

Dermatitis Herpetiformis Presenting as Chronic Urticaria

Gavin R. Powell, M.D., Anna L. Bruckner, M.D., and William L. Weston, M.D.

Department of Dermatology, University of Colorado Health Sciences Center, Aurora, Colorado

Abstract: Childhood dermatitis herpetiformis (DH) is an immunobullous disease associated with gluten-sensitive enteropathy. This disease is rare in children and is typically characterized by intensely pruritic vesicles on the extensor surfaces. Definitive diagnosis of DH depends on the direct immunofluorescence finding of granular or fibrillar IgA deposits along the basement membrane zone of biopsied perilesional skin. We report an 11-year-old boy with an unusual presentation of DH characterized by a 7-month history of chronic urticaria-like skin lesions. He had evanescent, largely asymptomatic, urticarial wheals on his trunk, face, and extremities that were unresponsive to conventional therapy for urticaria. Skin biopsy specimen findings were consistent with DH and direct immunofluorescence of perilesional skin was diagnostic. The patient had no symptoms of gluten-sensitive enteropathy at the time of diagnosis, and his skin lesions rapidly cleared with dapsone therapy. This patient serves to highlight an unusual presentation of childhood DH and the need to consider this diagnosis when evaluating chronic urticarial lesions in children.

CASE REPORT

A previously healthy 11-year-old Caucasian boy presented to our pediatric dermatology practice with a 7-month history of persistent, urticaria-like lesions. These first appeared 5 weeks after the patient was treated with intramuscular benzathine penicillin for culture-positive group A streptococcal pharyngitis. The cutaneous lesions were reported as hives on the trunk, face, and extremities. By history, most of the skin lesions were transient, lasting less than 24 hours. A few would persist for several days prior to resolution. Gastrointestinal and other constitutional symptoms were not present. Pruritus and vesiculation were notably absent.

The initial diagnosis was streptococcal-associated urticaria and management included oral diphenhydramine and loratadine, which failed to clear the lesions. The patient was then referred to an allergist for evaluation of chronic urticaria.

Initial laboratory evaluations included a normal complete blood count (CBC), liver function tests, urinalysis, creatinine, thyroid-stimulating hormone (TSH), and serum IgE. C4 and C1 esterase inhibitor levels were also within normal limits. Anti-streptolysin O (ASO) titer was elevated at 1060 IU/ml (normal 0–200 IU/ml). Skin prick tests for common environmental allergens were negative. The patient was subsequently treated with oral prednisone for 5 days, which transiently cleared the eruption.

Address correspondence to Gavin R. Powell, M.D., Department of Dermatology, University of Colorado Health Sciences Center, P.O. Box 6510, Mail Stop F703, Aurora, CO 80045-0510.



Figure 1. Right forearm shows urticarial wheals with blanching halos.

Soon after, the patient continued to have exacerbations of his condition despite chronic suppression with H_1 and H_2 antagonists. Plain film radiographs of the chest were unremarkable. Sinus films were interpreted as consistent with sinusitis. Although asymptomatic for sinus disease, the patient was treated with oral clarithromycin, which failed to improve his cutaneous eruption. Other interventions, instituted by the patient's mother, including the elimination of dairy products, a "yeast-free" diet, and homeopathic remedies, also failed to improve his skin disease. The eruption continued in an evanescent but otherwise asymptomatic pattern and again cleared transiently with a second course of oral prednisone. Six months after initial presentation, rare blistering of individual skin lesions was reported. Laboratory studies were repeated and remained unremarkable, including a negative antinuclear antibody (ANA) test. A computed tomography (CT) scan of the sinuses was normal.

As months of evaluation and treatment had not produced improvement, the patient was referred to dermatology. Physical examination at our clinic found a healthy-appearing 11-year-old boy in the 50th percentile for weight and the 30th percentile for height. Mucous membranes were unremarkable. Cutaneous examination revealed more than a hundred 4–12 mm wheals with blanching halos, distributed over his face, trunk, and extremities (Fig. 1) and positive dermatographism. No vesicles, erosions, or excoriations were noted. The clinical differential diagnosis included chronic urticaria, urticaria pigmentosa, urticarial vasculitis, dermatitis herpetiformis, and other bullous disorders.

Two 4 mm punch biopsy specimens were taken from the right upper arm. Lesional skin was submitted for routine histologic examination. Hematoxylin-eosin-stained sections revealed neutrophilic microabscesses in the

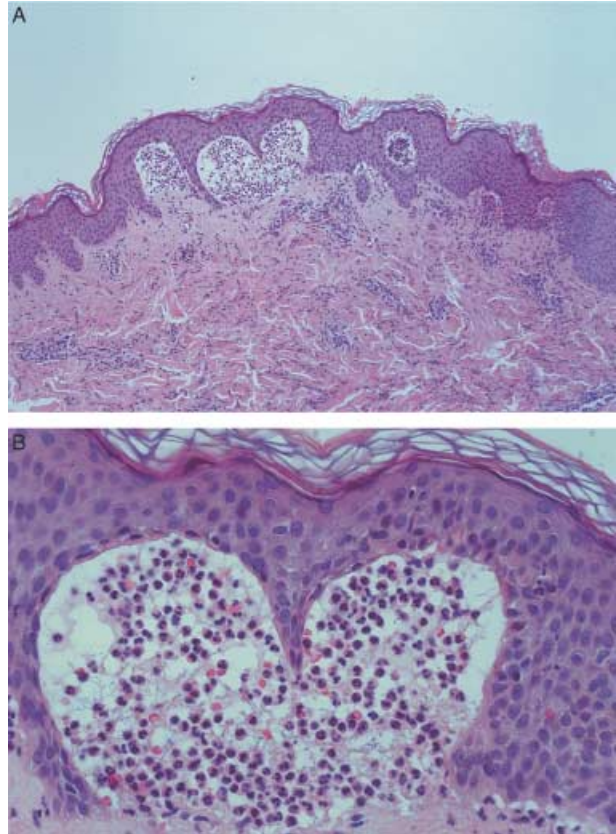


Figure 2. (A) Subepidermal blister formation and a superficial and deep perivascular and interstitial mixed inflammatory infiltrate consisting of lymphocytes and neutrophils (hematoxylin-eosin; original magnification 40 $\times$). (B) High-power view shows a "stuffed papilla," with papillary dermal neutrophilic microabscesses with blister formation (hematoxylin-eosin; original magnification 200 $\times$).

dermal papilla with subepidermal blister formation, suggestive of DH (Fig. 2). A superficial and deep perivascular and interstitial infiltrate consisting of lymphocytes and neutrophils was also noted. Perilesional skin was submitted for direct immunofluorescence studies, and these demonstrated marked deposition of fibrillar IgA along the basement membrane zone (BMZ) with papillary accentuation, diagnostic of DH. IgA antigliadin, antiendomysial, and tissue transglutaminase antibodies, all markers for gluten-sensitive enteropathy, were not measured.

The patient was subsequently started on dapsone 25 mg/day and complete clearing of skin lesions was noted in 48 hours. A gluten-free diet was also instituted at the time of diagnosis. Follow-up for this patient has revealed mild exacerbations of his skin disease, which now demonstrates more typical vesicular lesions and pruritus. Titration of the dapsone dose has been effective in managing these exacerbations.

DISCUSSION

Childhood DH is rare. Its true incidence and prevalence have been difficult to determine due to previous failure to differentiate this condition from linear IgA bullous dermatosis (1). In more than 20 years of experience in the immunofluorescence laboratory at the University of Colorado Health Sciences Center, only three instances of diagnostic immunofluorescence findings for DH have been identified in prepubertal children (2). Childhood DH typically occurs between the ages of 2 and 7 years and has been reported in children as young as 10 months of age (3). Clinical findings in most instances resemble the adult form of the disease, with intensely pruritic papulovesicular lesions showing a predilection for the extensor surfaces of the knees and elbows, the buttocks, posterior neck, and scalp, although any part of the skin may be involved. Mucous membrane involvement is rare and often asymptomatic. Cutaneous lesions are often preceded by an 8- to 12-hour prodrome of stinging and burning at the site of the impending eruption. The primary lesions most commonly present as 1–5 mm grouped papules and vesicles. Due to the intense pruritus, excoriated papules and erosions are often seen, as scratching rapidly unroofs vesicles.

Urticarial skin lesions are not a common clinical feature of DH. In our patient, urticaria-like wheals were the predominant lesions for the first 6 months of presentation. The lack of pruritus and the paucity of vesicular lesions are also unusual features. But the superficial and deep perivascular and interstitial inflammatory infiltrate noted on histologic examination provides an explanation for the urticarial appearance of this patient's skin lesions. This histologic pattern is more commonly seen in urticaria, and is a rare finding in DH. Review of the literature revealed no other reports that describe urticarial wheals as the primary clinical feature. Other unusual presentations of childhood DH reported include nonpruritic, deep dermal papules and nodules of the buttocks, hands, and extensor surfaces in a 5-year-old child (4), isolated erythematous palmar and plantar plaques (5), and isolated palmar purpura (6).

The differential diagnosis for diseases that may clinically mimic urticaria in children include DH, chronic bullous disease of childhood, lupus erythematosus, bullous pemphigoid, vasculitis, erythema multiforme, papular urticaria, and urticaria pigmentosa. It should be noted that a majority of the above dermatoses, excluding papular urticaria and urticaria pigmentosa, also have characteristic direct immunofluorescence findings. Granular and/or fibrillar IgA deposits along the BMZ with papillary accentuation are diagnostic of DH (7). Therefore direct immunofluorescence studies of the skin

should be considered when evaluating atypical urticarial lesions.

Dermatitis herpetiformis is intimately associated with gluten-sensitive enteropathy, with 100% of patients demonstrating subclinical or latent celiac disease (CD) (8). The pathogenesis of gluten-sensitive enteropathy involves genetically susceptible individuals in whom the deamidation of gluten by tissue transglutaminase (TG) leads to the production of autoantibodies, including antibodies to TG (9). The exact mechanism producing skin disease in DH is unknown, but it has been shown that in both CD and DH, circulating antibodies to both tissue and epidermal TG are present (10). In addition, evidence suggests that epidermal TG-specific antibodies occur in DH, and that the IgA immune complexes found in DH skin contain epidermal TG, suggesting that epidermal TG is the autoantigen in DH (10). Furthermore, the production of autoantibodies in both DH and CD directly correlates with the ingestion of gluten, with reduced antibody levels occurring with a gluten-free diet.

Hence the maintenance of a gluten-free diet is the ideal long-term treatment for childhood DH, with a majority of patients having clearing of skin lesions within 1–6 months of starting treatment (3). Strict maintenance of this diet can be challenging, especially for children, and requires a significant commitment. Early in the treatment course and/or in the absence of a strict gluten-free diet, disease control may require medical management. Dapsone is the drug of choice for DH and is highly effective for controlling skin lesions and pruritus, often clearing the eruption within 48–72 hours. The drug is started at 2 mg/kg/day for childhood disease and titrated, depending on clinical response (1).

Dapsone is associated with dose-related hemolytic anemia and methemoglobinemia in all patients; glucose-6-phosphate dehydrogenase deficiency is a contraindication to its use. Agranulocytosis is a rare complication and can occur early in the treatment course. Weekly CBC and reticulocyte counts should be done until hemoglobin levels are stable, then monthly to bimonthly testing is appropriate. Our patient responded rapidly to dapsone therapy and has maintained adequate disease control with this drug.

Childhood DH is a rare blistering disease that usually presents with the typical features of the adult form of the disease. Although other atypical presentations have been noted in previous reports, none describe urticaria-like wheals as the primary cutaneous lesion. We describe a boy with childhood DH in whom chronic asymptomatic urticarial wheals were the predominant feature. Clinicians should consider the diagnosis of DH and other immunobullous diseases when evaluating children with chronic urticarial lesions that have not responded to

therapy and utilize skin biopsy and direct immunofluorescence as part of the evaluation.

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