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Case report

Severe congenital syphilis as cause of unexpected prematurity: 2 case reports and recommended management

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Abstract

Epidemiologic data suggest an increasing incidence of congenital syphilis (CS) in developed countries in recent years. Fetal infection by *Treponema pallidum* can cause a wide spectrum of clinical manifestations, including stillbirth and prematurity. The physician should always consider infections caused by toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and other agents (TORCH) when facing a severely ill preterm neonate.

The authors describe 2 very similar cases of severe CS in preterm newborns, both of whom were admitted to the Neonatal Intensive Care Unit. At birth, in addition to severe respiratory distress needing invasive ventilation, the neonates presented with ascites, hepatosplenomegaly, and hydrocele. The preliminary evaluation revealed anemia and thrombocytopenia, which required aggressive transfusion support. Increased inflammatory parameters and cholestasis were also noted. Based on the clinical signs and analytic alterations, TORCH infections were suspected. An investigation was conducted and both neonates had treponemal and non-treponemal positive tests. Both mothers had reactive serologies at the time of delivery, which was previously unknown. Other viral and bacterial infections were excluded. Ultrasonograms of the brains were unremarkable. Ophthalmologic, audiologic, and bone screenings were negative. The neonates received a course of treatment with aqueous crystalline penicillin G for 14 days, and had good outcomes.

The diagnosis of CS can be difficult because most infants are asymptomatic at birth and rarely present with severe disease, as shown by our cases. To make a correct diagnosis, it is important to compare treponemal and non-treponemal tests from the mother and newborn because serologies are difficult to interpret.

The cases described herein are a reminder of the importance of screening and treatment for these infections during pregnancy and at the time of delivery. It is essential to prioritize health investments in screening programs and to allocate specialized healthcare staff so that syphilis can be treated earlier in the population of reproductive age.

Keywords

Congenital syphilis, congenital and perinatal infections, fetal infections, syphilis, *Treponema pallidum*, TORCH infections, management.

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Introduction

Once believed to be a rare disease in developed countries, recent data suggest a massive increase in the number of congenital syphilis (CS) cases since 2012 [1]. This finding reflects the rising trend in syphilis among women of reproductive age in recent decades, mainly due to defunding on public health and screening programs [2].

Routine serologic screening during pregnancy is extremely important to prevent CS. According to the Centers for Disease Control and Prevention (CDC) guidelines, screening should be performed at the 1st prenatal visit, at 28 weeks gestation, and at the time of delivery for women living in communities with a high rate of syphilis, women infected with human immunodeficiency virus (HIV), or women who are at increased risk for exposure to syphilis [3].

Fetal infection with *Treponema pallidum* (*T. pallidum*) can result in stillbirth, prematurity, and a wide spectrum of clinical manifestations. The majority of infants infected with *T. pallidum* are asymptomatic at birth, but when symptomatic, signs are non-specific or subtle [4]. A severely ill preterm newborn should signify the possibility of an infection caused by toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and other agents (TORCH) [5].

The authors describe 2 similar cases of severe CS in preterm newborns who were admitted to the Neonatal Intensive Care Unit (NICU).

Case reports

Case 1

The first case had normal prenatal screening and an uncomplicated pregnancy. At 34 weeks of gestation, the mother was admitted via the Emergency Department due to decreased fetal movements. An ultrasound (US) revealed ascites, hyperechogenic bowel, a unilateral hydrocele, and oligohydramnios. Cardiotocography (CTG) was significant for fetal heart rate decelerations. Therefore, an emergency C-section was performed. The newborn had spontaneous breathing, an Apgar score of 9 at the 1st and 5th minutes of life and an adequate somatometry for gestational age. He presented with jaundice, hepatosplenomegaly, and a left hydrocele. He was admitted to the NICU and started on ampicillin and gentamicin for suspected early sepsis. During the first hour of life, he developed worsening respiratory distress that required mechanical ventilation.

The initial evaluation revealed anemia (hemoglobin = 7.8 g/dL), thrombocytopenia (1,800/μL), an elevated C-reactive protein (CRP) level (63 mg/L), and cholestasis. The indirect Coombs test was negative. Abdominal US showed hepatosplenomegaly with a normal gallbladder, ascites, a splenic-renal shunt, and a left hydrocele. Cerebral US was normal.

Based on the preliminary evaluation, TORCH infections were suspected and extensive testing was performed. The maternal pregnancy serologies were reviewed. A positive venereal disease research laboratory test (VDRL) result was missed in the 1st trimester, for which she received no treatment. Additional maternal tests were positive for *T. pallidum* immunoglobulin G and M (IgG+IgM) using enzyme immunoassay (EIA) and a rapid plasma reagin (RPR) titer of 1/16. The newborn had positive *T. pallidum* IgG+IgM (EIA), positive fluorescent treponemal antibodies-absorbed (FTA-Abs), and an RPR titer of 1/32.

A pathologic examination in a severely ill neonate with positive treponemal and non-treponemal tests (mother and son) made a diagnosis of CS highly probable. He started treatment on day 2, with aqueous crystalline penicillin G (50,000 U/kg intravenous for 14 days).

A lumbar puncture was performed on the 16th day of life due to instability and thrombocytopenia. The cerebrospinal fluid (CSF) analysis showed a normal protein level and leucocyte count, as well

as a negative VDRL and culture. The remaining cultures and serologies, including cytomegalovirus, human immunodeficiency virus, and sexually transmitted infections, were negative. The ophthalmologic, audiologic, and bone screening were unremarkable.

He presented a maximum CRP of 136 mg/L on day 2 of life. The RPR began to decline on the 12th day of life, was negative at 2 months of age, and remained negative at 4 months of age. He presented a favorable course and is periodically evaluated in the Pediatric Infectious Disease Clinic.

Case 2

The second case had normal prenatal screening (negative VDRL in the 1st trimester) and an uncomplicated pregnancy. At 32 weeks of gestation, the mother was admitted to the hospital for abdominal pain and vomiting. The fetal US revealed hydrops fetalis with pleural and pericardial effusions, ascites, hepatosplenomegaly, and a right hydrocele. Maternal testing at the time of admission revealed positive *T. pallidum* IgG+IgM (EIA) and an RPR titer of 1/16. An emergency C-section was performed because the CTG showed persistent fetal heart rate decelerations. The neonate was hypotonic, bradycardic, and had no spontaneous breathing following delivery. The Apgar score was 3 at the 1st minute and 8 at the 5th and 10th minutes. He required aggressive ventilatory and vasoactive support during the first hour of life.

The examination was significant for jaundice, a grade III/VI systolic heart murmur, hepatosplenomegaly, and a desquamative rash on the torso (**Fig. 1**). The somatometry was adequate for the gestational age. The preliminary tests showed pancytopenia with severe anemia (hemoglobin = 4.6 g/dL), thrombocytopenia (5,000/μL), an elevated CRP level (110 mg/dL), hyperbilirubinemia, and hypoalbuminemia. The blood smear was normal and the indirect Coombs test was negative. Abdominal US confirmed the hepatosplenomegaly, ascites, and right hydrocele. Cardiac US showed biventricular dilation, mitral and tricuspid insufficiency, persistent arterial ductus, but no pericardial effusion. Cerebral US was unremarkable.

With a symptomatic newborn whose mother had newly-positive treponemal and non-treponemal tests, the suspicion of CS was high, so he was treated with aqueous crystalline penicillin G (50,000 U/kg intravenous for 14 days). The neonate was positive for *T. pallidum* IgG+IgM (EIA), had a negative FTA-Abs, and an RPR titer of 1/32.

A lumbar puncture was performed on the 20th day of life after hemodynamic and platelet count stability were achieved. The CSF analysis

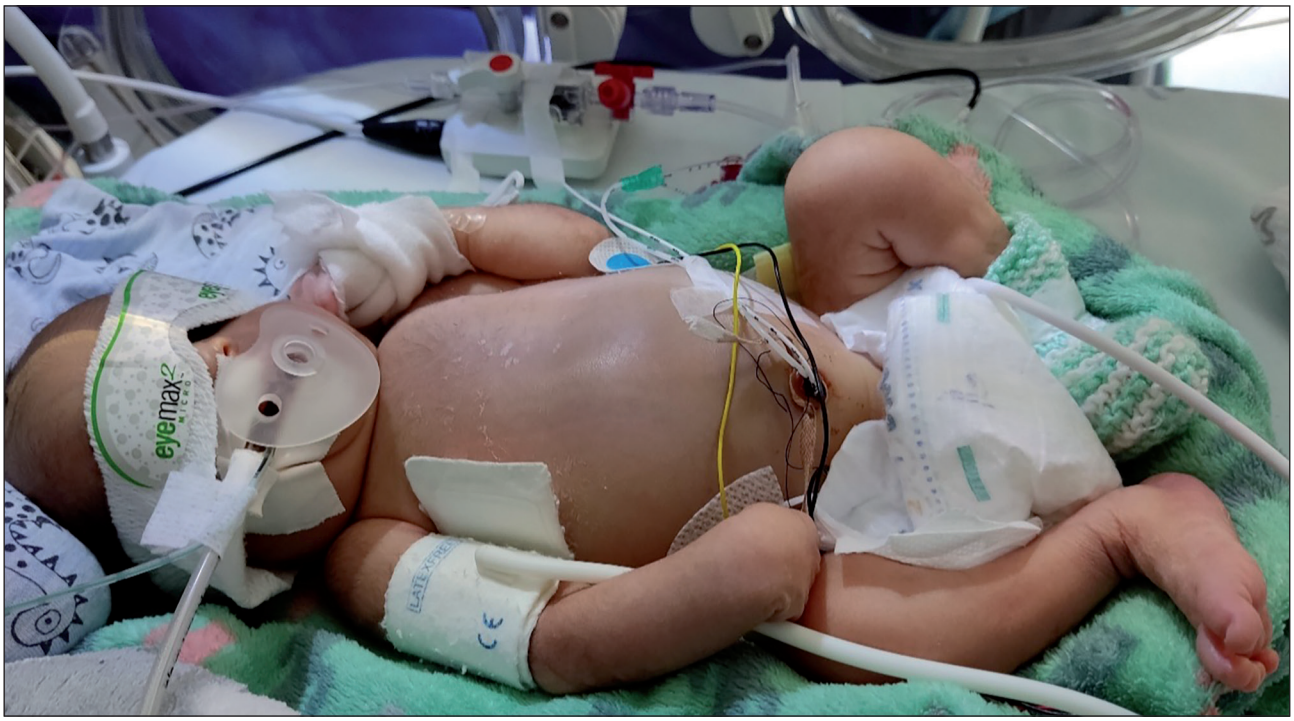

Figure 1. Desquamative rash on the torso in the second case.

showed a normal protein level and leucocyte count, as well as a negative VDRL and culture. Ophthalmologic, audiologic, and bone screening showed no abnormalities. The remaining cultures and serologies were negative.

Throughout the NICU stay, aggressive transfusion support was needed. The maximum CRP was 154 mg/dL on day 2 of life, followed by a progressive decline. The baby had complete regression of cardiac abnormalities during the 1st week of life.

On day 26 of life we observed an increasing RPR titer of 1/64, even though his clinical status had improved and the inflammatory markers were negative. At 2 months of life, the RPR titer began to decline and at 3 months of life the titer was 1/8. Currently, he is under clinical surveillance and regular RPR testing.

Discussion

Both cases occurred within a 1-month interval at the end of 2021, probably the result of the recent increase in incident cases of CS worldwide. The latest European Centre for Disease Prevention and Control (ECDC) annual epidemiologic report revealed an increase in CS cases, with Portugal having the second highest rate in Europe (12 cases per 100,000 live births) [1]. In our country, Portugal, we have a free National Health System that recommends VDRL screening to all women in the 1st and 3rd trimesters, as recommended by the CDC [3]. Despite compliance with prenatal screening, the first case had a 1st trimester positive screening test result that was missed, thus no treatment was initiated and the fetus was infected early in the pregnancy. The second case underwent recommended screening, had a negative VDRL in the 1st trimester, and a positive VDRL at the time of delivery at 32 weeks of gestation. Therefore, the infection occurred after the 1st trimester. Several factors are thought to contribute to the increase in CS incidence. The authors point out the increasing number of migrants in the last 2 years, mainly from South America, where the prevalence of CS is much higher, therefore contributing to the increase in CS cases in Portugal and Europe [6]. The recent coronavirus pandemic also contributed to an unexpectedly higher number of cases during 2020 and 2021 because of decreased in-person care with social distancing, reduced syphilis screening, and reassignment of health care staff to pandemic work [7]. During this period, we observed a defunding of public health screening programs and health services that focus on the prevention, identification, and treatment of sexually transmitted diseases (STDs). This change has led to gaps in testing, treatment, and follow-up during prenatal care [2]. Maternal screening should be improved by facilitating access to healthcare facilities and improving health literacy. The World Health Organization has also recognized this important matter and released a global guidance for the elimination of mother-to-child transmission of syphilis and other STDs, with a global goal to eliminate CS and maternal STD transmission to fetuses worldwide [8]. Because we see a rise in the incidence CS in our country as well as globally, the authors propose to add syphilis screening during the 2nd trimester, thus avoiding diagnoses close to birth.

The diagnosis of CS can be difficult because maternal IgG antibodies are transferred through the placenta to the fetus, thus complicating the interpretation of reactive serologies among neonates. Neonates born to mothers with reactive treponemal and non-treponemal tests should undergo non-treponemal testing (RPR or VDRL) because the treponemal test is difficult to interpret (passively transferred maternal IgG can persist > 15 months). Therefore, treatment decisions must be made on the basis of the following [3]:

1. identification of syphilis in the mother and adequacy of maternal treatment;
2. presence of clinical, laboratory, and radiographic evidence of syphilis in the neonate;
3. comparison of maternal (at delivery) and neonatal non-treponemal serologic titers (RPR or VDRL) by using the same test, preferably conducted by the same laboratory.

Both our cases presented with characteristic clinical features of CS, including massive hepatosplenomegaly, ascites, cholestasis, anemia, and thrombocytopenia [5]. Despite not having a high RPR titer (≥ 4-fold) in comparison to the maternal titer, the diagnosis in both cases was supported by the neonatal abnormal physical examination consistent with CS, and later confirmed by the neonatal non-treponemal reactive test result [3, 5]. **Tab. 1** summarizes the evaluation and treatment recommendations for neonates born to women who have reactive serologic tests according to CDC guidelines [3].

Both babies were unstable and had severe thrombocytopenia, thus a lumbar puncture was

Table 1. Recommended congenital syphilis (CS) evaluation and treatment of neonates born to women who have reactive serologic tests during pregnancy and a reactive non-treponemal test at the time of delivery (original table, based on the recent CDC guidelines [3]).

Diagnosis	Evaluation	Treatment
Confirmed proven or highly probable CS. Any neonate with: • abnormal physical exam consistent with CS; • neonate serum quantitative non-treponemal serologic titer ≥ 4 x mother's titer at delivery; or • positive darkfield test or PCR of placenta, cord, lesions, body fluid, or a positive silver stain of the placenta/cord.	• CSF for VDRL, cell count, protein; • CBC; • long bone radiographs.	• Aqueous crystalline penicillin G IV, 10 days; or • procaine penicillin G IM, 10 days.
Possible CS. Any neonate with: • normal physical exam; • neonate serum quantitative non-treponemal serologic titer ≤ 4 x mother's titer at delivery; • mother inadequately or not treated.		• Aqueous crystalline penicillin G IV, 10 days; or • procaine penicillin G IM, 10 days; or • benzathine penicillin G IM, single dose (only if normal CSF, radiographs, and CBC).
Less likely CS. Any neonate with: • normal physical exam; • neonate serum quantitative non-treponemal serologic titer ≤ 4 x mother's titer at delivery; • mother adequately treated during pregnancy; • mother has no evidence of reinfection or relapse.	None.	• Benzathine penicillin G IM, single dose; or • no treatment and follow-up (every 2-3 months).
Unlikely CS. Any neonate with: • normal physical exam; • neonate serum quantitative non-treponemal serologic titer ≤ 4 x mother's titer at delivery; • mother adequately treated before pregnancy; • mother's non-treponemal serologic titer remained low and stable during pregnancy and at delivery.		• No treatment; or • if neonate's reactive non-treponemal tests: follow-up or benzathine penicillin G IM, single dose (if follow-up is uncertain).

CBC: complete blood count; CS: congenital syphilis; CSF: cerebrospinal fluid; IM: intramuscular; IV: intravenous; PCR: polymerase chain reaction; VDRL: venereal disease research laboratory test.

contraindicated as part of the preliminary evaluation, so they received treatment for 14 days to cover central nervous system involvement. We faced a challenge when the second baby presented with an increasing RPR titer to 1/64 (4-fold the maternal titer) on day 26 of life after completing the course of antibiotic treatment. We therefore asked: "Should he receive another course of treatment?". The case was discussed with the infectious diseases consultants taking into account the CDC guidelines, and we decided to wait and re-evaluate because the RPR titer could take some time to decrease. Moreover, the clinical response was favorable and inflammatory markers were negative. In these cases, it is recommended to perform non-treponemal tests every 2-3 months until negative. If positive titers persist at 6-12 months, a CSF examination should be repeated and a course of treatment might be necessary [3, 5].

Pediatricians should always consider the diagnosis of TORCH infections when facing a severely ill preterm neonate because the signs can vary and are non-specific [4]. These cases are a reminder of the importance of recommended screening and treatment for these infections during pregnancy and at the time of delivery [5]. It is essential to prioritize the prevention of STDs worldwide by investing in screening and educational programs, as well as allocation of specialized healthcare staff so that syphilis can be identified and treated earlier in the population of reproductive age [7].

Ethics declaration

The Authors confirm that this manuscript is in accordance with the ethical standards of the institutional, national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of interest

The Authors declare no conflicts of interest. The Authors confirm that they did not receive financial or other kinds of support from any organization or institution to write or publish this manuscript.

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