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CASE STUDY

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A case of reactive granulomatous dermatitis associated with neonatal lupus erythematosus

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Abstract

Neonatal lupus erythematosus (NLE) is an uncommon disorder affecting approximately one out of 20 000 live births in the United States. Common manifestations of NLE include cutaneous eruptions and cardiac involvement. The typical rash of NLE most closely resembles the rash of subacute cutaneous lupus erythematosus both clinically and histopathologically. We present a case of reactive granulomatous dermatitis (RGD) associated with NLE in a 3-month-old male in whom the initial histopathology and immunohistochemistry were concerning for hematologic malignancy. RGD is a unifying term used to describe cutaneous granulomatous eruptions that occur in response to a variety of stimuli, including autoimmune connective tissue diseases. Our case demonstrates the range of histopathological findings that may be present in the setting of NLE.

KEYWORDS
histiocyte infiltration, neonatal lupus erythematosus, rash, reactive granulomatous dermatitis

1 | INTRODUCTION

Neonatal lupus erythematosus (NLE) is an uncommon disorder affecting approximately 1 out of 20 000 live births in the United States.[1,2] NLE is acquired through transplacental passage of maternal autoantibodies to Sjögren syndrome A or B (SSA and SSB) autoantigens and rarely, anti-U1-ribonucleoprotein antibodies.[1,2] Mothers who are seropositive for SSA and SSB antibodies have a 2% chance of having a child affected with NLE.[1] Anti-SSA antibodies are the laboratory hallmark of NLE, and are more commonly associated with cardiac manifestations of NLE.[3] Additionally, in cases of NLE skin manifestations, anti-SSB and U1-ribonucleoprotein antibodies are more likely to be detected.[1]

While the most common manifestations of NLE include cutaneous eruptions and cardiac involvement, the hematological, neurological, pulmonary, and hepatobiliary systems can be involved.[4,5] The typical rash of NLE most closely resembles that of subacute cutaneous lupus erythematosus (SCLE) both clinically and histopathologically. The classic clinical features are erythematous thin scaly plaques and annular pink plaques most often distributed periocularly with extension into the scalp. The histopathology typically demonstrates epidermal atrophy with vacuolization of the basal layer and a sparse lymphohistiocytic infiltrate at the dermal–epidermal junction. Nonspecific cutaneous lesions can also occur in lupus erythematosus in general, and rarely in NLE. Reactive granulomatous dermatitis (RGD) is a unifying term used to describe cutaneous granulomatous eruptions that occur in response to autoimmune connective tissue diseases such as lupus erythematosus, as well as to medications and malignancies.[6] The three main subtypes include interstitial granulomatous dermatitis (IGD), palisaded neutrophilic and granulomatous dermatitis (PNGD), and interstitial granulomatous drug reaction (IGDR). We present a case of RGD associated with NLE.

2 | CASE

A 3-month-old male with a family history of maternal lupus erythematosus presented for evaluation of an asymptomatic extensive whole-body rash since 6 weeks of age. Past history was significant for premature delivery at 32-week gestation via emergency cesarean section due to maternal vaginal bleeding and breech presentation followed by a 1-month course in the neonatal intensive care unit. During this time, the patient was treated for jaundice, apnea, and respiratory distress syndrome. The rash initially appeared on the face at 6 weeks of age, described as a few red patches that gradually spread to the rest of the body. Prior to presentation to dermatology, the patient had been treated for eczema and skin infection with cephalexin for 1 week and hydrocortisone 2.5% ointment for 2 weeks with minimal improvement. Skin examination revealed widespread erythematous papules coalescing into small annular plaques with fine white scale involving the face, scalp, ears, trunk, and extremities (Figure 1). Background patchy hypopigmentation was noted on the forehead and cheeks. The remaining physical exam findings were normal.

Due to the extensive nature of the eruption, a punch biopsy from the left thigh was obtained. Histopathology revealed a superficial and deep perivascular and interstitial infiltrate composed of medium-sized round to oval cells with scant cytoplasm and basophilic, indented nuclei (Figure 2A,B). Immunohistochemical staining revealed that the interstitial infiltrate was positive for CD33, CD68, CD163, and myeloperoxidase (MPO) (Figure 2C,D). The infiltrate was negative for CD3, CD4, CD19, CD56, CD117, FXIIIa, TDT, and TCL-1. An initial histopathologic diagnosis of atypical myeloid/monocytic infiltrate was made. The patient was evaluated by the hematology/oncology service and underwent a bone marrow biopsy with cytogenetic analysis to exclude a hematologic malignancy with no abnormal histopathologic or pathogenic molecular findings. Serology was confirmatory for neonatal lupus (ANA 1:640; SSA Ab, RNP Ab, SMRNP Ab+). Additional laboratory findings were notable for elevated liver function tests with an aspartate aminotransferase value of 136 U/L (normal: 8–37 U/L) and alanine aminotransferase value of 108 U/L (normal: 8–35 U/L). Complete blood count and platelet counts were normal and electrocardiogram studies were all normal.

At 1-month follow-up, the red papules had flattened somewhat with the development of hyperpigmented scaly patches and thin plaques with less of an annular configuration (Figure 3). Based on the features concerning malignancy in the first biopsy, a repeat punch biopsy from a plaque on the right thigh was obtained. Histopathology revealed a diffuse interstitial and perivascular infiltrate composed of histiocytes surrounding foci of degenerated collagen and focal collections of karyorrhectic debris (Figure 4A,B). Based on clinical and histopathologic findings, the patient was diagnosed with RGD associated with NLE. Treatment with hydrocortisone 2.5% ointment was recommended if the child appeared itchy or uncomfortable. By 5 months of age, the rash had mostly cleared leaving scattered hypopigmented patches and a few ill-defined erythematous plaques of fine papules. The liver enzyme levels were trending downward.

3 | DISCUSSION

NLE is an autoimmune disorder that results from the transplacental transfer of autoantibodies from mother to fetus. Though NLE typically self-resolves within 8 months as maternal autoantibodies degrade, early diagnosis is important as non-cutaneous symptoms including heart block, cardiomyopathy, cytopenias, hepatobiliary disease, and hydrocephalus can cause serious morbidity and mortality.[2] Maternal or infant seropositivity for NLE-associated antibodies and one or more clinical manifestations of NLE can establish a diagnosis.[2] One of the most common presentations is cutaneous lesions, which occurs in 40% of cases.[7]

Cutaneous manifestations of NLE are typically present in the first few months of life. The characteristic rash is composed of annular or elliptical erythematous plaques with central clearing and fine scaling. The rash most often involves the face in a distribution around the eyes, temples, and forehead[1,2,4,5] and is described as an "eye-mask" pattern.[4] However, the rash may also involve the scalp, trunk, and extremities. Similar to the rash of SCLE, NLE may demonstrate

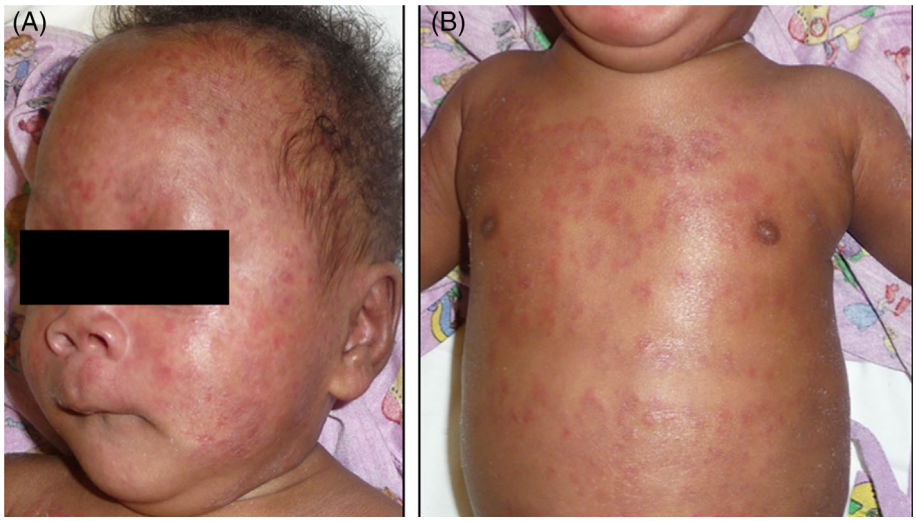

FIGURE 1 Erythematous papules coalescing into small plaques, some with annular configuration with fine white scale, on the (A) head and (B) trunk.

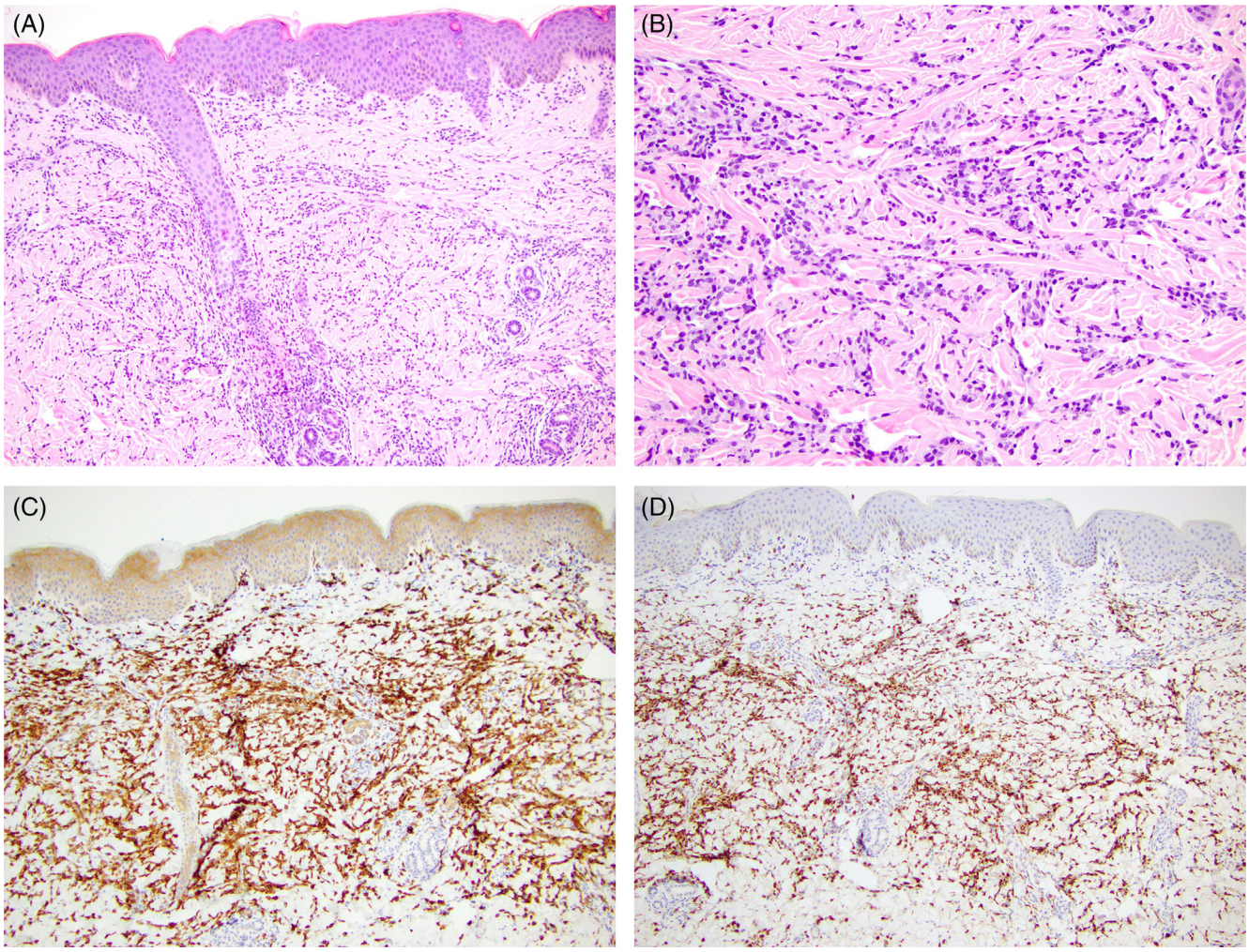

FIGURE 2 (A) Superficial and deep perivascular and interstitial infiltrate (H&E, ×100). (B) The infiltrate is composed of medium-sized round to oval cells with scant cytoplasm and basophilic, indented nuclei (H&E, ×200). Immunohistochemical staining demonstrated expression of (C) CD163 (CD163, ×100) and (D) myeloperoxidase (MPO, ×100).

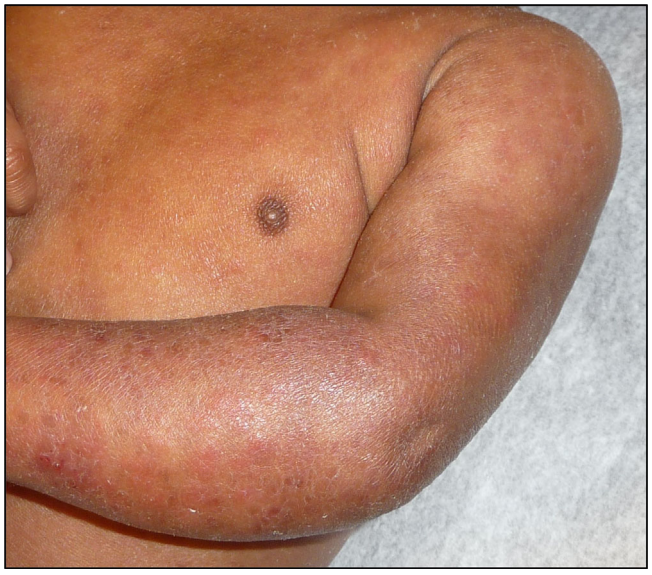

FIGURE 3 Improved rash at 1-month follow-up.

photoexacerbation, although some newborn infants exhibit the rash even in photo-protected sites. The differential diagnosis for the skin lesions may include seborrheic dermatitis, tinea capitis, erythema marginatum, and other annular eruptions. The rash of NLE is most commonly misdiagnosed as eczema, fungal infection, or trauma.[2]

The histopathological features of cutaneous NLE mirror those of SCLE, demonstrating an interface dermatitis with vacuolar alteration of basal keratinocytes and basement membrane thickening, as well as a lymphocytic infiltrate in the upper dermis and around adnexal structures with increased deposition of mucin in the dermis.[1,2,4,8] Little information is available on the immunohistochemical staining of NLE.

Only two other cases of NLE with histiocyte infiltration and accompanying immunohistochemical investigations have been reported (Table 1).[9,10] The more histiocytic dominant infiltrate observed in those reports closely resembles the histopathological patterns underlying highly reactive immune states, including RGD, histiocytoid Sweet syndrome, and leukemia cutis/acute myeloid leukemia.[6,11–13] The combined expression of CD68, CD163, and MPO in a poorly differentiated cutaneous infiltrate,

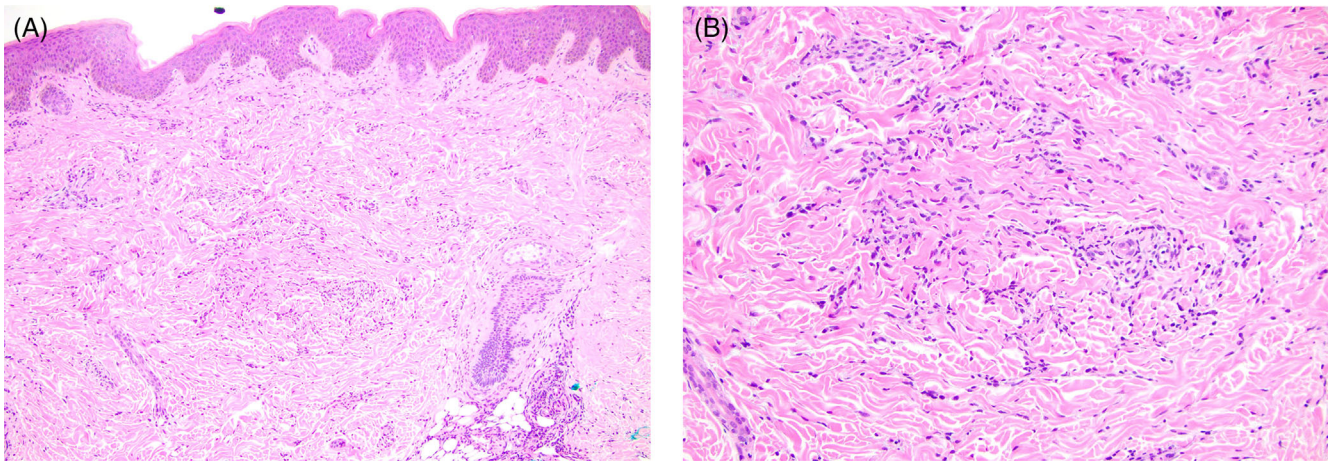

FIGURE 4 (A) Diffuse interstitial and perivascular infiltrate (H&E, ×100), (B) composed of histiocytes surrounding foci of degenerated collagen and focal collections of karyorrhectic debris (H&E, ×200).

TABLE 1 Cases of neonatal lupus with histiocyte infiltration reported in the literature.

Authors	Year	Age/sex	Histopathological findings	IHC staining
Sitthinamsuwan[9]	2014	1 mo/M	• Diffuse interstitial dermal infiltration by mononuclear cells with some segmented neutrophils	Positive for CD33, CD68, CD123, myeloperoxidase
Okada[10]	2014	25 do/M	• Vacuolar alteration at the dermoepidermal interface • Mild edema in the upper dermis • Interstitial and periadnexal mononuclear cell infiltration • Nuclear dust in the dermis	Positive for CD33, CD68, CD163
Current case	2022	3 mo/M	• Interstitial infiltrate composed of medium-sized round to oval cells with scant cytoplasm and basophilic, indented nuclei • Sparse lymphohistiocytic inflammation	Positive for CD33, CD68, CD163, myeloperoxidase

Abbreviations: do, day-old; IHC, immunohistochemical; M, male; mo, month-old.

as seen in our case, poses significant diagnostic challenges in differentiating a reactive histiocytic proliferation from a myeloid neoplasm. Careful consideration of the clinical scenario in conjunction with knowledge of the hematopathologic differential diagnosis is necessary. The use of additional immunohistochemical markers, such as CD34[14] and nucleophosmin,[15] may be of additional benefit in assessing for a malignant process. The co-expression of CD68, CD163, and MPO may favor a diagnosis of a reactive process such as RGD.[16] Previous authors have also reported histiocytic infiltrates with a similar immunophenotype (CD68+/CD163+/MPO+) in histiocytoid Sweet syndrome.[17,18] The histopathologic differential diagnosis of RGD includes interstitial granuloma annulare, histiocytoid Sweet syndrome, leukemia cutis, interstitial granulomatous mycosis fungoides and metastatic breast carcinoma.

From the clinical perspective, in adult patients with RGD, approximately 10% have underlying systemic lupus.[12] This subset may be even higher in pediatric patients. In a multicenter retrospective review of seven pediatric cases of RGD, all cases were associated with either active systemic lupus or led to its diagnosis, with resolution of cutaneous disease upon initiation of systemic treatment.[12]

The pathogenesis of RGD is still not fully understood. As granulomatous dermatitis has been found in the setting of autoimmune diseases such as systemic lupus, rheumatoid arthritis, ulcerative colitis, vasculitis, chronic uveitis, and incomplete Sjögren syndrome, some authors hypothesize that it is due to immune complex deposition or pathogenic factors of systemic disease.[11,19] Alternative etiopathologies include abnormal neutrophil activation, delayed-type hypersensitivity reaction, and low-grade small-vessel vasculitis.[6] RGD has also been documented in the setting of lymphoproliferative diseases (e.g., acute myelogenous leukemia, lymphoma, and multiple myeloma), solid organ malignancies (e.g., breast and endometrial), drug reactions (e.g., tumor necrosis factor (TNF)-inhibitors, angiotensin-converting enzyme (ACE)-inhibitors, and allopurinol), and infectious diseases (e.g., Lyme disease and coccidiomycoses).[6]

4 | CONCLUSION

Especially in the neonatal setting, atypical rashes may exhibit morphologic features overlapping a myeloid malignancy and reactive dermatosis. Knowledge of the various differential diagnostic entities for such lesions is critical for both hematopathologists and dermatopathologists to arrive at an accurate diagnosis. Our case expands the range of histopathological findings that may be seen in the setting of NLE.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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