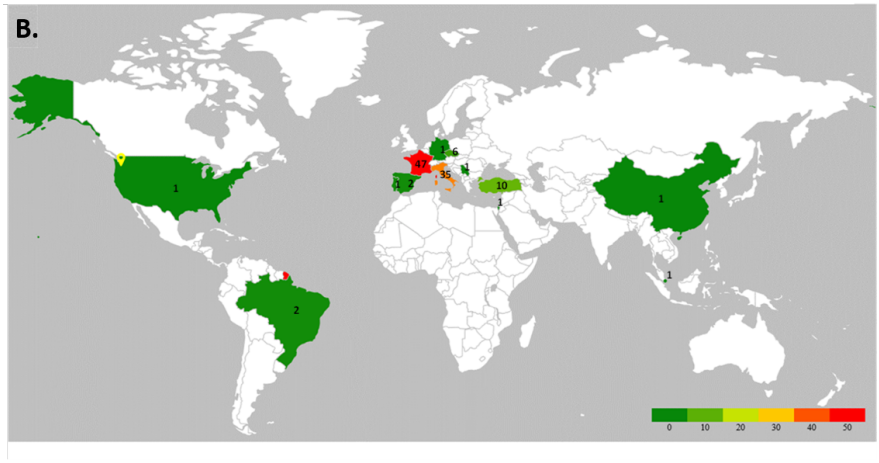
Figure 1: A. MRI Brain showing left superior parietal lobule leptomeningeal enhancement seen with FLAIR hyperintensity.**B.** CT Chest, abdomen and pelvis with contrast showing hepatosplenomegaly with innumerable nodules in the liver, spleen, kidneys, and pancreas without discrete drainable abscess. **C.**MRI brain showing a peripherally enhancing lesion in left parietal region involving cortex and extra-axial space with surrounding edema and numerous punctate foci of enhancement both supra and infratentorial likely representing foci of disseminated fungemia. **D.** Repeat CT Chest, abdomen and pelvis ~6 weeks later with ongoing hepatosplenomegaly with worsening of liver lesions, no change to splenic lesions, and improvement of lesions in lungs, pancreas, and kidneys.

Figure 2: A. The patient's daily recorded temperature correlating with treatment. First yellow arrow was the patient's first fever with her seizure. Second arrow identifies when voriconazole (VCZ) and amphotericin-B (Amp-B) was started. Third arrow identifies the last positive blood culture. Fourth arrow was when flucytosine (5-FC) was added. Fifth arrow represents the time at which surgery was performed to drain the intracranial abscess. Sixth arrow is when blinatumomab was initiated. Final arrow is when the patient was discharged after over 7 days without fevers on three antifungal agents. **B.** Reported*Magnusiomyces clavatus*

infections by country of origin. This report highlighted with a yellow pin.







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