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T2Candida® to guide antifungal and lengh of treatment of candidemia in a pediatric multivisceral transplant recipient

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ABSTRACT

A case of 1-year- old male multivisceral transplant recipient with candidemia diagnosed by the T2Candida® test is presented. Optimal management of the candidemia complemented the treatment of the global clinical episode. Duration of treatment might be established much more precisely with the T2Candida® test than with blood cultures.

1. Introduction

Candidemia is the most common cause of invasive fungal disease in hospitalized children. It prolongs hospital length of stay, increases costs, contributes to morbidity and has an attributable mortality of 10%. Studies have shown rapid diagnosis leads to an early initiation. Mortality rate is reduced from 40% to 11% when antifungal treatment is started in less than 12 h [1,2].

The current clinical gold standard for the diagnosis of candidemia is blood culture, but it has low sensitivity (50–60%) and requires 2–5 days of culture growth with viable circulating *Candida* cells [3]. Molecular diagnostic techniques, such as PCR or RT-PCR, have been developed. However, a majority of these methods are not fully automated, they are time-consuming, they need DNA extraction and purification steps and are not commercially available [4,5]. In addition, PCR techniques do not differentiate between DNA in blood or viable yeast cells.

T2Candida® is the first diagnostic test able to provide cells species-specific *Candida* rapid detection and identification directly from whole blood in 3–5 h, without the requirement for prior growth of the organism in contrast to blood culture. T2Candida® enables more rapid turnaround times than previously reported *Candida* PCR assays (≤ 12 h) and blood cultures (≤ 5 days), being crucial for the early management of the candidemia [6].

2. Case

Here we reported a case of 1-year-old male multivisceral transplant recipient due to microvillus inclusion disease. He was on immunosuppressive therapy with tacrolimus and methylprednisolone for 5 months due to his condition of solid organ transplant recipient. The patient was admitted to Pediatric Intensive Care Unit for 40 days after an exploratory laparotomy for abdominal sepsis suspicion. Intestinal obstruction was suspected after 6 fecaloid vomiting in a day. The patient had persistent leukopenia (2600/μL) and high acute phase reactants (CRP: 170.7 mg/L) maintained throughout admission due to peritonitis secondary to intestinal perforation. Upon admission (day 0), a simultaneous blood culture and whole blood (EDTA) sample for T2Candida® test were obtained. Empiric antibiotherapy with meropenem, vancomycin and micafungin had been given for about 1 month. Abdominal echography showed some collections in the surgical area. Peritoneal fluid and collections were drawn. These samples were cultured and multiresistant *Pseudomonas aeruginosa* (non-carbapenemase) and *Enterococcus faecalis* were isolated (day +1 and +3 respectively). *P. aeruginosa* was only susceptible to colistin, amikacin and ceftolozane-tazobactam. This strain was also isolated in the surgical wound and in a bronchial aspirate, which caused cellulitis and nosocomial pneumonia. Treatment was replaced for 25 days by ceftolozane-tazobactam and colistin for treating the *P. aeruginosa* infections and linezolid for treating the *E. faecalis* isolate.

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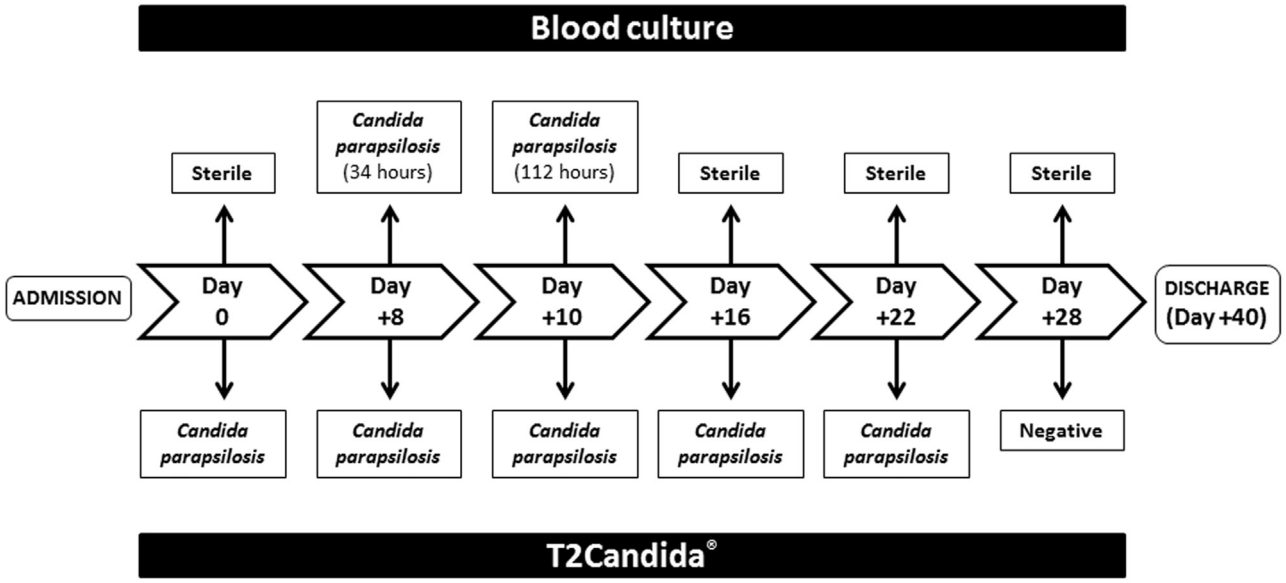

Fig. 1. Timeline of candidemia diagnosis and candidemia clearance through simultaneous blood cultures and T2Candida® tests.

The blood culture was sterile after 5 days of incubation in a continuously monitored non-invasive system BD BACTEC FX (Becton Dickinson, Franklin Lakes, NJ). However, T2Candida® test (T2 Biosystems©, Lexington, MA) in whole blood was positive for *Candida parapsilosis*. At that time, micafungin was switched to liposomal amphotericin B. As part of the candidemia management, central venous catheters were removed and cultured and extension studies were performed (fundoscopic exam, transthoracic echocardiogram, abdominal echography and thoracic-abdominal CT scan). They were all negative. Two more consecutive samples (Fig. 1 – Timeline of blood cultures and whole blood samples for T2Candida® test) were drawn and *C. parapsilosis* was isolated in both blood cultures (1 and 4 days after incubation). Both T2Candida® tests were also positive for *C. parapsilosis* (4 h). Due to blood culture isolate was susceptible in vitro to fluconazole, amphotericin B was switched to fluconazole. Cultures of catheters were negative. Additional simultaneous samples (Fig. 1) were drawn in successive days for blood cultures and T2Candida® tests. These samples were evaluated in order to detect clearance of candidemia. T2Candida® tests were persistently positive while blood cultures were sterile in two additional samples (Fig. 1). The last sample reported negative results for both analysis. The final date of treatment with fluconazole was based on the resolution of the primary focus (day + 28) of infection and the first negative sample. The last day of candidemia treatment was defined two weeks from the day of the first T2Candida® negative result. After 40 days of admission, the patient was transferred to Gastroenterology Unit for 36 days and finally he was discharged from the hospital due to improvement of his general condition.

3. Discussion

In this case, the first positive result of T2Candida® test with negative blood culture allowed to guide the antifungal therapy immediately after the result was available (4 h) micafungin was switched to amphotericin B. It has been shown that in 89% of patients with candidemia empirical antifungal therapy is not started on the same day when blood cultures are drawn [7]. Moreover, this rapid diagnostic method has the potential to reduce the administration of empiric antifungal treatment to patients with negative test, reducing the adverse effects and additional costs of unnecessary antifungal therapy [8], as well as the antifungal pressure that is associated with development of resistance to antifungal agents [9–11]. For patients without metastatic complications, a minimum of two weeks of therapy after blood cultures become negative and resolution of symptoms attributable to candidemia has been used in most clinical trials. This is the recommended duration in the 2016 Infectious Diseases Society of America (IDSA) guidelines [12]. T2Candida® allows a close monitoring of the candidemia episode because of its high sensitivity. The sensitivity and specificity values have been also validated in a clinical trial that included analysis of both prospectively collected blood samples of more than 1800 patients with symptoms of bloodstream infection and blood samples technically spiked with known clinically relevant concentrations of the 5 *Candida* spp. The overall sensitivity per assay of the T2Candida® was found to be 91.1% and the overall specificity 99.4%. Further, using quantified spiked samples, the limit of detection was estimated to be 1 colony forming unit per milliliter (CFU/mL) for *C. tropicalis* and *C. krusei*, 2 CFU/mL for *C. albicans* and *C. glabrata*, and 3 CFU/mL for *C. parapsilosis* [13]. These low values makes this test more reliably than a blood culture (between 1 and 100 CFU/mL) [6] in order to ensure the clearance of *Candida* in bloodstream when a negative result is reported. The length of treatment after the last negative result might be established much more precisely than with blood cultures. As shown in Fig. 1, before the first negative sample of the patient for both methods, there were two samples with positive T2Candida® tests with negative blood cultures. This allowed to establish the length of treatment for two weeks after the negative T2Candida® result (last sample) and not after the first negative blood culture (day + 16), in which T2Candida® result remained positive. The focus of infection (abdominal) was partially controlled until the final days of PICU stay, therefore an antifungal length treatment guided by blood cultures might had not be optimal and might had have influence in the appearance of a possible recurrence episode.

However, *C. parapsilosis* candidemia was not the unique infectious disease of this patient. He presented a multi resistant *P. aeruginosa* disseminated infection. *C. parapsilosis* presents less virulence than other *Candida* species, but it must be suitably diagnosed and treated due to the influence that it can have on the morbidity and mortality of these complex patients (in this case multivisceral transplant recipient, broad spectrum antibiotherapy, mechanical ventilation, venous central catheters, immunosuppression, abdominal surgery) [14].

In conclusion, T2Candida® provided an optimal management of candidemia in this patient. Although the rapid diagnosis of the candidemia episode could not be definitive for the healing of the patient due to comorbidities (multiresistant bacteria infections and primary focus of the infection were also cleared up) it defined the correct antifungal treatment by allowing the correct election of the antifungal agent and

the adequate duration of treatment and management of the candidemia episode.

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Conflict of interest

There are none.

Ethical Form

Submitted.

Ethical approval

This clinical case is part of the study approved by the Ethics Committee of La Fe de Valencia Hospital with number 2016/0241. It was also ratified by the Ethics Committee of University Hospital La Paz.

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