

1. Sfikakis PP, Iliopoulos A, Dalmau J, Ricart E, Roe E, Alomar A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. *Arthritis Rheum*. 2005;52:2513-2518.
2. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. *Ann Rheum Dis*. 2006;65: 405-407.
3. Peramiqnel L, Puig L, Worm M, et al. Onset of flexural psoriasis during infliximab treatment for Crohn's disease. *Clin Exp Dermatol*. 2005;30:713-714.
4. Thurber M, Feasel A, Stroehlein J, Hymes SR. Pustular psoriasis induced by infliximab. *J Drugs Dermatol*. 2004;3:439-440.
5. Vere MM, Del Pozo J, Yebra-Pimentel MT, Porta A, Fonseca E. Psoriasiform eruption induced by infliximab. *Ann Pharmacother*. 2004;38:54-57.

Clinical Evidence of an Intermolecular Epitope Spreading in a Patient With Pemphigus Foliaceus Converting Into Bullous Pemphigoid

Pemphigus foliaceus and bullous pemphigoid are 2 distinct forms of autoimmune blistering disorders with unique clinical, histologic, and immunologic features. We describe a patient with pemphigus foliaceus that converted into bullous pemphigoid, providing evidence of clinical intermolecular epitope spreading.

Report of a Case. An 86-year-old African American man presented in 2001 with crusted lesions in his scalp and widespread erosions involving the face, back, chest, abdomen, and extremities. No intact blisters were observed; the mucous membranes were uninvolved. Histopathologic analysis revealed acantholysis and intraepidermal blister formation within the upper epidermis, consistent with pemphigus foliaceus (**Figure**). Direct immunofluorescence showed epithelial cell surface IgG and C3 deposits without any skin basement membrane deposition; an indirect immunofluorescence study was not performed. The patient was treated for the next 1.5 years with prednisone (up to 60 mg/d) and azathioprine (up to 150 mg twice daily) and showed clinical improvement but then was lost to follow-up.

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Two years after his last follow-up visit, the patient developed tense bullae on the right foot. An empirical trial of doxycycline and niacinamide was begun because his clinical picture was more consistent with bullous pemphigoid. Eight months later, the patient developed extensive tense bullae on all extremities and urticarial plaques on the torso. The scalp, face, and mucous membranes were spared. A biopsy specimen revealed a subepidermal blister, intact epidermis, and numerous eosinophils, consistent with bullous pemphigoid. Linear IgG, C3, and fibrinogen deposits were observed at the dermoepidermal junction on direct immunofluorescence, without any epithelial cell surface deposit. Indirect immunofluorescence on human sodium chloride–split skin showed IgG binding exclusively to the epidermal side (roof) of the split, but indirect immunofluorescence on monkey and guinea

pig esophagus showed no epithelial cell surface staining. Enzyme-linked immunosorbent assay detected no IgG autoantibodies to desmoglein 1. Treatment with prednisone, 40 mg/d, and azathioprine, 50 mg/d, was started; doxycycline and niacinamide treatments were discontinued. Four weeks later, all blisters had resolved (**Figure**).

Comment. While rare, reports of coexisting pemphigus foliaceus and bullous pemphigoid or pemphigus vulgaris and bullous pemphigoid have been described in the literature.¹⁻³ Reported cases had a pemphigus-pemphigoid combination that either developed simultaneously or was preceded (by a few years) by pemphigus or pemphigoid and had features of both conditions concurrently as documented by clinical examination, histopathologic analysis, and immunopathologic analysis.^{1,2}

However, an extensive literature search failed to reveal any similar cases of pure pemphigus foliaceus or vulgaris converting into a pure bullous pemphigoid, or vice versa, making our patient unique compared with those with a mixed picture of pemphigus and pemphigoid. We hypothesize that an intermolecular epitope spreading mechanism may have triggered our patient to develop bullous pemphigoid years after pemphigus foliaceus. Epitope spreading occurs when tissue damage caused by an autoimmune or inflammatory skin disease can expose protein components normally undetectable by the immune system, leading to the production of autoantibodies against the exposed protein components and formation of another autoimmune skin disease. Intermolecular epitope spreading occurs between epitopes from 2 different proteins; clinical evidence of intermolecular epitope spreading has been described in a variety of situations in which one autoimmune bullous disease converted into another, but all cases were contained within the pemphigus or pemphigoid group.^{4,5}

Another possible explanation of this case is that these were 2 independent events, and our patient was more vulnerable to develop bullous pemphigoid because he had tendencies toward autoimmune disease. However, we believe that this theory is less likely given the short duration between the outbreak of the 2 diseases. We further suspect that the patient had achieved a cure of pemphigus foliaceus because no antidesmoglein 1 antibodies were detected by enzyme-linked immunosorbent assay or on indirect immunofluorescence of monkey or guinea pig esophagus, and no epithelial cell surface staining was seen on direct immunofluorescence.

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1. Sami N, Ahmed AR. Dual diagnosis of pemphigus and pemphigoid: retrospective review of thirty cases in the literature. *Dermatology*. 2001;202:293-301.

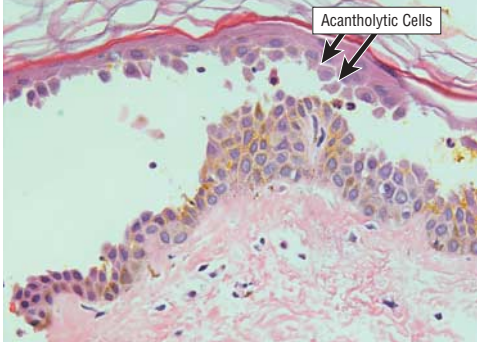
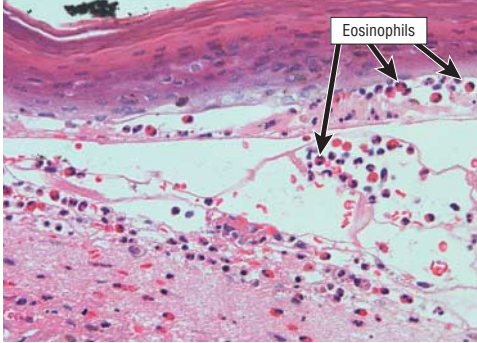
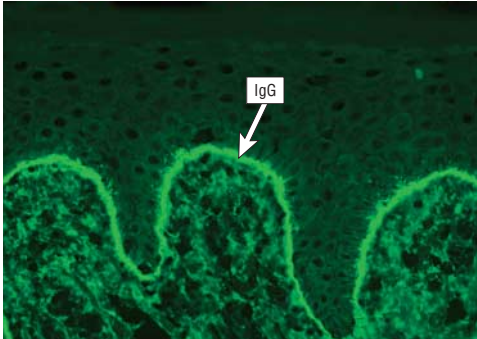
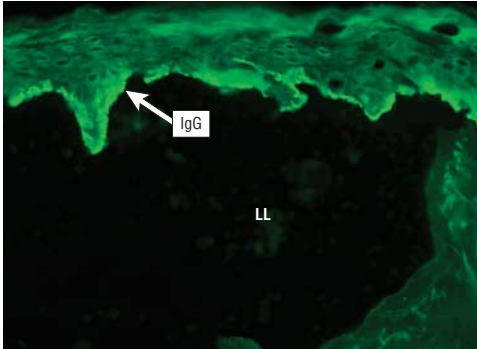
	2001	2006
Clinical Findings	Crusted Lesions in the Scalp; Widespread Erosions Involving the Face, Back, Chest, Abdomen, and Extremities; No Intact Blisters; Mucous Membranes Uninvolved	
Lesional Histopathologic Findings		
Perilesional Direct Immunofluorescence	Epithelial Cell Surface IgG and C3 Deposits; Without Any Basement Membrane Deposition	
Indirect Immunofluorescence	Not Done	
ELISA Findings	Not Done	No Reaction to Desmoglein 1
Treatment Response	Partial Clearing (1.5 y); High Doses of Immunosuppressants (Prednisone up to 60 mg/d; Azathioprine up to 150 mg Twice Daily)	Complete Clearing (4 wk); Moderate Doses of Immunosuppressants (Prednisone 40 mg/d; Azathioprine, 50 mg/d)

Figure. Contrasting features of 2001 and 2006 patient presentations. In 2001, the clinical findings were superficial erosions without intact blisters; histopathologically, an intraepidermal acantholytic blister; and under direct immunofluorescence, IgG deposits at epithelial cell surfaces. In 2006, the clinical findings were tense blisters and erosions; histopathologically, subepidermal blister with infiltrating eosinophils; under direct immunofluorescence, linear deposits of IgG at the skin basement membrane zone; and under indirect immunofluorescence, binding of IgG antibodies to the epidermal side of 1.0M sodium chloride-split skin (LL indicates the lamina lucida space). Original magnification $\times 40$ for all histopathologic photographs. Photographs not available for the clinical presentation and direct immunofluorescence in 2001; indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) were not done in 2001.

2. Harrington CI, Sneddon IB. Coexistence of bullous pemphigoid and pemphigus foliaceus. *Br J Dermatol*. 1979;100:441-445.
3. Korman NJ, Stanley JR, Woodley DT, et al. Coexistence of pemphigus foliaceus and bullous pemphigoid. *Arch Dermatol*. 1991;127:387-390.
4. Chan LS, Vanderlugt CJ, Hashimoto T, et al. Epitope spreading: lessons from autoimmune skin disease. *J Invest Dermatol*. 1998;110:103-109.
5. Fairly JA, Woodley DT, Chen M, et al. A patient with bullous pemphigoid and epidermolysis bullosa acquisita: an example of intermolecular epitope spreading. *J Am Acad Dermatol*. 2004;51:118-122.

Neurovascular Instability Syndrome: A Unifying Term to Describe the Coexistence of Temperature-Related Vascular Disorders in Affected Patients

Temperature-related vascular disorders including pernio, erythromelalgia, and Raynaud phenomenon present a diagnostic and therapeutic challenge. We describe the unusual cooccurrence of perniosis and erythromelalgia. Although these conditions are aggravated by disparate environmental conditions, their coexistence may help to elucidate their pathophysiologic characteristics.

Report of a Case. A 37-year-old woman was referred to our institution 2 years after the onset of erythema, pain, and dusky papules on the feet for which extensive diagnostic workup and therapeutic trials had been unsuccessful. Initially, she had developed painful red papules on the toes triggered by cold temperature. Evaluation of a skin biopsy specimen showed findings consistent with pernio.

Her symptoms improved slightly under treatment with prednisone, but several months later, she developed episodic swelling, redness, and burning pain of her feet triggered by extended periods of walking and hot baths. On physical examination, she had tender red papules and macules on the toes and feet (**Figure**). Findings of another biopsy specimen evaluation were again consistent with pernio.

Laboratory findings were either normal or negative for the following: complete blood cell count; metabolic and hepatitis panels; erythrocyte sedimentation rate; Lyme titer; and levels of antinuclear antibody, double-stranded DNA antibody, cryofibrinogen, cryoglobulin, antiphospholipid antibodies, immunoglobulins, and thyroid-stimulating hormone. Findings from neurologic tests including lumbar puncture, magnetic resonance imaging of the brain and spine, and large-fiber nerve conduction velocities were normal. Small-fiber nerve conduction velocity test results are pending.



Figure. Tender red papules and macules on the toes.

Mild improvement in the patient's symptoms occurred with the use of gabapentin. However, trials of nifedipine, nortriptyline hydrochloride, tiagabine hydrochloride, misoprostol, prednisone, and duloxetine hydrochloride have failed.

Comment. Inflammatory, vascular, and neuropathic mechanisms have been proposed to explain the pathogenesis of temperature-related vascular disorders. Our case of concomitant cold- and heat-induced dermatoses suggests that these conditions may share a common pathophysiologic cause related to abnormal neurovascular control.

Pernio, characterized by painful, erythematous acral lesions, may be divided into a primary and/or idiopathic form and a secondary form associated with medications or underlying conditions including cryoproteinemia, lupus erythematosus, leukemia, and hypercoagulability. The underlying pathogenesis seems to be related to an abnormal vascular response to cold or damp conditions. It has been suggested that the vasculopathic changes lead to inflammation and thrombosis along the dermal vessels at areas of aberrant vasoconstriction.¹

Erythromelalgia, characterized by episodes of erythema and pain of acral skin induced by exercise or heat and relieved by exposure to cold, can also be divided into a primary familial form and secondary forms associated with underlying comorbidities. Recently, a defect in the Na_v1.7 sodium channel has been described in primary erythromelalgia. The defect results in decreased thresholds for impulses in pain-sensing neurons.² Other studies have shown that most patients with erythromelalgia have small-fiber neuropathy that leads to redness and pain after an increase in local blood flow and temperature.³

Our patient's heat-induced erythema and pain are consistent with erythromelalgia, but at the same time she has the persistence of pernio lesions, although these are no longer triggered by cold. Overlap of other temperature-associated vascular disorders including the coexistence of erythromelalgia and Raynaud phenomenon has been documented⁴; however, this is the first report to our knowledge of the coexistence of pernio and erythromelalgia.

While our patient's dual diagnoses may be coincidental, the cooccurrence of 2 or more clinically distinct temperature-associated vascular disorders suggests that they may share a common pathogenesis. We hypothesize that small-fiber neuropathy causes inappropriate neural responses to temperature, which in turn lead to abnormal vascular responses. When cold temperature is the trigger and vasculopathy ensues, Raynaud phenomenon or pernio may develop. If heat is the trigger, then erythromelalgia may occur. We suggest the designation *neurovascular instability syndrome* as a unifying term to describe cases of aberrant neurovascular response to environmental stimuli manifesting as pernio, erythromelalgia, or Raynaud phenomenon.

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