CASE REPORT

Acquired Cytomegalovirus Infection in an Extremely Low-Birth Weight Infant Presenting with a Severe Sepsis-Like Syndrome

Mafalda Rebordão Crisóstomo[1], Marta Póvoas[2], Ana Maia Pita[1], Ema Leal[1], José Nona[2]

Port J Pediatr 2022;53:523-7
DOI: https://doi.org/10.25754/pjp.2022.24216

Abstract

Cytomegalovirus infection is one of the most common congenital infections worldwide. Moreover, it seems to be an important cause of postnatally acquired infection. Perinatal transmission can occur intrapartum (from the birth canal), from a blood transfusion, via maternal breast milk, or from close contact with infected people. The risk of breast milk-acquired cytomegalovirus infection is higher in countries with a high prevalence of cytomegalovirus immunoglobulin G-positive women. Usually, acquired cytomegalovirus infection is asymptomatic, especially in term infants. However, preterm infants can present with a sepsis-like syndrome and multiple organ involvement. A high index of suspicion is required to make an early diagnosis. Therapeutic guidelines for symptomatic postnatal cytomegalovirus infection are not yet available. More studies are required to understand the long-term sequelae of postnatally acquired cytomegalovirus infection and know which is the best strategy to avoid cytomegalovirus post-natal transmission.

Keywords: Cytomegalovirus Infections/complications; Cytomegalovirus Infections/transmission; Infant, Extremely Premature; Infectious Disease Transmission, Vertical; Milk, Human

Keypoints

What is known:
- Screening for cytomegalovirus infection in preterm neonates should be performed more frequently.
- Diagnosis of postnatal cytomegalovirus infection in the preterm neonate may be challenging and implies a negative polymerase chain reaction before three weeks of age.

What is added:
- Refrigeration of breast milk decreases the rate of transmission but does not eliminate it completely, maintaining its beneficial properties.
- Further studies are required to determine the timing and optimal duration of treatment, as well as long-term follow-up to ascertain the impact of the disease.

Introduction

Cytomegalovirus (CMV) infection is the most common congenital infection worldwide[1] and seems to be an important cause of postnatal-acquired infection. Mother to child virus transmission can occur during pregnancy (congenital cytomegalovirus infection), childbirth (perinatal cytomegalovirus infection), or after birth (postnatal cytomegalovirus infection) from maternal breast milk, blood transfusion, or horizontal transmission by close contact. Infected breast milk is the major source of infection during the first year of life.[4] The risk of acquired-CMV infection transmitted through breast milk is higher in countries with a high prevalence of cytomegalovirus immunoglobin (Ig) G positive women, with CMV deoxyribonucleic acid (DNA) being detected in breast milk of about 95% of cytomegalovirus seropositive mothers.[4] Usually, acquired-CMV infection is asymptomatic, especially in term infants. However, preterm infants may present with a sepsis-like syndrome and multiple organ involvement. We report a case of severe cytomegalovirus infection, presenting as a sepsis-like syndrome with pneumonitis, colitis, hepatomegaly, and thrombocytopenia in an extremely low birth weight infant, following postnatal viral acquisition. The aim of this report is to call attention for this rare, but potentially fatal entity.

1. Hospital Dona Estefânia, Centro Hospitalar Universitário, Lisboa Central, Lisboa, Portugal
2. Maternidade Alfredo da Costa, Centro Hospitalar Universitário, Lisboa Central, Lisboa, Portugal
Corresponding Author
Mafalda Rebordão Crisóstomo| E-mail: mafalda.rsrc@gmail.com
Address: Hospital Dona Estefânia, Rua Jacinta Marto 8A Lisboa
Received: 03/05/2021 | Accepted: 10/12/2021 | Published online: 01/04/2022 | Published: 01/04/2022

Case Report

A 42-year-old twin pregnant woman, an Indian native, was admitted to the hospital with premature rupture of membranes at a gestational age of 23 weeks. Extremely low birth weight first twin male infant was delivered by cesarean section at 26 weeks of gestation, weighing 875 g. He required treatment with surfactant on the first day of life and invasive mechanical ventilation until day 19. He was extubated following a course of systemic steroids. Enteral nutrition with own mother breast milk and donor human milk was started on day two. Expressed breast milk was frozen at -20ºC for at least 72 hours from the seventh day of life, before administration, according to the local protocol. Donor milk was first frozen at -20ºC for at least 72 hours, followed by a pasteurized process, where breast milk was heated at 62ºC for 15 seconds. In the first days of life (days two, 10, and 24), he received irradiated and leucodepleted red blood cell transfusions for anemia.

On day 25, his general condition started to deteriorate with decreased activity, poor peripheral perfusion, severe episodes of apnea, bradycardia requiring re-intubation, and invasive ventilation. Late sepsis was suspected, and empiric antibiotic treatment with vancomycin and gentamycin was started after obtaining one peripheral blood culture, tracheal aspirate, and urine cultures. By this time, he had a percutaneous central venous catheter inserted on day five of life. *Staphylococcus capitis* was isolated in blood cultures, and treatment was adjusted.

Despite adequate antibiotic treatment, his condition worsened. Chest radiography showed new lung infiltrates, and laboratory results revealed sustained thrombocytopenia (minimum 14 x 10^9 cells/L), in need of twice-daily platelet transfusion, and increased C-reactive protein (maximum 125.7 mg/L). At this point, cytomegalovirus and fungal infections were suspected. However, cytomegalovirus polymerase chain reaction in urine and fungal polymerase chain reaction in blood were both negative. On day 32, he developed severe abdominal distension and hepatomegaly, along with hypoalbuminemia (17 g/L), worsening respiratory distress, and increased oxygen requirements. Abdominal ultrasound showed large-volume ascites, intestinal wall thickening with hypomotility, but no signs of bowel perforation.

Empirical antibiotic treatment for necrotizing enterocolitis was started, with piperacillin-tazobactam and metronidazole. Since then, there was a significant clinical deterioration, with refractory hypoxemia (but no signs of pulmonary hypertension on cardiac ultrasound) and hypotension requiring aminergic support. As a result, a paracentesis was performed.

Ascitic fluid was clear, without any signs of blood, feces, or pus, and on the laboratory analysis, it presented the characteristics of a transudate. Cultures of ascitic fluid were sterile. Despite broad-spectrum antibiotics, his condition kept worsening, with increasing inflammatory markers (leukocytosis 20.45 x 10^9 cells/L, neutrophiles 10.8 x 10^9 cells/L, C reactive protein 113.2 mg/L), persistent thrombocytopenia, pneumonitis, hepatomegaly (with a slight increase in transaminases), and colitis. Considering the infant atypical clinical picture for necrotizing enterocolitis and despite a previous negative result, CMV polymerase chain reaction in urine was repeated and turned out to be positive with a high viral load: urine 98 482 707 IU/mL, blood 78 000 IU/mL (4.9 $\log_{10}$). His mother was cytomegalovirus IgG seropositive, and polymerase chain reaction testing for CMV in the blood of Guthrie card taken on the sixth day of life was negative. Cytomegalovirus analysis of the mother milk was not performed.

Other important routes of transmission were considered less probable. Donor milk underwent a freezing process and short-term pasteurization before administration, and all transfused blood was submitted to leukoreduction, both inducing a virtually total cytomegalovirus eradication. Horizontal transmission of the virus was difficult to roll out and could not be completely excluded.

Considering the patient critical condition, antiviral therapy with intravenous ganciclovir was started on day 45 (12 mg/kg body weight in two daily doses), with a rapid and sustained improvement. One week after the beginning of anti-viral therapy, the infant had a complete resolution of ascites and hepatomegaly, with laboratory tests back to normal range, including platelets count, as well as C reactive protein, and liver function tests. The respiratory status also improved, being extubated to nasal continuous positive airway pressure on the 12th day of treatment. He completed a total of three weeks of intravenous ganciclovir, switching to oral valganciclovir (16 mg/kg body weight twice a day) on day 68, which was maintained for a total of six months, with parental consent.

After 18 days of treatment, viral load significantly decreased to 560 IU/mL (2.70 $\log_{10}$). There were no side effects related to ganciclovir or relapse of the infection. The patient was discharged on the 101st day of life (8 days of corrected age), weighing 2445 g (percentile 1), with moderate bronchopulmonary dysplasia and sequelae of treated bilateral stage IV retinopathy of prematurity. Cerebral ultrasound examination at 40

weeks of corrected gestational age was normal, and cerebral magnetic resonance obtained at 12 months of age (9 months of corrected age) revealed discrete signs of periventricular leukomalacia. Acoustic evoked potentials were normal at 6 months of corrected age. At 11 months of age (8 months of corrected age), neurological and developmental assessments showed mild abnormalities in muscle tone, maintaining the physiotherapy intervention program.

Discussion

Postnatal cytomegalovirus infection transmitted by human milk is estimated to occur in 22.8% of the premature infants of seropositive mothers, with a symptomatic disease in 0%-34.5% of them.[5] As maternal antibodies are passively acquired mainly after 28 weeks of gestation,[6] the disease is more severe in very preterm babies. In addition, the developmentally immature preterm immune system may facilitate viral pathogenicity.[3] Diagnosis of postnatal cytomegalovirus infection in preterm may be challenging because its unspecific symptoms are frequently attributed to other infectious causes that are common in this age group.

The most common manifestations are hepatitis, bone marrow suppression (thrombocytopenia and/or neutropenia), bowel inflammation (necrotizing enterocolitis, volvulus, colitis), and pneumonitis.[1,4,7-9] Cytomegalovirus-related sepsis-like syndrome is a rare condition, with a median incidence of only 4%,[9] which implies a high level of suspicion to make the diagnosis.

In this case report, the clinical presentation resembled sepsis, which was supported by *Staphylococcus capitis* identification in blood cultures. Worsening symptoms despite adequate treatment led to cytomegalovirus screening at 4 weeks of age, which came back negative. Two weeks later, in face of severe refractory multisystemic disease, cytomegalovirus polymerase chain reaction testing was repeated, and a high viral load was detected. In congenital cytomegalovirus infections, higher CMV load was thought to be associated with late-onset disease and adverse clinical outcomes.[10] However, to our knowledge, there are no robust data describing any association between cytomegalovirus viral load and adverse clinical outcomes in post-natal acquired CMV infections.[7,9]

Differential diagnosis between congenital and postnatal cytomegalovirus after 3 weeks of age is difficult. Retrospectively diagnosing congenital cytomegalovirus relies on detecting the virus on the dried blood spot, collected as part of screening for congenital conditions. Diagnosis of postnatal acquired cytomegalovirus is based on the exclusion of congenital cytomegalovirus infection and detection of cytomegalovirus DNA, after day 21 of life from body fluids (blood, urine, cerebrospinal fluid, saliva, or respiratory secretions).[7] In this case, cytomegalovirus DNA polymerase chain reaction was negative in Guthrie card and also in the first urine sample tested for cytomegalovirus taken on the 31st day of life. These two findings together support the hypothesis of acquired postnatal cytomegalovirus infection.

Prevention of cytomegalovirus transmission through breast milk in preterm neonates has been a concern, and several methods have been tested. Freezing has proven to be effective in reducing the cytomegalovirus infection rate by about 78%, without modifying its beneficial nutrients and immunological properties.[11] However, it does not completely eliminate the virus, and some neonates will still be infected. Short-term (62ºC-72ºC for 5-15 seconds) and long-term (62.5ºC for 30 minutes) pasteurization are both effective in preventing cytomegalovirus transmission.

Nevertheless, only the short-term method allows the conservation of nutritional properties and immunological components of human milk. In our unit, all mothers of premature infants (born with less than 34 weeks of gestational age or less than 1500 g) are tested for cytomegalovirus serological status. Our prevention policy consists of refrigerating breast milk from seropositive mothers at -20ºC for 72 hours after the first week of lactation, following the beginning of viral shedding.[4] Breast milk from donors was first frozen and then treated by the short-term pasteurization method (62ºC for 15 seconds) before administration. The risk of acquiring cytomegalovirus from banked breast milk from cytomegalovirus-positive donors is near zero.

However, freezing milk does not completely eliminate breast milk infectivity, and preterm born with a gestational age lower than 30-32 weeks or with less than 1500 g are at higher risk.[4,9] There is no international consensus about the best strategy for this group of infants. The position of the American Academy of Pediatrics is that the benefits of fresh breast milk from seropositive mothers outweigh the risk of postnatal cytomegalovirus infection.[12] However, the French Neonatal Society advises pasteurization of breast milk from seropositive mothers for infants born at less than 28 weeks gestation (or 1000 g) until aged 31+6 weeks equivalent.[13] A third of German and Austrian neonatal intensive care units also give pasteurized milk to infants less than 32 weeks gestational age or 1500 g.[14] The risk of cytomegalovirus transmission from blood transfusions

nowadays is residual, but virtually possible. However, the universal use of leucodepleted and/or cytomegalovirus-negative blood, nearly eliminates the risk of acquisition via this route,[3] making it much less probable. Horizontal transmission of the virus, via close contact with an infected person is a possibility difficult to roll out in this case. This fact is a limitation in our report, and because breast milk from the mother was not tested. Although it cannot be completely excluded, it seems less probable, given all the infection prevention measures applied in neonatal intensive care units. Furthermore, in extremely low birth weight infants, the first source of postnatal cytomegalovirus transmission is through breast milk,[4] even if frozen before administration.

Evidence for treatment in postnatal cytomegalovirus is sparse and based purely on case reports.[3,9] The indication for treatment in postnatal cytomegalovirus infection would be to suppress active viremia and prevent destructive end-organ complications in severe life-threatening diseases.[7,9] In preterm infants with severe life-threatening symptomatic postnatal cytomegalovirus infection, the use of ganciclovir and valganciclovir have been reported.[3] In this patient, there was sustained improvement with ganciclovir, along with progressive and sustained reduction of viral load (560 IU/mL after four weeks of therapy). The long persistence of cytomegalovirus in body fluids could be due to the immaturity of the immune system in newborns, who are unable to mount an effective cellular immune response.[10] Oral valganciclovir was started, making a total of six-month therapy. There were no significant side effects.

Long-term sequelae of postnatal cytomegalovirus infection are yet to be determined.[9] However, so far, the prognosis seems favorable. A recent cohort study showed no adverse effects on the neurodevelopment of postnatal cytomegalovirus infection within the first six years of life, including sensorineural hearing loss.[15] Further studies are required to fully ascertain the long-term effects of acquired cytomegalovirus infection and differentiate these from the consequences of extreme prematurity.

Author Contribuitions

MRC, MP, AMP, EL and JN participated in the study conception or design. MRC and MP participated in acquisition of data. MRC and MP participated in the analysis or interpretation of data. MRC and MP participated in the drafting of the manuscript. AMP, EL and JN participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Fischer C, Meylan P, Bickle Graz M, Gudinchet F, Vaudaux B, Berger C, et al. Severe postnatally acquired cytomegalovirus infection presenting with colitis, pneumonitis and sepsis-like syndrome in an extremely low birthweight infant. Neonatology 2010;97:339-45. doi: 10.1159/000260137.

2. Romero-Gómez M, Cabrera M, Montes-Bueno M, Cendejas-Bueno E, Segovia C, Pastrana N, et al. Evaluation of cytomegalovirus infection in low-birth weight children by breast milk using a real-time polymerase chain reaction assay. J Med Virol 2015;87:845-50. doi: 10.1002/jmv.24101.

3. Montasser M, Bhushan S. Postnatally acquired cytomegalovirus infection in preterm infants: When we need to treat? EC Paediatrics 2017;4:23-9.

4. Bardanzellu F, Fanos V, Reali A. Human breast milk-acquired cytomegalovirus infection: Certainties, doubts and perspectives. Curr Pediatr Rev 2019;15:30-41. doi: 10.2174/1573396315666181126105812.

5. Kurath S, Halwachs-Baumann G, Müller W, Resch B. Transmission of cytomegalovirus via breast milk to the prematurely born infant: A systematic review. Clin Microbiol Infect 2010;16:1172-8. doi: 10.1111/j.1469-0691.2010.03140.x.

6. Gunkel J, de Vries LS, Jongmans M, Koopman-Esseboom C, van Haastert IC, Eijsermans MC, et al. Outcome of preterm infants with postnatal cytomegalovirus infection. Pediatrics 2018;141:e20170635. doi: 10.1542/peds.2017-0635.

7. Kadambari S, Whittaker E, Lyall H. Postnatally acquired cytomegalovirus infection in extremely premature infants: How best to manage? Arch Dis Child Fetal Neonatal Ed 2020;105:334-9. doi: 10.1136/archdischild-2019-317650.

8. Takahashi R, Tagawa M, Sanjo M, Chiba H, Ito T, Yamada M, et al. Severe postnatal cytomegalovirus infection in a very premature infant. Neonatology 2007;92:236-9. doi:

10.1159/000103982.
9. Osterholm EA, Schleiss MR. Impact of breast milk-acquired cytomegalovirus infection in premature infants: Pathogenesis, prevention, and clinical consequences? Rev Med Virol 2020;30:1-11. doi: 10.1002/rmv.2117.
10. Forner G, Abate D, Mengoli C, Palù G, Gussetti N. High cytomegalovirus (CMV) DNAemia predicts CMV sequelae in asymptomatic congenitally infected newborns born to women with primary infection during pregnancy. J Infect Dis 2015;212:67-71. doi: 10.1093/infdis/jiu627.
11. Balcells C, Botet F, Gayete S, Marcos MÁ, Dorronsoro I, de Alba C, et al. Vertically transmitted cytomegalovirus infection in newborn preterm infants. J Perinat Med 2016;44:485-90. doi: 10.1515/jpm-2015-0325.
12. Johnston M, Landers S, Noble L, Szucs K, Viehmann L. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-41. doi: 10.1542/peds.2011-3552.
13. Picaud JC, Buffin R, Gremmo-Feger G, Rigo J, Putet G, Casper C. Review concludes that specific recommendations are needed to harmonise the provision of fresh mother's milk to their preterm infants. Acta Paediatr 2018;107:1145-55. doi: 10.1111/apa.14259.
14. Buxmann H, Falk M, Goelz R, Hamprecht K, Poets CF, Schloesser RL. Feeding of very low birth weight infants born to HCMV-seropositive mothers in Germany, Austria and Switzerland. Acta Paediatr 2010;99:1819-23. doi: 10.1111/j.1651-2227.2010.01954.x.
15. Gunkel J, de Vries LS, Jongmans M, Koopman-Esseboom C, van Haastert IC, Eijsermans MC, et al. Outcome of preterm infants with postnatal cytomegalovirus infection. Pediatrics 2018;141:e20170635. doi: 10.1542/peds.2017-0635.

Infeção Adquirida por Citomegalovírus em Recém-Nascido de Peso ao Nascimento Extremamente Baixo com Síndrome Semelhante a Sepsis Grave

Resumo

A infeção por citomegalovírus é uma das infeções congénitas mais comuns a nível mundial, mas é também uma importante causa de infeção adquirida pós-natal. A transmissão perinatal pode ocorrer durante o parto, através de transfusões sanguíneas, do leite materno ou por contacto próximo com pessoas infetadas. O risco de infeção por citomegalovírus adquirido através do leite materno é superior em países com maior prevalência de mulheres positivivas para imunogloblina G para citomegalovírus. A infeção adquirida por citomegalovírus é geralmente assintomática, principalmente em recém-nascidos de termo. No entanto, em recém-nascidos pré-termo pode apresentar-se como um quadro semelhante a sepsis, com envolvimento multiorgânico. É necessário um alto índice de suspeição para fazer um diagnóstico precoce. Não existem orientações terapêuticas consensuais para a infeção sintomática pós-natal por citomegalovírus. São necessários mais estudos para compreender as sequelas a longo prazo da infeção adquirida por citomegalovírus e saber qual a melhor estratégia para evitar a sua transmissão pós-natal.

Palavras-Chave: Infecções por Citomegalovirus/complicações; Infecções por Citomegalovirus/transmissão; Lactente Extremamente Prematuro; Leite Humano; Transmissão Vertical de Doenças Infecciosas