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AMPHOTERICIN B IN THE TREATMENT OF CANDIDA MENINGITIS IN THREE NEONATES*

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Candidiasis is an opportunistic infection and may result in significant morbidity and mortality in neonates. Cerebral candidiasis is rare and usually associated with systemic candidiasis. Information concerning the toxicity and efficacy of antifungal therapy for neonates is limited. In this report, we present three neonates with candidiasis. All of the patients were premature with low birth weights, and received antibiotic therapy for one to four weeks before the onset of candidiasis. Candida albicans was isolated from cerebrospinal fluid cultures. Amphotericin B was given administered at an initial dose of 0.25 mg/kg/day intravenously (IV) and increased to a dosage of 2 mg/kg/day, and therapy was continued for three to four weeks. A transient and mild elevation in hepatic enzyme concentration was observed in two patients, and transient thrombocytopenia occurred in all of them. *Key words: candida meningitis, amphotericin B, neonate.*

Candida infections appear to be an increasing problem among neonates, and may result in serious neonatal morbidity including meningitis, cerebritis, osteomyelitis, endocarditis and abscesses[1]. The risk factors include low birth weight, aggressive chemotherapy, parenteral hyperalimentation, corticosteroids, venous catheters, endotracheal tubes and ventriculo-peritoneal or ventriculo-atrial shunts[2].

Although amphotericin B is the drug of choice in the treatment of candidiasis, little is known about its toxicity and efficacy in neonates[3]. In this paper, we report three neonates with candida meningitis treated with amphotericin B and review the relevant literature.

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Case Reports

Case 1

A premature (34-week gestation) male infant was delivered by caesarean section due to vaginal bleeding of his mother. He was admitted to the hospital with the diagnosis of respiratory distress syndrome. On day three, his general condition was deteriorating, and the clinical and laboratory findings were compatible with sepsis. Ceftriaxone and amikacin were given for sepsis. On day six, a lumbar puncture was performed and cerebrospinal fluid (CSF) examination revealed meningitis. After the isolation of Candida albicans from the CSF, treatment with amphotericin B was started (initially 0.25 mg/kg/day and increasing to 2 mg/kg/day). Transfontanelle ultrasonography revealed bilateral dilated ventricles and multiple echogenic areas. Cranial computed tomography (CT) was suggestive of multiple cerebral abscesses (Figs. 1, 2). Nonspecific antibiotic administration was stopped by the tenth day of treatment. A mild and transient thrombocytopenia was determined during antifungal treatment. CSF findings improved on the twentieth day of treatment. Administration of amphotericin B was continued for four weeks and stopped after clinical improvement was sufficient. The patient was discharged within eight weeks. After six months, physical examination revealed motor and mental retardation. Cranial CT displayed hydrocephalus and multiple calcified lesions in both hemispheres (Fig. 3).

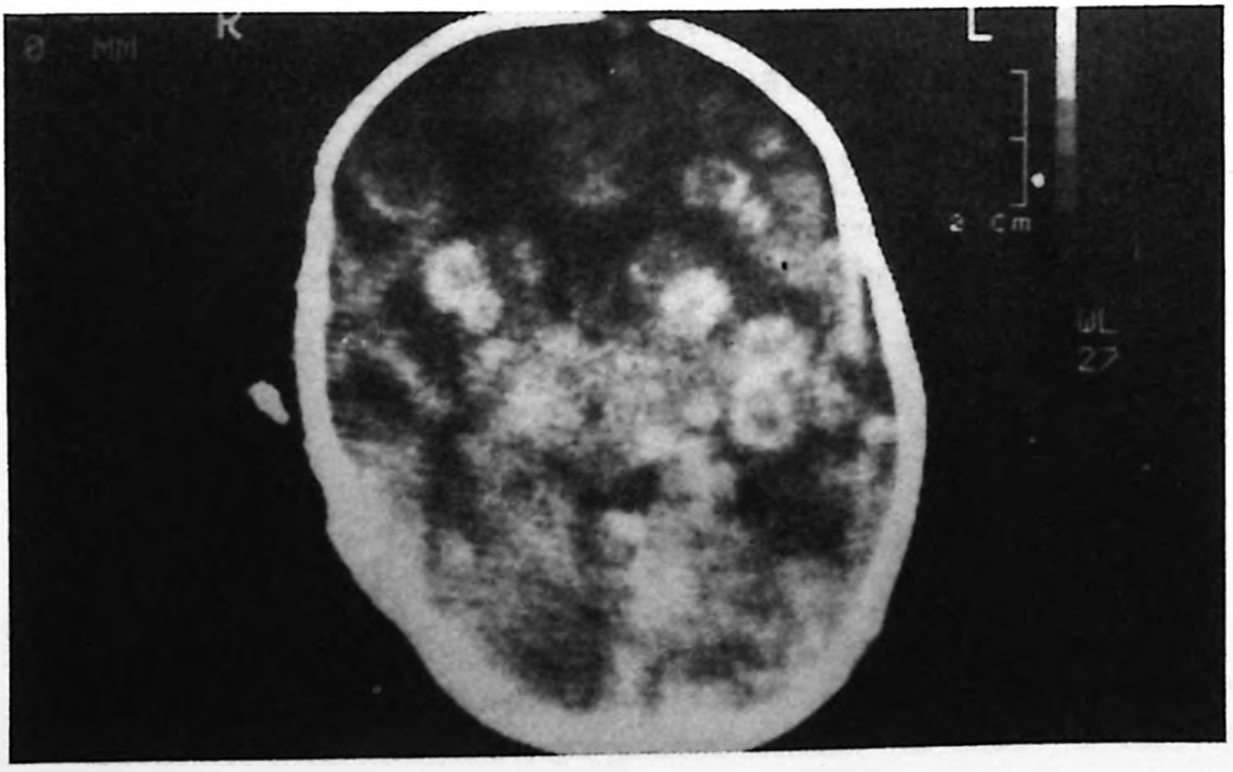

Fig. 1: Initial contrast-enhanced computed tomography (CECT) scan showing multiple nodular lesions of different sizes with good enhancement (Case 1).

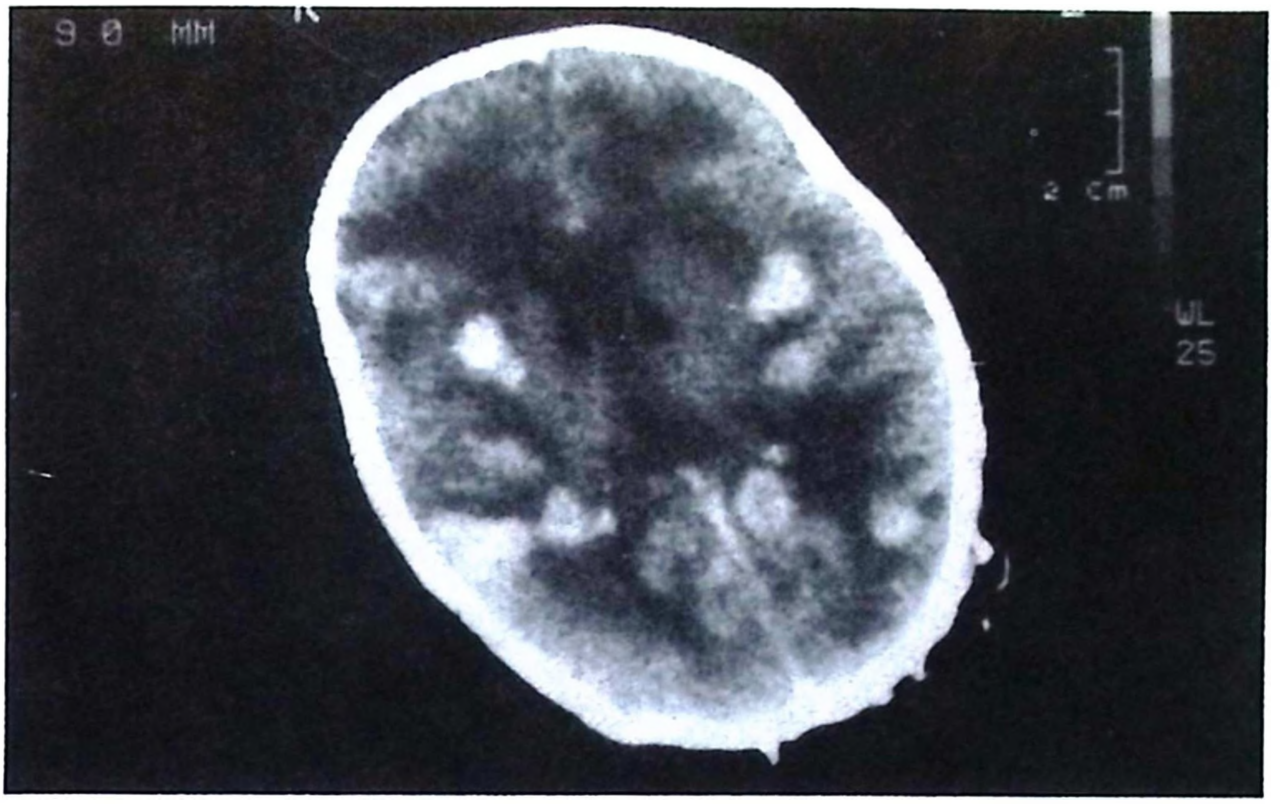

Fig. 2: CECT on the fifteenth day, illustrating marked resolution of lesions with respect to size and quantity (Case 1).

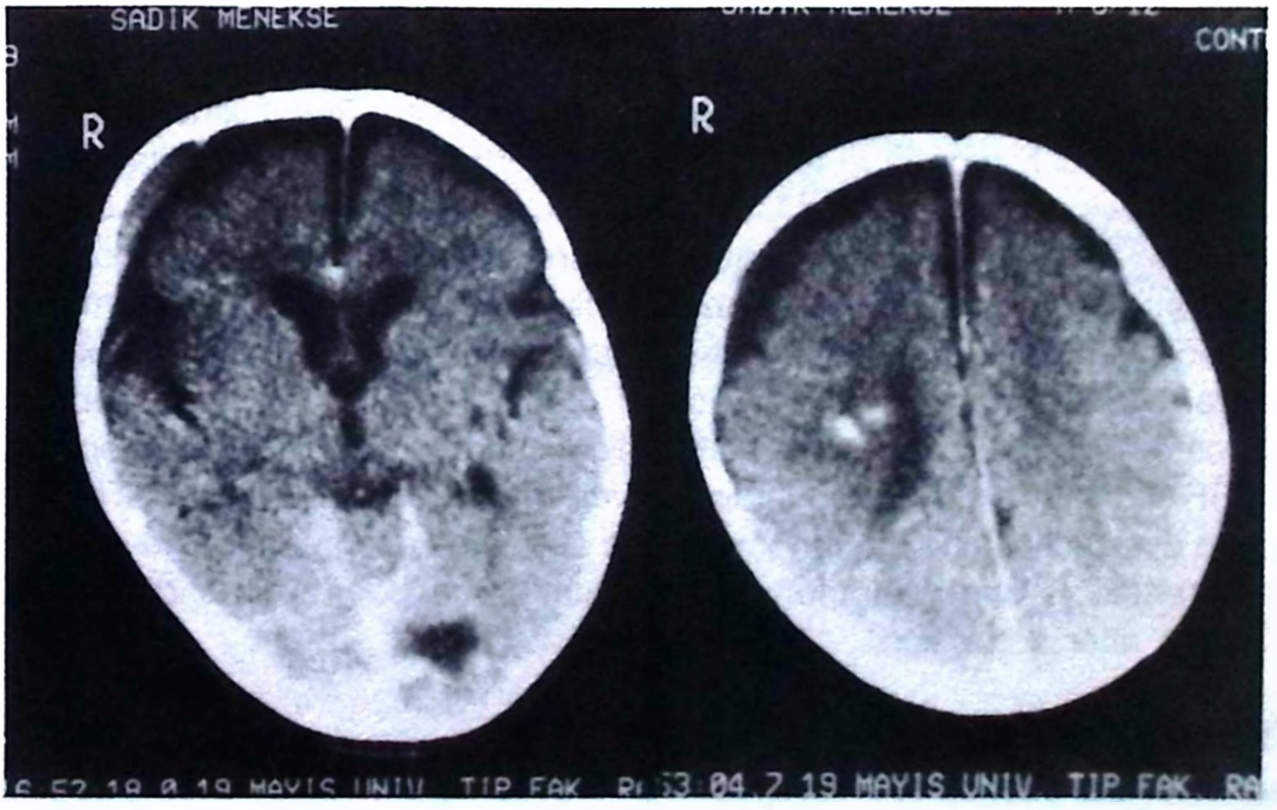

Fig. 3: Post-contrast CT at five months, demonstrating small hyperdense lesions in the right paraventricular white matter, encephalomalacic focus in the left occipital lobe, and minimal subdural effusion (Case 1).

Case 2

A premature female baby was delivered at 33 weeks gestation by cesarean section weighing 1800 g. Jaundice was observed on the first day and phototherapy begun. Because of increasing serum bilirubin levels, two exchange transfusions were performed. After these procedures, clinical and laboratory findings were suggestive of sepsis, and ceftazidime and amikacin were started empirically. Later, cefotaxime was substituted for ceftazidime due to isolation of ceftazidime-resistant enterobacter from the blood on the twelfth day of treatment. Clinical findings did not improve sufficiently during antibiotic therapy. On day 32, Candida albicans was isolated from CSF. At that point the treatment regimen was reevaluated; antibiotic administration was stopped and treatment with amphotericin B initiated. Transfontanelle ultrasonography and cranial CT findings were normal. Seven days after the start of antifungal treatment the patient had improved moderately, and amphotericin B was stopped at the end of the third week. A transient increase in hepatic enzymes was observed from the second to third weeks of treatment. She was discharged nine weeks after admission. Good neurological development was noted at a clinic visit three months later.

Case 3

A preterm female infant was delivered by cesarean section for maternal preeclampsia at 35 weeks gestation. Her birth weight was 1900 g. She was diagnosed with neonatal sepsis on the third day of life, and received ceftriaxone and amikacin. Five days later, oligoanuria was observed. Renal ultrasonography showed adrenal hemorrhage and papillary hypertrophy. Peritoneal dialysis was performed twice for acute renal failure, and the antibiotics were changed. In the fourth week of broad-spectrum antibiotics administration, Candida albicans was isolated from the blood, CSF, urine and joint fluid of the left wrist. CSF examination revealed meningitis. Transfontanelle ultrasonography and cranial CT showed bilateral hydrocephaly. Administration of other antibiotics was stopped, and amphotericin B was commenced with clinical improvement and improvement in the CSF and affected joint fluid findings over the course of four weeks. Transient hepatic dysfunction and thrombocytopenia appeared, caused by side effects of amphotericin B during antifungal treatment. The patient was discharged 10 weeks after admission.

Discussion

Neonates are susceptible to systemic infection because of less adequate anatomic barriers, low serum immunoglobulins and complement levels, deficient cell-mediated immunity, impaired opsonic ability and defective phagocytic function, such as chemotaxis, intracellular killing and oxidative burst[4].

Coupled with chronic antibiotic use, which suppresses normal bacterial flora thus allowing Candida and other nosocomial pathogens to flourish, the neonate becomes a prime candidate for fungal invasion[5,6].

Candida species cause late-onset systemic infection in neonates, especially in premature infants[3]. Common signs and symptoms of systemic candidiasis include respiratory deterioration (an increase in oxygen requirement or ventilatory support), acidosis, apnea and bradycardia, carbohydrate intolerance, abdominal distention, guaiac-positive stools, lethargy, hypotension, hepatosplenomegaly and nonspecific maculopapular rashes[2,3]. These nonspecific signs do not allow for distinction of bacterial from fungal infection. Involvement of the central nervous system is not uncommon, and cerebral candidiasis is frequently secondary to systemic candidiasis. In all three of our patients, the clinical picture resembled nonspecific meningitis. Only the culture results demonstrated Candida albicans as the responsible microorganism.

For the treatment of systemic candidiasis, amphotericin B, flucytosine, itraconazole, fluconazole and ketoconazole are the recommended drugs; however, neither the optimal dosage nor duration of therapy with these drugs is known in neonates. Recent reports suggest that amphotericin B and flucytosine should be used in neonates, although they have also been reported as potentially toxic agents[2,7]. Butler et al.[3] and other researchers[2,8] have suggested that amphotericin B might be a contributing factor in the morbidity and mortality of neonates with systemic candidiasis. Azotemia, hepatotoxicity and thrombocytopenia have been reported with amphotericin B therapy[3,8-10]. In our patients, no significant side effects were observed other than a transient elevation in liver enzymes in two of them, and transient thrombocytopenia in all three (Table I).

Table I: Laboratory Findings at the Onset, During and at the End of Amphotericin B Treatment

							Cerebrospinal Fluid			
	SGOT (U/L)	SGPT (U/L)	GGT (U/L)	BUN (mg/dl)	Cr (mg/dl)	Thromb (/mm3)	Prot (mg/dl)	Gluc (mg/dl)	PNL (/mm3)	Lymp (/mm3)
Case 1										
OT	37	40	131	5	0.4	365,000	201	34	200	10
DT	40	52	375	10	0.4	147,000	740	46	270	140
ET	18	23	92	15	0.6	350,000	414	43	10	10
Case 2										
OT	28	14	116	23	0.5	300,000	310	57	330	10
DT	85	104	246	36	1.1	65,000	157	57	0	0
ET	50	55	187	21	0.8	380,000	110	70	0	0
Case 3										
OT	28	19	—	27	1.2	110,000	264	19	140	150
DT	66	82	1665	54	2.4	34,000	180	14	60	30
ET	30	40	160	12	0.5	370,000	124	84	5	

OT: At onset of therapy; DT: At any time during therapy; ET: At end of therapy; ALT: Alanine aminotransferase; AST: Aspartate aminotranasferase; GGT: Gamma glutamyl transferase; BUN: Blood urea nitrogen; Cr: Creatinine; Thromb: Thrombocytes; Prot: Protein; Gluc: Glucose; PNL: Polymorphonuclear leukocytes; Lymp: Lymphocytes.

In conclusion, amphotericin B may be used as a single drug in candidal infections of neonates, but because of its toxicity caution should be used in prescribing and administering this drug.

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