Case Report

Breakthrough disseminated *Saprochaete capitata* infection in a child with acute myeloid leukaemia receiving caspofungin therapy

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Introduction: We present a fatal case of disseminated infection in a child with leukaemia, caused by *Saprochaete capitata*, an ascomycetous yeast.

Case presentation: The aetiological role of disseminated infection by *S. capitata* in a child with relapsed acute myeloid leukaemia following bone-marrow transplantation was established by its repeated isolation from blood, tracheal secretion and urine samples. The identity of *S. capitata* was confirmed by phenotypic and molecular methods. The isolate showed reduced susceptibility to caspofungin.

Conclusion: This report indicates that patients receiving echinocandin prophylaxis are at risk of breakthrough infections caused by *S. capitata* or other arthroconidial yeast species. To the best of our knowledge, this is the first well-documented case of *S. capitata* infection from the Middle East.

Keywords: Breakthrough infection; echinocandins; fungaemia; *Saprochaete capitata*.

Received 23 March 2014

Accepted 24 March 2014

Introduction

Saprochaete capitata, an anamorph of *Magnusiomyces capitatus* (de Hoog & Smith, 2004), previously known as *Geotrichum capitatum* or *Blastoschizomyces capitatus*, is a rarely reported cause of disseminated disease (Girmenia *et al.*, 2005). It is known to colonize the respiratory and digestive tracts of humans and appears to have similar pathogenesis to other yeast species colonizing mucosal surfaces (Birrenbach *et al.*, 2012). Most cases of *S. capitata* infection have occurred in patients with haematological malignancies and persistent neutropenia receiving chemotherapy (Fouassier *et al.*, 1998; Martino *et al.*, 2004; Girmenia *et al.*, 2005; Miceli *et al.*, 2011; Lafayette *et al.*, 2011; Özkaya-Parlakay *et al.*, 2012; García-Ruiz *et al.*, 2013). Disseminated *S. capitata* infection is associated with high mortality, thus underscoring the need for accurate identification, prior antifungal susceptibility testing and early initiation of specific therapy (Girmenia

et al., 2005). Here, we describe a fatal case of breakthrough *S. capitata* infection in a child who was on empirical caspofungin therapy.

Case report

An 11-year-old Egyptian female, a known case of acute myeloid leukaemia since December 2009, underwent allogeneic bone-marrow transplantation in August 2011. She was admitted for a relapse and received chemotherapy with fludarabine, L-asparaginase and idarubicin. During chemotherapy, she developed fever, cough, renal impairment and bacteraemia with *Stenotrophomonas maltophilia* (susceptible to cotrimoxazole and colistin), and she was transferred to the paediatric intensive care unit (PICU) and started on colistin, caspofungin and metronidazole. During her PICU stay, she remained severely neutropenic (absolute neutrophil count $<100 \text{ mm}^{-3}$) and experienced two more episodes of bacteraemia, one due to *Staphylococcus epidermidis* and the other due to

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; ITS, internal transcribed spacer; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; PICU, paediatric intensive care unit.

The GenBank/EMBL/DBJ accession number for the ITS region and D1/D2 sequences are HG313853 and HG313854, respectively.

Stenotrophomonas maltophilia from blood drawn through the Port-A-Cath. For these infections, she was treated with teicoplanin, colistin, meropenem, clarithromycin and cotrimoxazole. Caspofungin was added empirically in the treatment regimen. The Port-A-Cath was not changed due to the low platelet counts. Tests for *Clostridium difficile* toxin and cytomegalovirus DNA were negative. As she became stable and afebrile for 5 days, meropenem and teicoplanin were discontinued and the patient was shifted back to the ward with continued treatment with caspofungin, clarithromycin and cotrimoxazole. A week later she developed bacteraemia with *Enterobacter cloacae* (an AmpC and extended-spectrum β -lactamase producer) and *Klebsiella pneumoniae*, for which meropenem and amikacin were added to caspofungin, cotrimoxazole and clarithromycin.

As her condition deteriorated with signs and symptoms of tachycardia, tachypnoea, generalized petechiae and sepsis, she was shifted back to the PICU. This time, her peripheral venous blood (on two consecutive days) and repeated cultures of urine and tracheal secretions grew a fungus, identified as *Geotrichum capitatum* by the Vitek 2 system (bioMérieux). The Port-A-Cath was removed and liposomal amphotericin B (AmBisome; Gilead Sciences) was started, but the patient remained drowsy and her oxygen saturation dropped to 85 %, requiring intubation and mechanical ventilation. The laboratory parameters showed haemoglobin at 100 g l^{-1} , white blood cells at 0.048 mm^{-3} , platelets at $7.4 \times 10^9 \text{ l}^{-1}$, blood glucose at 7.8 mmol l^{-1} and creatinine at 118 mmol l^{-1} . A chest X-ray showed features of acute respiratory distress syndrome. In spite of the full inotropic support with dopamine, dobutamine and noradrenaline, she did not respond to the treatment and succumbed to the infection 2 days after removing the Port-A-Cath and starting AmBisome. At the time of her death, she had received meropenem, clarithromycin and colistin for varying durations along with caspofungin for 24 days and AmBisome for 3 days.

The colonies of the yeast isolate on Sabouraud dextrose agar were creamy white and slightly hairy with a fruity odour. On ageing, hyphal growth was predominant at the periphery of the colony. The hyphae were hyaline and disarticulated into arthroconidia. The isolate was able to grow at 42°C . The identity of the isolate as *M. capitatus* was confirmed using a Vitek MS matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) system (bioMérieux) with a confidence value of 99.9 and by sequencing of the internal transcribed spacer (ITS) and D1/D2 regions of rRNA genes, performed according to previously described methods (Al-Sweih *et al.*, 2005; Khan *et al.*, 2008). The D1/D2 region sequence of our isolate showed 100 % identity with reference *M. capitatus* strain CBS 197.35 whilst the ITS region sequence showed four nucleotide difference compared with corresponding sequences from *M. capitatus* strains CBS 162.80 and CBS 197.35, thus establishing the identity of our isolate as *M. capitatus*.

Three isolates, one each from blood, urine and tracheal aspirate, were tested for MICs by Etest against amphotericin B, fluconazole, voriconazole and caspofungin. The test was performed according to manufacturer's instructions as described previously (Al-Sweih *et al.* 2005). Reference strains of *Candida parapsilosis* (ATCC 22019) and *Candida albicans* (ATCC 90028) were used for quality control. Although there are no susceptibility breakpoints available for *S. capitata* or other arthroconidial yeast species, the isolates were considered susceptible to amphotericin B (MIC $0.094\text{--}0.19 \text{ }\mu\text{g ml}^{-1}$), fluconazole (MIC $0.75\text{--}1.0 \text{ }\mu\text{g ml}^{-1}$) and voriconazole (MIC $0.094\text{--}0.25 \text{ }\mu\text{g ml}^{-1}$) but showed reduced susceptibility to caspofungin (MIC $>32 \text{ }\mu\text{g ml}^{-1}$) (Pfaller & Diekema, 2012; García-Ruiz *et al.*, 2013).

Discussion

A case of disseminated *S. capitata* in a child with relapsed acute myeloid leukaemia following bone-marrow transplantation is described. The aetiological role of the fungus was established by its repeated isolation from blood, tracheal secretion and urine. It was unfortunate that by the time the fungus was isolated from blood and antifungal susceptibility results were available, it was too late to manage the patient appropriately. In fact, this is a case of breakthrough *S. capitata* infection, where the patient was treated empirically with caspofungin for more than 3 weeks. Consistent with our case, there are previous reports of breakthrough *S. capitata* infections in leukaemic patients on caspofungin/micafungin prophylaxis (Giacchino *et al.*, 2006; Bonini *et al.*, 2008; Chittick *et al.*, 2009; Schuermans *et al.*, 2011). All these cases succumbed to *S. capitata* infection (Schuermans *et al.*, 2011). More recently, García-Ruiz *et al.* (2013) reported five cases of disseminated *S. capitata* infection in patients with advanced haematological malignancies. Four of these patients received antifungal therapy with caspofungin and one with fluconazole. All the isolates showed reduced susceptibility to caspofungin (8 to $>16 \text{ }\mu\text{g ml}^{-1}$) and fluconazole ($2\text{--}32 \text{ }\mu\text{g ml}^{-1}$). Based on the above reports, it is imperative that the prophylactic or empirical use of fluconazole and caspofungin is not advisable for the treatment of neutropenic fever in high-risk patients, particularly in institutions where this yeast is frequently isolated from clinical specimens.

There is a paucity of data on the antifungal susceptibility of *S. capitata* (Miceli *et al.*, 2011). Girmenia *et al.* (2003) performed antifungal susceptibility testing on 23 *Geotrichum capitatum* strains comparing the Clinical and Laboratory Standards Institute (CLSI) microdilution method with Sensititre and agar diffusion methods. According to the authors, amphotericin B and voriconazole were the most active drugs, with MIC₉₀ values of 0.125 and $0.25 \text{ }\mu\text{g ml}^{-1}$ by the CLSI method, respectively. In this study, echinocandins were not tested. In a subsequent study, Cuenca-Estrella *et al.* (2006) reported antifungal

susceptibility results for 25 strains of *Dipodascus capitatus* and 12 strains of *Galactomyces geotrichum*. Both these species showed reduced susceptibility to caspofungin with a MIC₉₀ value of >16 µg ml⁻¹. This report suggests that caspofungin has only limited activity against ascomycetous yeast species with arthroconidial characteristics, and thus may not be an effective prophylactic agent in leukaemic patients receiving cytotoxic therapy. Here attention may also be drawn to the reports of breakthrough *Trichosporon* infection in leukaemic patients receiving caspofungin therapy (Matsue *et al.*, 2006; Chitasombat *et al.*, 2012). *Trichosporon* spp., although belonging to the basidiomycetous lineage, are similar in their arthroconidial morphological characteristics as well as in susceptibility profile to echinocandins (Cuenca-Estrella *et al.*, 2006; Miceli *et al.*, 2011). As echinocandins are now being used as first-line drugs for the treatment of *Candida* infections, it is important that yeast isolates are accurately identified and antifungal susceptibility determined before an echinocandin is prescribed. It is reasonable to speculate that, in centres where caspofungin or other echinocandins have replaced fluconazole, cases of breakthrough infections due to *S. capitata* or other arthroconidial yeasts may be encountered with greater frequency. In this context, recent reports of the isolation of multidrug-resistant strains of *S. capitata* are noteworthy (Savini *et al.*, 2011; Villa López *et al.*, 2013). Although reports on the emergence of multi-drug-resistant strains are sporadic, it is a cause of concern to clinicians because of the availability of limited choices of antifungal drugs for optimal management.

Due to taxonomic changes supported by phenotypic and molecular characteristics, the species previously considered in the genus *Geotrichum* have now been assigned to different teleomorphic genera, such as *Geotrichum capitatum* (*S. capitata*) under *Magnusiomyces* as *M. capitatus* and *Geotrichum candidum* to *Galactomyces* as *G. candidus*, whereas *Dipodascus geotrichum* is a synonym of *Galactomyces geotrichum* within the genus *Galactomyces* (Kurtzman *et al.*, 2011). Although the taxonomic position of our isolate was established unequivocally by sequencing of the ITS and D1/D2 regions of rRNA genes, as well as by MALDI-TOF MS analysis, we had difficulty in its identification, as the Vitek2 assimilation profile of all three strains (from blood, endotracheal secretion and urine) showed it as urease positive, even though it was identified as *G. capitatum* (bionumbers 7510124002025511/7510104002005110) with 93–96 % probability. However, when these three strains were tested on Christensen's urea agar, they were urease negative. Recently, Kolečka *et al.* (2013) evaluated a MALDI-TOF MS system for identification of 72 strains of arthroconidial yeasts belonging to the genera *Galactomyces*, *Geotrichum*, *Saprochaete* and *Magnusiomyces*. Concordant results in comparison with molecular identification based on ITS and/or large subunit rRNA gene sequences were obtained in 98 % of the isolates.

S. capitata is widely distributed in the environment and occurs in diverse natural substrata including dairy

products (Bouakline *et al.*, 2000; Pottier *et al.*, 2008). However, it is unclear why most of the cases (>87 %) of disseminated infections have been reported from Mediterranean region countries in Europe, mainly from Italy, Spain and France (Girmenia *et al.*, 2005; Birrenbach *et al.*, 2012). Recently, five cases of *S. capitata* (*B. capitatus*) have been reported from the temperate zone of Switzerland. Environmentally, the species may be more prevalent in geographic areas of relatively high humidity and temperature, and its geographic distribution may gradually extend to other areas, possibly as a consequence of global warming (Birrenbach *et al.*, 2012). Like other opportunistic yeasts colonizing the gastrointestinal tract, it is reasonable to infer that *S. capitata* infection originates from the gastrointestinal tract, where damaged mucosa as a result of cytotoxic therapy facilitates invasion and haematogenous dissemination. In this context, a recent report of a nosocomial outbreak of *S. capitata* infection in a haematological unit linked to consumption of contaminated milk is noteworthy (Gurgui *et al.*, 2011). Infections with arthroconidial yeast species yield higher recovery rates in blood cultures (~80 %), show a greater propensity to cause tissue invasion and are associated with higher mortality (Martino *et al.* 2004; Girmenia *et al.*, 2005; Birrenbach *et al.*, 2012).

In conclusion, to the best of our knowledge, this is the first documented case of disseminated *S. capitata* from the Middle East. The report highlights the fact that patients receiving echinocandins for prolonged periods may be susceptible to breakthrough infection with *S. capitata* or other arthroconidial yeasts, which tend to exhibit reduced susceptibility to these drugs.

Acknowledgements

The authors gratefully acknowledge the technical help of Sandhya Vayalil.

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