Systemic lupus erythematosus—associated neutrophilic dermatosis with palmoplantar involvement

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Key words: autoimmune connective-tissue disorders; neutrophilic dermatosis; neutrophils; nonbullous; palmoplantar; systemic lupus erythematosus.

INTRODUCTION
Neutrophilic infiltrates in the setting of systemic lupus erythematosus (SLE) are commonly associated with bullous or vasculitic disease. Recently, an increasing number of reports describe a nonbullous, nonvasculitic SLE-associated neutrophilic dermatosis. Prior cases of SLE-associated neutrophilic dermatosis describe an urticarial eruption involving the trunk and extremities. Here we report the case of a 27-year-old woman with SLE-associated neutrophilic dermatosis with palmoplantar involvement, thus, expanding the clinical spectrum of this disease. Neutrophilic dermatosis may represent the initial cutaneous manifestation of systemic disease in one-third of patients. Thus, prompt recognition of this distinct cutaneous entity should promote screening for SLE.

CASE REPORT
A 27-year-old woman with a 9-month history of SLE was admitted to the hospital with 4 days of worsening pleuritic chest pain, dyspnea, and arthralgias. She also had a 1-day history of a burning, annular eruption on her trunk, palms, and soles. Upon admission, the patient was found to have recurrent pericardial and bilateral pleural effusions in the setting of an acute SLE flare. Although complete blood count and basic metabolic panel were unremarkable, the patient’s anti–double-stranded DNA antibody was 266 IU/mL, C3 was 41.4 mg/dL (laboratory-specific reference range, 90–180 mg/dL), and C4 was 6.62 mg/dL (laboratory-specific reference range, 10–40 mg/dL).

From prior workup of SLE, antinuclear antibody was 1:640 with speckled pattern and was anti-Smith antibody positive and antinucleoprotein antibody positive. Anti–SS-A antibody was 7.3 (normal ≤0.9 antibody index) and anti–SS-B antibody was 0.6 (normal ≤0.9 antibody index). Erythrocyte sedimentation rate was 45 mm/h.

On physical examination, the patient had blanchable, erythematous macules and annular, urticarial papules and plaques bilaterally distributed on the palmoplantar surfaces (Fig 1). Additionally, there were faint, blanchable, erythematous macules on the chest and back. Shave biopsy findings of the left plantar surface showed neutrophils aligned along the dermoepidermal junction (DEJ) associated with vacuolar alteration and rare dyskeratosis (Fig 2). There was also a superficial, perivascular, and interstitial predominantly neutrophilic infiltrate with lymphocytes and leukocytoclasis, without vasculitis or a significant increase in dermal mucin (Fig 3).

At the time of presentation, the patient was taking hydroxychloroquine (200 mg twice daily), prednisone (50 mg/d), omeprazole, atovaquone, and cholecalciferol. She was treated with intravenous methylprednisolone and underwent a thoracentesis.
with improvement in respiratory status and resolution of chest pain. Palmoplantar surfaces were treated with clobetasol ointment twice daily with only modest improvement; however, shortly after an increase in systemic glucocorticoids and the initiation of mycophenolate mofetil, the eruption subsided. At 5-month follow-up, the patient remained free of the cutaneous eruption while maintained on hydroxychloroquine (200 mg twice daily) and mycophenolate mofetil (1500 mg twice daily). Methylprednisolone had been tapered down to 10 mg daily.

DISCUSSION

Ackerman was among the first to consider SLE in the histologic differential diagnosis of nonbullous, nonvasculitic neutrophilic inflammatory dermatosis.\(^1,2\) He described the presence of neutrophils and neutrophilic dust immediately beneath the epidermis of an interface dermatitis and postulated that these histopathologic features may represent a “muted” expression of bullous SLE.\(^2\) The first clinical case of SLE associated with a Sweet’s syndrome–like dermatosis was reported in 1985.\(^3\) Since then, close to 50 cases of SLE-associated neutrophilic dermatosis distinct from Sweet’s syndrome, pyoderma gangrenosum, and bullous lupus erythematosus (LE) have been reported.\(^3\)–\(^8\)

The literature on neutrophil-dominant manifestations of SLE is fraught with confusion, in part because of the overlap in terminology. A variety of terms have been used to describe nonbullous, nonvasculitic, neutrophilic dermatosis and include nonbullous neutrophilic dermatosis, nonbullous neutrophilic LE, Sweet’s syndrome–like neutrophilic dermatosis, and SLE-associated neutrophilic dermatosis. However, reproducible clinical and histopathologic reports confirm that SLE-associated neutrophilic dermatosis represents a distinct entity that is closely associated with and may herald the development of systemic disease.\(^4\)–\(^8\) Clinical and histopathologic differential diagnoses of SLE-associated neutrophilic dermatosis are vast (Table 1).\(^8\)–\(^10\) Although there are no known prognostic or therapeutic differences for SLE-associated neutrophilic dermatosis, recognition of this distinct cutaneous entity should prompt screening for SLE.

The cutaneous findings of SLE-associated neutrophilic dermatosis include erythematous papules and plaques, many of which are described as urticarial and some of which have an annular morphology, without bulla formation or mucosal involvement. Histopathologic features include an interstitial and perivascular predominantly neutrophilic infiltrate with leukocytoclasis and variable vacuolar alteration along the DEJ, without the presence of vasculitis or bullae.\(^5\) The degree of neutrophilic infiltrate varies from paucicellular to cell rich Sweet’s syndrome like, which suggests a spectrum
| Diagnosis | Clinical features | Histopathologic features |
|-----------|-------------------|--------------------------|
| SLE-associated neutrophilic dermatosis | • Erythematous papules and plaques<br>• Urticarial or annular morphology<br>• Trunk or extremities | • Interstitial neutrophilic infiltrate, leukocytoclasia<br>• Vacuolar interface alteration, increased dermal mucin, BMZ thickening, positive DIF (C3, IgG, IgM along DEJ) | No vasculitis or bulla formation |
| Generalized eruption | Neutrophilic urticarial dermatosis*9 | • Erythematous macules or thin plaques<br>• Resolve within 48 hours<br>• Trunk or extremities | • Interstitial neutrophilic dermal infiltrate, leukocytoclasia | No vasculitis |
| | Neonatal lupus erythematosus* | • Erythematous macules, papules, plaques<br>• Head and neck, ± trunk, extremities<br>• Maternal history of anti-Ro/SS-A lupus | • Interstitial neutrophilic infiltrate<br>• Vacuolar interface alteration, increased dermal mucin |
| | Bullous SLE* | • Widespread, symmetric, vesiculo-bullous eruption<br>• History of SLE or SLE-related manifestations<br>• Mucosal involvement often observed | • Subepidermal neutrophil-mediated separation | Interstitial neutrophilic infiltrate |
| | Dermatitis herpetiformis | • Erythematous excoriated papules, plaques<br>• Symmetric distribution over extensor surfaces | • Neutrophilic microabscesses in papillary dermis<br>• Leukocytoclasia<br>• Eosinophils<br>• Granular IgA deposits in dermal papillae |
| | Linear IgA bullous dermatosis* | • Vesicles or bulla on erythematous or urticarial skin, often annular or polycyclic<br>• Trunk and limbs, ± mucosal involvement | • Neutrophils aligned along DEJ<br>• Interstitial neutrophilic infiltrate with admixed eosinophils<br>• Subepidermal blistering<br>• IgA deposits in linear pattern along DEJ |
| | Still's disease | • Evanescent, salmon-pink erythema that waxes and wanes with fever<br>• Favor the extremities<br>• Intermittent high fevers ± arthralgia | • Paucicellular to moderately cellular neutrophilic infiltrate in papillary dermis<br>• Vacuolar interface alteration |
| | Behcet's disease | • Aphthous or herpetiform ulcers in oral cavity and genitalia<br>• Pseudofolliculitis, acneiform lesions<br>• Erythema nodosum | • Cell-rich or Sweet's-like neutrophilic infiltrate<br>• Suppurative folliculitis or vasculitis |
| | Pyoderma gangrenosum* | • Deep ulceration with violaceous, undermined border<br>• Pathergy | • Cell-rich pan-dermal neutrophilic infiltrate<br>• No vasculitis |
| | Sweet's syndrome* | • Erythematous to violaceous edematous papules, plaques, nodules<br>• Fever<br>• Leukocytosis | • Cell-rich neutrophilic infiltrate with leukocytoclasia<br>• Papillary dermal edema<br>• No vasculitis |
of neutrophilic dermatoses within SLE patients. Perivascular lymphocytes are also typically present in small numbers. Histopathologic changes that are consistent with SLE, such as interface changes, dermal mucin, and basement membrane thickening, are variably present. When performed, direct immunofluorescence is positive for immunoreactants at the DEJ in 50% of cases, with deposition of C3, IgG, and IgM along the DEJ. Currently, treatment is targeted at the underlying disease, and the eruption usually responds to immunomodulatory or immunosuppressive therapy.

The pathogenesis of these nonbullous lesions remains unclear. Many patients develop the eruption while on immunosuppressive therapy, which may inhibit the formation of bullae and supports the idea of a forme fruste variant of bullous LE, as suggested by Ackerman. Other patients have the eruption as the presenting symptom of SLE without concurrent systemic therapy, suggesting that this could be a distinct cutaneous manifestation of SLE. Although absent in some cases, histopathologic findings characteristic of SLE, such as vacuolar alteration and immunoreactants along the DEJ, raise the possibility of an antibody-mediated pathogenesis. The occurrence of this entity in patients with other autoimmune connective-tissue disorders, such as rheumatoid arthritis, Still’s disease, and Sjögren’s syndrome, has been reported, suggesting that the disorder represents a clinicopathologic response in individuals predisposed by diverse autoimmune connective-tissue disorders and not exclusively SLE.

This case shows unique palmoplantar involvement of SLE-associated neutrophilic dermatosis. Increased awareness and recognition of the clinical spectrum of neutrophilic dermatoses in the setting of SLE is imperative, particularly in the one-third of cases in which cutaneous manifestations are the presenting symptoms of systemic disease.

REFERENCES
1. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. Br J Dermatol. 1996;135(3):355-362.
2. Ackerman AB. Histologic Diagnosis of Inflammatory Skin Diseases: An Algorithmic Method Based On Pattern Analysis. 2nd ed. Baltimore: Williams & Wilkins; 1997. P.525, 542.

Table I. Cont’d

| Diagnosis | Clinical features | Histopathologic features |
|-----------|-------------------|-------------------------|
| Palisaded neutrophilic and granulomatous dermatitis | • Symmetrically distributed umbilicated papules | • Palisaded granulomas with neutrophils |
| | • Favor extensor surfaces of the extremities | • Variable small vessel leukocytoclastic vasculitis |
| Leukocytoclastic vasculitis | • Palpable purpura | • Perivascular small vessel neutrophilic infiltrate with extension into vessel walls |
| | • ±Urticarial lesions | • Leukocytoclasia |
| | | • Fibrinoid necrosis of vessel walls |
| | | • Extravasation of erythrocytes |
| Hypocomplementemic urticarial vasculitis | • Painful, pruritic urticarial papules | • Small vessel leukocytoclastic vasculitis |
| | • Persist for >24 hours | • Variable, perivascular neutrophilic infiltrate |
| | • Hyperpigmentation after resolution | |
| | | Hypocomplementemia with low C1q, C3, C4 |
| | | Positive C1q antibody |
| Palmoplantar eruption | | |
| Palmpoplantar eccrine hidradenitis | • Abrupt onset of erythematous, tender papules, nodules | • Neutrophil peri-ecrine infiltrate |
| | • Most commonly in children | • ±Mixed perivascular infiltrate |
| Palmoplantar pustulosis | • Persistent, painful sterile pustules that coalesce | • Intraepidermal pustules |
| | • Resolve to brown macules and hyperkeratosis | • Spongiform alterations |
| | | • ±Mixed perivascular infiltrate |
| Erythema multiforme | • Erythematous targetoid papules and plaques | • Vacuolar interface dermatitis with conspicuous keratinocyte necrosis |
| | • ±Mucosal ulceration | • Sparse superficial perivascular lymphocytic infiltrate |

BMZ, basement membrane; DIF, direct immunofluorescence.
*Neutrophil-dominant dermatoses that may occur in association with SLE.
3. Goette DK. Sweet’s syndrome in subacute cutaneous lupus erythematosus. Arch Dermatol. 1985;121(6):789-791.
4. Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. J Cutan Pathol. 2006;33(11):721-725.
5. Brinster NK, Nunley J, Pariser R, Horvath B. Nonbullous neutrophilic lupus erythematosus a newly recognized variant of cutaneous lupus erythematosus. J Am Acad Dermatol. 2012;66(1):92-97.
6. Saeb-Lima M, Charl-Joseph Y, Rodríguez-Acosta ED, Dominguez-Cherit J. Autoimmunity-related neutrophilic dermatosis: a newly described entity that is not exclusive of systemic erythematosus. Am J Dermatopathol. 2013;35(6):655-660.
7. Larson AR, Granter SR. Systemic lupus erythematosus-associated neutrophilic dermatosis—an under-recognized neutrophilic dermatosis in patients with systemic lupus erythematosus. Hum Pathol. 2014;45(3):598-605.
8. Larson AR, Granter SR. Systemic lupus erythematosus-associated neutrophilic dermatosis: A review and update. Adv Anat Pathol. 2014;21(4):248-253.
9. Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease. Report of 9 new cases and review of the literature. Medicine (Baltimore). 2009;88(1):23-31.
10. Grotz W, Baba HA, Becker JU, Baumgärtel MW. Hypocomplementemic urticarial vasculitic syndrome: an interdisciplinary challenge. Dtsch Arztebl Int. 2009;106(46):756-763.