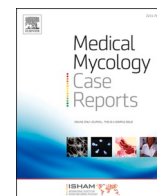


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Obstructive hydrocephalus and intracerebral mass secondary to *Epicoccum nigrum*

Taylor L. Charron^a, Michelle A. Gill^b, Laura M. Filkins^c, Veena Rajaram^{d,g},
Christian A. Wysocki^e, Brett A. Whittemore^{f,h,*}

^a Department of Neurosurgery, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390, USA

^b Departments of Pediatrics and Immunology, Washington University School of Medicine in St. Louis, 660 S Euclid Ave, St. Louis, MO, 63110, USA

^c Department of Pathology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390, USA

^d Division of Pediatric Pathology and Neuropathology, Department of Pathology, Children's Health, 1935 Medical District, Dallas, TX, 75235, USA

^e Division of Allergy and Immunology, Departments of Internal Medicine and Pediatrics, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390, USA

^f Division of Pediatric Neurosurgery, Department of Neurosurgery, Children's Health, 1935 Medical District, Dallas, TX, 75235, USA

^g Division of Pediatric Pathology and Neuropathology, Department of Pathology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390, USA

^h Division of Pediatric Neurosurgery, Department of Neurosurgery, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX, 75390, USA

ARTICLE INFO

Keywords:

Epicoccum nigrum
Fungal CNS infection
Intracerebral fungal mass
Obstructive hydrocephalus

ABSTRACT

Here we report a case of a 14-week-old girl with a history of intrauterine drug exposure and hypoxic ischemic encephalopathy secondary to cardiac arrest requiring prolonged resuscitation at birth presented with irritability and a bulging anterior fontanelle. After neurosurgical resection, pathologic examination showed fungal hyphae, and *Epicoccum nigrum* was detected by fungal PCR and sequencing. To our knowledge, this is the first reported case of a central nervous system infection due to *Epicoccum nigrum*.

1. Introduction

Among fungal CNS infections, the most common causative organisms are *Cryptococcus*, *Aspergillus*, and *Candida* [1]. Although less common, dematiaceous fungi have been shown to cause cerebral infections [2]. Dematiaceous fungi consist of a large group of molds that contain melanin in their hyphae and are found ubiquitously in the soil [3]. One such dematiaceous fungus is *Epicoccum nigrum*. A limited number of reports cite *Epicoccum nigrum* as the cause of infection and predominantly involve immunocompromised patients. *Epicoccum nigrum* has generally been reported as an airborne fungus causing allergic manifestations such as allergic fungal sinusitis or hypersensitivity pneumonitis [4]. There have also been singular case reports identifying this fungus in a renal bezoar [5] and in an intramuscular abscess [6]. Here, we report a case of a pediatric patient who presented with obstructive hydrocephalus secondary to a right frontal brain nidus later identified to be an *Epicoccum nigrum* infection that was successfully treated with neurosurgical resection and anti-fungal therapy.

2. Case presentation

A 14-week-old girl presented to the ED (day 0) with a chief complaint of irritability at the recommendation of her pediatrician, who also noted that her frontal occipital circumference (FOC) had increased across percentiles. She was born at 37 weeks gestation by emergency Caesarian section with pregnancy complicated by intrauterine drug exposure. CPR for 30 minutes with 4 doses of epinephrine, intubation, and umbilical catheterization were required at delivery with resultant hypoxic-ischemic injury.

Physical exam showed a bulging anterior fontanelle with diastatic cranial sutures. The patient's FOC was at the 90th percentile with previous measurements in the 3rd then 50th percentiles. Her gaze was conjugate with no sunsetting, though she had a right gaze preference and kept her head turned to the right. There was no history of recent fevers or respiratory symptoms. She did not have a history of frequent infections.

CT showed supratentorial hydrocephalus with marked asymmetric enlargement of the right lateral ventricle, leftward shift of the third ventricle, and a cystic collection in the inferomedial part of the right

* Corresponding author. Division of Pediatric Neurosurgery, Department of Neurosurgery, Children's Health, 1935 Medical District, Dallas, TX, 75235, USA.

E-mail address: brett.whittemore@utsouthwestern.edu (B.A. Whittemore).

<https://doi.org/10.1016/j.mmcr.2022.01.002>

Received 17 November 2021; Received in revised form 16 December 2021; Accepted 3 January 2022

Available online 6 January 2022

2211-7539/© 2022 Published by Elsevier B.V. on behalf of International Society for Human and Animal Mycology. This is an open access article under the CC

BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

frontal lobe inferior to the frontal horn. MRI showed a 2 cm diameter FLAIR-hyperintense cystic mass with a diffusion-restricting enhancing mural nodule and a large CSF-isointense cyst in the right lateral ventricle that extended across midline (Fig. 1). MRI of the full spine showed no spinal lesions.

On day 3 post-admission, the patient underwent a right frontal transcortical transventricular approach for resection of the mass, fenestration of the intraventricular cyst, and placement of an external ventricular drain. A tubular retractor was used to prevent collapse of the thin frontal cortex. The operative trajectory was planned with frameless stereotactic navigation. Under the operating microscope, the cyst cavity containing the mass was entered, and the solid mural nodule was removed. The solid tissue consisted of avascular, white, friable material, and the cyst fluid was comparable to CSF. The large cyst within the right lateral ventricle was fenestrated to the left lateral ventricle through the septum pellucidum. An external ventricular drain was passed into the ventricular system through the tubular retractor. Intraoperative frozen section showed abnormal tissue but was not diagnostic. The external ventricular drain was removed two days after surgery, and there has been no sign of progressive hydrocephalus on follow up imaging.

Pathology results on day 8 showed fungal hyphae seen on H&E and PAS stains, and no neoplastic tissue (Fig. 2). Empiric IV liposomal amphotericin B, 5 mg/kg daily, was administered on day 9, then continued for six weeks. *Epicoccum nigrum* DNA was detected on day 23 by broad range PCR and Sanger sequencing of partial 26S rRNA gene, ITS 1, and ITS 2 regions from formalin fixed paraffin embedded brain tissue from the right frontal cyst wall (testing performed at University of Washington Medical Center Molecular Microbiology Laboratory). Bacterial and fungal cultures were not performed due to low preoperative suspicion for infection. Oral voriconazole 12.8 mg/kg was added on day 17, once the identification of *Epicoccum* was made, and continued for sixteen weeks.

Further workup for disseminated infection included blood and fungal blood cultures, lumbar puncture with cultures, aspiration of subgaleal

fluid with cultures, skin biopsy of subcutaneous nodules by dermatology, ophthalmology exam, abdominal ultrasound, chest CT, echocardiogram, and nasal endoscopy. Of note, while *Epicoccum nigrum* DNA was found in the tissue, this organism was never isolated in fungal CSF or subgaleal cultures. Basic lab studies showed normal kidney function and electrolytes, and negative inflammatory markers. The fungal markers beta-D-glucan and aspergillus galactomannan were negative. Immunologic workup included normal neutrophil counts and neutrophil oxidative burst (Dihydrorhodamine) test. Flow cytometry did not reveal cellular deficiencies. Tests of antibody production and vaccine responsiveness were normal. Proliferative responses of lymphocytes to mitogenic stimuli were normal. Testing of cytokine responses to Toll-like receptor stimuli showed depressed cytokine response to TLR2/6 ligand, but normal responses to all others. Next generation sequencing of a panel of 407 genes with involvement in immune development and function did not reveal causative mutations.

There were no postoperative complications, and the patient began to make significant developmental progress. Amphotericin was stopped after 6 weeks, and voriconazole after 16 weeks, and MRI 4 months after presentation showed no signs of recurrent infection. She continued to progress well 9 months after presentation, though she was delayed. Her head control was improving. She had some residual left-sided weakness and continued with physical and occupational therapies. The head circumference decreased in percentile, consistent with brain atrophy and ex vacuo ventricle dilation rather than progressive hydrocephalus.

3. Discussion

Dematiaceous fungi are a diverse group of organisms identified by their dark-colored hyphae due to melanin pigment in the cell wall and have been shown to cause a range of clinical presentations primarily involving allergic diseases [2]. *Epicoccum nigrum*, a dematiaceous fungus, is an opportunistic pathogen that can be found in the soil and decaying plants [7]. It is also airborne and is an uncommon cause of

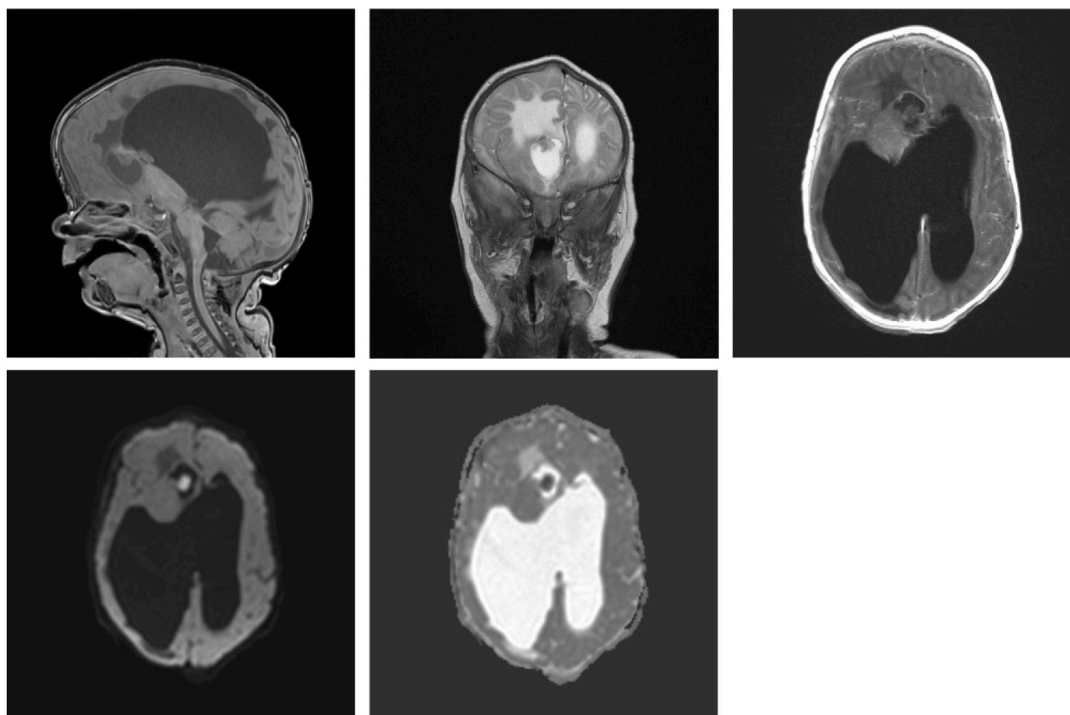


Fig. 1. MRI (A) T1 pre-contrast sagittal image showing a cystic and solid mass measuring 2.4 x 2.4 cm with marked enlargement of the right lateral ventricle. (B) T2 coronal image demonstrating right to left midline shift that caused mass effect on the cerebral aqueduct. (C) T1 post-contrast axial image shows enhancement about the periphery of the cystic portion of the tumor. DWI axial image (D) and ADC axial image (E) demonstrate restricted diffusion centrally in the solid portion of the tumor.

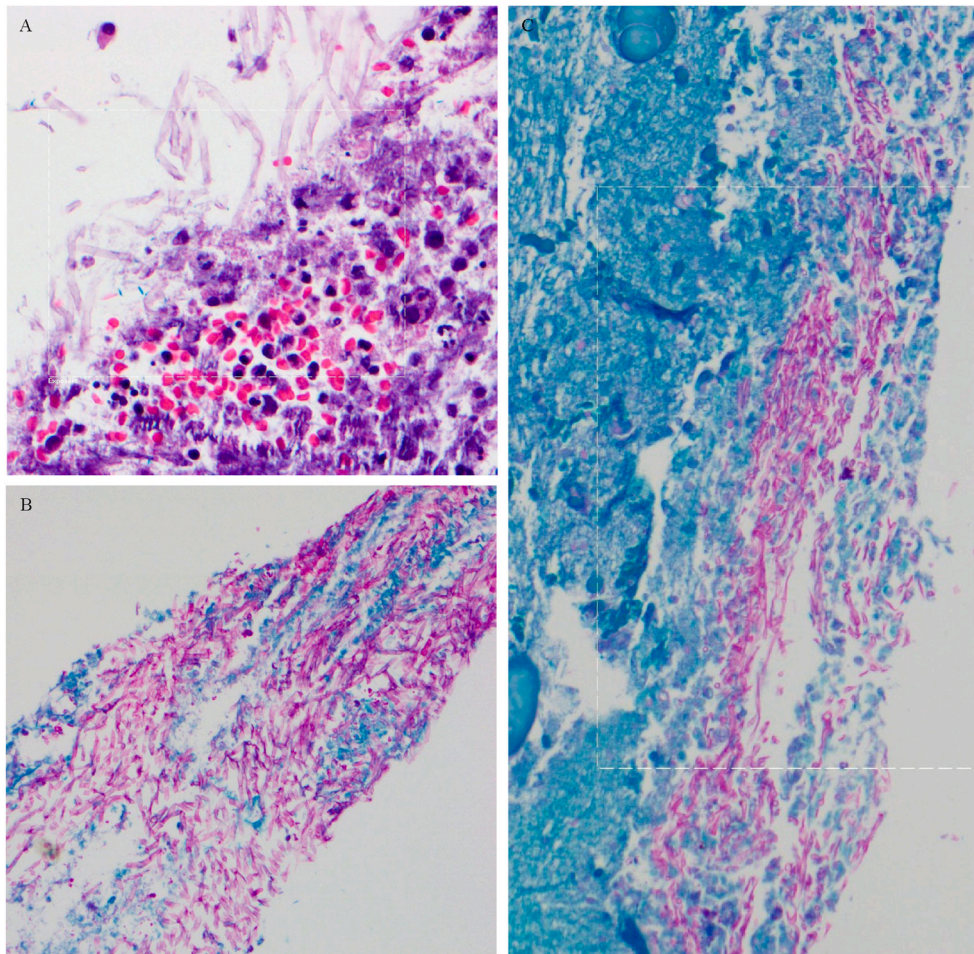


Fig. 2. (A) H&E stain shows fragments of necrotic tissue with scattered fragments of brain parenchyma with reactive gliosis, infiltrated by neutrophils and macrophages. Several pale hyphal structures are seen in areas of necrosis. Histology (B, C) PAS-fungus stains highlight clusters of hyphae and areas of necrosis.

allergic fungal sinusitis [4].

A case report described an intramuscular abscess due to *Epicoccum nigrum* in an immunocompromised patient with chronic lymphocytic leukemia, who was treated with amphotericin B, caspofungin, and voriconazole for two weeks before being transitioned to voriconazole for eight weeks [6]. Another case report described pyelonephritis due to *Epicoccum nigrum* in a patient who had previously undergone an endourological procedure for renal stones, who was treated with amphotericin B and voriconazole for 2 weeks [5]. *Epicoccum nigrum* has also been isolated as a causative agent in superficial skin mycosis coinfecting with *Aspergillus flavus*, *Emericella nidulans*, *Epicoccum* sp, and *Pestalotiopsis* sp. [8].

When isolated from patient specimens, *Epicoccum nigrum* is often considered a contaminant or colonizing organism with limited clinical significance; in rare cases this organism causes invasive human infection. In this case, the invasive hyphae seen on histopathology and the patient's response to therapy were strong evidence that this was not a contaminant.

Regarding the case presented here, no known underlying primary immunodeficiency was identified that predisposed her to this infection. One possible explanation for this unusual fungal infection is that the patient was more susceptible to infection due to her traumatic birth and hypoxia which required prolonged resuscitation. Another possible explanation is that this infection was acquired prenatally due to the maternal history of drug use, which could have possibly introduced environmental spores in the bloodstream [9], though intrauterine dematiaceous mold infections have not been documented. *Epicoccum*

nigrum has been shown to colonize the nasal sinuses which could lead to dissemination, but there was no evidence of infection beyond the brain. The depressed cytokine response to zymosan in PMBCs could possibly be reflective of a broader issue with innate responses to fungal cell wall components and is being examined.

Fungal CNS infections can present in a variety of ways, such as meningitis, intracranial mass lesions, or hydrocephalus (communicating or obstructive) [10], and can mimic brain tumors on imaging and clinical presentation [11,12]. In our case, surgical resection of the mass provided a diagnosis and adequately treated the hydrocephalus, though the role for neurosurgery in disseminated or surgically inaccessible fungal CNS infections may be only for biopsy (if extra-CNS sites are not amenable) or CSF diversion.

The location and pathogen associated with this patient's infection posed a challenge in terms of choice of antimicrobial therapy given the sparsity of clinical literature and no reports previously describing a brain nidus with *Epicoccum nigrum*. In the case reports reviewed above, combination antifungal therapy with amphotericin B and voriconazole was favorable since triazoles have good activity against many dematiaceous fungi [7]. Therefore, a prolonged course of combination antifungal therapy with amphotericin B and voriconazole was chosen for our patient. Based on the case presented here, *Epicoccum nigrum* is an organism capable of infecting the brain and can present as a solid and cystic intracerebral mass with hydrocephalus and no other systemic signs of infection.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report/case series from the patient(s) or legal guardian(s).

Declaration of competing interest

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.**

Acknowledgements

Not applicable.

References

- [1] A. Dubey, R.v. Patwardhan, S. Sampth, V. Santosh, S. Kolluri, A. Nanda, Intracranial fungal granuloma: analysis of 40 patients and review of the literature, *Surg. Neurol.* 63 (2005) 254–260, <https://doi.org/10.1016/j.surneu.2004.04.020>.
- [2] K. Góralska, J. Blaszkowska, M. Dzikowiec, Neuroinfections caused by fungi, *Infection* 46 (2018) 443–459, <https://doi.org/10.1007/s15010-018-1152-2>.
- [3] M.E. Brandt, D.W. Warnock, Epidemiology, clinical manifestations, and therapy of infections caused by dematiaceous fungi, *J. Chemother.* 15 (2003) 36–47, <https://doi.org/10.1179/joc.2003.15.supplement-2.36>.
- [4] J.A. Noble, S.A. Crow, D.G. Ahearn, F.A. Kuhn, Allergic fungal sinusitis in the southeastern USA: involvement of a new agent *Epicoccum nigrum* Ehrenb, ex Schlecht 1997 (1824). <https://academic.oup.com/mmy/article/35/6/405/978257>.
- [5] S.M. Suchitra, P.G.G. Laxman, B. Shrikala, B.M. Ashok, A renal bezoar of *Epicoccum nigrum*: an unusual clinical curiosity, *J. Clin. Diagn. Res.* 6 (2012) 905–907.
- [6] N. Azira, M. Zeehaida, Z. Nazli, S. Suraiya, A case report of intramuscular abscess secondary to *Epicoccum nigrum* infection, *J. Clin. Health Sci.* 1 (2016) 48–51.
- [7] S.G. Revankar, D.A. Sutton, Melanized fungi in human disease, *Clin. Microbiol. Rev.* 23 (2010) 884–928, <https://doi.org/10.1128/CMR.00019-10>.
- [8] A. Devi, S. Kaul, An Opportunistic Fungal Consortium Causes Superficial Skin Mycosis: A Case Study, 2015. <http://www.cibtech.org/cjb.htm>.
- [9] R.K. Whyte, Z. Hussain, Antenatal Infections with *Candida* Species, 1982.
- [10] R.F. Young, G. Gade, V. Grinnell, Surgical Treatment for Fungal Infections in the Central Nervous System, 1985.
- [11] J.H. Hur, J.H. Kim, S.W. Park, K.G. Cho, Cryptococcal brainstem abscess mimicking brain tumors in an immunocompetent patient, *J. Kor. Neurosurg. Soc.* 57 (2015) 50–53, <https://doi.org/10.3340/jkns.2015.57.1.50>.
- [12] A. Caceres, M.L. Avila, M.L. Herrera, Fungal infections in pediatric neurosurgery, *Child's Nerv. Syst.* 34 (2018) 1973–1988, <https://doi.org/10.1007/s00381-018-3942-3>.