Cutaneous sequelae in neonatal lupus: A retrospective cohort study

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Background: Cutaneous eruptions in neonatal lupus erythematosus (NLE) are thought to be self-resolving. Limited literature suggests cutaneous changes may persist.

Objective: To characterize cutaneous residua in NLE and identify predictors for their development.

Methods: A retrospective cohort study of patients with cutaneous NLE born between January 1980 and May 2017 was performed. Primary outcome was the proportion of patients with cutaneous residua. Secondary outcomes included associations/predictors of sequelae.

Results: At the last follow-up, at a mean age of 4 years (range, 0.5-18.7 years), 34% of 106 patients had cutaneous sequelae, 13% had telangiectasia, 17% had dyspigmentation, and 9% had atrophic scarring. Scarring at the last follow-up was significantly associated with the presence of skin lesions at birth ($P < .001$).

Limitations: This study was limited by the retrospective design, short follow-up duration in a subset of patients, and small sample size.

Conclusion: Cutaneous NLE can exhibit long-term cutaneous residua. These findings underlie the importance of accurate diagnosis, long-term monitoring, and appropriate counseling. (J Am Acad Dermatol 2020;83:440-6.)

Key words: atrophy; cutaneous sequelae; dyspigmentation; neonatal lupus erythematosus; scarring; telangiectasia.

Neonatal lupus erythematosus (NLE) is a rare autoimmune condition occurring in newborns secondary to transplacental passage of maternal anti-Ro/La and rarely anti-U_1 ribonucleoprotein (RNP) autoantibodies during pregnancy.[1] Although multisystem involvement, including hepatobiliary, hematologic, cardiac, neurologic, and cutaneous findings, can variably be seen, skin lesions are among the most common features, seen in 15% to 25% of neonates with NLE.[2-4] Lesions are classically described as annular or polycyclic, erythematous plaques favoring periorbital and photodistributed sites; however, lesions may be highly heterogeneous in appearance, and more generalized presentations and involvement of non-photoexposed areas have also been described.[5,6] Indeed, the heterogeneity of presentation may lead to misdiagnosis and underrepresentation of cutaneous NLE (CNLE) in the literature.[4]

Although NLE is largely described as a self-resolving cutaneous entity,[2,3,5,7] limited literature has documented the presence of cutaneous sequelae, including telangiectasia,[3] hypopigmentation, hyperpigmentation,[5,7] and atrophic scars.[1,5,8,9]

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Isolated case reports have postulated that the presence of cutaneous lesions at birth may be a risk factor for eventual scarring.[8,10]

We, therefore, sought to describe the presence and range of cutaneous sequelae documented in patients with NLE and to determine whether specific risk factors modify susceptibility to these cutaneous sequelae.

CAPSULE SUMMARY

- Cutaneous eruptions are a common manifestation of neonatal lupus erythematosus. Traditionally, skin manifestations are thought to be self-resolving, but our study demonstrated sequelae, including scarring, in a significant number of patients.
- Patients should be monitored for and counselled about the possibility of long-term residua.

METHODS

Study design and population

A retrospective cohort study design was used to identify all patients with CNLE presenting to a specialized NLE clinic at a quaternary pediatric referral center between January 1980 and May 2017. Patients were excluded if there was no follow-up identified, if patients were aged younger than 6 months at the last follow-up, or if comorbid potentially scarring cutaneous disease was present, including burns, significant skin infections, blistering conditions other than lupus, and aplasia cutis congenita. While limited numbers of sibling sets were included in the study population, maternal factors were considered separately for each child, because the antibody profile or health status may have changed with subsequent pregnancies. Data were extracted retrospectively from the patient record. Corresponding clinical photography from the patient record was accessed when available. This study was approved by the Hospital for Sick Children Research Ethics Board (REB# 1000061561).

Outcomes

The primary outcome measure was the proportion of patients with residual cutaneous lesions, such as telangiectasia, pigmentary alterations, or atrophic scarring. Secondary outcomes included predictors for the presence of residual cutaneous lesions at follow-up, including demographic factors, the presence and type of maternal autoantibodies, extent of cutaneous disease quantified by specific sites of skin involvement, treatment of lesions, and extracutaneous involvement.

Statistical analysis

Data were summarized using descriptive statistics. Risk factors for atrophic scarring were explored with χ^2, analysis of variance, and linear regression analysis. A multiple regression analysis was performed using the variables that showed less than 2.5% significance in the linear modeling. The overall significance level was set at 5%. Statistical analysis was performed using Stata 14.0 software (StataCorp, College Station, TX).

RESULTS

We identified 144 patients with CNLE. Of these, 106 patients (57% female) met inclusion criteria and were therefore included in the study. Patient characteristics are summarized in Table I. All patients were seen in the specialized NLE rheumatology clinic, and 45 (42%) were additionally seen by the pediatric dermatology service. Rash onset occurred at a mean age of 5.5 (standard deviation, 4.8) weeks, and diagnosis of NLE was made at a mean age of 11.6 (standard deviation, 7.7) weeks. Extracutaneous features included hepatitis in 44 of 106 patients (43%), hematologic involvement in 34 of 106 (33%), congenital heart block in 10 of 106 (9%), and hydrocephalus in 10 of 106 (9%).

Maternal connective tissue disease was documented in 69 patients (65%), of whom 71% had systemic lupus erythematosus (SLE). Anti-Ro antibodies were identified in the mothers of 99 patients (94%), and 72 (69%) demonstrated anti-La antibody positivity. Anti-U_1RNP antibodies were present in 14 (13%), of whom 5 (5%) had exclusively anti-U_1RNP antibodies without anti-Ro or anti-La antibodies.

NLE rash morphology was heterogeneous, but annular (71%) and papulosquamous (71%) rashes were found in most patients. Rash in a periorbital distribution was found in 43 patients (41%). The scalp was similarly involved in 44 patients (42%). Lesions were isolated to the head and neck in 41 patients (39%), whereas widespread involvement was seen in 57 (54%). Mild to midpotency topical corticosteroids were prescribed to 57 patients, and 8 were prescribed topical calcineurin inhibitors.

Cutaneous residua were present in 36 of 106 patients (34%) at the last follow-up at a mean age of 4 (range, 0.5-18.7) years (Table I). Of these patients, 14 (13%) had telangiectasia, 18 (17%) had dyspigmentation, and 10 (9%) had atrophic scarring. Telangiectasias were seen on the temples in 6 of 14 patients (43%), and the face and scalp were affected in all but 1 patient, who demonstrated telangiectasia

Abbreviations used:

CNLE: cutaneous neonatal lupus erythematosus
NLE: neonatal lupus erythematosus
RNP: ribonucleoprotein
SLE: systemic lupus erythematosus

on the palm (the only patient with no prior NLE rash at the site of telangiectasia development). One patient with previously widespread CNLE had extensive telangiectasias involving the lip, glabella, axillae, thighs, and diaper area. Of the patients with dyspigmentation, hyperpigmentation was seen in 9 of 18 patients (50%), hypopigmentation in 6 of 18 (33%), and both hyper- and hypopigmentation in 3 of 18 (17%). Dyspigmentation was seen periorbitally in 3 of 9 patients (33%), and 4 of 9 patients (44%) had widespread dyspigmentation involving the torso and limbs. Clinical features of those patients who demonstrated atrophic scarring at the last follow-up are presented in Table II.

The rash completely resolved in 70 of 106 patients (66%) at a mean age of 5.7 months (data available for 31 of 70 patients). Risk factors and predictors for atrophic scarring are presented in Table III. On univariate analysis, the presence of atrophic scarring at the last follow-up was significantly associated with female sex ($P = .025$), presence of NLE rash at birth ($P < .001$), topical treatment of NLE lesions ($P = .019$), and absence of maternal anti-Ro antibodies ($P = .041$). In the multiple regression model, only the presence of the rash at birth remained significant ($P < .001$).

DISCUSSION

NLE is an uncommon condition seen in infants born to mothers with anti-Ro, anti-La, or less commonly, anti-U_1RNP antibodies. The clinical presentation is heterogenous, but cardiac and cutaneous manifestations occur most frequently. Owing to the rarity of the illness, NLE is likely underdiagnosed and possibly under-reported in the literature. In CNLE specifically, the rash is often initially misdiagnosed as eczema or fungal infection.[4]

CNLE has traditionally been described as a self-resolving entity, and lesions are thought to spontaneously resolve by age 6 to 8 months as maternal IgG antibodies are gradually cleared.[11] However, limited case reports and small series have posited that cutaneous sequelae, including telangiectasias, dyspigmentation and scarring, may persist long-term. In one of the largest series to date, Neiman

Table I. Patient and material characteristics

Variables*	Data
Demographic features	(N = 106)
Female	60 (56.6)
Gestational age at birth, mean (SD), wk	37.9 (2.7)
Prematurity	21/104 (20.2)
Age at diagnosis, mean (SD), wk	11.6 (7.7)
Age at rash onset, mean (SD), wk	5.5 (4.8)
Age at last follow-up, mean (range), y	4.0 (0.5-18.7)
Maternal connective tissue disease	(n = 106)
Known connective tissue disease	69 (65.1)
Systemic lupus erythematosus	49 (46.2)
Sjogren syndrome	16 (15.1)
Rheumatoid arthritis	6 (5.7)
Other	7 (6.6)
Maternal autoantibodies	(n = 105)
Anti-Ro	99 (94.2)
Anti-La	72 (68.6)
Anti-U_1RNP	14 (13.3)
Anti-U_1RNP only	5 (4.8)
Extracutaneous NLE features	(n = 106)
Congenital heart block	10 (9.4)
Hepatitis	44 (42.5)
Hematologic involvement	34 (32.0)
Thrombocytopenia	7 (6.6)
Leukopenia	1 (1.0)
Neutropenia	27 (25.5)
Hydrocephalus	10 (9.4)
Morphology at rash onset	(n = 99)
Pink/red macules	11 (11.1)
Annular	70 (70.7)
Atrophic	14 (14.1)
Bullous	1 (1.0)
Petechial	1 (1.0)
Papulosquamous	70 (70.7)
Site of cutaneous involvement	(n = 106)
Periorbital	43 (40.6)
Scalp	44 (41.5)
Upper extremities	27 (25.4)
Lower extremities	22 (20.8)
Palms and soles	8 (7.6)
Torso	56 (52.8)
Diaper area	20 (18.9)
Cutaneous residua at last follow-up	(n = 106)
Any cutaneous residua	36 (34.0)
Telangiectasia	14 (13.2)
Dyspigmentation	18 (17.0)
Hypopigmentation	9 (8.5)
Hyperpigmentation	15 (14.2)
Atrophic scarring	10 (9.4)

NLE, Neonatal lupus erythematosus; *No*, number; *RNP*, ribonucleoprotein; *SD*, standard deviation.
*Categorical data are presented as number (%) and continuous data as indicated.

Table II. Characteristics of patients with atrophic scarring at last follow-up

Pt	Sex	Age at rash onset	Maternal autoantibodies	Extracutaneous NLE features	Rash morphology	Rash location	Treatment used	Age at last follow-up, y	Location of atrophy
1	F	Birth	Ro positive La positive U_1RNP negative	Hematologic	Annular, atrophic, papulosquamous	Periorbital, other facial, scalp	TCS	1.6	Face, temples
2	F	Birth	Ro positive La positive U_1RNP positive	Hepatitis, hematologic	Atrophic, papulosquamous	Other facial, scalp, torso	TCS	18.7	Face
3	F	1 mo	Ro positive La positive U_1RNP positive	None	Annular, papulosquamous	Periorbital, scalp	TCS	1.6	Forehead
4	F	2 mo	Ro positive La positive U_1RNP negative	None	Annular, papulosquamous	Periorbital, UE, LE, torso	TCS	5.0	Back
5	F	Birth	Ro positive La positive U_1RNP negative	None	Not recorded	Other facial, scalp, torso	None	3.8	Face, scalp, chest, back
6	F	Birth	Ro negative La negative U_1RNP positive	None	Erythematous macules, atrophic, papulosquamous	Periorbital, other facial, scalp	TCS TCNI	2.0	Temples
7	F	Birth	Ro negative La positive U_1RNP negative	Hepatitis, hydrocephalus	Atrophic, papulosquamous	Other facial, scalp, torso	TCS	3.1	Temples, perinasal
8	M	1 mo	Ro positive La positive U_1RNP negative	Hepatitis	Annular, papulosquamous	Periorbital, other facial, UE, LE, torso, diaper	TCS	0.9	Behind ear, forehead
9	F	2 mo	Ro positive La positive U_1RNP negative	Hepatitis, hematologic	Papulosquamous	Periorbital, other facial, UE, LE, torso, diaper	TCS TCNI	0.5	Temples
10	F	Birth	Ro positive La positive U_1RNP negative	Hepatitis	Annular, atrophic, papulosquamous	Periorbital, scalp, UE, LE, torso, diaper	TCS	1.7	Scalp, behind ears

F, Female; *LE*, lower extremities; *M*, male; *NLE*, neonatal lupus erythematosus; *Pt*, patient; *RNP*, ribonucleoprotein; *TCNI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids; *UE*, upper extremities.

Table III. Predictors for skin scarring/atrophy

Variable	Without scarring (n = 96), No. (%)	With scarring (n = 10), No. (%)	*P* value
Sex			.025
Male	45 (46.9)	1 (10)	
Female	51 (53.1)	9 (90)	
Maternal connective tissue disease	64 (66.7)	5 (50.0)	.293
Anti-Ro antibodies in mother	91/95 (95.8)	8 (80.0)	.041
Anti-La antibodies in mother	63/95 (66.3)	9 (90.0)	.125
Anti-U_1RNP antibodies in mother	11/95 (11.6)	3 (30.0)	.103
Prematurity	19/95 (20)	2 (20.0)	.874
Presence of NLE rash at birth	5/84 (6.0)	6 (60.0)	<.001*
Hepatitis	39 (40.6)	5 (50.0)	.431
Hematologic involvement	31 (32.3)	3 (30.0)	.849
Congenital heart block	10 (10.4)	0 (0)	.284
Site of cutaneous involvement			.554
Head and neck only	38 (39.6)	3 (30.0)	
Body only	8 (8.3)	0 (0)	.342
Diffuse (head/neck and body)	50 (52.1)	7 (70.0)	.279
Treatment of cutaneous lesions	49 (51.0)	9 (90.0)	.019

NLE, Neonatal lupus erythematosus; *No.*, number; *RNP*, ribonucleoprotein.
*The only factor significantly associated with atrophic scarring in multiple regression analysis was the presence of NLE rash at birth.

et al[9] reported that 27% (14 of 51) of patients had residual skin abnormalities. Our study similarly found that 34% of patients with CNLE demonstrated cutaneous sequelae at the last follow-up visit; 13% had persistent telangiectasia, 17% had dyspigmentation (hypo- or hyperpigmentation), and 9% had atrophic scarring. In those patients in whom the rash completely resolved, this occurred at a mean age of 5.7 months, although the specific date of resolution was missing in a large proportion of patient records. In the 36 patients with cutaneous sequelae, residua were documented to be present at a mean age of 3.1 years (range, 6 months-18.7 years; median, 1.6 years).

Telangiectasias are the most well-characterized cutaneous complication of CNLE. In a case series including 18 patients with CNLE, residual telangiectasia were seen in 4 (22%), all at sites of prior inflammation, but these eventually resolved in 2 of these patients.[7] Neiman et al[9] reported a similar rate of telangiectasia, seen in 10 of 51 patients (20%).[9] Thornton et al[12] reported 5 patients in whom telangiectasias were seen in sites not previously affected by an inflammatory eruption, including in the diaper area. In our cohort, telangiectasias were seen in 13%, and frequently found around the temples, a common site of CNLE. However, telangiectasia developed on the palms in 1 patient in our cohort, where CNLE lesions were not previously seen.

The pathogenesis of this complication remains unknown, but authors have postulated that possible mechanisms may include immune complex deposition, hormonal factors, photodamage, or possible secretion of angiogenic factors from affected cells.[3] Pulsed-dye laser therapy has been used successfully in the treatment of persistent NLE-related telangiectasia.[13]

Dyspigmentation was seen in 17% of our patients at the last follow-up. The incidence of long-term dyspigmentation after CNLE is unknown, because this complication is not well-quantified in the literature. Postinflammatory pigmentary changes may be under-reported given the general view that dyspigmentation often improves, or even resolves, over time. Weston et al[7] reported 3 of 18 patients with secondary dyspigmentation after CNLE, although they report resolution of both hypo- and hyperpigmentation in all by age 5 years. More persistent dyspigmentation has also been documented in CNLE.

High and Costner[5] reported a 12-year-old girl with classical CNLE present from birth who demonstrated hyperpigmentation (in addition to atrophic scars) in areas of neonatal rash. She was treated successfully with hydroquinone 4% cream and tretinoin 0.025% cream, and the hyperpigmentation reportedly improved significantly.[5] A subset of patients in our cohort were lost to follow-up in early childhood, which limited our ability to determine whether their dyspigmentation was truly persistent; however, 3 patients had ongoing hyperpigmentation beyond 5 years of age, including 1 patient who was 18 years old at the last follow-up.

Atrophic scarring is the most worrisome complication of CNLE given the higher likelihood of persistence and lack of effective therapies available. Scarring is scarcely reported in CNLE; Weston et al[7] found no atrophy or scarring developed in their 18 patients. Neiman et al,[9] however, found that 10 of 51 patients had pitting, scarring, or atrophy after a minimum 2 years of follow-up. In our cohort, atrophic scarring was similarly noted at the last follow-up in 9% of patients, with ages ranging from 6 months to 18 years (mean age, 3.9 years).

The limited literature available has suggested that the presence of CNLE lesions at birth may confer an increased risk of atrophic scarring. Our cohort demonstrated a significant association existed between atrophic scarring at the last follow-up and the presence of skin lesions at birth ($P < .001$). This finding has been described in previous case reports and small case series.[5,8,10] Interestingly, the 6 patients in our cohort with congenital onset of rash and eventual scarring all demonstrated an initial atrophic morphology (with the exception of 1 patient in whom initial rash morphology was not described in the record). The remaining 5 patients with presence of rash at birth but no scarring on follow-up had CNLE lesions that were not atrophic. Similarly, the 9 patients presenting with atrophic rash morphology and lack of eventual scarring almost universally presented after birth. Therefore, there appears to be a potential link between congenital NLE rash, atrophic morphology, and eventual atrophic scarring. It has been suggested that an inflammatory insult in utero may account for the presence of atrophic skin lesions at birth,[10] but the relationship between these factors and eventual scarring, as well as the pathogenesis of this phenomenon, likely merits further exploration.

Although no additional factors were significantly associated with scarring in the multiple regression model, the risk of atrophic scarring may also be elevated in female patients and in the absence of maternal anti-Ro antibodies. Similarly, treatment of lesions with topical steroids or topical calcineurin inhibitors may be a nonsignificant predictor for atrophic scarring, likely as a surrogate marker for more significant or widespread rash at presentation rather than as a true causative predictor for scarring. Some authors have advocated for use of systemic steroids for widespread cutaneous rash,[14] but none of the patients in our cohort received this therapy.

Limitations of this study include the limited duration of follow-up in a subset of patients. Some patients who were lost to follow-up at an early age may have ultimately gone on to experience resolution of their cutaneous residua, particularly those with postinflammatory dyspigmentation.

We were also limited by the retrospective nature of the study, with some variability in the recording of data in the patient record. Selection bias may have led to inclusion of more severe presentations given that patients presented to a quaternary site, which in turn may lead to an over-represented risk of cutaneous complications. The rarity of the outcomes examined coupled with the relatively small sample size meant that we were not adequately powered to reliably identify all potential predictors of scarring.

CONCLUSION

Still, to our knowledge, this remains the largest cohort of patients with CNLE and one of few specifically examining cutaneous residua. As demonstrated previously,[9] our cohort confirms that long-term complications, such as telangiectasia, dyspigmentation, and atrophic scarring, are likely more common than previously described; ongoing monitoring may therefore be indicated. Furthermore, given the rarity of CNLE and frequency of misdiagnosis, it remains critical that clinicians not only accurately diagnose this condition but also remain aware of potential cutaneous complications, so parents can be effectively counselled. Further study is certainly required to elucidate potential risk factors for development of cutaneous sequelae, such as the presence of the NLE rash at birth, presence or absence of specific autoantibodies, and whether specific treatment alters clinical outcomes.

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