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

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A R T I C L E   I N F O

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A B S T R A C T

Two cases of fungemia caused by Magnusiomyces capitatus, an arthroconidial yeast-like fungus, in non-hematologic immunocompromised patients are described. Both patients died before definitive 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 variably 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 arthroconidial 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 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 x10⁹/L and 23 x 10⁹/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/...
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 $18 \times 10^9$/L, increased neutrophils $13 \times 10^9$/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 $\geq 32 \, \mu g/mL$) 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 capitata*) 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] (Schuemans 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. capitata* 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 Magnusiomyces fungemia [18] (Garey et al., 2006).

To the best of our knowledge, the value of direct microscopy in diagnosing Magnusiomyces 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 (Schemans 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 fluconazole 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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