

# Chronic fungal meningitis caused by *Aureobasidium proteae*

---

**Kutleša, Marko; Mlinarić-Missoni, Emilija; Hatvani, Lóránt; Vončina, Darko; Simon, Silvio; Lepur, Dragan; Baršić, Bruno**

*Source / Izvornik:* **Diagnostic Microbiology and Infectious Disease, 2012, 73, 271 - 272**

**Journal article, Accepted version**

**Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)**

<https://doi.org/10.1016/j.diagmicrobio.2012.03.007>

*Permanent link / Trajna poveznica:* <https://urn.nsk.hr/urn:nbn:hr:105:493767>

*Rights / Prava:* [In copyright](#) / [Zaštićeno autorskim pravom.](#)

*Download date / Datum preuzimanja:* **2025-01-15**



*Repository / Repozitorij:*

[Dr Med - University of Zagreb School of Medicine  
Digital Repository](#)





## Središnja medicinska knjižnica

**Kutleša M., Mlinarić-Missoni E., Hatvani L., Vončina D., Simon S., Lepur D., Baršić B. (2012) *Chronic fungal meningitis caused by *Aureobasidium proteae**. *Diagnostic Microbiology and Infectious Disease*, 73 (3). pp. 271-2. ISSN 0732-8893**

<http://www.elsevier.com/locate/issn/07328893>

<http://www.sciencedirect.com/science/journal/07328893>

<http://dx.doi.org/10.1016/j.diagmicrobio.2012.03.007>

<http://medlib.mef.hr/1707>

University of Zagreb Medical School Repository

<http://medlib.mef.hr/>

# Chronic fungal meningitis caused by *Aureobasidium proteae*

Marko Kutleša<sup>1</sup>, Emilija Mlinarić-Missoni<sup>2</sup>, Lóránt Hatvani<sup>3</sup>, Darko Voncina<sup>4</sup>, Silvio Simon<sup>5</sup>, Dragan Lepur<sup>6</sup>, and Bruno Baršić<sup>1</sup>

**RUNNING TITLE:** *Aureobasidium proteae* meningitis

<sup>1</sup>University of Zagreb School of Medicine, University Hospital for Infectious Diseases “Dr. Fran Mihaljević”, Department of Intensive Care Medicine and Neuroinfectology

<sup>2</sup>Croatian National Institute of Public Health, National Reference Laboratory for systemic mycoses, Zagreb, Croatia

<sup>3</sup>Department of Microbiology, Faculty of Pharmacy and Biochemistry, University of Zagreb, Schrottova 39, 10000 Zagreb, Croatia

<sup>4</sup>Department of Plant Pathology, Faculty of Agriculture University of Zagreb, Svetosimunska 25, 10000 Zagreb, Croatia

<sup>5</sup>Department of Plant Breeding Genetics, Biometrics and Experimentation, Faculty of Agriculture, University of Zagreb, Svetosimunska 25, 10000 Zagreb, Croatia

<sup>6</sup>University Hospital for Infectious Diseases “Dr. Fran Mihaljević”, Department of Intensive Care Medicine and Neuroinfectology

*Corresponding author:*

Marko Kutleša, M.D.

Department of Neuroinfections and Intensive Care Medicine, University Hospital for Infectious

Diseases “Dr. Fran Mihaljević”, Mirogojska 8, 10000 Zagreb, Croatia

tel.: +385 1 2826 254

fax: +385 1 2826 255

E-mail: mkutlesa@bfm.hr

***Word count of the abstract: 45***

***Word count of the text: 1325***

**Key words:** *Aureobasidium proteae*, meningitis, cerebral phaeohyphomycosis

**Conflict of interest:** none

**Authors' contribution:**

All authors wrote, reviewed and revised the article and approved the final version of the manuscript.

Dr. Kutleša was primarily responsible for data collection and writing the manuscript.

**Abstract**

We present a case of chronic meningitis due to the mold *Aureobasidium proteae*. Clinical features, the disease course, as well as the diagnostic methods and optimal treatment options are discussed. This case confirms neuroinvasiveness of *Aureobasidium proteae* and introduces it as a new human pathogen.

## 1. Introduction

Cerebral phaeohyphomycosis is central nervous system (CNS) infection caused by dematiaceous fungi. Specific characteristic of these fungi is the presence of melanin pigments in the cell walls and spores. They are found throughout the world in soil and decaying vegetation. The usual pathogens that are clinically significant include: *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Ochroconis gallopavum*, *Fonsecaea pedrosoi*, *Ramichloridium mackenziei* and *Aureobasidium* species (Chang et al., 2000; Tintelnot et al., 1991; Vukmir et al., 1994; Sides et al., 1991; al-Hedaithy et al., 1988; Sutton et al., 1998).

Most common pathogenesis of cerebral phaeohyphomycosis is the extension of infection from adjacent paranasal sinuses after the inhalation of spores. In one case report hematogenous dissemination from a localized skin lesion has been suggested (Fletcher et al., 2000). The usual clinical presentation of cerebral phaeohyphomycosis is a brain abscess with seizures and focal neurological deficits.

Cerebral phaeohyphomycosis can occur in immunocompetent and immunocompromised patients equally and overall mortality in a major review article was 73% (Revankar et al., 2004). Suggested medical treatment of this disease consists of amphotericin B in combination with an azole. Surgical resection is mandatory if the brain abscesses are present (Revankar et al., 2004).

*Aureobasidium* species are molds known to cause fungemia, eye and skin infections (Hawkes et al., 2005). The only member of the species reported to cause meningitis is *Aureobasidium mansonii* (Krcméry et al., 1994; Huttova et al., 1998)

We present a case of chronic meningitis caused by *Aureobasidium protae*. This mold has not been reported as a human or CNS pathogen in the literature thus far.

## 2. Case report

A 53-year old white male was admitted to our hospital because of suspected chronic meningitis. His illness started three months prior to the admission with fever, weight loss, headache, dark colored facial skin lesion and progressive hearing loss. He is an agricultural worker in charge of planting and harvesting crops.

At admission he was febrile with preserved consciousness and severe bilateral hearing loss without any signs of the vestibular system involvement. Neurologic examination was otherwise unremarkable. Dark colored painless skin ulcer with elevated erythematous edges was noticed on his left cheek. Remaining physical examination was normal.

Lumbar puncture yielded normotensive opalescent cerebrospinal fluid (CSF) containing 420 white cells per cubic millimeter, with 54% neutrophils and without eosinophils. CSF-blood glucose ratio was 0.36, protein content was 1.337 g/L and chloride level was normal. Gram and acid-fast stain of the CSF were negative and the CSF remained sterile. White blood cell count was  $7.3 \times 10^9/L$  with normal differential, platelet count  $291 \times 10^9/L$ , and hemoglobin level 9.0 g/dL. Erythrocyte sedimentation rate (ESR) was 100 mm/h with C-reactive protein of 104.3 mg/L. A native and contrast-enhanced brain computed tomography scan and the Magnetic Resonance Imaging (MRI) of the brain at admission were normal.

Excision biopsy specimen of the facial lesion showed granulomatous inflammation on hematoxylin-eosin stain. The attempt of fungal isolation from this specimen was unsuccessful.

CD4 count was normal and the patient tested negative on the anti-HIV antibody assay. Electrophoresis of the serum proteins as well as immunoelectrophoresis revealed normal results.

Pathological uptake of fluorodeoxyglucose was not detected on the positron emission tomography - computed tomography of the whole body.

Anti-nuclear and anti double-stranded DNA antibodies were negative. Anti-neutrophil cytoplasmic antibodies and rheumatoid factor were negative as well.

CSF formula was compatible with tuberculous meningitis, thus CSF samples were taken daily for four consecutive days in order to increase the sensitivity of *Mycobacterium tuberculosis* cultures.

All four CSF samples grew *Aureobasidium pullulans*. Sabouraud's glucose agar with chloramphenicol and Brainheart infusion agar were used for fungal isolation from the CSF.

Further molecular biology analysis of the isolated pathogen ensued. Suspensions were prepared from the cultures in double distilled water (10<sup>8</sup> cells/ml) and used as template DNA for subsequent polymerase chain reaction (PCR) amplification. PCR-amplification of the internal transcribed spacer region was carried out (Rigó et al., 2002). The sequences of the PCR products were determined as described in the literature (Voncina et al., 2011). The gained sequences were analyzed by NCBI Standard Nucleotide BLAST (<http://blast.ncbi.nlm.nih.gov/>), then aligned by the aid of softwares ClustalX2 and GeneDoc in comparison with the corresponding sequences of 2-2 *A. pullulans* and *A. proteae* strains (GenBank accession numbers: JN400825.1, EF567985.1 and JN712493.1, JN712492.1, respectively). BLAST analysis revealed 99% homology of the ITS sequences of the isolates both to those of *A. pullulans* and *A. proteae*. Results of the alignments showed clear difference from *A. pullulans* while complete identity with each other and with both *A. proteae* strains tested, suggesting that all the four isolates belong to this species.

Three weeks after admission the susceptibility testing confirmed that the isolate was sensitive to both amphotericin B and voriconazole. The E-test was performed and revealed minimal inhibitory concentrations of 0.06 and 0.03 µg/ml for amphotericin B and voriconazole respectively.

After the samples were collected the empirical antifungal treatment with amphotericin B and voriconazole commenced. Subsequently, the patients' condition gradually improved. His hearing started to improve after 12 day of treatment and was clinically completely recovered at the discharge from the hospital. The fever resolved after 10 days of treatment and the CSF examination was normal after a month. Inflammation markers, ESR and C-reactive protein returned to normal values at discharge. Facial skin lesion resolved promptly and completely on topical twice daily clotrimazole treatment and systemic antifungal treatment. The patient was discharged from the hospital after two months without any signs of the disease. Peroral voriconazole treatment of 400 mg bid was recommended for additional four months.

After four months patient was hospitalized again for reevaluation of the disease and was found to be cured from the meningitis. However, during the hospital stay he suffered from the ruptured



aneurysm of the abdominal aorta and died of hemorrhagic shock. The only significant finding on the post-mortem analysis was ruptured aneurysm of the abdominal aorta and large retroperitoneal hematoma.

### 3. Discussion

We report a case of *A. proteae* cerebral phaeohyphomycosis that presented as chronic meningitis. Extensive search was undertaken in order to detect any medical condition that could predispose the patient to the *A. proteae* infection and unveiled nothing significant. Consequently, it can be concluded that this pathogen can cause infection in immunocompetent adult patients.

Proposed pathogenesis in the presented case is hematogenous dissemination to the CNS. Facial lesion could be the source of the infection since the biopsy specimen confirmed granulomatous inflammation compatible with the fungal etiology. Regardless of the exact pathogenic mechanism, this case definitely confirms neuroinvasiveness of *A. proteae* and introduces this mold as a new human as well as CNS pathogen.

The new-onset of deafness does not indicate any etiology and can be a consequence of bacterial, fungal and tuberculous meningitis. However, since it affected our patient it could be perceived as one of the features that occur during the *A. proteae* meningitis and could be attributed to the basal form of meningitis. Furthermore, the skin biopsy of any suspicious lesion could be helpful in similar patients since it might indicate the fungal etiology.

The prompt etiological diagnosis is required for the implementation of the most effective antifungal treatment. Due to the absolute lack of experience with this mold as a human pathogen, we can only propose the treatment protocol used in the described patient. The treatment consisted of conventional amphotericin B 1 mg/kg daily for two weeks. Voriconazole was added concomitantly with initial dose of 6 mg/kg every 12 hours for 2 doses, afterwards the maintenance dose of 4 mg/kg every 12 hours for four weeks was administered. Initial parenteral treatment was followed by peroral voriconazole (400 mg bid) for the next four months. Voriconazole has the best CNS penetration and is thus preferred over the other extended-spectrum azoles. This treatment approach should be reevaluated if the cases of *A. proteae* meningitis occur in the future. However, until the time arrives we can recommend the treatment presented since it completely cured meningitis in our patient without any significant side-effects occurring.

## References

1. Chang CL, et al. (2000) Acute cerebral phaeohyphomycosis due to *Wangiella dermatitidis* accompanied by cerebrospinal fluid eosinophilia. *J Clin Microbiol* 38:1965-6.
2. Fletcher H, et al. (2000) Systemic phaeohyphomycosis in pregnancy and the puerperium. *West Indian Med J* 49:79-82.
3. Hawkes M, et al. (2005) *Aureobasidium pullulans* infection: fungemia in an infant and a review of human cases. *Diagn Microbiol Infect Dis* 51:209-13.
4. al-Hedaithy SS, et al. (1988) Cerebral phaeohyphomycosis caused by *Fonsecaea pedrosoi* in Saudi Arabia. *APMIS Suppl* 3:94-100.
5. Huttova M, et al. (1998) Prospective study of nosocomial fungal meningitis in children--report of 10 cases. *Scand J Infect Dis* 30:485-7.
6. Krcméry V Jr, et al. (1994) *Aureobasidium mansonii* meningitis in a leukemia patient successfully treated with amphotericin B. *Chemotherapy* 40:70-1.
7. Revankar SG, et al. (2004) Primary central nervous system phaeohyphomycosis: a review of 101 cases. *Clin Infect Dis* 38:206-16.
8. Rigó K, et al. (2002) Phylogenetic analysis of *Aspergillus* section *Flavi* based on sequences of the internal transcribed spacer regions and the 5.8 S rRNA gene. *J. Gen. Appl. Microbiol* 48:9-16.
9. Sides EH, et al. (1991) Phaeohyphomycotic brain abscess due to *Ochroconis gallopavum* in a patient with malignant lymphoma of a large cell type. *J Med Vet Mycol* 29:317-22.
10. Sutton DA, et al. (1998) U.S. case report of cerebral phaeohyphomycosis caused by *Ramichloridium obovoideum* (*R. mackenziei*): criteria for identification, therapy, and review of other known dematiaceous neurotropic taxa. *J Clin Microbiol* 36:708-15.
11. Tintelnot K, et al. (1991) Cerebral phaeohyphomycosis caused by an *Exophiala* species. *Mycoses*; 34:239-44.
12. Voncina D, et al. (2011) Differential properties of Grapevine virus B isolates from Croatian autochthonous grapevine cultivars. *Journal of Plant pathology* 93: 283-289.

13. Vukmir RB, et al. (1994) Successful therapy for cerebral phaeohyphomycosis due to *Dactylaria gallopava* in a liver transplant recipient. *Clin Infect Dis* 19:714-9.