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Case Report

Should arboviruses be the only diagnosis hypothesis in pregnant women in endemic areas presenting with a rash?

Maria Dolores Salgado Quintans*[1]*, *Angela Cristina Gouvêa Carvalho*[2]*, *Vanessa de Sousa Neves Guimarães*[1], *Marcelo Rodrigues Coppo*[1], *Alexandre Ribeiro Fernandes*[1], *Vania Glória Silami Lopes*[2], *Arnaldo Costa Bueno*[1] and *Claudete Aparecida Araújo Cardoso*[1]

[1]. Departamento Materno Infantil, Faculdade de Medicina, Universidade Federal Fluminense, Niterói, RJ, Brasil.
[2]. Departamento de Patologia, Faculdade de Medicina, Universidade Federal Fluminense, Niterói, RJ, Brasil.

Abstract

Listeria is an unusual pathogen that causes neonatal infection with high morbidity and mortality. We present the case of a premature newborn whose mother had a rash during pregnancy; the newborn had severe early sepsis because of *Listeria monocytogenes* and histopathologically suggestive findings of the placenta. Obstetricians and neonatologists should suspect listeriosis in cases with compatible epidemiological history, clinical features, and examination findings of the placenta.

Keywords: Rash. Pregnancy. Neonatal listeriosis.

INTRODUCTION

Listeriosis is a relatively rare and potentially fatal disease transmitted by food contaminated with *Listeria monocytogenes* and less frequently with *L. ivanovii*. These bacteria are motile, gram-positive bacilli that are non-spore forming, facultative anaerobes[1].

Infection is more prevalent in pregnant women than in those at the extremes of age (neonates and the elderly) and immunocompromised patients. The estimated neonatal occurrence is 8.6 per 100,000 live births in the USA, and the disease is one of the commonest causes of neonatal meningitis. Of the total cases, 16%-27% occur in pregnant women who are at a high risk of developing the disease. However, because the clinical symptoms are non-specific, such as rashes, the diagnosis is often clinically challenging[1].

Gastrointestinal tract colonization is common and may be present in 44% of pregnant women. In one report, one-third of pregnant women with severe listeriosis had positive blood cultures, half of whom were hospitalized for treatment[1]. This condition is rare because most pregnant women present mild aspects of the disease similar to influenza with fever, headache, and myalgia and less frequently with abdominal cramps and diarrhea. Lumbar pain may resemble a urinary tract infection, which is common in these patients. Up to 30% of pregnant women are asymptomatic[2].

Listeriosis occurs more frequently in the third trimester of pregnancy, which is associated with a lower cell-mediated immune response from 26 weeks, but there are records of its occurrence in the early pregnancy stages. Approximately 22% of perinatal listeriosis cases result in fetal death and 1.6% result in premature birth or miscarriage[2]. Direct invasion by extracellular bacteria is less likely to occur than is cell-to-cell spread as the main mechanism for the traffic of infected maternal phagocytes to the placenta. The predominance of one mechanism depends on the infectious dose and degree of infection of the primary target organs (liver and spleen) after intestinal bacterial translocation[3].

Preventive measures for foodborne diseases such as listeriosis include advice on how to handle foods of animal origin and recommendations to avoid consuming unpasteurized

*These authors contributed equally to this work.
Corresponding author: Claudete Aparecida Araújo Cardoso.
e-mail: claudetecardoso@id.uff.br / claudete@huap.uff.br
Orcid: http://orcid.org/0000-0002-7638-6814
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milk. Specific preventive measures for pregnant women include avoiding the ingestion of soft cheeses such as feta, brie, camembert, blue cheese, and Mexican-style cheese (i.e., "fresh cheese")[4].

Because listeriosis is rare and is associated with high neonatal mortality rates, case reports are relevant because they increase obstetrician and pediatrician suspicion of the disease. The case reported here demonstrates the disease severity in a newborn with early-onset *Listeria* sepsis.

The study was approved by the Research Ethics Committee of the Universidade Federal Fluminense.

CASE REPORT

The male patient was born at a gestational age of 32 weeks and 6 days after an operative delivery owing to acute fetal distress. His birth weight, 1,945 g, was suitable for his gestational age by Fenton; his head perimeter (29.5 cm) was normal for his gestational age.

The mother was 24 years of age, previously healthy, and had an incomplete prenatal examination history; serology was performed only at admission for delivery (Venereal Disease Research Laboratory and anti-HIV non-reactive; hepatitis B surface antigen and anti-hepatitis C virus-negative; anti-HB-positive; and rubella, cytomegalovirus, and toxoplasmosis serology positive for IgG and negative for IgM). During her pregnancy, she had worked in a butchery without adequate protection while handling meat and reported exanthema and arthralgia during the first month of gestation, when serum was collected for Zika virus assessment by real-time reverse polymerase chain reaction (RT-qPCR).

The newborn required resuscitation in the delivery room (Apgar 1/4/7) and was referred to the neonatal intensive care unit (ICU).

In the neonatal ICU, the patient received mechanical ventilation and surfactant, venous hydration, vasoactive amines, sedation, and antibiotic therapy with ampicillin for 28 days and gentamicin for 15 days. His early seizures were controlled with phenobarbital. *L. monocytogenes* was isolated from the blood culture collected at admission and the RT-qPCR test for Zika virus was negative in serum collected from the newborn. The admission cerebral spinal fluid (CSF) examination showed 10 leukocytes (100% mononuclear), 261 mg/dL protein, 37 mg/dL glucose, and a negative culture. During his four-month hospitalization, the meningoencephalitis evolved into tetraventricular hydrocephalus requiring a ventriculoperitoneal shunt. At discharge, the neurological examination showed quadriplegia and swallowing abnormalities. These changes were related to lesions in the subcortical and pseudobulbar areas of the brain. A computed tomography (CT) scan of the skull showed tetraventricular hydrocephalus.

Macroscopic examination of the placenta showed a high weight and membranes with chronic meconial impregnation as well as subchorionic microabscesses in the cut surfaces. Microscopy showed chorioamnionitis with necrosis, funisitis, intervillositis, necrotizing villitis, diffuse subchorionic microabscesses with a predominance of mononuclear leukocytes and intracellular gram-positive bacilli in the membranes and microabscesses in the umbilical cord, suggestive of placental listeriosis (**Figure 1**).

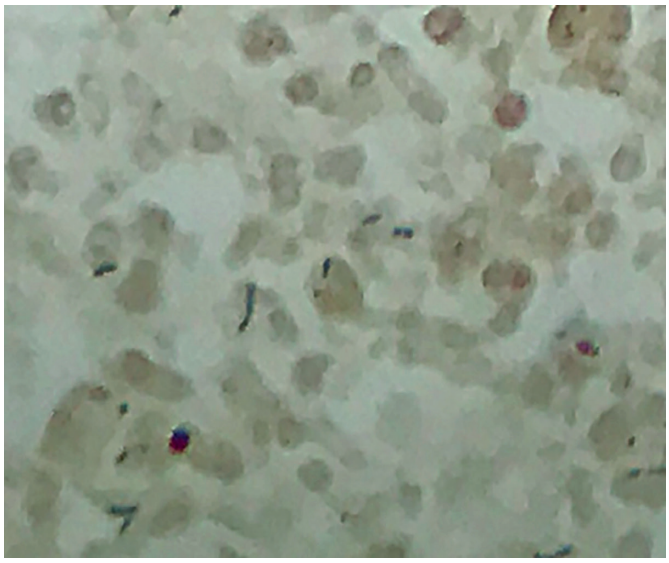

FIGURE 1: Gram stain showing Gram-positive bacilli in violet/blue (100×).

DISCUSSION

Neonatal listeriosis is often severe and potentially fatal and results from the vertical transmission of *L. monocytogenes* by inhaling infected amniotic fluid, the transplacental route, or ascending colonization of the vagina[5].

Vaginal colonization is a rare finding; however, nearly half of asymptomatic mothers of newborns with listeriosis have positive *L. monocytogenes* cultures[5].

Listeriosis remains an underreported and often under-treated disease. One reason for this is that *Listeria* is morphologically similar to *Corynebacterium*, *Clostridium,* and other gram-positive bacillii[6]. Positive blood culture for diphtheria or *Haemophilus* in a septic neonate should alert physicians to possible *Listeria* infection. Cultures should be carefully examined to ensure that there is no mistake regarding differentiation from other microorganisms[4]. The suspicion of *Listeria* infection should be reinforced with the laboratory so that specific tests can be performed to differentiate this group of microorganisms. The motility test rapidly differentiates *Listeria* from diphtheroid members of the normal flora of the skin, as it has tumbling end-over-end motility at 22-28°C but not at 37°C[6].

There are two forms of disease presentation in the newborn (early onset and late onset), which suggest different modes of transmission; namely, vertical and healthcare-associated infections, respectively. The symptoms of early-onset listeriosis occur an average 36 hours after birth. In approximately 50%-74% of cases, the mother presents prodromes with an influenza-like profile and symptoms of a fever, headache, and myalgia. Maternal fever associated with meconium-stained amniotic

fluid may be a characteristic presentation of this infection[7]. Newborns are often preterm and have a profile associated with chorioamnionitis. They present with clinical characteristics such as sepsis (81%-88%), respiratory distress or pneumonia (38%), meningitis (24%), and disseminated inflammatory granulomas[1]. *Granulomatosis infantisepticum* is a pathognomonic feature of listeriosis that corresponds to small, pale granulomatous nodules or pustules; however, these signs may be absent[8]. The late stage tends to occur between five days and two weeks postpartum and typically presents in term newborns[2].

Immune responses to *Listeria* are cell-mediated, which explains its higher frequency in pregnancy, AIDS, organ transplantation patients, and newborns, as these conditions are commonly associated with cellular immunosuppression. Due to pregnancy-induced immunosuppression, pregnant women are approximately 13 times more likely to become infected. Investigations of the fetal and neonatal immune systems have shown that deficient synthesis of interleukin (IL)-2, interferon-gamma, IL-4, tumor necrosis factor-alpha, and MyD88 results in poor modulation of immune responses such as macrophage and NK cell activation. This scenario contributes to the increased susceptibility of neonates to *Listeria*. The serotypes associated with early-onset neonatal listeriosis are types Ia, Ib, and (occasionally) IVb. Late-onset disease is caused most often by serotype IVb[9].

Ampicillin is the drug of choice for treating neonatal listeriosis. Treatment is recommended to be associated with gentamicin, aiming at synergism between the drugs. Cephalosporins and chloramphenicol are not active against *Listeria* and empirical treatment schemes for neonatal meningitis including these antimicrobials do not provide effective coverage[7]. With an appropriate clinical response, ampicillin alone may be continued for 14 days and a course of 21 days is recommended for more severe infections or meningitis treatment[4].

In our case, there was an initial suspicion of Zika virus infection due to the disease epidemics in Rio de Janeiro at the time of this report and the maternal manifestations at the beginning of gestation, which were more commonly related to the greater severity of clinical presentations of the disease. Although a maternal serum sample collected for RT-qPCR to detect Zika was collected at the time of the rash, the material was not processed for logistical reasons, which made the diagnosis of the pathogen impossible during pregnancy. The RT-qPCR for Zika was performed using serum from her newborn soon after birth and the virus was not detected. The strong maternal epidemiological history, premature birth, and the ready isolation of *L. monocytogenes* in blood culture were fundamental for the correct administration of antibiotic therapy. We also observed severe neurological sequelae due to meningitis in our patient. The preferential involvement of areas at the base of the brain and other granulomatous infections, including tuberculosis, can explain the unfavorable evolution and high risk of hydrocephalus. Tomographic findings were those commonly described in the literature[10,11].

Macroscopic examination of the placenta revealed thick and whitish membranes with subchorionic abscesses on the cut surface. Histological examination is a valuable tool to reinforce the diagnosis of listeriosis by the presence of mononuclear leukocytes predominantly in the abscessed areas. The diagnosis was compatible and could be associated with the blood culture and gram-positive bacilli findings in the placenta.

Obstetricians and neonatologists must suspect this disease when the epidemiological history, clinical features, and placental examination are compatible with *Listeria* infection. Careful interpretation of cultures is also key for correct treatment. Preventive measures in pregnant women with guidance on the correct handling and consumption of foods potentially contaminated with the bacteria are effective in reducing infection rates in pregnant women[1].

Conflict of Interest

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Lamont RF, Sobel J, Mazaki-Tovi S, Kusanovic JP, Vaisbuch E, Kim SK, et al. Listeriosis in human pregnancy: a systematic review. J Perinat Med. 2011;39(3):227-36.
2. Posfay-Barbe KM, Wald ER. Listeriosis. Pediatr Rev. 2004;25(5):151–9.
3. Vázquez-Boland JA, Krypotou E and Scortti M. Listeria placental infection. MBio. 2017;8(3):e00949-17.
4. Kylat RI, Bartholomew A, Cramer N and Bader MY. Neonatal listeriosis: Uncommon or misdiagnosed? J Neonatal Perinatal Med. 2016;9(3):313-6.
5. Becroft DMO, Farmer K, Seddon RJ, Sowden R, Vines A and Wattie DA. Epidemic listeriosis in the newborn. Br Med J. 1971;3(5777):747-51.
6. Brooks GF, Carroll KC, Butel JS, Morse SA and Mietzner TA. Aerobic nonspore-forming Gram-positive bacilli: Corynebacterium, Listeria, Erysipelothrix, Actinomycetes, & related pathogens. In: Brooks GF, Carroll KC, Butel JS, et al., eds. Jawetz, Mel- nick, & Adelberg's Medical Microbiology. 27th ed. New York, NY: McGraw-Hill; 2010:213-9.
7. McKinney JS. Listeria Infections in Neonates. Neoreviews. 2016;17(9):e515-20.
8. Kelly CS and Gibson JL. Listeriosis as a cause of fetal wastage. Obstet Gynecol. 1972;40(1):91–7.
9. Bortolussi R and Mailman TL. Listeriosis. In: Remington JS, Klein JO, Wilson CB, et al, eds. Infectious diseases of the fetus and newborn infant. 8th ed. Philadelphia, PA: Elsevier Saunders; 2016:470-86.
10. Antal A, Løberg E, Dietrichs E and Mæhlen J. Neuropathological findings in 9 cases of Listeria monocytogenes brain stem encephalitis. Brain Pathol. 2005;15(3):187-91.
11. Posfay-Barbe KM and Wald ER. Listeriosis. Semin Fetal Neonatal Med. 2009;14(4):228–33.