Prematurity due to maternal brucella infection and review of the literature

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Brucellosis is a zoonosis caused by ingestion of unpasteurized milk or other dairy products from infected animals or through close contact with their secretions. Human-to-human transmission, which is rare, has been reported in association with blood transfusion, bone marrow transplantation, transplacental or perinatal exposure, and breastfeeding. In the neonatal period, congenital brucellosis, which is an extremely rare condition, can lead to serious clinical consequences with a high morbidity and mortality rate. The case presented here is a premature baby born at 25 weeks' gestation to a mother suffering from severe oligohydramnios, premature rupture of membranes and untreated acute brucellosis. The baby had severe respiratory distress and radiological findings compatible with pulmonary infection. The blood cultures of the baby and the mother were positive for Brucella melitensis, supporting the diagnosis of brucellosis with presumed transplacental transmission.

Key words: brucellosis, transplacental, congenital, oligohydramnios.

Brucellosis is a zoonotic disease with a worldwide distribution. It is transmitted from animals to humans through unpasteurized milk and other improperly cooked dairy products; meat and meat products from infected animals; direct contact with the contaminated area; and the inhalation of contaminated animal feces, which dry off and become dust-like[1]. Human-to-human transmission is rare. Only 20 neonatal cases with congenital brucellosis caused by transplacental exposure have been reported in the literature thus far[2]. The majority of these cases exhibited non-specific symptoms and findings. Here, we report a case of congenital brucellosis with presumed transplacental transmission in a premature newborn suffering from severe pulmonary involvement in the course of the disease.

Case Report

The male neonate was born to a 27-year-old woman at 25 weeks' gestation by spontaneous vaginal delivery as the second liveborn child of the mother, weighing 810 g and with an Apgar score of 5/8. He was transferred to the neonatal intensive care unit (NICU) after initiating nasal continuous positive airway pressure (CPAP) in the delivery room. Prenatal history provided that the mother was not followed by a clinician, and she had premature rupture of membranes (PROM) (>24 hours before birth), high sedimentation rate (95 mm/h), increased C-reactive protein (CRP) level (13 mg/dl), and oligohydramnios (fetus and placenta were both normal), which was defined by ultrasonography performed at 23 weeks' gestation (the first ultrasonography performed during her pregnancy). The physical examination revealed that the patient had poor general status; his body temperature (36.6°C) and heart rate (145 beats/min) were within normal limits, but oxygen saturation was low, with a SaO2 of 81%. The chest radiograph showed diffuse reticulonodular interstitial opacities (Fig. 1). There was no increase in oxygen saturation despite mechanical ventilation with 95% inspired oxygen. Then, one dose of surfactant (100 mg/kg beractant, Survanta®) was administered via an endotracheal cannula.

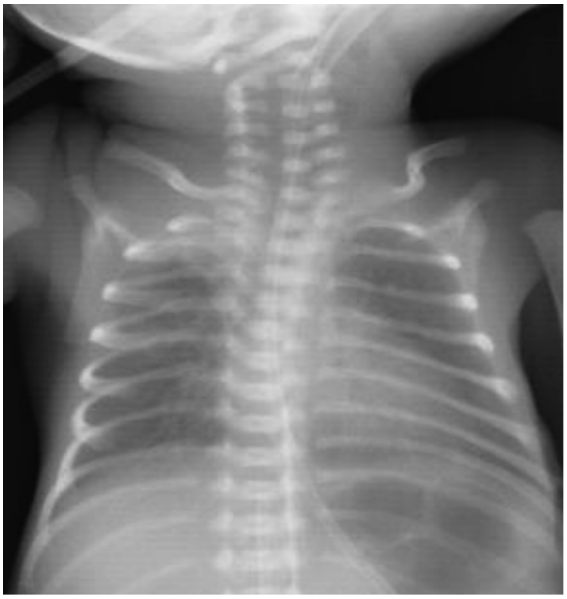

Fig. 1. Anteroposterior radiography of the chest. The chest X-ray of the patient showing diffuse reticulonodular interstitial opacities.

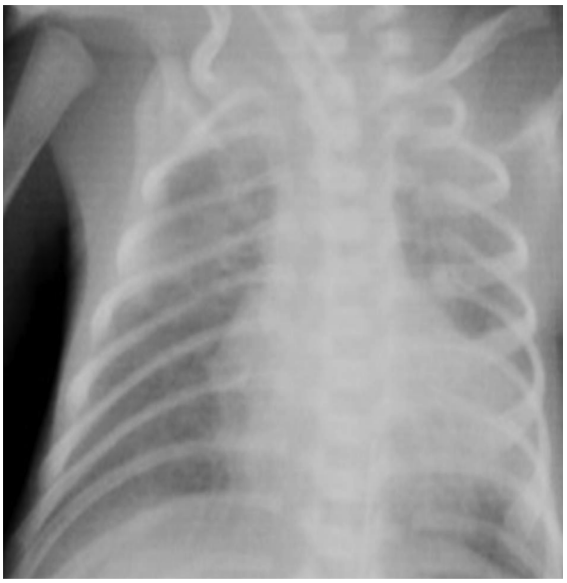

Fig. 2. Anteroposterior radiography of the chest. Follow-up chest X-ray of the patient showing lobar consolidation.

The patient, whose umbilical artery and vein were catheterized, was commenced on ampicillin, gentamicin, and fluconazole prophylaxis. The echocardiography showed the presence of a patent ductus arteriosus and a patent foramen ovale. No pathology was detected in the cranial and abdominal ultrasound examinations. The findings of the laboratory investigation were as follows: hemoglobin: 14.2 g/dl, white blood cell count: 63700/mm^3, platelet count: 212000/ mm^3, and CRP: 14 mg/dl. Just after his admission to the NICU, a blood culture was performed using the automated BACTEC 9120 system (Becton Dickinson, Maryland, USA). After five days, *Brucella melitensis* (*B. melitensis*) grew on the blood culture. Therefore, cefotaxime and rifampicin were added to the treatment according to the results of the antibiogram. Serologic tests for brucellosis were taken at the beginning of the treatment, and revealed standard tube agglutination (STA) titer: 1/1280 (+), specific immunoglobulin (Ig) M: 63.08 NTU (+), and specific IgG: 29.51 NTU (+). The history of the patient revealed that his family was engaged in farming and sheep trade and had consumed cheese from raw milk; the father had received treatment for brucellosis two years ago; and the mother was not followed by an obstetrician and had experienced excessive sweating and arthralgia during her pregnancy, but was not examined for brucellosis. The results of the serum sample taken from the mother for brucellosis were as follows: STA titer: 1/320 (+), specific IgM: 77.56 NTU (+), and specific IgG: 36.39 NTU (+). The mother's blood culture was also positive for *B. melitensis*. The patient was diagnosed with congenital brucellosis and commenced on rifampicin. The mother was directed to the Department of Infectious Diseases.

On the second day of treatment, the baby had an abnormal liver function test, and rifampicin was changed to trimethoprim and sulfamethoxazole. No clinical or radiological improvement could be achieved despite appropriate treatment. Furthermore, repeated chest X-ray showed lobar consolidation (Fig. 2). *B. melitensis* grew again in the follow-up blood culture. On the 10th day of admission, pneumothorax developed and a chest tube was inserted. Subsequently, the disease was complicated with severe metabolic and respiratory acidosis. The patient's general condition gradually deteriorated and he died due to multiple organ failure on the 14th day of admission. The family did not consent to an autopsy.

Discussion

Brucella is a genus of gram-negative, non-motile, non-sporing, and non-encapsulated

Table I. Characteristics of Our Case and Other Cases with Congenital Brucellosis Reported in PubMed

First author and year	Country	Number of affected cases	Gestational age (week)	Birth weight (g)	Age at admission (day)	Presenting symptom & sign	Brucella serotype	Outcome
Lubani, 1988[13]	Kuwait	3	>38	-		Late neonatal hyperbilirubinemia Sepsis-like picture Respiratory distress	*B. melitensis*	Survived
Singer, 1991[14]	Israel	1	39	3100	23	Splenomegaly	*B. melitensis*	Survived
Al-Eissa, 1992[15]	Saudi Arabia	4	NA	NA	NA	NA	NA	NA
Carbajo-Ferreira, 1995[16]	Spain	1	38	2510	30	Asymptomatic, maternal infection during the 5th month of gestation	*B. melitensis*	Survived
Chheda, 1997[17]	USA	2	24	650	1	Chorioamnionitis, respiratory distress, intraabdominal hematoma Septic emboli, neutropenia thrombocytopenia	*B. melitensis*	Survived
Shamo'on et al. 1999[18]	Jordan	1	35	2550	1	Premature rupture of membranes, Hypoglycemia, indirect hyperbilirubinemia, leukocytosis, CRP ↑	Brucella spp	Survived
Giannacopoulos, 2002[19]	Greece	1	39	3100	27	Fever, feeding intolerance, Vomiting, bloody feces	*B. abortus*	Survived
Mosayebi et al. 2005[20]	Iran	1	26	NA	1	Sepsis-like picture, hyperbilirubinemia, hypocalcemia, thrombocytopenia, pneumothorax	*B. melitensis*	Exitus
Poulou, 2006[21]	Greece	1	37	3200	5	Feeding intolerance, respiratory distress, fever, leukocytosis, CRP ↑	*B. melitensis/*	NA
Koklu, 2006[22]	Turkey	1	32	1100	5	Respiratory distress, hepatosplenomegaly, direct bilirubinemia, liver dysfunction	*B. melitensis*	Survived
Sarafidis et al. 2007[23]	Greece	1	37	3260	1	Severe respiratory distress, hepatosplenomegaly, rash	*B. melitensis*	Survived
Mesner, 2007[24]	Israel	1	24	NA		Progressive respiratory distress, interstitial emphysema, pulmonary hypertension, shock, patent ductus arteriosus	Brucella spp.	Exitus
Glocwicz, 2010[2]	USA	1	24	480	1	Premature rupture of membranes, early neonatal sepsis	*B. melitensis*	Survived
Dogan, 2010[25]	Turkey	1	31	1480	1	Premature rupture of membranes, severe respiratory distress, HSM	Brucella spp	Survived
Our case	Turkey	1	25	810	1	Oligohydramnios, premature rupture of membranes, prematurity, respiratory distress	*B. melitensis*	Exitus

HSM: Hepatosplenomegaly. NA: Not available.

coccobacilli. The majority of the cases that have been reported across the world are related to *B. melitensis*, which is the most invasive and pathological of all species of brucella. Once brucella enters the body through mucosal surfaces, they are phagocytized by polymorphonuclear leukocytes, and carried by lymphatic vessels to localized lymph nodes. They then spread throughout the body via the bloodstream[3]. Human-to-human transmission, which is very rare, has been reported in association with sexual intercourse, blood transfusion, and organ transplantation[4-6]. The number of cases with neonatal brucellosis that have been reported in the literature is extremely limited, and there is not much information as to the modes of transmission of this disease. Akçakuş et al.[7] reported two neonatal cases with brucellosis caused by *B. melitensis* following exchange transfusion. Similarly, Al-Kharfy et al.[5] reported that brucella was isolated in their patient after blood transfusion.

It is known that brucellosis can also be transmitted to neonates through breastmilk[8]. In our patient, the blood culture showing brucella was taken just after delivery. He was not breastfed during the first days after delivery, and he did not receive any kind of blood transfusion. The serological markers and the blood cultures of both the patient and the mother suggested that the mode of transmission was transplacental, although the placental pathology was unknown.

Little is known about the effects of brucellosis in pregnant women on the pregnancy or about its complications. It is known, however, that this condition leads to abortus, PROM, and preterm birth. It is believed that the underlying reason is erythritol, which is found in the placenta of animals and which is a growth stimulant for brucella[9]. As the human placenta does not contain erythritol, it has been claimed that the risk of miscarriage due to brucellosis is not high, but there are also publications in which the opposing view has been expressed[10]. It has been reported that pregnant women with untreated brucellosis are at risk for preterm birth, PROM, chorioamnionitis, postpartum endometritis, and intrauterine growth restriction, and it has been asserted that these complications can be prevented with the treatment of brucellosis[11]. The mother of our case was not examined for brucellosis during her pregnancy as she did not exhibit any of the specific symptoms associated with brucellosis and as no relevant findings were present. The mother was examined in the postpartum period after our case was diagnosed with brucellosis, and she was diagnosed with brucellosis serologically. In vitro studies have shown that brucella increases the frequency and intensity of uterine contractions by means of an oxytocin-like endotoxin. This endotoxin also produces a decrease in placental glycogen, leads to vascular changes that involve an increase in fragility and permeability, and decreases platelet numbers. All these changes may be considered to induce uteroplacental insufficiency[12].

A total of 20 neonates suffering from congenital brucellosis from nine countries have been reported to date, since the first case was reported in 1988 (Table I)[2,13-25]. Congenital brucellosis does not produce any specific symptoms, and it is not detectable by any specific findings. Furthermore, it is very difficult to distinguish brucellosis clinically from other bacterial infections. The correlation between congenital brucellosis and pulmonary involvement is not very clear. Despite the fact that the majority of the cases reported in the literature suffered from respiratory distress, this condition has, as a rule, been considered to be related to sepsis, preterm birth and meconium aspiration syndrome[20,21,24,25]. Our patient presented with severe respiratory distress due to pulmonary infiltration. It makes one think that brucellosis might be an underlying reason for pulmonary involvement. Pulmonary brucellosis is very rare in adults. It has been reported that it can cause bronchopneumonia, pulmonary abscess, empyema, pleural effusions, solitary pulmonary nodules, and hilar and/or paratracheal lymphoadenopathy[26]. Even though pulmonary brucellosis is mostly transmitted by inhalation, it can also occur by hematogenous spread[27]. Hence, there is the possibility that the pulmonary involvement developed in our case may have been caused by intrauterine aspiration of the amniotic fluid infected with brucella. As far as we know, only two cases of brucellosis with pulmonary involvement have been reported. Köklü et al.[22] reported a newborn presenting with respiratory distress on postnatal day 5. The patient was diagnosed to be interstitial pneumonia caused by *B.*

melitensis. Antibiotic combination including trimethoprim and sulfamethoxazole, rifampicin and gentamicin was commenced. He began to show considerable clinical and radiological improvement on the fifth day of the therapy. Likewise, Sarafidis et al.[23] reported another case in which a term neonate, diagnosed with congenital brucellosis based on radiological findings such as severe respiratory distress, lobar consolidation, and diffuse interstitial infiltration, showed rapid clinical and radiological improvement after being treated with trimethoprim and sulfamethoxazole, rifampicin and gentamicin. We believe that our case did not respond to supportive and antimicrobial therapy because his pulmonary and systemic involvement was severe due to the fact that he was born too prematurely.

In conclusion, congenital brucellosis is a rare condition with fatal consequences. This condition can cause severe pulmonary involvement. It is important that necessary preventive measures be taken in order to protect pregnant women living in high-risk areas where brucellosis is endemic. Oligohydramnios accompanying sweating and arthralgia may be symptoms of brucellosis. These women should be screened carefully, and if deemed necessary, a treatment should be commenced immediately.

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