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Candida nivariensis, an emerging fungus causing peritonitis in a patient receiving peritoneal dialysis

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ABSTRACT

Fungal peritonitis (FP) is usually associated with poor patient outcomes and is mostly caused by non-*albicans Candida* species. We present a *Candida nivariensis*-associated peritonitis in a 68-year-old woman with end-stage kidney disease on peritoneal dialysis (PD). Biochemical profiling of the cultured yeast of the effluent sample did not adequately identify the yeast. Hence, molecular phylogeny and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-TOF) mass spectroscopy were employed which correctly identified the causative species, *C. nivariensis*. PD catheter was removed and oral fluconazole was promptly started according to the 2022 International Society for PD (ISPD) Peritonitis Guidelines. However, the patient achieved only a partial clinical response and eventually died. The susceptibility test showed that the pathogen was susceptible to amphotericin B and voriconazole but resistant to other triazoles. This report underlines the importance of identifying the species, though rarely reported, and the drug susceptibility of the organism.

1. Introduction

Candida species are common human pathogenic yeasts, causing invasive candidiasis and mucosal *Candida* infections [1]. *Candida nivariensis* is an emerging pathogenic yeast genetically related to *Candida glabrata* [2]. In 2005, this *Candida* species was isolated in the broncho-alveolar lavage, blood, and urine over 3 years of three patients from a Spanish hospital [3]. Subsequently, it was described as a causative agent of candidemia, oropharyngeal candidiasis, and vulvovaginal candidiasis [4,5]. Previous studies based on isolations from deep, usually sterile body fluids/sites such as pleural fluid, ascitic fluid, peritoneal dialysis (PD) effluent (PDE), pelvic abscess, and lower respiratory tract indicate that this pathogen is widely distributed in clinical specimens and relevant in human infections [2,6,7]. Furthermore, *C. nivariensis* frequently exhibit multidrug resistance to azole antifungal agents [5]. Heretofore, only 2 cases of *C. nivariensis* have been isolated from PD patients (an exit-site swab and PDE), but without clinical information [2]. Herein, we report the case of *C. nivariensis*-associated peritonitis from PDE. The patient had an unfavorable outcome, albeit adequate treatment according to the 2022 International Society for PD (ISPD) Peritonitis Guidelines [8].

2. Case presentation

A 68-year-old woman with end-stage kidney disease (ESKD), who had been on continuous ambulatory PD (CAPD) for 12 years and had a

Abbreviations: PD, Peritoneal dialysis; PDE, Peritoneal dialysis effluent; ESKD, End-stage kidney disease; CAPD, Continuous ambulatory peritoneal dialysis; ISPD, International Society for Peritoneal Dialysis; IP, Intraperitoneal; KCMH, King Chulalongkorn Memorial Hospital; ITS, Internal transcribed space; MIC, Minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute.

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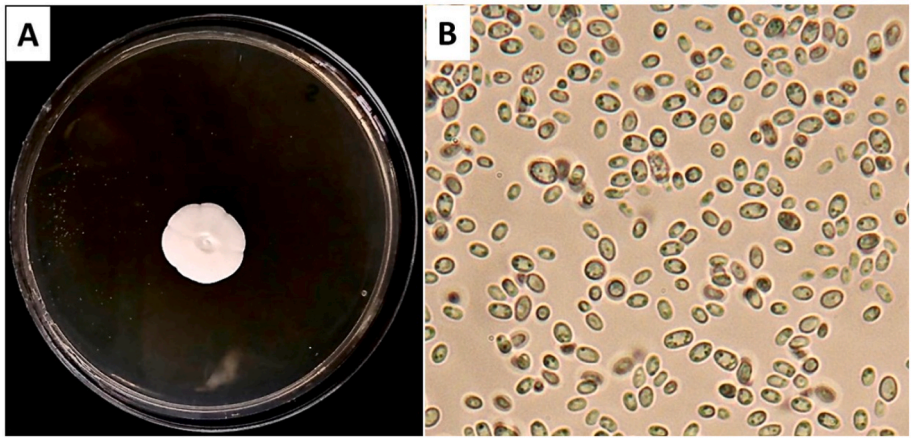

Fig. 1. (A) *Candida nivariensis* colony on SDA after 10 days of incubation at 25 °C. (B) *C. nivariensis* yeast cells by using KOH examination viewed under a microscope (× 1000).

history of three prior episodes of peritonitis presented with cloudy effluent, abdominal pain, and diarrhea for 1 day. PDE leukocyte count on day 0 was 484 cells/μl (92% neutrophils). The patient was initially diagnosed with PD-related peritonitis and immediately started a 2-week empirical antibiotic therapy with intraperitoneal (IP) cefazolin and ceftazidime at dosages of 1 gm daily each. PDE culture from day 0 demonstrated no microbial growth (day +7). Treatment with cefazolin and ceftazidime proved ineffective as the patient still had cloudy dialysate with a rising PDE leukocyte count of 1474 cells/μl (neutrophil 93%)(day +12). Therefore, the treatment was changed to IP vancomycin (1 gm) for 3 days. The PD bag was submitted to the King Chulalongkorn Memorial Hospital (KCMH) Microbiology Laboratory for microbial identification (day +13). On day +16, the PDE inoculated media depicted yeast growth (Fig. 1). Hence, she was diagnosed with fungal peritonitis. The PD catheter was removed and the patient was transferred to hemodialysis.

Oral fluconazole at a dosage of 200 mg daily was prescribed according to the 2022 ISPD Peritonitis Guidelines for14 days (day +16 to day+29). Unfortunately, her abdominal pain persisted, and abdominal imaging was done resulting in generalized bowel swelling without specific pathology. She was discharged from the hospital on day +30 for out-patients hemodialysis 3 times/week and passed away on day +34 from an unknown etiology, possibly due to peritonitis-associated death according to the 2022 ISPD Peritonitis Guidelines (defined as death occurring within 30 days of peritonitis onset or death during hospitalization due to peritonitis) [8].

Initially, identification was based on VITEK-2® yeast identification system. The system showed a low discrimination organism between *C. magnoliae* and *C. norvegensis* and gave a numerical bionumber code of 4001104000000111. Hence, the system could not be trusted and was deemed as unable to identify the pathogen. Then, the ancillary assessment with VITEK-MS (IVD Knowledgebase v.3.0) (bioMérieux, Marcy l' Etoile, France) using Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology was employed and the result indicated that the pathogen was *C. nivariensis* (99.9% confidence value).

To confirm species identification, molecular phylogeny was used. The molecular phylogenetic analysis was based on DNA sequence data of the internal transcribed spacer (ITS) regions and the D1-D2 hypervariable region. The two genes were amplified using polymerase chain reactions (PCR) with the universal fungal primer, ITS1/ITS4 (White et al., 1990) and 5.8SR/LR7 primer (Vilgalys lab, Duke University). Raw reads from the sequencing company demonstrated 98.3% (1242/1653, accession number KP131741.1) and 100% (905/905, accession number MK503937.1) similarity to *C. nivariensis* (ITS and LSU, respectively) when subjected a blast search against the GenBank nucleotide base.

To determine the minimum inhibitory concentrations (MIC), Epsilometer test (E-test) (bioMérieux, Marcy l' Etoile, France) were performed. In brief, 0.5 McFarland yeast suspension was prepared in sterile saline (0.85% sodium chloride, pH 6.0). Then, the yeast suspension was streaked onto Roswell Park Memorial Institute (RPMI) agar plates, antifungal strips were applied onto the agar, and plates were incubated at 25 °C. The MICs against the antifungal agents was based on the Clinical and Laboratory Standards Institute (CLSI) M27-A2 and determined at 48 Hr [9]. The susceptibility to antifungal agents of the pathogen was referenced to microbroth dilution values of *Candida* species. The pathogen was considered highly susceptible to amphotericin B and voriconazole with MICs of 0.038, and 0.125 μg/mL, respectively. While the inoculation exhibited resistance to fluconazole, itraconazole, and caspofungin with MICs of above 24, 3, and 0.5 μg/mL, respectively.

3. Discussion

The case of PD-related peritonitis from *C. nivariensis* is reported here with an unfavorable outcome, albeit an adequate treatment following the 2022 ISPD Peritonitis Guidelines [8]. The patient died of PD-related peritonitis after the complete course of antifungal medication. This pathogen posed a challenging diagnosis, automated platforms for pathogenic yeast identification could not specify the species, but broad-range PCR targeting ITS and 28S rDNA followed by DNA sequencing successfully solved the etiology.

Although many *C. nivariensis* infections have been reported since 2005, only one case was isolated from PDE but without clinical information. Conventional assimilation methods were not able to discriminate in *C. glabrata* complex (*C. bracarensis, C. nivariensis,* and *C. glabrata*) [2,3,5,10–16]. There are highly similar phenotypic characteristics often misidentification as reported in our presented case.

Furthermore, *C. nivariensis* has become multidrug-resistant, particularly azole antifungal agents [5]. Previous reports show that *C. nivariensis* isolates have varying susceptibility to the azoles. *C. nivariensis* isolates from previous reports exhibited alarming *in-vitro* resistance to itraconazole, voriconazole, and fluconazole [2]. Due to no previous record of antifungal treatment in *C. nivariensis*-associated PD patients, oral fluconazole administration for two weeks with early catheter removal was provided. Unfortunately, the patient died after a complete 2-week course of antifungal treatment in the hospital indicating peritonitis-related death according to the 2022 ISPD Peritonitis Guidelines' definition [8].

Although *C. nivariensis* is rare, correct identification is clinically important for clinicians to choose a suitable antifungal agent for their patients since each species has its own specific antifungal agent susceptibility patterns [17]. Misidentification may lead to inappropriate management resulting in poor outcomes. Biochemical profiling is

currently the primary method for yeast identification in most diagnostic laboratories. However, carbon assimilated identification methods using VITEK-2® (bioMérieux) systems posed unidentification of this strain. Possibly, *C. nivariensis* is not incorporated into the databases for commercially available assays. VITEK-MS system (bioMérieux), a yeast identification system employing mass spectrometry may prove capability in the identification of the pathogen as *C. nivariensis*. Nonetheless, confirmation of yeast identification remains reliant on DNA sequencing of the ITS region or the D1/D2 region of the 28S rRNA gene [7].

In conclusion, *C. nivariensis* should call for medical importance. Not only is it multi-antifungal resistant, causing a fatal outcome despite the treatment according to the 2022 ISPD Peritonitis Guidelines [8]. This work also alerts the limitations of the current routine diagnostic platform in the identification of yeast.

Declaration of competing interest

TK has received consultancy fees from VISTERRA, ELEDON, Otsuka OLE, and Otsuka VISIONARY as country investigators and current recipient of the National Research Council of Thailand and received speaking honoraria from Astra Zeneca and Baxter Healthcare. The other authors declare that they have no relevant financial interests.

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