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Candida haemulonii: An emerging opportunistic pathogen in the United States?

Michael Coles*, Kayla Cox, Andrew Chao

Augusta University, 1120 15th Street, Augusta, GA, 30912, USA

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ABSTRACT

Candida species are ubiquitous fungal pathogens that exhibit increasing resistance to anti-fungal agents. *Candida haemulonii*, a rare subtype, is an emerging and virulent yeast pathogen. Species identification is difficult due to phenotypic similarity to other *Candida* subtypes, such that there is a high risk of inappropriate antimicrobial administration and worsening of emerging resistance patterns. *Candida haemulonii* has a proclivity for infection of chronic lower extremity wounds particularly in diabetic patients, as exemplified in our case. This case raises awareness about the necessity for expeditious identification and antimicrobial stewardship directed to a highly resistant emerging pathogen.

Introduction

Candida species have emerged as potentially deadly opportunistic pathogens among hospital and other health care settings, in part due to resistance to azoles and amphotericin B. Invasive candidiasis caused by atypical non-*albicans* species is increasingly reported [1,2]. Reports of *C. haemulonii* infection have been wide spread, ranging from South America, Asia, the Middle East and Europe [3]. The first case report of *C. haemulonii* infection in the United States was in 1991 [3]. To our knowledge, our patient is the second reported case of *C. haemulonii* infection in the United States, and highlights the diagnostic and therapeutic challenges specific to this organism.

Case presentation

Our patient is a 61-year-old African-American man with a past medical history significant for uncontrolled type-2 diabetes mellitus with polyneuropathy and diabetic ulcers, end-stage renal disease on hemodialysis, multi-vessel coronary artery disease post-bypass grafting, chronic systolic heart failure with reduced left ventricular ejection fraction, and peripheral vascular disease. He had a known chronic non-healing wound over his left foot third digit which over time became persistently painful and developed skin changes concerning for dry gangrene. He was referred for a vascular surgery evaluation, however prior to his appointment he noted increasing pain, swelling with development of purulent drainage. He was then hospitalized for further treatment. The clinical impression was that of progression of dry gangrene into wet gangrene, requiring amputation. No intraoperative cultures from the amputation were sent. Intraoperative cultures were not obtained. Histopathology showed evidence of extensive soft tissue infection but no osteomyelitis. The patient underwent right and left lower limb angioplasty and stenting of left superficial femoral artery/popliteal artery, and angioplasty of left anterior tibial artery. He was discharged home on oral cephalexin.

He presented back to the hospital 8 days later due to bleeding and purulent drainage from his amputation site with necrotic skin changes of his left 2nd and 4th toes. He was well-appearing with stable vital signs and without leukocytosis but did have an ESR elevated at 135 mm/hr. CT imaging demonstrated a soft tissue tract from the surgical amputation site tracking to the left third metatarsal head with mild lucency of the distal most portion of the third metatarsal, concerning for osteomyelitis. He subsequently underwent amputation of left foot 2nd and 4th digits with debridement of the 3rd toe surgical site. He was treated with empiric intravenous vancomycin and piperacillin/tazobactam. Intra-operative tissue was sent for culture and *Candida haemulonii* was identified using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Intravenous micafungin was then added to his antimicrobial regimen. The pathology report of his 3rd toe surgical margins indicated findings of osteomyelitis in the proximal bony margins despite prior debridement. One week post-operatively the patient's left 5th toe began showing signs of necrosis despite antifungal medication, thus necessitating further surgical intervention. The patient was then taken back to operating room for left 5th digit amputation

* Corresponding author.
E-mail address: micoles@augusta.edu (M. Coles).

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Table 1
In vitro antifungal susceptibility panel of *Candida haeumulonii* performed *via* broth microdilution.

Drug	MIC (mg/L)
5-Flucytosine	4
Amphotericin B	1
Anidulafungin	0.12
Caspofungin	0.03
Fluconazole	0.06
Itraconazole	0.25
Micafungin	0.06
Posaconazole	0.06
Voriconazole	0.12

with further surgical debridement of the 3rd toe stump. The cultures grew *Candida haeumulonii*.

In vitro antifungal susceptibility testing (Table 1) was performed *via* broth microdilution. There are currently no standard antifungal susceptibility breakpoints for *Candida haemulonii* from either CLSI or EUCAST recommendations. The most recent version of EUCAST breakpoints (2020-02-04) does have fluconazole susceptibility and resistance breakpoints for *Candida* species other than *C. glabrata* or *C. krusei*, under which an MIC of $\leq$2 mg/L would be considered susceptible.

Based on culture data and organism susceptibilities, the patient was discharged on fluconazole 200 mg daily (adjusted for his dialysis dependence) with outpatient follow up in 6 weeks. At follow up he had incomplete wound healing and fluconazole was to be continued for 6 more weeks. The patient experienced cardiac arrest during dialysis shortly after his follow up visit and expired.

Discussion and conclusions

This case raises awareness about the necessity for expeditious identification and antimicrobial stewardship regarding a frequently emerging and resistant pathogen. Clinical disease can vary, ranging from superficial infection to invasive candidiasis; several cases of *C. haemulonii* candidemia have also been reported [5]. *C. haemulonii* candidiasis is associated with peripheral vascular disease, diabetes mellitus and chronic leg ulcers [6]. One study found a 60 % incidence in patients with chronic foot infections, all of whom had uncontrolled diabetes [7]. This has concerning implications for the U.S. given the prevalence of diabetes and its complications.

Closely-related species include *Candida auris* and *Candida pseudohaemulonii,* both notoriously drug-resistant. Several commercial yeast identification systems, particularly traditional phenotypic identification methods, have proven unreliable in differentiating these species [7]. *C. auris* has been misidentified as *C.haemulonii;* identification using the Vitek system was only able to identify 29 % of *C. haemulonii* isolates compared to 100 % identification using MALDI-TOF MS [8]. This highlights the challenges in accurate and timely diagnosis of *C. haemulonii*. There is limited data on misidentification of *C. haemulonii* and we cannot discount the possibility that it has a higher incidence within North America than reported.

Infection with *C. haemulonii* is associated with resistance to amphotericin B [9], itraconazole and fluconazole [10]. Echinocandins, posaconazole and voriconazole have demonstrated potent *in vitro* activity against this species [11], although high MICs to echinocandins have been reported in individual cases [3]. In our patient *C haemulonnii* was found to be fully susceptibility to all azoles and echinocandins; the amphotericin B MIC was borderline susceptible. A standard treatment regimen has yet to be established due to the highly variable resistance pattern and limited treatment data. This highlights the need for timely identification and antifungal susceptibility testing, and for detailed documentation of accruing clinical experience with this organism.

In conclusion, *C. haemulonii* is difficult to identify using conventional methods and challenging to treat due to its wide, yet variable, resistance to many common antifungals. Our patient is the second reported case of *C. haemulonii* in the US, with the first case reported in 1991. The proclivity of this species for chronic lower extremity wounds in diabetic patients highlights the importance of recognition of this pathogen in light of the growing population of diabetics in the U.S.

Author contribution

Michael Coles: Drafted and assembled the manuscript
Kayla Cox: Drafted and assembled the manuscript
Andrew Chao: Edited the manuscript and revised for important intellectual content

Declaration of Competing Interest

No conflict of interest exists.

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-Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request

CRediT authorship contribution statement

Michael Coles: Conceptualization, Writing - original draft. **Kayla Cox:** Conceptualization, Writing - review & editing, Visualization. **Andrew Chao:** Supervision, Writing - review & editing.

References

[1] Pfaller MA, Diekema DJ. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of Candida. Clin Microbiol Infect 2004;10(Suppl. 1):11–23.
[2] Garcia-Martos P, Dominguez I, Marin P, Garcia-Agudo R, Aoufi S, Mira J. [Antifungal susceptibility of emerging yeast pathogens]. Enferm Infecc Microbiol Clin 2001;19(6):249–56.
[3] Kumar APA, Singh A, et al. Candida haemulonii species complex: an emerging species in India and its genetic diversity assessed with multilocus sequence and amplified fragment-length polymorphism analysis. Emerg Microbes Infect 2016;5(5).
[5] Kim S, Ko KS, Moon SY, Lee MS, Lee MY, Son JS. Catheter-related candidemia caused by Candida haemulonii in a patient in long-term hospital care. J Korean Med Sci 2011;26(2):297–300.
[6] Ben-Ami RB, Berman J, Novikov A. Multi-drug resistant candida haemulonii and c. auris, Tel Aviv, Israel. Emerg Infect Dis. 2017;23(2):195–203.
[7] Kathuria S, Singh PK, Sharma C, Prakash A, Masih A, Kumar A, et al. Multidrug-resistant Candida auris misidentified as Candida haemulonii: characterization by matrix-assisted laser desorption ionization-time of flight mass spectrometry and DNA sequencing and its antifungal susceptibility profile variability by Vitek 2, CLSI broth microdilution, and etest method. J Clin Microbiol 2015;53(6):1823–30.
[8] Hou X, Xiao M, Chen SC, Wang H, Cheng JW, Chen XX, et al. Identification and antifungal susceptibility profiles of Candida haemulonii species complex clinical isolates from a multicenter study in China. J Clin Microbiol 2016;54(11):2676–80.
[9] Shin JH, Kim MN, Jang SJ, Ju MY, Kim SH, Shin MG, et al. Detection of amphotericin B resistance in Candida haemulonii and closely related species by use of the Etest, Vitek-2 yeast susceptibility system, and CLSI and EUCAST broth microdilution methods. J Clin Microbiol 2012;50(6):1852–5.
[10] Khan ZU, Al-Sweih NA, Ahmad S, Al-Kazemi N, Khan S, Joseph L, et al. Outbreak of fungemia among neonates caused by Candida haemulonii resistant to amphotericin B, itraconazole, and fluconazole. J Clin Microbiol 2007;45(6):2025–7.
[11] Ruan SY, Kuo YW, Huang CT, Hsiue HC, Hsueh PR. Infections due to Candida haemulonii: species identification, antifungal susceptibility and outcomes. Int J Antimicrob Agents 2010;35(1):85–8.