Neonatal lupus erythematosus presenting with cholestatic hepatitis: a case report and review of the literature

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Neonatal lupus erythematosus (NLE) is a disease primarily characterized by cardiac and/or cutaneous involvement. Hepatic, hematological, neurological and pulmonary involvement are rare manifestations and normally considered as mild and transient complications. But recent studies have shown more frequent hepatic involvement in NLE. We report a two month-old male infant, born to a clinically asymptomatic mother, presenting with significant hepatic involvement and annular, erythematous plaques with hyperkeratotic borders at the eyebrow region and anterior surface of trunk. Both the infant and his mother were positive for anti-Ro (SS-A) and anti-La (SS-B).

Key words: neonatal lupus erythematosus, cholestatic hepatitis.

Neonatal lupus erythematosus (NLE) is a disease primarily characterized by cardiac and/or cutaneous involvement. Hepatic, hematological, neurological and pulmonary involvement are rare manifestations and normally considered as mild and transient complications. These children have mothers with systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), other systemic rheumatic diseases, or their mothers are asymptomatic. NLE is characterized by the transplacental passage of auto antibodies, in particular anti-Ro (SS-A), and anti-La (SS-B), or both, from the mother to the fetus[1]. We report a case of NLE who presented with cholestatic hepatitis.

Case Report

A two-month-old male infant, 15 days after birth, presented with annular, erythematous plaques of several millimeters in diameter with sharp, hyperkeratotic borders at the eyebrow region and anterior surface of trunk (Fig. 1). Physical examination revealed hepatosplenomegaly and jaundice. Liver function studies revealed a mild increase of aspartate aminotransferase (AST: 403 U/L), alanine aminotransferase (ALT: 155 U/L), and gamma glutamyl transpeptidase (GGT: 358 U/L). His bilirubin levels, with a predominance of direct billirubin (9.1 mg/dl), were also increased. A hepatobiliary scintigraphy showed a decreased hepatic uptake with no passage through the intrahepatic bile

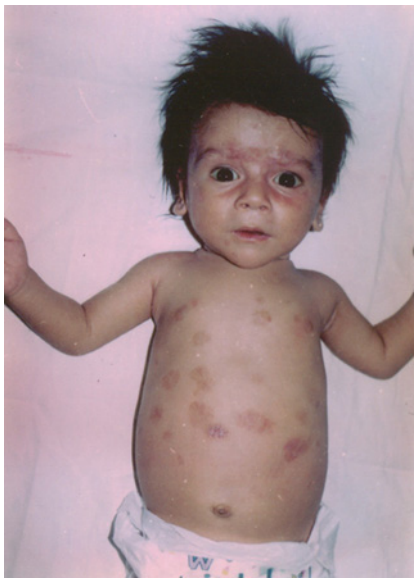

Fig. 1. A two-month-old male infant presented with annular, erythematous plaques of several millimeters in diameter with sharp, hyperkeratotic borders at the eyebrow region and on the anterior surface of the trunk.

ducts. His complete blood count, electrocardiogram and echocardiography were normal. No proteinuria was seen in urine analysis. Histopathological examinations of the skin biopsy showed hyperkeratosis in epidermis, basal cell liquefaction, a mild perivascular and periadneal mononuclear infiltration, minimal edema, and dermal collagen degeneration in dermis (Fig. 2). Immunohistochemical staining of the skin specimen showed IgG deposition at the dermoepidermal junction, and granular deposition of IgG, IgA and IgM at the vascular wall. Both the infant and his mother were positive for anti-Ro (SS-A) and anti-LA (SS-B). In addition, the mother had positive antinuclear antibodies (ANA). He was treated with topical steroid creams.

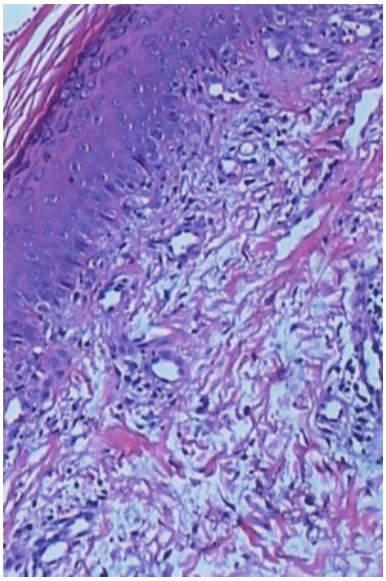

Fig. 2. Epidermal hyperkeratosis, basal cell liquefaction, and dermal perivascular and periadneal lymphocyte and plasmocyte infiltration are seen; degeneration at dermal collagen is also noted (HE X 200).

When the patient was four months old, AST, ALT and, direct bilirubin levels were 179 U/L, 104 U/L and 3.8 g/dl, respectively. Hepatosplenomegaly and milder skin lesions were still present. Systemic steroid treatment was started with a dose of 2 mg/kg/day. One month after beginning systemic steroid therapy, direct bilirubin level had decreased to 0.65 g/dl and hepatosplenomegaly regressed, but AST and ALT levels were still high. At the 2nd month of systemic steroid therapy, due to development of pneumonia and cushingoid appearance. Systemic steroid treatment was stopped until control of infection was achieved. At 4th month of therapy anti-La (SS-B) was negative, and splenomegaly and skin lesions had resolved. Hepatomegaly and high levels of AST and ALT were still present. Systemic steroid dose was halved to 1 mg/kg/day and two weeks later continued with a dose of 1 mg/kg every two days. Because of persistent hepatomegaly and elevated AST and ALT levels, liver biopsy was done, and histopathological examinations of the liver biopsy showed nodular regenerative hyperplasia and microvesicular fatty degeneration (Fig. 3). At 10th month of treatment (age: 14 months), (Fig. 4), anti-Ro (SS-A) was negative, and AST and ALT levels had regressed to 60 U/L, respectively. Tapering of systemic steroid therapy was started. During follow-up of the patient, no cardiac, hematological or any other abnormal findings was observed.

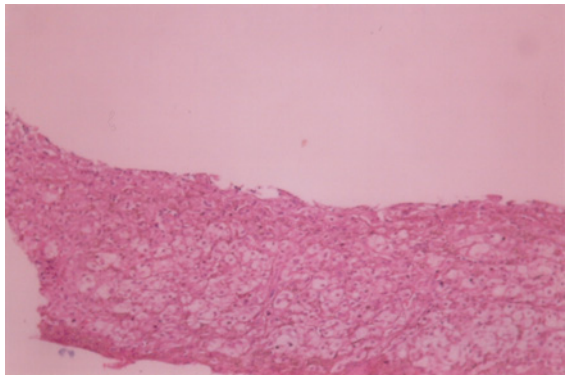

Fig. 3. Nodular regenerative hyperplasia and microvesicular fatty degeneration in the liver (HE X 100).

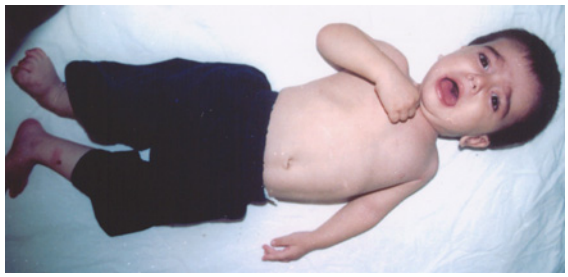

Fig. 4. A picture of the patient at 10th month of treatment (aged 14 months), showing complete resolution of the skin lesions.

His mother had only a positive ANA test as a sign of SLE. She is currently being followed for SS and/or SLE/SS due to positive anti-Ro (SS-A) and anti-La (SS-B).

Discussion

Neonatal lupus erythematosus is a rare disease of cutaneous lupus, congenital complete heart block (CHB), or both, and/or other systemic manifestations, which appear in children of women with SLE, SS, other systemic rheumatic diseases, or in children of asymptomatic mothers[1]. NLE is characterized by the transplacental passage of auto antibodies, in particular anti-Ro (SS-A) and anti-La (SS-B), or both, from mother to fetus. In our case, the mother was asymptomatic and both the boy and his mother were positive for anti-Ro (SS-A) and anti-La (SS-B).

Almost half of NLE patients have CHB, and two-thirds of these habies are females. The CHB is complete in most reported cases. Other described rare cardiac inflammatory forms are pericarditis, myocarditis, cardiomyopathy and Libman-Sacks endocarditis[1]. CHB carries a significant mortality (15-30%) and morbidity: two-thirds of children require permanent pacing[2].

Approximately 40-50% of patients with NLE have cutaneous findings, and three-fourths are females. The skin rashes consist of annular, erythematous, scaly, hyperkeratotic, macular, papular or plaque-like lesions with central clearing on mostly sun-exposed areas, such as face, scalp, trunk and extremities. These rashes are similar to those seen in SLE and/or discoid lupus erythematosus. Cutaneous manifestation of NLE usually does not require much treatment beyond the avoidance of sun exposure and use of sunblock and topical hydrocortisone cream. They typically last for 2-6 months and disappear without leaving a scar; sometimes minimal atrophy, telangiectasis, or hyperpigmentation is reported. The skin biopsy of rashes reveals findings of hyperkeratosis, follicular plugging, acanthosis, atrophy, and liquefactive degeneration of keratinocytes[1,3,4].

In our case, skin lesions were annular, hyperkeratotic with sharp borders and located on face and trunk, and appeared in the first month of life. The skin biopsy examination with histopathological and immunohistochemical studies confirmed the diagnosis of NLE. Skin lesions repond to moderate-to-potent topical steroid treatment.

In previous studies, liver involvement in NLE has been mentioned as a rare condition. A total of 294 babies with NLE had been described by the end of the 1991. Of these babies, 54.4% had CHB, 37.1% had cutaneous NLE, 7.1% had both, and only 1.4% had other manifestations. Hepatic involvement was seen in 7.8% of patients having cardiac and/or cutaneous involvement[1]. In recent studies it has been reported that at least 10% of NLE cases have liver involvement[5]. Rosh et al[6]. reported hepatomegaly and elevation of transaminases in 20-40% of infants with NLE. Lee et al[7]. found hepatic disease in 4 of 35 (114%) NLE patients. Laxer et al[8]. reported that the liver involvement is more frequent than previously described. Especially in prospective studies, mothers of infants with idiopathic neonatal hepatitis should be explored for auto antibodies[8]. In hepatic involvement, hepatomegaly, splenomegaly, elevations of transaminases, jaundice, cholestasis, cirrhosis and serious gastrointestinal bleedings can be seen. But the major clinical picture is cholestasis[5,7]. The liver biopsy shows non-infectious hepatitis, neonatal giant cell hepatitis, intra and extracellular cholestasis, ductal and ductular hyperplasia, portal septal fibrosis, cirrhosis, excessive extramedullary hematopoiesis, and IgG deposits[1,7].

Lee et al.[5] described three clinical variants of hepatobiliary disease in their recent series: 1- severe liver failure presenting during gestation or in the neonatal period, often with the phenotype of neonatal iron storage disease; 2- conjugated hyperbilirubinemia with mild or no elevations of aminotranferases, occurring in the first few weeks of life; and 3- mild elevations of aminotransferases occurring at approximately two to three months of life. They reported that the prognosis for children in the latter two categories is excellent, and frequently they do not need treatment[5]. Evans et al[9]. reported that patients with hepatic involvement heal spontaneously in six months[9]. The liver biopsy revealed nodular regenerative hyperplasia and microvesicular fatty degeneration. Nodular regenerative hyperplasia is a rare liver biopsy finding of SLE patients. Matsumota et al[10]. found nodular regenerative hyperplasia in liver biopsy materials taken from 3 of 52 SLE patients. Colina et al.[11] defined autoimmune disease in 5 (20.8%) of 24 patients who had liver pathology findings of nodular degenerative hyperplasia. Liver biopsy findings of our case were compatible with NLE, but there was no sign of cholestasis. We should keep in mind that the liver biopsy of the case

was performed during steroid treatment and elevated direct bilirubin level had decreased to normal before the biopsy.

The literature on long-term follow-up of children with NLE is limited. Fox et al[12]. described a patient with cutaneous lupus as a neonate who developed SLE at[19] years of age. Jackson and Gulliver[13] reported an infant with NLE who developed SLE at 13 years of age. Neiman et al[3]. followed up affected children for a mean period of 77 months (range, 1-204 months). In four children, signs or symptoms of autoimmune disease were noted. One child developed Hashimoto's thyroiditis at seven years of age. Two developed juvenile rheumatoid arthritis (at 2 years and 5 years). Another developed Raynaud's phenomenon.

Buyon et al[14]. reported that in 37 (71%) of 52 subsequent pregnancies, no signs of NLE were reported in the children. Ten (19%) pregnancies resulted in a second child with a skin rash. In three additional families, the next younger siblings having cutaneous manifestation of NLE was seen in 25%. Twenty of the 47 mothers became pregnant after the birth of the child with cutaneous NLE. Seven (35%) children had no manifestations of NLE. Notably, six (30%) subsequent children had CHB, two in isolation and four in association with a skin rash. Seven (35%) of the subsequent children had cutaneous manifestations alone[3]. Julkunen et al[15]. reported that the risk of having a child with CHB after a previous birth of an affected child (with CHB) was 8%.

Both this case and his mother are being followed for development of possible disorders.

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