

Pemphigoid Nodularis: A Case Report

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Several variants of bullous pemphigoid have been reported including pemphigoid nodularis. Patients with pemphigoid nodularis have clinical features of prurigo nodularis in combination with clinical or immunologic characteristics of bullous pemphigoid. We report the case of a 71-year-old woman with pemphigoid nodularis. The diagnosis was suspected clinically and established by positive indirect immunofluorescence (IIF) findings characteristic of pemphigoid. Results of direct immunofluorescence (DIF) testing were negative, which emphasizes the importance of conducting both DIF and IIF when pemphigoid nodularis is suspected.

Cutis. 2011;88:224-226.

Pemphigoid nodularis is a rare distinct clinical variant of bullous pemphigoid. It is characterized by clinical features of prurigo nodularis in combination with clinical or immunologic features of bullous pemphigoid.^{1,2} Prurigo nodularis often precedes the development of bullae, thus hindering an early diagnosis unless immunofluorescence studies are performed. We describe a case of pemphigoid nodularis in which direct immunofluorescence (DIF) findings were negative, but clinical suspicion and positive results of indirect immunofluorescence (IIF) testing on monkey esophagus and human salt-split skin established the diagnosis.

Case Report

A 71-year-old woman sought care in February 1997 for severe generalized pruritus of approximately 1 year's duration. Her internist considered the

eruption to be a drug reaction and discontinued the patient's use of atenolol, losartan, ranitidine, conjugated estrogen, hydroxyzine, and vitamin C; after 3 months, no improvement was noted. Subsequent treatment included topical corticosteroids, a topical anesthetic agent, systemic doxepin, cetirizine, hydroxyzine, and a methylprednisolone dose pack during the next 13 months without improvement.

On examination in June 1998 in our department of dermatology, the patient had multiple erythematous papules and plaques with excoriations, excoriated nodules, and superficial ulcerations involving her trunk, thighs, and buttocks (Figure 1). No oral lesions, lymphadenopathy, or blisters were present. Findings from a skin biopsy of a lesion on her right thigh revealed chronic dermatitis. Results of DIF



Figure 1. Large erythematous plaques with excoriated nodules on the lateral surface of the right leg.

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The authors report no conflict of interest.

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testing of 2 biopsy specimens were nondiagnostic. However, IIF testing with monkey esophagus showed strong linear basement membrane zone staining with IgG with a titer of 1:640. Furthermore, serum tested with human salt-split skin showed an epidermal staining pattern.

On the basis of the patient's clinical presentation and IIF test results, a diagnosis of pemphigoid nodularis was established. The patient was subsequently treated with prednisone and azathioprine and returned to the care of her referring dermatologist, with complete remission noted after 4 months of therapy. Subsequently, the prednisone dosage was tapered and discontinued, and the patient was maintained on 50 mg of azathioprine twice weekly.

Comment

Many clinical variants of pemphigoid exist.³ In 1979, Provost et al⁴ first described bullous pemphigoid presenting in patients with prurigo nodularis lesions and diagnostic DIF and IIF findings. The term *pemphigoid nodularis* was coined in 1981.¹

Clinically, prurigo lesions most commonly develop several months to years before blisters, and blisters develop either on normal skin or sites of prurigo lesions.⁴⁻¹⁰ Most patients with pemphigoid nodularis are female and tend to be older than 50 years,¹¹ though exceptional cases have been reported.^{12,13} Mucosal involvement appears to be rare but has been reported to occur at the anterior nares.⁷

Because prurigo nodularis lesions may present before blisters develop, immunofluorescence testing is crucial in establishing the diagnosis. Direct immunofluorescence results typically are positive in cases of pemphigoid nodularis. Specifically, a linear basement membrane zone staining pattern with IgG or C3, or both, usually is observed. Linear basement membrane zone staining with IgA also has been observed in a few cases but has never been the sole conjugate.^{7,8,10} Our patient's case was unique in that the diagnosis rested on correlation of clinical findings with a positive IIF result (1:640 titer) and epidermal staining pattern with the salt-split skin assay (Figure 2), in the absence of positive DIF findings. We speculate that the DIF results in our patient may have been falsely negative because one biopsy specimen was from a well-developed hyperkeratotic plaque in which substantial inflammation may have obfuscated immunofluorescence findings; the other specimen was taken 1 cm away from an early lesion to exclude dermatitis herpetiformis.

Indirect immunofluorescence testing has been positive in most of the reported patients with pemphigoid nodularis, which is consistent with prior reports of positive IIF results in approximately 70%

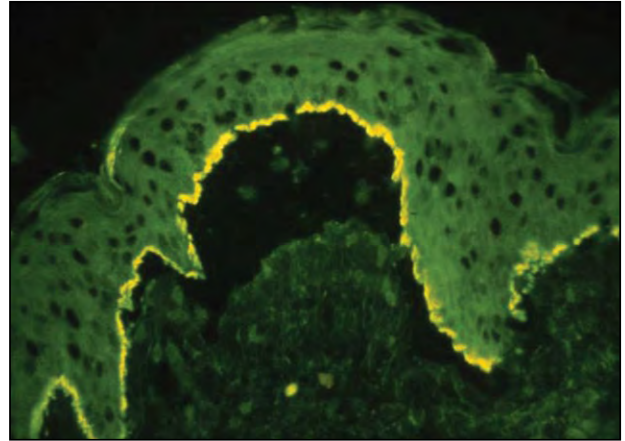


Figure 2. Representative image of an epidermal staining pattern on indirect immunofluorescence with IgG using human salt-split skin. This finding is consistent with pemphigoid (original magnification $\times 20$).

of patients with classic bullous pemphigoid.^{14,15} Imperfect test sensitivity may result from low circulating antibody titers. As highlighted by our case, IIF findings may be critical in proving the diagnosis of pemphigoid nodularis, which also was exemplified by a patient reported by Grolleau-Rochiccioli et al¹⁶ with perilesional biopsy specimens that demonstrated 5 negative DIF results and 3 positive IIF results. These cases emphasize the importance of performing both DIF and IIF studies for all patients with prurigo nodularis or elderly patients with generalized pruritus.

In addition to immunofluorescence testing, immunoblotting studies¹⁷⁻²⁰ and enzyme-linked immunosorbent assay for IgG antibodies to the 230-kDa bullous pemphigoid antigen^{19,21} and the 180-kDa bullous pemphigoid antigen^{20,22,23} may confirm the diagnosis. On immune electron microscopy, gold-labeled antibodies demonstrate deposits at the intracellular or extracellular hemidesmosome in pemphigoid nodularis.²⁰

The pathogenesis of pemphigoid nodularis is not well-understood. It has been postulated that pemphigoid antibodies are induced by physical trauma to the skin and basement membrane in patients with prurigo nodularis lesions. However, this hypothesis does not explain why pemphigoid nodularis bullae develop before prurigo lesions in some patients.^{3,12,24} Another plausible theory is that nodules develop subsequent to scratching in patients who have generalized pruritus with subclinical bullous pemphigoid.²

The treatment of pemphigoid nodularis is challenging. Systemic immunosuppressive therapy

typically is required. Many patients, including ours, have been treated with a combination of prednisone and azathioprine. Sulfamethoxypyridazine, dapsone, intravenous immunoglobulin, rituximab, and suplatast tosilate (a selective helper T cell [T_H2] cytokine inhibitor) have been effective in isolated case reports.^{13,18-21}

Conclusion

Our case illustrates the need to consider pemphigoid nodularis in the differential diagnosis of prurigo nodularis-like eruptions in older patients. Furthermore, because prurigo nodularis lesions precede bullae in most patients with pemphigoid nodularis, immunofluorescence testing may be required to establish the diagnosis. Because neither DIF nor IIF testing is entirely sensitive in pemphigoid variants, we recommend performing both studies when clinical suspicion for immunobullous disease exists. Although serum was not available from our patient to check for autoantibodies to BP180 and BP230, this investigation also may be helpful in establishing the diagnosis of pemphigoid nodularis.

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