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Note

Exophiala dermatitidis as a cause of central line associated bloodstream infection in an infant: Case report and literature review

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ABSTRACT

Background: *Exophiala dermatitidis* is a dematiaceous fungus known to cause superficial, subcutaneous, cutaneous and deep seated infections, and rarely central line associated bloodstream infection (CLABSI). A case of CLABSI due to *E. dermatitidis* in an infant is described.
Case report: Clinical and laboratory data were extracted from patient's chart and laboratory records. The isolate was identified as *E. dermatitidis* by phenotypic characterization and sequencing of the ITS and LSU regions of the ribosomal DNA. Medline search was done to review all cases of CLABSI due to *E. dermatitidis*. Among the azoles tested, posaconazole (0.06 mg/l), voriconazole (0.03 mg/l) and itraconazole (0.03 mg/l) showed very low MICs when compared to fluconazole (4 mg/l)
Conclusions: As we did not found in the literature any case of CLABSI due to *E. dermatitidis* in an infant, we report the first one. Sequencing is a mandatory method for accurately identifying this species. Prompt removal of the central line, followed by a treatment with amphotericin B or an azole, seems to be the most effective treatment.

Exophiala dermatitidis como causante de infección del torrente sanguíneo asociada a catéter central en un lactante: reporte de un caso y revisión de la literatura

Palabras clave:
Exophiala dermatitidis
Fungemia
Catéter central
Lactante
Feohifomicosis

RESUMEN

Antecedentes: *Exophiala dermatitidis* es un hongo dematiáceo conocido por causar infecciones superficiales, subcutáneas, cutáneas y profundas, y rara vez infección del torrente sanguíneo asociada a catéter central (*central line associated bloodstream infection* [CLABSI]). Se describe un caso de CLABSI debido a *E. dermatitidis* en un bebé.
Caso clínico: Los datos del paciente se extrajeron de la historia clínica y de los registros de laboratorio. El aislamiento se identificó como *E. dermatitidis* mediante caracterización fenotípica y la secuenciación de las regiones ITS y LSU del ADN ribosómico. Se realizó una búsqueda en Medline para revisar todos los casos de CLABSI debidos a *E. dermatitidis*. Entre los azoles evaluados, el posaconazol (0,06 mg/l), el voriconazol (0,03 mg/l) y el itraconazol (0,03 mg/l) mostraron valores de MIC muy bajos en comparación con el fluconazol (4 mg/l).
Conclusiones: Tras la revisión de todo lo publicado en la literatura, presentamos el primer caso de CLABSI debido a *E. dermatitidis* en un lactante. La secuenciación es necesaria para identificar con precisión esta especie. La retirada inmediata del catéter venoso central seguida de un tratamiento con anfotericina B o un azol es el tratamiento más efectivo.

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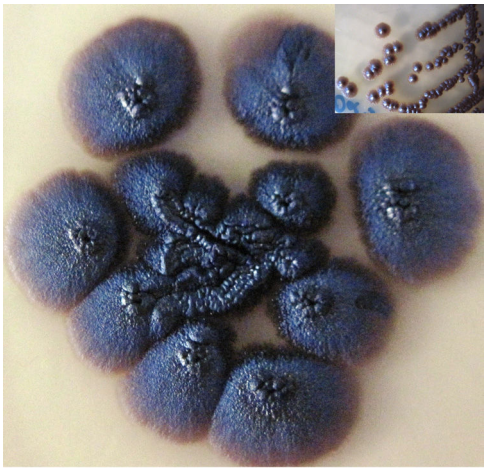

Fig. 1. Jet black yeast-like colonies of *Exophiala dermatitidis* on day 4 (inset) and colonies with filamentous growth on day 14 on Sabouraud dextrose agar incubated at 37 °C.

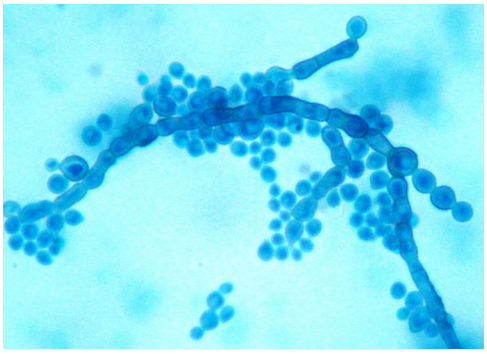

Fig. 2. Smear of an old culture showing septate, brown hyphae, conidiophores and phialides without collarettes. Conidia are pale brown, one-celled, and round to oval in shape; they gather in balls at the apices of the phialides and down the side of the conidiophore.

Exophiala dermatitidis is a dark-pigmented yeast-like organism with a worldwide distribution, and has been found in the environment and wild animals.[22] It is a well-known cause of local and disseminated pheohyphomycosis in immunocompromised patients but is an uncommon cause of fungemia.[17] *E. dermatitidis* is also known to colonize the airways of patients with cystic fibrosis.[10] In this report we describe a case of central line associated bloodstream infection (CLABSI) due to *E. dermatitidis* in a two-month-old female child with suspected mitochondriopathy and an inborn error of metabolism.

Case report

A two-month-old female infant, born near term, small for gestational age with failure-to-thrive and developmental delay, was admitted with bronchopneumonia, septicaemia and multi-organ dysfunction. Blood investigations showed increased concentrations of lactic acid, pyruvate, succinic acid, fumaric acid and ethylmalonic acid, suggestive of a mitochondriopathy and an inborn error of metabolism. Fluorescent *in situ* hybridization for DiGeorge syndrome was negative. The patient was treated with broad spectrum antibiotics. Paired blood specimens from the central line and peripheral vein were inoculated into BacT/Alert PF aerobic bottles and incubated in a BacT/ALERT 3D (bioMérieux, Marcy l'Etoile, France) system. Both bottles flagged as positive for budding yeast cells, and grew as light gray, yeast-like colonies at 48 h, which on further incubation turned black (Fig. 1). Slide cultures prepared on potato dextrose agar at 37 °C revealed long, slender conidiophores with clusters of oval conidia at the tips of the phialides, and aggregates of conidia along the sides of the conidiophores (Fig. 2). The isolate grew at 40 °C but failed to grow at 42 °C. Based on the macroscopic morphology, microscopic appearance and physiological features, the isolate was identified as *Exophiala* spp. Since the patient had CLABSI, the catheter was removed and fluconazole therapy was started. Clinical, radiological and ophthalmologic evaluation did not reveal any evidence of disseminated fungal infection. Subsequent blood cultures were negative. The patient was discharged from the hospital after 21 days of fluconazole therapy.

The *in vitro* antifungal susceptibility of the isolate was determined by a broth microdilution test performed according to the M27-A3 CLSI document.[9] *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 were used as quality control strains. The minimum inhibitory concentration (MIC) of amphotericin B, fluconazole, voriconazole, itraconazole, posaconazole, flucytosine, caspofungin, micafungin and anidulafungin were 1, 4, ≤0.03, ≤0.03, 0.06, 4, 2, 2 and 4 μg/ml respectively.

To confirm the identification, one representative isolate from blood was subjected to sequencing of the internal transcribed spacer (ITS) and the large ribosomal subunit (LSU) D1/D2 regions.[27] Both strands of the amplified DNA were sequenced on an ABI 3130XL Genetic analyzer using the BigDye Terminator Kit. Sequences were aligned using the Sequencing Analysis 5.3.1. Searches with GenBank basic local alignment search tool (BLAST) were done for species identification. ITS and LSU sequences of our strain revealed 100% identity with the standard strain of *E. dermatitidis* (CBS 748.88; accession AF050270.1 and CBS 129657; accession MH 876940.1). The nucleotide sequences of ITS and LSU regions were deposited in GenBank with the accession numbers KF996500 and KF996499, respectively.

Discussion

E. dermatitidis is a melanized yeast-like fungus that produces phialides without collarettes and belongs to the ascomycete order Chaetothyriales.[6] This species is distributed worldwide and has been isolated from several environmental sources like sauna facilities, humidifiers, sludge of bathroom pipes and bathwater.[1] Colonies are darkly pigmented because of the presence of dihydroxynaphthalene melanin.[1] Microscopically *E. dermatitidis* shows budding yeast cells at first, but pseudohyphae, moniliform hyphae, true hyphae, and sclerotic forms can also be observed. Smears from the same colony show a mix of yeasts and hyphal forms.[7,23] The switch between morphotypes can be activated by several environmental factors.[7] *E. dermatitidis* is known to cause localized and disseminated phaeohyphomycosis; reports of fungaemia are uncommon.[25] Systemic phaeohyphomycosis caused by *E. dermatitidis* includes respiratory, intestinal, cardiac, and cerebral diseases.[16,22] This species has often been reported as a colonizer of the respiratory tract in patients with cystic fibrosis and is occasionally involved in fungal pneumonia and pulmonary phaeohyphomycosis.[10] Asymptomatic carriage in the gastrointestinal tract has also been documented.[8] Localized infections are due to traumatic implantation into the skin without dissemination into deep organs.[8,22] Alternatively, acquisition can be due to inhalation and rarely due to hematogenous seeding.[8,18] High mortality rates (80%) due to a disseminated infection by *E. dermatitidis* have been reported; the spreading may be attributed to its neurotropic behavior and the high MICs to conventional antifungal agents like fluconazole.[8,16,18]

Searching in the Medline database for published articles using the keywords '*Exophiala dermatitidis*', '*E. dermatitidis* and infection',

Table 1
Summary of the published cases of *E. dermatitidis* CLABSI excluding outbreaks.

No.	Age (years)/gender	Underlying condition	Treatment/Outcome	Susceptibility MIC (μg/ml)	Diagnostic method	Author/country/year/ reference
1	3.5/M	ALL	CL removal, AMB, 5FC, 3 weeks/Survival	ND	Morphotype	Blashke-Hellmessen/Germany/1994[4]
2	53/F	Colectomy, parenteral nutrition	CL removal, FLC, 4 days/Survival	ND	Morphotype	Simpson/United Kingdom/1994[21]
3	5/M	ALL	CL removal, ITC, 8 weeks/Survival	ND	Morphotype	Kabel/Netherlands/1994[11]
4	3/M	HIV	CL removal, AMB (4 weeks), ITC (20 weeks)/Survival	ND	Morphotype	Nachman/USA/1996[17]
5	61/F	Metastatic breast cancer	CL removal, AMB, ITC, 8 weeks/Survival	ND	Morphotype	Larocco/USA/2002[15]
6	58/F	Lung cancer	CL removal, AMB, 17 days/Survival	FLC 48 AMB 0.19	Morphotype	Tseng/Taiwan/2005[24]
7	57/M	Lymphoma, graft-*versus*-host disease	CL removal, VRC, AMB, 10 days/Death	FLC 8; ITC 0.25; VRC 0.125; POS 0.125; AMB 1; 5FC >64; CAS 8; AFG 8; MFG 8; TRB 0.06	Morphotype	Chalikas/USA/2014[5]
8	47/F	Metastatic lingual and oesophageal cancer Chemotherapy	CL removal, MFG, 12 days/Death	MFG >16	Morphotype	Kakuya/Japan/2014[12]
9	45/M	Myelofibrosis Acute myeloid leukemia Prolonged neutropenia	CL removal, AMB/Death	AMB 0.5; MFG > 16; FLC 16	Morphotype, MALDI-TOF	Watanabe/Japan/2018[26]
10	75/M	Cirrhosis COPD	CL removal, AFG/Death	AMB 0.125; CAS 0.008; AFG 0.008	Morphotype MALDI-TOF ITS sequencing	Vila/Argentina/2019[25]
11	2 months/F	Mitochondriopathy, inborn errors of metabolism	CL removal, FLC, 3 weeks/Survival	AMB 1; FLC 4; VRC ≤ 0.03; ITC ≤ 0.03; POS 0.06; 5FC 4; CAS 2; MFG 2; AFG 4	Morphotype ITS, LSU, sequencing	Present case

ND: not done; CL: central line; HIV: human immunodeficiency virus; ALL: acute lymphocytic leukemia; COPD: chronic obstructive pulmonary disease; AMB: amphotericin B; ITC: itraconazole; FLC: fluconazole; VRC: voriconazole; 5FC: flucytosine; MFG: micafungin; POS: posaconazole; CAS: caspofungin; AFG: anidulafungin; TRB: terbinafine; MALDI-TOF: matrix-assisted laser desorption/ionization-time of flight; ITS: internal transcribed spacer; LSU: large ribosomal subunit.

'*Wangiella dermatitidis*', '*W. dermatitidis* and infection', 'CLABSI', 'central venous catheter', 'catheter-associated' and 'nosocomial', was done. A total of ten cases, whose details are summarized in Table 1, were found. Adding up our case, four patients out of eleven (36.36%) were pediatric. CLABSI due to *E. dermatitidis* in an infant is being reported for the first time. A solitary case of CLABSI due to *Exophiala oligosperma* in a three year old leukemic child was reported from Kuwait.[2] All the patients had underlying risk factors, the central line was removed, and were treated with systemic antifungals. Most of the patients received amphotericin B with or without an azole with 66.6% (4/6) survival. Overall mortality in patients with CLABSI due to *E. dermatitidis* was 40% (4/11) and was seen exclusively in adult patients. Though *E. dermatitidis* is believed to have higher MICs to fluconazole, two cases (including the present one) responded well to monotherapy with fluconazole. Notably, all patients on echinocandins died. Withdrawal of central line and the administration of antifungals are the mainstay of the treatment in cases of central line associated fungemia.[25] The increase in the incidence of CLABSI due to *E. dermatitidis* can be attributed to its propensity to form biofilms.[14] A review of 40 cases from 1990 to 2011 by Patel et al. found that 70% of the cases had an identifiable underlying condition.[18] Steroid therapy, cystic fibrosis, cancer, transplantation, intravenous drug abuse and the use of long-term catheter were risk factors for the disseminated disease.[18] They also reported that cerebral infection proved fatal in 90% of the cases and had the highest mortality.[18] The source of the infection in our case could not be identified. Since there were no other cases during this period an outbreak was ruled out.

The phenotypic characteristics that differentiate *E. dermatitidis* from other species of the genus are its ability to grow at 42 °C, inability to utilize nitrite or nitrate and the absence of annelides on microscopy.[18] The monoclonal antibody used in Pastorex *Aspergillus* antigen test for the detection of *Aspergillus* galactomannan antigen may cross-react with *E. dermatitidis*.[13] The differentiation of *E. dermatitidis* from other species of *Exophiala*, like *Exophiala phaeomuriformis*, solely on the basis of morphological features is difficult. ITS1 sequencing should be used to differentiate closely-related black yeast species.[2,14,18,25] Recent studies have found that matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) can also accurately identify *E. dermatitidis*.[3,25]

E. dermatitidis has been found to have high MICs to fluconazole and 5-fluorocytosine, whereas amphotericin B, itraconazole, voriconazole and posaconazole seem to be more effective *in vitro*.[19] In the present case, the isolate was susceptible to amphotericin B, voriconazole, itraconazole and posaconazole, and had a higher MIC of fluconazole in comparison with other azoles tested. The isolate was non-susceptible to 5-fluorocytosine and echinocandins. Treatment of localized lesions includes complete surgical excision followed by antifungal therapy with amphotericin B or voriconazole. Monotherapy with echinocandins has been reported to be suboptimal.[25,26] However, in case of systemic infection and involvement of the central nervous system, addition of amphotericin B to the treatment regimen is recommended. Posaconazole has the broadest spectrum of any oral agent and can be considered in cases of central nervous system disease.[20]

We report the first case of CLABSI due to *E. dermatitidis* in an infant with a review of all cases of CLABSI published in literature. Sequencing was found to be a reliable method to accurately identify this species. Prompt removal of the central line followed by

treatment with amphotericin B or an azole seems to be the most effective treatment.

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Conflict of interest

We certify that there are no entities with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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