Congenital Systemic Fungus Infection in Twin Prematurity—A Case Report and Literature Review

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Abstract

Congenital candidemia sepsis is a serious condition especially for the prematurity. Early recognition is always not the scenario and this leads to high morbidity and mortality. Twin pregnancy complicates the problems further. This report presents a case of congenital candidiasis in a twin preterm and literatures review of five twin pairs with the same scenario. In conclusion, for twin prematurity, if one is suspected to have invasive candidiasis, both of them should receive a full course of antifungal therapy through the intravenous route.

Keywords
- congenital candidemia
- twin
- prematurity
- sepsis

Congenital candida sepsis is a serious illness especially for the prematurity. Early recognition is not easy and this leads to grave outcome.[1,2] Twin pregnancy further complicates the problems further; if one of the twins is infected, how risky another twin is? Besides, twin pregnancy always results in prematurity and low birth body weight (BBW); both render them more risky in comparison with the term babies. This report presents a case of invasive congenital candidiasis in a twin preterm and literatures of five twin pairs with the same scenario are reviewed.

Case Report

This case was a twin A baby, G3P1A2, gestation age (GA) 30 weeks, BBW 1664 g; meconium stain of amniotic fluid was noted at birth and Apgar score were 2, 6, and 8 at 1, 5, and 10 minutes respectively. This gestation was achieved via in vitro fertilization (IVF) technique. At gestation 13 weeks, embryo reduction from quadruplets to twins was performed. The mother had received tocolysis treatment since gestation 24 weeks. She had no vaginal candidiasis or other significant history such as cerclage suture. At gestation 30 weeks, rupture of membrane happened. After 1 hour, dichorionic-diamniotic twins were born by spontaneous vaginal delivery.

The baby was apnea at birth; cardiopulmonary resuscitation (CPR) was performed. At admission, several reddish papules over anterior chest wall were noted, but these lesions disappeared soon. Initial therapy included high-frequency oscillation ventilation, use of surfactant, and antibiotics. The baby was very sick and CRP was 10.1 mg/dL. The condition got downhill in spite of various aggressive therapies. At 36 hours of age, cardiac arrest happened to the baby; pulse was regained after chest compression. Afterward, the baby's pupils were fully dilated without light reflex. Brain sonography showed intraventricular hemorrhage (IVH) grade IV with midline shift. At 40 hours of age, amphotericin B (1 mg/kg/day) for blood culture yield Candida was used. Finally, patient expired at 81 hours of age. The culture from blood, urine, sputum, and placenta all yielded *Candida albicans*.

Twin B was a female baby, BBW was 1,488 g, and Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. Fluconazole (12 mg/kg/day) was used at 40 hours of age and lasted for 14 days until negative blood culture was informed when twin B's urine culture was positive. The

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baby's urine culture grew *C. albicans*. She was discharged after hospitalization for 55 days.

Review of the Literature

Five twin pairs were collected through the MEDLINE search as far back as to 2000.[2–6] Plus this case report, there were six twin pairs in total. Their clinical data are summarized in ►**Tables 1** and **2**. The mean GA was 30 ± 2 weeks (29∼33 weeks), mean BBW was 1,421 ± 560 g (425 ∼ 2,362 g). Among the six twin A babies, five cases including one intrauterine fetal death (IUFD) had candidemia sepsis and four of them died. The only survivor (twin pair 3) received antifungal treatment promptly at the presentation of symptoms and signs because culture of the amniotic fluid grew *C. glabrata* at gestation 26 weeks. Among the six twin B babies, two cases had candidemia and resulted in one mortality. One case had candiduria; two cases had skin rashes consistent with congenital cutaneous candidiasis, and the remaining one was well.

In the seven cases with systemic candidiasis, the initial manifestation was sepsis in five babies. One case was IUFD and the remaining one was free from symptoms. This case, twin B of pair 6, received antifungal therapy at 7 hours of age because maternal blood culture grew *non-albicans Candida*. Skin rashes consistent with congenital cutaneous candidiasis were present in two twin B babies.

As for the five mortality cases, one was IUFD; three cases died before antifungal therapy, which included the IUFD case, because the condition deteriorated too rapidly to start treatment. Two cases received antifungal medication after blood culture yielded *Candida*. Two cases including the IUFD case had autopsy; disseminated fungus infection involving the lung, pleural fluid, liver, and blood was demonstrated.

As for maternal culture, five cases were positive: three from placenta, one from amniotic fluid, and one from blood. The status of the remaining ones was not mentioned. In the seven babies with fungal sepsis, four cases were of *C. albicans*, one *C. glabrata*, one *C. kyfer*, and one *C. parapsilosis*. Except twin pair 3 whose mother's culture was not mentioned, species of the babies' culture were the same as the mothers (►**Table 2**).

Discussion

Congenital candidiasis in preterm infants is a severe infection requiring antifungal treatment and the need of antifungal therapy in term infants is pending evaluation. Congenital cutaneous candidiasis should be considered an invasive *Candida* infection, especially in preterm. In preterm infants, the skin rashes represent not only superficial rashes or colonization, but an invasive disease caused by their immature, compromised mucocutaneous barrier and systemic host defenses.[7,8] Diagnosis of invasive congenital candidiasis can be confirmed by fungal culture from a sterile body fluid (blood, urine, or cerebrospinal fluid [CSF]…etc.) in a newborn.[9,10] Although hematogenous route has been reported,[6,11] generally, it is an ascending infection from vagina resulting in chorioamnionitis. The infected amniotic fluid results in cutaneous candidiasis of fetus via direct contact and invades the body through the amniotic fluid circulation pathway. The fetal swallowing movement leads to colonization of the gastrointestinal (GI) tract, and the occasional deep breathing may cause aspiration of the infected amniotic fluid into the lungs.[12] Though the severity of illness varies, *Candida* infection of the placenta, amniotic fluid, maternal bloodstream infected, and infant skin involvement (congenital cutaneous candidiasis), in addition to infant blood, urine, or CSF involvement, should prompt treatment of both twins (or other multiples). Risk of systemic involvement increases in prematurity and low BBW infants, whose inadequate skin barrier and impaired cellular immunity may be the causes.[7] The mortality of untreated systemic candidiasis ranges from 39 to 94%.[12] Therefore, early diagnosis and early treatment are crucial.

Table 1 Demographic data of the twins with congenital systemic Candidiasis

		Chen[a]	Bender	ARAI	Krallis	Carmo	Pineda
		Taiwan	USA	Japan	Greece	Australia	USA
		2012	2000	2002	2006	2007	2012
GA (wk)		30 + 6	33	29	26 + 4	32	29
BBW (g)	A	2,362	1,664	1,118	425	1,694	1,440
	B	2,055	1,488	1,169	535	1,740	1,370
Delivery		NSD	CS	CS	NSD	CS	CS
Sex		M/F	M/F	M/M	F/M	F/F	b
Chorioamnionic status		DCDA	DCDA	b	DCDA	MCDA	DCDA
Chorioamnionitis		+	+	+	b	+	b
PROM		1 h	b	b	b	No	13 h

Abbreviations: BBW, birth body weight; CS, cesarean section; DCDA, dichorionic diamniotic twins; F, female; GA, gestation age; M, male; MCDA, monochorionic diamniotic twins; NSD, normal spontaneous delivery; PROM, premature rupture of membrane; +, mother had chorioamnionitis.
[a]Chen index case.
[b]Not mentioned.

Table 2 Summary of the clinical course and culture results of the twins with congenital candidiasis

		Chen[a]	Bender	ARAI	Krallis	Carmo	Pineda
Manifestation	A	Sepsis, skin rash	IUFD	Sepsis	Sepsis	Sepsis	None
	B	None	Skin rash	None	Sepsis	Skin rash	None
Day of presentation	A	Day 1	IUFD	Day 1	Day 1	Day 1	None
	B	None	Day 6	None	Day 1	Day 3	None
Day of therapy started	A	Day 2	N/A	Day 1	Day 1	No treatment	Day 1
	B	Day 2	Day 6	b	No treatment	Day 3	Day 1
Therapy	A	Amphotericin B 1 mg/kg/d 2 d	N/A	Fluconazole 6 mg/kg/day	Amphotericin B 2 days	No treatment	AmBisome 5 mg/kg/d 14 d
	B	Fluconazole 12 mg/kg/d 14 d	Oral nystatin and local clotrimazole	b	No treatment	Amphotericin B 14 days	AmBisome 5 mg/kg/d 21 d
Outcome	A	Died	IUFD	Alive	Died	Died	Alive
	B	Alive	Alive	Alive	Died	Alive	Alive
[c]Day of hospitalization	A	4 d	IUFD	About 2 months	3 d	1 day	24 d
	B	55 d	b	About 2 months	1 d	b	44 d
Culture species/site	A	*Candida albicans*/ blood, urine, sputum	*C. albicans*/ autopsy	*Candida glabrata*/ blood	*Candida parapsilosis*/ blood	*C. albicans*/ blood, autopsy	Not yield
	B	*C. albicans*/ urine	No growth	No growth	*C. albicans*/ blood	*C. albicans*/ skin and nose swab	*C. kefyr*/ blood
Culture of mother species/site		*C. albicans*/ placenta of twin A	*C. albicans*/ placenta of twin A	*C. glabrata*/ amniotic fluid	b	*C. albicans*/ placenta of twin A, vaginal swab	*C. kefyr*/ blood

Abbreviations: IUFD, intrauterine fetal death; N/A, not applicable.
[a]Chen index case.
[b]Not mentioned.
[c]length of days from birth to discharge/died.

In the six pairs of twins of this review, the most common manifestation of congenital candidiasis was sepsis with respiratory distress. Once there were symptoms and signs, the clinical course was so fulminant that in-time antifungal treatment was always impossible.[1,2,12–14] The time to initiate of antifungal treatment is crucial for the outcome. In our review, only two cases survived from congenital candidiasis. One case received treatment before clinical manifestation and the baby was well at discharge. The other received treatment immediately after manifestation of symptoms and signs, and the baby had neurologic sequelae.[3] The survival of these two cases gave credit to the early initiation of antifungal therapy based on the maternal history. In the four fatal cases, in two cases the antifungal therapy was given after positive culture informed and the other two had no therapy at all.[2,5] The grave outcome was probably due to delayed recognition of *Candida* sepsis.

The recognition of congenital cutaneous candidiasis may arouse the suspicion of *Candida* sepsis. It has been reported that "White dots on the placenta and red dots on the baby" are a hallmark of congenital *Candida* sepsis.[11] However, the skin manifestation is so diverse that early diagnosis is difficult. In many of these cases, the skin rash was not cultured and both the opportunity of making the diagnosis and important antifungal therapy were delayed. It is known that the lack of skin rash does not indicate that neither the fungus is invasive nor the infant is heavily colonized by the fungus at other sites.[2,15] In contrast, the maternal history of fungal infection is a solid clue for early suspicion of fungal sepsis in newborns. Invasive procedures such as amniocentesis, embryo reduction, maternal intrauterine device, and cervical cerclage are risk factors of congenital systemic candidiasis.[12,16,17] Manifestation at the placenta or umbilical cord is a hint of congenital candidiasis. In addition, maternal culture from vaginal, placenta, or amniotic fluid may also help us recognize the infection early.[3,6,15] These are all indications to start empiric antifungal therapy pending evaluation.

To decrease the mortality and morbidity of congenital candidiasis, cultures from baby, such as samples from blood, urine, skin, nasopharynx secretion, or bronchoalveolar lavage fluid are important. It has been demonstrated that antigen assay accelerates detection of candidal infection.[9,18,19] Furthermore, if a baby has cutaneous finding, skin culture and microscopic examination of fungi and bacteria from the skin rash are needed.[7] Last, if a prematurity has septic signs and symptoms but does not get improvement upon antibacterial agents, fungal infection should be considered and repeat cultures have to be sent and empirical antifungal agents should be started right away.[2]

For twin prematurity, this review revealed twin A was riskier than twin B. Theoretically, twin A is considered the first to be affected by ascending infection and constitutes a barrier for twin B, who usually gets *Candida* infection during delivery. The illness of twin B was thus proposed to be less severe. This phenomenon was also recognized in previously.[4] Despite the possibility that the severity of infection of twin B was less or none, owing to a prematurity, the risk of invasive candidiasis was still high and 14-day period of systemic antifungal therapy was needed.

In this review, *C. albicans* accounted for two-thirds of the nine positive fungal cases and *C. glabrata*, *C. kyfer*, and *C. parapsilosis* for the remaining three cases. As *C. albicans* is the most prevalent *Candida* species in congenital candidiasis, the empirical antifungal therapy for prematurity suspected of *Candida* sepsis is amphotericin B or liposomal amphotericin B for at least 14 days.[20] In term babies, systemic antifungal therapy is also suggested if there is a generalized skin involvement, sepsis, or respiratory signs, because the risk of invasive fungal infection is high and could not be ignored.[7,20]

Conclusion

Congenital systemic candidiasis should be suspected in newborns with unaccountable illness severity and poor response to antibiotics treatment especially in the presence of risk factors. If mothers have history of significant fungal infection before delivery, antifungal therapy to high-risk babies should be considered prior to placental pathology/culture or skin rashes/cutaneous involvement. For twin prematurity, if one is suspected to have invasive candidiasis, both of them should receive a full course of antifungal therapy through the intravenous route.

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