SKIN

IN-DEPTH REVIEW

Neonatal Lupus Erythematosus: A Case Report and Review of the Literature

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ABSTRACT

Neonatal lupus erythematosus (NLE) is a rare autoimmune condition caused by transplacental passage of maternal IgG autoantibodies to the fetus. It often presents with erythematous annular lesions on the scalp and periorbital area that appear after exposure to sunlight. Clinicians should be aware of the broad manifestations of neonatal lupus erythematosus, including cutaneous, cardiac, hematologic, hepatic and neurological manifestations. We present a case of cutaneous neonatal lupus erythematosus with rare central nervous system findings and perform a literature review on the subject.

CASE REPORT

A 3-month-old female patient with a past medical history of premature birth (34 weeks) and intrauterine growth restriction, initially presented to the Emergency Department due to concern over poor feeding and labored breathing. While in the ED, the patient arrested, requiring cardiopulmonary resuscitation and intubation, and was subsequently admitted to the intensive care unit. The patient's presenting symptoms were accompanied by a rash which had appeared following minimal sun exposure 6 weeks prior to presentation. The patient had no family history of diagnosed autoimmune disorders, although the mother experienced a facial rash during pregnancy and had a history of recurrent miscarriages, frequent dental caries, and chronic dry eyes, consistent with Sjogren's syndrome-like symptoms.

Physical examination was remarkable for thin scaly pink annular papules and plaques on the scalp, forehead, malar cheeks, arms, trunk, and extremities (**Figure 1**). A punch biopsy demonstrated vacuolar interface dermatitis, dyskeratosis, and focally increased mucin (**Figure 2 & 3**). Lab work was remarkable for the presence of anti-SSA and anti-SSB antibodies, as well as elevated anticardiolipin and B2 glycoprotein antibodies. The histologic findings and laboratory abnormalities confirmed the diagnosis of neonatal lupus erythematosus. Increased levels of alanine transaminase (60, normal range 0-40 U/L) and aspartate transaminase (97, normal range 1-40] U/L) were also present. Ultrasound of the head showed enlargement of extra-axial CSF spaces, with subsequent CT imaging of the brain noted widened subarachnoid space, diffuse white matter atrophy and chronic bilateral hygromas. These findings were confirmed with an MRI of the brain, which

revealed volume loss of both grey and white matter, widened subarachnoid space and bilateral subdural collections. Brain myelination was found to be normal for the patient's age and no evidence of vasculopathy was found. Further workup for Menke's disease and glutaric aciduria was negative. A neonatal crisis panel showed no genetic abnormalities, though an inherited variant of uncertain significance in the IGF1R gene was found. No evidence of arrhythmia or conduction disease on ECG or telemetry were found, and an ophthalmological exam which showed no inflammation of the optic nerve.

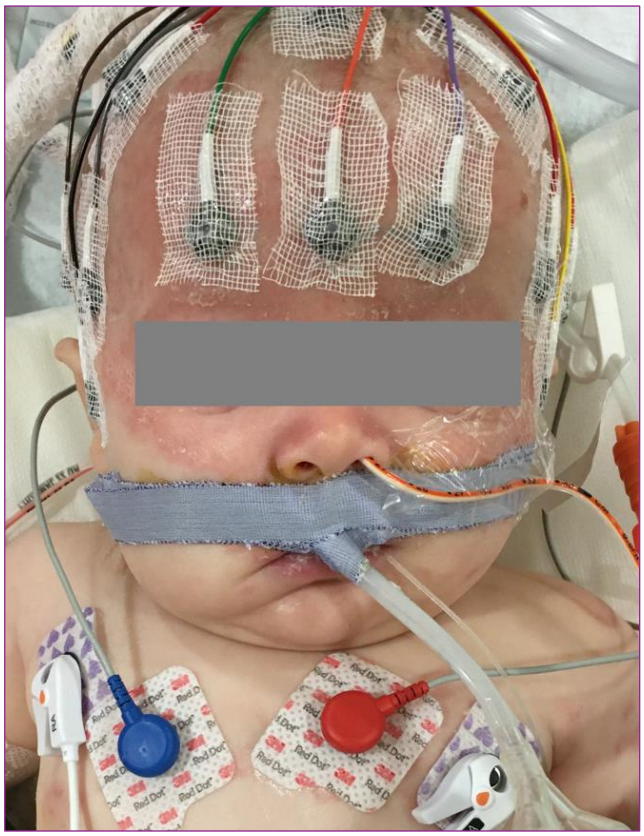

Figure 1. Thin scaly pink annular papules and plaques on the scalp, forehead, malar cheeks, arms, trunk, and extremities

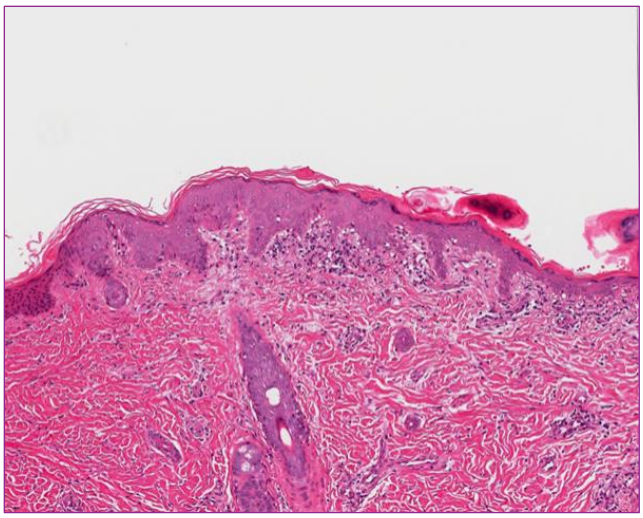

Figure 2. Vacuolar interface dermatitis, dyskeratosis, and focally increased mucin

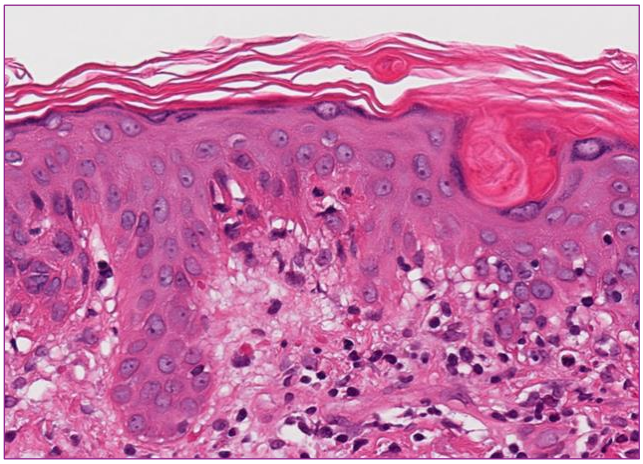

Figure 3. Closer view of punch biopsy

NEONATAL LUPUS ERYTHEMATOSUS

Neonatal lupus erythematosus (NLE) is an autoimmune disease caused by transplacental passage of maternal IgG autoantibodies against intracellular ribonucleoproteins Ro (SSA) and/or La (SSB) to the fetus. The pathogenesis of NLE is unclear, although evidence suggests the maternal antibodies bind to specific cells in neonatal organs and cause inflammation. The inflammation can progress to fibrosis and calcification, especially in the conduction system of the heart.[1] The passive antibodies

are most frequently associated with maternal systemic lupus erythematosus (SLE) or Sjogren's syndrome, but are often present in the absence of maternal autoimmune disease or autoimmune-like symptoms.[2] Approximately 50% of asymptomatic mothers with these autoantibodies end up developing symptoms suggestive of autoimmune disease within years of delivery, with the most common symptoms being dry eyes, dry mouth, Raynaud's syndrome, or rashes.[3]

NLE most commonly causes cutaneous and cardiac manifestations, though hepatic,[4] neurologic,[5] and hematologic[6] manifestations have been described. Complete heart block is a serious complication of NLE that can develop before or after the time of diagnosis.[7,8] Most clinical manifestations of the disease progressively resolve as the transferred maternal antibodies are cleared and disappear 6-9 months after birth.[9,10]

After excluding conditions that present similarly, the diagnosis of NLE is established when compatible clinical manifestations and anti-Ro (SSA), anti-La (SSB), or anti-ribonucleoprotein (RNP) antibodies are present. The anti-Ro (SSA) antibody targets proteins of the Ro family, namely Ro52 and Ro60. Ro52 is a regulatory protein that negatively moderates the inflammatory response. Acting separately from Ro52, Ro60 regulates the fate of misfolded RNA within cells.[11] The anti-La (SSB) antibody targets the La protein, which is involved in numerous aspects of RNA metabolism.[12,13] Cases of NLE with anti-U1 RNP (small nuclear ribonucleoproteins) antibodies and no anti-Ro (SSA) or anti-La (SSB) have been reported and typically present with cutaneous findings and lack cardiac manifestations.[14,15]

The cutaneous manifestations of NLE commonly involve erythematous annular lesions or arcuate macules with slight central atrophy and raised active margins with a predilection for the scalp and periorbital area (Figure 1).[16] The distinctive periorbital distribution is often described as an 'owl eye' or 'eye mask' appearance.[17] The lesions occasionally exhibit scaling and sometimes affect the palms, soles, or diaper area.[18,19] Cutaneous manifestations may be present at delivery but are most often observed after exposure to ultraviolet light anywhere from a few days to weeks after birth.[20] Though uncommon, prominent lesions may undergo blistering or crusting. Lesions are typically nonscarring and remain for a few weeks to months before resolving, though atrophic lesions may persist even after the levels of maternal antibodies have fallen.[17] Approximately 10% of NLE patients may exhibit telangiectasia on the face or genitals between 6 and 12 months of age.[21]

The polycyclic skin lesions of NLE can present similarly to urticaria, tinea corporis, seborrheic dermatitis, annular erythemas of childhood, Langerhans cell histiocytosis, and autoinflammatory syndromes. Urticarial lesions are raised, pruritic, and erythematous, and can be distinguished from NLE lesions by their transient nature and raised centers. In contrast to urticarial lesions, NLE lesions tend to have atrophied center.[22] Lesions of NLE can be distinguished from tinea corporis by having less scale and absent fungal hyphae on a potassium hydroxide (KOH) preparation of skin scrapings.[22] In addition to its typical manifestation of non-inflammatory greasy yellow scales on the scalp, informally referred to as "cradle cap," seborrheic dermatitis can manifest as yellow greasy scales on the face that are accompanied by erythematous, scaly, salmon-colored plaques. The latter manifestation may appear similarly to NLE lesions, though NLE lesions are less scaly and darker purple in color.[22,23]

Annular erythemas of childhood are rare diseases such as erythema annulare centrifugum, familial annular erythema, erythema multiforme, and annular erythema of infancy. These diseases can be differentiated from cutaneous NLE by their migrating course, lack of central atrophy, presence of peripheral lesions, long duration, and unusual history of new lesion development after the disappearance of lesions at different locations.[24]

Langerhans cell histiocytosis may present with pustular, purpuric, petechial, vesicular, or papulonodular lesions, and may appear similar to those of NLE. The majority of patients with Langerhans cell histiocytosis are found to have multi-system disease affecting the liver, spleen, and/or bone. Additionally, skin biopsy will distinguish lesions of Langerhans cell histiocytosis from those of NLE.[22,25]

Autoinflammatory diseases may closely resemble cutaneous NLE manifestations, but commonly present with multisystem involvement and severe fevers. Autoinflammatory diseases most likely to resemble NLE include stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI), chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome (CANDLE syndrome), autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID), and C1q deficiency.[22,26]

The histopathological findings of NLE skin lesions commonly resemble those of subacute cutaneous lupus erythematosus and include vacuolar alterations at the dermo-epidermal interface and adnexal structures.[27] Urticaria-like lesions that have superficial and deep perivascular and periadnexal lymphocytic infiltrates can also occur.[27]

Hepatic manifestations of NLE range from liver failure and hepatitis to asymptomatic elevated liver enzymes, cholestasis, and mild hepatosplenomegaly.[4,17] Hyperbilirubinemia and increased liver transaminases can occasionally be the only presentation of NLE.[28] When NLE causes liver failure *in utero* or at birth, the clinical presentation is similar to that of neonatal storage disease or neonatal hemochromatosis.[17] Hepatic manifestations other than liver failure are associated with a good prognosis and undergo spontaneous resolution with no long-term sequelae.[17]

Though uncommon, neurologic manifestations of NLE such as hydrocephalus and macrocephaly have been described.[5] Imaging with CT scans has shown that infants with NLE can have reduced attenuation of white matter, increased subarachnoid space, ventriculomegaly, and basal ganglia calcifications, with normal grey matter.[2,29] There is currently no literature on brain MRIs in infants with NLE.[2] A case of abnormal periventricular white matter signals on MRI. in a patient with a history of NLE has been reported, though the patient was 3 years old.[30] Transient and permanent vasculopathies of the central nervous system due to NLE have also been reported, though these findings are less common.[31] Despite CT findings, clinical findings of neurologic disease are typically absent, though spastic paraparesis, myelopathy, focal seizure, and hydrocephalus have been reported.[2,30] The neurological imaging findings in our patient are unique because volume loss of grey matter was present, in addition to the previously reported findings of white matter volume loss, widened subarachnoid space, and bilateral subdural collections on imaging.

The mechanism for these subclinical central nervous system findings remains unclear, but it is likely a transient phenomenon that occurs due to maternal antibodies.[30]

Congenital heart block is a well-known and serious complication of NLE, as the mortality rate for complete congenital heart block is 4% to 29%.[32,33] In fact, many cases of NLE are diagnosed after noting bradycardia in the fetus or newborn.[1] Heart block, which occurs due to autoimmune injury and secondary fibrosis of the atrioventricular (AV) node and its surrounding tissue, usually happens *in utero* during the second or third trimester. Cases of first- or second-degree heart block progressing to complete heart block have been reported.[34] While non-cardiac manifestations of NLE are generally transient and fade as maternal antibodies are cleared from the blood, the effects on the conduction system are permanent. Approximately two-thirds of patients with autoimmune congenital heart block receive a pacemaker before reaching adulthood.[35]

Though congenital heart block is the most widely recognized cardiac manifestation of NLE, many other cardiac manifestations have been recognized. These other cardiac manifestations include diffuse myocardial disease, structure defects, and other electrophysiologic anomies.[32] Diffuse myocardial disease can occur with or without conduction disturbances, suggesting it may be a separate manifestation from the congenital heart block manifestation of NLE.[36] While heart block is often diagnosed before or at birth, myocardial disease may not be detected until months or years after birth.[17] The clinical symptoms of diffuse myocardial disease may be severe enough to persist despite pacemaker therapy and can lead to heart failure, death, or transplantation.[37,38] Structural congenital heart defects, including patent ductus arteriosus, atrial and ventricular septal defects, and semilunar and atrioventricular valvular abnormalities, have been reported to occur in 16-42% of patients with congenital heart block.[39,40] Additional electrophysiological abnormalities include transient and persistent sinus node dysfunction, prolonged QT interval, ventricular and junctional tachycardia, and atrial flutter.[37,41]

Typical hematological manifestations of NLE include anemia, neutropenia, or thrombocytopenia.[6] The incidence of hematological manifestations of NLE may be underestimated, as it is not routine for healthy infants to undergo complete blood counts. Thrombocytopenia is the most common hematological manifestation, which occurs in at least 10% or cases.[42] The thrombocytopenia is transient and typically of no clinical importance, though one case of gastrointestinal bleeding had been attributed to NLE-associated thrombocytopenia in 1999.[43] Neutropenia is less commonly reported and may be associated specifically with the anti-Ro (SSA) antibody.[44] Of note, no cases of neonatal sepsis occurred in the children with neutropenia.[9] A few cases of pancytopenia have also been reported.[45,46]

CONCLUSION

Neonatal Lupus Erythematosus (NLE) is an autoimmune disorder caused by the transplacental passage of maternal anti-SSA/SSB antibodies to the fetus. NLE frequently demonstrates cutaneous and cardiac manifestations, although clinicians should be aware of hematologic, hepatic, and neurologic manifestations. Most clinical manifestations of NLE progressively resolve as the maternal antibodies are cleared and tend to disappear 6-9 months after birth (with the exception of congenital heart block). CT

imaging of infants with NLE has demonstrated attenuation of white matter, increased subarachnoid space, ventriculomegaly, and basal ganglia calcifications with normal grey matter. MRI performed on our patient revealed unique findings of grey matter volume loss in addition to bilateral subdural collections. While the significance of these MRI findings is unknown at this point, serial MRIs in the future may clarify potential implications.

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