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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.

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 Thiotepa (3×5 mg/kg). Anti-thymocyte globulin (3×15 mg/kg), cyclosporine 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

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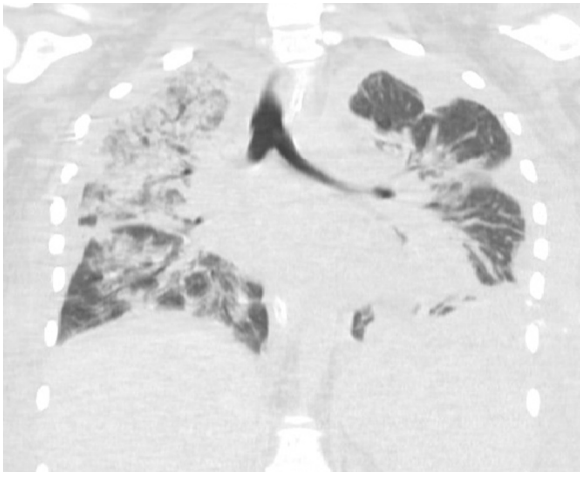
Table 1
Minimum inhibitory concentrations (MIC) of the *Magnusiomyces capitatum* isolate as reported by Department of mycology, HPL Ltd. a Member of Medirex Group, Bratislava, Slovakia Bratislava, Slovakia.

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
Caspofungin	R 32
Anidulafungin	R 32
Micafungin	C 0.003

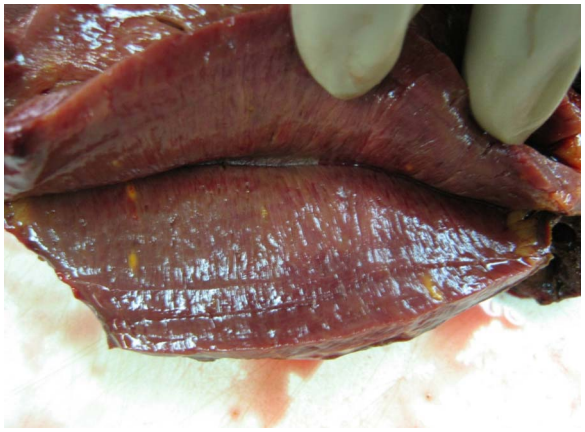


Picture 1. Lungs CT scan with multiple areas of hypodensities.

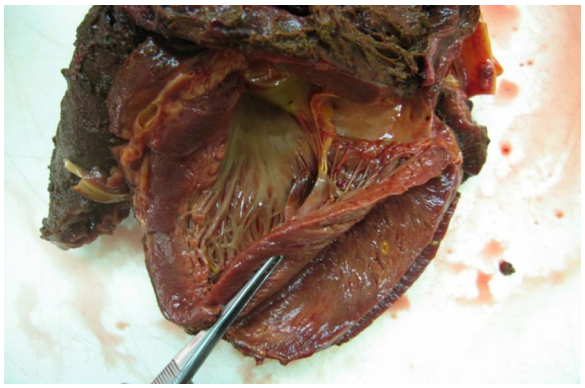
mechanical ventilation (MV). The deteriorating condition continued with renal failure, and the patient received haemodialysis starting on D +14. Leukocytes engraftment occurred on D+17, with complete donor chimerism in peripheral blood. The molecular adsorbents recirculating system (MARS) was required for liver failure from D+19. The first negative blood culture for *P. aeuroginosa* 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, liver and kidneys (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*)

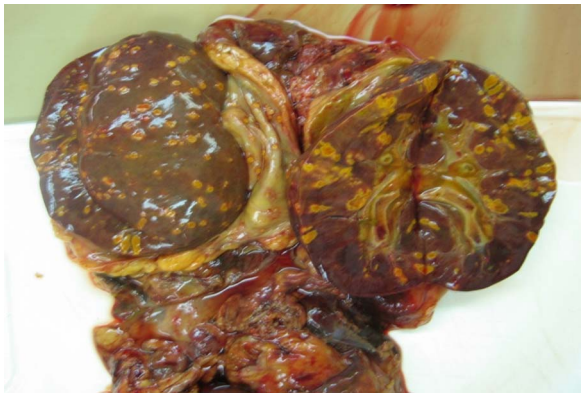
Picture 2. Lungs.



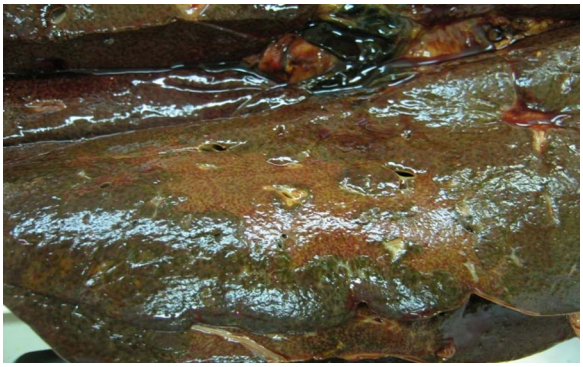
Picture 3. Heart.



Picture 4. Heart.



Picture 5. Kidneys.



Picture 6. Liver.

Picture 7. Brain.

Table 2
Primers for Saprochaete specific PCR.

Primer	Sequence (5´→ 3´)
SCMC-1	CAATTCTTGAACGCACATGG
SCMC-R	GCGGGTAGTCTTGCTTGATA

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

Magnusiomyces capitatus (previously known *as Geotrichum capitatum* or *Blastoschizomyces capitatus* or *Trichosporon capitatum*) and its anamorph *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 haemato-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 resistent to anidalufungin 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 antifungals 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 antimycotic 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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None.

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