Dermatitis herpetiformis (DH) is an autoimmune blistering disease with a classical clinical presentation characterized by intensely pruritic polymorphous lesions symmetrically located on extensor surfaces, with a concentration on the elbows, knees, scapulae, shoulders, sacrum, hairline, and scalp. Mucous membranes are uncommonly involved. Papillary dermal neutrophilic microabscesses are characteristically seen on routine biopsy, and a similar distribution of granular deposition of immunoglobulin A (IgA) detected with direct immunofluorescence (DIF) confirms the diagnosis. Nearly all patients will have clinical or subclinical evidence of small bowel villous atrophy, and it is now known that DH is the cutaneous manifestation of gluten-sensitive enteropathy (also known as celiac sprue or celiac disease), with both conditions being associated with human leukocyte antigens (HLAs) DQ2 DQ8. Both conditions are caused by an immunologic reaction to ingested gliadin, the fraction of gluten found in wheat, rye, and barley, and both conditions are associated with circulating IgA antibodies against endomysium and tissue transglutaminase (tTG), which serve as a surrogate marker of gluten-free diet (GFD) compliance. Patients with DH also have IgA antibodies directed against epidermal transglutaminase (eTG), which is homologous to tTG. A population of non-cross reactive anti-eTG IgA antibodies are found only in DH patients, suggesting that eTG is the target in DH.

A diagnosis of DH may be straightforward; however, there are some nonclassic presentations with which clinicians should be familiar. Although the name reflects the clinical presentation of herpetiform vesicles, these are often immediately excoriated, resulting in erosions, crusted papules, or areas of postinflammatory dyschromia, or there may be erythema or urticarial plaques and papules. Severe pruritus, burning, and/or stinging, alone or preceding the eruption by 8 to 12 hours, are often the presenting symptoms, simulating scabies. Localized scalp lesions and palmar petechiae are other unusual presentations. DH usually occurs in patients between 20 and 40 years of age, but the condition is not restricted to adults. Children with recalcitrant eczematous lesions, urticaria, pruritic impetigo, and papular urticaria may escape diagnosis if one does not consider a diagnosis of DH in this population.

The criterion standard for diagnosing DH remains DIF, but often one will first obtain a screening biopsy for histology, and the presence of papillary dermal microabscesses may either support the clinicopathologic diagnosis or will prompt confirmatory DIF sampling. Unfortunately, the biopsy specimen may show atypical features, such as acantholysis of the...
basal keratinocytes, or misleading histology, such as “normal skin,” secondary changes related to excoriation, or nonspecific inflammation, erroneously excluding a diagnosis of DH. In fact, in one series, nine of 24 patients with DH had nonpapillary dermal perivascular lymphocytic inflammation, with variable fibrosis and/or eosinophils. Deeper sectioning showed classic DH features in only one of three. To avoid this pitfall, one should consider routinely submitting portions of the perilesional skin when performing a biopsy for the diagnosis of DH.

One must also be aware of the pitfalls of DIF. While granular IgA in the dermal papillae is the classic finding, these deposits may also be seen contiguously along and beneath the basement membrane zone. Moreover, in about 2% of cases, there will be a fibrillar pattern of IgA deposition along the basement membrane zone, where the IgA presents as linear streaks instead of fine granules. These cases may clinically differ from classic DH, because some of these patients have had urticarial or psoriasisform lesions. It is important to use a reputable laboratory, because both false positive and false negative results may be seen. If there is a strong suspicion for DH and a negative DIF is encountered, serial sections should be taken through the specimen, because this may reveal diagnostic findings. In addition, a prolonged GFD should be excluded as an explanation for a false DIF in a patient suspected of having DH. Approximately one quarter of patients on a GFD for 3 to 16 months may lose the skin deposits after clearance of the rash. If DH cannot be confirmed with DIF, the diagnosis can be made by documenting the circulating autoantibodies against tissue tTG (anti-tTG). Anti-eTG may be a more sensitive serologic marker for DH than anti-tTG. In study published by Rose et al, anti-eTG was detected in 95% of patients versus 79% with positive anti-tTG in patients with DH on a normal diet or a GFD. Of note is the fact that in patients who had been able to discontinue suppressive dapsone therapy while on a GFD, no tTG- or eTG-specific antibodies were found.

A GFD is the treatment of choice for DH, and has several advantages. After about 1 to 2 years, it may reduce or eliminate the need for medication, it treats the enteropathy, which is usually present, and it has been shown to have a protective effect against the development of small bowel lymphoma. Details of products to avoid and gluten alternatives can be found in a review by Rottmann. Oats may be cautiously consumed, but often are in contaminated with gluten-containing cereals. Strict adherence to this diet is crucial but difficult. Rigorous scrutinization of food labels for ingredients that would not be expected to contain gluten, such as preservatives, thickening agents, stabilizers, and distilled white vinegar—often added to condiments—is important. In this Dialogue, Dr Heymann warned us that even the flour found in gum wrappers may trigger a relapse. Other nonfood items to avoid include some shampoos, toothpastes, toothpowder, and some medications.

As we heard in this Dialogue, dapsone is the only medicine for DH that has been approved by the US Food and Drug Administration. The dose is 1 mg/kg per day, starting at 25 mg to 50 mg, with an average dose of 75 mg to 100 mg/day. Hemolysis is common and noted within about 2 weeks of onset of dapsone. Methemoglobinemia is also a common dose-dependent toxicity, but rare cases of this occurring at therapeutic doses have been reported.

Methemoglobinemia occurs when iron is oxidized from the oxygen-carrying ferrous state to the ferric state. The normal level is 1%. Cyanosis is seen at 15% methemoglobin, and is differentiated from other causes of cyanosis by brown pasty mucous membranes, in contrast to blue, brown venous blood, and brown or black urine—hence the term “chocolate cyanosis.” It is often asymptomatic and does not require intervention or discontinuation of dapsone until levels of 20% to 45% methemoglobin, where dizziness, fatigue, headache, tachycardia, and weakness set in. Above 45%, there may be acidosis, dyspnea, seizures, arrhythmias, and coma. Symptoms may occur at lower concentrations with premorbid states, such as anemia or cardiopulmonary compromise. The diagnosis requires arterial blood gas, because pulse oximeters are insensitive to hypoxia and overestimate oxygen saturation. Treatment is intravenous methylene blue 1 to 2 mg/kg, repeated 1 hour later if needed. Dapsone should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency, because they have decreased concentrations of nicotinamide adenine dinucleotide phosphate, which is needed to prevent conversion of hemoglobin to methemoglobin. Methylene blue is ineffective in these patients and also causes delayed hemolytic anemia. Ascorbic acid and cimetidine are possible alternative treatment options for methemoglobinemia.

Dr Heymann warned us of the rare but severe dapsone hypersensitivity syndrome. This may occur 2 to 6 weeks after the onset of treatment and includes fever, rash, lymphadenopathy, and visceral involvement, including a delayed hypothyroidism. Dapsone-induced photosensitivity eruptions are non–dose-related reactions to the sulfone, which can be documented with photopatch testing. Clinicians should be aware of this rare side effect,
because it may mimic a variety of photodermatoses and may also present as a component of the dapsone hypersensitivity reaction.

Dermatologists are familiar with the classic presentation of DH but must be aware of pitfalls in diagnosis and management of this disease. Although the most common toxicities of hemolysis and methemoglobinemia are usually dose-dependent, close monitoring is crucial to avoid any unexpected idiosyncratic adverse events. In this Dialogue, we were encouraged to be aware of the risk of small bowel lymphoma and DH-associated autoimmune disorders, such as pernicious anemia, Sjögren syndrome, lupus erythematosus, thyroiditis, and diabetes mellitus.

REFERENCES

Additional topics from the August 2010 issue of the Dialogues in Dermatology:
1. Diagnosis and management of hair loss
   With Kimberly Salkey, MD, interviewed by Marguerite Thew, MD
2. Update in psychocutaneous medicine
   With Jason Reichenberg, MD, interviewed by Jacqueline M. Junkins-Hopkins, MD

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