Dermatitis herpetiformis

Relevance of the physical examination to diagnosis suspicion

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Dermatitis herpetiformis (DH) is a vesicobullous eruption that appears on the elbows, knees, buttocks, neck, and scalp, and less commonly on the upper back, abdomen, groin, and face.[1] The main symptoms are severe itch, followed by small blisters resembling those caused by herpes simplex virus. They are often scratched, creating eroded and crusted secondary lesions, resembling the cutaneous lesions of excoriated prurigo. The appearance of vesicobullous eruptions and excoriated prurigo–like eruptions can delay the diagnosis of DH for several months or years. Even less common, DH can cutaneously manifest urticarial papules[2] or purpuric or petechial lesions on the hands and feet.[3-13]

Celiac disease (CD) is a gastrointestinal disease that manifests as small-intestinal inflammation, villous atrophy, and crypt hyperplasia after the ingestion of gluten.[1] However, much evidence shows that gluten-induced manifestations of CD can also appear outside the intestinal tract.[1] Dermatitis herpetiformis is the most widely recognized of these extraintestinal disorders, and today it is accepted as a particular type of CD.[1]

Diagnosis of DH is established on the basis of clinical, histologic, serologic, and direct immunofluorescence findings.[1,2,14] These include polymorphic eruptions with vesicles and intense itching on the elbows, knees, and buttocks. Symptoms and family history of CD might be present. Neutrophilic microabscesses at the papillary dermis tips and subepidermal bullae are typical but not diagnostic findings. Presence of granular immunoglobulin (Ig) A deposits on the papillary dermis is a diagnostic criterion that differentiates DH from linear IgA dermatosis. Serologic measurements include IgA tissue transglutaminase and IgA endomysial antibodies.

This article describes 4 clinical cases collected during the past 6 years, in which the presence of excoriated papules on the skin of the hands and feet plus acral purpuric lesions contributed to the correct diagnosis of DH. All 4 patients had histories of multiple previous medical appointments during which proper investigations for gluten intolerance were not done.

Case

The main characteristics of the 4 patients are summarized in **Table 1** and **Figures 1** to **4**. Patient 1 was a 44-year-old white man with hypothyroidism, pruritus, and prurigo-like papules and petechiae on his elbows. Patient 2 was a 19-year-old white woman with severe itching and

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EDITOR'S KEY POINTS

- Diagnosis of dermatitis herpetiformis (DH) is established on the basis of clinical, histologic, serologic, and direct immunofluorescence findings. These include severe itch, followed by small blisters resembling those caused by herpes simplex virus; measurement of tissue transglutaminase; and presence of immunoglobulin A on direct immunofluorescence.
- Because DH is a cutaneous form of celiac disease, it is best treated with a gluten-free diet. Dapsone can be taken until the gluten-free diet takes effect. For patients who cannot tolerate or are unresponsive to dapsone or other sulfonamide drugs, alternative therapies include heparin, tetracycline and nicotinamide, or cyclosporine.
- Patients with celiac disease who have even minor itching lesions should be referred to dermatologists. The presence of petechial or purpuric lesions on the hands and feet strongly indicates DH.

POINTS DE REPÈRE DU RÉDACTEUR

- On pose le diagnostic de la dermatite herpétiforme (DH) sur la base des constatations cliniques, histologiques, sérologiques et de l'immunofluorescence directe. Parmi celles-ci se trouvent une démangeaison sévère, suivie de l'apparition de petites cloques qui ressemblent à celles causées par le virus de l'herpès simplex, la mesure de la transglutaminase des tissus et la présence de l'immunoglobuline A à l'immunofluorescence directe.
- Parce que la DH est une forme cutanée de la maladie céliaque, le meilleur traitement est un régime alimentaire sans gluten. On peut prendre de la dapsone jusqu'à ce que l'alimentation sans gluten fasse effet. Chez les patients qui ne tolèrent pas la dapsone ou d'autres médicaments sulfamidés, ou qui n'y répondent pas, les autres thérapies à envisager sont l'héparine, la tétracycline et le nicotinamide ou la cyclosporine.
- Il faudrait demander une consultation en dermatologie pour les patients atteins de la maladie céliaque qui ont des lésions avec démangeaisons, même mineures. La présence de pétéchies ou de purpuras aux mains et aux pieds laissent fortement présager une DH.

excoriated papules and hematic crusts on the extensor surfaces of her forearms, elbows, and legs; intergluteal region; scalp; and submandibular skin. Patient 3 was a 58-year-old white man with hypothyroidism and gastrointestinal symptoms. He had itching and excoriated papules on the extensor surfaces of the limbs, lumbar area, and buttocks. Patient 4 was a 22-year-old white male with

Table 1. Patient characteristics

CASE	AGE, SEX, AND ETHNICITY	GIS, DURATION OF DISEASE, AND ASSOCIATED DISEASES	CLINICAL FEATURES AND DIFFERENTIAL DIAGNOSIS	ANTI-tTG LEVELS, TITRE, AND G6PD BLOOD LEVELS*	HISTOLOGIC ASPECTS AND DIRECT IMMUNOFLUORESCENCE RESULTS	TREATMENT AND FOLLOW-UP
Patient 1	44 y Male White	No 1 y Hypothyroidism	• Pruritus and prurigo-like papule vesicles and petechiae on the elbows • Bullous pemphigoid	• 196.8 U/mL (ELISA; normal level below 20 U/mL) • 1:160 • 44.9 mU/billion red blood cells	• Subepidermal bullae containing numerous neutrophils and neutrophilic microabscesses at the papillary dermal tips • Granular IgA deposits on the upper dermis	• Gluten-free diet and tetracycline 2 g/d plus oral nicotinamide 1.5 g/d • Improvement after 2 wk
Patient 2	19 y Female White	No 1.5 y None	• Severe itching all over the body and excoriated papules and hematic crusts on the extensor surfaces of the forearms, elbows, and legs; lumbar area; intergluteal region; scalp; and submandibular skin • Scabies	• 90 U/mL (normal level below 35 U/mL) • Not done • Normal	• Subepidermal bullae with neutrophilic infiltrate • Granular IgA deposition on the upper dermis	• Oral dapsone 100 mg/d • Free of itch after 4 d
Patient 3	58 y Male White	Yes 10 y Hypothyroidism	• Itching and excoriated papules on extensor surfaces of the limbs, lumbar area, and buttocks • Scabies and atopic dermatitis	• 175 U/mL (normal level below 35 U/mL) • Not done • Normal	• Subepidermal cleavage with neutrophilic infiltrate and microabscess on the papillary dermis • Granular IgA deposition on subepidermal area	• Gluten-free diet for 4 mo • After 6 mo, free of lesions and gained 3.6 kg
Patient 4	22 y Male White	No 1.5 y Hypothyroidism	• Numerous excoriated papules and crusts distributed on the dorsum of the hands, scalp, neck, extensor surfaces of the limbs, lumbar area, and intergluteal region; and several new and old petechial lesions at the volar aspect of the hands and feet • Scabies	• 18 U/mL (ELISA; normal level below 10 U/mL) • Not done • Normal	• Subepidermal vesicle with neutrophilic infiltrate • Granular IgA deposits on the upper dermis	• Oral dapsone 100 mg/d • Not reported

ELISA—enzyme-linked immunosorbent assay, G6PD—glucose-6-phosphate dehydrogenase, GIS—gastrointestinal symptoms, Ig—immunoglobulin, tTG—tissue transglutaminase.
*A normal G6PD level is greater than 118.0 mU/billion red blood cells.

hypothyroidism and numerous excoriated papules and crusts on the dorsum of the hands, scalp, neck, extensor surfaces of the limbs, lumbar area, and intergluteal region. He had several new and old petechial lesions at the volar aspect of the hands and feet. For each patient, anti–tissue transglutaminase levels and glucose-6-phosphate dehydrogenase levels were measured, and direct immunofluorescence was performed.

Discussion

The cutaneous lesions in DH can be extensive, but in mild cases only a few scattered lesions can be seen on the skin,[1] making the diagnosis of DH difficult. The activity of the eruption might fluctuate in different patients but, without any treatment, the rash rarely disappears for longer than a few weeks.[1] Each of our patients fulfilled 4 out of 5 criteria for DH diagnosis.

Differential diagnosis of DH is made against other autoimmune blistering conditions (such as linear IgA disease and bullous pemphigoid), itchy dermatoses (such as atopic dermatitis, nummular [discoid] eczema, and scabies[1]), and psychiatric conditions like neurotic excoriations and dermatitis artefacta. In mild cases, DH might not often be suspected, especially when the patient concomitantly has atopic dermatitis or some other itching skin disease.[1]

Figure 1. Clinical photographs of patient 1, a 44-year-old white man: *A) Excoriated papules and crusts on the forearm and extensor surface of the elbow. B) Meticulous clinical examination showed small vesicles on the skin of the elbow. C) Purpuric lesions on the volar aspect of the fingers. D) Purpuric lesions on the volar aspect of the toes. E) Dermoscopy of a petechial lesion on the finger demonstrating violaceous globules. F) Direct immunofluorescence of a lesion on the skin of the forearm. Notice the granular deposits of immunoglobulin A–fluorescein-marked complex at the dermal-epidermal junction of the skin (papillae of dermis).*

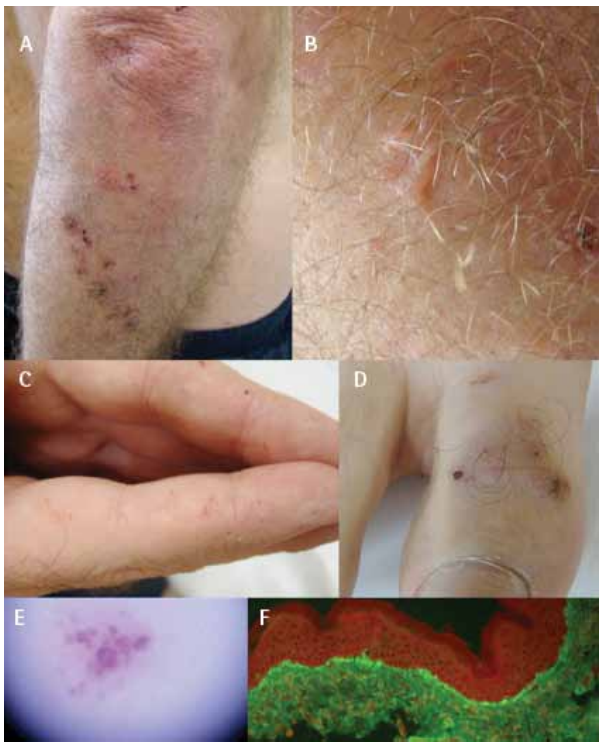


Figure 2. Clinical features of patient 2, a 19-year-old white woman: *A) Excoriated papules and plaques on the back. B) Detail of the excoriated papules and crusts on the back. C) Papules and urticarial plaques on the buttocks and sacral area. D) Erythematous papules and urticarial lesions on the elbows. E) Excoriated papules and plaques on the submandibular area. F) Histopathologic examination of a skin lesion on the elbow showing small vesicles (hematoxylin and eosin stain, original magnification × 100). G) Detail of the subepidermal vesicle (hematoxylin and eosin stain, original magnification × 200). H) Direct immunofluorescence of a lesion on the back. Note the granular deposits of immunoglobulin A–fluorescein-marked complex at the dermal-epidermal junction of the skin (papillary dermis).*

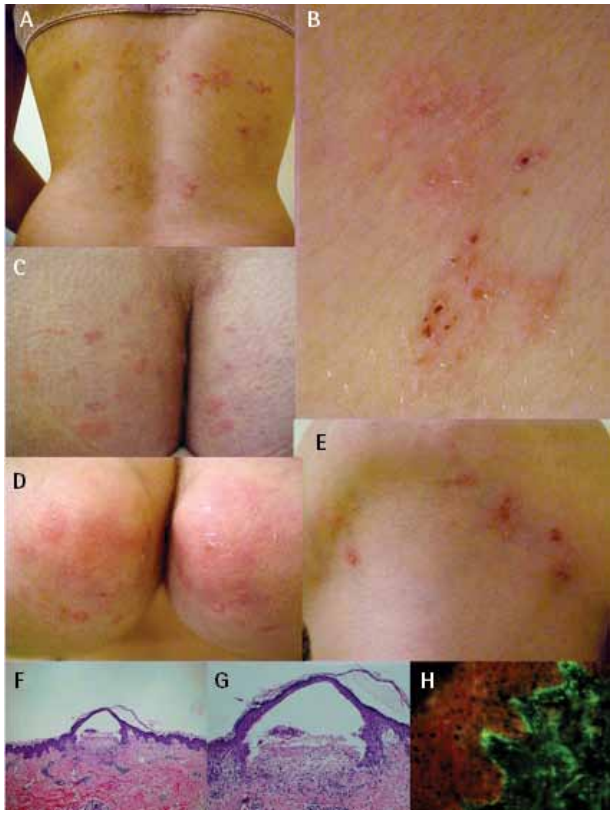


Figure 3. Clinical features of patient 3, a 58-year-old white man. *A) Excoriated papules and crusts on the extensor surface of the elbow; B) knee; and C) buttocks. D) Histopathologic examination of a skin lesion on the dorsum of the foot showing a small subepidermal vesicle (hematoxylin and eosin stain, original magnification × 400). E) Detail of the subepidermal vesicle leading to a microabscess filled with neutrophils (hematoxylin and eosin stain, original magnification × 1000). F) Direct immunofluorescence of the back skin. Note the granular deposits of immunoglobulin A–fluorescein-marked complex at the dermal-epidermal junction of the skin (papillary dermis).*

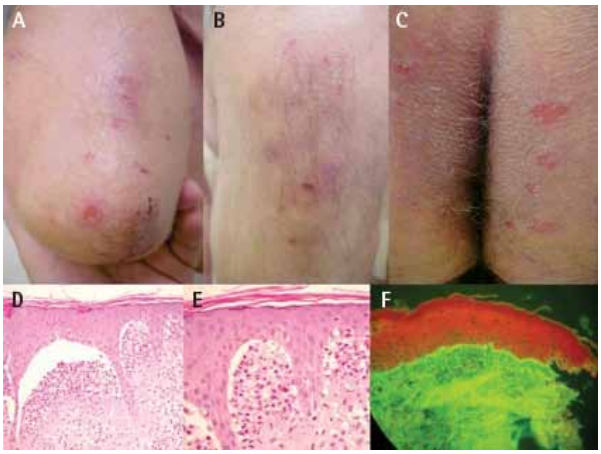
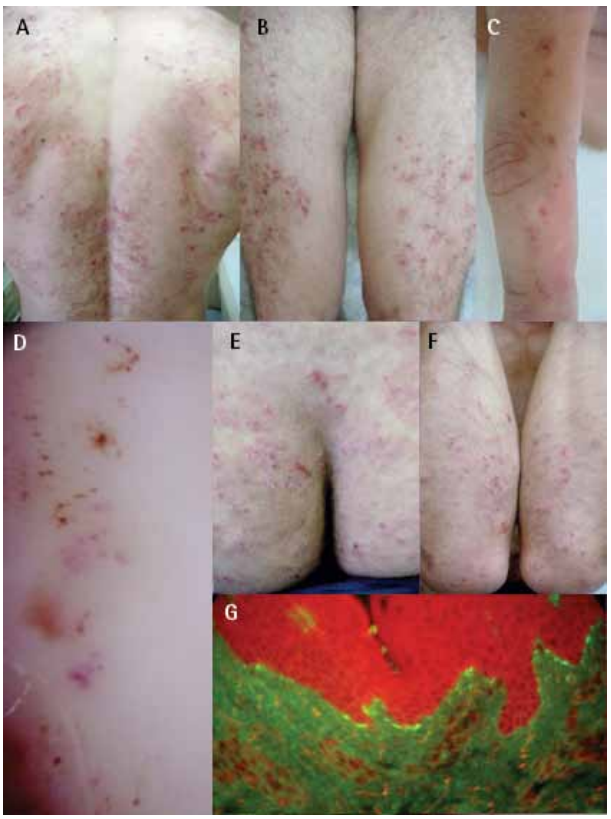


Figure 4. Clinical features of patient 4, a 22-year-old white man. *A) Extensive excoriated papules and crusts on the back and B) legs. C) Purpuric lesions on the volar aspect of the fingers. D) Dermoscopy of petechial lesions on the finger demonstrating violaceous globules (newest lesions) and brownish dots and globules (oldest lesions). E) Excoriated papules and residual lesions on the buttocks. F) Excoriated papules and crusts on the extensor surface of the elbow. G) Direct immunofluorescence of the forearm skin. Note the granular deposits of immunoglobulin A–fluorescein-marked complex at the dermal-epidermal junction of the skin (papillary dermis).*



Similarly, even minor itching lesions in patients with CD warrant dermatologic consultation to confirm or exclude DH, as there are some differences in the management and follow-up of these 2 phenotypically distinct gluten-sensitivity disorders.[1]

Dermatitis herpetiformis, the skin's expression of CD, is induced by the presence of IgA antibodies and epidermal transglutaminase (the main autoantigen) stored in the papillary dermis and vessel walls.[15]

Both diseases might appear in the same family and share a strong association with class II histocompatibility locus antigens DR3 and DQw2, and with alleles DQA1*0501 and B1*0201 of chromosome 6.[15] The physiopathogenic mechanism of CD seems to be related to a T-cell response to gluten peptides and the ubiquitous enzyme tissue transglutaminase, which acts as an autoantigen and enhances the immunogenicity toward gluten peptides.[15] This immune response leads to a Th2 cytokine release and to activation of metalloproteinases and of the humoral system, which induces production of IgA and IgM antibodies against gliadin and other modified peptides.[15] The triggered immune system–induced gut mucosal changes range from complete disruption of the mucosal architecture with villous flattening and crypt hyperplasia, to a slight increase in the inflammatory infiltrate, both in the epithelium and the lamina propria.[15]

In DH the immune complexes are composed of IgA antibodies, and epidermal transglutaminase is considered the main autoantigen.[15] A cascade of events follows the immune complex deposition, such as activation of neutrophil chemotaxis, cytokine synthesis in the skin with complement activation, and release of metalloproteinases that break down the connective tissue of the dermis and lead to cleavage of the dermal-epidermal junction, which then leads to vesicle formation.[15] This pathophysiologic scenario was evident from the histology examinations of our 4 patients.

Other atypical clinical findings in DH are the presentation in childhood of nonpruritic, deep dermal papules and nodules on the buttocks, hands, and extensor surfaces,[16] isolated erythematous palmar and plantar plaques,[17] and isolated palmar purpura.[3] In our cases, patients 1 and 4 displayed several 1- to 2-mm purpuric lesions on the hands and feet, similar to those described by McGovern and Bennion.[3] Cutaneous biopsies of the purpuric lesions were conducted, which revealed focal epidermal necrosis, papillary edema with numerous neutrophils and extravasated erythrocytes, and superficial and mild perivascular lymphocytic infiltrate.[3] In one area of the slide there was a subepidermal cleavage filled with neutrophils and fibrin, suggesting DH.[3] Similar purpuric, pseudopurpuric, and hemorrhagic palmar lesions associated with DH have been reported by other authors.[3-13] This cutaneous sign (purpuric or petechial lesions) on the hands or feet should alert physicians to the possibility of a DH diagnosis when associated with cutaneous itching and excoriated lesions in a DH distribution pattern.

Because DH is considered the cutaneous form of CD, a proven diagnosis of DH in a patient should be used as a diagnostic marker for bowel damage recognition.[3] Therefore, small-bowel biopsy might be unnecessary even in DH patients with gastrointestinal symptoms. Diet adherence can be monitored by serologic testing and skin lesion observation, as DH features usually reappear within a few days after gluten ingestion.[3]

The absence of gastrointestinal symptoms in our patients saved them having bowel biopsies. A gluten-free diet is the treatment of choice for patients with CD and DH because both enteropathy and cutaneous eruption are dependent on gluten ingestion.[14] Dapsone is a valid therapeutic option for patients with DH during the first 2 years after diagnosis, until the gluten-free diet becomes effective.[14] Patient 1 had glucose-6-phosphate dehydrogenase deficiency, and was therefore treated with a combination of tetracycline and nicotinamide, resulting in satisfactory symptomatic control. For patients who cannot tolerate or are unresponsive to dapsone or other sulfonamide drugs, some authors propose alternative therapies such as heparin,[18] tetracycline and nicotinamide,[19] or cyclosporine.[20]

Conclusion

We have reported cases of uncommon purpuric acral lesions associated with DH to alert physicians to the possibility of a precise DH diagnosis based on clinical signs such as excoriated and eroded skin lesions associated with chronic itch. The presence of petechial or purpuric lesions on the hands or feet increases the suspicion of this diagnosis.

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Competing interests
None declared

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