

Positive Syphilis Serologies after Intravenous Immunoglobulin (IVIG) Treatment: A Diagnostic Confusion That Needs Emphasis

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CASE DESCRIPTION

The patient under evaluation was a 33-year-old pregnant woman who sought maternal fetal medicine consultation. Her previous neonate developed petechial rash and thrombocytopenia (platelet count: $2.4 \times 10^{10}/L$, reference range: 15 to $45 \times 10^{10}/L$). Following a referral to genetic counseling, the patient underwent testing for antihuman platelet antigen (HPA)-1a antibody and was positive, while her spouse underwent genetic testing indicating he did not have any variants in the ITGB3 gene encoding HPA-1a. Therefore, alloimmunization was confirmed and her previous neonate was diagnosed with neonatal autoimmune thrombocytopenia (NAIT). Although most cases of NAIT are mild, severe cases can cause intracranial hemorrhage that may result in death or long-term disability (1). Given the high risk of NAIT to the fetus, the patient received prophylactic intravenous immunoglobulin (IVIG) treatment of 1 g/kg/week and prednisone 0.5 mg/kg/day from 20 weeks of gestation, which were increased to 2 g/kg/week and prednisone 0.5 mg/kg/day from 32 weeks of gestation. The patient's early pregnancy screening for syphilis was performed by following a reverse algorithm (described later), which was initially negative for total antibody by enzyme immunoassay (Abbott). However, 6 weeks after starting IVIG treatment, the patient tested positive for syphilis total antibody. Subsequent testing revealed a negative result with the Venereal Disease Research Laboratory (VDRL) test (BD Diagnostics) and a positive result with the *Treponema pallidum* particle agglutination (TPPA) test (Fujirebio). Additional syphilis tests at 32 weeks of gestation (12 weeks after IVIG initiation) showed positive syphilis total antibody, inconclusive TPPA, and negative VDRL, whereas a test conducted at delivery (37 weeks of gestation or 17 weeks after IVIG initiation) showed positive syphilis total antibody and TPPA and negative VDRL. The IVIG treatment was discontinued at the time of delivery, and a repeat syphilis test performed 6 weeks later returned negative results for syphilis total antibody. TPPA and VDRL tests were not performed as they were not indicated based on the negative syphilis total antibody result.

The patient did not receive syphilis treatment during pregnancy as the positive syphilis tests were interpreted to be false positive. This was due to her negative early pregnancy syphilis screening test, low-risk sexual history, absence of a history of sexually transmitted infections or infectious symptoms throughout her current pregnancy, and the chronological relationship between her IVIG treatment and positive syphilis test results. Such interpretation was confirmed by the negative syphilis total antibody test after IVIG discontinuation.

QUESTIONS TO CONSIDER

1. How is commercially manufactured IVIG made and what it is composed of?
2. Can IVIG cause a false-positive syphilis test?
3. How can you differentiate between a true syphilis infection and IVIG-related false-positivity?

REFERENCE

1. Kamphuis MM, Paridaans NP, Porcelijn L, Lopriore E, Oepkes D. Incidence and consequences of neonatal alloimmune thrombocytopenia: a systematic review. *Pediatrics* 2014;133:715–21.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the December 2023 issue of *Clinical Chemistry*. To view the case and comments online, go to <https://academic.oup.com/clinchem/issue/69/12> and follow the link to the Clinical Case Study and Commentaries.

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