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ORIGINAL RESEARCH ARTICLE

Dermatitis Herpetiformis: Clinical Presentations Are Independent of Manifestations of Celiac Disease

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Abstract
Background Dermatitis herpetiformis (DH) is a skin manifestation of celiac disease (CD), and is often the presenting and only complaint. There are few data comparing those with DH who present only with DH and those with DH who present mainly due to CD.
Objective We compared the prevalence of features usually associated with CD in those who presented with DH with patients in whom DH was part of a typical CD presentation.
Methods A cross-sectional study of a prospectively maintained database of 1,050 patients with CD was analyzed. Only biopsy-diagnosed patients were analyzed for small bowel findings. All patients were included in the analysis of autoimmune diseases and lymphoma incidence. Small bowel biopsies were classified into mild and severe.
Results The prevalence of villous atrophy was significantly higher in the patients who presented with CD than in those who presented with DH alone (61.8 vs. 12.5 %; $p = 0.005$). However, the prevalence of nutritional deficiencies, autoimmune diseases, and lymphoma occurred at a similar rate in patients with DH and patients with CD without DH.
Conclusions Patients who present with CD and concurrent DH are more likely to have more severe pathology than those with predominantly DH, although nutritional deficiencies are similar between the two groups. It is important to screen for nutritional deficiencies in patients with DH, irrespective of the presence of typical CD manifestations.

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1 Introduction

Dermatitis herpetiformis (DH) is a chronic disease consisting of an intensely pruritic papulovesicular eruption primarily involving the extensor surfaces and characterized histologically by neutrophils in the dermal papillae and characteristic deposition of immunoglobulin (Ig)-A. Since the first report of the association of DH and celiac disease (CD) in 1967 [1], evidence of the close links between the two disorders has accumulated. CD is an autoimmune disease induced by the ingestion of the cereal grains, wheat, rye, and barley [2]. Originally it was thought that DH was a condition associated with CD; it is now recognized as an extra-intestinal manifestation of CD [3]. Fry et al. [4] showed that a gluten-free diet could clear the cutaneous manifestation of the disease, whereas a challenge with gluten would exacerbate the pruritic eruption. There have also been documented similarities, including the prevalence of human leukocyte antigen (HLA)-B8 and DR3 phenotypes, circulating IgA antibodies directed against the endomysium of smooth muscle (EMA), transglutaminase in skin and sera, coexisting autoimmune disease, and the predisposition to the development of lymphoma [4].

The prevalence of CD has increased almost fivefold in the last 50 years in the USA [5], though the rate of clinical diagnosis lags far behind that of the actual prevalence of the disease. This is demonstrated in the analysis of the most recent National Health and Nutrition Examination Survey (NHANES) data set, in which only 17 % of those with CD were diagnosed [6]. A recent study published in 2011 by Salmi and colleagues [7] showed the highest prevalence yet

of 75.3 per 100,000. However, this study only addressed the issue of prevalence and incidence and did not address the management dilemmas often encountered.

While the associations between DH and CD are not in dispute, management of DH has been a little more controversial. Some investigators have observed normal jejunal mucosa in about one-third of patients [8], whereas others have claimed that enteropathy is almost always demonstrable and the studies showing response to a gluten-free diet are from more than 20 years ago [9]. While in CD there is an increasing trend to screen for vitamin deficiencies, there is no evidence as to the prevalence of malabsorption in patients with DH.

The aims of this study were to explore the clinical, nutritional, and associated conditions in patients with DH seen at a Celiac Disease Center, comparing those presenting primarily with DH versus patients presenting with predominant symptoms related to CD.

2 Materials and Methods

2.1 Clinical Review

We performed a cross-sectional study of patients seen at the Celiac Disease Center at Columbia University in New York; all patients, after informed consent, were prospectively enrolled in a database. The Celiac Center at Columbia University, a specialist referral center, is one of the few dedicated centers in the country and draws patients from both the New York Metropolitan region as well more distant sites in the USA. Of 1,050 patients with biopsy-confirmed CD, 98 with DH were identified; of these, only 84 patients who had data available from duodenal biopsy at the time of diagnosis were included in the analysis for small bowel findings and evidence of malabsorption. All 1,050 patients were included in analysis of incidence of autoimmune disease and lymphoma. As well as demographic information, we assessed the incidence of autoimmune disease and lymphoma in the entire database of patients without DH compared with the incidence in patients with DH. We obtained histological findings, vitamin deficiencies, and other evidence of malabsorption, presence of other autoimmune disorders, and development of lymphoma. A careful review of clinical charts and pathology slides allowed for unequivocal confirmation of the diagnosis of DH in all cases, and presence of autoimmune disease was confirmed with appropriate serology and clinical findings.

2.2 Histopathology

Formalin-fixed, paraffin-embedded skin specimens from most of the patients were available. In a few instances, skin biopsy had been performed at other institutions and a written report was available in the chart. Classical findings, such as a collection of neutrophils or leukocytoclasia in the dermal papillae with the formation of subepidermal clefting, were considered to be consistent with the diagnosis of DH. However, to be included in this study, we required confirmation of the diagnosis by direct immunofluorescence.

Small intestinal biopsies were classified based on Marsh criteria, ranging from increased intraepithelial lymphocytes to complete villous destruction. For this analysis, we then divided small bowel findings into two categories, those with minimal lesions (Marsh 0, 1, or 2), and those with villous atrophy (Marsh 3a, 3b, or 3c) [10]. CD was defined as positive serology (anti-tissue transglutaminase antibodies [anti-tTG IgA] and/or deamidated gliadin peptides) in the presence of consistent pathological findings. In patients with negative serology but classic findings on small bowel biopsy, the diagnosis was maintained. Patients who only had positive serology but not histologic findings, and were not on a gluten-free diet, were considered to not have CD.

2.3 Statistical Methods

All results were analyzed using Chi-square and Fisher's exact test when applicable. P values <0.05 were considered statistically significant.

3 Results

A total of 84 patients with DH were identified from the database that had been prospectively maintained since 1990. Mean length of follow-up was 8 years. The age at diagnosis ranged from 18 to 87 (mean 43) years (Table 1). A total of 68 patients (81 %) in this group were diagnosed with CD, preceding the diagnosis of DH, with presentations including anemia, diarrhea, osteoporosis, or screening in high-risk individuals. Sixteen patients (19 %) presented with DH and had no other clinical manifestation of CD. Of these patients, there was a male predominance in patients with a DH-predominant presentation compared with those diagnosed initially with CD (71 vs. 40 %; $p = 0.44$, Table 1).

In all 84 patients with DH and CD, small bowel biopsy was performed. We divided histopathologic findings, assessed at the time of diagnosis, prior to the initiation of a gluten-free diet, into two categories: those with mild lesions (classified as Marsh 0, 1, or 2) and those with villous atrophy (Marsh 3a, 3b, or 3c). In the 68 patients with symptomatic CD preceding DH, 26 (38.2 %) had mucosal alterations consistent with milder lesions compared with 14 (87.5 %) patients with a DH-predominant presentation.

Table 1 Characteristics of patients with DH and CD

Characteristic	CD diagnosed before DH ($n = 68$)	DH-predominant presentation ($n = 16$)
Men (%)	40	71
Age at diagnosis (years); mean (SD)	43.1 (19.6)	42.5 (19.9)
Serology		
tTG IgA positivity (%)	52 (76.4)	14 (87.5)
DGP positivity (%)	47 (69.1)	10 (62.5)

CD celiac disease, *DGP* deamidated gliadin peptides, *DH* dermatitis herpetiformis, *SD* standard deviation, *tTG IgA* anti-tissue transglutaminase antibody

Table 2 Results of small bowel biopsy at the time of diagnosis

Marsh criteria	CD diagnosed before DH ($n = 68$)	DH-predominant presentation ($n = 16$)
0, 1, or 2 (%)	26 (38.2)	14 (87.5)*
3a, 3b, or 3c (%)	42 (61.8)**	2 (12.5)

CD celiac disease, *DH* dermatitis herpetiformis

* $p = 0.05$; ** $p = 0.005$

The prevalence of significant small bowel pathology (Marsh 3a, 3b, or 3c) was significantly higher in the patients who presented with CD than in patients who presented with DH alone (61.8 vs. 12.5 %; $p = 0.005$) (Table 2).

In all 84 patients with DH and CD, vitamin and mineral levels were measured, including vitamin D, iron, vitamin B_{12}, and folate. There was no significant difference between the two groups in any of these parameters (Table 3).

Other autoimmune disorders were diagnosed in 190 patients with CD and no history of DH compared with 23 patients with DH and CD (19.9 vs. 23.4 %; $p = 0.59$). On further sub-analysis, no significant difference was noted in the incidence of any autoimmune disorder (Table 4). There was no increased rate of other dermatological conditions (psoriasis, vitiligo, or alopecia). Lymphoma occurred at a similar rate in patients with CD and DH and in patients with CD without DH (1.0 vs. 0.2 %; $p = 0.07$) (Table 4).

Upon analysis of control of DH with diet alone versus medication, we found that a significant percentage of patients (76.5 %) with CD preceding the diagnosis of DH had resolution of skin findings on a gluten-free diet, with only 5.9 % requiring dapsone, whereas in the group with a DH predominant-presentation, only 37.5 % of patients resolved with diet alone ($p < 0.05$), and 37.5 % required therapy with dapsone. However, overall resolution rates of DH were similar between groups (88.2 vs. 87.5 %) (Table 5).

4 Discussion

Few studies in the literature have reported the prevalence of typical manifestations of CD in patients with DH. We sought to classify these patients based on histological findings, nutritional status, and risk of other autoimmune diseases or malignancy, and noted a similar rate of nutritional deficiencies and associated conditions in those who present with DH compared with those who presented with typical manifestations of CD.

Most of the existing literature on DH originates from centers primarily seeing patients for the dermatological aspects. Gawkrodger et al. [11], in a series of 282 patients with DH, reported 15 patients whose diagnosis of CD preceded the onset of DH. The series of Buckley et al. [12] and Davies et al. [13] yielded a total of 161 patients with DH, but only six had been previously diagnosed with CD. Egan et al. [14] reported six patients diagnosed with CD before the diagnosis of DH in a cohort of 54 patients (11.1 %), showing the limited data on patients with a diagnosis of DH followed by CD and recommendations for follow-up and screening for other associated illness.

We are aware of the limitations of this study in that current criteria used to establish a diagnosis of CD might have resulted in a higher prevalence of patients with both

Table 3 Nutritional status

Vitamin/mineral	CD diagnosed before DH ($n = 68$)	DH-predominant presentation ($n = 16$)	Reference range
Vitamin D (ng/mL); mean (SD)	30.88 (14.6)	25.67 (15.42)	20–80
Iron (μg/dL); mean (SD)	81.4 (25.5)	64.6 (33.4)	50–170
Vitamin B_{12} (pg/mL); mean (SD)	682.8 (353.3)	557.4 (338.9)	110–800
Folate (ng/mL); mean (SD)	12.49 (8.0)	10.24 (5.5)	3–20

No significant difference between groups in any measurements

CD celiac disease, *DH* dermatitis herpetiformis, *SD* standard deviation

Table 4 Associated autoimmune disorders, other disorders, and lymphoma in patients with CD with and without DH

Disorder	Number of patients (%)	
	CD without DH ($n = 952$)	CD and DH ($n = 98$)
Thyroid disease	97 (10.2)	12 (12.2)
Hypothyroidism	88 (9.2)	9 (9.2)
Hyperthyroidism	1 (0.1)	0 (0)
Hashimoto's thyroiditis	4 (0.4)	1 (1.0)
Goiter	2 (0.2)	1 (1.0)
Grave's disease	4 (0.4)	1 (1.0)
Connective tissue disorders	27 (2.8)	2 (2.0)
Rheumatoid arthritis	5 (0.5)	1 (1.0)
Sjogren's syndrome	10 (10.5)	1 (1.0)
Systemic lupus erythematosus	7 (0.7)	0 (0)
Polymyalgia rheumatica	4 (0.4)	0 (0)
Polymyositis	1 (0.1)	0 (0)
Other autoimmune disorders	22 (2.3)	0 (0)
Addison's disease	3 (0.3)	0 (0)
Pernicious anemia	1 (0.1)	0 (0)
Type 1 diabetes mellitus	18 (1.9)	0 (0)
Liver disease	7 (0.7)	3 (3.1)
Autoimmune hepatitis	3 (0.3)	3 (3.1)
Primary biliary cirrhosis	3 (0.3)	0 (0)
Wilson's disease	1 (0.1)	0 (0)
Dermatologic conditions	34 (3.6)	5 (5.1)
Psoriasis	17 (1.8)	2 (2.0)
Vitiligo	12 (1.3)	2 (2.0)
Alopecia	3 (0.3)	1 (1.0)
Malignancies	3 (0.3)	1 (1.0)
Lymphoma	2 (0.2)	1 (1.0)
Chronic lymphocytic leukemia	1 (0.1)	0 (0)

No significant difference between groups in any measurements

CD celiac disease, *DH* dermatitis herpetiformis

DH and CD. In addition, the patients were seen in a specialist CD center and may not be representative of patients with DH in the community.

In regards to small bowel pathology, patients who present with CD and concurrent DH are more likely to have more severe intestinal damage (Marsh 3a or greater pathology) than those with a DH-predominant presentation. Previous studies have shown that up to 20 % of patients with DH can have minimal pathological lesions in duodenal biopsies [14]. Despite this, we found that the nutritional deficiencies are similar between the two groups. It is therefore important that patients with DH are assessed for

Table 5 Treatment of DH with resolution

Treatment	CD diagnosis prior to DH ($n = 68$)	DH-predominant presentation ($n = 16$)
Gluten-free diet [*n* (%)]	52 (76.5)	6 (37.5)*
Medications		
Dapsone [*n* (%)]	4 (5.9)	6 (37.5)*
Sulfapyridine [*n* (%)]	4 (5.9)	2 (12.5)

CD celiac disease, *DH* dermatitis herpetiformis

* $p < 0.05$

nutritional deficiencies both at diagnosis and during follow-up. We continue to screen all patients with any form of CD, including DH, for nutritional deficiencies and provide supplements when necessary. Even findings of minimal histological change can be misleading, due to the patchy nature of the disease, and can mislead the clinician as to the risks of nutritional deficiency. In addition, nutritional deficiencies may be contributed to by the gluten-free diet itself, as the diet can be deficient in B vitamins, calcium, and iron, as well as fiber [15]. Patients with CD and DH are also recommended by the National Institutes of Health (NIH) Consensus Development Conference on Celiac Disease to be assessed by an experienced dietitian on an ongoing basis [15, 16].

Those with CD have a greater incidence of other autoimmune diseases than the general population [17]. This increase may be reduced by early diagnosis of CD [18, 19] and, after diagnosis, adherence to a gluten-free diet reduces the risk of further acquisition of more autoimmune diseases [20]. Patients with DH have also been shown to have increased rates of autoimmune disease. Collin et al. [21] reported an incidence of 5.2 % (16/315) of endocrinologic disorders in patients with DH, most commonly thyroid-related diseases (4.3 %). In their series of 115 and 100 patients with DH, Christensen et al. [22] and Weetman et al. [23] reported 9 and 5 % incidences of thyroid disorders, respectively. Our data showed a similar incidence of thyroid disease in 10.2 % in patients with CD alone and a 12.2 % incidence in patients with DH and CD. In addition, we demonstrated an overall similar rate of autoimmune disease among both those with CD alone and those with CD and DH.

Liver disease, predominantly autoimmune hepatitis, has been shown to be associated with CD, but no clear connection exists with DH. In our study, only 0.7 % of patients with CD had associated liver diseases, including autoimmune hepatitis, primary biliary cirrhosis, and Wilson's disease. In the subset of patients with DH, 3.1 % of patients were found to have autoimmune hepatitis. Although the difference has a trend towards significance ($p = 0.056$), the numbers are too small to make a clear connection.

Patients with CD have increased mortality compared with the general population, and an increased rate of lymphoma [24]. Studies have shown an association between DH and an increased rate of malignancies [25]; however, fewer than 100 cases of lymphoma associated with DH have been reported. The 1.0 % incidence of lymphoma in our series is in agreement with previously published reports of <2 %. Both T- and B-cell non-Hodgkin's lymphoma occur in CD [26]. The T-cell lymphomas, especially the enteropathy-associated T-cell lymphoma (EATL), carry a very poor prognosis [27]. In our cohort, no significant difference was seen in the incidence of lymphoma in patients with CD only versus those with CD and DH (0.2 vs. 1 %). Recently, a reduced mortality has been reported in patients with DH compared with the general population in Finland [28]. This could well be attributed to strict adherence to a gluten-free diet that is necessary in some patients to control their DH symptoms.

5 Conclusions

It is assumed that patients with DH have CD with some form of enteropathy; however, the establishment of the status of the small intestinal mucosa is not necessary to confirm the diagnosis of DH. Even though a minority of patients with DH lack gastrointestinal complaints consistent with CD, we observed similar incidences of vitamin and mineral deficiencies, incidence of autoimmune disease, and lymphoma risk in patients with CD diagnosis prior to DH and DH alone. However, patients with a more classical presentation of CD have more severe changes in the intestinal mucosa than those who present with DH alone.

In the population of patients presenting with only DH, it is important to encourage a gluten-free diet and to continue routine nutritional screening similar to in those patients presenting with other forms of CD, as the course of the disease, and incidence of co-morbidities, is similar.

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