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Case Report

Congenital tuberculosis in an extremely preterm infant and prevention of nosocomial infection☆

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ABSTRACT

Congenital tuberculosis is a rare disease, especially in non-endemic countries. We present a preterm infant who developed congenital tuberculosis in a neonatal intensive care unit (NICU). The male patient, weighing 1140 g was born by cesarean section at 26 weeks gestation. The baby's respiratory condition suddenly deteriorated at 18 days old, and he was diagnosed with congenital tuberculosis after Gram stain revealed “ghost bacilli” in his tracheal aspirate. The mother, who was born in an endemic country, had fever with unknown cause during labor and was diagnosed with miliary tuberculosis after the infant was diagnosed. Both were successfully treated for tuberculosis with a four-drug regimen. The genotyping profiles of *Mycobacterium tuberculosis* were identical in both mother and baby based on variable number of tandem repeat (VNTR) analysis. The lineage was considered to be East-African Indian. To prevent nosocomial infection in the NICU, 23 potentially exposed infants received isoniazid for 2 months. Two infants showed a transient liver enzyme elevation that seemed to be due to isoniazid. For 10 months after the incident, there were no infants and medical staff who developed tuberculosis. Although the incidence of tuberculosis has steadily decreased in Japan, the percentage of foreign-born individuals has increased yearly, especially those of reproductive age. The evaluation of active tuberculosis should be considered in pregnant women with unexplained fever, history of tuberculosis, or emigration from high-burden areas.

1. Introduction

Tuberculosis is one of the deadliest infectious diseases worldwide, especially in Africa and Asia. Congenital tuberculosis is a rare disease caused by transmission from maternal circulation to fetal circulation or from aspiration and ingestion of amniotic fluid or maternal blood [1]. The incidence rate of congenital tuberculosis is not well delineated and depends on the epidemic situation in an area [1]. Clinical signs of congenital tuberculosis are neither distinctive nor specific [1,2]. Additionally, almost all mothers who deliver an infant with congenital tuberculosis are only diagnosed when their infant is diagnosed [2]. Although early diagnosis is difficult, nosocomial exposure could be a serious problem in the neonatal intensive care unit (NICU) or pediatric ward.

In this report, we describe a preterm infant who developed congenital tuberculosis during hospitalization and the management of nosocomial infection in the NICU.

2. Case report

A 34-year-old woman from Southeast Asia, HIV-negative, was transferred to our hospital because of clinical chorioamnionitis and

Abbreviations: EAI, East-African Indian; IGRA, interferon-gamma release assay; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; TST, tuberculin skin test; VNTR, variable number of tandem repeat.

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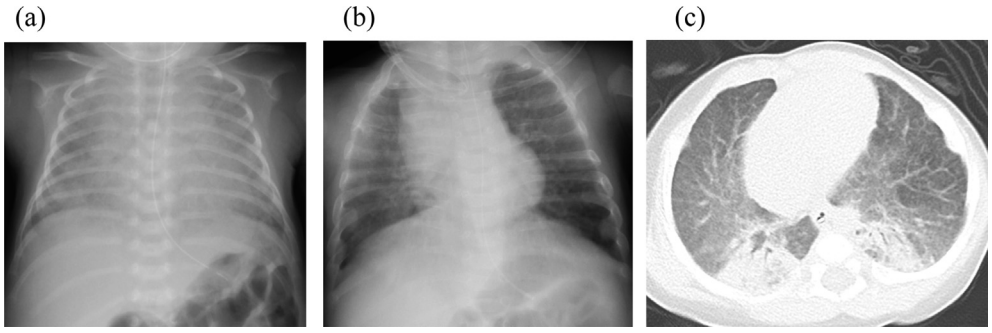

Fig. 1. a) Chest radiograph at diagnosis. An infiltrative shadow and heart enlargement were detected. b) c) Chest radiograph and CT image at discharge. The infiltrative shadow on chest radiograph showed improvement. Chronic aspiration was suspected due to consolidation of the bilateral posterior lung field on chest CT scan.

threatened preterm labor at 26 weeks gestation. Although she had received ritodrine as an intravenous tocolytic agent and cefmetazole for antibiotic therapy, she delivered a male infant by emergency cesarean section at 26 weeks gestation weighting 1140 g. Apgar scores were 2 (1 min) and 5 (5 min). The preterm infant was intubated immediately and admitted to the NICU. He did not have signs of respiratory distress syndrome and bacterial infection; therefore, he was extubated and treated by nasal continuous positive airway pressure after day 1 of age. Levels were normal at birth for C-reactive protein (CRP), natural immunoglobulin M, and white blood cells. The baby's course was good during his first 2 weeks as an infant with very low birth weight.

He was reintubated at 18 days of age because of respiratory deterioration and apnea. Chest radiograph revealed an infiltrative shadow and heart enlargement (Fig. 1a), and echocardiography showed a recurrence of patent ductus arteriosus (PDA). Because bacterial infection and symptomatic PDA were suspected, he was immediately treated by intravenous cefazolin, amikacin, and indomethacin. The PDA was closed the next day; however, his respiratory status did not improve, and CRP level was elevated to 6.1 mg/dL. At 21 days of age, Gram staining showed unstained bacillus footprints or “ghost bacilli” in his tracheal aspirate (Fig. 2a). Additional Ziehl–Neelsen staining confirmed acid-fast bacilli (Fig. 2b). PCR and tracheal aspirate cultures were also positive for *M. tuberculosis*. Cultures of blood were also positive; however, cultures of cerebrospinal fluid were negative. The strain was sensitive to isoniazid, rifampin, ethambutol, and pyrazinamide.

Upon review of the mother's medical history from the previous hospital, it was noted that the mother came to Japan 13 years ago and delivered a term newborn 3 years ago. After the labor, she underwent an interferon-gamma release assay (IGRA) test because of respiratory problems in the newborn. Although the IGRA was positive, the possibility of tuberculosis in this newborn was excluded by later examination. At that time, the mother was observed without any anti-tuberculosis drugs, because she refused treatment. In our present case, after the infant was diagnosed with tuberculosis, the mother's sputum smear and PCR results were both negative; however, the sputum culture subsequently grew *M. tuberculosis* that had the identical variable number of tandem repeat (VNTR) patterns as the infant (24 loci, Table 1). The PCR and culture of blood were both negative, and pathology examination of the placenta did not reveal dry necrosis. Computed tomography of the mother's lungs revealed miliary infiltrates.

The infant was moved into an isolated room equipped with negative air pressure and started on isoniazid (10 mg/kg), rifampin (15 mg/kg), ethambutol (15 mg/kg), and pyrazinamide (30 mg/kg). After rifampicin resistance mutations were not detected by cartridge-based nucleic acid amplification test (Xpert® MTB/Rif, Cepheid, Sunnyvale, CA, USA), ethambutol was discontinued to avoid adverse effects in the eyes. Treatment was successful, and the patient was extubated at 50 days of age. PCR and culture of gastric juice were negative at 58 days of age. Although isoniazid and rifampin were continued for another 4 months, the drugs were temporarily discontinued for 3 weeks because of liver enzyme and

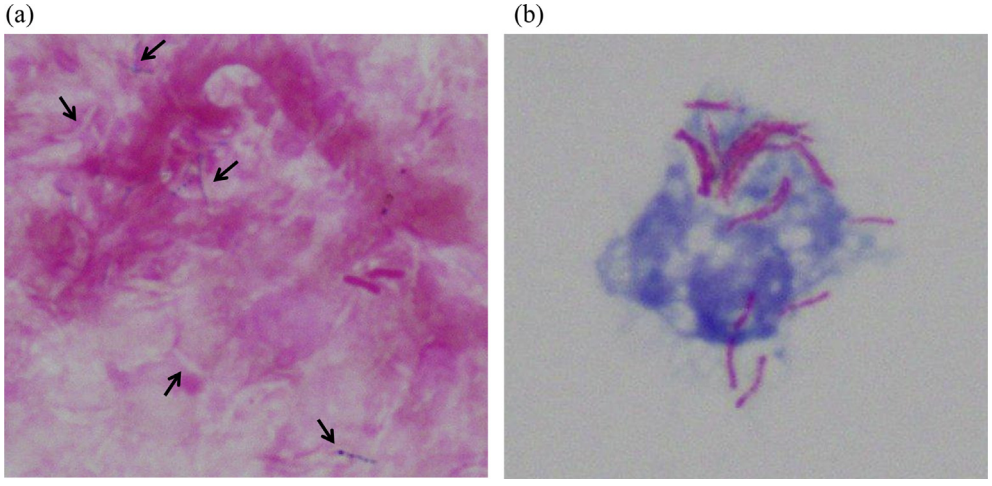

Fig. 2. Microscopic examination of tracheal aspirate. a) Gram-ghost bacilli are noted in the tracheal aspirate (arrow), Gram stain, x 1000. b) Ziehl-Neelsen stain, x 1000.

Table 1
The VNTR patterns of the mother and the infant. The patterns were completely identical. Related strains were detected by using of MIRU-VNTR plus [6].

Isolates	JATA (12)											JATA (15)			Hypervariable			Locus for international comparison[a]				
	0424	M10	1955	2074	2163b	2372	M26	Q15	M31	3336	Q26	4156	Q11a	EA	Q18	3232	3820	4120	M04	M16	M40	EC	t30	t39
mother	1	4	7	3	7	1	2	4	4	7	7	2	11	4	10	1	10	4	5	3	2	4	2	2
infant	1	4	7	3	7	1	2	4	4	7	7	2	11	4	10	1	10	4	5	3	2	4	2	2
related strain	1	4	10		9		2		4		7	1		4		1	10	4	5	3	2	4	2	2
	1	4	10		8		2		4		7	1		4		1	10	4	5	3	2	4	2	2

Abbreviations: JATA, Japan Anti-Tuberculosis Association; MIRU-VNTR, mycobacterial interspersed repetitive units-variable number of tandem repeat.
[a] The six loci composed the international Supply's 15MIRU-VNTR by combination with JATA12-VNTR.

bilirubin elevation. Eventually, the baby was transferred a local hospital at 129 days (44 weeks corrected gestational age), then discharged home with supplemental oxygen via nasal cannula. No hepatic lesions were detected by ultrasonography during hospitalization. The infiltrative shadow on chest radiograph showed improvement at discharge (Fig. 1b). Cranial MRI and chest CT at discharge revealed no complications of tuberculosis. Chronic aspiration was suspected due to consolidation of the bilateral posterior lung field on chest CT scan (Fig. 1c).

2.1. Prevention of nosocomial infection in the NICU

2.1.1. Exposed infants in the NICU

The infectious period was defined as 21 days from the patient's date of birth to the date of isolation. Exposed infants were defined as infants who were in the same room with the index case during the infectious period. There were 24 exposed infants during that period. Preventive therapy with isoniazid (10 mg/kg) was started in 23 exposed infants with supplementation of vitamin B6 (pyridoxine) to prevent peripheral neuropathy. The one remaining infant did not receive prophylaxis, because isoniazid was contraindicated because of severe liver dysfunction; thereafter, he died of original disease. After 2 months of prophylaxis, tuberculin skin test (TST) was negative in all cases, and preventive therapy was discontinued. Two infants showed a transient liver enzyme elevation that seemed to be due to isoniazid [3]. Afterward, one infant died of original cardiac disease. Finally, the remaining 22 infants did not develop tuberculosis during 10 months of follow-up.

2.1.2. Exposed medical staff

Of the 84 medical staff members who were identified as having potential exposure to the index case, 53 were defined as close contact that were in frequent or continuous contact in the NICU. IGRA was immediately administered to the group of close contacts, and it was repeated 2 months later for comparison. There were no medical staff members with positive IGRA results.

3. Discussion

The diagnosis of congenital tuberculosis is often delayed because clinical signs are not specific, and it is difficult to distinguish from other infections [1,2]. Furthermore, most infected mothers are not diagnosed with tuberculosis until their children are diagnosed [2]. In the present report, it was fortunate that Gram-ghost bacillus were seen in the tracheal aspirated sample (Fig. 2). Although *M. tuberculosis* was considered a Gram-positive bacillus, crystal violet led to no appreciable staining of bacilli because of the thick cell wall [4]. Finding “ghost bacillus” on Gram stain sometimes provides an early and helpful diagnostic clue [4]. Regarding treatment of tuberculosis in children, published regimens vary widely and depend on various factors, including infection site, bacillary load and drug susceptibility [5,6]. In the present case, the infant had been treated with a four-drug regimen and ethambutol was discontinued to avoid optic neuritis after rifampicin resistance mutations were not detected. However, recent recommendations say that ethambutol is safe in children of all ages [5,6]. There are also opinions that the duration of two drug regimen (isoniazid and rifampicin) following initial treatment should be longer for severe case [6].

In the present case, the mother was diagnosed with latent tuberculosis infection 3 years earlier. If a pregnant woman has a positive IGRA result, the provider should evaluate whether the tuberculosis is active by using chest X-ray or bacteriological examination [7]. Since active tuberculosis in pregnant women is strongly associated with both maternal and neonatal mortality,

such women should start treatment during pregnancy, and the newborn should also be evaluated and treated [7].

In the present study, the VNTR pattern was similar to East-African Indian (EAI) lineages (Table 1), and spoligo patterns of the lineages were EAI-Manilla [8]. The result indicated that the mother was infected in her country of origin. According to a recent review, most infants who develop congenital tuberculosis are born to foreign-born mothers in low-incidence areas [1]. In Japan, the incidence rates of tuberculosis decreased from 40 cases per 100,000 population in 1990 to 13.9 in 2016 [9]. The rate is much lower than neighboring countries such as the Philippines, China, or Vietnam and approaching the incidence rates of Europe and the United States. However, there are an increasing number of young patients in Japan from abroad who could be pregnant. In 2017, 57.7% of patients in their 20s with newly developed tuberculosis were born in foreign countries [9]. There may be increased risk of congenital tuberculosis from foreign-born mothers in Japan. Tuberculosis screening of high-risk pregnant women may become necessary, as in the United States and Europe [10,11]. Further research is needed to determine whether the screening such as an IGRA test for pregnant women from endemic countries is effective in decreasing the incidence rates of tuberculosis in Japan.

Several reports have described transmission of tuberculosis from infected neonates to other hospitalized infants or health care workers [12–14]. However, there are few established guidelines for the management of neonates after exposure. The present case was considered a high risk of transmission due to frequent suctioning and mechanical ventilation. Consequently, all exposed infants received preventive therapy with isoniazid as previously reported [12–15]. TST was performed on all exposed infants in the NICU after preventive therapy. However, examination may not be reliable, because of the immature immune system of infants <6 months of age [16]. Recently, high sensitivity and specificity of IGRA to detect tuberculosis in children was reported [17]; however, IGRA was not performed in the current case because of limited evidence for neonates and high sample volume requirements. Further research is required to determine a useful evaluation method for horizontal transmission in exposed infants.

In summary, we diagnosed congenital tuberculosis by Gram stain of tracheal aspirate in a preterm infant. Once an infant develops congenital tuberculosis in the NICU, management to prevent nosocomial infection is crucial. We strongly suggest that pregnant women with risk factors for tuberculosis such as history of tuberculosis, unexplained fever, or mother's country of origin being a high-burden country should be managed carefully.

Declarations of interest

None.

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