Cerebral and renal abscess and retino-choroiditis secondary to candida albicans in preterm infants: eight case retrospective study

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Summary

Objectives: To assess the tissues and organs commonly involved and the clinical features in the invasive fungal infection (IFI) of candida albicans in the preterm infants. *Materials and Methods:* Eight preterm infants who developed IFI with positive blood culture for candida albicans were retrospectively studied. All infants received selected clinical and laboratory parameters evaluation, such as blood culture, cerebral magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) biochemical test, routine urine test, urine culture, renal ultrasonography, renal computer tomography (CT), and fundus examination. The re-examinations were performed after one to two months follow-up. *Results:* Cerebral abscesses were detected in six infants. Five cases developed renal systemic fungal infection, among which one had renal abscess. Three cases were complicated with fungal retino-choroiditis. *Conclusions:* Preterm infants, especially very-low-birth-weight (VLBW) and extremely-low-birth-weight (ELBW) infants are susceptible to fungi. The majority of preterm late-onset fungal infections are due to candida albicans. The organs commonly involved in the IFI of candida albicans are central nervous system (CNS), kidney and fundus, among which renal systemic fungal infection are prone to recur, calling for a prolonged anti-fungi treatment course.

Key words: Candida albicans; Preterm neonates; Invasive fungal infection; Cerebral abscess; Renal abscess; Retino-choroiditis.

Introduction

The neonatal intensive care unit (NICU) is rapidly developing. The application of mechanical ventilation, nutritional support through peripherally inserted central catheter (PICC), umbilical artery and vein catheters, and broad-spectrum antibiotics has increased the survival of the very-low-birth-weight (VLBW) and the extremely-low-birth-weight (ELBW) infants. However, fungi have become part of the major pathogens leading to the late-onset infection of VLBW and the ELBW infants. Genus candida accounts for the majority of invasive fungal infection (IFI). Since it is difficult to differentiate disseminated infection of candidemia from bacteremia, early diagnosis and prompt management of fungal infection are delayed. The delay and the properties of adherence and proliferation lead to the dissemination to multiple end organs like brain, kidney, lung, intestinal tract, heart, eye, liver and joints. To assess the tissues and organs commonly involved and the clinical features in the IFI of candida albicans in the preterm infants, the authors retrospectively studied a case series of eight preterm children who developed IFI with positive blood culture for candida albicans and complications of cerebral abscess, renal abscess or retino-choroiditis.

Materials and Methods

Patients

Retrospective studies were done in eight cases diagnosed as candida albicans IFI between January 2011 and February 2012 in the First Hospital of Jilin University. This study was conducted in accordance with the Declaration of Helsinki and was conducted with approval from the Ethics Committee of First Hospital of Jilin University. Written informed consent was also obtained from all participants. All cases were preterm infants, with the gestational age of 27 to 32 weeks, birth weight of 940 g to 2,200 g, and main pre-existing conditions of premature and respiratory distress syndrome (RDS). One case was ELBW infant, two cases were VLBW infants, and the other five were low-birth-weight (LBW) infants. Five cases required invasive mechanical ventilation. All infants received nutritional support through PICC for 15 to 53 days. Positive blood cultures for fungi occurred between days 7 to 40 after admission. The catheters were all removed as soon as possible after the positive culture. Table 1 summarizes the clinical data.

Imaging evaluation

Eight preterm infants who developed IFI with positive blood culture accepted selected imaging evaluation like cerebral magnetic resonance imaging (MRI), renal ultrasonography, renal computer tomography (CT), and indirect ophthalmoscopy examination. Cerebral abscesses were detected by cerebral MRI in six infants. The observations of the cerebral MRI: multiple punctate, relatively small, disseminated wide lesions performed higher signal in bilateral frontal, temporal, occipital, and parietal lobes (Figure 1). After the administration of fluconazole for four to six weeks, multiple cerebral abscesses disappeared after one to two months. Five cases developed renal systemic fungal infection, among which one had renal abscess. Kidney CT showed enlarged bilateral kidneys, with multiple well-defined, low-density parenchymal lesions. Renal Doppler ultrasonography showed multiple parenchymal echoless areas in bilateral kidneys. Punctate hyperechoic areas were detected in the renal pelvis (Figure 2). Three cases were complicated with fungal retino-choroiditis. Fluffy white retinal balls were detected by indirect ophthalmoscopy (Figure 3).

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Table 1. — *Clinical data of eight preterm infants.*

Case number	1	2	3	4	5	6	7	8
Gestational age (weeks)	30	28^{+6}	30	32	28	32^{+4}	32^{+4}	27
Birth weight (kg)	1.68	1.8	1.64	2.2	1.44	1.65	1.42	0.94
Pre-existing condition	Premature; RDS	Premature; twins	Premature; RDS	Premature; RDS; BPD	Premature; RDS; PDA; Premature;	Premature; twins Premature;	Premature; twins PDA; BPD	Premature; twins; RDS;
Nutritional support through PICC (days)	20	25	18	15	50	15	12	53
Ventilation support (days)	10	3		7	52			60
Timing of positive blood culture (days)	18	16	11	22	15	40	7	21
Organs involved	Brain; Kidney; Fundus	Fundus	Brain	Brain; Kidney;	Kidney	Brain; Kidney;	Brain; Kidney; Fundus	Brain
Course of anti-fungi medication (days)	32	28	28	56	45	35	14	35
Outcome	Recurred	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Died

NOTE: RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; Recurrenced cases: renal systemic infection recurred.

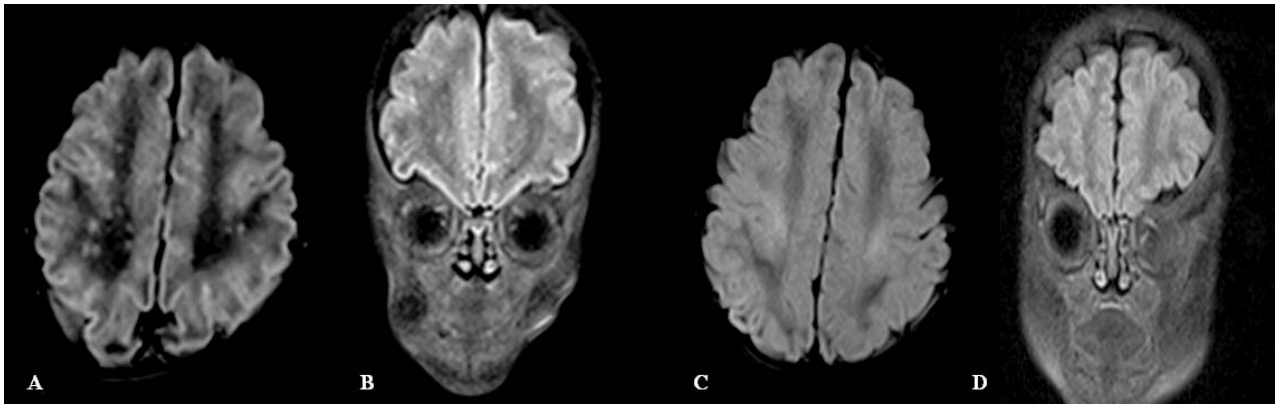

Figure 1. — Fungal cerebral abscesses. Case 7: T2-weighted dark flare cerebral MRI. A, B: the multiple punctate lesions performed higher signal in bilatural frontal, temporal, occipital, and parietal lobes. C, D: one month later, the multiple punctate higher signal lesions disappeared.

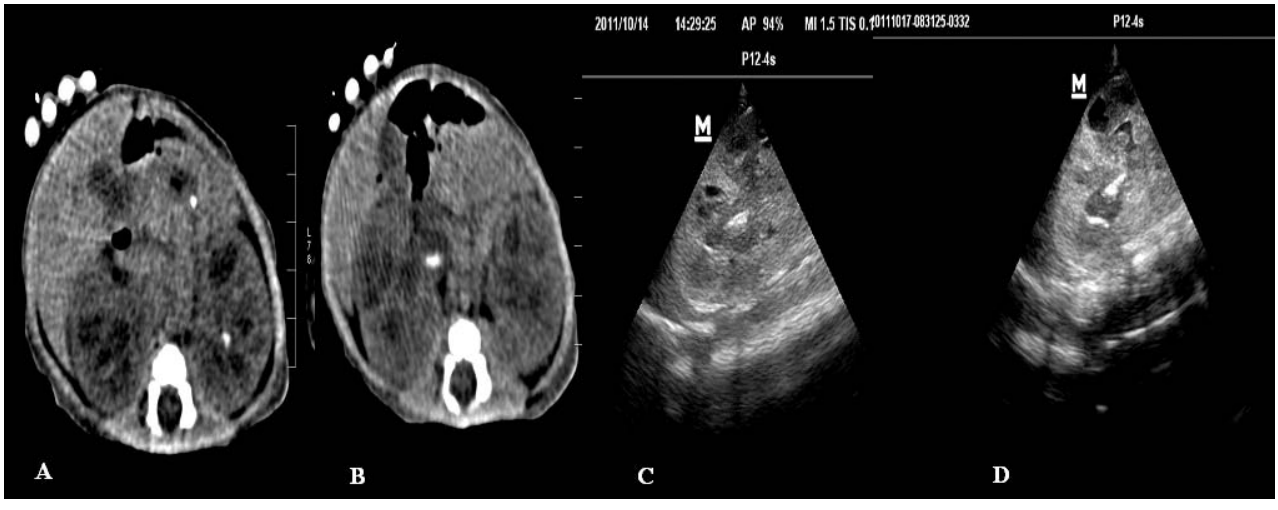

Figure 2. — Renal systemic fungal infection complicated with kidney abscess. Case 7: Kidney CT and renal Doppler ultrasonography. A, B: kidney CT showing enlarged bilateral kidneys, with multiple well-defined, low-density parenchymal lesions. High-density mass in the bilateral renal pelvis and upper nephritic ducts. C, D: renal Doppler ultrasonography showing multiple parenchymal echoless areas in bilateral kidneys. Punctate hyperechoic areas in the renal pelvis.

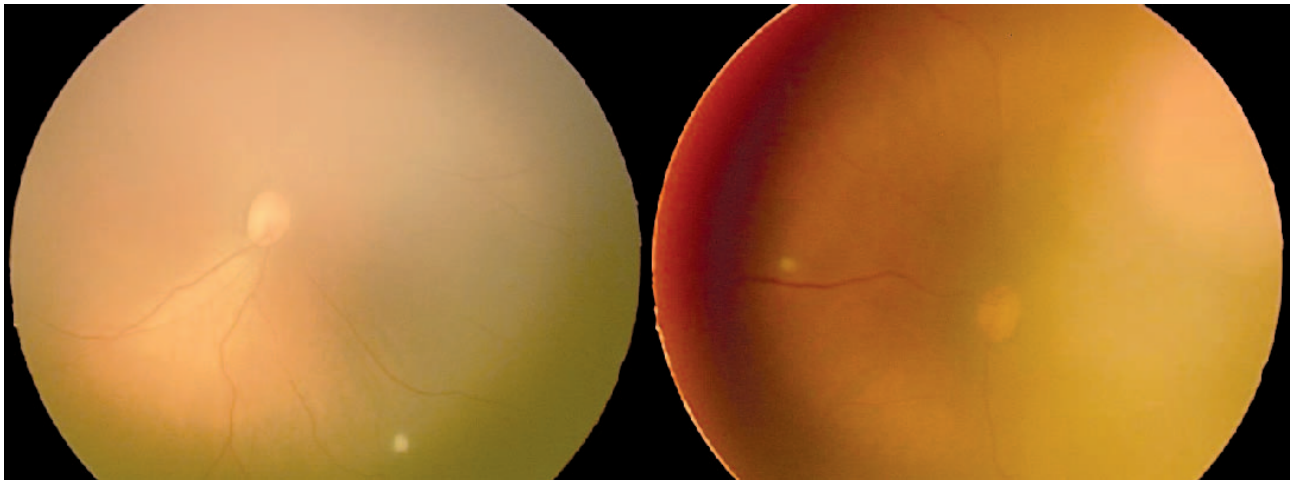

Figure 3 — Fungal retino-choroiditis. Case 7: indirect ophthalmoscopy examination showing fluffy white retinal balls.

Results

Cerebral abscesses were detected in six infants (Figure 1). Five cases developed renal systemic fungal infection, among which one had renal abscess (Figure 2). Three cases were complicated with fungal retino-choroiditis (Figure 3).

Discussion

NICUs are rapidly developing. The application of mechanical ventilation, nutritional support through PICC, umbilical artery and vein catheters, and broad-spectrum antibiotics has increased the survival of the VLBW and the ELBW infants. However, fungi had become part of the major pathogens leading to the late-onset infection of VLBW and the ELBW infants. Genus candida accounts for the majority of IFI. Since it was difficult to differentiate disseminated infection of candidemia from bacteremia, early diagnosis and prompt management of fungal infection were delayed. The delay and the properties of adherence and proliferation lead to the dissemination to multiple end-organs like brain, kidney, lung, intestinal tract, heart, eye, liver and joints [1]. Course of anti-fungi medication were prolonged and outcomes were poor.

Candida albicans is considered an opportunistic pathogen. Whether people become ill or not depends on the immunity and the defense of the host, as well as the virulence of the pathogen. In normal conditions, candida albicans in the body is yeast-like and non-pathogenic. However, when the immunity and defense of the host decreases, candida albicans proliferates and transforms to an invasive, multicellular filamentous form (also called pseudohyphae) to infect the host tissue, thus people will become ill and clinical manifestations arise. candida albicans has several known virulence factors contributing to its pathogenicity: adherence to epithelial and endothelial cells: virulence is parallel with adherence and candida albicans adheres most strongly to epithelial cells among the genus candida. Pseudohyphae formation: When infection occurs, candida albicans is in the multicellular filamentous form, which is of greater virulence than the yeast-like morph. Toxin: the polycose toxin on the surface and another kind called 'candida toxin' may be the pathogenic factors. The components of the cell wall; extracellular membrane-damaging enzymes: candida albicans can excrete some species of enzymes like lysophospholipase, phospholipase, acid protease, etc, among which extracellular acid protease is the most important, which can hydrolyze not only protein, but also keratin and collagen, leading to the promotion of the ability of adherence of candida albicans.

The process of the candida albicans infection is as follows: The fungus adheres to the epithelial cells and forms infectious focus with the help of the aforementioned pathogenic factors. The process of adherence is accomplished by the combination of collagen and adherence acceptors, which are located on the surface of the candida albicans and the host cells respectively. The collagen widely distributes in vascular walls, inflammation and trauma, making the candida albicans adhere and invade the host's tissues much more easily. Compared to other candida species, candida albicans demonstrates increased adherence and penetration of vascular endothelium, possibly accounting for its higher incidence as a cause of IFI. Since the kidney, ocular fundus and central nervous system are abundant in blood vessels, which are the destination of candida albicans' adherence, these organs are prone to be involved.

What are the clinical features of preterm end-organ dissemination of candida albicans infection? The authors demonstrate the clinical data of the eight cases infected with candida albicans, with the involvement of central nervous system (CNS), kidney, choroidal and/or retina as follows.

CNS candida infection may involve disseminated minor abscesses (diameter < three mm), meningitis, ventriculitis, cerebral infarction, mycotic aneurysm, and subarachnoid hemorrhage [2]. In the present study, six of eight

cases had CNS infection, with the clinical manifestations of fever, decreased responsiveness, and apnea in all, convulsion in only one case, CSF changes in three cases of increased of protein, and white blood cells and negative culture, and multiple minor abscesses in all the CNS involved cases' MRI except for one who could not undergo the examination because of the severity of the disease. Thus, the CNS candida albicans infection cannot be excluded even the cerebral spinal fluid (CSF) is normal, and the infants with the clinical manifestations of IFI should routinely accept cerebral MRI screening. The present observations that foci of abscesses, numerous and relatively small, disseminate widely and coordinate well with Mueller's study [3]. After the administration of fluconazole for four to six weeks, multiple cerebral abscesses disappeared after one to two months. Among the cases are a couple of twins who are nine-month-old now and normally developed their CNS, left with no sequelae.

Five cases during the study developed candida albicans infection in the urinary system, with positive urine culture in all the five cases, the same with the blood culture. Other auxiliary examinations included urine routine test, renal Doppler ultrasonography, and renal CT. White blood cells increased in the urine. With ultrasonography, multiple parenchymal echoless areas and hyperechonic areas were detected respectively in parenchyma and renal pelvis bilaterally in several cases. Corresponding with CT, the renal abscesses appeared as parenchymal oval low-density lesions. Also, high-density masses appeared in the renal pelvis and upper renal duct. One case with renal abscesses developed renal dysfunction, and recovered after peritoneal dialysis, urinary tract flushing and anti-fungal medication. Candida albicans adheres easily to epithelial cells of vessels and other tracts because of the ability of adherence. Since the glomerulus and nephric tubules are abundant in vessels, candida albicans infection easily involves urinary system and forms abscess, which are difficult to eradicate. The clinical symptoms of fungal infection in urinary tract are always insidious, so it should be routine for the patient with candidemia to accept the urine test, urine culture, and image examination to clear whether the patient has fungal urinary infection [4-6]. It should also be noted that central venous catheters create a unique surface for proliferation of candida albicans, so the catheters should be removed for any preterm infant with candidemia. As for management, medicine-like fluconazole that has a high concentration in the urinary system should be administrated. In case of recurrence, the course should be prolonged [7-8]. In the present study, the five cases accepted fluconazole for two to three weeks until the urinary culture turned negative. However, two of them relapsed after the drug withdrawal. The short course may account for the recurrence. So in case of recurrence, the course of urinary tract fungal infection should last for at least four to six weeks until the several negative urine culture results.

Three cases caused fungal retino-choroiditis with the white fluffy balls in the fundus examination. According to the reference, candida albicans infection, the main part of the endogenous endophthalmitis, may occur at any age, have no gender difference, and 70% of the patients develop the disease in binoculus [9-11]. Fungal retino-choroiditis has the following characteristics: the infective process develops gradually. The posterior segment lesions are mainly caused by invasion via the choriocapillaries, crossing the pigment epithelium affecting the retina. If the organism penetrates the internal limiting membrane of retina, the lesions break free and disseminate to form 'satellite foci'. If the fungus gains access to the vitreous cavity, multiple clumps may form within the vitreous. The multiple clumps in the vitreous are often connected by thread-like strands, thus their aspect is referred to as having 'string of pearls appearance [12]. The posterior hyaloid fixed by inflammatory foci, around which granulation and organization form, results in the severe sequel of hemorrhage or traction retinal detachment [13]. The course of the disease can be divided into two phases [14]: retino-choroiditis phase and endophthalmitis phase involving vitreous and sometimes anterior uvea. Medical treatment varies according to the tissues involved in the candida albicans infection: systemic administrations through the venous route of antifungal agents like fluconazole or amphotericin B for retino-choroiditis; as for the endophthalmitis, injection of amphotericin B in the vitreous cavity or vitrectomy is performed, and the simultaneous administration of antifungal agents helps. Because of the insidious clinical symptoms and the severe sequel-like retinal necrosis, traction retinal detachment, bulbus oculi atrophy, and visual loss of the fungal retino-choroiditis [15-16], infants who are suspected to have fungal infection especially IFI, should accept routine screening through indirect ophthalmoscope after mydriasis [17-18]. Since the fungal infection can be detected in the retinal phase, endophthalmitis and the severe results may be prevented under proper and prompt treatment. The three cases were administrated with fluconazole for two to four weeks, resulting in the gradual disappearance of the white dots. No visual loss was detected during the follow-up.

Preterm infants, especially smaller and more immunocompromised ones, are susceptible to fungal infection [19]. In the present study, fungal end-organ infection of cerebral abscess, urinary infection, and retino-choroiditis in the eight preterm infants with IFI have obvious and specific signs detected through imaging examination. Candida species can also cause fungal arthritis, dermatitis, cardiac valvulitis, and fungal abscesses may form in skin and liver, etc [20]. When the neonates develop candida albicans invasive infection, they should accept the auxiliary examination to identify whether they are complicated with end-organ infection in CNS, kidney, fundus, skin and joints, which are necessary for the determination of the management and the prediction of the prognosis.

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