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Magnusiomyces capitatus fungemia: The value of direct microscopy in early diagnosis

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ABSTRACT

Two cases of fungemia caused by *Magnusiomyces capitatus,* an arthroconidial yeast-like fungus, in non-hematologic immunocompromised patients are described. Both patients died before definite diagnosis of *M. capitatus* was made. The report highlights that pending confirmation of the isolate by phenotypic and/or molecular methods, the characteristic morphologic features observed in Gram-stained smears of blood culture positive bottles can lead to early preliminary diagnosis, thus significantly reducing time required for initiating appropriate antifungal therapy.

1. Introduction

Magnusiomyces capitatus is an uncommon yeast that has undergone multiple taxonomic revisions in the last few decades [1] (De Hoog et al., 2004). It is an *Ascomycetous* yeast-like fungus and belongs to the order *Saccharomycetales* in family *Dipodascaceae*. In literature, it has been variedly described as *Blastoschizomyces capitatus*, *Geotrichum capitatum*, *Trichosporon capitatum* and *Dispodascus capitatus* [1] (de Hoog et al., 2004). *M. capitatus* can cause invasive infections among immunosuppressed patients especially those with hematologic disorders [2,3] (Mazzcato et al., 2015; Tanuskova et al., 2017). It can also infect non-neutropenic and immunocompetent patients [4,5] (Shah, 2017; D'Assumpcao et al., 2018). In immunocompromised patients, infections with *M. capitatus* are associated with increased risk of dissemination and high rates of mortality. In addition, *Magnusiomyces* species, along with other arthoconidial yeasts, are intrinsically resistant to echinocandins which are often used as a first line therapy for invasive candidiasis [6] (Kaplan et al., 2018). Here, we describe two cases of *M. capitatus* in non-hematologic immunocompromised patients, who died before definitive diagnosis was made. In this case report, we explore the important role of direct microscopy in rapid diagnosis of *Magnusiomyces* species, which has significant treatment implications.

2. Cases

Case 1. An 85-year-old woman with a long history of bronchial asthma, hypertension, ischemic heart disease, and chronic renal disease, was admitted (day 0) on May 2018 because of chest infection. Empirically, she was prescribed cefepime, linezolid, and oseltamivir (day +1). Two days following admission (day +2), she developed respiratory failure requiring intensive care with mechanical ventilation. Concomitantly, she also developed acute liver failure and severe renal impairment. Her total white blood cell count and neutrophils were raised: 24 x10/^{9}/L and 23×10^{9}/L respectively. Because she remained critically ill, hydrocortisone (day +2) and Caspofungin (day +3) were started. As she had acute hepatic impairment, she received only 35mg maintenance dose of caspofungin. On day + 9, hemodialysis was initiated due to progressive renal failure, and cefepime was replaced with meropenem and colistin. On day +12, a new set of blood culture was collected, which yielded a yeast growth (day +15) by automated blood culture system (BD BACTEC FX). Gram-stained smears from the blood culture bottles showed numerous arthroconidia fragmenting into rectangular forms (Figs. 1 and 2). Subculture on Sabouraud dextrose agar (Oxoid, Basingstoke, UK) yielded whitish, dry, wrinkled yeast like colonies with radiating edges. The isolated yeast was identified as *Saprochaete capitata* by VITEK 2 with 99% confidence. However, before accurate identification and antifungal susceptibility of the yeast isolate could be determined, the patient succumbed to infection (day +15). Antifungal susceptibility data by Etest (bioMérieux) showed resistance to caspofungin (MIC ≥32 μg/ml), micafungin (MIC ≥32 μg/ml) and somewhat reduced susceptibility to fluconazole (MIC 3 μg/ml), however, the isolate appeared susceptible to voriconazole (0.19 μg/

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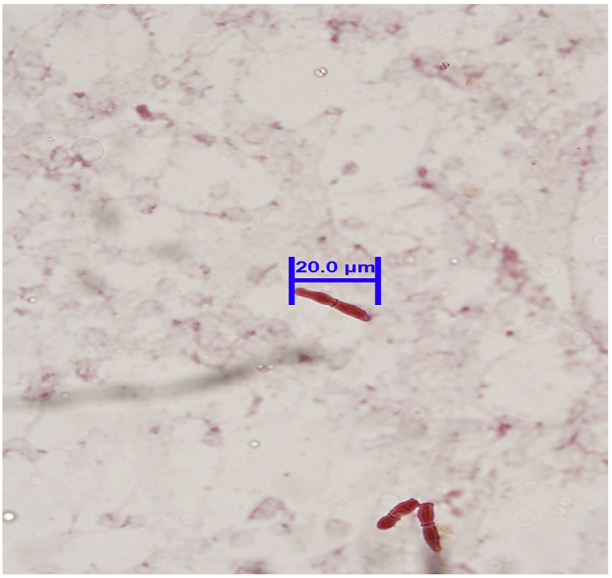

Fig. 1. Gram-stained smears from positive blood cultures showing typical arthroconidial forms of *M. capitatus,* magnification, x 100. Occasionally, the yeast appears red in color, which suggests its weak ability to retain crystal violet stain.

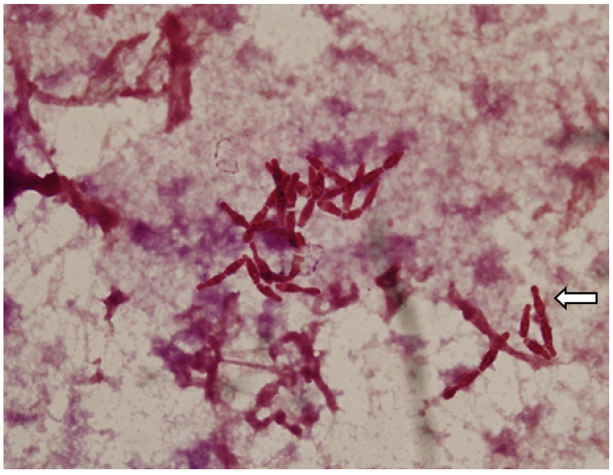

Fig. 2. Some conidia have rounded apex and flat base.

ml) and amphotericin B (0.5 µg/ml). The identity of the isolate as *M. capitatus* was confirmed by PCR amplification followed by DNA sequencing (PCR sequencing) of the internal transcribed spacer (ITS) region of rDNA, performed as described in detail previously [7,8] (Al-Sweih et al., 2005; Khan et al., 2010). The ITS region sequence the isolate showed 100% identity with the sequence from reference *M. capitatus* strain CBS 197.35, thus establishing the identity as *M. capitatus*.

Case 2. A 67-year-old woman with a history of diabetes, hypertension, ischemic heart disease, left ventricular failure, peripheral vascular disease, bronchial asthma and obstructive sleep apnea presented (day 0) with a decreased oral intake, and reduced level of consciousness. On examination, she was afebrile but hypotensive. CT scan of the head ruled out acute brain insult. Blood investigations revealed a high total white cell count of 18×10^9/L, increased neutrophils 13×10^9/L, normal procalcitonin (0.65 ng/mL) and raised serum creatinine (159 µmol/L) indicating acute kidney injury. The patient was in septic shock, so inotropic support was given and she was shifted to intensive care unit (day 0). A central line was inserted, and ceftriaxone and clarithromycin were started. Despite optimal supportive care, patient died next day (day +1). The blood cultures which were collected shortly after admission (day 0) grew a yeast, which was identified *as Saprochaete capitata* by VITEK2 (VITEK2, bioMérieux) and VITEK MS (confidence value 99%). The isolate was tested by Etest (bioMérieux) to determine antifungal susceptibility. It was resistant to caspofungin (MIC ≥32 µg/ml)) and fluconazole (MIC =16 µg/ml), but susceptible to amphotericin B (MIC = 0.5 µg/ml) and voriconazole (MIC = 0.5 µg/ml). By doing PCR amplification followed by DNA sequencing of the ITS region of rDNA, the identity of the isolate as *M. capitatus* was confirmed.

3. Discussion

This report is noteworthy in that it conveys three important messages, firstly, *M. capitatus* fungemia occurred in non-neutropenic and non-hematologic patients, secondly, initial diagnosis was made by characteristic morphological feature of the yeast in blood cultures, and thirdly, it emphasizes the need of prior identification and susceptibility testing since arthroconidial yeast-like fungi are intrinsically resistant to echinocandins. *M. capitatus* (anamorph: *Saprochaete capitate*) is an emerging yeast pathogen associated with considerable mortality in immunocompromised patients [2,3,9–11] (Mazzacato et al., 2015; Tanuskova et al., 2017; Martino et al., 2004; Girmenia et al., 2005, Garcia-Ruiz et al., 2013). The species has acquired considerable clinical significance since several cases of breakthrough *M. capitatus* fungemia, have recently been reported in patients receiving echinocandins [12,13]. (Schuermans et al., 2011; Purohit et al., 2014). Although one of our patients died before antifungal therapy was started, the other patient died 9 days after receiving echinocandin therapy. Incidentally, both of our isolates (Kw1449/18 and Kw2241/18) also showed reduced susceptibility to fluconazole (MIC of 3 µg/ml and 16 µg/ml), respectively.

A study conducted by Kaplan et al., which included 21 *M. capitatus* isolates, revealed that they were resistant to fluconazole and micafungin, but highly susceptible to voriconazole [6]. These findings are consistent with susceptibility results of our two isolates and also with some other reports [9,10,12,14] (Martino et al., 2004; Girmenia et al., 2003; Schuemans et al., 2010; Fernandez-Ruiz et al., 2017).

Mazzacato et al. (2015) [2] reviewed 104 cases of *S. capitate* infection reported between 1977 and 2013. The most common risk factor for *M. capitatus* infection was prolonged neutropenia and majority of them (82%) had hematologic malignancies. Around 75% of the cases were diagnosed by blood cultures, while in the remaining cases (25%), the organism was isolated from other sterile sites, such as CSF, peritoneal fluid or tissue biopsies. Interestingly, 43% of the cases had more than one site involved, including brain, lung, liver, spleen, kidney, gut, bone, and/or bone marrow [2] (Mazzacato et al., 2015). The outcome depended upon the immune status and degree of neutropenia of the host. In patients with profound neutropenia, mortality may exceed 90% [15] (Bouza et al., 2014).

Blood culture is currently the main method for diagnosing patients with fungemia or candidemia. It has the advantage of isolating the etiologic agent to be identified at species level and also to perform susceptibility testing. However, it has a long turn-around time. On average, it takes around 24–48 hours from positive blood culture to identify the species. To shorten this time, the role of direct microscopy using Gram stain has been re-examined in several publications. Harrington et al. [16] have examined the use of yeast morphology by Gram-stained smears in differentiating *Candida albicans* from other yeasts. They have found that the presence of clustered pseudohyphae had a sensitivity, specificity, positive predictive value, and negative predictive value of 85, 97, 96, and 89%, respectively. Likewise, Meretuk & Hamprecht [17] have also assessed the usefulness of microscopic morphologic features of common *Candida* spp. from positive blood

culture in identifying the species. Features such as pseudohypal clusters, the degree of branching, cylindrical and oval blastospores were used to form an algorithm for species identification. The authors reported that 92% of the tested *Candida* isolates were correctly identified using this algorithm. It is well known that a delay in institution of antifungal therapy even by few hours increases mortality several folds in candidemia cases and the same may also apply to *Magnusionmyces* fungemia [18] (Garey et al., 2006).

To the best of our knowledge, the value of direct microscopy in diagnosing *Magnusionmyces* bloodstream infection has not been highlighted in previous studies. The characteristic microscopic features characterized by arthroconidial forms offers a distinct advantage in achieving rapid diagnosis and may help clinicians to choose appropriate antifungal therapy and avoid echinocandins, to which *M. capitatus* and other closely related arthroconidial yeast species are intrinsically resistant (Schuemans et al., 2011; Arendrup et al., 2014) [12,19]. The other arthroconidial yeasts include *Saprochaete clavata, Geotrichum candidum*, and *Trichosporon* spp. which all have high MICs against echinocandin. Currently, no clinical breakpoints or therapeutic guidelines are available for treating *M. capitatus* infection. Based on antifungal susceptibility profiles and limited clinical experience, amphotericin B with, or without flucytosine could be recommended (Arendrup et al., 2014) [19]. It is pertinent to emphasize here that with increasing use of echinocandins in clinical practice, the frequency of infections caused by arthroconidial yeast-like filamentous fungi is likely to increase, warranting greater understanding of their epidemiology, virulence attributes and management strategies.

In conclusion, this report underscores the value of Gram-stained smear from positive blood cultures in the early presumptive diagnosis of *M. capitatus* fungemia. Prompt initiation of appropriate antifungal therapy, while avoiding echinocandin usage, is crucial to improve therapeutic outcome of patients with fungemia caused by arthroconidial yeast-like fungi.

Conflict of interest

There are none.

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