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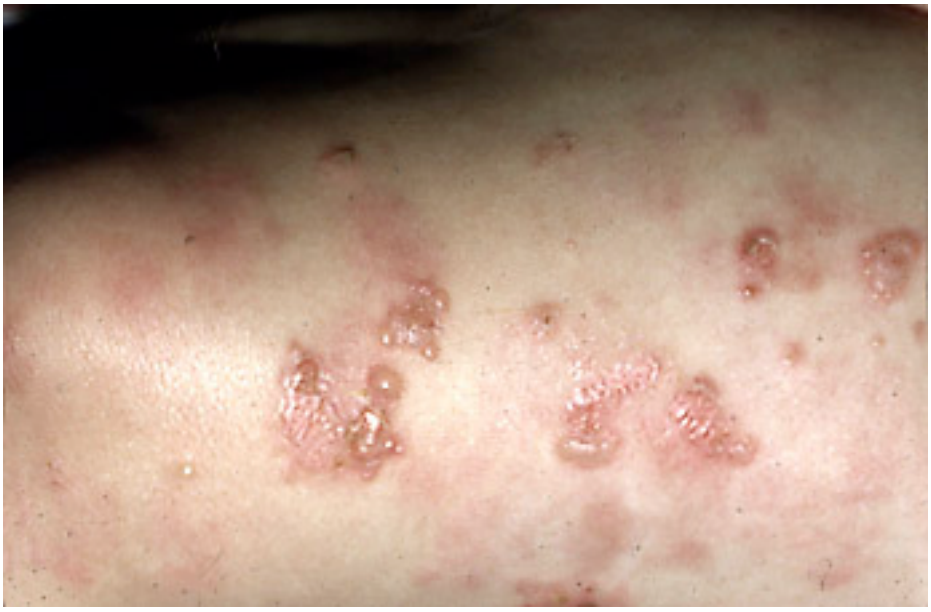
Dermatitis Herpetiformis

Jami L Miller, MD, Assistant Professor, Division of Dermatology, Department of Internal Medicine, Vanderbilt University Medical School; Director of Phototherapy Unit, Vanderbilt University Medical Center; Consulting Attending Physician, Nashville Veterans Affairs Medical Center

Updated: Aug 14, 2009

Introduction



Classic vesicles of dermatitis herpetiformis.

Background

Dermatitis herpetiformis (DH) is an autoimmune blistering disorder associated with a gluten-sensitive enteropathy (GSE). The disease was described and named in 1884 by Dr. Louis Duhring at the University of Pennsylvania.[1] Dermatitis herpetiformis is characterized by grouped excoriations; erythematous, urticarial plaques; and papules with vesicles. The classic location for dermatitis herpetiformis lesions is on the extensor surfaces of the elbows, knees, buttocks, and back. Dermatitis herpetiformis is exquisitely pruritic, and the vesicles are often excoriated to erosions by the time of physical examination.

Diagnosis requires direct immunofluorescence of a skin biopsy specimen showing deposition of immunoglobulin A (IgA) in a granular pattern in the upper papillary dermis. Although most patients are asymptomatic, greater than 90% have an associated gluten-sensitive enteropathy upon endoscopic examination. Among patients with celiac disease, 15-25% develop dermatitis herpetiformis. The mainstays of treatment are dapsone and a gluten-free diet.

Pathophysiology

Dermatitis herpetiformis is a disease of the skin caused by the deposition of IgA in the papillary dermis, which triggers an immunologic cascade, resulting in neutrophil recruitment and complement activation. Dermatitis herpetiformis is the result of an immunologic response to chronic stimulation of the gut mucosa by dietary gluten.

An underlying genetic predisposition to the development of dermatitis herpetiformis has been demonstrated. Both dermatitis herpetiformis and celiac disease (CD) are associated with an increased expression of HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes. Environmental factors are also important; monozygotic twins may have dermatitis herpetiformis, celiac disease, and/or gluten-sensitive enteropathy with variable symptomatology.

Evidence is mounting that epidermal transglutaminase 3 (eTG) is the dominant autoantigen of dermatitis herpetiformis.[2] eTG is a cytosolic enzyme involved in cell envelope formation during keratinocyte differentiation. Theoretically, dermatitis herpetiformis is caused by dermal deposition of circulating immune complexes containing both IgA and eTG. This is supported by the finding that precipitates of skin-bound IgA from dermatitis herpetiformis lesions contain eTG.

In addition, serum from dermatitis herpetiformis patients contains high-affinity anti-eTG IgA autoantibodies. eTG is highly homologous with tissue transglutaminase (TG2), which is found in the gut, and serum from patients with gluten-sensitive enteropathy, with or without skin disease, contains IgA antibodies to both skin and gut types.[3] levels of these circulating antibodies have been found to correlate with each other, and both appear to correlate with the extent of enteropathy.[4]

Co-localized IgA and eTG deposits have been demonstrated in the papillary dermis in patients with dermatitis herpetiformis and, to lesser extent, in healthy skin of gluten-sensitive enteropathy patients.[5] eTG has not been demonstrated in normal papillary dermis, suggesting it is part of the circulating complex that is deposited in the papillary dermis, rather than originating from the papillary dermis.

The leading theory for dermatitis herpetiformis is that a genetic predisposition for gluten sensitivity, coupled with a diet high in gluten, leads to the formation of IgA antibodies to gluten-TG2 complexes. These antibodies cross-react with eTG, and IgA/eTG complexes deposit within the papillary dermis to cause the lesions of dermatitis herpetiformis. These IgA deposits alvato da Windows Internet Explorer 8> Subject: Dermatitis Herpetiformis: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 00:44:21 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_0132_01CA2CF8.D7743830" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_0132_01CA2CF8.D7743830 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1062640-print

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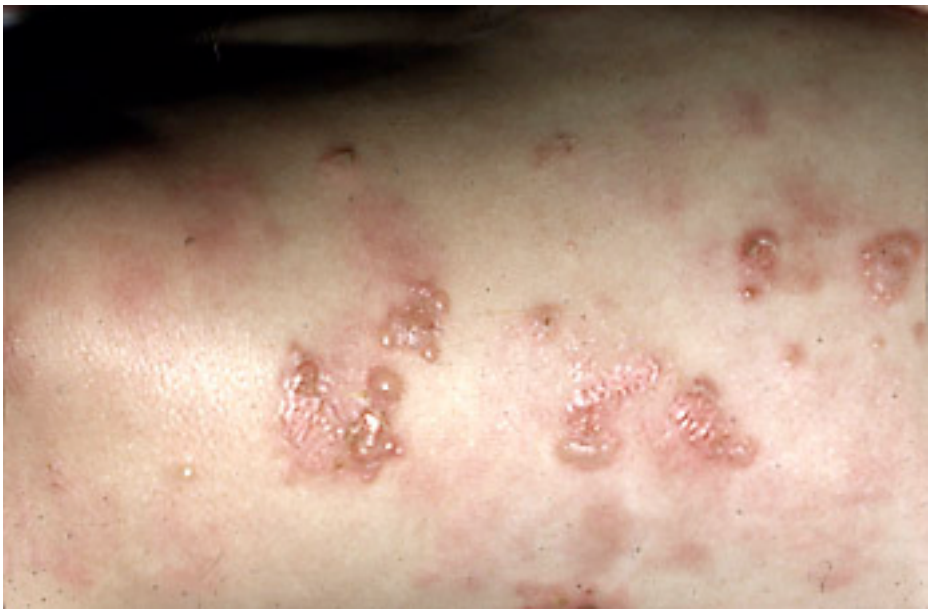

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Cutaneous IgA deposits in dermatitis herpetiformis have been shown to function in vitro as a ligand for neutrophil migration and attachment. Although IgA deposition is pivotal for disease, an increased serum IgA is not necessary for pathogenesis; in fact, case reports describe dermatitis herpetiformis in patients with a partial IgA deficiency.[6] When the disease is active, circulating neutrophils have a higher level of CD11b and an increased ability to bind IgA. The characteristic histologic finding of dermatitis herpetiformis is neutrophil accumulation at the dermoepidermal junction, frequently localizing to the papillary tips of the basement membrane zone.

Collagenase and stromelysin 1 may be induced in basal keratinocytes either by cytokines released from neutrophils or by contact with keratin from damaged basement membrane matrix. Stromelysin 1 may contribute to blister formation.

One study found levels of E-selectin mRNA expression in normal-appearing skin of patients with dermatitis herpetiformis to be 1271 times greater that that of controls.[7] Additionally, the same study observed increased soluble E-selectin, IgA antitissue transglutaminase antibodies, tumor necrosis factor-alpha, and serum interleukin 8 (IL-8) levels in patients with dermatitis herpetiformis, providing further evidence of endothelial cell activation and a systemic inflammatory response as part of the pathogenic mechanism of the disease. Mild local trauma may also induce the release of cytokines and attract the partially primed or activated neutrophils, which is consistent with the typical location of dermatitis herpetiformis lesions on frequently traumatized areas, such as the knees and elbows.

Deposits of C3 also may be present in a similar pattern at the dermoepidermal junction. The membrane attack complex, C5-C9, also has been identified in perilesional skin, although it may be inactive and not contribute to cell lysis.[8]

Hormonal factors may also play a role in the pathogenesis of dermatitis herpetiformis, and reports describe dermatitis herpetiformis induced by treatment with leuprolide acetate, a gonadotropin-releasing hormone analog.[9] Androgens have a suppressive effect on immune activity, including decreased autoimmunity, and androgen deficient states may be a potential trigger for dermatitis herpetiformis exacerbation. Exacerbation of dermatitis herpetiformis by oral contraceptives has also been reported.

Apoptosis may contribute to the pathogenesis of epidermal changes in dermatitis herpetiformis, and research demonstrates a markedly increased apoptotic rate within the epidermal compartment in dermatitis herpetiformis.[10] In addition, Bax and Bcl-2 proteins are increased in the dermal perivascular compartment and Fas proteins showed epidermal staining in dermatitis herpetiformis lesions.

Most patients with dermatitis herpetiformis have histologic evidence of enteropathy, even in the absence of symptoms of malabsorption. In one study, all dermatitis herpetiformis patients had increased intestinal permeability (as measured by the lactulose/mannitol ratio) and up-regulation of zonulin, a regulator of tight junctions.[11] Thus, increased expression of zonulin may be involved in the pathogenesis of enteropathy in patients with dermatitis herpetiformis.

Frequency

United States

The only US study showed a dermatitis herpetiformis prevalence of 11.2 cases per 100,000 population.

International

Prevalence of dermatitis herpetiformis has been reported as high as 10 cases per 100,000 population.

Mortality/Morbidity

In an English study, patients with dermatitis herpetiformis (152 total) were followed from the date of diagnosis to the end of 1989 for mortality and from 1971 or the date of diagnosis (if later) to 1986 for cancer incidence.[12] Death occurred in 38 patients younger than 85 years, slightly fewer than expected on the basis of national general population rates. Cancer incidence was significantly increased. Cancer of the small intestine caused 1 death, and lymphoma caused 1 death. Another English study, which compared 846 dermatitis herpetiformis patients with 4225 controls, found that dermatitis herpetiformis conferred no increased risk of lymphoproliferative cancer and no increase in fracture, malignancy, or mortality.[13]

A 30-year population-based study of 1147 celiac disease and dermatitis herpetiformis patients in Finland also revealed an overall good prognosis for patients with dermatitis herpetiformis.[14] The total occurrence of malignancies was equal to that of the general population in both celiac disease and dermatitis herpetiformis patients, but an increased incidence of non-Hodgkin lymphoma was noted among both celiac disease and dermatitis herpetiformis patients, with standardized incidence ratios of 3.2 and 6.0, respectively. Overall mortality was actually decreased in dermatitis herpetiformis patients compared with that in the general population.
Dermatitis herpetiformis lesions are extremely pruritic. Morbidity results from scarring, discomfort, and insomnia due to itching. Secondary infection may also develop, requiring antibiotic therapy.

Race

Dermatitis herpetiformis occurs more frequently in individuals of Northern European ancestry and is rare in Asians and persons of African descent. Dermatitis herpetiformis is most common in Ireland and Sweden. This can be attributed to the shared HLA associations of dermatitis herpetiformis and celiac disease including DQA1*0501 and B1*-02, which encode HLA-DQ2 heterodimers.

Sex

US studies show a male-to-female ratio of 1.44:1, but international studies have demonstrated a male-to-female ratio up to 2:1. In one study of patients with gluten-sensitive enteropathy, 16% of the men and 9% of the women had dermatitis herpetiformis.[15]

Age

Typically, the onset of dermatitis herpetiformis is in the second to fourth decade; however, persons of any age may be affected.[16] Dermatitis herpetiformis is rare in children.

Clinical

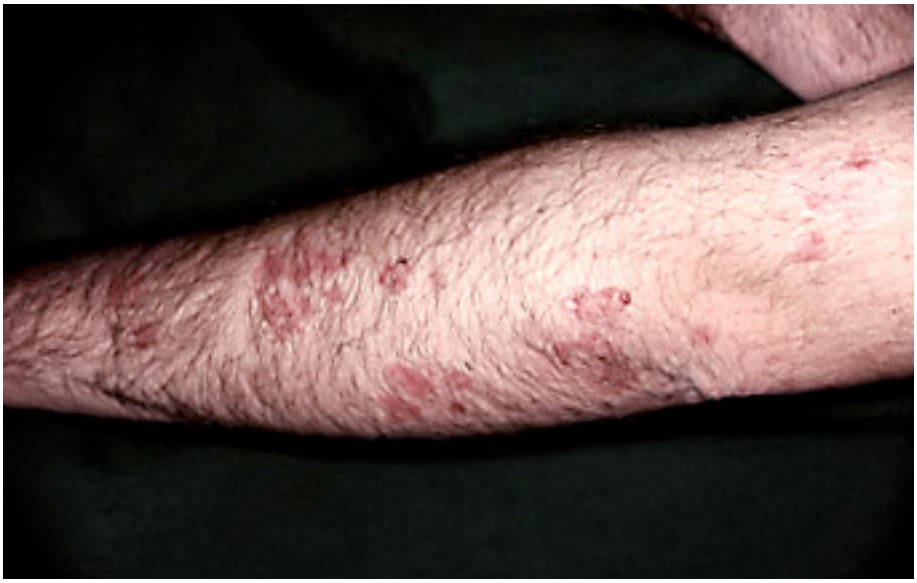
History

Patients typically present with a waxing and waning, pruritic eruption on the extensor surfaces of the arms, knees, and buttocks. It may become generalized. Small vesicles may have been noted but have often been excoriated by the time of presentation to the physician. They may have associated worsening of disease with dietary intake of gluten. Many do not report any GI symptoms, even when prompted.

Physical

The diagnosis is suspected based on the distribution of the eruption.

- Flesh-colored–to–erythematous excoriated papules or plaques with herpetiform (ie, small, clustered) vesicles are symmetrically distributed over extensor surfaces, including the elbows, knees, buttocks, and shoulders.
    - Dermatitis herpetiformis rarely occurs on the posterior (nuchal) scalp and face. Lesions occur infrequently on the oral mucosa, but males are more likely than females to have involvement of the oral and genital membranes.[17] Palms and soles are spared. Digital purpura resembling vasculitis can occur. Erythematous papules and urticarialike plaques occur less frequently; bullae are rare.
    - The eruption is intensely pruritic; patients often present with erosions and crusts in the absence of vesicles, which have ruptured due to excoriation.
    - Typical symptoms include burning, stinging, and intense itching. Rarely, if ever, are patients totally asymptomatic, although the degree of itching varies.
    - Dermatitis herpetiformis is a lifelong disease, although periods of exacerbation and remission are common.



Polymorphic lesions on extensor surface of arm.

Causes

Dermatitis herpetiformis is generally accepted as a cutaneous manifestation of celiac disease. The genetic predisposition to the development of gluten sensitivity underlies the disease.

- Gluten is a protein present in grasses of the species *Triticeae,* which includes barley, rye, and wheat. Rice and oats belong to different species and are generally well tolerated.[18,19] Strict compliance with a gluten-free diet results in normalization of the small bowel mucosal changes and control of the cutaneous manifestations of dermatitis herpetiformis in most patients. Levels of circulating antibodies also tend to normalize.
- The gluten-sensitive enteropathy does not cause symptoms in most dermatitis herpetiformis patients. Less than 10% exhibit symptoms of bloating, diarrhea, or malabsorption. However, greater than 90% show abnormalities upon endoscopic examination. Two thirds have villous atrophy detected on intestinal biopsy specimens. The other third shows elevated intraepithelial lymphocyte counts, increased T-cell receptor gamma/delta intraepithelial lymphocyte counts, or both.
    - The critical role of associated gluten-sensitive enteropathy in the pathogenesis of dermatitis herpetiformis is confirmed by the fact that resumption of a gluten-containing diet in patients with dermatitis herpetiformis results in a return of the characteristic skin disease.
    - Mild steatorrhea or other signs of mild malabsorption (eg, altered D-xylose absorption, iron or folate deficiency) can be demonstrated in 20-30% of patients with dermatitis herpetiformis.
    - Patients with dermatitis herpetiformis and no apparent GI disease can be induced into developing dermatitis herpetiformis by increasing gluten intake, which is often termed latent gluten-sensitive enteropathy.
- IgA circulating immune complexes are present in 25-35% of patients with dermatitis herpetiformis, although no association with disease severity has been noted. These immune complexes also have been noted in patients with isolated gluten-sensitive enteropathy and are believed to be related to the presence of the gut disease.[4]
    - IgA antibodies to gliadin (a portion of wheat protein), reticulum, and smooth muscle endomysium have also been noted in patients with dermatitis herpetiformis and in those with isolated gluten-sensitive enteropathy.
    - IgA endomysial antibodies are most specific for gluten sensitivity and are found in 80% of patients with dermatitis herpetiformis and greater than 95% of patients with celiac disease. The presence of IgA antiendomysial antibodies correlates with the extent of the gut disease[4,20]; however, some dermatitis herpetiformis patients do not have detectable IgA antiendomysial antibodies, even during episodes of active skin disease.
    - The criterion standard for the diagnosis of dermatitis herpetiformis remains the presence of granular deposits of IgA in normal-appearing perilesional skin. It is positive in 92.4% of patients.
    - Patients with bullous pemphigoid, cicatricial pemphigoid, Henoch-Schönlein purpura, and alcoholic liver disease also may have IgA deposits in normal skin; however, the pattern of IgA deposits is different from that seen in patients with dermatitis herpetiformis.
- In patients with dermatitis herpetiformis, 10-15% of their first-degree relatives have dermatitis herpetiformis or celiac disease. HLA studies have conclusively established the presence of a genetic predisposition for dermatitis herpetiformis. Patients with dermatitis herpetiformis have an increased expression of the HLA-A1, HLA-B8, HLA-DR3, and HLA-DQ2 haplotypes. This is identical to the HLA association found in patients with isolated gluten-sensitive enteropathy. Most persons with these HLA types do not have dermatitis herpetiformis or gluten-sensitive enteropathy. Associations of HLA and dermatitis herpetiformis are as follows:
    - For HLA-B8, the association with dermatitis herpetiformis is 58-87%, versus 20-30% for control patients.
    - For HLA-DR3, the association with dermatitis herpetiformis is 90-95%, versus 23% for control patients.
    - For HLA-DQ2, the association with dermatitis herpetiformis is 95-100%, versus 40% for control patients.
- Other associations include the following:
    - Associated GI conditions include gluten enteropathy, gastric atrophy, gastric hypochlorhydria, and pernicious anemia.
    - Associated autoimmune diseases include dermatomyositis, type 1 diabetes mellitus, myasthenia gravis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, and thyroid abnormalities. Thyroid abnormalities are present in as many as 50% of dermatitis herpetiformis patients and include hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer.[21]
    - Neurologic manifestations such as ataxia have been rarely described.[22]

- Associated neoplastic conditions include GI lymphomas and non-Hodgkin lymphoma; patients are at increased risk of developing these cancers.[23] A gluten-free diet may reduce the incidence of dermatitis herpetiformis–associated lymphomas.
- Celiac disease usually involves more severe and widespread intestinal involvement. Celiac disease has been associated with genetic abnormalities, including Down syndrome, Turner syndrome, and William syndrome. Liver disease, neurologic disorders, and other skin diseases are also increased in celiac disease, possibly due to common HLA regions on chromosome 6 or immune molecule cross-reactivity.
- Gastric manipulation (surgery) may induce dermatitis herpetiformis.
- Several chemicals have been associated with induction of dermatitis herpetiformis, including potassium iodide and cleaning solutions.
- Case reports have described dermatitis herpetiformis induced by medications. Leuprolide acetate, inhibitors of tumor necrosis factor-alpha, anti-influenza medications, and progesterone-containing contraceptives have been reported in association with development of dermatitis herpetiformis.[9,24]

Differential Diagnoses

Bullous Pemphigoid

Erythema Multiforme

Linear IgA Dermatosis

Neurotic Excoriations

Scabies

Transient Acantholytic Dermatosis

Other Problems to Be Considered

Eczema[25]

Papular urticaria

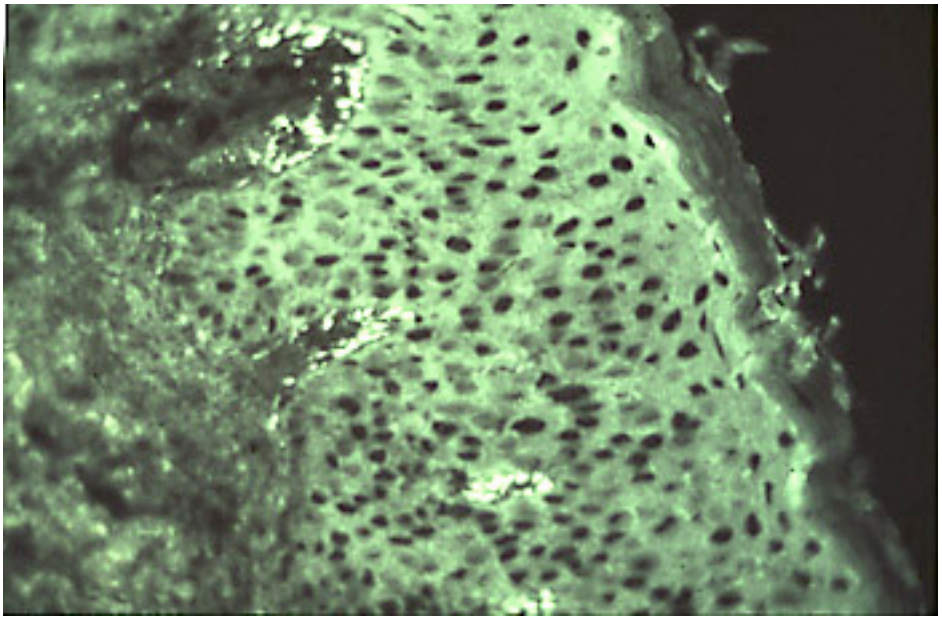
Workup

Laboratory Studies

- The diagnosis of dermatitis herpetiformis (DH) is made on the basis of skin biopsy results. However, other tests should be performed depending on the presence of symptoms of associated syndromes. Serum markers, such as IgA endomysial antibodies, are negative in as many as 10-37% of patients with dermatitis herpetiformis.[26] Arguments have been made in favor of testing for tissue transglutaminase for diagnosis,[27] but tissue transglutaminase enzyme-linked immunosorbent assay positivity can occur in many autoimmune diseases because of impurities and cross-reactivity.[28]

Procedures

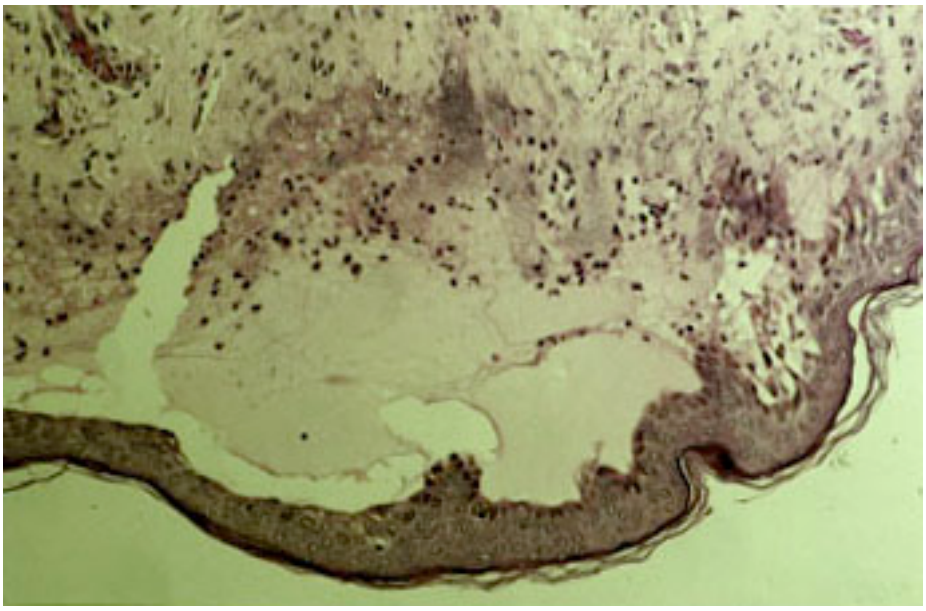
- The diagnosis is made after observing characteristic findings from skin biopsy specimens. The biopsy sample should be taken from the edge of a lesion for hematoxylin and eosin staining and from normal-appearing perilesional skin for direct immunofluorescence staining.
- Results of direct immunofluorescence of lesional skin are often falsely negative. The vigorous immune response degrades the IgA antibody at the site. Therefore, biopsy specimens for the direct immunofluorescence studies should be taken from healthy-appearing skin.



Immunofluorescence showing immunoglobulin A at the dermoepidermal junction (direct immunofluorescence stain).

Histologic Findings

Biopsy specimens of lesional skin reveal neutrophils in the dermal papillae, with fibrin deposition, neutrophil fragments, and edema. Eosinophils may be present. Papillary microabscesses form and progress to subepidermal vacuolization and vesicle formation. Vesicles form in the lamina lucida, the weakest portion of the dermoepidermal junction, due to neutrophil lysosomal enzymes.[25] See Media File 2.



Papillary microabscesses form and progress to subepidermal vacuolization and vesicle formation in the lamina lucida, the weakest portion of the dermoepidermal junction (hematoxylin and eosin stain).

The histologic differential diagnosis of early skin lesions includes bullous lupus erythematosus, bullous pemphigoid, epidermolysis bullosa acquisita, and linear IgA disease.[30] The histologic differential diagnosis of late skin lesions includes bullous drug eruption, bullous pemphigoid, erythema multiforme, and herpes gestationis.

Granular IgA deposits in dermal papillae of perilesional skin observed by direct immunofluorescence is the criterion standard of diagnosis. However, the presence of both granular and linear IgA deposits has been reported on direct immunofluorescence testing in a patient with dermatitis herpetiformis.[31]

Inflammation in lesional skin degrades the immunoreactants and is usually negative for the diagnostic granular pattern. Because deposits are found more reliably in the surrounding normal-appearing skin, the standard practice is to obtain biopsy specimens from normal-appearing perilesional skin for direct immunofluorescent staining.

Treatment

Medical Care

Control of dermatitis herpetiformis (DH) skin disease can be achieved with medications, dietary avoidance of gluten, or both.

- A gluten-free diet is very difficult to achieve; however, limiting intake of wheat, barley, or rye products can lessen the symptoms. Oats may be eaten in moderate quantities.
- Dapsone (diaminodiphenyl sulfone) and sulfapyridine are the primary medications used to treat dermatitis herpetiformis.
    - Before easy availability of direct immunofluorescence, rapid improvement after dapsone therapy was a chief diagnostic criterion for the disease. However, many diseases respond to dapsone, and this should not be used as the only diagnostic criterion. Dapsone is readily available at most pharmacies and is the first-line drug therapy.
    - For patients unable to tolerate dapsone, particularly those who develop hemolysis, sulfapyridine may be substituted.
    - The mechanism for therapeutic effect of dapsone in dermatitis herpetiformis is unclear. It may be related to the inhibition of neutrophil migration into the area, thus, decreasing the inflammatory response.
    - Improvement may be dramatic; symptomatic improvement of skin lesions often begins within hours. No new lesions form for up to 2 days after a dose of dapsone; however, dapsone does not improve GI mucosal pathology.
- Other, less effective treatments for dermatitis herpetiformis include colchicine, cyclosporine, azathioprine, and prednisone.[29] Ultraviolet light may provide some symptomatic relief. Cyclosporine should be used with caution in patients with dermatitis herpetiformis because of a potential increase in the risk of developing intestinal lymphomas.
- One case report described resolution of dermatitis herpetiformis after initiation of the Atkins diet.[32]
- Nonsteroidal anti-inflammatory drugs may exacerbate dermatitis herpetiformis; however, ibuprofen appears to be safe.[33]
- Iodides may elicit or exacerbate dermatitis herpetiformis.

Consultations

- Consider consultation with a gastroenterologist for evaluation and for recommendations regarding gluten-sensitive enteropathy (GSE).
- Consult with a dietitian regarding patients who are modifying dietary intake to avoid gluten or who are instituting an elemental diet.

Diet

Dietary intake of gluten causes the disease, and elimination of gluten from the diet improves it.

- A position statement by the American Gastroenterological Association (AGA) Institute advises that treatment for patients with dermatitis herpetiformis, like that of all patients with celiac disease, requires a strict, lifelong adherence to a gluten-free diet. The AGA stresses the importance of patient education, motivation, and support in maintaining adherence, and recommends consultation with an experienced dietician, referral to a support group, and clinical follow up for compliance, as well as treatment of nutritional deficiency states.[34] See the guideline summary, AGA Institute medical position statement on the diagnosis and management of celiac disease.
- Most patients (as many as 80%) who can maintain a gluten-free diet respond with control of their skin disease. Some patients are able to discontinue dapsone therapy. Compliance with a gluten-free diet is difficult and requires a motivated patient, and the best treatment response occurs with absolute gluten restriction in the diet.
- Strict dietary vigilance may be required for 5-12 months before the dapsone dose can be reduced.
- Maintaining a gluten-free diet is the only sustainable method of eliminating the disease, not only from the skin, but also from the GI mucosa.
- Patients on a gluten-reduced diet may experience a decrease in symptoms; therefore, such a diet can reduce the dosage of dapsone required for disease control.
- Neither IgA deposition nor circulating antibodies correlate with gluten intake in short-duration studies; however, some studies have suggested a correlation with complement deposition. Avoidance of dietary gluten for 10 years or more has resulted in loss of cutaneous IgA deposits, which then return upon reinstitution of gluten in the diet.
- Elemental diets may improve the disease within weeks.[35,36] These diets consist of free amino acids, small amounts of triglycerides, and short-chain polysaccharides; they are marketed by pharmaceutical companies. One report has suggested that this improvement may be independent of gluten ingestion; however, this finding has not been confirmed.[36]
- A summary guideline from the American College of Allergy, Asthma, and Immunology, Food allergy: a practice parameter, may be helpful.[37]

Follow-up

Further Outpatient Care

- Dietitians and gastroenterologists are helpful in addressing the gluten-sensitive enteropathy (GSE).

Complications

- Complications are related to the gluten-sensitive enteropathy, the risk of developing lymphomas, and the potential adverse effects of medications, particularly dapsone.

Prognosis

- Dermatitis herpetiformis (DH) is an ongoing disease process of variable severity.
- The prognosis is good for patients who can tolerate dapsone and the few who can maintain a gluten-free diet (which may decrease the risk of lymphoma).

Patient Education

- Educate patients regarding the use of a gluten-free diet as well as the adverse effects and complications of dapsone.

Miscellaneous

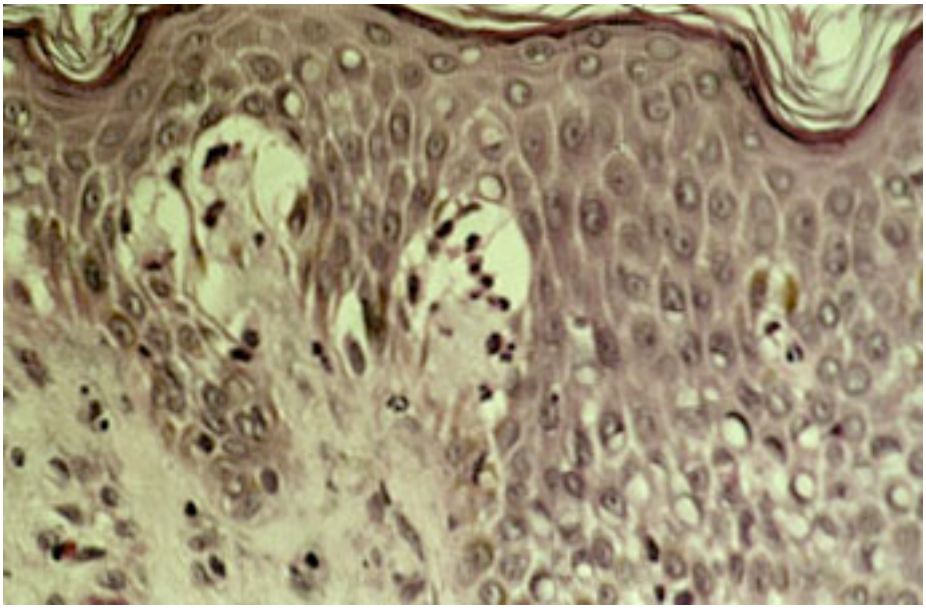
Medicolegal Pitfalls

- Failure to consider and diagnose dermatitis herpetiformis can result in the continuation of a distressing disease in a patient who can be treated successfully with dapsone.
- Failure to mention the association of dermatitis herpetiformis with gluten sensitivity and the association with lymphoma can result in further distress to the patient. Although maintenance of a gluten-free diet demands a motivated patient, it should always be offered as an option.
- Patients must be monitored when using dapsone or sulfapyridine. Very commonly, patients' hemoglobin levels drop by 1-2 g/dL during dapsone therapy, and larger decreases may be seen. Patients should be counseled regarding the signs of a pronounced hemolytic anemia or methemoglobinemia, including malaise, shortness of breath, tachycardia, or jaundice. Most patients can continue the dapsone if the anemia is mild and they are asymptomatic.

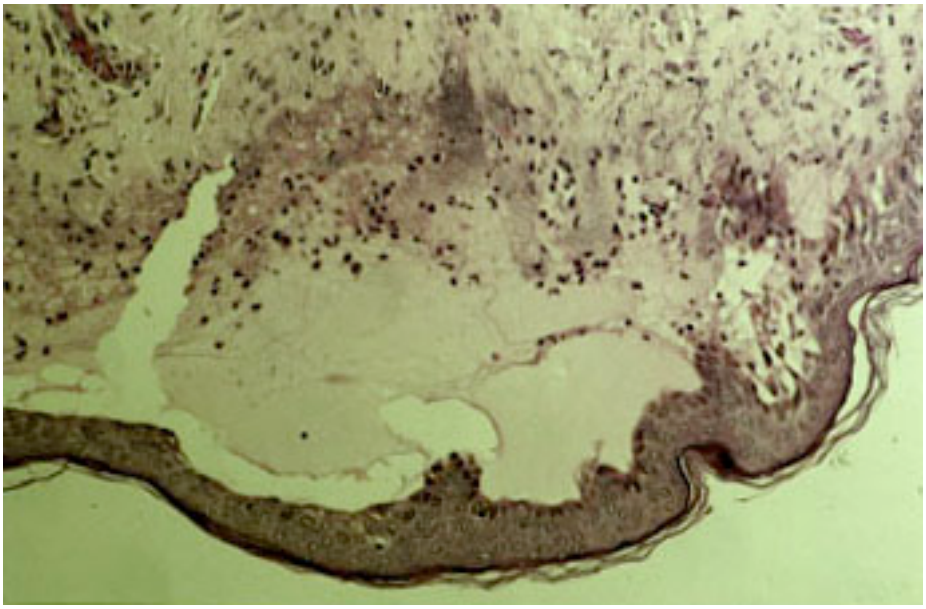
Special Concerns

- Polymorphic lesions and an atypical presentation, including a paucity of the characteristic vesicles, may make clinical diagnosis difficult.
- Histopathologic and immunologic confirmation of clinically suspected disease is mandatory for diagnosis.

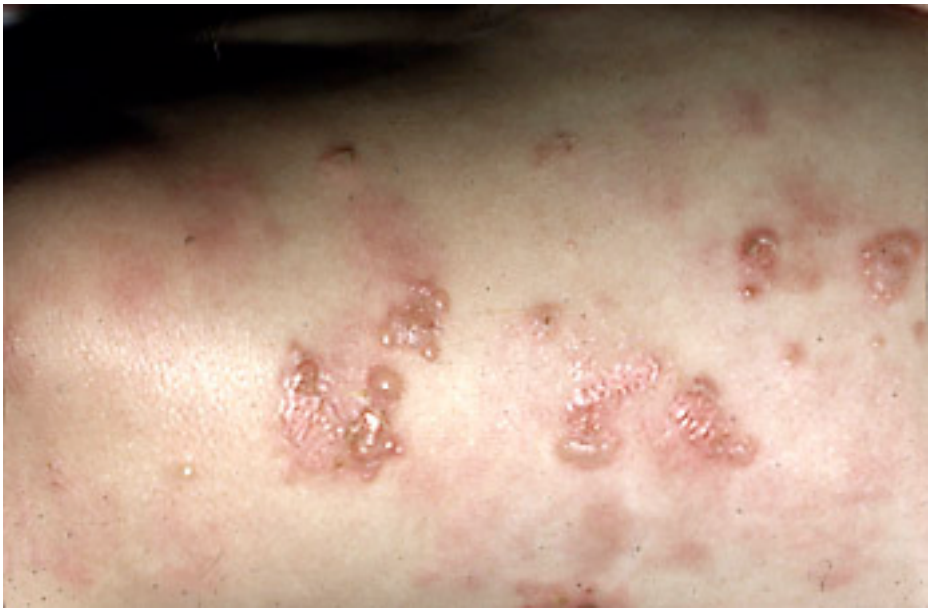
Multimedia



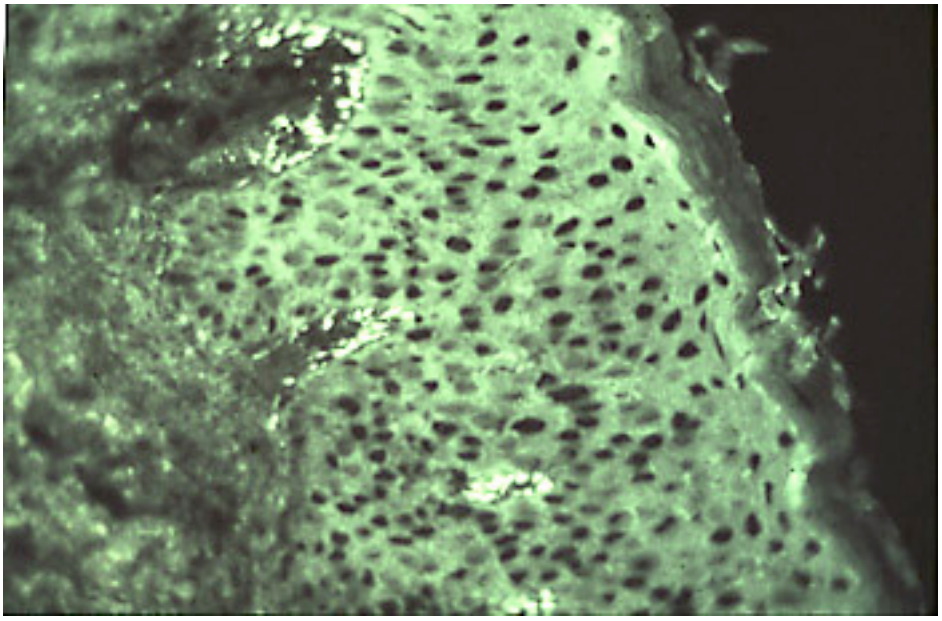
Media file 1: Light micrograph shows neutrophils in the dermal papillae, with fibrin deposition, neutrophil fragments, and edema (hematoxylin and eosin stain).



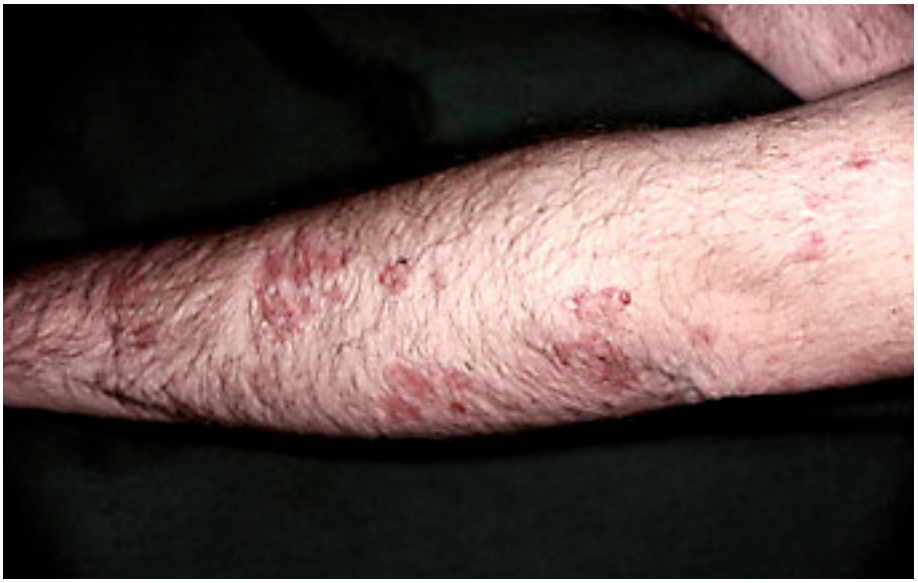
Media file 2: Papillary microabscesses form and progress to subepidermal vacuolization and vesicle formation in the lamina lucida, the weakest portion of the dermoepidermal junction (hematoxylin and eosin stain).



Media file 3: Classic vesicles of dermatitis herpetiformis.



Media file 4: Immunofluorescence showing immunoglobulin A at the dermoepidermal junction (direct immunofluorescence stain).



Media file 5: Polymorphic lesions on extensor surface of arm.

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