Dermatitis herpetiformis with fibrillar IgA deposition and unusual histologic findings

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INTRODUCTION
Dermatitis herpetiformis (DH) is an autoimmune, subepidermal blistering disease associated with gluten sensitivity. It commonly manifests as intensely pruritic papules and vesicles on the extensor surfaces of extremities in a symmetric distribution. Classic histologic findings and data from direct immunofluorescent (DIF) staining often permit for a prompt diagnosis; however, dermatopathologists should be aware of rare and misleading histologic features and DIF patterns that can delay the diagnosis. We present an exceedingly rare case in which there was reasonably strong clinical suspicion for DH but misleading histologic and DIF stain findings. Clinicopathologic correlation allowed for a proper diagnosis and subsequent biopsies showed classic findings.

CASE
A 55-year-old woman with a reported history of celiac disease and poor adherence to her gluten-free diet presented with a 2-month history of intensely pruritic pink papules over her knees, arms, back, and abdomen (Fig 1, A). Serum antibodies against tissue transglutaminase were found in high concentration (119 μ/mL; reference range 0.1-10.0 μ/mL). A punch biopsy from the right lateral knee (Fig 1, B) revealed superficial dermal perivascular lymphohistiocytic inflammation underlying excoriation-related epidermal changes (Fig 2, A and B). No papillary dermal neutrophils or dermal edema were identified on serial step-leveled sections through the tissue block. DIF staining of a biopsy of perilesional skin revealed fine, fibrillar deposition of IgA and IgG along the dermoepidermal junction (Fig 2, C and D, respectively).

The diagnosis of DH was established in light of the clinical presentation, an established diagnosis of celiac disease, and the unusual, albeit diagnostic findings from the DIF stain. However, the patient initially adhered poorly to treatment with dapsone 100 mg daily and to her gluten-free diet. This resulted in only modest improvement over 6 months and the diagnosis was called into question. A repeat punch biopsy of the right upper arm revealed a similar perivascular lymphohistiocytic infiltrate with occasional neutrophils that focally extended to the dermal-epidermal junction. Serial step-leveled sections through the tissue block revealed no subepidermal neutrophilic microabscesses (Fig 3, A and B). A DIF stain performed on another perilesional skin sample revealed the classic appearance of granular IgA deposition in the dermal papillae (Fig 3, C and D). The patient adhered to a gluten-free diet, continued therapy with dapsone, and experienced improvement.

DISCUSSION
Histopathologic findings of DH depend on timing of the biopsy. Early lesions show edema with the accumulation of neutrophils and occasional eosinophils in the dermal papilla. Subepidermal vesicles between rete ridges become more apparent as lesions age. The histologic differential diagnosis depends on the age of the lesion and might include bullous pemphigoid when there are eosinophils.

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linear IgA disease, epidermolysis bullosa acquisita, or bullous lupus.

A small number of cases have been described showing a dermal perivascular lymphohistiocytic infiltrate with vessel ectasia and subtle dermal fibrosis as was seen in our initial biopsy. In a series of 24 cases described by Warren and Cockerell, 9 biopsies revealed such findings; however, all of the patients

Fig 1. A, Clinical photographs of pruritic, pink papules on the right lateral knee. B, Biopsy site, right lateral knee.

Fig 2. A and B, Perivascular lymphohistiocytic inflammation without the classic histologic features of dermatitis herpetiformis. Fibrillar IgA (C) and IgG (D) deposition present in the companion biopsy submitted for direct immunofluorescent (DIF) staining. (A and B, Hematoxylin-eosin stain; C and D, DIF stain; original magnifications: A, C, and D, ×200; B, ×400.)
in their series had granular IgA deposition seen by DIF staining in addition to classic clinical manifestations that permitted for an appropriate diagnosis. Lesions with these rare and unusual findings would in the absence of clinical correlations or a positive DIF suggest a histologic differential diagnosis of subacute spongiotic dermatitis versus a drug- or virus-related dermal hypersensitivity reaction.

A diagnosis of DH is further supported by DIF identification of granular IgA deposition in the papillae or below the dermal-epidermal junction of perilesional and uninvolved skin, but this finding is not found in the skin of patients with celiac disease who do not have DH. The granular deposits exhibit some morphologic variability between cases; however, they are most evident within the dermal papillae and appear as small aggregates or clumps in sharp contrast with the smooth, linear deposition present along the basement membrane exemplified by linear IgA disease. There are rare reports of DH showing a distinct fibrillar IgA deposition by DIF stain. In our initial biopsy of perilesional skin, DIF staining revealed this rare pattern, characterized by variably intense IgA labeling of irregular, elongated strands deposited broadly and perpendicularly along the dermal-epidermal junction without confluence or accentuation in the papillae. This distinct fibrillar pattern was predominant in the initial specimen submitted for DIF. This unexpected finding together with an absence of conventional histologic features raised some uncertainty about the diagnosis of DH. In contrast with our patient, 2 of the 3 patients described in a series by Ko and colleagues had no detectable serum transglutaminase or endomysial antibodies. Their third patient, like our own, had circulating autoantibodies to transglutaminase and clinical features to further substantiate the diagnosis of DH despite this unusual finding. All patient biopsies in the series reported by Ko and colleagues had clusters of neutrophils at the dermoepidermal junction. This helpful, characteristic finding was absent from our case, which lead to the consideration of an alternative diagnosis of a dermal hypersensitivity reaction when the patient initial showed no evidence of improvement.

There are exceedingly rare mentions in the literature of cases like ours in which there is an absence of both classic histologic and DIF findings, and this is, to our knowledge, the first report of DH in which a classic granular DIF pattern was identified on a repeat

**Fig 3.** A, Similar perivascular lymphocytic infiltrate present in the repeat biopsy with occasional neutrophils and focal extension to the junction without edema or neutrophilic microabscess formation. C and D, Granular IgA deposition at junction. (A and B, Hematoxylin-eosin stain; C and D, direct immunofluorescent stain; original magnifications: B, ×400; A, C, and D, ×200.)
biopsy of perilesional skin following prior identification of the fibrillar pattern. Although the chronologic order of our DIF findings raises the question of whether or not fibrillar immune complex deposition could represent an early feature in developing lesions of DH, a majority of the rare reported cases with fibrillary deposition have been associated with well-developed histologic features of DH on biopsy. These observations would argue against a temporal relationship linking the DIF pattern to the age of the lesion. Nonetheless, they raise awareness of an alternative pattern that may be seen in DH even in the absence of classic histologic features.

The diagnosis of DH was clinically suspected in our case; however, the histologic and DIF findings were highly unusual and misleading, which lead to the decision to repeat biopsy after there had been no significant clinical improvement. In retrospect, we understand that this lack of improvement was caused by variable adherence to diet and medication. We present this case and a review of the literature to raise awareness of these rarely reported histologic and DIF findings, to emphasize that they are not mutually exclusive and to illustrate how they can potentially delay diagnoses. Such a scenario also illustrates the importance of correlating clinical, laboratory, histopathologic, and DIF data in the evaluation of suspected immunobullous disease.

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