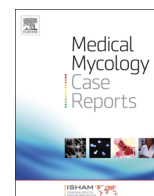




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## Ventriculitis due to infection with *Rhizopus arrhizus*

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### ABSTRACT

A 52-year-old heart–lung transplant patient presented to the emergency department with acute onset of neurologic symptoms. MRI showed ballooning of the left ventricle, midline shift and contrast enhancement in the anterior horn of the left ventricle. Ventricle neuroendoscopy revealed whitish, floccose aerial structures within the left ventricle. Brain biopsy cultures grew *Rhizopus arrhizus*. Therapy with liposomal amphotericin B and posaconazole was performed. Except for hemianopsia and deficits in minute motor activity, the patient completely recovered.

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### 1. Introduction

Mucormycosis is a very aggressive invasive fungal disease caused by Zygomycetes of the order Mucorales. Granulocytopenia, immunosuppression, diabetes and penetrating trauma are the most prevalent predisposing diseases associated with mucormycosis. Severe infection of the facial sinuses, which may extend into the brain, is the most common presentation. Cerebral mucormycosis is a devastating infection and associated with a high case-fatality rate, especially in immunocompromised patients. Pulmonary, cutaneous, and gastrointestinal infections are also recognized. [1–3] Herein, we present a patient with ventriculitis due to infection with *Rhizopus arrhizus* (*Rhizopus oryzae*) that was initially clinically diagnosed as intracerebral aspergillosis but failed under empiric voriconazole therapy. After identification of *R. arrhizus*, the patient was successfully treated with intrathecal amphotericin B and systemic combination therapy of high-dose liposomal amphotericin and posaconazole.

### 2. Case

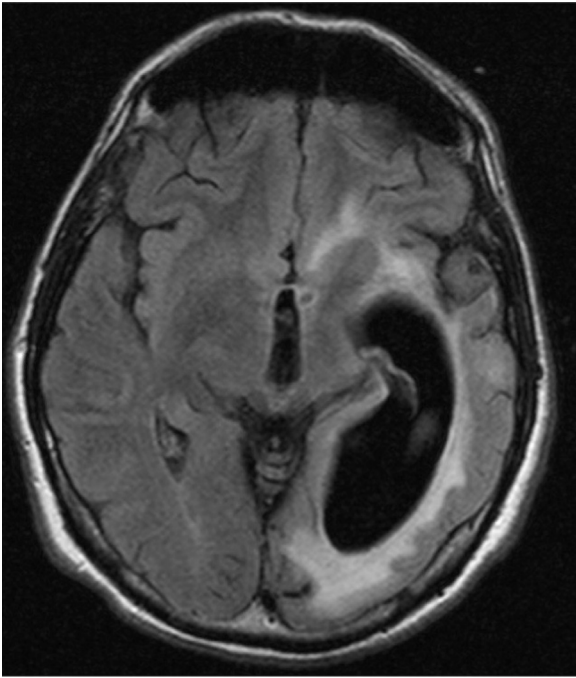
A 52-year-old man presented to the emergency department

with acute onset of confusion, dysarthria and tendency to fall in July 2012. He reported no fever. The patient was on immunosuppressive therapy because of a combined heart–lung transplantation in June 2011.

Laboratory data on hospital admission (day 0), were normal besides of low hemoglobin (reference range in brackets): WBC 6.4 Gpt/l (4.4–11.3), platelets  $227 \times 10^9/l$  (150–360), hemoglobin 7.8 mmol/l (8.7–10.9) and C-reactive protein (CrP) < 2.0 mg/l (< 7.5). MRI on admission showed ballooning of the left ventricle, midline shift over 11 mm and contrast enhancement in the anterior horn of the left ventricle with obstruction of the inter-ventricular foramen (of Monro) (Fig. 1). Initial cerebrospinal fluid (CSF) examination on day 0 showed a cell count of 377 cells/ $\mu$ L (0–5) and a protein level of 340 mg/L (150–400); no organisms were observed on Gram stain. Furthermore, 16S and 18S ribosomal RNA gene targeting PCR performed on CSF was negative. Likewise Aspergillus (Galactomannan) antigen and cryptococcal antigen test of CSF was negative. The patient was started on meropenem, vancomycin and voriconazole on day 0, but did not respond to this treatment. Therefore, for further diagnosis and therapy, ventricle neuro-endoscopy was performed on day 12 after admission. Ventricle neuroendoscopy revealed whitish, floccose aerial structures within the left ventricle (Fig. 2).

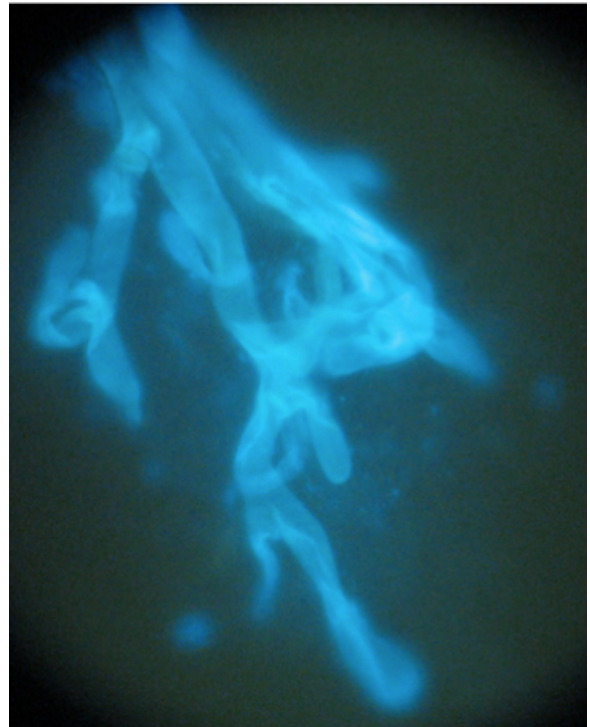
Calcofluor-white stain of the ventricular biopsy showed ribbon-like hyphae (Fig. 3). PAS staining showed numerous ribbon-like

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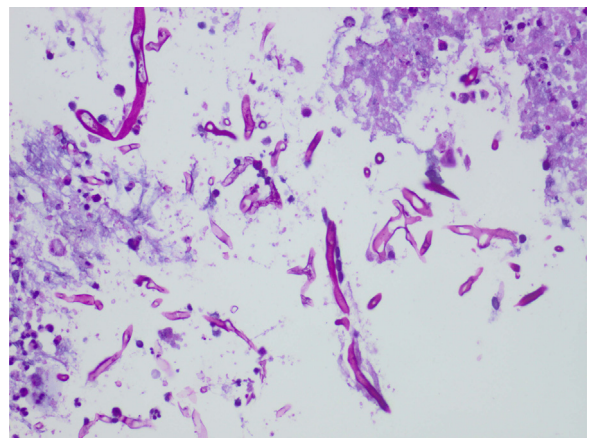


**Fig. 1.** MRI showing ballooning of the left ventricle, midline shift over 11 mm and contrast enhancement in the anterior horn of the left ventricle with obstruction of the interventricular foramen (of Monro).

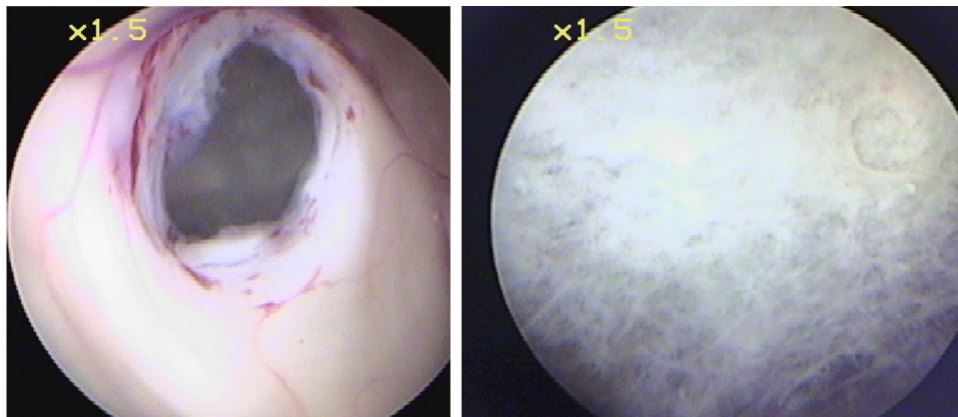
haphazardly branched fungal hyphae with PAS positive thick walls and little or no septation (Fig. 4). Species identification was performed on histological tissue biopsy and microbiological cultures by molecular diagnostic technique based on 18s-PCR (primers and protocol used for amplification and sequencing according to [4], length of resulting sequence 339 bp, 100% identity to Acc. No. KM527239.1) which revealed *R. arrhizus* (*R. oryzae*). Empiric therapy of meropenem, vancomycin and voriconazole was stopped and therapy with intravenous liposomal amphotericin B (5 mg/kg/day with stepwise increase to 10 mg/kg/day), intrathecal amphotericin B (0,5 mg/day) and posaconazole (1200 mg/day) was initiated on day 14. Intrathecal amphotericin B was terminated due to neurologic side effects including fluctuating level of consciousness on day 21. Therapy with intravenous liposomal amphotericin B and high-dose posaconazole was continued until day 35, respectively day 55 after admission. Thereafter suppressive therapy with posaconazole (600 mg/day) has been continued until now. Except for hemianopsia and deficits in minute motor activity, the patient completely recovered. He presented the last time for follow up in our outpatient clinic in May 2015.



**Fig. 3.** Calcofluor-white stain, native tissue ventricular biopsy showing ribbon-like hyphae. (Magnification, approximately  $\times 500$ .)



**Fig. 4.** PAS staining showed numerous ribbon-like, haphazardly branched fungal hyphae with PAS positive thick walls and little or no septation (staining, PAS; magnification,  $\times 200$ ).



**Fig. 2.** Ventricle neuro-endoscopy from the right side through the fenestrated septum pellucidum showing whitish, floccose aerial structures within the left ventricle.

### 3. Discussion

Overall, *Rhizopus* species are the most common cause of mucormycosis in humans. *Rhizopus* grow profusely on decaying vegetables, seeds, fruits and soil. Humans can be infected through inhalation, ingestion and skin inoculation. [5] Zygomycetes such as *Rhizopus* species can invade the CNS by either direct extension or hematogenous spread. [6] An European guideline for the diagnosis and management of mucormycosis was published recently. [1] For diagnosis, direct microscopy of clinical specimens and culture is strongly recommended. Colonies of *Rhizopus* are characterized by rapid growth, coarse and floccose aerial mycelia, similar to the structures visualized during ventricle neuroendoscopy in our patient. To best of our knowledge this is the first report showing pictures of colonies of *R. arrhizus* (*R. oryzae*) within the ventricle of a patient. Histopathological examination may allow differentiation between hyphae of *Aspergillus* or morphologically related fungi, and hyphae of Mucorales, which is important for treatment decisions as latter are intrinsically non-susceptible to voriconazole and echinocandins. Hyphae of Mucorales have a variable width (6–25 µm), are non-septate or pauci-septate and have an irregular, ribbon-like appearance. Interestingly, repeatedly performed CSF cultures showed no growth of *R. arrhizus* in our patient, only the tissue biopsy sampled during ventricle neuroendoscopy was positive finally. This emphasizes the importance of performing different modes of diagnostics including tissue biopsy. In our case, the failure of empiric voriconazole and the negative CSF-galactomannan prompted us to invasive diagnostics that revealed the correct diagnosis. Recommended treatment strategy comprises surgical debridement whenever possible combined with medical treatment. Liposomal amphotericin B is the drug of choice, dose should be at least 5 mg/kg/day. In the case of CNS infection 10 mg/kg/day is recommended for the initial 28 days. For salvage therapy posaconazole 200 mg four times daily is strongly recommended, the clinical significance of combination therapy however is uncertain according to the guideline [1]. However, in a recent report on 32 patients with mainly hematological diseases the analysis suggested that a combined antifungal treatment with liposomal amphotericin B and posaconazole may be considered in patients with very aggressive forms of invasive mucormycosis [7]. Due to rapid deterioration of general condition and worsening of neurologic symptoms combination therapy of liposomal amphotericin B

and posaconazole was performed in our patient. Because of unreliable absorption rates of oral posaconazole suspension and no possibility for therapeutic drug monitoring of posaconazole we decided to administer high-dose posaconazole (1200 mg/daily) in our patient. This treatment regime was well tolerated by our patient and a probably devastating surgical focus control was not required.

### Conflict of interest

SH and MWP received lecture fees from MSD SHARP & DOHME, Germany. All other authors report no conflicts of interest relevant to this article.

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