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Septic shock due to *Candida famata* (*Debaryomyces hansenii*) candidemia in an ICU immunocompetent trauma-patient

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ABSTRACT

Sepsis related to *Candida famata (C. famata)* fungemia is extremely rare in immunocompetent patients. Moreover, septic shock has not been reported due to this yeast.

A previously healthy young multi-trauma male, presented septic shock from C. famata, after he had been admitted in the Intensive Care Unit (ICU) due to haemorrhagic shock. Risk factors for candidemia in ICU patients are the presence of a central venous catheter (CVC), Total Parenteral Nutrition (TPN), use of broad-spectrum antimicrobials, immunosuppression and the length of ICU stay. The presence of CVCs, prior use of antibiotics, prolonged hospitalization, disruption of skin flora and immunocompromised states have been identified as predisposing risk factors for *C. famata* fungemia. It is worth noting that the present case concerns a non-immunocompromised patient, but long ICU stay and brain injury may indicate a state of immunoparalysis.

Identification of the yeast was performed by partial amplification and sequencing of the 26S ribosomal DNA gene [hypervariable region D1/D2; partial sequencing of the *act1* gene confirmed the identity of the strain as *Debaryomyces hansenii* (GenBank submission ID: 1688297)]

The patient quickly recovered from sepsis after initiation of amphotericin B and was discharged on the 60th day.

Case presentation

A 25-year-old male, otherwise healthy, was admitted in the ICU with haemorrhagic shock after a car accident. He suffered from severe traumatic brain injury, left-sided haemothorax with multiple lung contusions (a chest tube was placed) and fractions of the pubic and hip branches, stabilized with external fixation. Splenectomy and embolization of the right internal iliac artery was performed for haemodynamic stabilization. Fifteen units of packed red blood cells were administered in the first two days. Acute Respiratory Distress Syndrome (ARDS) of moderate severity (PaO_2/FiO_2: 140) quickly improved.

During the first month of ICU stay the patient required broad-spectrum antibiotics for the multiple severe infections that he suffered (Ventilation Associated Pneumonia, VAP), complicated urinary tract infection and surgical site infection, as a deep wound at the point of the left external fixation required repeated surgical debridement. The isolated pathogens were: multidrug-resistant *Acinetobacter baumannii* (bronchial aspirates), *Proteus mirabilis* (urine), and multidrug-resistant *Klebsiella spp* (tissue debridements). On the 35th day, being afebrile and off antibiotics for the last 5 days, his condition deteriorated, developing high fever (39 °C) and hypotension. Tigecycline, colistin and metronidazole were administered. Blood, bronchial, urine samples and central venous catheter tips cultures were negative. As the patient remained febrile, daptomycin and anidulafungin (200 mg load-

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BSI, Blood Stream Infection; C. famata, Candida famata; CLSI, Clinical and Laboratory Standards Institute; CRBSI, Catheter Related Blood Stream Infection; CVC, Central venous catheter; EUCAST, European Committee on Antimicrobial Susceptibility Testing; ICU, Intensive Care Unit; ITS, Internal Transcribed Spacer; MDR, Multi Drug Resistant; MIC, Minimal Inhibitory Concentration; PICC, Peripherally Inserted Central Catheter; TPN, Total Parenteral Nutrition.

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Table 1
The table summarizes the cases of Candida famata severe infections reported in the literature. The primary disease and clinical presentation of the infection, risk factors, therapeutic options and outcome is presented for each case.

References Infection site	Primary disease Clinical presentation of the infection	Risk factors	Treatment/outcome
Quindos et al. [3] Peritonitis	76-year old male Chronic renal failure Peritoneal dialysis (peritoneal catheter) Initially misdiagnosed as C. guilliermondii	Chronic renal failure Peritoneal dialysis Peritoneal catheter Broad spectrum antibiotics	Fluconazole/ Death (respiratory failure)
Carrega et al. [4] CRBSI Pleural fluid Urine	69-year old female Cephalo-duodeno −pancreasectomy	Surgery Broad-spectrum antibiotics	Fluconazole (18 days)/ Discharged in good condition
Krcmery and Kunova [5] BSI	24-year old female Liver carcinoma	Chemotherapy Central venous catheter Broad-spectrum antibiotics	Amphotericin-B (11 days) Microbiological eradication Death (septic shock due to S. aureus, S. viridans, E. faecalis BSI)
Wagner et al. [6] CRBSI Invasive pulmonary infection	66-year old Severe aplastic anemia Myelodysplastic syndrome Hematopoietic stem cell transplantation	Immunosuppression Broad spectrum antibiotics	Liposomal amphotericin-B Caspofungin Switch to voriconazole/ Death
Gupta et al. [7] Peritonitis	35-year old Renal transplant on peritoneal dialysis Sclerosing peritonitis	Immunosuppression Peritoneal dialysis	Fluconazole plus intraperitoneal amphotericin-B Switch to voriconazole/ Death
Struck et al. [8] Disseminated C. famata infection [C. famata invasion detected on histological examination in stomach, heart, kidneys, spleen, leptomeninges, lung, liver] Central line tip	20-year old male Burn injury (26% of Total Body Surface Area) Septic Shock −Multiorgan Failure	Necrosectomy −mesh graft transplantation Multi-transfusions of blood products ARDS Hydrocortisone Broad spectrum antibiotics Hemodialysis Severe neutropenia (800/μL) after surgery	Death
Turunc et al. [9] 7 burn patients	Mean age 22,2 years Burn injury	Central venous catheter Broad spectrum antibiotics	Amphotericin-B/UNK
Beyda et al. [2] CRBSI	60-year old Acute myelogenous leukemia	Chemotherapy Broad spectrum antibiotics PICC	Micafungin, amphotericin-B Clinical and microbiological cure.
Beyda et al. [2] CRBSI	Elderly (>80-year old) male Recent hospitalization for pneumonia, megacolon (TPN, rectal tube placement)	Chronic Kidney disease Chronic Obstructive Pulmonary Disease TPN Broad-spectrum antibiotics Hemodialysis	Micafungin/clinical and microbiological cure

CRBSI: Catheter Related Blood Stream Infection, BSI: Blood Stream Infection, ARDS: Acute Respiratory Distress Syndrome, PICC: Peripherally Inserted Central venus Catheter, TPN: Total Parenteral Nutrition, UNK: unknown.

ing dose followed by 100 mg daily) were empirically started until the 45th ICU day, when *Pseudomonas aeruginosa* (MIC 0.25 mg/L for ciprofloxacin and MIC <0.5 for colistin) was identified in the blood. Antimicrobial therapy was de-escalated to colistin and ciprofloxacin. Despite appropriate antibiotic therapy, his condition did not improve (fever of 38.4 °C, tachycardia and positive daily fluid balance). Three days later, his condition deteriorated further, presenting severe septic shock (white blood cells 21.900 cells/mm^3, C-reactive protein 7 mg/dl; normal value <0.5 mg/dl). Tigecycline and metronidazole were re-administered and liposomal amphotericin-B, 300 mg/daily, was added.

Blood cultures obtained on the 48th day turned positive for yeast. Antifungal susceptibility of the isolate was not available until five days had passed. The patient's clinical condition improved two days after the introduction of liposomal amphotericin-B (given for 21 days), while antipseudomonal treatment was continued (colistin and ciprofloxacin for 11 days in total). All subsequent blood cultures turned negative. The patient was discharged on the 60th day.

The yeast growing from the blood cultures was identified as *C. famata.* Subsequent sequencing of the Internal Transcribed Spacer (ITS) (GenBank Accs. Nos KF726845;KF726846), of the 26S ribosomal DNA gene hypervariable D1/D2 region (KF726845) and partial sequencing of the *act1* gene (GenBank submission ID: 1688297) confirmed the identity of the strain as *Debaryomyces hansenii*. Antifungal susceptibility of the isolate, as determined by the EDef

7.2 European Committee on Antimicrobial Susceptibility Testing (EUCAST) microdilution method [1], was as follows: amphotericin-B 0.5 mg/L; anidulafungin and micafungin 1 mg/L; caspofungin 2 mg/L; flucytosine 0.12 mg/L; fluconazole > 64 mg/L; voriconazole, posaconazole and itraconazole 0.25 mg/L.

Discussion

This is the first reported case of septic shock in a previously healthy, immunocompetent patient caused by *C. famata.*

The presence of CVCs, prior antibiotic prescription, prolonged hospitalization, disruption of skin flora and immunocompromised states have been identified as predisposing risk factors for *C. famata* fungemia [2]. Interestingly, in all reported cases (summarized in Table 1) the infection concerned immunocompromised hosts and burn patients; while immunocompetent considered patients had chronic renal disease requiring hemodialysis [2–9]. A patient with burn injuries suffered fulminant invasive C. famata fungemia after having undergone transplantation, also presenting severe neutropenia [8]. In our case, *C. famata* fungemia evolved in an immunocompetent multi-trauma patient with brain injury. His condition was complicated with ARDS and hemorrhagic shock after multi blood transfusions, and had a long ICU stay. Moreover, he presented multiple severe septic episodes and received broad spectrum antibiotics against MDR pathogens, including an antifungal agent, and had undergone repeated surgical debridements, which probably further worsened a state of immunoparalysis existing in ICU multi-trauma patients; yet, central venous and arterial catheters as well as urinary catheters were always present, as this is mandatory in critically-ill patients.

C. famata, anamorph *of D. hansenii*, is present in the normal microbiota, in sea water and dairy products like cheese and it is considered an opportunistic pathogen. It accounts for only 0.08-0.5% of isolates in invasive candidiasis [2,10]. Severe trauma and surgical patients, especially when splenectomy and multiple blood transfusions are needed, present higher risk for candidemia among other ICU patients [11–13]. In these patients, both innate and adaptive immune dysfunction has been described, leading to immunoparalysis. In particular, tissue injury due to trauma or surgery causes a selective depression of T_H1 function and a shift towards a T_H2 response pattern thus leading to cell-mediated immune suppression [14,15].

C. famata exhibits high osmotolerability. Other candida spp., especially *C. guilliermondii* and *C. parapsilosis*, could be misidentified phenotypically as *C. famata.* Misidentification may impact the clinical course of the patients as different species present differences in antibiotic susceptibility profiles. Lack of clinical improvement should alert clinicians to revise the diagnosis, the implicated pathogens or the therapeutic choices. Only 3 out of 26 isolates initially identified by phenotypic methods as *C. famata*, were finally confirmed, by sequencing the ITS and D1/D2 region of rRNA gene. Therefore, *C. famata* fungemia may be even rarer than it is believed as, in most of the reported cases, the species were identified using phenotypic parameters [16]. Proteomic-based identification methods such as the matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS), may become interesting alternatives to DNA-based methods [17]. Usually, the fungus is detected in the anamorph state. In our subject, candida strain was isolated in its teleomorphic state *D. hansenii*. There are no data, regarding to whether the teleomorphic state plays a role in its virulence.

C. famata appears to exhibit reduced in vitro susceptibility to echinocandines and azoles [1]. In our case, the isolate had an MIC of 1 mg/L to anidulafungin; however, breakpoints for *C. famata* are not yet set either by Clinical and Laboratory Standards Institute (CLSI) or EUCAST, so MIC values are only indicative and do not predict the therapeutic outcome [1]. Possibly, anidulafungin limited but did not resolve sepsis; the septic shock appeared when the echinocandin was stopped. Liposomal amphotericin-B administration resulted in excellent response. Until now, prompt initiation of therapy with liposomal amphotericin-B seems the most suitable antifungal agent for *C. famata* Blood Stream Infections [2].

In conclusion, prolonged ICU stay after severe trauma, multiple catheter presence, and prolonged use of antibiotics, are risk factors for developing fungemias not only from usual fungi, but also for developing sepsis and septic shock from rare ones, such as *D. hansenii (C. famata),* even in immunocompetent considered subjects. Accurate recognition of *D. hansenii* requires expert laboratory identification procedures. Liposomal amphotericin seems to be the best antifungal treatment.

Competing interests

None declared.

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