Abstract

Dermatitis herpetiformis (DH) is an autoimmune bullous disease, which represents the cutaneous manifestation of gluten sensitivity, in the setting of celiac disease. Although classical DH is characterized clinically by grouped, vesicles on an erythematous base, primary lesions often are absent owing to the intense, associated pruritus. Instead, many cases present only with erythematous erosions with numerous overlying excoriations. As in celiac disease, the core pathogenic mechanisms of DH are likely mediated by immunoglobulin A class autoantibodies against one of several transglutaminase enzymes. As the production of these autoantibodies is directly correlated with gastrointestinal exposure to gliadin, which is an alcohol-soluble fraction of gluten, a gluten-free diet represents the cornerstone of a DH management regimen. In cases refractory to dietary management alone, dapsone is the first-line agent for the treatment of DH, although many other agents have been anecdotally reported as effective.
Case synopsis

History: A 54-year-old man was referred to the NYU Dermatologic Associates for a nine-month history of pruritus that affected the back, arms, legs, and thighs. Past medical history included a recent unintended 20 pound weight loss, diabetes mellitus, and hypothyroidism. The patient denied any other recent changes in his health and a review of systems was negative for diarrhea, nausea, bloating, or dyspepsia.

A punch biopsy was obtained from a representative lesion on the right thigh.

Physical examination: A few, scattered, erythematous erosions with numerous overlying erythematous-to-hyperpigmented, linear excoriations and lichenification were present on the medial aspects of the thighs, back, and lateral aspects of the arms.

Laboratory data: Serum tissue transglutaminase IgA levels were 15 U/mL (normal range <6 U/mL). Serum endomysial antibody was detected at a titer of 1:20 (normal < 1:5).

Histopathology: There is a superficial, perivascular, lymphocytic infiltrate with a predominantly sub- and intraepidermal collection of neutrophils. Rare eosinophils also are noted. A periodic acid-Schiff with diastase stain fails to reveal fungal hyphae.

Discussion

Diagnosis: Dermatitis herpetiformis

Comment: Initially described by Louis Duhring in 1884, dermatitis herpetiformis (DH) is an autoimmune bullous disease, which represents the cutaneous manifestation of gluten hypersensitivity, in the setting of celiac disease [1]. Whereas DH is characterized clinically by grouped, fragile vesicles on an erythematous base, primary lesions often are absent owing to the intense, associated pruritus. Instead, many cases present only with erythematous erosions, with numerous overlying excoriations. In most cases, the disease distribution is relatively symmetric, with the extensor surfaces of the upper and lower extremities, scalp, and buttocks being the most affected areas [2]. Less commonly, DH may present with palmoplantar purpura and petechiae, with complete sparing of the dorsal aspects of the extremities [2]. Furthermore, although associated mucosal lesions are rare, emerging evidence suggests that dental abnormalities, which include pits of the enamel, are relatively common, but likely underreported [3-5].

As in celiac disease, the core pathogenic mechanisms of DH are likely mediated by immunoglobulin A (IgA) class autoantibodies against one of several transglutaminase enzymes. In celiac disease, the pathogenic autoantibody targets tissue transglutaminase (tTG), which is a ubiquitous cytoplasmic, calcium-dependent enzyme that catalyzes crosslinks between glutamine and lysine protein residues [2,6]. In the setting of celiac disease, tTG modifies gliadin, which is an alcohol-soluble fraction of gluten, into a potent autoantigen with a distinct specificity for T cell stimulation via gut-derived antigen presenting cells [2,6,7]. The resulting autoimmune response is further enhanced by highly immunogenic tTG-gliadin complexes that are formed via protein-protein cross-linking [2,6,7]. This latter mechanism appears to represent the key event in the pathogenesis of DH, with epidermal transglutaminase (eTG) acting as the primary autoantigen. In contrast to tTG, which is largely ubiquitous, eTG only occurs in the small intestine, brain, testes, and epidermis where it functions to facilitate and maintain cornified envelope integrity [2,8,9]. Whereas the relationship between the development of autoantibodies to tTG and eTG remains unclear, emerging data suggests that the two enzymes share a common epitope, which may function as the primary autoantigen [2,10,11].
Because DH is now regarded as a cutaneous manifestation of gluten hypersensitivity, a gluten-free diet represents the cornerstone of management. Although its precise pathogenesis remains unclear, neutrophil and eosinophil degranulation at superficial dermal papillae is pathognomonic for DH. A biopsy for histopathologic examination should include an intact vesicle. The classic histopathologic features that are associated with DH include a subepidermal cleft that contains neutrophils and a few sparse eosinophils as well as a perivascular inflammatory infiltrate, although these findings may occur in linear IgA bullous dermatosis and bullous lupus erythematosus. Although a direct immunofluorescence analysis that shows granular deposits of IgA at the superficial most aspects of dermal papillae is pathognomonic for DH, the sensitivity of direct immunofluorescence only approaches 90%. Since DH is now believed to represent a cutaneous manifestation of gluten intolerance, serologic testing for autoantibodies associated with celiac disease often proves vital in diagnostically challenging cases. These tests include total serum IgA, anti-tTG IgA, IgG, and anti-endomysial IgA and IgG.

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As in many dermatologic conditions, the diagnosis of DH requires clinicopathologic correlation, which includes clinical features, serologic tests, and a biopsy for both routine histopathologic and immunofluorescence analysis. As with most other vesiculobullous diseases, biopsy specimens obtained for histopathologic examination should include an intact vesicle. The classic histopathologic features that are associated with DH include a subepidermal cleft that contains neutrophils and a few sparse eosinophils as well as a perivascular inflammatory infiltrate, although these findings may occur in linear IgA bullous dermatosis and bullous lupus erythematosus. Although a direct immunofluorescence analysis that shows granular deposits of IgA at the superficial most aspects of dermal papillae is pathognomonic for DH, the sensitivity of direct immunofluorescence only approaches 90%. Since DH is now believed to represent a cutaneous manifestation of gluten intolerance, serologic testing for autoantibodies associated with celiac disease often proves vital in diagnostically challenging cases. These tests include total serum IgA, anti-tTG IgA, IgG, and anti-endomysial IgA and IgG.

References

13. Spurkand A, et al. Dermatitis herpetiformis and celiac disease are both primarily associated with the HLA-DQ (alpha 1*0501, beta 1*02) or the HLA-DQ (alpha 1*03, beta 1*0302) heterodimers. Tissue Antigens 1997;49:29 [PMID: 9027962].