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Case report: candidemia in a child with cystic fibrosis with fatal course

Relato de caso: candidemia em criança portadora de fibrose cística com curso fatal

Relato de caso: candidemia en niño con fibrosis quística de curso fatal

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Gleiciere Maia Silva
ORCID: https://orcid.org/0000-0003-1372-799X
Federal University of Pernambuco, Brazil
E-mail: gleicieremaia@gmail.com
Alice Cristiane Rangel Silveira
ORCID: https://orcid.org/0000-0002-5532-5983
Federal University of Pernambuco, Brazil
E-mail: cris_silveira4@yahoo.com.br
Reginaldo Gonçalves de Lima Neto
ORCID: https://orcid.org/0000-0002-8846-877X
Federal University of Pernambuco, Brazil
E-mail: goncalves_reginaldo@hotmail.com
Rejane Pereira Neves
ORCID: https://orcid.org/0000-0003-4184-7366
Federal University of Pernambuco, Brazil
E-mail: rejadel@yahoo.com.br

Abstract
In the present study we report a case of candidemia in an infant with cystic fibrosis admitted to a Pediatric Intensive Care Unit (PICU) with a fatal course. Six-month-old male patient with a history of productive cough and persistent fever. He was admitted to the PICU of a public hospital in the city of Recife, PE, Brazil, with a diagnosis of dyspnea and cystic fibrosis, with a respiratory infection. Antibiotics were administered, however without success, peripheral blood and transcatheter blood cultures were requested, the isolated agents were *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*, respectively. After seven days, the patient presented lesions on the genitalia and persistent fever. Blood and genital lesions were collected, the samples were identified as *Candida albicans* through the classical taxonomy and the VITEK 120 automated system. The antifungal sensitivity test followed the protocol by the broth microdilution method (CLSI- Clinical and Laboratory Standard Institute, 2008b). The isolates from blood samples were sensitive to amphotericin B with a Minimal Inhibitory Concentration (MIC) of 0.03 µg/mL, 0.12 µg/mL for anidulafungin and 0.25 µg/mL for voriconazole, exhibiting resistance to fluconazole with MIC of 64 µg/mL. *C. albicans* isolated from the genitalia lesion was sensitive to all the drugs used. The patient was administered nystatin 4 times a day and amphotericin B. The patient improved from the genital lesion and fever. However, after three days, the patient presented cardiac and respiratory deficit that led to cardiac arrest, leading to death.
Keywords: Candidemia; Children; Cystic fibrosis.

Resumo
No presente estudo relatamos um caso de candidemia em lactente portador de fibrose cística internado em Unidade de Terapia Intensiva Pediátrica (UTIP) com curso fatal. Paciente com seis meses de idade, do sexo masculino com histórico de tosse produtiva e febre persistente. Foi admitido na UTIP de um hospital público da cidade do Recife, PE, Brasil, com diagnóstico de dispneia e fibrose cística, apresentando um quadro infeccioso respiratório. Foi administrado antibióticos, entretanto sem sucesso, foi solicitada hemocultura de sangue periférico e de transcateter, os agentes isolados foram *Staphylococcus epidermidis* e *Pseudomonas aeruginosa*, respectivamente. Após sete dias o paciente apresentou lesão na genitália e febre persistente. Foi realizada coleta de sangue e da lesão da genitália, as amostras foram identificas como *Candida albicans* através da taxonomia clássica e do sistema automatizado VITEK 120. O teste de sensibilidade a antifúngicos seguiu protocolo pelo método de microdiluição em caldo (CLSI- *Clinical and Laboratory Standard Institute,* 2008b). Os isolados de amostras de sangue foram sensíveis a anfotericina B com Concentração Inibitória Mínima (CIM) de 0,03 µg/mL, 0,12 µg/mL para anidulafungina e ao 0,25 µg/mL para voriconazol, exibindo resistência ao fluconazol com CIM de 64 µg/mL. *C. albicans* isolada da lesão da genitália foi sensível a todas as drogas utilizadas. Foi administrado ao paciente nistatina 4 vezes ao dia e anfotericina B. O paciente obteve melhora da lesão da genitália e da febre. Contudo, após três dias o paciente apresentou déficit cardíaco e respiratório que conduziu a parada cardíaca, indo ao óbito.
Palavras-chave: Candidemia; Criança; Fibrose cística.

Resumen
En el presente estudio reportamos un caso de candidemia en un lactante con fibrosis quística ingresado en una Unidad de Cuidados Intensivos Pediátricos (UCIP) con evolución fatal. Paciente masculino de seis meses de edad con antecedentes de tos productiva y fiebre persistente. Ingresó en la UCIP de un hospital público de la ciudad de Recife, PE, Brasil, con diagnóstico de disnea y fibrosis quística, con infección respiratoria. Se administraron antibióticos, sin embargo, sin éxito, se solicitaron hemocultivos de sangre periférica y transcatéter, los agentes aislados fueron *Staphylococcus epidermidis* y *Pseudomonas aeruginosa*, respectivamente. Después de siete días, el paciente presentó lesiones en los genitales y fiebre persistente. Se recolectó sangre y lesiones genitales, las muestras se identificaron como *Candida albicans* mediante la taxonomía clásica y el sistema automatizado VITEK 120. La prueba de sensibilidad antifúngica siguió el protocolo por el método de microdilución en caldo (CLSI- Clinical and Laboratory Standard Institute, 2008b). Los aislados de muestras de sangre fueron sensibles a la anfotericina B con una Concentración Mínima Inhibitoria (MIC) de 0,03 µg/mL, 0,12 µg/mL para anidulafungina y 0,25 µg/mL para voriconazol, presentando resistencia a fluconazol con MIC de 64 µg/mL. *C. albicans* aislado de la lesión de los genitales fue sensible a todos los fármacos utilizados. Se le administró nistatina 4 veces al día y anfotericina B. La paciente mejoró de la lesión genital y fiebre. Sin embargo, después de tres días, el paciente presentó un déficit cardíaco y respiratorio que lo llevó a un paro cardíaco que lo llevó a la muerte.
Palabras clave: Candidemia; Niño; Fibrosis quística.

1. Introduction

Fungal infections exhibit variable clinical presentations ranging from the outermost layer of the epidermis to severe and disseminated infections (Blyth et al., 2011; Zhang, et al., 2020). Estimates suggest that 25% of the population are affected by any type of fungal skin infection (Cock & Van Vuuren, 2020; Xiao et al., 2019).

The incidence of diseases caused by fungi has become increasing in recent decades, especially in children who are in hospital environments. The infection can be of community origin present or incubated at the time of hospital admission, defined by the appearance after forty-eight hours of hospitalization (Hota, 2004; ANVISA, 2013; Paho, 2017).

Risk factors such as prematurity, low birth weight, immature skin structure, length of hospital stay, prolonged use of antibiotics, insertion of central venous catheters, parenteral nutrition, mechanical ventilation, and steroid use increase the frequency of infections in children (Borges et al., 2009).

The species most commonly found as an etiologic agent in children is Candida albicans, although other yeast species have emerged in recent years, such as *C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis* (Rocha et al., 2008; Zeichnner; Pappas, 2006; Pappas et al., 2018).

The complexity of pediatric patients and the most varied underlying diseases increase the risks for fungal infections. Thus, opportunistic mycoses present considerable challenges for diagnosis and therapy in this group of patients. In this sense, cystic fibrosis (CF), which is an autosomal recessive disease, resulting from a disturbance in the Fibrosis Transmembrane Conductance Regulatory Protein, characterized by an increase in viscosity and in the amount of mucus secreted, can contribute to the development of infections, in particular respiratory tract (O'brien; et al., 2012; Lubovich et al., 2019).).

Therefore, studies in neonatal patients with cystic fibrosis in association with fungal infections are necessary, since the underlying disease and fungal diseases increase the severity of any pathology. Early diagnosis contributes to an effective treatment, reducing complications resulting from CF and increasing the expectation and quality of life of these patients.

2. Methodology

The present study is a case report was approved by the Ethics Committee for Research with Human Beings under registration number 0366.0.172.106-11 of the Oswaldo Cruz University Hospital, and is in accordance with CNS Resolution number 196/96.

3. Case Report

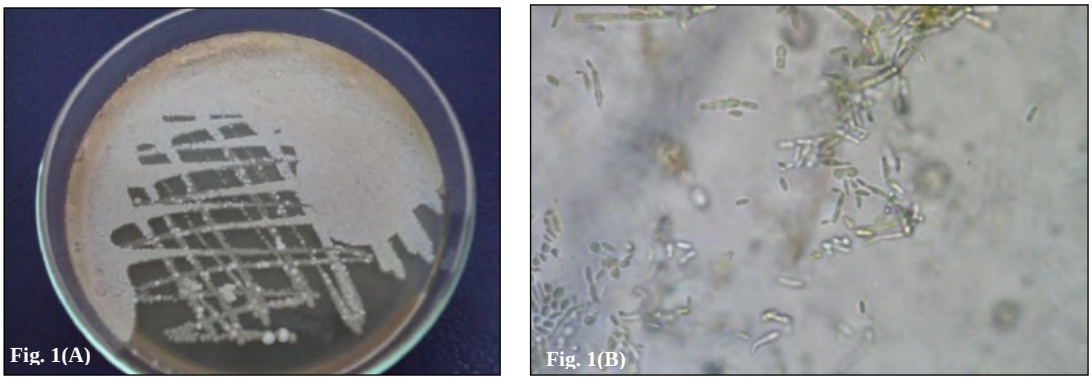
A six-month-old male infant with a 15-day history of productive cough, nasal congestion, and fever was referred to a public hospital in Recife, Brazil, with a diagnosis of cystic fibrosis (CF), dyspnea, breathing and dehydration. He was admitted to the Pediatric Intensive Care Unit. He was initially treated with ampicillin and erythromycin and developed diarrhea, vomiting with worsening symptoms.

To elucidate the infection, peripheral and transcatheter blood cultures were requested for laboratory diagnosis. In the culture, *Staphylococcus epidermidis* resistant to azithromycin, ciprofloxacin, gentamicin, oxacillin, penicillin G, trimethoprim and sulfamethoxazole was identified and in the transcatheter material *Pseudomonas aeruginosa* resistant to imipenem and meropenen was identified.

After seven days, the patient presented a lesion on the genitalia and clinical samples of the lesion and blood culture were requested. The collected samples were sent to the Medical Mycology Laboratory of the Federal University of Pernambuco. Direct examination of the epidermal scales was clarified with 20% potassium hydroxide (KOH), facilitating direct microscopy observation of fungal structures. Were visualized numerous oval and hyaline yeast cells with pseudomycelium.

Blood samples and epidermal scales were seeded on Sabouraud Dextrose agar (Difco), supplemented with chloramphenicol (50 mg/L), incubated at 28°C and 35°C for up to 15 days. Identification was performed according to morphophysiological criteria, described by Barnett et al. (2000) and through the automated system VITEK 120. *C. albicans* was identified as an agent of lesions in the genitalia and blood cultures, by all the methods used. The figure below illustrates macroscopic and microscopic aspects of the *Candida albicans* culture obtained from a blood culture sample.

Figure 1 - Macroscopic appearance culture of *Candida albicans* on Sabouraud agar (A) and microscopy of the culture showing numerous oval and hyaline yeast cells and pseudomycelium (B).



Source: Author of the manuscript.

The antifungal susceptibility profile of *C. albicans* isolates was performed by the broth microdilution method, according to the standardization published in M27-A3 documents (CLSI 2008b). The antifungal drugs tested were amphotericin B (UnitedMedical) (0.03-16µg/mL), anidulafungin (Pfizer) (0.015-8µg/mL), voriconazole (Pfizer) (0.03-16µg/mL) and fluconazole (Pfizer) (0.125-64µg/ml). Strains from the American Type Culture Collection (ATCC), *C. parapsilosis* ATCC 22019 and *C. albicans* ATCC 200955 were included in the assays.

From the skin samples, the isolates exhibited the same pattern of sensitivity, being sensitive to all drugs tested. Cultures obtained from blood were sensitive to amphotericin B with a minimum inhibitory concentration (MIC) of 0.03 µg/mL, for anidulafungin 0.12 µg/mL and for voriconazole 0.25 µg/mL, however, the isolates showed a resistance profile with a MIC of 64 µg/mL against fluconazole.

Treatment was performed with nystatin (4 times a day) and liposomal amphotericin B (Ambisome®) for 30 days (300mg/day). The patient showed improvement in genital lesions and fever. However, after three days, he developed cardiac and respiratory deficits, leading to death.

4. Discussion

The incidence of fungemia has increased considerably in hospitalized patients. The fungi most commonly recovered from blood samples are species of the genus *Candida*, of which 50% of the episodes of candidemia are due to *Candida albicans*, which is also associated with superficial and/or systemic infections, especially in neonatal patients (Karam et al., 2005).

According to Rex and Sobel (2001), in Brazil the main species causing candidemia are *Candida albicans, Candida parapsilosis* and *Candida tropicalis*. Even so, *C. albicans* is one of the most frequent species isolated from superficial and invasive infections at different anatomical sites. It is a yeast with well-known pathogenic potential, presenting as main factors of pathogenicity and virulence the ability to adhere to different mucous membranes and epithelia, dimorphism with the production of filamentous structures that help tissue invasion, and the production of enzymes such as proteinases and phospholipases (França; et al., 2008).

As for cystic fibrosis (CF), the underlying disease of the patient in the study, the World Health Organization drew attention to this fact in 1997, recommending several actions in services that treated patients with CF, such as neonatal screening to determine the incidence and identify the affected newborns, implementation of laboratories to identify CF mutations, development of diagnostic and treatment centers with a multidisciplinary team (Raskin et al., 2008; Ferreira; et al., 2019).

Individuals with CF suffer repeated infections with bacteria, initially *Staphylococcus aureus* and *Haemophylus influenzae*, *Pseudomonas aeruginosa* and, in some cases, *Burkholderia cepacia* and other *Pseudomonas* species. The organism responds to chronic infection by increasing the production of specific immunoglobulin G which in turn does not eliminate the bacteria, however it combines with bacterial antigen forming an immune complex that promotes a continuous inflammatory reaction (Burke, 2003)

When the patient with CF acquires in addition to infections by bacteria associated with fungi, the clinical picture worsens. According to Colombo (2003) it is believed that most cases of candidemia are acquired endogenously through the translocation of yeast through the gastrointestinal tract, however cases of candidemia can also be acquired exogenously through contact with the hands of professionals. healthcare with patients with central vascular catheters, implantation of contaminated prostheses, as well as parenteral administration of contaminated solutions.

The sources of invasive candidiasis are usually endogenous from the colonization of the mucous membranes, mainly intestinal, of the neonate. The critically ill newborn is colonized very early, about 10% of these become colonized in the first week of life, and more than 64% are colonized after four weeks of hospitalization, although there is evidence of a correlation between fungal colonization and invasive disease in children. as low weight (Borges et al., 2009).

Candidemia is one of the leading causes of death from infections, especially in pediatric patients with a severe underlying disease, and the third most common cause of late-onset sepsis. It is believed that these indices may be related to late diagnosis in addition to late or ineffective antifungal treatment (Mondeli et al 2012).

Mondeli et al (2012) in a study at a tertiary hospital in São Paulo, Brazil, identified 98 cases of candidemia, 33.67% were caused by *C. albicans* and 66.33% by other *non-albicans Candida* species. Of these, *C. parapsilosis* had the highest percentage rate (37.7%), followed by *C. tropicalis* (7.1%), C. glabrata (4.1%), *C. guilliermondii* (3.1%), *C. lusitaniae* (2.1%).

5. Conclusion

The association of candidemia and the severe underlying disease of a pediatric patient usually does not have a favorable clinical course, fungemia, when not properly treated without an early diagnosis, worsens the clinical picture and can be a cause of mortality. It is essential to take greater care of pediatric patients with a serious history so that they do not develop fungemia, further aggravating the situation.

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