abstract

Dermatitis herpetiformis (DH) is a pruritic and chronic autoimmune blistering skin disease associated with varying degrees of gluten-induced enteropathy. Associated symptomatic celiac disease (CD) occurs in a minority of patients, but the pathogenesis of both diseases shares several features. In addition to some features of enteropathy, patients with DH also form specific antibodies to epidermal transglutaminase not typically found in patients with only CD. Although incidence is highest in middle age, because it is a life-long condition its prevalence is highest in the older population. Chronic complications of DH, including gastrointestinal lymphomas, are more likely to present in the geriatric group. Similarly, common comorbid disease associations including pernicious anemia, splenic atrophy and thyroid disease should be routinely assessed in this population. Long-term treatment of DH requires strict adherence to a gluten-free diet. Symptomatic treatment of this skin disease commonly uses dapsone to inhibit neutrophil accumulation and disease expression. Older patients may be more susceptible to toxic side effects of dapsone metabolites, and both careful patient selection and close monitoring should be undertaken with dapsone treatment.

Key words: dermatitis herpetiformis, autoimmunity, anemia, comorbidities, dapsone.

Dermatitis Herpetiformis in Older Adults

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Introduction

Dermatitis herpetiformis (DH) is a chronic pruritic gluten-induced symmetric autoimmune blistering skin disease associated with varying degrees of jejunal enteropathy. Although the majority of patients with DH manifest with very mild or asymptomatic intestinal disease, approximately 20-30% of genetically predisposed individuals go on to have symptoms consistent with celiac disease (CD). [1-3] The pathogenesis of these two gluten-associated diseases is quite similar such that DH can really be thought of as a cutaneous manifestation of some degree of underlying celiac disease.

CD involves gluten-induced autoimmune damage to the jejunal mucosa and typically presents with diarrhea, flatulence, abdominal bloating and weight loss.[4] Malabsorption can become severe and result in anemia from B12, iron or folate deficiency, and osteoporosis from ineffective vitamin D metabolism in the intestine. Approximately 5% of patients with CD also have DH with gluten-induced auto-immune damage to the papillary dermis resulting in pruritic polymorphous lesions.[1] In linking these two diseases together, all patients with DH have either jejunal pathology consistent with mild or asymptomatic CD, or have latent celiac sprue where CD pathology can be induced by large quantities of dietary gluten intake.[5]

Although DH and CD characteristically present in mid-life, approximately one-third of cases present in the over 65 age group.[6] Furthermore, this disease is generally considered to involve a chronic, often life-long sensitivity to gluten, and thus the prevalence of this relatively infrequent disease becomes more significant in older adults. Finally, many of the long-term complications associated with DH, including lymphoma, tend to manifest in the older age group.

Epidemiology and Pathogenesis

DH is most prevalent in people of European ethnicity at a rate of 1-4/10, 000, being relatively rare in Asian and African-Americans.[1-3,7,8] Slightly more prevalent in males, DH is strongly associated with specific major histocompatibility complex alleles.[2] These human leukocyte antigens (HLA) may be intimately involved in the development of the disease. Ninety per cent of patients with DH have the HLA-DQw2 alleles (HLADQ2A1*0501B1*02) while the majority of the rest express the HLADQ8 alleles (HLADQ8A1*03B1*0302).[5]

Gluten is a plant elastin that is found in wheat, rye, and barley, but not oats.[9, 10] Gliadin is the alcohol-soluble fraction of gluten and is believed to be the key antigenic component. Gliadin is metabolized by an enzyme produced in the endomysium (the connective tissue covering the smooth muscle layers of the stomach and jejunum) called tissue transglutaminase (TG2).[11] This enzyme is also involved in tissue-repairing functions within the intestine. In some people who express the HLA-DQw2 or HLA-DQ8 haplotypes, the binding of tissue transglutaminase in the deamidation of gliadin produces a neoepitope that can then be presented in the context of these MHC class II molecules and stimulate gut-

derived T-cells in an autoimmune response. Subsequent generation of IgA-class antibody to tissue transglutaminase impairs its normal tissue-repairing function and varying degrees of enteropathy can develop. Persistent stimulation by gluten in the diet can maintain high levels of both specific anti-transglutaminase IgA antibody and T-cell activation and result in celiac disease with ongoing intestinal damage. Several similar yet distinctive transglutaminases involved in tissue repair are also expressed in other tissues of the body. Epidermal transglutaminase (TG3) is expressed in the papillary dermal tips of the skin. Patients with either CD, DH or both CD and DH have some antibodies which can cross-react between the similar TG2 in the intestine and TG3 in the papillary dermis. However, patients with DH not only express varying titres of antibody to TG2, but also develop high affinity/avidity IgA antibodies to TG3.[12] These specific anti-TG3 IgA antibodies are not found in celiac disease without DH. These IgA antibodies deposit in the papillary tips, bind complement, and are chemotactic for activated neutrophils. Neutrophils then appear in the papillary tips and release their enzymatic granule contents including gelatinase and collagenase, which results in a cleavage through the overlying lamina lucida. This clinically presents as vesicles overlying erythematous papules (Table 1).[11, 12]

Specific testing for anti-TG3 antibodies in the serum is not yet available. Current serological assays are markers of gut pathology only and are not markers of skin disease.[13] Anti-gliadin antibodies do not have any clear pathological significance and simply represent antibody made to the alcohol-soluble portion of the plant elastin. Anti-reticulin, anti-jejunal and anti-endomysial antibodies are indicators of damage to the jejunal connective tissue. Anti-transglutaminase (TG2) is a specific type of anti-endomysial antibody that is most suggestive of gut pathology. Furthermore, titres of this antibody appear to correlate with the degree of enteropathy. The role of serological studies in DH would be to help exclude significant underlying intestinal disease.[13]

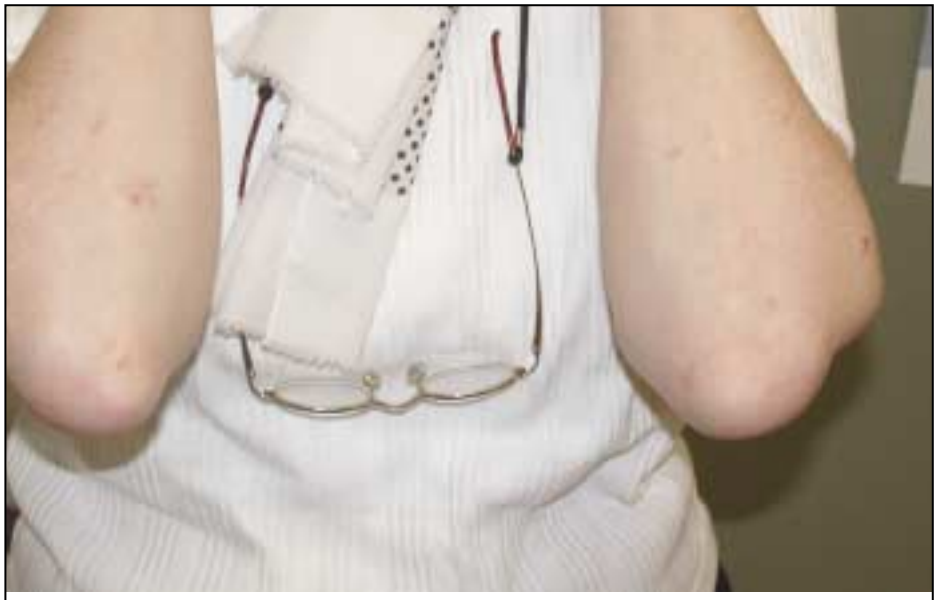

Figure 1: Dermatitis herpetiformis. Pruritic erythematous papules and excoriations on the extensor elbows of a 68-year-old woman.

Clinical Features

DH typically presents with intensely pruritic urticarial to purpuric plaques, papules, papulo-vesicles, vesicles or excoriations symmetrically over extensor surfaces. The intense pruritus, distribution and symmetry are often the key features of the disease. Classic areas of involvement include the extensor elbows (Figure 1), knees (Figure 2), buttocks, posterior shoulders, nucha, sacrum, and scalp. Vesicles, when present, tend to be grouped in a "herpetiform" arrangement. With the intensely pruritic nature of the disease, typically only excoriations are seen (Figure 1, 2). This is generally a non-scarring condition, but the chronicity of the disease can result in significant post-inflammatory hyper- or hypo-pigmentation.

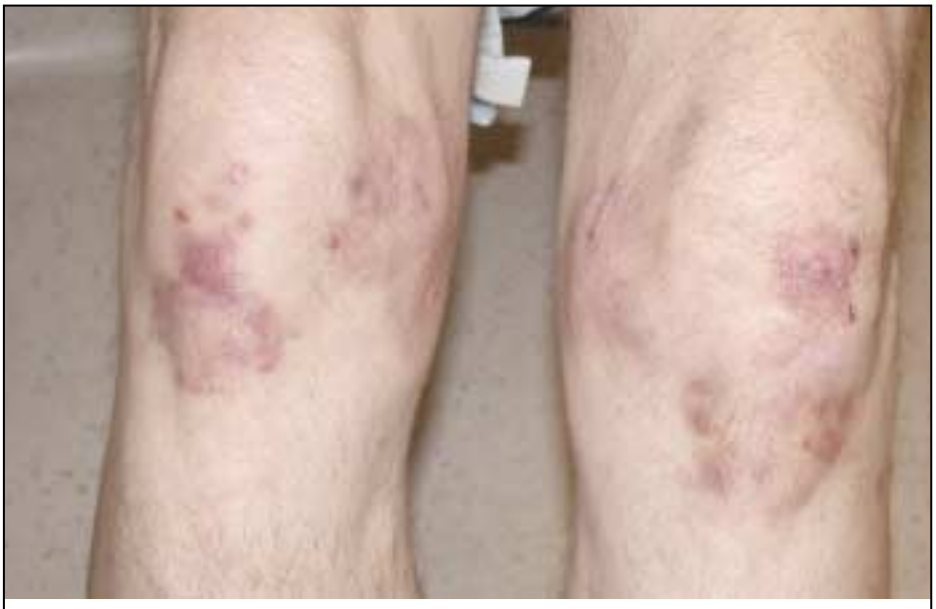

Figure 2: Dermatitis herpetiformis. Onset of intensely pruritic purpuric papules, plaques and excoriations over the knees in a 79-year-old man.

Table 1: Pathophysiology of Celiac Disease (CD) and Dermatitis Herpetiformis (DH)

Celiac Disease:
1. Gliadin from plant gluten binds to tissue transglutaminase (TG3) produced by jejunal connective tissue
2. Neo-epitope formed from TG3-gliadin binding is presented to T-cells in context of HLA-DQw2/-DQ8
3. Intraepithelial cytotoxic T-cells and IgA autoantibody produced to endomysium and TG3
4. Normal jejunal repair function of TG3 is inhibited
5. Enteropathy develops and progresses
6. Some cross-reacting IgA antibodies bind to epidermal transglutaminase (TG2) in epidermal papillary tips
Dermatitis Herpetiformis:
1-6 as above.
7. High affinity/avidity IgA autoantibodies are generated specifically to TG2
8. Granular or fibrillar deposition of these autoantibodies in papillary tips where TG2 islocated
9. Complement binds to precipitated IgA
10. Neutrophils are attracted to both precipitated IgA and complement and accrue in the papillary tips
11. Neutrophils express tissue destructive enzymes and oxygen radicals
12. Cleavage occurs at weakest point in basement membrane zone (lamina lucida)
13. Results in subepidermal vesiculation

With the polymorphous clinical presentation, DH can be easily confused with other pruritic dermatoses, including neurotic excoriations, eczema, insect bite reactions, urticarial bullous pemphigoid, transient acantholytic dermatosis (Grover's disease), linear IgA bullous dermatosis, and infestations, including scabies.

Diagnosis of DH

Clinical suspicion of DH based on symptoms and symmetric characteristic distribution should be followed with a skin biopsy of an erythematous lesion for histopathology. Clinically-involved skin often shows dermal papillary edema, with accumulation of neutrophils and fibrin resulting in separation of the papillary tips with the formation of subepidermal bullae (Figure 3). This pathologic feature is suggestive of DH, but is not diagnostic. Similar changes can be seen in bullous lupus erythematosus, variants of cicatricial pemphigoid, bullous pemphigoid and linear IgA bullous dermatosis.

Confirmation of DH requires a biopsy of peri-lesional skin for direct immunofluorescence (DIF). Skin biopsies for DIF should be sent to the laboratory either fresh for snap freezing or in appropriate immunofluorescence transport media, such as Michel's solution. DIF reveals either a granular (85-95%) or a fibrillar pattern of IgA deposits concentrated in the papillary tips. These may have associated C3 or IgM. The false negative rate of DIF is elevated in lesional skin where immunoreactants may be degraded by inflammation. Similarly, the false negative rate of DIF increases sharply with distance away from an active lesion; thus, it is important to biopsy true perilesional skin (within one centimetre of erythema).[8, 14]

Assessment and Surveillance for Comorbid Disease in DH

With chronic T-cell activation occurring in the intestinal connective tissue, patients with DH, CD or both are at an increased lifetime risk for the development of non-Hodgkin's (primarily T-cell) gastrointestinal lymphomas.[15,16] The risk of this event may be decreased by avoidance of further T-cell activation through the elimination of gluten antigen from the diet.[17-19] Onset of lymphoma can present as a change in an otherwise controlled disease, weight loss, abdominal pain, development of pruritus while on treatment, or even as obstruction or perforation.[20] Lymphoma most commonly develops approximately 15 years after diagnosis and is most prevalent in the older population.[5,18] A CT scan should be considered in any older patient with DH and a change in symptoms.

Although there is uncertainty as to the pathogenic mechanisms, approximately one-third of patients with DH develop splenic atrophy. Hence, all patients with DH should receive pneumococcal vaccination. Howell-Jolly bodies seen on blood film are an indication of splenic atrophy.[21]

Non-goitrous Hashimoto's thyroiditis is commonly associated with DH and should be periodically screened for on history, physical and laboratory examinations.[22] Similarly, atrophic gastritis and achlohydria often lead to both B12 deficiency and pernicious anemia. Any laboratory signs of anemia in the face of DH should precipitate a search for possible symptomatic enteropathy and malabsorption. In diagnosed CD, bone densitometry should be considered to search for treatable osteopenia, as the enteropathy may result in ineffective vitamin D metabolism.

Several other auto-immune diseases may be more weakly associated with DH or CD (Table 2).[23]

Treatment

Management of DH includes both behavioural and systemic treatments (Table 3). The skin lesions associated with DH appear to be induced primarily by the neutrophilic infiltrate. Medications that exacerbate neutrophilic activation, such as iodides or non-steroidal anti-inflammatory agents (NSAIDs), may aggravate lesions of DH.[2] Similarly, cigarette smoking can also activate neutrophils. Medications that inhibit neutrophil chemotaxis and activation (sulfones, sulfonamides, colchicine) are the mainstay of symptomatic treatment in DH. These medications inhibit the neutrophil effector arm but do not address the underlying disease or pathology.

Strict adherence to a gluten-free diet is by far the best treatment for both DH and CD. Both skin and intestinal disease respond to the absence of further antigenic stimulation.[24] However, the time frame for improvement of skin disease (i.e., the slow resorption of IgA complexes and complement in the papillary dermis) averages 25 months on a gluten-free diet.[5] This often necessitates the use of anti-neutrophilic agents to inhibit cutaneous symptoms during this time.

The sulfone dapsone (4′, 4′ diaminodiphenyl sulfone) is the first-line treatment for the symptoms of DH. Patients typically respond within 48-72 hours of starting therapy at 50mg per day. Dose range may vary from 25mg per week to 300mg per day to adequately control disease. Dapsone inhibits neutrophil chemotaxis, adherence, myeloperoxidase expression, and binding to IgA antibody complexes.[25] It is degraded by liver cytochromes CYP2E and CYP2C to both toxic hydroxylamine and non-toxic acetylated intermediates which undergo glucuronidation and subsequent excretion in the urine. Many of the potential adverse effects of dapsone treatment are due to hydroxylamines (Table 4). The hydroxylamine intermediates react with hemoglobin to form methemoglobin which cannot effectively deliver oxygen to the tissues. On average, 5% of the hemoglobin may be converted to methemoglobin. This may be important in older patients with comorbid pulmonary or cardiac disease that are dependent upon all of their cardiac reserve. Symptoms of methemoglobinemia include headache, lethargy and eventually, dyspnea. [25, 26]

Hydroxylamine intermediates also pose an oxidative stress on the red blood cell (RBC) membrane and cause hemolysis of aged RBCs. On average, the hemoglobin drops 10% on dapsone therapy. This drop is at least doubled in those patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency who cannot properly respond to oxidative stress. Hemolysis outside of G6PD-deficiency may be minimized by the co-administration of cimetidine (400 mg po tid) and vitamin E (800 IU po qd), which inhibit the hydroxylamine pathway and oxidative stress, respectively. [27, 28]

Idiopathic reactions to dapsone can include agranulocytosis, which occurs in response to hydroxylamine-induced hapten-immunologic destruction of granulocytes. This presents most commonly in older non-Caucasian patients at approximately seven weeks of therapy with a

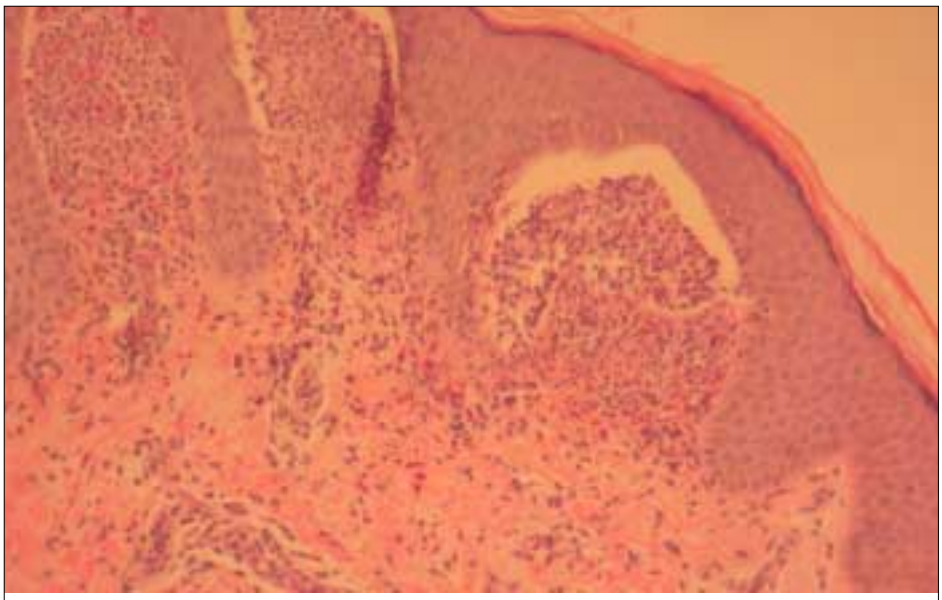

Figure 3: Histopathology of dermatitis herpetiformis. Neutrophilic microabscesses and fibrin are found in the papillary dermal tips and result in subepidermal separation and vesicle formation. There is also a superficial perivascular lymphohistiocytic infiltrate with scattered neutrophils and eosinophils in the papillary dermis (Hematoxylin and Eosin staining; 100X magnification).

Table 2: Disease Associations Observed with DH and CD

Strong Associations:
– Malabsorption associated anemia (folic acid, iron, B12)
– Pernicious anemia (B12 and atrophic gastritis)
– Osteopenia and osteoporosis (vitamin D)
– Splenic atrophy
– Non-Hodgkin's lymphoma (T-cell, gastrointestinal)
– Hashimoto's thyroiditis
– Type I diabetes
Weak Associations:
– Sjogren's syndrome
– Systemic Lupus erythematosus
– Scleroderma
– Vitiligo
– Alopecia areata
– Addison's disease
– Autoimmune hepatitis
– Myasthenia gravis
– Sarcoidosis

Table 3: Treatment Options for Dermatitis Herpetiformis

Behavioural:
1. Avoid systemic iodides and NSAIDs
2. Avoid cigarette smoking
3. Strict avoidance of glutens in diet
Systemic†:
1. Dapsone (start 25-50mg po qd and titrate up to disease control)
2. Sulfapyridine
3. Colchicine
Adjunctive Agents:
1. Potent topical corticosteroids
2. Phototherapy
†With observance of a strict gluten-free diet, systemic therapy may be tapered

frequency of 1:240-1:425 patients treated with dapsone.[29] Often presenting with fever and pharyngitis, this complication usually resolves within several days of stopping the medication. Other possible idiopathic adverse reactions to dapsone include a drug hypersensitivity syndrome, pancreatitis, peripheral neuropathy, hepatitis, psychosis, gastrointestinal upset, renal toxicity and various cutaneous reactions (Table 4).[5, 25]

Table 4: Potential Adverse Effects of Dapsone Therapy

Hydroxylamine-mediated and dose-dependent:
– Methemoglobinemia
– Hemolysis
Hydroxylamine-mediated and dose-independent:
– Agranulocytosis
Idiopathic:
– Hypersensitivity syndrome
– Peripheral neuropathy
– Gastrointestinal upset
– Cutaneous eruptions
– Hepatitis
– Psychosis
– Pancreatitis
– Renal toxicity

Appropriate selection of patients for dapsone treatment (i.e., no underlying untreated anemia, significant cardiopulmonary disease, G6PD deficiency, renal disease, progressive peripheral neuropathy, or concomitant medications causing significant oxidative RBC stress) will minimize adverse events associated with this medication. Similarly, starting at a relatively low dose (25-50mg) in older patients, with frequent and close monitoring of both physical and laboratory values, may permit the clinician to quickly identify any symptomatic adverse events and stop therapy.

Frequently, patients are placed on dapsone while attempting to adhere to a gluten-free diet and may eventually be able to discontinue the dapsone. However, many patients continue to have gluten in their diet and are on dapsone treatment indefinitely to control skin symptoms. It should be remembered that dapsone only treats the symptoms of the skin disease and does not change the pathology of any underlying enteropathy or the long-term risk of lymphoma. Continued gluten consumption while skin symptoms are controlled by dapsone may in fact, increase the lifetime risk of lymphoma.

Second-line options for the treatment of DH include potent topical corticosteroids for temporary symptomatic relief, sulfapyridine, colchicine, or phototherapy. Sulfapyridine and colchicine are not as effective as dapsone, and this is likely due to sporadic absorption; however, these drugs do not have such significant effects on RBC hemolysis. Treatment of the skin with ultraviolet light may temporarily improve skin symptoms (Table 3).

Summary and Recommendations

DH is a chronic autoimmune pruritic skin disease associated with varying degrees of enteropathy. As it is a life-long condition, prevalence is highest among older adults. Suspicion of DH based on symmetric pruritic lesions on extensor surfaces is confirmed by histopathology and direct immunofluorescence of skin biopsies and subsequent rapid response to dapsone (Table 5). Comorbid diseases and complications of DH, including non-Hodgkin's lymphoma, thyroiditis, splenic atrophy, and pernicious anemia, are most likely to present as the person ages in the presence of the disease. Ultimately, treatment of both the skin disease and any underlying enteropathy requires exclusion of gluten-containing foods from the diet.

Symptomatic treatment of the skin disease is most commonly accomplished with dapsone. Older patients are at highest risk for significant and potentially life-threatening side effects of this medication, so one must proceed at low doses and with close monitoring. A diagnosis of DH should be considered in any patient with symmetric and pruritic lesions on classic sites such as the elbows,

Table 5: Criteria Suggestive for a Diagnosis of Dermatitis Herpetiformis

Diagnosis of Dermatitis Herpetiformis:
– Symmetric pruritic papules, vesicles or excoriations over elbows, knees, buttocks, nucha, posterior shoulders or hair-line
– Histopathology showing subepidermal vesicle formation with neutrophilic papillary dermal microabscesses containing fibrin
– Direct immunofluorescence (DIF) showing granular or fibrillar deposits of IgA +/- complement in the dermal papillary tips†
– Rapid response of skin symptoms to dapsone treatment
†DIF showing granular or fibrillar IgA papillary deposits is diagnostic of DH

knees and buttocks. It is not uncommon for a patient to have a diagnosis of neurotic excoriations for many years before direct immunofluorescence confirms the true diagnosis—dermatitis herpetiformis. ◆

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