

Nonbullous neutrophilic lupus erythematosus: A newly recognized variant of cutaneous lupus erythematosus

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Background: Neutrophils in the setting of systemic lupus erythematosus (SLE) are commonly associated with bullous disease. Rare cases of nonbullous neutrophilic lesions have been reported in patients with SLE.

Objective: This study used clinical and histologic findings of 4 patients to further define the newly emerging entity of nonbullous neutrophilic lupus erythematosus (LE).

Methods: We reviewed the clinical and pathological findings of 4 patients with known SLE who developed urticarial papules, plaques, subcutaneous nodules, or a combination of these.

Results: All patients were women with established SLE. Histopathological findings in all patients included an interstitial and perivascular neutrophilic infiltrate with leukocytoclasia, and variable vacuolar alteration along the dermoepidermal junction. Direct immunofluorescence study results in two patients were positive for C3, IgG, and IgM along the basement membrane zone. One patient also presented with neutrophil-rich lupus panniculitis. All clinical lesions resolved with immunomodulating/immunosuppressive agents.

Limitations: This study was limited by the small number of cases.

Conclusions: Nonbullous neutrophilic LE is an important entity to consider in the differential diagnosis of neutrophil-mediated eruptions. In addition, the histologic finding of neutrophils in the setting of lupus should alert one to the possibility of systemic disease. (J Am Acad Dermatol 10.1016/j.jaad.2009.05.019.)

Key words: direct immunofluorescence; lupus erythematosus; neutrophils; panniculitis.

Rare reports in the literature have described a nonbullous neutrophilic dermatitis in the setting of lupus erythematosus (LE).¹⁻³ To our knowledge, the existing literature describes 6 cases.^{2,3} We describe 4 additional patients with nonbullous neutrophilic LE. All 4 patients had the clinical findings of pruritic, urticarial papules and plaques, and one patient also had the newly described pattern of neutrophil-rich lupus panniculitis.

METHODS

We reviewed the clinical records and histopathological specimens of 4 patients seen during a 2-year

Abbreviations used:

bid: twice a day
 DEJ: dermoepidermal junction
 LE: lupus erythematosus
 SLE: systemic lupus erythematosus

period of time (2006-2008) at the dermatology clinics of the Virginia Commonwealth University (cases 1-3) and Eastern Virginia Medical School (case 4). Hematoxylin and eosin-stained sections and direct immunofluorescence studies were reviewed.

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RESULTS

For all patients, pertinent clinical data including age, race, gender, duration, distribution and morphology of skin lesions, history of systemic lupus, serologic data, and medications at the time of diagnosis were reviewed (Table I). All patients were women aged 18 to 50 years (mean age 35.5 years). They presented with recent onset urticarial papules and plaques on the trunk and extremities. One patient simultaneously had subcutaneous nodules. None developed blisters. In all 4 patients histologic examination revealed intradermal perivascular and interstitial neutrophils with leukocytoclasia and variable degrees of vacuolar alteration along the dermoepidermal junction (DEJ). There was no leukocytoclastic vasculitis. For all patients, immunomodulating medications resulted in resolution of the lesions.

Case 1

An 18-year-old Peruvian woman with a 1-year history of systemic LE (SLE) presented with pruritic, erythematous papules on her trunk and hands, present for 1 month (Fig 1, A). Pertinent serologies are listed in Table I. Skin biopsy specimen showed a superficial perivascular and interstitial infiltrate of neutrophils with leukocytoclasia, and a brisk neutrophil-mediated vacuolar alteration along the DEJ (Fig 2, A). Direct immunofluorescence studies showed strong C3 and IgG and weak IgM staining along the DEJ in a granular pattern (Fig 3). IgA and fibrinogen were negative.

At the time of her initial biopsy, the patient was taking mycophenolate mofetil (500 mg twice a day [bid]), hydroxychloroquine (200 mg bid), and prednisone (15 mg daily). Shortly after an increase in mycophenolate mofetil to 1000 mg bid, her lesions resolved.

Case 2

A 38-year-old white woman with a 7-year history of SLE presented with 3 weeks of urticarial papules on her trunk and arms (Fig 1, B). The lesions were pruritic and burning. Relevant serologies are listed in Table I. Skin biopsy specimen showed a superficial perivascular and interstitial infiltrate of neutrophils,

with extensive leukocytoclasia and mild vacuolar alteration along the DEJ (Fig 2, B). Direct immunofluorescence showed strong granular staining of IgG and IgM, with weak C3 and IgA along the DEJ. Fibrinogen was negative.

At the time of presentation the patient was taking mycophenolate mofetil (1000 mg bid), prednisone (20 mg daily), and hydroxychloroquine (200 mg bid). Subsequent increase in prednisone to 40 mg daily resulted in resolution of the lesions.

CAPSULE SUMMARY

- Nonbullous neutrophilic lupus erythematosus is a reproducible entity, typically seen in association with systemic disease.
- Histologic features include dermal neutrophils with leukocytoclasia and no vasculitis or bulla formation.
- Direct immunofluorescence studies may show C3 and immunoglobulin deposition along the basement membrane zone.
- Neutrophils in the setting of lupus panniculitis may indicate systemic disease.

Case 3

A 36-year-old African American woman with type 2 diabetes mellitus and a 10-year history of SLE presented with 3 weeks of urticarial papules and tender subcutaneous nodules on her legs (Fig 1, C and D). Serologies are listed in Table I. Biopsy specimen of a papule showed a sparse superficial and perivascular infiltrate of neutrophils, with mild vacuolar alteration along the DEJ (Fig 2, C). Biopsy specimen of a nodule revealed a mixed septal and lobular panniculitis with broad, fibrotic septa and paraseptal lymphoid follicles (Fig 2, D). Hyalinization of fat lobules was present. There was also a superficial and deep perivascular infiltrate of lymphocytes, eosinophils, and neutrophils. Neutrophils were also present within the lymphoid follicles and in septa (Fig 2, E). Tissue stain findings for micro-organisms (Gram, periodic acid-Schiff, and Ziehl-Neelsen) were negative. Direct immunofluorescence examination produced negative findings.

At the time of presentation she was taking prednisone (20 mg daily). The subsequent addition of dapson (50 mg daily) rapidly resolved the clinical lesions.

Case 4

A 50-year-old white woman with a 2-year history of SLE presented with mildly pruritic urticarial, pink plaques on the torso and proximal upper and lower extremities, of a few weeks duration. Pertinent serologies are listed in Table I. Although she was previously taking hydroxychloroquine, the patient was not taking immunomodulating medications at the time of diagnosis. Skin biopsy specimen showed a perivascular and interstitial neutrophil-predominant infiltrate with leukocytoclasia (Fig 2, F) and focal vacuolar alteration along the DEJ. Direct immunofluorescence

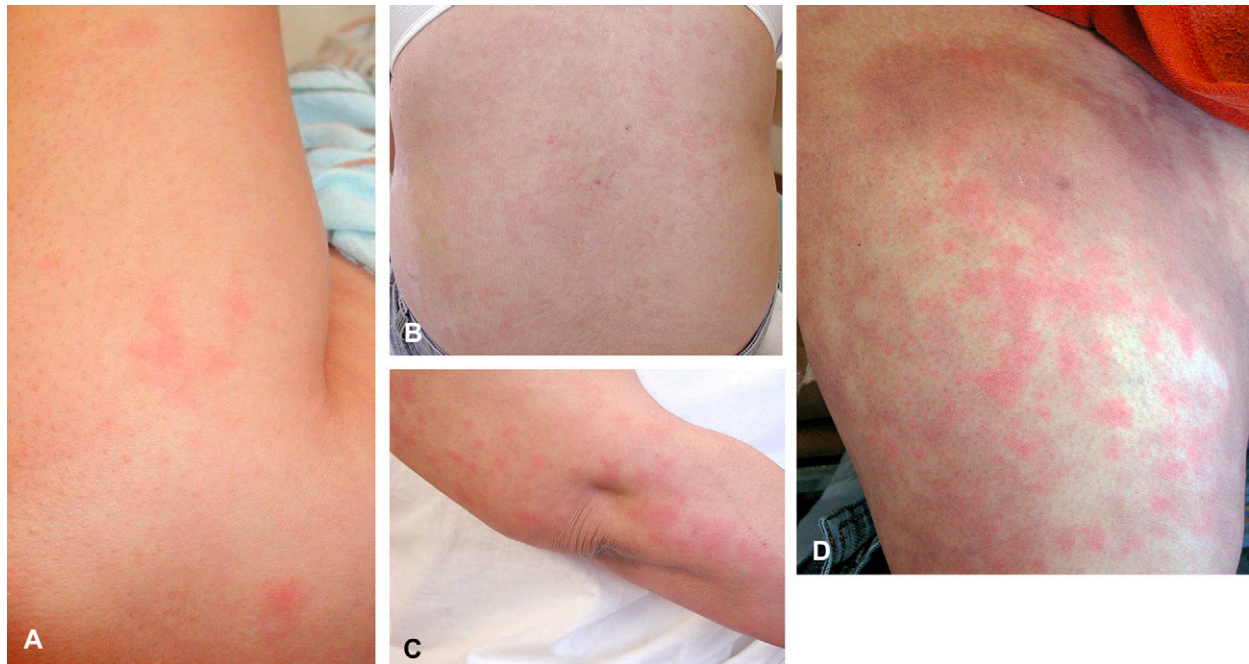


Fig 1. **A**, Case 1: urticarial plaques on arm. **B**, Case 2: ill-defined urticarial plaques on back. **C**, Case 3: urticarial papules and plaques on arm. **D**, Case 3: violaceous ill-defined subcutaneous nodules within background of urticarial papules and plaques on front of thigh.

Table I. Clinical findings

Case	Gender	Age, y	History of SLE, y	Clinical lesions	Distribution	Duration of lesions	Serologies	Medications at diagnosis
1	Female	18	1	Pruritic urticarial papules and plaques	Trunk, arms	1 mo	Positive ANA (1:320 homogenous), dsDNA, anti-RNP; negative SSA, SSB	Mycophenolate mofetil, hydroxychloroquine, prednisone
2	Female	38	7	Burning and pruritic urticarial papules	Trunk, arms	3 wk	Positive ANA (1:2560 speckled), anti-Smith, low complement components C3 and C4, positive LAC	Mycophenolate mofetil, prednisone
3	Female	36	10	Urticarial papules and subcutaneous nodules	Legs	3 wk	Positive ANA (1:1280 nucleolar), anti-RNP; negative SSA, SSB, dsDNA	Prednisone
4	Female	50	2	Pruritic, urticarial pink plaques	Trunk, arms, legs	A few weeks	Positive ANA (1:640 speckled), low C4, normal C3 level	None

ANA, Antinuclear antibody; dsDNA, double-stranded DNA; LAC, lupus anticoagulant; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SSA, extractable nuclear antigen Sicca syndrome A; SSB, extractable nuclear antigen Sicca syndrome B.

studies were not performed. The lesions improved with topical betamethasone cream.

DISCUSSION

We describe 4 patients with nonbullous neutrophilic LE. These cases share clinical features of an established diagnosis of SLE with subsequent

development of pruritic urticarial papules and plaques. One patient simultaneously presented with subcutaneous nodules. None of the patients developed blisters. In 3 of 4 cases, clinical lesions developed in the setting of chronic immunosuppression.

The urticarial lesions in these cases share the histologic findings of an interstitial neutrophilic

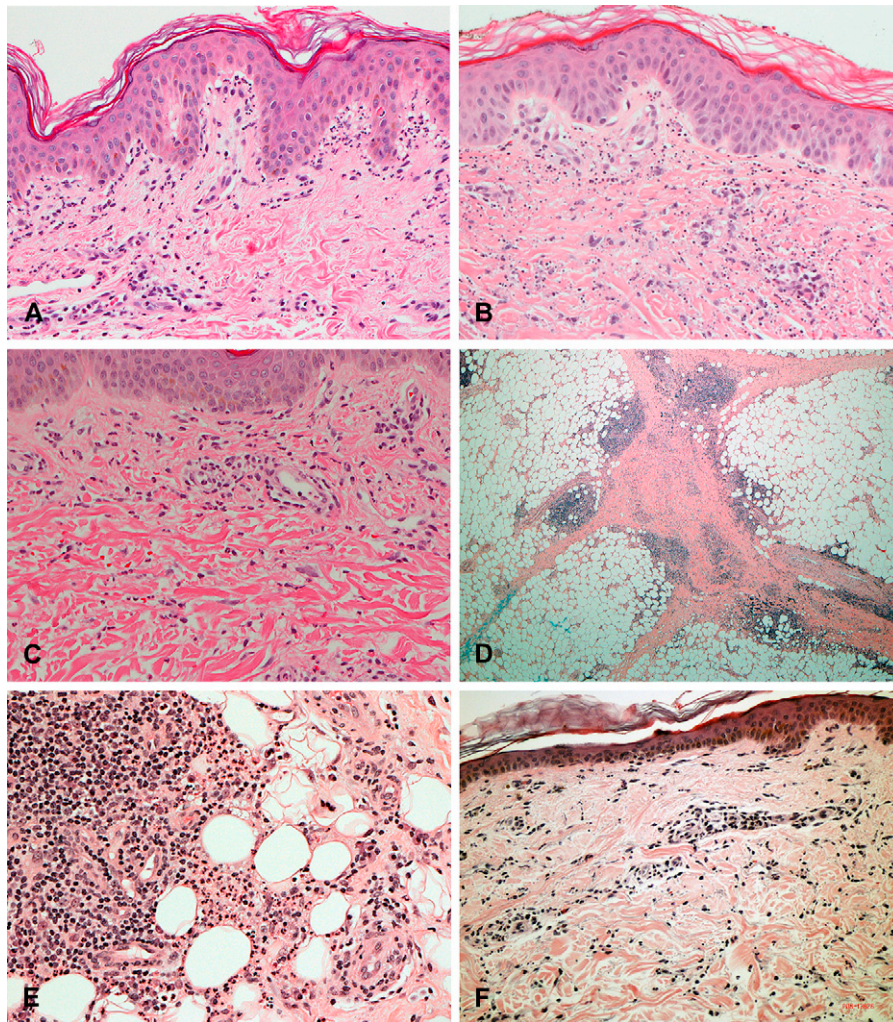


Fig 2. **A**, Case 1: interstitial neutrophils and neutrophil-mediated vacuolar alteration along dermoepidermal junction (DEJ). Leukocytoclasia is present. **B**, Case 2: neutrophilic infiltrate with extensive leukocytoclasia in dermis and along DEJ. Focal apoptotic keratinocyte also present. **C**, Case 3: biopsy specimen from arm with interstitial neutrophils and slight leukocytoclasia. **D**, Case 3: biopsy specimen from front of thigh showing septal widening with fibrosis, paraseptal lymphoid follicles, and hyalinization of fat lobules. **E**, Case 3: higher-power magnification of **D** showing lymphoid follicle with neutrophils within and adjacent to the follicle, extending into fat lobules. **F**, Case 4: intradermal neutrophils with lymphocytes and leukocytoclasia. (**A** to **F**, Hematoxylin-eosin stain; original magnifications: **A** to **C**, **E**, and **F**, $\times 200$; **D**, $\times 20$.)

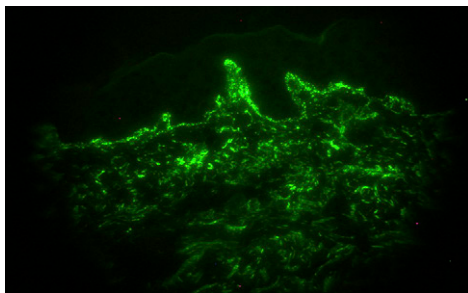


Fig 3. Case 1: Direct immunofluorescence. IgG in granular pattern along dermoepidermal junction. (Original magnification: $\times 100$.)

infiltrate with leukocytoclasia and variable vacuolar interface alteration. The subcutaneous nodules demonstrate classic features of lupus panniculitis in addition to neutrophils in the dermis and fat, not typically present. Our cases support the previous reports and present additional evidence that non-bullous neutrophilic LE is a real and reproducible disorder that may indicate the presence of systemic disease.

Although neutrophilic dermatoses in association with LE are well known historically, this has been seen in the setting of bullous or vasculitic disease.⁴⁻⁹

Table II. Key clinical and histologic features of nonbullous lupus erythematosus and Sweet syndrome

	Nonbullous neutrophilic lupus erythematosus	Sweet syndrome
Clinical features	Erythematous papules and plaques No vesicles, bullae, or pustules Clinical background of systemic/neonatal lupus erythematosus	Erythematous papules and plaques May vesiculate or become bullous/pustular Variable clinical background including leukemia, infection, and inflammatory bowel disease
Histologic features	Neutrophilic infiltrate with leukocytoclasia No vasculitis Vacuolar alteration along dermoepidermal junction Direct immunofluorescence studies may demonstrate complement and/or immunoglobulin deposition along basement membrane zone	Neutrophilic infiltrate with leukocytoclasia Low-grade vasculitis may be present No vacuolar alteration Negative direct immunofluorescence study results

The description of neutrophilic nonbullous plaques and panniculitis in the setting of LE is relatively new to the literature.

Ackerman¹ originally described “scattered neutrophils and neutrophilic dust immediately beneath the epidermis of an interface dermatitis” in the setting of SLE. He conjectured that these lesions may represent a muted form of bullous LE.¹

The first clinical cases were reported by Gleason et al² who described 4 patients with SLE and urticarial lesions. Satter and High³ subsequently described two cases of neonatal LE. Histopathology in all these cases showed interstitial neutrophils with leukocytoclasia, and vacuolar alteration along the DEJ. No vasculitis was noted.

The precise classification of nonbullous neutrophilic lupus is uncertain. It may represent an abortive or early form of bullous LE, as postulated by Ackerman.¹ The fact that 3 of 4 of our patients were on immunosuppressive therapy may have inhibited their ability to form bullae. Our fourth patient developed lesions in the absence of systemic treatment, which alternatively raises the possibility that nonbullous lesions could be a manifestation of the disease process itself: ie, a forme fruste variant of bullous SLE.

Alternatively, nonbullous neutrophilic lupus may represent a variant of febrile neutrophilic dermatitis (Sweet syndrome). The literature contains 6 reports of “Sweet’s like” eruptions in patients with SLE similar to our cases.¹⁰⁻¹⁵

Our cases exhibit some clinical and histologic features commonly seen in Sweet syndrome, such as erythematous plaques and intradermal neutrophils with leukocytoclasia, respectively.¹⁶ However, the neutrophilic infiltrate in our cases is not as dense as is commonly seen in Sweet syndrome and there is an

absence of papillary dermal edema. Our cases also demonstrate vacuolar alteration and immunoglobulin and complement deposition along the DEJ, features not part of Sweet syndrome (Table II).

The pathogenesis underlying nonbullous neutrophilic lupus is also unclear. The presence of vacuolar alteration along the DEJ in our cases, characteristic of cutaneous SLE, combined with immunoreactants along the basement membrane zone in 2 of 3 of the cases, suggests the possibility of a similar antibody-mediated cause.

In conclusion, we present 4 additional cases of nonbullous neutrophilic LE. Our cases confirm the previously recognized clinical features of urticarial papules and plaques, and present the new finding of a neutrophil-rich lupus panniculitis. Increased awareness of these presentations of cutaneous LE may aid clinicians caring for patients with LE and neutrophilic dermatoses.

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REFERENCES

1. Ackerman AB. Histologic diagnosis of inflammatory skin diseases: an algorithmic method based on pattern analysis. 2nd ed. Baltimore: Williams and Wilkins; 1997. p. 525, 542.
2. Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. *J Cutan Pathol* 2006;33: 721-5.
3. Satter EK, High WA. Non-bullous neutrophilic dermatosis within neonatal lupus erythematosus. *J Cutan Pathol* 2007; 34:958-60.
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
5. Berti S, Moretti S, Lucin C, Amato L, Massi D, Fabbri P. Urticarial vasculitis and subacute cutaneous lupus erythematosus. *Lupus* 2005;14:489-92.

6. Crowson AN, Magro C. The cutaneous pathology of lupus erythematosus: a review. *J Cutan Pathol* 2001;28:1-23.
7. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunol Allergy Clin North Am* 2004;24:183-213, vi.
8. Drenkard C, Villa AR, Reyes E, Abello M, Alarcon-Segovia D. Vasculitis in systemic lupus erythematosus. *Lupus* 1997;6: 425-35.
9. Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Clin Rev Allergy Immunol* 2007;33:85-106.
10. Goette DK. Sweet's syndrome in subacute cutaneous lupus erythematosus. *Arch Dermatol* 1985;121:789-91.
11. Ramsey-Goldman R, Franz T, Solano FX, Medsger TA Jr. Hydralazine induced lupus and Sweet's syndrome: report and review of the literature. *J Rheumatol* 1990;17:682-4.
12. Sequeira W, Polisky RB, Alrenga DP. Neutrophilic dermatosis (Sweet's syndrome): association with a hydralazine-induced lupus syndrome. *Am J Med* 1986;81:558-60.
13. Servitje O, Ribera M, Juanola X, Rodriguez-Moreno J. Acute neutrophilic dermatosis associated with hydralazine-induced lupus. *Arch Dermatol* 1987;123:1435-6.
14. Hou TY, Chang DM, Gao HW, Chen CH, Chen HC, Lai JH. Sweet's syndrome as an initial presentation in systemic lupus erythematosus: a case report and review of the literature. *Lupus* 2005;14:399-402.
15. Choi JW, Chung KY. Sweet's syndrome with systemic lupus erythematosus and herpes zoster. *Br J Dermatol* 1999;140: 1174-5.
16. Ratzinger G, Burgdorf W, Zelger BG, Zelger B. Acute febrile neutrophilic dermatosis: a histopathological study of 31 cases with review of the literature. *Am J Dermatopathol* 2007;29:125-33.