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■ Case report ■

High-dose caspofungin salvage in a very-low-birth-weight infant with refractory candidemia

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= Abstract =

Candidiasis is one of the most common causes of late-onset infection among very-low-birth-weight infants (VLBW) in most neonatal intensive care units and is associated with significant morbidity and mortality. Standard therapy consists of the administration of amphotericin B, amphotericin B complex, and fluconazole. In many cases, candidiasis is not easily eradicated, despite the administration of these drugs. We report our experience of the addition of high-dose caspofungin to the conventional antifungal drugs in a VLBW infant with refractory candidemia. (Korean J Pediatr 2010;53:239-243)

Key Words : Candidiasis, Caspofungin, Infant, Very low birth weight

Introduction

Invasive *Candida* infection is a significant cause of late-onset sepsis, especially in very low birth weight infants (VLBWs) in the neonatal intensive care unit (NICU)[1]. Despite administration of conventional amphotericin B alone or in combination with fluconazole, invasive candidiasis in VLBWs has a higher mortality and more frequent complications[1, 2]. Recently, it was reported that successful treatment of invasive candidiasis by a new antifungal echinocandin agent, caspofungin, in cases untreatable to these conventional antifungal agents[3, 4]. However, the optimal dose of caspofungin in pediatric patients, especially VLBW infants, is controversial. We report our successful experience of the addition of high-dose caspofungin in a critically ill VLBW with persistent, refractory candidemia who failed to conventional antifungal therapy.

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Case report

A preterm newborn girl developed an abdominal distension and respiratory distress at 18-day-old of age. She was born at 33^{+1} weeks gestation by cesarian section. At the time of conception, the mother was 27 years old with the history of two previous elective abortions, was referred to our hospital because of abruptio placenta and premature uterine contractions. No abnormal findings were noted on placental biopsy except a villus hematoma. There were no congenital malformations in the neonate or genetic disorders in her parents. There were no medical conditions or diseases requiring medication during pregnancy. Her birth weight was 1,140 g (10th percentile), the height was 38 cm (10-25th percentile), and the head circumference was 27.5 cm (25th percentile). Apgar scores were 2 at 1 minute and 3 at 5 minutes, respectively. She received artificial surfactant replacement therapy for respiratory distress syndrome. Antibiotic therapy with ampicillin and gentamicin was started empirically. At 3 days of age, she was noted to have a patent ductus arteriosus and was treated with indomethacin. Gentamicin was changed to cefotaxime because the C-reactive protein (CRP) increased to 22.90 mg/L. The umbilical venous catheter was removed at 6 days of age, and total parenteral nutrition was continued through a percutaneous central venous catheter (PCVC) inserted in

the right cephalic vein. At 9 days of age, antibiotics were discontinued because both the CRP and leukocyte count were in the normal range and the blood, urine, and cerebrospinal fluid cultures were negative. At 16 days of age, severe apnea developed. Her condition was deteriorated at 17 days of age with hypoglycemia, hypotension, and respiratory difficulty. Antibiotic therapy with ampicillin and amikacin was restarted. However, at 18 days of age, the apnea became more severe and abdominal distention developed. Her weight increased to 1,160 g since birth. A complete blood cell count showed a white blood cell (WBC) count of 8,610/mm^3 (neutrophils, 43%; lymphocytes, 35%; monocytes, 15%), hemoglobin level of 13.2 g/dL, and platelet count of 345,000/mm^3. Blood, urine, and PCVC cultures were obtained. Chest x-ray showed increased diffuse ground glass opacities in both lungs compared to the previous x-ray (Fig. 1A, 1B). Cultures from blood, urine and PCVC at 20 days of age were reported as positive for *C. albicans*. After removing the PCVC, antifungal drug therapy was stated with liposomal amphotericin B at 7 mg/kg/day from 20 days of age. She continued to deteriorate clinically with worsening of apnea and a reduction in the oxygen saturation. Repeat blood cultures performed at 22 days of age remained positive for *C. albicans* in spite of 48 hours of antifungal therapy. At 24 days of age, fluconazole was added with loading dose of 12 mg/kg/day followed by a maintenance dose of 6 mg/kg/day. At 26 days of age, excessive pulmonary hemorrhage occurred (Fig. 1C). Even though a high-frequency ventilator was used with 100 % FiO_2 and high MAP (18 cm H_2O), severe respiratory distress per-

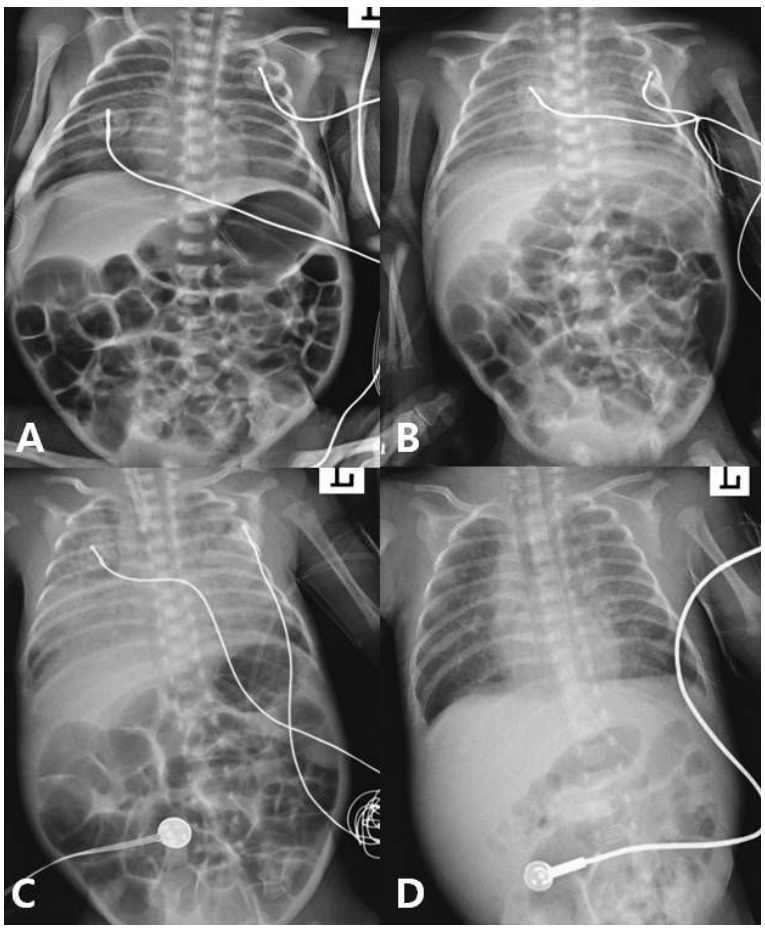

Fig. 1. (A) A chest x-ray of a 9-day-old infant showing ground-glass opacities in the central region of both the lungs (before candidemia) (A), diffuse haziness without zonal predominance at day 19 (onset of candidemia) (B), total lung opacity, except at both the costophrenic angles at day 26 (progression of candidemia) (C), and clearing of haziness in both the lungs, but presence of ground-grass opacities and granular densities in the central regions of the lungs at day 63 (recovery of candidemia) (D).

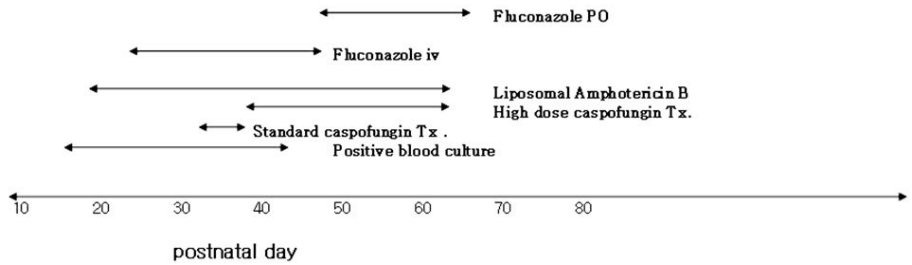

Fig. 2. Time course of antifungal dosing. The dosage of standard caspofungin treatment was 2 mg/kg/day, and that of high-dose caspofungin treatment was 50-70 mg/kg/day.

sisted. In spite of the combination therapy with fluconazole and liposomal amphotericin B, *C. albicans* persisted for 2 weeks. Caspofungin was added with the dose of 2 mg/kg/day at 32 days of age. Despite of additional caspofungin treatment, the clinical condition deteriorated. The dose of caspofungin was increased to 4-6 mg/kg/day (50-70 mg/m^2/day). The blood culture became sterile after the 5th day of high-dose caspofungin. During candidemia, drug sensitivity tests (MIC test) were performed two times (day 22, day 31) by an AST-YS01 card in VITEK®2 (bioMerieux Inc, Durham, NC, USA). The MIC results for amphotericin B and fluconazole were ≤0.5 and ≤1.0 μg/mL, respectively for both occasions. She received 5 weeks of caspofungin (4 weeks of high-dose), 6 weeks of liposomal amphotericin B, and 6 weeks of fluconazole [oral fluconazole for 2 weeks after intravenous fluconazol for 4 weeks; (Fig. 2)]. Following the 5 weeks of caspofungin treatment, the candidemia completely resolved without drug-related adverse effects. Chest x-ray showed clearing of hazziness in both lung fields at 63 days of age (Fig. 1D). She had bronchopulmonary dysplasia and was O_2-dependent until postmenstrual age at 40^{+4} weeks. She was discharged from the hospital on day 143 with a weight of 4,350 g (10th percentile).

Discussion

Candida infections can be life-threatening problem in long-term hospitalized adult and pediatric patients, especially in NICU[5, 6]. The identified risk factors for neonatal candidemia are low-birth weight, use of central venous catheters, parenteral nutrition, and broad-spectrum antibiotics[7-10]. Our case had several risk factors for a *Candida* infection, such as VLBW, endotracheal intubation, a history of exposure to antibiotics before the onset of candidemia (ampicillin, 10 days; gentamicin, 3 days; and cefotaxime, 7 days), the presence of PCVC (11 days before the onset candidemia), and the use of aminophylline. In cases of immunosuppressed patients, such as premature infants, many organs are involved and *Candida* infections cause serious systemic diseases, including endophthalmitis, meningitis, renal involvement, osteoarthritis, and pneumonia. Our patient had severe pneumonitis with candidemia without involvement of other solid organs.

In view of treatment of invasive candidiasis, Amphotericin B has been considered the mainstay of antifungal therapy. Fluconazole recommends for use as a second-line drug[11]. Liposomal amphotericin, a lipid complex of amphotericin B, reduces adverse drug reactions resulting from amphotericin B, but dose not improve the successful treatment rate[13]. Caspofungin was developed in the background of a necessity for a new antifungal agent which has high therapeutic effects and low adverse reactions, which is the echinocandin class, inhibiting the synthesis of 1,3 β D-glucan, a component of the fungal cell wall[13, 14]. Caspofungin is effective against a broad range of fungi, including many strains that are resistant to amphotericin B and fluconazoles [13]. In addition to this therapeutic effect, several studies have shown that caspofungin has fewer adverse reactions and synergistic effect with fluconazole[3, 15, 16]. The frequent adverse drug reactions are fever, erythema, nausea, headache, vomiting, and phlebitis and occur with a frequency of 3%. Approximately, 3% of patients have hepatic dysfunction or eosinophilia[4]. High-dose caspofungin treatment has been reported to result in hypercalcemia, hyperphosphatemia and hypermagnesema in an extremely low birth weight infant[17]. Our case did not show above mentioned side effects of caspofugin.

In regard to dosage and effect of caspofungin, many reports have suggested that caspofungin treatment is effective in VLBW who is unresponsive to combination therapy with amphotericin B and fluconazole[4, 17-19]. However, there is insufficient data regarding to the effective dosage and

length of therapy of caspofungin in children, especially in newborn until now. Odio et al[18] reported standard doses (2 mg/kg/day followed by 1 mg/kg/day) had good microbiologic activity. But, Walsh et al[20] suggested that dosing caspofungin at 1.0 mg/kd/day in pediatric patients may be suboptimal because the area under concentration-time curve over 24 hour (AUC_{0-24}) with this dose of caspofungin in pediatric patients was significantly lower than that observed in adults receiving 50 mg/day and a scheme based on body surface area dosing (maintenance dose of 50 mg/m^2/day) was found to better approximate levels of adults given 50 mg/day. Based on this study, subsequent dosing in children has been proposed to include a loading dose of 70 mg/m^2 followed by daily maintenance dosing of 50 mg/m^2/day[21]. Also it was suggested that a successful treatment case with high-dose caspofungin (loading dose of 100 mg/m^2/day [8 mg/kg/day] followed by a maintenance dose of 70 mg/m^2/day [6 mg/kg/day])[17]. In our case, patient recovered from severe and refractory candidemia when high-dose caspofungin treatment (50-70 mg/m^2/day) instead of standard caspofungin treatment (2 mg/kg/day) was added to conventional drugs. We added caspofungin to conventional antifungal drugs when clinical condition of the patient seriously deteriorated despite the usage of conventional antifungal drugs of sufficient duration to show effect, which is similar to the findings of previous studies[4,17-19]. Although it is unclear that the clinical improvement in this case was secondary to high-dose caspofungin or combined effect with other conventional antifungal drugs, we suggest that caspofungin played significant role in the treatment of persistent candidemia in VLBW. The in vitro resistance to classical antifungal drugs, especially for *C. albicans* and C. parapsilosis is 2 to 7%[22]. Our patient did not show resistant to amphotericin B and fluconazole as shown by the results of MIC tests of VITEK2, which was not consistent with that of Smith et al[4].

To our best knowledge, this case is the first report in Korea regarding to successful experience of the addition of high-dose caspofungin in a critically ill VLBW with persistent candidemia refractory to conventional antifungal therapy. For wider usage of caspofungin in the cases with persistent, refractory candidemia in VLBWs, studies on the dosage and possible combination with other antifungals are needed.

한 글 요 약

극소 저체중 출생아의 난치성 칸디다혈증에서 고용량 Caspofungin 구제요법

부산성모병원 소아청소년과, 부산성모병원 영상의학과 부산성모병원 진단검사의학과†*

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저자들은 고식적인 항진균제에 반응하지 않는 극소 저체중 출생아에서 발생한 지속적인 전신 칸디다증에서 이들 고식적인 항진균제에 고용량의 caspofungin을 병용 투여하여 국내에서 처음으로 특별한 약물 부작용 없이 치유한 1례를 경험하였기에 문헌고찰과 함께 보고하는 바이다.

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