Early identification and treatment of perinatal listeriosis: A ret-rospective case analysis

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Abstract: Neonatal listeriosis is a rare but extremely fatal perinatal disease. Its prevalence is underestimated due to misdiagnosis, undiagnosed stillbirths, and insufficient single-case reports, resulting in inadequate attention. Herein, we report a case of a mother, whose twice *Listeria* tests were negative by blood culture, subsequently giving birth to a newborn suffering from listeriosis. The infant presented complications such as premature birth, sepsis, necrotizing enterocolitis, and septic shock. Despite aggressive empirical rescue and treatment, the infant's death could not be averted. The case warns us of the severe threat *Listeria* poses to newborn health. In this case where a pregnant woman showed the symptom of *Listeria* infection, but twice blood cultures fail to isolate the pathogen. Our aim is to enhance the awareness that perinatal physicians should heighten their vigilance towards rare pathogens that can cross the placental barrier. Given the high proportion of false negatives in blood cultures, there is an urgent need to establish a more sensitive and comprehensive detection system for these types of pathogens.

Keywords: *Listeria* monocytogenes; congenital infection; early diagnosis.

1. Introduction

Listeriosis is an acute infectious disease caused by the bacterium*Listeria* monocytogenes. Compared with other populations, the incidence of listeriosis in pregnant women is elevated. *Listeria*infection can lead to

serious consequences in pregnant women such as miscarriage, stillbirth, premature delivery, and congenital perinatal infections [1]. Between 2011 and 2017 in China, 562 cases of listeriosis were reported, the probability death among pregnant women with listeriosis is as high as 32.68% [2]. However, limited data are available on previous cases of congenital *listeria* infection [3, 4]. The available literature on congenital listeriosis also rarely focuses on treatment of patients for whom early diagnosis is difficult or impossible to achieve. The objective of this manuscript is to summarize disease progression, diagnosis, and treatment strategies in premature infants with *L. monocytogenes* infection. We focus on the reasons for treatment delays to provide a reference for clinicians.

2. Case Presentation

The mother

A 32-year-old pregnant woman was admitted to the emergency department because of irregular abdominal pain and fever at 33 weeks and 3 days gestation. Her body temperature was 38.2 °C on admission. Fetal heart rate monitoring showed a fetal heart rate of 110 to 180 beats/minute, reflecting intrauterine distress. The baby was delivered by lower uterine cesarean section under general anesthesia. The amniotic fluid was turbid (II°) but no abnormalities were observed in the umbilical cord or placenta.

When the mother was admitted to the hospital, her white blood cell count was 24.65×10^9/L with a neutrophil percentage of 86.4%. The patient was administered cefoperazone and tazobactam as antimicrobial therapy. Her detailed laboratory data are shown in Table 1. Bacteria were cultured from blood, sputum, and vaginal secretions. Duplicate bacterial cultures of the mother's blood during admission and hospitalization revealed no pathogenic bacterial organisms.

The infant

The infant was born with cyanotic skin; she was not crying and showed hypotonia, poor responsiveness, a heart rate of 80 beats/minute, and a birth weight of 1600 g. Apgar scores of 3, 7, and 8 at 1, 5, and 10 min, respectively, were recorded. Resuscitation treatments for neonatal asphyxia were administered including respiratory tract cleaning, physical stimulation, and endotracheal intubation. Blood was collected for bacterial culture. A chest radiograph showed an excessive decrease in pulmonary dialysis (Figure 1). Arterial blood gas analysis showed a pH of 7.10. Her blood count showed a white blood cell count of 11.13×10^9/L. (Table 1). Because the infant could not establish regular spontaneous breathing, she was transferred to the neonatal intensive care unit (NICU) after tracheal intubation for further treatment. In the NICU, an invasive ventilator was used to assist breathing. Blood gas analysis was performed every 4 hours. Flomoxef was administered as antimicrobial therapy, the intravenous infusion was used to correct hypoglycemia, and symptomatic and supportive treatments were used to protect the heart and brain.

Twenty-four hours after birth, the infant gradually developed body edema, pale skin with patterns, weak bowel sounds, dark green stools, and a positive fecal occult blood test. The infant's condition improved and the results of the blood gas analysis became normal (Table 1). Continued symptomatic supportive therapy along with routine stool tests and abdominal ultrasound.

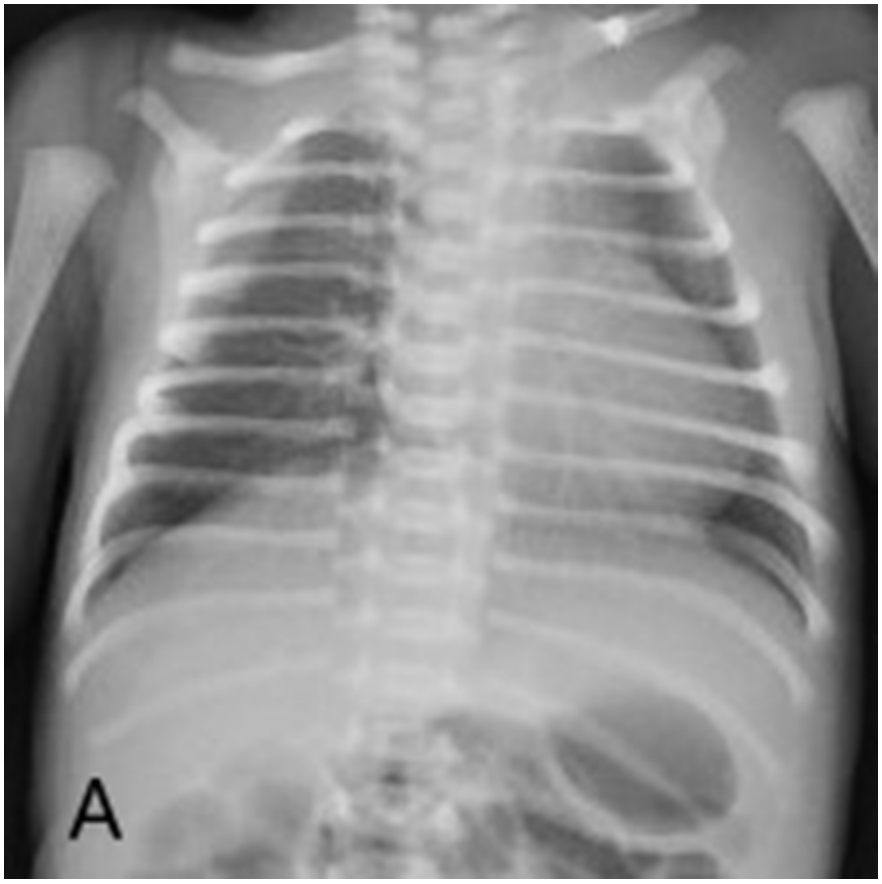

Figure 1. **A** Chest radiograph taken on birth showing reduced lung permeability and RDS (respiratory distress syndrome).**B** Chest radiograph taken on 24 hours after birth showed the ventilation status of the lungs was good with using a PS^{+} invasive ventilator. **C** Chest radiograph taken on 48 hours after birth showed no obvious abnormality. **D**Chest radiograph was taken on 72 hours after birth showing the infant's chest penetration is reduced, pulmonary infection, RDS secondary to an infection, and pulmonary hemorrhage are suspected.

Table 1 Laboratory examination of the mother and the infant

Laboratory examination of the mother

Variable	**On admission**	**Two days after admission**	**Six days after admission**	**On discharge**
White blood cell count	24.65	18.89	8.37	8.50
Neutrophil percentage	86.4	90.4	67.2	64.3
CRP	156	192	165	¡0.8
Temperature	38.23	38-40	37-38	36-37
Laboratory examination of the infant	Laboratory examination of the infant	Laboratory examination of the infant	Laboratory examination of the infant	Laboratory examination of the infant
Variable	**0 hours after birth**	**24 hours after birth**	**60 hours after birth**	**72 hours after birth**

Parameters of blood routine examination	Parameters of blood routine examination	Parameters of blood routine examination	Parameters of blood routine examination	Parameters of blood routine examination
White blood cell count	11.13	7.06	-	-
Neutrophil percentage	38.1	70.64	-	-
Hb	156	112	-	-
CRP	38.23	-	-	-
AST	72	-	-	-
CK-MB	312	-	-	-
APTT*	65.4	-	-	-
Blood gas analysis parameters	Blood gas analysis parameters	Blood gas analysis parameters	Blood gas analysis parameters	Blood gas analysis parameters
PH	7.10	7.36	6.84	<6.8
Glu	0.9	3.4	24.4	-
Lac	>15	2.7	>15	-
BE	-19.1	1.5	-26.2	-
Blood culture identification	NA	NA	Suspected *Listeria* monocytogenes	*Listeria* monocytogenes
Stool analysis	-	Red blood cell 0-2/HP, white blood cell 6-12/HP	-	-
Anteroposterior chest radiograph	Decreased lung permeability	The lungs are well ventilated	-	RDS and hemorrhage are suspected
Abdominal ultrasound	-	liquid dark area range 2.0 cm×1.0cm	liquid dark area range 2.1 cm×1.4cm	-

Note: White blood cell count (per dm^3); Neutrophil percentage N%); CRP, C-reactive protein (mg/ liter); Temperature (); White blood cell count (per dm^3); Hb (g/liter); AST, Aspartate aminotransferase, (U/liter); CK-MB, Creatine kinase isoenzyme, (U/liter) ;*APTT, activated partial thromboplastin time(sec); Glu (mmol/liter); Lac (mmol/liter); BE (mmol/liter); bowel sounds(beats/min).

Forty-eight hours after birth, the infant's skin was pale yellow and systemic edema was unchanged. Bowel sounds were weak. Mucus stools and a liquid dark area on abdominal ultrasound were observed (Table 1). Neonatal necrotizing enterocolitis was suspected, and we presume that it was caused by circulatory disturbances and secondary organ damage due to a severe congenital infection. To avoid serious multi-organ infection, circulatory failure, shock, and even death, a decision was made to administer imipenem/cilastatin as antimicrobial therapy.

Bacterial culture was still underway preliminary findings were suggestive of *Listeria* infection. Therefore, 62 hours after birth, the infant was given imipenem/cilastatin combined with intravenous amoxicillin sulbactam as antimicrobial therapy. Additional treatments administered included dopamine to improve circulation, an erythrocyte suspension to correct anemia, and parenteral nutrition. However, 70 hours after birth, the infant's condition deteriorated and she gradually developed shortness of breath accompanied by a triple concave sign. The aspiration sounds of both lungs were symmetrical and scattered wet rales could be heard. Thirty minutes later, her anterior fontanel became slightly dilated and she developed meningitis symptoms including gazing, twitching of limbs, and clenching both fists. The infant was given intramuscular injections of phenobarbital for sedation and furosemide to reduce intracranial pressure. Her heart rate dropped to

60 beats/minute. Blood gas analysis showed a pH < 6.8. The infant died 72 hours after admission to the hospital. On the second day after her death, the results of blood culture and drug sensitivity tests confirmed L. monocytogenes infection.

In the mother, antimicrobial therapy was switched to piperacillin and sulbactam. After 40 hours, the mother's temperature and blood cell counts returned to normal (Table 1).

3. Discussion

In this case report, a premature infant was infected in utero with L. monocytogenes from her mother. The mother experienced headaches at 6 months gestation, then developed symptoms of fever and abdominal pain at 33 weeks. These symptoms were consistent with maternal antenatal symptoms presented in a report of 12 cases of perinatal listeriosis: mothers had clear neutropenia during their illness, which was also present in the case reported here [5]. Therefore, cases of antepartum fever with abdominal pain should be treated cautiously.

The infant in this case had early onset listeriosis; she was born prematurely at 33 weeks and died 72 hours after birth. The clinical features were typical of early-onset neonatal listeriosis, including preterm delivery and sepsis at birth [6]. The causes of death included sepsis, secondary meningitis, necrotizing enterocolitis, and septic shock.

We administered emergency treatment for perinatal infection, but the L. monocytogenes was not detected early enough. We made the judgment that neonatal infection was likely on the basis of the clinical symptoms of neonatal respiratory distress, lethargy, and poor responsiveness. Because most of the pathogenic bacteria responsible for early neonatal sepsis are Gram-positive cocci [7], we administered flomoxef because of its wide antibacterial spectrum and safety [8]. After L. monocytogenes was suspected, antimicrobial therapy was switched to amoxicillin and sulbactam combined with imipenem/cilastatin. Although the infant died 10 hours later, the mother improved significantly within 1 to 2 days of treatment with piperacillin and sulbactam following the identification of L. monocytogenes in the infant's blood culture. Generally, early diagnosis of mother-to-child *Listeria* infection is challenging. In this case, the mother's blood cultures were twice as negative. In a retrospective case study, only 36% of 11 pregnant women with perinatal listeriosis had positive blood cultures [9]; thus, false negatives are very common. We speculate that the high false negative rate may be related to the collection conditions of blood cultures. In principle, blood samples should be collected at the patient's body temperature above 38.5 °C without using antibiotics and submitted for testing within 30 min. However, this condition is not easy to achieve in most situations.

Several factors may explain the different results of treatment of the infant and mother with antibiotics effective against *Listeria* . Most importantly, neonatal immune function is poor, the disease progresses faster, the complications are critical, and the mortality rate is high. Moreover, in clinical diagnosis, a negative blood culture should not be interpreted as non-septicemia. When neonatal infection progresses rapidly and accurate results of blood cultures are unavailable, empirical diagnosis is more important. Ampicillin can simultaneously cover L. monocytogenes, beta-hemolytic streptococci, and*E. coli* , the latter two bacteria are the most common and harmful pathogens associated with neonatal early-onset sepsis [10].

In the treatment of this case, a multi-pronged approach was applied in addition to antimicrobial therapy that included the use of an incubator, sterilization, ventilator-assisted breathing, heart-brain protection, and so on. These interventions are vital to ensure the operation of the organs and maintain circulation. Before the onset of complications (e.g., 24 hours after birth, Table 1), the infant's condition improved slightly.

There were some limitations to this retrospective case report that require clarification. First, *Listeria* shows placental tropism and placental specimen culture is the most sensitive method for diagnosing neonatal listeriosis [11]. However, the placenta was not cultured in this case and the results of the mother's blood culture were twice negative. In this case, the infant was born with symptoms of sepsis, and the mother's improvement following the administration of antibiotics effective against *Listeria* along with negative blood cultures was sufficient to demonstrate that the infection was congenital. The failure to identify listeriosis earlier is a major

factor preventing the rescue of newborns. Second, without detailed epidemiological information, including the mother's medical history, it was not possible to determine the source of *Listeria* infection.

The diagnosis of neonatal *Listeria* infection has three characteristics. No specific clinical symptoms. The diagnosis of biological samples has different degrees of false negatives [12]. In addition, newborns have experienced circulatory failure, shock, and death before *Listeria* can be isolated and identified.

Considering our experience with this case, we conclude that although bacterial culture is vital for the diagnosis of listeriosis [13], clinicians should not wait for final confirmation of the pathogen when the infant is in critical condition. Instead, clinicians should assess the medical history of the mother and the infant at the same time and monitor changes in their conditions. Bacterial culture and identification results should be evaluated in combination with clinical experience. Clinicians should remain alert to the possibility of specific bacterial infections and be ready to change antimicrobial therapy in a timely fashion.

4. Conclusions

This pathological report demonstrates that monocytosis caused by*Listeria* monocytogenes poses a significant threat to the lives of newborns. The bacterium can cross the placental barrier, leading to neonatal listeriosis when transmitted from infected mothers. This disease progresses rapidly, has a poor prognosis, and carries an extremely high mortality rate. Furthermore, the empirical use of cephalosporins and carbapenems has shown resistance. These findings highlight the importance of early identification of the pathogen in the treatment of neonatal listeriosis. However, blood culture identification is associated with long turnaround times and a high false-negative rate, necessitating the establishment of an early and sensitive comprehensive testing system for this bacterium. It is particularly crucial to strengthen screening for high-risk pregnant women during the perinatal period. More importantly, healthcare professionals should increase their awareness and attention to rare pathogens that can traverse the placental barrier.

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