6 Liver Failure and Rash in a 6-week-old Girl

Rishi Mediratta, MD, MSc, MA,* Hayden Schwenk, MD, MPH,† Anoop Rao, MD,‡ Ritu Chitkara, MD, FAAP‡

*Department of Pediatrics, †Division of Pediatric Infectious Diseases, and ‡Division of Neonatal-Perinatal Medicine, Stanford University School of Medicine, Stanford, CA

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PRESENTATION

A 6-week-old girl is admitted to the NICU with liver dysfunction and jaundice. One week before presentation she had developed an erythematous macular rash on the chest and extremities, oral thrush, and a low-grade fever. Physical examination reveals jaundice, hepatosplenomegaly, and a desquamating macular rash on the left lower extremity. Her vital signs are normal for age. She was born to a 34-year-old G7P2321 woman via normal spontaneous vaginal delivery at 37 weeks' gestation. Birthweight was 3,060 g (35th percentile). The infant's mother had routine prenatal care, and her course was complicated by intrahepatic cholestasis of pregnancy. Results of first-trimester maternal *Treponema pallidum* enzyme immunoassay were negative.

Laboratory evaluation reveals acute liver failure, coagulopathy, conjugated hyperbilirubinemia, lymphocyte-predominant leukocytosis, disseminated intravascular coagulation, anemia, and thrombocytopenia. Laboratory test results are notable for hemoglobin level, 7.2 g/dL (72 g/L); total leukocyte count, 25,000/μL (25.0×10^9/L) with 68% lymphocytes and 18% neutrophils; platelet count, $20 \times 10^3/\mu$L (20×10^9/L); aspartate aminotransferase, 1,164 U/L (19.4 μkat/L); alanine aminotransferase, 536 U/L (8.9 μkat/L); albumin, 1.8 g/dL (18 g/L); international normalized ratio, 1.8; and partial thromboplastin time, 34.9 seconds. Her C-reactive protein level was elevated at 19.1 mg/L (181.9 nmol/L).

The Case Discussion and References appear with the online version of this article at http://pedsinreview.aappublications.org/content/39/6/315.

DISCUSSION

The differential diagnosis includes sepsis due to bacteria such as *Escherichia coli, Enterococcus, Klebsiella*, methicillin-resistant *Staphylococcus aureus,* and *T pallidum*. Potential viral pathogens include enterovirus, echovirus, adenovirus, parvovirus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human herpesvirus 6, and other viral hepatitides. Noninfectious possibilities include α_1-antitrypsin deficiency, hemophagocytic lymphohistiocytosis, and acetaminophen toxicity.

Treatment with vancomycin, cefotaxime, and acyclovir was initiated on hospital admission. Vitamin K, fresh frozen plasma, platelets, and packed red blood cells were administered. Acyclovir therapy was discontinued based on negative HSV polymerase chain reactions from mucosal, blood, and cerebrospinal fluid (CSF) samples. Results of CSF VDRL testing and plasma HIV RNA polymerase chain reaction were also negative. Three days later, liver dysfunction, anemia, and thrombocytopenia resolved. Antibiotic therapy was narrowed to ampicillin based on a blood culture with growth of *Enterococcus faecalis*. Syphilis was confirmed by serum *T pallidum* particle agglutination assay (TPPA) and rapid plasma reagin (RPR) titer (1:64). After the diagnosis of congenital syphilis, the infant received 10 days of intravenous aqueous penicillin G followed by 1 intramuscular dose of benzathine penicillin G. Both parents subsequently tested positive for syphilis (TPPA, RPR) and were treated. The infant was discharged after a normal ophthalmologic and audiology evaluation, with anticipation of periodic follow-up and serial nontreponemal antibody testing. The infant continues to be followed in the Pediatric Infectious Disease Clinic and had a greater than 4-fold reduction in RPR titer 3 months after hospital discharge (RPR titer of 1:8).

The Condition

This infant has congenital syphilis despite negative maternal first-trimester treponemal test results. Congenital syphilis is caused by transplacental transfer of *T pallidum*, a spirochete that is sensitive to penicillin. The incidence of congenital syphilis in the United States increased between 2012 and 2014. In 2014, there were 12 cases of congenital syphilis per 100,000 live births. (1) The incubation period of syphilis is typically 3 weeks but ranges from 10 to 90 days. (2) Risk factors for congenital syphilis include lack of prenatal care, substance abuse, sexual promiscuity, history of sexually transmitted infections, or contact with anyone with sexually transmitted infections. (3) Syphilis infection can occur throughout pregnancy and can result in miscarriage, stillbirth, prematurity, neonatal death, and congenital syphilis. (4)

The involvement of the placenta and subsequent hematogenous dissemination of *T pallidum* to the infant helps explain the multitude of clinical manifestations of congenital syphilis. Congenital syphilis is classified as early congenital syphilis, affecting infants from birth to 2 years old, and late congenital syphilis, affecting infants older than 2 years. Most infants with early congenital syphilis are asymptomatic at birth but can develop poor feeding, hepatomegaly, splenomegaly, jaundice, hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia, pneumonitis, nephrotic syndrome, rhinitis, maculopapular rash, generalized lymphadenopathy, fever, central nervous system dysfunction, and osteochondritis during the first few weeks after birth. (5) Manifestations of late congenital syphilis include interstitial keratitis, saddle nose, saber shins, Hutchinson teeth, eighth nerve deafness, mental delay, and convulsive disorders. (5) Concurrent bacterial sepsis, secondary to bacterial translocation across the gastrointestinal mucosal barrier, has also been reported. (6)

Diagnosis

Because *T pallidum* cannot be readily cultured, syphilis is typically diagnosed using a screening nontreponemal test followed by a confirmatory treponemal test. Nontreponemal testing includes the VDRL and RPR tests. Treponemal tests include TPPA, *T pallidum* enzyme immunoassay, *T pallidum* chemiluminescent assay, and fluorescent treponemal antibody absorption. A reactive nontreponemal test result needs to be confirmed by treponemal testing because the sensitivity of RPR and VDRL tests to detect primary syphilis is 86% and 78%, respectively. (7) The RPR test works by detecting lipoidal material released by cells that are infected with *T pallidum*. The RPR test results can become positive from treponemal infections as well as nontreponemal conditions. False-positives for nontreponemal tests occur in 1% to 2% of the US population and can be due to other infections, including hepatitis, varicella, measles, HIV, and mononucleosis; pneumonia; autoimmune disease; injection drug use; lymphoma; tuberculosis; malaria; and pregnancy. (8)(9) Because nontreponemal test results parallel disease activity, they are also used to monitor response to therapy. In congenital syphilis, the RPR and VDRL tests should show at least a 4-fold reduction in titer by the third month after treatment. (7) Fluorescent treponemal antibody absorption is the most commonly used treponemal confirmatory test, and it has sensitivity of 84% and specificity of 97% to detect primary syphilis. (7) Unlike nontreponemal tests, the titers from treponemal tests do not correlate with disease activity and cannot be used to monitor response to therapy.

Treatment

The *Red Book* has recommendations, summarized herein, about the evaluation of infants who are born to mothers with a reactive serologic test for syphilis. (2) Mothers who have positive results of nontreponemal testing, such as RPR or VDRL, should receive a treponemal test. A negative treponemal test result strongly excludes the possibility of congenital syphilis. If a mother has a reactive treponemal test during the pregnancy, then evaluation of the infant is influenced by the mothers' treatment of syphilis.

If a mother who had syphilis was adequately treated with penicillin before the pregnancy, has either a low VDRL titer of 1:2 or less or a low RPR titer of 1:4 or less during the pregnancy, and the infant has normal examination findings, then the infant does not need an evaluation or treatment.

If the mother with syphilis was treated with penicillin more than 4 weeks before delivery and there is no evidence of maternal reinfection during the pregnancy based on maternal syphilis titers, then the infant should be tested for syphilis by RPR/VDRL testing. If the infant has abnormal physical examination findings and the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemal test, then the infant needs to be evaluated and treated for congenital syphilis. Infants who have 4-fold or greater nontreponemal titers also need to be evaluated and treated. Evaluation includes complete blood cell count, CSF examination for cell count, protein, glucose, and quantitative VDRL testing. Other tests should be ordered if clinically indicated, such as chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response.

Penicillin remains the drug of choice for the treatment of congenital syphilis. Treatment for congenital syphilis includes aqueous penicillin G 50,000 U/kg every 12 hours if 1 week of age or younger or every 8 hours if older than 1 week. Another option is procaine penicillin G 50,000 U/kg intramuscularly as a single daily dose for 10 days. If the infant's nontreponemal test is not 4-fold or greater than the mother's nontreponemenal test, then the infant can be treated with one single dose of benzathine penicillin G 50,000 U/kg intramuscularly if the infant has normal physical examination findings. These infants' nontreponemal titers should be followed monthly until the results are negative.

If a mother is not treated with penicillin for syphilis during the pregnancy, if the treatment is not documented, if the treatment occurred 4 weeks or less before the delivery, if a nonpenicillin drug was used, or if there is a 4-fold or greater increase in maternal syphilis titers, then the infant needs to be evaluated for congenital syphilis. If the infant's physical examination findings are normal, if the syphilis evaluation results are normal, and if the infant's nontreponemal titers are the same or less than 4-fold the maternal nontreponemal titers, then the infant should be treated with 10 days of penicillin G, either intravenously or intramuscularly, or with a single dose of benzathine penicillin G 50,000 U/kg intramuscularly. Most experts recommend 10 days of treatment. If the infant's physical examination findings are abnormal, if the evaluation results are abnormal, or if the infant's nontreponemal titer is at least 4-fold greater than the maternal nontreponemal titer, then the infant should be treated with 10 days of either aqueous or procaine penicillin. All infants with congenital syphilis should also be tested for other coinfections, including HIV, hepatitis B, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.

Infants with skin or mucus membrane lesions should be cared for with gloves until 24 hours of therapy has been completed because nasal secretions, blood, and discharge from lesions are potentially infectious. (6) A mother with syphilis may continue to breastfeed her infant as long as she does not have active lesions on her breast. There is no evidence that syphilis is transmitted through human milk among mothers without active breast lesions. (10) Laboratory follow-up after treatment includes VDRL/RPR testing every 3 months until the titer is negative or has decreased at least 4-fold.

Lessons for the Clinician

- A negative maternal first-trimester test for syphilis during pregnancy does not negate the risk of infants developing congenital syphilis.
- The Centers for Disease Control and Prevention (CDC) recommends that all pregnant women be tested for syphilis during the first trimester of pregnancy. Women at high risk for syphilis, including those who live in areas of high syphilis morbidity, who are previously untested, or who had a positive screening test result, should be screened for syphilis during the third trimester and at delivery. (11)
- The rise of congenital syphilis presents an opportunity for pediatricians and neonatologists to partner with obstetricians, family practitioners, internists, and public health departments about how to best screen for and prevent congenital syphilis.
- As long as syphilis continues to spread among adults, congenital syphilis will continue to pose a serious threat for infants.

References

1. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(44):1241–1245
2. Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2015 Report of the Committee on Infectious Diseases*. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:755–768
3. Saloojee H, Velaphi S, Goga Y, Afadapa N, Steen R, Lincetto O. The prevention and management of congenital syphilis: an overview and recommendations. *Bull World Health Organ*. 2004;82(6):424–430
4. Wallace HE, Isitt CE, Broomhall HM, Perry AE, Wilson JD. Adverse pregnancy outcomes following syphilis treatment in pregnancy in the UK. *Int J STD AIDS*. 2016;27(12):1108–1113
5. Darville T. Syphilis. *Pediatr Rev*. 1999;20(5):160–164, quiz 165
6. Kollmann TR, Dobson SR. Syphilis. In: Wilson CBNV, Maldonado YA, Remington JS, Klein JO, eds. *Remington & Klein's Infectious Diseases of the Fetus and Newborn Infant*. 8th ed. Philadelphia, PA: Elsevier; 2016
7. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev*. 1995;8(1):1–21
8. Birnbaum NR, Goldschmidt RH, Buffett WO. Resolving the common clinical dilemmas of syphilis. *Am Fam Physician*. 1999;59(8):2233–2240, 2245–2246
9. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. *JAMA*. 2003;290(11):1510–1514
10. Lamounier JA, Moulin ZS, Xavier CC. Recommendations for breastfeeding during maternal infections [in Portuguese]. *J Pediatr (Rio J)*. 2004;80(5)(suppl):S181–S188
11. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1–137