First case of invasive *Magnusiomyces capitatus* infection in Slovakia

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**ABSTRACT**

*Magnusiomyces capitatus* (previously known as Geotrichum capitatum or Blastoschizomyces capitatus or *Trichosporon capitatum*) is a rare cause of fungal infection in immunocompromised patients. Most of these cases (87%) have been reported from the Mediterranean region, as it is extremely rare to recognize it in other regions. Here we report a first case of disseminated *M. capitatus* infection in Slovakia. The patient – 19 year old woman with myelodysplastic syndrome was diagnosed with *M. capitatus* fungemia after allogeneic stem cell transplantation. The infection occurred despite antifungal prophylaxis with micafungin, which was in vitro sensitive to the yeast. The treatment according to minimal inhibitory concentrations (micafungin, voriconazol) and granulocyte transfusions were administered. *M. capitatus* was cleared out from the bloodstream. However, patient died of multiple organ failure. Autopsy showed multiple lesions in organs, but did not prove presence of yeast by histopathology. *M. capitatus* was confirmed by polymerase chain reaction from all tested organs: heart, brain, lungs, spleen, liver and kidneys. We present the post mortem pictures showing the yeast lesions in affected organs. 2012 Elsevier Ltd. All rights reserved.

1. Introduction

*Magnusiomyces capitatus* is a rare cause of fungal infection in immunocompromised patients, occurring almost exclusively in the Mediterranean region, with only a few case reports from outside this region. This paper presents the first case of disseminated *M. capitatus* infection in Slovakia. We present the post mortem pictures showing the lesions in affected organ, in which *M. capitatus* was confirmed by polymerase chain reaction (PCR).

2. Case

A 19-year old woman with refractory cytopenia type of myelodysplastic syndrome (RCC/MDS) was admitted to our unit for planned allogeneic stem cell transplantation. Multiresistant *Pseudomonas aeruginosa* from stool and rectum and *Candida glabrata* from vulva were found in routinely performed pretransplant swabs, however the patient had no signs of infection. Peripheral blood stem cell transplantation from a 9/10 HLA- matched unrelated donor was performed (D 0) following the conditioning consisting of Fludarabine (4×40 mg/m\(^2\)) and Thiopeta (3×5 mg/kg). Anti-thymocyte globulin (3×15 mg/kg), cyclosporin A and methotrexate (10 mg/m\(^2\)) were used for T cell depletion and graft-versus-host disease (GvHD) prophylaxis. Micafungin (1 mg/kg/daily) was used for antifungal prophylaxis. On D +2 the patient became febrile and on D +3 a yeast - *M. capitatus* was identified in blood cultures from central venous catheter (CVC). This yeast was found in several consecutive blood cultures. From D +8 multiresistant, yet sensitive to colimycine *P. aeruginosa* was identified in blood cultures from CVC and from peripheral blood as well (being colonized with the bacteria – the swab from rectum and stool). At this point the patient had suffered from agranulosis for 4 months for what we know. In-vitro susceptibility testing of *M. capitatus* showed sensitivity to azoles, amphotericin B and micafungin (Table 1) and combined micafungin (2 mg/kg) and voriconazole (1.day 6 mg/kg, then 4 mg/kg) treatment began. The sensitivity was valued according to CLSI breakpoints for *Candida spp.*, there are none specifically set for this pathogen. Lung high resolution computed tomography (HRCT) showed inflammatory infiltrates in the both lungs with fluidothorax. Treatment with granulocytes infusions began on D +10. Patient's condition started to deteriorate, respiratory failure occurred and she was febrile despite the targeted antifungal and antibacterial treatment. On D +12 the patient was transferred to paediatric intensive care unit (PICU) due to required...
mechanical ventilation (MV). The deteriorating condition continued with renal failure, and the patient received haemodialysis starting on D +14. Leukocytes engraftment occurred on D+17, with complete donor chimerism in peripheral blood. The molecular adsorbents recirculating system (MARS) was required for liver failure from D+19. The first negative blood culture for *P. aeruginosa* was recorded on D+18, for *M. capitatus* the first negative blood culture was found on D+19. Nevertheless, *P. aeruginosa* was still found in swabs from rectum and throat and *M. capitatus* in the urine and in the swabs from nose and from tongue (D+26). On D+38 computed tomography of brain, lungs and abdomen showed multiple areas of hypodensity in following organs: brain, liver, spleen, kidneys, and lungs (Picture 1). These were the assumed infectious emboli of the yeast, however the unstable and critical condition of the patient made it impossible to perform biopsy. The patient suffered another complications – left thoracoscopic revision due to fluidothorax and haemothorax (D +33), which was complicated with haemorrhagic shock after the thoracoscopy, left thoracotomy with haematoma evacuation and drainage (D +40), diffuse bleeding from the gastrointestinal tract. Cultivations of pleural effusions (D +33) and from bronchoalveolar lavage specimen (D +53) were both tested negative for bacterial and mycotic agents as well. The patient died D +71 of multiple organ failure. The autopsy showed multiple lesions in heart, brain, lungs, spleen, kidneys, and lungs (Picture 2, 3, 4, 5, 6, 7), but did not prove any mycotic infection in the morphological picture. Autopsy samples were tested with two different panfungal PCR methods [1,2].

Regarding the tissue samples neither of our methods was positive despite our expectations. Consequently, we designed a novel specific PCR (Table 2) for detection of *Saprochaete capitata* and *S. clavata* followed by species identification based on sequencing. After PCR products sequencing we confirmed *M. capitatus* (Anamorph *S. capitata*)

![Picture 1. Lungs CT scan with multiple areas of hypodensities.](image1)

![Picture 2. Lungs.](image2)

![Picture 3. Heart.](image3)

![Picture 4. Heart.](image4)

![Picture 5. Kidneys.](image5)

**Table 1**
Minimum inhibitory concentrations (MIC) of the *Magnusiomyces capitatum* isolate as reported by Department of mycology, HPL Ltd., a Member of Medirex Group, Bratislava, Slovakia.

| Antifungal agent | MIC (μg/mL) |
|------------------|-------------|
| Fluconazole      | C 6.0       |
| Itraconazole     | C 0.125     |
| Voriconazole     | C 0.094     |
| Posaconazole     | C 0.75      |
| Amphotericin     | C 0.38      |
| Amphotericin     | R 32        |
| Anidulafungin    | R 32        |
| Micafungin       | C 0.003     |
as an aetiological agent of disseminated invasive fungal infections in all affected tissues. On the contrary, culture samples (cultivated from blood) were positive by all used methods. In our opinion this was caused by significantly different loads of fungal DNA in tissue samples and culture samples. High amount of DNA in a sample can lead to a positive amplification despite a few mismatches between primers and targeted DNA sequences.

3. Discussion

_Magnusiomycetes capitatus_ (previously known as _Geotrichum capitatum_ or _Blastoschizomyces capitatus_ or _Trichosporon capitatum_) and its ana-morph _Saprochaete capitata_ [3], is a rare cause of disseminated disease [4]. _M. capitatus_ can be isolated from the environment and may be a constituent of the microflora of the skin and the mucosa of the respiratory and digestive tracts [5]. It is an opportunistic mycotic pathogen and can cause an infection, especially in neutropenic haematoto-oncology patients, typically in the Mediterranean region- Italy, Spain, and France report 87% of the cases in Europe [4,6]. However, the case reports have been recently published from other countries, that are not typical for this infection - Kuwait, Switzerland, Nepal [7–9]. To our knowledge, this is the first case of _M. capitatus_ infection in Slovakia. The reason why this infection has been found in such atypical regions has not been recognised [10,11].

The clinical presentation is similar to the other fungi, usually persistent fever despite antibacterial treatment. The yeast causes fungemia, but deep organs can be involved as well - the lungs, kidneys, liver, spleen, brain and endocardium [4], which was proved in our case as well.

Treatment should be started as soon as possible. There are not enough clinical data to assess the optimal treatment for _M. capitatus_ in haematology patients. However, based on _in vitro_ susceptibility and the limited clinical data available, any amphotericin B formulation with or without flucytosine can be recommended [12,13]. Similarly, voriconazole can be used as well, alone or in combination [8]. _M. capitatus_ is considered intrinsically resistant to echinocandins [14], in our case the yeast was resistant to anidulafungin and caspofungin, however sensitive to micafungin that had been administered to the patient at the time of the appearance of infection. This finding suggests that _in vitro_ and _in vivo_ activity of antifungal may differ. There are several publications on cases of infections in patients receiving echinocandins (caspofungin and micafungin) [7,15,16]. The removal of central venous catheter also seems to be an important aspect of treatment, as removal was shown as a prognostic indicator for success in one study [6]. Other adjuvant therapies to improve the phagocytic activity such as colony-stimulating factors, granulocyte transfusions and interferon-γ have been combined with antifungal drugs with some success [17–19].

The outcome of invasive disease caused by _M. capitatus_ depends mainly on patient immunity. In patients with profound neutropenia, mortality is greater than 90% and survival has largely coincided with the recovery of the neutrophil count [5]. Despite the targeted combined antymycotic treatment and administration of granulocyte transfusions until the engraftment, the infection disseminated and was fatal in our case.

Conflict of interest

There are none.

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References

[1] M. Bezdíček, M. Lengrová, D. Rieca, B. Weinbergerová, I. Kocmanova, P. Volfova, L. Drgona, M. Poczočka, J. Mayer, Z. Racil, Rapid detection of fungal pathogens in bronchoalveolar lavage samples using panfungal PCR combined with high resolution melting analysis, Med. Mycol. 54 (2016) 714–724, http://dx.doi.org/10.1093/mmy/myw092.

[2] C. Ferrer, F. Colom, S. Frasés, E. Mulet, J.L. Abd, J.L. Alió, Detection and identification of fungal pathogens by PCR and by ITS2 and 5.8S ribosomal DNA typing in otolar infections, J. Clin. Microbiol. 39 (2001) 2873–2879, http://dx.doi.org/10.1128/JCM.39.8.2873-2879.2001.

[3] G. Sybren De Hoog, M.T. Smith, Ribosomal gene phylogeny and species delimitation in Geotrichum and its teleomorphs, Stud. Mycol. 50 (2004) 489–515.

[4] C. Girmenia, L. Pagano, B. Martino, D. D’Antonio, R. Fanisi, G. Specchia, L. Melillo, M. Buelli, G. Pizzarelli, M. Venditti, P. Martino, GIMEMA infection program, invasive infections caused by trichosporon species and geotrichum capitatum in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature, J. Clin. Microbiol. 43 (2005) 1818–1828, http://dx.doi.org/10.1128/JCM.43.4.1818-1828.2005.

[5] E. Bouza, P. Muñoz, Invasive infections caused by Blastoschizomyces capitatus and Scedosporium spp, Clin. Microbiol. Infect. 10 (2004) 76–85, http://dx.doi.org/10.1011/j.1470-9465.2004.00842.x.

[6] R. Martino, M. Salavert, R. Parody, J.F. Tomas, R. de la Camara, L. Vazquez, I. Jarque, E. Prieto, J.L. Sastre, I. Gadea, J. Peman, J. Sierra, Blastoschizomyces capitatus infection in patients with leukemia: report of 26 cases, Clin. Infect. Dis. 38 (2004) 335–341, http://dx.doi.org/10.1086/380643.

[7] P. Purohit, I. Al-Obaid, E. Al-Oneizi, O. Al-Hindi, L. Joseph, S. Ahmad, Z. Khan, C.Z. Khan, Breakthrough disseminated Saprochaete capitata infection in a child with acute myeloid leukaemia receiving caspofungin therapy, (n.d.).

[8] T. Birrenbach, S. Bertschy, F. Aebersold, N.J. Mueller, Y. Achermann, K. Muechlehaler, S. Zimmerli, Emergence of Blastoschizomyces capitatus yeast infections, Central Europe, Emerg. Infect. Dis. 18 (2012) 98–101, http://dx.doi.org/10.3201/eid1801.111192.

[9] H. Subramanya Supram, S. Gokhale, A. Chakrabarti, S.M. Rudramurthy, S. Gupta, P. Honnavar, Emergence of _Magnusiomycetes capitatus_ infections in Western Nepal, Med. Mycol. 54 (2016) 103–110, http://dx.doi.org/10.1093/mmy/myv075.
[10] V.A. Robert, A. Casadevall, Vertebrate endothermy restricts most fungi as potential pathogens, J. Infect. Dis. 200 (2009) 1623–1626, http://dx.doi.org/10.1086/644642.

[11] M.A. Garcia-Solache, A. Casadevall, Global warming will bring new fungal diseases for mammals, MBio 1 (2010) http://dx.doi.org/10.1128/mBio.00061-10.

[12] I. Gadea, M. Cuenca-Estrella, E. Prieto, T.M. Diaz-Guerra, J.I. Garcia-Cia, E. Mellado, J.F. Tomas, J.L. Rodriguez-Tudela, Genotyping and antifungal susceptibility profile of Dipodascus capitatus isolates causing disseminated infection in seven hematological patients of a tertiary hospital, J. Clin. Microbiol. 42 (2004) 1832–1836, http://dx.doi.org/10.1128/JCM.42.4.1832-1836.2004.

[13] E. Cofrancesco, M.A. Viviani, C. Boscetti, A.M. Tortorano, A. Balzani, D. Castagnone, Treatment of chronic disseminated Geotrichum capitatum infection with high cumulative dose of colloidal amphotericin B and itraconazole in a leukaemia patient, Mycoses 38 (2016) 377–384, (http://www.ncbi.nlm.nih.gov/pubmed/25781171) (accessed 16 December 2016).

[14] M.C. Arendrup, T. Boekhout, M. Akova, J.F. Meix, O.A. Cornely, O. Lortholary, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, European Confederation of Medical Mycology, ESCMID® and ECMM† joint clinical guidelines for the diagnosis and management of rare invasive yeast infections, Clin. Microbiol. Infect. 20 (2014) 76–98, http://dx.doi.org/10.1111/1469-0691.12360.

[15] D. Yılmaz Karapinar, N. Karadağ, Z. Önder Siviş, P. Yazıcı, M. Duyu, D. Metin, B. Karapinar, Y. Aydinok, D.Y. Karapinar, N. Karadağ, Z.O. Sivis, P. Yazici, M. Duyu, D. Metin, B. Karapinar, Y. Aydinok, Rare severe mycotic infections in children receiving empirical caspofungin treatment for febrile neutropenia, Braz. J. Infect. Dis. 19 (2015) 549–552, http://dx.doi.org/10.1016/j.bjid.2015.06.008.

[16] P. Chittick, E.L. Palavecino, B. Delashmit, J. Evans, J.E. Peacock, Case of fatal blastoschizomyces capitatus infection occurring in a patient receiving empirical micafungin therapy, Antimicrob. Agents Chemother. 53 (2009) 5306–5307, http://dx.doi.org/10.1128/AAC.00710-09.

[17] J. DeMaio, L. Colman, The use of adjuvant interferon- therapy for Hepatosplenic Blastoschizomyces capitatus infection in a patient with leukemia, Clin. Infect. Dis. 31 (2000) 822–824, http://dx.doi.org/10.1086/314047.

[18] L. Pagano, G. Morace, E. Ortu-La Barbera, M. Sanguinetti, G. Leone, Adjuvant therapy with rhGM-CSF for the treatment of Blastoschizomyces capitatus systemic infection in a patient with acute myeloid leukemia, Ann. Hematol. 73 (1996) 33–34, <http://www.ncbi.nlm.nih.gov/pubmed/8695721> (accessed 16 December 2016).

[19] I. Pérez-Sanchez, J. Anguita, P.M. Rabahad, P. Muízor, D. Serrano, A. Escudero, T. Pintado, Blastoschizomyces capitatus infection in acute leukemia patients, Leuk. Lymphoma 39 (2000) 209–212, http://dx.doi.org/10.3109/10428190009053506.