Neonatal lupus erythematosus with cholestatic hepatitis

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Neonatal lupus erythematosus (NLE) is an uncommon passive autoimmune disease in which maternal autoantibodies are transferred across the placenta. These antibodies can be detected in the affected infant for the first few months of life. The major clinical manifestations of NLE are cutaneous lupus lesions, congenital heart block, and hematologic problems (e.g. anemia, thrombocytopenia). During the past decade, however, it has become clear that hepatobiliary disease may also occur as a manifestation of neonatal lupus erythematosus. We report a case of neonatal lupus erythematosus in a male infant who had lupus hepatitis with jaundice in addition to cutaneous lupus, anemia, and thrombocytopenia. Other diseases in the differential diagnosis of conjugated hyperbilirubinemia, including metabolic, infectious, and inherited anatomic conditions were all ruled out. The infant had a high titer of antinuclear antibodies (titer 1:640) with a speckled pattern, anti-Ro/SSA and anti-La/SSB antibodies, and no anti-dsDNA antibodies. Treatment with prednisolone (2 mg/kg/day) for 14 days resulted in dramatic improvement of the thrombocytopenia. Hemoglobin and bilirubin returned to normal 2 months later, and transaminases were normal by 10 months of age.

Key words: Cholestasis, hepatitis, lupus erythematosus, newborn infant

Neonatal lupus erythematosus (NLE) is a passive autoimmune disease in which maternal autoantibodies are transferred across the placenta. These antibodies can be detected in the affected infant for the first few months of life. The major clinical manifestations of NLE are cutaneous lupus lesions, congenital heart block, and hematologic problems (e.g. anemia, thrombocytopenia and leukopenia). During the past decade, however, it has become clear that hepatobiliary disease may also occur as a manifestation of NLE [1]. The diagnosis of NLE liver disease is based on bilirubin levels and liver enzyme abnormalities consistent with cholestasis and hepatitis in a case in which metabolic, infectious, and inherited anatomic liver abnormalities have been ruled out. We report a case of NLE hepatitis in a 55-day-old male infant.

Case Report

A male patient was born at 38 weeks of gestation to a gravida 1, para 1 mother via vaginal delivery. The birth weight was 2690 g and length 50 cm. His mother was 31 years old and had a history of systemic lupus erythematosus (SLE) regularly treated with hydroxychloroquine and prednisolone. During pregnancy, she had a high titer of antinuclear antibodies (1:640) with a speckled pattern, positive anti-Ro/SSA anti-La/SSB antibodies, but no anti-dsDNA antibodies. C3 (133 mg/dL) and C4 (33 mg/dL) were normal, and there were no anticardiolipins detected.

After birth, the boy was well except for some red spots on the face which did not concern his mother. However, at the age of 55 days, the infant was brought to the hospital due to jaundice for over a week (Fig. 1). His level of activity had been fair. He had been feeding well, taking 14% regular formula, 90 mL every 3 h. He had not been breast fed, had no clay-colored stool or fever, and had not been given any drugs. The father, mother and the infant were all blood group B.

On admission, physical examination showed pale conjunctiva, icteric sclera, and generalized jaundice. There were multiple annular skin lesions in the periorbital area and on the trunk and extremities. These lesions had an erythematous, scaly border with a depressed, ecchymotic central area.

Hemogram revealed anemia (hemoglobin 6.7 g/dL) and thrombocytopenia (platelets 24,000/mm³). The prothrombin time and partial thromboplastin time were not prolonged. Direct hyperbilirubinemia (direct bilirubin 6.1 mg/dL, total bilirubin 13.3 mg/dL), cholestatis (alkaline phosphatase 423 U/L, gamma-glutamyl transferase 370 U/L) and elevated transaminases (aspartate aminotransferase 199 U/L, alanine aminotransferase 92 U/L) were found. No culture or serologic evidence...
Fasting abdominal ultrasound revealed a normal-sized liver and gall bladder, no bile duct dilation or cysts, and no sludge in the biliary tree. Technetium 99m-labelled diisopropyliminodiacetic acid analogue (DISIDA) cholescintigraphy showed poor hepatic uptake at 5 minutes without tracer flow into the intestine up to 24 hours. This indicated slow hepatic uptake of the isotope and no excretion into the bowel, consistent with hepatocyte dysfunction. There was a high titer of antinuclear antibodies (1:640) with a speckled pattern. Anti-Ro/SSA antibodies and anti-La/SSB antibodies were positive and anti-dsDNA antibodies were negative. NLE with cholestatic hepatitis, anemia, and thrombocytopenia was diagnosed. Prednisolone (2 mg/kg/day) was prescribed for 14 days combined with ursodeoxycholic acid and silymarin. The patient’s parents were advised to avoid exposing the infant to the sun. He was followed in the outpatient department and gradually improved. Platelet count increased dramatically within half a month to 103,000/mm³ and hemoglobin normalized within 2 months, to 10.7 g/dL. By the end of 2 months, both the jaundice and discoid rash had resolved. At 10 months of age, liver function tests were all within the normal range (Fig. 2).

Discussion

NLE is an uncommon disease caused by passage of anti-Ro/SSA and/or anti-La/SSB or anti-U1RNP maternal autoantibodies across the placenta. The incidence of NLE is about 1 in 20,000 live births and it has been found of pathogens that might be responsible for hepatitis, including hepatitis A, B and C viruses, *Toxoplasma* spp., rubella, cytomegalovirus, syphilis, herpes simplex, or Epstein-Barr virus. There was no growth on blood or urine culture. Tests for the following metabolic diseases were all negative or normal: glucose-6-phosphatedehydrogenase, hypothyroidism, galactosemia and phenylketonuria.
reported in a number of different ethnic groups [2]. Ninety eight percent of NLE babies have anti-Ro antibody [3], but only 1 to 2% of mothers with SSA/Ro antibodies have babies with NLE, regardless of whether the mothers are symptomatic [4]. Overall, 13% of mothers with SLE have babies who develop NLE [5]. Of these mothers, 40 to 60% are asymptomatic, while the remaining women have clear evidence of SLE, Sjögren’s syndrome, or undifferentiated connective tissue disease [6].

The earliest report of apparent hepatic involvement in NLE was by McCuistion and Schoch [7] in 1954. However, the hepatomegaly and transient elevation of hepatic transaminases were not thought to be clinically important [7,8]. Lee et al [1] reported that approximately 10% of cases of NLE have significant hepatobiliary involvement. The actual incidence was probably underestimated because jaundiced neonates may have been assumed to have physiologic jaundice. Hepatomegaly with liver function test abnormalities may be attributed to congestive heart failure or extramedullary hematopoiesis. Weston et al [9] noted that crusted skin lesions are more likely to occur in male babies with NLE and are highly associated with hepatic and hematologic abnormalities.

The major antibodies in NLE target SSA/Ro, SSB/La and U1RNP antigens. SSA/Ro consists of a 52-kDa and a 60-kDa polypeptide while SSB/La consist of one 47- to 50-kDa polypeptide. These Ro and La antigens are widely distributed in the skin, fetal cardiac conducting system, myocardium, and other organs, including the liver. The skin rash of NLE usually occurs from hours to several days after delivery, presumably in response to exposure to sunlight. Ultraviolet radiation and estradiol have been found to promote the appearance of Ro antigen on the surface of keratinocytes [10]. Autoantibodies also play a role in mediating platelet destruction or suppression of bone marrow production in NLE. There is evidence that thrombocytopenia caused by specific autoantibodies may be related to suppression of thrombopoiesis, analogous to red cell aplasia [11]. Similarly, the maternally-derived autoantibodies are thought to be responsible for neonatal hepatitis in NLE [12]. Lee et al [13] found immunoglobulin G (IgG) deposition in an NLE liver which reacted with anti-SSA/Ro-containing serum in guinea pigs. Therefore, the anti-SSA/Ro autoantibody seems to play an important role in liver damage.

The characteristic skin lesions of NLE have a predilection for the upper and lower eyelids, giving rise to a typical “owl-eye” appearance in the majority of babies. These lesions may be erythematous, annular or elliptical, raised or flat, sometimes with a fine scale. In addition to the periorbital area, the rash frequently involves other areas of the face, the scalp, trunk and extremities. As noted above, these lesions may develop from hours to several days after delivery, following sun exposure.

Despite being less common, hepatic involvement is a well-documented manifestation of neonatal lupus characterized by elevated transaminases, cholestatic liver disease with conjugated hyperbilirubinemia in the absence of structural abnormalities, and/or hepatosplenomegaly. The usual finding is conjugated hyperbilirubinemia with mild or no elevation of aminotransferases occurring in the first weeks of life and mild elevations of aminotransferase at approximately 2 to 3 months old [1]. NLE liver disease may present as an isolated disorder or in association with cutaneous lesions, congenital heart block, or any other manifestations of NLE. It may be the only manifestation of NLE in the baby of a mother with anti-Ro and anti-La autoantibodies [8]. In patients with idiopathic neonatal hepatitis, i.e., those in whom all other known causes of cholestasis have been excluded, NLE hepatitis should be considered.

The diagnosis of NLE liver disease requires bilirubin and liver enzyme levels consistent with cholestasis and hepatitis, along with detection in the infant of maternal antibodies to SSA/Ro and/or SSB/La. The differential diagnosis of conjugated hyperbilirubinemia includes a number of metabolic, infectious, inherited anatomic conditions, and idiopathic neonatal hepatitis (INH). One of the most common conditions in patients with a diagnosis of neonatal cholestasis is INH. It is quite likely that some cases labeled as INH have, in fact, been due to NLE [14]. NLE may cause intrahepatic cholestasis severe enough to mimic extrahepatic biliary atresia. Histological liver abnormalities in NLE are similar to idiopathic neonatal giant cell hepatitis with mild bile duct obstruction, occasional giant cells, and mild portal fibrosis [12]. Typically, such patients are unable to excrete bilirubin into the bowel on DISIDA scan. Liver biopsy is usually not indicated and should be reserved for infants with clinical evidence of severe dysfunction or with persistent, moderate dysfunction [15].

Our patient had typical cutaneous features of NLE with the classic “owl-eye” distribution and his mother had an obvious history of SLE. Anemia and severe thrombocytopenia were also present. The presence of
NLE with cholestatic hepatitis

anti-Ro/SSA and anti-La/SSB antibodies with a high antinuclear antibody titer helped confirm the diagnosis. It has been observed that elevation of antinuclear antibody titer may be an important risk marker for liver involvement in NLE [12,16]. This is compatible with the findings in our patient.

In general, strict avoidance of sun exposure and topical steroids are recommended for patients with cutaneous NLE. Abnormal liver function usually resolves spontaneously, with full recovery within 6 to 12 months in 80% of cases [12]. Although the hematologic problems usually resolve in 2 to 3 weeks without treatment, they can persist in some cases and be so severe as to be life-threatening. There is evidence that steroids are beneficial for patients with persistent cholestasis and pancytopenia. Lee et al [13] used systemic steroid in a case of NLE with persistent liver disease and thrombocytopenia with good results. Seip [17] reported a case of NLE-induced thrombocytopenia unresponsive to exchange transfusion but resolving with 1 month of steroid therapy. Intravenous immune globulin (1 g/kg/day) and steroids (dexamethasone 0.3 mg/kg 3 times per day) have also been used successfully in treating NLE with microvascular hemolysis [18]. Our patient received prednisolone for 14 days with dramatic improvement of thrombocytopenia. The anemia and bilirubin resolved 2 months later, and transaminases were completely normal by 10 months.

The long-term prognosis is usually good in NLE with hepatic involvement, unless liver failure occurs during gestation or in the neonatal period [1]. There have been no reported instances of late liver failure or cirrhosis developing in children with NLE hepatic involvement [15]. In the only reported case of an infant followed with repeat liver biopsy because of persistent liver function abnormalities, there was persistence of mild fibrosis but a good long-term outcome [15]. Cutaneous lupus rashes usually disappear several months after birth without scar or atrophy. Anemia may resolve spontaneously without blood transfusion. In NLE, congenital complete heart block is the main cause of death.

In summary, NLE should be considered in a jaundiced infant with conjugated hyperbilirubinemia, particularly if there are other features suggestive of NLE.

References