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Congenital syphilis after maternal macrolide therapy in a presumed penicillin allergic patient. Time to change the Chilean governmental normative

Sífilis congénita después de la terapia materna con macrólidos en paciente presuntamente alérgica a la penicilina. Hora de cambiar la normativa gubernamental chilena

Dear Editor,

Syphilis during pregnancy has a high risk of transmission from mother to fetus, especially during early phases of infection. Consequences are disastrous and include abortion, stillborn, premature birth, intrauterine growth retardation, perinatal death, and congenital syphilis[1].

Penicillin remains the drug of choice and is the only validated therapeutic option for maternal syphilis. Treatment failures are of rare occurrence and may be explained by reinfection, HIV infection, incomplete doses, or placental insufficiency impeding drug delivery to the fetus. Pregnant women allergic to penicillin impose a therapeutic challenge due to reported failures to prevent congenital infection after macrolide treatment either by a low transplacental passage of the antibiotic compound or antibiotic resistance[2,3]. Alternatives such as doxycycline and tetracycline are contraindicated. Due to the great dependence on penicillin to achieve a therapeutic success in the fetus, guidelines from the CDC and other countries advocate for penicillin desensitization every time is possible[4]. Contrary to this recommendation, the Chilean normative does not consider desensitization as an option and impose erythromycin treatment[5]. Unfortunately, this option was published as a rule and not as a guideline.

Recently, we observed a pregnant woman affected by latent syphilis with presumed penicillin allergy that was treated with 2 courses of oral erythromycin. Congenital syphilis was not prevented.

A 33-year-old, otherwise asymptomatic female, had a 1:2 routine VDRL screening test titer at the first trimester of her pregnancy confirmed by a reactive MHA/TP test. She reported being allergic to penicillin and received a 28-day course of erythromycin therapy. A serological follow-up performed one month later showed a VDRL titer increase to 1:4. A second course of oral erythromycin for 28 days was prescribed. Obstetric ultrasounds performed at 22 and 31 weeks of pregnancy did not show abnormalities. The couple was treated with benzathine penicillin G.

The patient was admitted at 36 weeks of pregnancy with labor symptoms but without fever or skin lesions. Her VDRL titer was 1:8. An ultrasound demonstrated fetal hydrops (Figure 1A) without cardiac abnormalities and a cesarean delivery was performed. At this time, a careful history on her penicillin allergy was obtained and discarded. One year before, she was treated by an acute febrile pharyngitis episode at an outpatient center with oral amoxicillin. She reported a non-itchy rash that affected the abdominal area but that appeared before the antibiotic course. After cesarean delivery, a penicillin desensitization protocol was applied successfully without any advert symptoms. Three weekly intramuscular doses of benzathine G penicillin (2.4 million IU each time) were prescribed, with the first dose applied before being discharged.

She gave birth to a preterm newborn appropriate for gestational age (36 weeks). The patient had an APGAR score 2-6 and was hyporeactive, hypotonic, bradychardic, and with axilar ecchymoses. She was admitted into the ICU with tachypnea, hepatomegaly, and bilateral lung crackles. At that time no skin lesions or peripheral edema were detected. The patient was connected to mechanical ventilation and evolved with respiratory failure with high oxygen requirements, metabolic acidosis, severe anemia, renal failure, hypocalcemia, hyponatremia and hypoalbuminemia. A chest x-ray showed right pleural effusion and pneumonia alba at the left side (Figure 1B). Besides supportive treatment, she received red blood cells transfusion and a combined antimi-

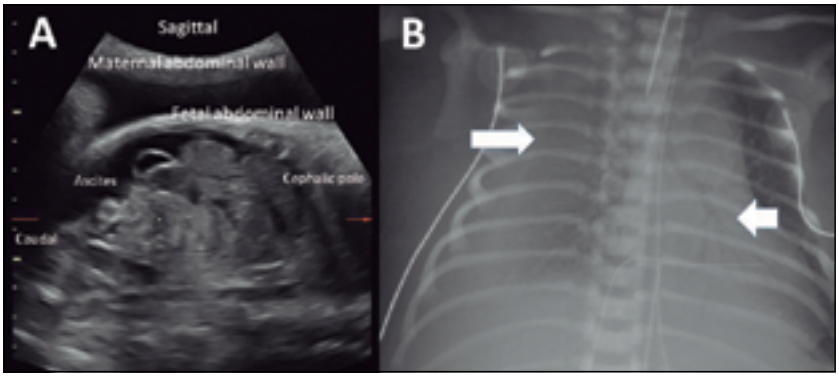

Figure 1. A: Sagittal view of an obstetric ultrasound taken at admission showing fetal ascites. Anatomical landmarks are indicated. **B:** Neonatal chest x-ray showing right pleural effusion with left lung compression (long arrow) and consolidation with air bronchogram at right (pneumonia alba; short arrow).

crobial treatment with intravenous sodium penicillin G (50,000 IU/Kg/day) and gentamicin (4 mg/kg/day). In the following days the patient evolved with edema, jaundice, hepatomegaly, non-nephrotic proteinuria and bilateral pleural effusion. A regenerative anemia persisted together with leukocytosis and thrombocypenia. A transthoracic echocardiogram was normal.

Peripheral blood VDRL titer showed higher values than those observed in her mother (1:16 and 1:64 lately), supporting the diagnosis of congenital syphilis with multisystemic involvement. On the fourth day, she presented vesiculobullous skin lesions, some of them involving palm and soles that evolved lately with peeling. Renal function as well as inflammatory and hematologic parameters improved. As blood cultures were negative, gentamicin was discontinued. A lumbar puncture was attempted several times without success and penicillin therapy was prolonged for 14 days. Complementary exams included fundoscopy, long-bones and skull x-rays and hearing screening studies that were normal. The patient was discharged alive after 26 days. Placental hystopathological analysis showed necrotizing funisitis.

We believe our case of congenital syphilis is well supported: a pregnant women with positive treponemal and non-treponemal tests, inappropriate antibiotic therapy with increasing VDRL titers during its application, compatible clinical findings both in the newborn and placental hystopatology, and finally, higher serological titers in the newborn when compared with those of her mother.

Early congenital syphilis as in this case, may include abdominal manifestations (hepatosplenomegaly, hepatitis, pancreatitis, ascites), hematological abnormalities (thrombocytopenia, leukocytosis), bone involvement (osteochondritis, periostitis), mucocutaneos manifestations (exanthema, pemphigus, mucous patches, pallor, petechia, purpura, jaundice), ocular disease (uveitis, chorioretinitis), and other manifestations such as fever, limphadenopathy, nephrotic syndrome, glomerulonephritis, and alveolar infiltration (pneumonia alba)[1]. In our case, several manifestations were present: fetal hydrops, hepatomegaly, hematological abnormalities, skin lesions, lung infiltrates, jaundice and necrotizing funisitis[6].

As stated above, the only effective treatment of syphilis during pregnancy is penicillin and international guidelines recommend a desensitization protocol every time is possible[4]. An updated version of the Chilean normative is urgently needed to avoid erythromycin use and damage to the fetus or newborn. Pharmacists are widely distributed along regional hospitals in Chile and have access and experience in desensitization protocols.

Penicillin is one of the most frequently compounds reported in allergies and desensitization was developed due to the pressing need to reintroduce it in a safe fashion in patients who had developed IgE type I hypersensitivity. The safety and efficacy of penicillin desensitization has been widely applied without reports of deaths or anaphylaxis even in high risk populations such as pregnant women who had positive penicillin allergy and required treatment for syphilis[7]. Patient is gradually exposed to escalating doses of a given drug and a transitory tolerance to the drug is obtained that assure treatment. In our patient, we use a protocol encompassing 3.5 hours[8].

In conclusion, a carefully history must be obtained in pregnant women with presumed penicillin allergy in order to confirm a hypersensitivity reaction. If confirmed, desensitization is the recommended step to assure penicillin treatment to a pregnant mother with syphilis as macrolides are not suitable alternatives. The Chilean normative should be modified in order to include penicillin desensitization protocols.

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