Dermatitis herpetiformis

Part II. Diagnosis, management, and prognosis

Diana Bolotin, MD, PhD, and Vesna Petronic-Rosic, MD, MSc
Chicago, Illinois

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Learning Objectives
After completing this learning activity, participants should be able to use the recent advances in understanding of the immunologic basis for dermatitis herpetiformis to identify and utilize appropriate diagnostic testing on dermatitis herpetiformis and to counsel patients and their families about the disease course and prognosis; describe the psychological implications of the disorder and its effect on quality of life; recognize the associated disorders and initiate appropriate multidisciplinary work up; identify and employ the optimal treatment options for patients with dermatitis herpetiformis; initiate adequate monitoring; and devise a follow-up plan for the patient.

Date of release: June 2011
Expiration date: June 2012

doi:10.1016/j.jaad.2010.09.776

The prompt recognition of the clinical features of dermatitis herpetiformis (DH) is important, but securing a definitive diagnosis requires further work-up. Recent advances in understanding of the immunologic basis for DH have led to the development and wider availability of serologic testing, which is rapidly becoming an essential part of the diagnosis and management of DH. Part II of this series will detail the diagnosis, treatment, and follow-up for patients with DH, and will particularly focus on recent advances in the field. (J Am Acad Dermatol 2011;64:1027-33.)

Key words: autoimmune bullous disease; celiac disease; dapsone; dermatitis herpetiformis; enzyme-linked immunosorbent assay; gliadin; gluten-free diet; gluten-sensitive enteropathy; human leukocyte antigen—DQ2; human leukocyte antigen—DQ8; immunofluorescence; immunoglobulin A; sulfapyridine.

DIAGNOSIS

Key points

- **Physical examination and routine histopathology are often suggestive of dermatitis herpetiformis, while direct immunofluorescence findings in perilesional skin are pathognomonic**
- **Serologic testing is a useful adjunct for diagnosis and may be used to monitor dietary adherence**
- **Genetic testing for human leukocyte antigens DQ2 and DQ8 is useful in ruling out dermatitis herpetiformis**

CAPSULE SUMMARY

- Direct immunofluorescence testing of perilesional skin shows pathognomonic findings
- Tissue and epidermal transglutaminases are serologic tests that may confirm the diagnosis of dermatitis herpetiformis and be used to monitor disease activity
- A gluten-free diet is the cornerstone of therapy, while dapsone provides the most rapid relief of skin signs and symptoms
- Extensive counseling and a multidisciplinary approach to care improve the outcomes of patients with dermatitis herpetiformis

The diagnosis of dermatitis herpetiformis (DH) is based on a constellation of findings on physical examination, routine histopathology, immunofluorescence studies, and serologic testing (Fig 1). Physical examination alone may be suggestive; however, given the varied morphologic presentation of DH, additional testing is usually required.[1] Biopsy specimens for routine histopathology should ideally contain an intact vesicle.[2] The classic histopathologic features of DH seen on light microscopy include a subepidermal cleft with neutrophils and a few eosinophils at the tips of dermal papillae (Fig 2, *A*).[1,2] These findings are often accompanied by a perivascular mixed inflammatory infiltrate (Fig 2, *A*).[1,2]

While routine histopathology may be highly suggestive of DH, other conditions, such as linear immunoglobulin A bullous dermatosis (LABD) and bullous lupus erythematosus, can present nearly identical histologic findings. Therefore, immunofluorescence studies are critical for definitive diagnosis. Granular deposits of IgA at the tips of dermal papillae are pathognomonic for DH (in contrast to the linear pattern of IgA deposition seen in LABD; Fig 2, *B*).[1-4] The IgA deposits in DH are thought to be polyclonal but are mainly composed of IgA1.[5] Occasionally, granular deposits along the basement membrane zone occur in DH, which can lead to misdiagnosis as LABD.[1]

Interestingly, these deposits are not altered by pharmacologic therapy for DH, but do slowly resolve on a gluten-free diet (GFD).[2,3] The site of biopsy for direct immunofluorescence is of vital importance. Although IgA deposition occurs in both lesional and nonlesional areas, a study comparing lesional, perilesional, and nonlesional skin in DH showed significantly greater IgA deposition in normal appearing perilesional skin.[3] In fact, biopsy specimens of lesional skin often yield false-negative results on direct immunofluorescence.[3,6]

Serologic testing is a useful adjunct to tissue-based studies. A number of serologic markers are shared between DH and CD, as might be expected given their close relationship. Circulating IgA antibodies to endomysium, the fine connective tissue sheath surrounding a muscle fiber, are detected in both conditions.[5] Testing for antiendomysial antibody is based on indirect immunofluorescence using monkey esophagus as substrate; despite some operator-dependent variability, it is a highly specific and moderately sensitive test for the diagnosis of DH.[1,5] IgA antitissue transglutaminase (tTG) testing is performed by a widely available enzyme-linked immunosorbent assay (ELISA)—based test and has a specificity range of 97.6% to 100% and sensitivity of 48.8% to 89.1%.[5,7,8] This test may be useful in differentiating DH from LABD and reflects the degree of mucosal changes on small bowel biopsy specimens in these patients.[7]

With the discovery that epidermal transglutaminase (eTG) is the key autoantigen in DH, serologic testing for autoantibodies against this protein has attracted increasing interest. Recent studies report a high sensitivity (60-80.8%) and specificity (92.8-100%) of serologic testing for DH with a commercially available ELISA-based assay to detect IgA anti-eTG antibodies.[8,9] Serologic testing offers the advantages of entailing a generally lower cost and being less invasive than a skin biopsy; pending more validation, it may become a useful initial screening method in patients in whom DH is suspected clinically. Levels of anti-tTG and anti-eTG IgA correlate with the extent of

From the Section of Dermatology, The University of Chicago.
Funding sources: None.
Reprint requests: Vesna Petronic-Rosic, MD, MSc, Section of Dermatology, The University of Chicago, 5841 S Maryland Ave, MC5067, Chicago, IL 60637. E-mail: vrosic@medicine.bsd.uchicago.edu.
0190-9622/$36.00