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Case report

Central line-associated blood stream infection (CLABSI) due to *Candida sojae* in an infant with short bowel syndrome: The first human case report

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ABSTRACT

Central line associated blood stream infections (CLABSIs) in infants and children with intestinal failure due to short bowel syndrome may be caused by different organisms due to intestinal translocation and skin contamination. We report what we believe the first case of candidemia in an infant with short bowel syndrome caused by the environmental yeast *Candida sojae* that was initially misidentified as *Candida tropicalis*. We discuss its possible sources including a central venous catheter (CVC) and gut translocation and the differences between the two *Candida* species.

Case report

The patient is a 6 –month old male, born at 34 weeks of gestation with subsequent multiple medial problems including chronic respiratory failure requiring tracheostomy and chronic mechanical ventilation. He also had a history of micorocolon and meconium peritonitis with pseudocyst and pneumoperitoneum that required bowel resection with ileostomy and mucous fistula creation that was later followed by intestinal reanastomosis and gastrostomy tube placement. In addition, he has feeding intolerance and chronically dependent on total parenteral nutrition (TPN) via a central venous access. At 4 months of age, he was diagnosed with postnatal acquired CMV infection.

The infant had received multiple courses of antibiotics after birth for meconium peritonitis, methicillin-susceptible *Staphylococcus aureus* (MSSA) pneumonia, and post-surgical wound infection. His most recent bacterial infection was methicillin-resistant *Staphylococcus aureus* (MRSA) tracheitis for which he was received a 14-day course of intravenous (IV) vancomycin.

One week into treatment, he developed fever (38.5 °C) associated with declining respiratory status requiring escalation of sedation and respiratory settings. He had diminished breath sounds and mild abdominal distension. He had a tunneled central internal jugular line in place; the site had no surrounding erythema, swelling or tenderness. The site of gastrostomy tube was clean with no erythema or drainage. Laboratory studies revealed C - reactive protein (CRP) 108.8 mg/L (increased from 16.0 mg/L the day earlier). Blood white blood cells were 12,100/mm^3 with neutrophils 73%. Platelet count dropped to 120,000 from 154,000 the day earlier. Blood, urine and respiratory cultures were sent. Of note, blood cultures could not be drawn from central line and was obtained from a peripheral vein puncture. Intravenous cefepime was added and IV vancomycin was continued. Respiratory viral PCR panel was negative. Respiratory culture revealed no organisms on Gram stain but grew few MRSA colonies and few yeast colonies that were not identified. Urine culture was negative. Peripheral blood culture subsequently grew *Candida* species that failed identification by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) but was identified by the API 20 C Yeast Identification System (bioMerieux, Durham, NC, USA) as *C. tropicalis*.

A repeat blood culture was obtained 2 days later also grew *Candida* species with preliminary identification as *C. tropicalis*. The patient had serial blood cultures taken on subsequent days (Table 1) that revealed no growth. However, all cultures were obtained by peripheral venous

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puncture due to inability to access his central venous catheter (CVC). Removal of the CVC was recommended, however, the neonatal intensive care unit team along with the interventional radiologist determined that it was not feasible to replace the central venous access. He was treated with IV micafungin 10 mg/kg daily which was continued for 14 days from the first negative blood culture (Table 1). In addition, because antifungal susceptibility testing was not available at the time, he also received IV fluconazole. The CVC was suspected to be the source candidemia, thus the catheter was locked with 70% Ethanol (the catheter lumen volume plus 0.1 mL) according to our institutional protocol for sterilizing CVCs without removal. This was instilled 4 h daily for 10 days. Table 1 illustrates culture results by date and site as well as antifungal treatment outline.

Five days after completion of antifungal therapy he became increasingly agitated, required increased respiratory settings, and became thrombocytopenic (51,000/mm^3). Blood culture was sent and IV micafungin was started. Blood cultures grew presumptive *Candida tropicalis* again and IV fluconazole was added. Blood cultures remained persistently positive over the next 6 days (Table 1). The patient had replacement of his double lumen right internal jugular venous catheter over a guidewire by an interventional radiologist. Ethanol lock therapy was not given due to inability to get a peripheral IV access and the need to continue using the CVC for TPN and antimicrobial therapy. A week later, ethanol locks were continued daily thereafter. All blood cultures afterwards were negative (Table 1). The patient received IV micafungin along with fluconazole for 14 days from the first negative blood culture. The antifungal susceptibility testing results revealed that the *Candida* species was susceptible to amphotericin B: Minimum inhibitory concentration (MIC) 0.5 μg/mL, fluconazole: MIC 0.5 μg/mL, voriconazole MIC: 0.016 μg/mL and micafungin MIC: 0.032 μg/mL.

Because of the discrepant identification and the unusual appearance of the isolated colonies compared to *Candida tropicalis*, a sample was sent to the Centers for Disease Control (CDC) for definitive identification. DNA sequencing revealed the organism to be *Candida sojae*.

The patient was evaluated for possible disseminated candidiasis during the two candidemia episodes. Ultrasound studies of the abdomen and kidneys were normal. Multiple eyes examinations did not reveal any evidence of endophthalmitis. Echocardiograms were also normal and did not reveal any thrombus or valvular vegetations.

Discussion

Infants and children with short bowel syndrome (SBS) have a higher incidence of central line associated blood stream infections (CLABSIs) than those without intestinal failure: 7.8 versus 1.3 per 1000 catheter days [1]. Factors affecting gut integrity increase the rate of CLABSI. This supports translocation as the main mechanism of infection in SBS patients [2]. Patients with SBS are also at high risk of polymicrobial infections, commonly due to organisms associated with gastrointestinal tract and the skin flora [2]. *Candida* infections are relatively common in this patient population, predominantly due to *Candida albicans*, and *C. parapsilosis* [3]. The rate of CLABSI due to *Candida* species at our institution during the last 10 years (2012–2020) was 0.14 per 1000 central line days.

The source of infection with *Candida sojae* in our patient is unknown. Our patient had multiple underlying conditions that increase the risk of invasive candidiasis including SBS, presence of tunneled double lumen CVC, dependence on TPN, multiple courses of broad-spectrum antibiotics and chronic mechanical ventilation in the presence of tracheostomy [4]. Possible mechanisms of infection include CVC colonization and subsequent infection that occurred following skin or respiratory colonization or secondary to bacterial gut translocation. The exit of the CVC was not erythematous or indurated and exhibited no discharge. The CVC was locked with ethanol according to our institutional guidelines for sterilizations of infected CVCs that remain in situ. This method has been found to be safe and effective method for decontamination and retention of CVCs [5].

We believe that the recurrence of infection after completion of the first course of antifungal therapy was due to *C. sojae* colonization of the CVC. Blood cultures were not checked from the CVC during the first episode of candidemia due to inability to withdraw blood from the catheter which may be due to malfunction. In cases of *Candida*-associated CLABSI, removal of the CVC is recommended [6]. However, patients with SBS frequently have limited IV access and clinicians attempt to treat CLABI with catheter in situ. In addition, replacing the CVC at the same site through a guide wire is not advisable, due to risk of persisting or recurrence of infection [6]. Candidemia in our patient cleared after catheter change, although clearance may also be due to a combination of factors that include antifungal therapy and ethanol locks.

Candida sojae was first identified as a new anamorphic yeast species in Japan by Nakase et al. in 1994 [7]. Two strains of this organism were isolated from a liquid fraction of water-soluble substances of defatted

Table 1
Timeline and results of blood cultures and treatment course.

Date	Blood culture Source	Culture result	Treatment		CVC replaced
7/16/2021	peripheral	*Candida sojae*	7/17/2021	7/20/2021	
7/18/2021	peripheral	*Candida sojae*	Micafungin	Fluconazole	
7/22/2021	Peripheral	Negative	8/4/2021	8/4/2021	
7/23/2021	Peripheral	Negative			
7/24/2021	Peripheral	Negative			
8/9/2021	Peripheral	*Candida sojae*			
8/11/2021	Peripheral	*Candida sojae*			
8/11/2021	CVC	*Candida sojae*			
8/12/2021	Peripheral	*Candida sojae*	8/12/2021		
8/13/2021	Peripheral	*Candida sojae*	Micafungin		
8/14/2021	Peripheral	*Candida sojae*	9/1/2021		
8/15/2021	Peripheral	Negative			
8/16/2021	CVC	*Candida sojae*			8/16/2021
8/18/2021	Peripheral	Negative		8/18/2021	
8/19/2021	Peripheral	Negative		Fluconazole	
8/20/2021	Peripheral	Negative		9/1/2021	
8/21/2021	Peripheral	Negative			
8/22/2021	Peripheral	Negative			
9/9/2021	Peripheral	Negative			

CVC: central venous catheter

soybean flakes [7]. Both strains showed close relation to *Candida tropicalis* based on similar mol% G+C and traditional taxonomic characteristics. However, they differed from *C. tropicalis* by lack of true hyphae, latent and weak fermentation of sucrose and lack of maltose fermentation, thus were classified as a different *Candida* species. Because these characteristics also resemble *Candida albicans*, further detailed comparative studies with type strains of *Candida tropicalis* and *Candida albicans* were undertaken and it was concluded that these two strains represent the new distinct species *Candida sojae*. Differences have been found in G+C content, DNA-DNA relatedness and in the electrophoretic enzyme pattern [7]. Microbiological features that help distinguish *Candida sojae* from *Candida tropicalis* and *Candida albicans* include the inability of *C. sojae* to ferment maltose. In addition, *Candida sojae* cannot grow at 40 °C, but the other two species can grow at a temperature of 40 °C or higher [7].

Borelli et al. have isolated *Candida sojae* from a plague insect in an energy-cane cultivar and demonstrated that this strain has fast xylose uptake and efficient xylitol production. They suggested that *Candida sojae* is yeast that may hold a biotechnological potential, since xylitol is a sugar-alcohol that is be used in food industries as a sweetener [8].

Candida sojae strain from our patient failed identification by MALDI-TOF and was identified by the API 20 C Yeast Identification System as *C. tropicalis*, which prompted further evaluation by gene sequencing. Whether other human cases due to *Candida sojae* have occurred but were misidentified as *Candida tropicalis* is unknown. The pathogenicity and invasiveness of *Candida sojae* in humans remain unknown. Our patient did not have evidence of disseminated infection despite prolonged candidemia. This may indicate that *C. sojae* is less invasive than *Candida albicans*. *Candida sojae* has not been previously recognized as a human pathogen. Using breakpoints for other *Candida* species, the isolate in our patient was susceptible to tested antifungals. *C. sojae* (CBS 7871 American Type and Collection strain) has been shown to be susceptible to amphotericin B, fluconazole and echinocandins including micafungin, caspofungin, anidulafungin and rezafungin [9].

In summary, we present what we believe is the first reported case of human infection due to *Candida sojae*, although others may have been misidentified as this one was initially. This *Candida* species failed identification by MALDI-TOF and was identified by the API 20C Yeast Identification System as *C. tropicalis.* Its colonial morphology was not distinct from usual *C. tropicalis* isolates. A similar result should prompt further evaluation of possible *Candida sojae* infection. Candidemia in this infant was likely related to intestinal failure and the presence of a CVC. Further studies are needed to clarify the pathogenesis of *Candida sojae* and its role in human disease.

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Authorship contribution statement

Authors NAH, BIA, JYA, GN, MF and HS contributed to either patient management, manuscript preparation and writing, editing, or commenting on the manuscript. All given consent for publication of the manuscript.

Ethics approval

Not applicable as no studies were conducted on the patient.

Consent

Not applicable. No personal identifiers, photography or imaging studies are published.

CRediT authorship contribution statement

Nahed Abdel-Haq: Data collection, manuscript writing and editing. **Basim I Asmar**: Manuscript editing and commenting. **Jocelyn Y Ang**: Manuscript editing and commenting. **Giriga Natarajan**: Manuscript editing and commenting. **Marilynn Fairfax**: Data collection, manuscript editing and commenting. **Hossein Salimnia**: Data collection, manuscript editing and commenting. All authors have given consent for publication of the manuscript.

Declaration of Competing Interest

The authors report no conflict of interest.

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