CASE REPORT

Disseminated candidemia refractory to caspofungin therapy in an infant with extremely low birth weight

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KEYWORDS
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Systemic fungal infections have high morbidity and mortality rates in neonates, especially neonates with an extremely low birth weight (ELBW). Here, we describe a 21-day-old ELBW female infant with an amphotericin B-unresponsive congenital Candida albicans infection that was treated with caspofungin. Blood sterilization was performed during the first episode, but a second episode of candidemia occurred after the discontinuation of caspofungin. Blood sterilization was again performed during the second round of caspofungin treatment, but fungal endocarditis and renal fungal balls still developed during the second episode. Caspofungin can be considered for invasive candidiasis in premature infants, especially in life-threatening situations. As for the focal lesions, more aggressive treatments other than just parenteral antibiotics should be considered. The literature regarding caspofungin therapy for neonatal candidiasis is also reviewed.

Introduction

Neonatal candidemia occurs in 4–15% of extremely low birth weight infants; the lower the birth weight, the higher the risk of developing neonatal candidemia.1 Preterm infants are predisposed to the development of invasive fungal infections because of their immature mucocutaneous barrier and systemic host defenses. Aggressive neonatal intensive care and prolonged courses of broad-spectrum antimicrobials are required in such cases.2–4 Candida albicans is the most prevalent pathogen among the invasive fungal infections that present in neonates (64–75%).3,5,6 Amphotericin B is often used as an empirical therapy and is most often the first-line agent for treating invasive candidiasis in neonates.7 However, despite initial therapy with amphotericin B, delayed sterilization has been reported.8

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Caspofungin is a newly developed echinocandin antifungal agent with proven effectiveness against candidemia and other invasive Candida infections in adults. Caspofungin is a fungicide for treating Candida spp, including some strains that are resistant to amphotericin B and triazoles. According to the updated guidelines published by the Infectious Diseases Society of America, echinocandins can be in situations where resistance or toxicity precludes the use of amphotericin B. Recently, clinical trials in children have shown that caspofungin is well tolerated and effective in pediatric patients with Candida infections aged 6 months through 17 years. However, the use of caspofungin to treat neonates or premature babies is limited.

Case report

A 770-g baby girl was delivered vaginally from a G1P1 mother at 26 weeks of gestation. The mother developed prematurely ruptured membranes 3 days before delivery and presented with a fever at delivery. Soon after birth, the baby suffered from respiratory distress that required intubation, surfactant replacement, and mechanical ventilation. Pneumothorax also presented with unstable vital signs and required chest tube insertion. Diffuse erythematous macules and papules, 2–4 mm in diameter, appeared over the trunk and extremities. Laboratory examinations showed a leukocyte count of 6,800 cells/mm³ consisting of 24% segmented neutrophils and 24% banded neutrophils. A platelet count of 207,000 cells/mm³ and C-reactive protein (CRP) of 0.6 mg/dL (normal: <0.8 mg/dL) were also noted. Ampicillin and gentamicin were administered after the blood cultures were obtained; the patient was then shifted to vancomycin and ceftazidime on the fifth day due to progressive hypotension. Meanwhile, scleroderma and diffuse desquamation with erosions were noted (Fig. 1A and B). A potassium hydroxide preparation of skin scrapings showed pseudohyphae; amphotericin B (1 mg/kg/day) was administered. Fungal cultures from skin scrapings and blood were positive for C. albicans; meanwhile, the bacterial blood culture was negative. An umbilical arterial and venous catheter was immediately removed. Due to the complicated and critical condition of this patient, a central venous catheter was inserted for vascular access. Minimum inhibitory concentrations of fluconazole and amphotericin B were administered at doses of 0.25 and 0.032 μg/mL, respectively. However, repeated blood cultures that were taken during the 14 days after amphotericin B therapy were all positive for C. albicans. A cerebral spinal fluid (CSF) study yielded no evidence of meningitis. No infection focus was identified by heart, renal, or brain sonography. Ocular examination did not indicate thrombi or endophthalmitis. The neonate had persistent thrombocytopenia that required frequent platelet transfusions and persistent...
results show that the \textit{C. albicans} (Fig. 2). A whole body survey showed that there were no cases of undetectable infection foci in the heart and/or kidneys. In our case, caspofungin indeed successfully controlled neonatal candidemia refractory to amphotericin B therapy\(^9,16\) and as a possible salvage therapy.\(^{10,17,18}\) However, the use of caspofungin to treat preterm babies is limited. We reviewed reports on caspofungin usage in preterm babies with \textit{Candida} infections as far back as 2003. In addition to our patient, 27 cases in the medical literature that included clinical data were found using a MEDLINE search (Table 1). All but three of these cases achieved blood sterilization using caspofungin. Focal infection foci, such as heart vegetation or renal fungal balls, were found in all cases that failed to respond to caspofungin treatment. The time periods needed to achieve blood sterilization varied between 1–21 days, but 3–7 days was typical. Five cases that achieved blood sterilization experienced a relapse of candidemia within 2–60 days after the discontinuation of caspofungin. Most of the relapsed cases (4 in 5) developed a focal fungal infection.

In our case, caspofungin indeed successfully controlled candidemia, which was unresponsive to amphotericin B treatment. The relapse of candidemia after the discontinuation of caspofungin was most likely due to the existence of undetectable infection foci in the heart and/or kidneys. The early use of antifungal agents might minimize the chances of disseminated lodged \textit{Candida} infections from the bloodstream by preventing persistent candidemia. In controlling neonatal candidemia refractory to amphotericin B therapy\(^9,16\) and as a possible salvage therapy.\(^{10,17,18}\)

Discussion

Congenital \textit{Candida} infections produce a wide spectrum of symptoms, ranging from diffuse skin eruptions to severe systemic disease resulting in fetal demise or early neonatal death.\(^{12}\) Diffuse skin rash was the most striking clinical manifestation in our case, which led to a strong suspicion of neonatal candidiasis.

Amphotericin B is often used empirically as a first-line agent to treat invasive candidiasis in neonates.\(^7,10\) We initially used 1 mg/kg/day amphotericin B, as recommended.\(^{15}\) Unfortunately, the patient did not show any improvement, and persistent candidemia and clinical deterioration manifested. Thus, we replaced amphotericin B with caspofungin, which has been reported as effective for hypotension that required inotropic support. On the 21\textsuperscript{st} day, caspofungin (1.5 mg/kg/day or 13.5 mg/m\textsuperscript{2}/day) was used to replace amphotericin B. The cumulative dose of amphotericin B was 11 mg/kg at that time. After 4 days of caspofungin therapy, the blood culture was negative for \textit{C. albicans}.

Acute renal failure with hyperkalemia and cholestasis developed on the 5\textsuperscript{th} and 6\textsuperscript{th} days after caspofungin usage, respectively; the dose of caspofungin was adjusted to 1 mg/kg/day (9 mg/m\textsuperscript{2}/day). Under the improved and stable conditions, caspofungin was discontinued for the total 28-day treatment course, with a total cumulative dose of 30 mg/kg. Repeated blood and urine cultures were all negative before caspofungin was discontinued. There was still no identifiable infection focus by heart, renal, or brain sonography. Follow-up fundus examination still showed no thrombi or endophthalmitis.

However, 15 days after the cessation of caspofungin, candidemia relapsed. This time, the echocardiogram showed a vegetative mass measuring 4.8 × 3.5 mm in size in the right atrium, adjacent to the superior vena cava (Fig. 1C). Renal ultrasound also showed multiple fungal balls over the calices and pelvis of both kidneys (Fig. 1D). All isolates were identified as \textit{C. albicans} by standard biochemical testing using the API 20C system (API BioMerieux Vitek Inc., Hazelwood, MO, USA). Genotyping for six isolates of \textit{C. albicans} from this patient was performed using random, amplified polymorphic DNA (RAPD) segments using primers M13 (5\textsuperscript{-}GAGGCTGGCTGGTTCT-3\textsuperscript{)}), ERIC1 (5\textsuperscript{-}GTGAAATCCCCAGAGCTTACAT3\textsuperscript{)}),\(^{13}\) OPA3 (5\textsuperscript{-}ACGTACGCCAC-3\textsuperscript{)},\(^{14}\) and OPH-15 (5\textsuperscript{-}AATGGCCGAG-3\textsuperscript{)} (Operon Technologies, Inc., Alameda, CA, USA). The results show that the \textit{C. albicans} samples isolated during the relapse were the same strain as the earlier isolates (Fig. 2). A whole body survey showed that there were no brain abscesses, ventriculitis, meningitis, or endophthalmitis. Caspofungin was administrated again and blood sterilization was achieved 4 days later. Additional blood cultures all revealed negative results. Follow-up cardiac and renal echocardiograms showed that the vegetation persisted while the renal fungal balls had resolved to stone formations. Unfortunately, the general condition of this patient progressively deteriorated thereafter. Episodes of sepsis were suspected but not documented. The neonate finally passed away at the age of 128 days due to multiple organ failure.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{RAPD patterns of the eight isolates of \textit{C. albicans} generated by the four primers: M13, ERIC1, OPA-3, and OPH-15. Lane M: molecular size markers (1-kb ladder; Gibco BRL, Gaithersburg, Md.); Lanes 1–8: patterns for isolates 1–8, respectively. Isolates 1–5 were isolated during the first episode and isolate 6 was isolated during relapse. Isolates 7 and 8 are control strains from different patients with candidemia.}
\end{figure}
Table 1  Summary of reports in the medical literature on the use of caspofungin therapy to treat 28 preterm babies with *Candida* infections.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cases (no.)</th>
<th>Gestational age (GA) (wk)</th>
<th>Birth body weight (g)</th>
<th>Isolate</th>
<th>Site</th>
<th>Dose of caspofungin</th>
<th>Outcome</th>
<th>Time to sterilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesseling et al</td>
<td>2003</td>
<td>1</td>
<td>24</td>
<td>Not available</td>
<td><em>C. guillermondii</em></td>
<td>Blood, heart</td>
<td>Loading dose of 50 mg/m², then 35 mg/m²/day for 7 days</td>
<td>Failure, death</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Odio et al</td>
<td>2004</td>
<td>10</td>
<td>31–37</td>
<td>1150–2610 (median: 1495)</td>
<td>4 <em>C. albicans</em></td>
<td>10 blood, 1 heart, 1 CSF, urine, kidney</td>
<td>1 case: 0.5 mg/kg/day for 3 days, then 1 mg/kg/day for 28 days Other cases: 1 mg/kg/day for 2 days, then 2 mg/kg/day for 15–21 days</td>
<td>10 sterilized, 1 relapsed, 1 death</td>
<td>Mean: 4.3 days</td>
</tr>
<tr>
<td>Natarajan G et al</td>
<td>2005</td>
<td>13</td>
<td>12 preterm (24–28wk), 1 full-term</td>
<td>530-5600 (median 800)</td>
<td>5 <em>C. albicans</em></td>
<td>13 blood, 8 kidney, 3 heart, 2 lung, 2 CSF, 3 skin</td>
<td>1 mg/kg/day 5 cases: loading dose of 1.5 mg/kg, (All cases combined with other conventional antifungal agents)</td>
<td>11 sterilized, 3 relapsed, 7 deaths</td>
<td>Median: 3 days (range: 1–21 days)</td>
</tr>
<tr>
<td>Manzar S et al</td>
<td>2006</td>
<td>1</td>
<td>23</td>
<td>660</td>
<td><em>C. glabrata</em></td>
<td>Blood</td>
<td>Not available</td>
<td>Sterilized, survived</td>
<td>3 days</td>
</tr>
<tr>
<td>Yalaz M et al</td>
<td>2006</td>
<td>1</td>
<td>27</td>
<td>980</td>
<td><em>C. parapsilosis</em></td>
<td>Blood</td>
<td>5 mg/kg/day for 3 days, then 2.5 mg/kg/day (total treatment: 21 days)</td>
<td>Sterilized, survive</td>
<td>7 days</td>
</tr>
<tr>
<td>Smith et al</td>
<td>2007</td>
<td>1</td>
<td>25</td>
<td>810</td>
<td><em>C. albicans</em></td>
<td>Blood, urine, kidney</td>
<td>Loading dose: 100 mg/m² (8 mg/kg), then 70 mg/m²/day (6 mg/kg/day)</td>
<td>Sterilized, survived</td>
<td>8 days</td>
</tr>
<tr>
<td>Present case</td>
<td>2008</td>
<td>1</td>
<td>26</td>
<td>770</td>
<td><em>C. albicans</em></td>
<td>Blood, heart, kidney, skin</td>
<td>1-1.5 mg/kg/day</td>
<td>Sterilized, but relapsed and died</td>
<td>4 days, relapse 15 days after discontinuing of treatment</td>
</tr>
</tbody>
</table>

Caspofungin for neonatal candidemia
addition to early treatment, a sufficiently long treatment duration is also important for preventing disseminated Candida infections. Currently, the recommended length of therapy for candidemia is 3 weeks. This patient was treated for a longer period of time that may be necessary, at least for cases with risk factors. Premature infants are at special risk because they have immature organ functions, poor immune responses, and prolonged hospitalization that is usually accompanied by a broad spectrum of antibiotics and invasive equipment. Furthermore, candidiasis may not be totally eradicated by antifungal treatment but only temporarily suppressed. Candidiasis may manifest again in high-risk hosts, especially in those with compromised immune systems. Regular and careful examinations that can detect infection foci before and after the discontinuation of antifungal therapy are warranted in cases with persistent candidemia. The failure to cure our patient in the second episode demonstrates the fact that antifungal agents are probably insufficient to cure focal infection foci due to poor penetrations into the vegetations or fungal balls. Once an infection focus has developed, elimination of the focus by surgical intervention should be considered.

The optimal dose of caspofungin in premature babies remains uncertain. Nilgun et al used a dose of 5 mg/kg/day (50 mg/m²/day) for 3 days, followed by 2.5 mg/kg/day (25 mg/m²/day). Walsh et al reported an initial caspofungin dosage of 1 mg/kg/day (9—14.5 mg/m²/day) for 2 days followed by 2 mg/kg/day (18—29 mg/m²/day) for 15—21 days. We used 1.5 mg/kg/day (13.5 mg/m²/day) to treat the first candidemia episode, and blood sterilization was rapidly achieved on the 4th day. During the second candidemia episode, we adjusted the dose to 1 mg/kg/day (9 mg/m²/day) due to impaired liver and renal functions. Sterilization was achieved after 4 days of caspofungin usage. For severe infections, higher dosages might lead to earlier sterilization and should be used under close surveillance due to potentially adverse effects.

In conclusion, disseminated neonatal candidiasis is a clinical challenge for physicians. Early detection, evaluation of the involvement of the systemic organs, and effective treatment are key to the successful treatment of neonatal candidiasis. Caspofungin is a new antifungal and is effective for invasive neonatal candidemia, especially in those that respond poorly to conventional antifungal drugs. Earlier intervention with higher or prolonged usage of caspofungin should be considered for complicated or critical cases. However, relapse after caspofungin therapy can occur and should be carefully monitored. Invasive candidiasis in neonates, especially in premature babies, should be considered early, treated seriously and completely, and carefully monitored.

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Ethical approval

No ethical approval was required to carry out this study.

References