

Celiac disease: from gluten to skin

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Celiac disease (CD) is an autoimmune gluten-dependent enteropathy characterized by atrophy of the intestinal villi that improves after a gluten-free diet. CD is often associated with extraintestinal manifestations. In the past few years, growing evidence has documented the involvement of skin diseases among the extraintestinal manifestations of CD. This association could be related to the impairment of intestinal absorption and motility, other than to immunological and hormonal changes. The aim of this review is to report all CD-associated skin manifestations described in the literature and to analyze the possible mechanisms involved in this association. The opportunity to evaluate the possible presence of CD in patients affected by skin disorders is discussed.

KEYWORDS: alopecia areata • celiac disease • dermatitis herpetiformis • malabsorption • psoriasis • skin

Celiac disease (CD) can be defined as a chronic immune-mediated gluten-dependent enteropathy, resulting from an inappropriate T-cell-mediated immune response against ingested gluten in genetically predisposed people [1]. CD is characterized by malabsorption in the small intestine, resulting in a loss of the body's ability to absorb nutrients through the villi, caused by wheat gluten and related cereal peptides [1–2]. Most affected individuals show sustained clinical remission when they are put on a strictly gluten-free diet (GFD) (FIGURE 1). The etiology of CD is not fully understood, but genetic and immunologic factors play an important role in its pathogenesis. CD may affect patients of any age; however, its incidence is bimodal, with peaks in early childhood and in the fourth and fifth decades [2]. The classic form of CD presents with several symptoms, such as diarrhea, abdominal pain, weight loss and nutritional deficiencies, particularly of iron, folate, calcium and vitamin D [1–3].

The use of serological tests has been suggested as a screening method for the diagnosis of CD as well as for the follow-up of dietary compliance. Immunological markers have been proposed as useful adjuncts for the diagnosis of CD by reducing the number of intestinal biopsies required for diagnosis. The IgA-class endomysial antibodies (EMAs) and IgA tissue transglutaminase antibodies (tTGAs) have high sensitivities (>93% for both) and specificities (>99 and >95%, respectively) for the diagnosis

of classical CD. The antigliadin antibodies (AGAs) have a sensitivity and specificity ranging between 82 and 100%, and 50 and 100%, and those of IgA–AGA between 52 and 99.9%, and 65 and 100%, respectively [4].

In the past few years, growing evidence has documented the involvement of skin diseases among the extraintestinal manifestations of CD [5]. The association between dermatitis herpetiformis (DH) and CD is well known. Other cutaneous manifestations accompanying CD have been reported in the literature (TABLE 1). However, at present, the data are not homogeneous, and most of the evidence for the association between CD and skin disorders is based on case reports, making it difficult to draw definitive conclusions on this topic.

A recent study was performed to detect the prevalence of mucocutaneous manifestations of CD in childhood and adolescence, and to investigate the relationship between these findings and the duration of disease and a GFD [6]. The study included 55 children and adolescents with a mean age of 10.0 ± 4.61 years (2–19 years of age). The most prevalent dermatologic diagnosis was xerosis (69.1%). No significant relationship was detected between the cutaneous findings and the duration of illness ($p > 0.05$). However, the duration was longer in patients with mucosal findings compared with those without mucosal findings ($p < 0.05$). It was found that all patients without cutaneous findings were on a strict GFD ($p < 0.05$).

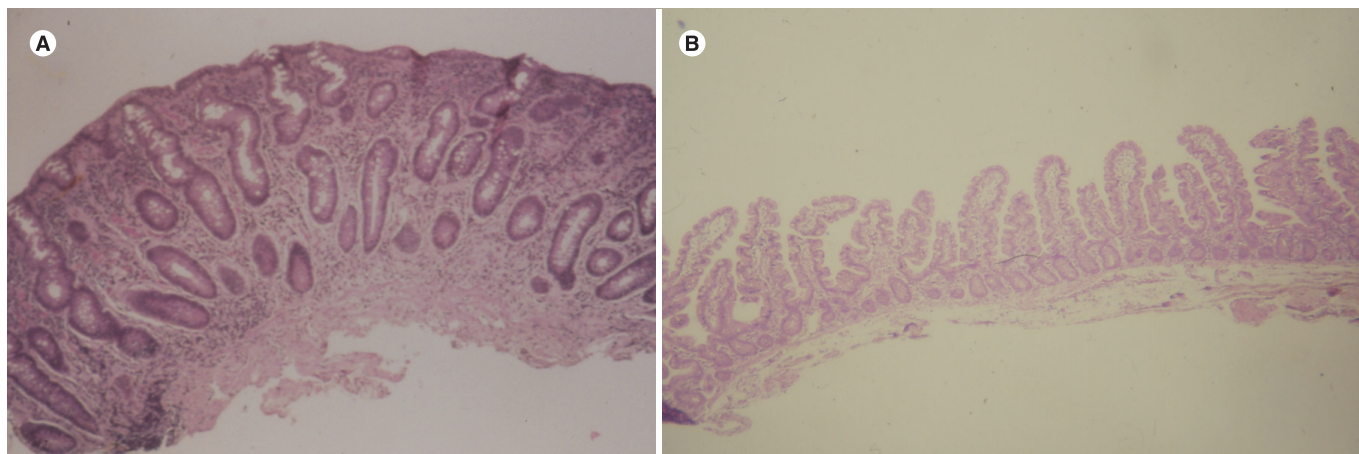


Figure 1. The effects of gluten-free diet in a celiac disease patient. (A) Biopsy section from the duodenum: villi are rudimentary and atrophic, with elongated hyperplastic crypts. The cellularity of the lamina propria is increased and numerous crypt mitotic figures are seen. **(B)** Small intestinal biopsy section obtained 3 months after the start of gluten-free diet: there is normalization of the abnormal architectural changes, the villi are elongated with shorter crypts and fewer mitotic figures are seen. Epithelial cells are more columnar and intraepithelial lymphocyte numbers are reduced. Lamina propria cellularity is markedly reduced.

The aim of this review is to report all CD-associated skin manifestations described in the literature and to analyze the possible mechanisms involved in this association.

Dermatitis herpetiformis

Dermatitis herpetiformis is an autoimmune intensely pruritic papulovesicular blistering rash typically located on the elbows, forearms, buttocks, knees and scalp (FIGURE 2) [7]. EMA and tTG antibodies have been detected in patients with DH [8]. CD and DH have characteristics of autoimmune disorders. These characteristics include a tight association with MHC class II molecules (HLA) and the production of circulating autoantibodies [9]. One quarter of patients with DH also have CD. Recently, a novel candidate gene, myosin *IXB* on chromosome 19p13, was shown to be associated with CD in Dutch and Spanish populations. It is a potential shared risk factor in these inflammatory disorders [10].

The histopathologic hallmarks of DH are the presence of neutrophils and eosinophils in dermal papillae with eventual vesiculation. Although granules of IgA that are believed to be pathogenic are located in the dermal papillae, the vesicle formed at the basement membrane occurs in the lamina lucida of the trilaminar basement membrane. This is believed to be the result of the degradation of the lamina lucida by neutrophil lysosomal enzymes. However, the exact target antigen is still unknown. These deposits are often associated with C3 to support the suggestion that complement is activated via the alternative pathway and C5 [11]. The activated fraction, C5a, is highly chemotactic for neutrophils and may contribute to the inflammatory change at the papillary tip. HLA studies in patients who have DH based on clinical and immunological criteria have shown that 85–90% are HLA B8-positive and that there is an even stronger association with HLA DW3 and DRW3. There is an immunogenetic association with HLA DR3 DQW2 (HLA class II alleles *DQA1 0501* and *DQB1 0201*), which is very much more common in Caucasians than in Orientals, and may be important for the different incidences of DH in different ethnic

populations [9]. Specific B-cell/macrophage antigens have been noted in patients with DH and CD [12]. One hypothesis is that both HLA and non-HLA disease genes are necessary for the development of lymphoid cell surface receptors that recognize gluten. These gluten-specific cells migrate to the gut mucosa where they mediate cytotoxic reactions involving epithelial cells.

Gluten must be present in the diet for the development of DH. The skin disease and the intestinal abnormality respond to gluten restriction within weeks to months. Skin disease and intestinal disease recur with the reinstitution of a diet containing gluten [13]. This strongly supports the belief that DH is an intestinal manifestation of CD. The severity of the skin disease and the level of responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. Although CD and DH may appear to be vastly different, they both share a unique intestinal sensitivity to gluten, with the rash of DH thought to be an external marker of the underlying intestinal sensitivity that is likely to be the result of molecular mimicry between autoantigen tissue transglutaminase resident in the gut- and skin-derived epidermal transglutaminase. Although patients with DH are unlikely to have gastrointestinal (GI) symptoms or features of malabsorption, they have small intestinal histopathologic changes, with either a classical atrophic appearance with complete villous atrophy or, more commonly, a more subtle infiltrative pattern with partial or no villous atrophy. When there is suspicion of DH but with a negative skin biopsy, and there is serologic evidence of CD, a skin biopsy should be repeated, given the patchy nature of the lesions, and referral to a gastroenterologist for small bowel biopsy should be pursued. Interestingly, topical skin application of gluten-containing products does not produce the rash of DH in susceptible patients; however, oral or rectal introduction of gluten has been found to result in the classic DH rash [14]. The DH rash is often treated with dapsone in conjunction with gluten withdrawal. In addition to improving the histological changes of the small intestine, a GFD may

Table 1. Cutaneous diseases in celiac patients.

Cutaneous diseases associated with CD	Study	EBM level	Ref.
Dermatitis herpetiformis	Seah <i>et al.</i>	B	[8]
	Spurkland <i>et al.</i>	B	[9]
	Preis <i>et al.</i>	B	[11]
	Nino <i>et al.</i>	C	[13]
Linear IgA bullous dermatosis	Caproni <i>et al.</i>	B	[34]
	Egan <i>et al.</i>	B	[35]
Urticaria	Hautekeete <i>et al.</i>	B	[37]
	Cooper <i>et al.</i>	B	[38]
	Scala <i>et al.</i>	B	[39]
Hereditary angioneurotic edema	Brickman <i>et al.</i>	C	[42]
	Farkas <i>et al.</i>	B	[43]
Cutaneous vasculitis	Alegre <i>et al.</i>	D	[46]
	Meyers <i>et al.</i>	D	[47]
Erythema nodosum	Cribier <i>et al.</i>	B	[48]
	Durand <i>et al.</i>	C	[49]
	Bartyik <i>et al.</i>	D	[50]
Erythema elevatum diutinum	Tasanen <i>et al.</i>	D	[53]
Necrolytic migratory erythema	Goodenberger <i>et al.</i>	D	[57]
	Kelly <i>et al.</i>	B	[58]
	Thorisdottir <i>et al.</i>	D	[59]
Psoriasis	Cardinali <i>et al.</i>	B	[24]
	Michaelsson <i>et al.</i>	B	[25]
	Ojetti <i>et al.</i>	B	[22]
	Ojetti <i>et al.</i>	C	[23]
Vitiligo disease	Collin and Regnala	D	[61]
Behçet's disease	Triolo <i>et al.</i>	B	[66]
Oral lichen planus	Fortune <i>et al.</i>	B	[68]
Dermatomyositis	Evron <i>et al.</i>	D	[74]
	Marie <i>et al.</i>	D	[75]
Porphyria	Twaddle <i>et al.</i>	B	[76]
Alopecia areata	Corazza <i>et al.</i>	C	[27]
	Fessatou <i>et al.</i>	C	[28]
Acquired hypertrichosis lanuginosa	Hovenden <i>et al.</i>	D	[79]
	Corazza <i>et al.</i>	D	[80]
Ichthyosiform dermatoses	Menni <i>et al.</i>	D	[83]
Pellagra	Schattner <i>et al.</i>	D	[85]
Generalized acquired cutis laxa	Lewis <i>et al.</i>	D	[88]
	Bodvarsson <i>et al.</i>	B	[89]
	Garcia-Patos <i>et al.</i>	D	[90]
Atypical mole syndrome and congenital giant naevus	Montalto <i>et al.</i>	D	[93]
Atopic dermatitis	Jafroodi M <i>et al.</i>	D	[100]

System with categories labeled A, B, C and D used by UK National Health Service to determinate EBM levels.

Level A: Consistent randomized, controlled clinical trial, cohort study, all or none, clinical decision rule validated in different populations.

Level B: Consistent retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study or extrapolations from level A studies.

Level C: Case-series study or extrapolations from level B studies.

Level D: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

CD: Celiac disease; EBM: Evidence-based medicine.



Figure 2. Dermatitis herpetiformis manifestations in a celiac patient, at the moment of diagnosis.

also allow a reduction in suppressive medication, as patients with CD are also at a higher risk of malignancies such as lymphomas.

Bardella *et al.* investigated the effects of long-term DH remission in patients who underwent a gluten challenge and subsequently reintroduced dietary gluten [15]. They found that the ingestion of small doses of gluten in childhood and/or the use of an anti-inflammatory drug may modify the immunological response inducing immune tolerance.

Psoriasis

Psoriasis is a chronic, relapsing dermatosis characterized by scaling, erythema and, less commonly, postulation (FIGURE 3) [16]. It has been demonstrated that psoriasis is an immunological disease with hyperproliferation of T-cell-mediated keratinocytes [17]. *HLA-Cw*0602* may play an important pathogenetic role in the majority of psoriasis patients [18]. Immune mechanisms have an important role in the pathogenesis of this disease. In particular, an overexpression of Th1 cytokines and relative underexpression of Th2 cytokines have been shown in psoriatic patients [19]. The treatment is often difficult; all currently available effective remedies are retinoids or immunosuppressant drugs, such as steroids or cyclosporin, except for topical treatments, photochemotherapy (psoralen plus ultraviolet A [PUVA] therapy) and biological treatments such as infliximab or etanercept [20].

In recent years, some reports have appeared regarding a probable connection between psoriasis and enteropathy, mainly CD, and about the association of the intestines with skin lesions [21]. Intestinal absorption disorders and enteropathy confirmed by intestinal mucosa histology were observed in psoriatics. Ojetti *et al.* have evaluated the prevalence of CD in patients affected by psoriasis, showing a high frequency of CD (4.34%) in psoriatic patients [22]. Moreover, the same group evaluated the prevalence of malabsorption in 55 psoriatic patients, and found that malabsorption was more prevalent among psoriatic patients than among controls, and hypothesized that CD and other diseases associated with psoriasis, for example, bacterial overgrowth, parasitic infestations and eosinophilic gastroenteritis, could be possible causes of

malabsorption in these patients [23]. In addition, increased titers of antibodies typical for CD, such as AGA for IgA, antireticuline (correlating to disease intensification) for tissue transglutaminase and smooth muscle endomysium for IgA, were found in patients affected by psoriasis. In psoriatic patients with positive AGA titers and chronic psoriatic lesions, a GFD had a beneficial effect, which could be supported by the fact that after returning to a normal diet, the skin lesions intensified. The presence of CD-associated antibodies in psoriatic patients correlated with greater disease activity, because a significantly higher proportion of patients with elevated CD-associated antibody levels was currently on or had previously required systemic immunosuppressants or PUVA therapy [24,25].

Recently, a Polish study estimated whether gluten intolerance appears more often in healthy people than in psoriatic patients [26]. Serum samples from 67 patients with intensified psoriatic lesions were investigated. Serum from healthy people at a comparable age and with no familial predisposition to psoriasis or CD was the control material. Antibodies against human tissue transglutaminase (recombinant antigen), tissue transglutaminase isolated from guinea pigs' livers and gliadin were determined by ELISA. Anti-EMAs were determined by an indirect immunofluorescence method. It was found that patients with psoriasis have significantly higher mean concentrations of human recombinant and guinea pig-derived antigen (tTGA) and AGA IgA. IgA tTGA (both antigens) and AGA positively correlate with psoriasis activity. No EMA IgA was found in any serum. The authors concluded that this result seems to imply an association between psoriasis and asymptomatic CD/gluten intolerance.

At present, the mechanisms implicated in the possible association between CD and psoriasis, and the effect of a GFD on psoriatic skin lesions are not known [21]. However, some hypotheses have been proposed:

- Abnormal small intestinal permeability could be a triggering factor between CD and psoriasis;
- An increased number of T cells, activated by gliadin could play a role in the pathogenesis of psoriatic skin lesions;

- Psoriatic lesions in CD patients could be related to vitamin D deficiency, which is present both in CD and in psoriasis.

Alopecia areata

Alopecia areata (AA) is a chronic autoimmune disease characterized by nonscarring alopecia. Histologically, it is possible to find perifollicular lymphocyte infiltration pointing to an immunologic etiology such as CD [27]. In both diseases, there is the presence of organ-specific autoantibodies, T-lymphocyte infiltration at the site of the lesion, an association with HLA genes, and the possible etiologic importance of viral cofactors [28]. Serological screening for CD has also been performed in AA patients. In the general population, the prevalence is one in 305 for CD and one in 819 for AA [5]. Corazza *et al.* found that the prevalence of CD in patients with AA was one in 85, and suggests that AA patients constitute a novel risk group of CD [27]. However, there are some reports that show a failure of a GFD in CD-associated AA [29,30]; however, some patients on a GFD showed complete regrowth of scalp hair and other body hair and no further recurrence of AA at follow-up [31,32].

The positive effects of a GFD on the pattern of autoimmune conditions, such as AA-associated CD, have been attributed to a normalization of the immune response. Because AA may be the only clinical manifestation, some authors suggest serological screening tests for CD in patients affected by alopecia.

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is a rare disease characterized by erythematous papules or groups of small vesicles [33]. The onset may be acute or gradual and the predominant symptom is usually pruritus. Immuno-electron microscopic studies have shown a linear deposition of IgA along the lamina lucida or in the sub-basal lamina area of stratified squamous epithelium [33]. Presently, LABD is considered as a distinct entity from DH and bullous pemphigoid. The incidence of gluten sensitivity enteropathy (GSE) in LABD has been described in the literature to range from 0 to 24%. The HLA haplotype (*A1*, *B8* and *DR3*) of LABD patients is often that found in classic DH, which is in over 85% of CD patients [34]. Although the prevalence of CD is low in LABD, some authors have suggested the diagnosis of GSE in these patients [35].

Urticaria

Urticaria is an eruption of transient erythematous or edematous swellings of the dermis or subcutaneous tissue, and is due to a local increase in permeability of the capillaries and small venules [36]. In recent years, many cases of chronic idiopathic urticaria associated with CD have been reported [37,38]. Placement on a GFD led to the resolution of intestinal and urticarial symptoms [39]. The passage of antigens and immune complex formation may be facilitated by an increased mucosal permeability. Theoretically, this mechanism might cause urticarial lesions and, by restoring the integrity of the mucosa, a GFD might resolve skin symptomatology. Some authors recommended screening for CD in all patients suffering from chronic urticaria [40].

Hereditary angioneurotic edema

Hereditary angioneurotic edema (HANE) is characterized by recurrent edematous attacks in the subcutis and submucous owing to a C1-esterase inhibitor (C1-INH) deficiency [41]. Brickman *et al.* [42] described HANE in association with inflammatory bowel diseases (IBDs). Subsequently, Farkas *et al.* first described the simultaneous occurrence of HANE and CD [43]. The classic activation pathway of the complement system plays a potential role in the immune regulation of both disorders: it is deficient in HANE and gluten is a potent activator of the alternative pathway in CD [44]. There might also be a genetically determined etiology of both diseases. Complement testing is justified whenever the GI symptoms of CD persist, despite the restoration of the damaged mucosa. Conversely, HANE that is unresponsive to adequate prophylaxis should prompt the completion of GI group tests [45].

Cutaneous vasculitis

Celiac disease may give rise to many skin manifestations, but vasculitic skin lesions have rarely been encountered. Leucocytoclastic vasculitis is characterized by the involvement of postcapillary venules. The skin is the most common organ involved, with the usual clinical appearance of a palpable purpura. In most cases, leucocytoclastic vasculitis is mediated by immunocomplex deposition and the antigen being either exogenous or endogenous [46]. The coexistence of cutaneous vasculitis and CD might be related to increased intestinal permeability, and immune complexes originating from exogenous or endogenous antigens might circulate owing to the impaired phagocytic function of the reticular endothelium system, and be deposited in the skin. Alternatively, an autoimmune sensitization may result owing to the release of endogenous antigens from damaged small bowel mucosa [21]. Meyers *et al.* described a case of cutaneous vasculitis complicating CD and the remission of skin lesions after treatment with a strict GFD [47]. Treatment of leucocytoclastic vasculitis has generally been difficult, but corticosteroids and a GFD may improve the dermatosis in cases associated with CD.



Figure 3. Celiac patient affected by psoriasis.

Erythema nodosum

Erythema nodosum (EN) is a chronic panniculitis characterized by inflammation of the fat septa, and its etiology seems to involve an allergic or immune complex-mediated reaction to many antigens [48]. Triggers include infections, sarcoidosis, adverse drug reactions, IBD and lymphomas. EN generally resolves in 5–8 weeks but if the antigenic stimulus persists, the disease may last for a long period. A linkage between CD and EN was first observed by Durand *et al.* [49]. They presented the case of a 17-year-old girl who had suffered from the disease for 6 months. Her skin lesions cleared completely without any recurrence after treatment with a strict GFD. The authors have suggested that EN in CD is the result of an altered intestinal permeability to endogenous or exogenous antigens, which provoke the immunologic response. The coexistence of EN with CD has also been subsequently observed by other authors [50]. EN is also a common finding in sarcoidosis, which frequently coincides with CD [51]. When EN skin lesions are chronically recurrent or persistent, it is advisable to search for underlying CD, even if it is difficult to estimate the true incidence of the coexistence of both diseases.

Erythema elevatum diutinum

Erythema elevatum diutinum (EED) is a rare variation of cutaneous leucocytoclastic vasculitis, originally described in 1894. Its lesions appear as soft erythematous papuleplaques and become hard nodules mainly affecting the backs of the hands in a symmetrical manner and other extensor surfaces overlying the joints [52]. Ulceration, arthralgia and pain can be other features of this disease. Even if it is presumed to be an immune reaction by bacterial antigens, the etiology of EED is unknown. EED has been described in association with several other immunological diseases, especially paraproteinemias (i.e., monoclonal IgA gammopathy). Tasanen *et al.* detected dermoepidermal IgA and complement deposits suggestive of EED in lesional skin of a patient affected by CD [53]. The EED skin lesions appear to result from an immune complex reaction, as suggested by the association of various infections or autoimmune diseases. Joint pains are often present in patients affected by autoimmune disease such as EED but are also often found in association with CD. Some authors have therefore suggested that it is important to warrant consideration of underlying CD in at least some patients with EED.

Necrolytic migratory erythema

Necrolytic migratory erythema (NME) is a characteristic skin condition seen in the presence of a pancreatic glucagonoma. The presence of NME in the absence of a pancreatic tumor has been termed the pseudoglucagonoma syndrome. In such cases, NME is commonly associated with conditions such as liver disease, IBD, pancreatitis, malabsorption disorders (i.e., celiac sprue) and other malignancies [54]. NME is a term used by Wilkinson to describe the characteristic skin disease related to glucagonoma [55]. Lesions typically start with figurate areas of erythema followed by erosions mainly over the trunk, perineum, lower extremities and perioral area. Eventual shedding is caused by superficial necrosis [56]. Most patients have angular cheilitis, stomatitis, glossitis, diffuse alopecia

and brittle nails. NME occasionally co-occurs with chronic liver disease or malabsorption with villous atrophy. Goodenberg *et al.* [57], Kelly *et al.* [58] and Thorisdottir *et al.* [59] have all separately described an association between CD and NME. Resolution of the rash occurs only upon treatment of the underlying cause of NME, such as excision of the pancreatic glucagonoma, a GFD in CD, and nutritional supplementation in zinc, amino acid and fatty acid deficiencies.

Vitiligo

Vitiligo is a specific, common and often heritable acquired disorder characterized by well-circumscribed milky white cutaneous macules devoid of identifiable melanocytes [60]. This disease appears to be more commonly observed in parts of the body exposed to the sun and in darker skin types, and may develop at any age. The etiology is complex; there appears to be a certain genetic predisposition and a number of potential precipitating causes (i.e., crisis, illness, physical injury, and so on). Numerous attempts to identify HLA markers have revealed certain ethnic-specific markers: *HLA-DR4* (Black people), *B13* (Jewish people) and *BW-35* (Yemenites). We have previously discussed three prevailing theories to explain vitiligo: the neural hypothesis, the self-destruct hypothesis and the immune hypothesis [5]. Vitiligo carries with it a risk for ocular abnormalities, particularly iritis, and a significant risk for thyroid disease, diabetes mellitus, Addison's disease and pernicious anemia. The relationship between CD and vitiligo is controversial. Although some authors have described some cases of vitiligo in patients affected by CD, a serological screening study for CD in patients with vitiligo did not show any correlation between these two immunological disorders [61,62]. This implies that the sporadic associated cases must be considered coincidental.

Behçet's disease

Behçet's disease (BD) is a chronic, relapsing inflammatory disorder characterized by recurrent oral and genital aphthosis together with several other systemic manifestations, including skin, ocular, articular, neurological and vascular lesions. The underlying cause of BD is unknown. As with other autoimmune diseases, BD may represent an aberrant immune activity triggered by exposure to an antigen in those with a genetic predisposition to develop the disease [63]. BD and CD share many clinical presentations, such as recurrent aphthous stomatitis, as well as GI, musculoskeletal and neurological involvement. In fact, a history of oral ulceration has been described in 25% of patients with CD, and approximately 2–4% of patients with recurrent oral ulceration also have CD [64]. Oral ulcers usually show only nonspecific inflammatory changes, although there may be an infiltration of the grossly thickened walls of thrombosed arterioles [65]. Triolo *et al.* described three cases of a coexistence of BD and symptomless CD in 11 patients with BD (defined according to International Study Group-ISG criteria) [66]. IgA and IgG class AGA and EMA were found in one patient; another two had IgG AGA alone. There is suggestive but as yet inconclusive evidence of a probable association between CD and autoimmune

diseases such as BD. It could be supposed that both diseases are likely the result of molecular mimicry between two undefined autoantigens or an action triggered by a virus. In patients affected by BD, it may therefore be important to search for underlying undiagnosed CD.

Oral lichen planus

The associations between CD and recurrent oral ulceration, glossitis, angular cheilitis and burning mouth are common [67]. A total of 3–6% of patients with these oral manifestations may have underlying undiagnosed CD. Fortune and Buchanan described the erosive type of oral lichen planus (OLP) in a patient with gluten enteropathy [68]. OLP is a common chronic autoimmune inflammatory condition frequently associated with other immune disorders and usually resulting in characteristic lacy white patches. It frequently involves the buccal mucosa, gingiva and tongue, and sometimes the throat or esophagus. While OLP usually begins during midlife, it can occur at any age [69]. Moreover, OLP is usually a chronic condition and can last for many years. OLP signs and symptoms may include pale raised areas or bumps that form a lacy network on the tongue or inside the cheeks, or red, open sores in the mouth. It can cause mouth pain, dryness, sensitivity to hot or spicy food, or a metallic taste sensation. Symptoms may be intermittent. OLP is more apparent where there is evidence of corrosion, and the etiology of lichenoid lesions is likely to be multifactorial (i.e. drugs, allergies, dental issues, stress, and so on) [69]. The histology may show features compatible with lichen planus or a nonspecific chronic superficial perivascular dermatitis [68,69]. In CD and OLP, the lesions have a mucosal T-cell infiltrate. It is not clear whether the oral lesions are a direct manifestation of CD or if they are due to the effect of malabsorption on the rapidly dividing mucosal cells already predisposed to soreness by a pre-existing disease [69]. Furthermore, the response of oral lesions to a GFD is controversial; while some authors report their amelioration or resolution after GFD [70], one double-blind, placebo-controlled trial discounted this [71].

Dermatomyositis

Dermatomyositis (DM) is a disorder mainly of the skin, muscle and blood vessels, in which characteristic erythematous and edematous changes in the skin are associated with muscle weakness and inflammation [72]. Juvenile DM (JDM) has a more favorable prognosis for life but functional disability is usually severe. Its pathogenesis is probably due to cell-mediated immunity to muscle antigens, humoral immunity and immune complex deposition [73]. Some authors have described an association between DM and CD. Both diseases share common HLA associations, including most notably the DQA1 0501 allele. DQA1 0501 may lead to the activation of CD4-positive T cells by the presentation of a still unidentified peptide that may induce CD or JDM. Evron *et al.* [74] and Marie *et al.* [75] have also described the association between DM and polymyositis (PM) and CD in adults. For these authors, CD was included within the spectrum of GI manifestations of DM/PM, and they showed that a GFD may resolve clinical and laboratory abnormalities [74,75].

Porphyria

The coincidental diagnosis of CD in porphyric patients has been reported in the literature [76]. Patients with CD and porphyria present particular problems in terms of their management. The porphyrias are a group of rare diseases affecting the enzymes of the heme biosynthetic pathway with a subsequent accumulation of porphyrins in the tissues. These substances are photosensitizers and their accumulation in the skin can cause bullae, erosions, increased fragility, scarring, hirsutism and pigmentation on photo-exposed areas. CD is often associated with DH, which has some features in common with skin lesions of porphyrias. In one type of porphyria, variegate porphyria (VP), the accumulation of porphobilinogen and 5-aminolevulinic acid is associated with GI symptoms and an acute neuropsychiatric syndrome. Some drugs such as dapsone are precipitants of these acute attacks [77]. It is essential that patients with bullous skin lesions are adequately investigated to distinguish VP from DH, as the administration of dapsone could have a potentially fatal outcome. Furthermore, the symptomatic control of CD (i.e., malabsorption, anorexia and calorie restriction) can prevent the precipitation of acute attacks of VP, and because gluten sensitivity itself may be associated with neurological and psychiatric disorders, neuropsychiatric porphyria could be one of the differential diagnoses [78].

Acquired hypertrichosis lanuginosa

Acquired hypertrichosis lanuginosa (AHL) is a rare disease and there are less than 40 cases in the literature [79]. This type of hypertrichosis is characterized in its extreme by the rapid growth of fine, down-like hair all over the body, occasionally associated with glossitis and loss of taste. A lesser degree of hypertrichosis, in which lanugo hair occurs only on the face, is more common. It is three times more common in females than in males and is most commonly associated with malignancy. Lymphomas, carcinoid tumors and the Zollinger–Ellison syndrome have also been associated with this pathology [79]. In 1988, Corazza *et al.* described the only reported case of AHL associated with CD [80].

Ichthyosiform dermatoses

The ichthyosiform dermatoses consist of a heterogeneous group of hereditary disorders, all of which are characterized by the accumulation of large amounts of scale on the cutaneous surface [81]. The earliest reports of ichthyosis have been traced to Indian and Chinese literatures several hundred years before Christ, and a dermatology text by William I also discussed the problem. Kinetic studies of the epidermis in the major forms of ichthyosis have shown an increased germinative cell hyperplasia and an increased transit rate through the epidermis in lamellar ichthyosis [82]. Menni *et al.* first reported a case of ichthyosis revealing CD [83], but the reason for this association is still unknown.

Pellagra

Pellagra is a disease characterized by lesions of the skin usually preceded by prodromal symptoms, especially of the digestive and nervous systems [84]. The dermatosis begins as erythema and edema on the back of the hands with pruritus and burnings,

especially determined by exposure to the sun and by localized pressure. In some patients, blisters appear several days after the onset of erythema; these run together to form bullae and then break. In the second stage, the dermatosis becomes hard and brittle. The skin may resemble that of a goose's. The usual sites are the face, neck, dorsal surfaces of the hands, arms and feet. The cause of pellagra is still not entirely clear. It may arise from a diet deficient in niacin or tryptophan, or more commonly deficient in both, and an amino acid imbalance may also play a part. In 1999, Schattner described a case of a man with a pellagra-like syndrome due to CD [85].

Generalized acquired cutis laxa

Cutis laxa (CL) is a heterogeneous group of inherited and acquired (generalized or localized) diseases characterized by a looseness of the skin with the development of inelastic folds that gives the affected person a prematurely senile appearance [86]. CL presents with a destructive phenomenon of previously apparently normal elastic fibers, with cephalocaudal progression. It occurs mainly in adults and the etiology is unknown. Immunological abnormality has been postulated to explain the destruction of elastic tissue [87]. Generalized acquired cutis laxa (GACL) has been reported in association with infectious disorders, drugs and autoimmune diseases. Many authors have described a dermal deposit of IgG (IgA) in various diseases, suggesting that the destruction of elastic tissue may be immunologically mediated [88]. Cases of association between GACL and CD have been reported. Bodvarsson *et al.* proposed that dietary intake of glutenin may induce the production of antibodies to elastin and mediate the adherence of neutrophils [89]. A cross-reaction is possible between gluten and some components of elastic fibers, since glutenin presents a amino acid sequence 22.3% similar to elastin. Garcia-Patos *et al.* described a case of GACL associated with CD, with evidence of IgA deposits on the dermal elastic fibers and a moderate improvement of eruption after treatment with GFD [90].

Rosacea

Rosacea is a fairly common skin disorder characterized by erythema, telangiectasia, papules and, occasionally, pustules on the face. In addition, there is a high incidence of 'flushing attacks'. Watson *et al.* found a group of 60 patients with rosacea to be underweight compared with a control group; 20 out of their 60 patients had some abnormality of their small intestinal mucosa on biopsy and they considered that four of their patients had confirmed CD [91]. They postulated that there was a high incidence of small intestinal disease in patients with rosacea and suggested there may be a hereditary basis for this disease. This findings were not confirmed by Marks *et al.* in a study of 62 patients with rosacea [92]. The authors not find any difference in the incidence of GI symptoms or weight of their patients compared with 62 control subjects, and there was no difference in the incidence of abnormality of the small intestinal mucosa in subjects with rosacea compared with a control group; they considered that an abnormal small mucosa was present in three out of the 34 patients with rosacea and in six out of 34 control subjects (subjects with

other skin disease including psoriasis and DH). However, the observations reported in the literature regarding this association are out of date.

Atypical mole syndrome & congenital giant naevus

Montalto *et al.* first described the association between CD, atypical mole syndrome and congenital giant naevus. They reported a case of a patient affected by a rare multiple disorder of the cutaneous pigmentary system, which increased the risk of melanoma, and by CD, which is frequently associated with some neoplasms [93].

Atopic dermatitis & xerosis

Atopy refers to the tendency to suffer from asthma, eczema, xerosis and hayfever. Atopy is largely inherited (genetic) and is characterized by an overactive immune response to environmental factors. Atopic dermatitis (AD) is a disease of the whole body that manifests in the skin. Events that upset the body in other ways (e.g., viral infections, teething or eating certain foods) may have an effect on the dermatitis. Flares may also occur without obvious provocation and can be very frustrating. Recently, there has been emerging evidence that inflammation in AD primarily results from inherited abnormalities in the skin (i.e., a skin 'barrier defect') [94]. The immune system develops in the first 6 months of life. There is a generally an equilibrium of the two main types of T-helper lymphocytes (small white blood cells), Th1 and Th2 cells. In AD, there is often an imbalance, with far more Th2 cells and their associated chemical messengers (cytokines). In some children there are also high levels of IgE antibodies and eosinophils (the white blood cells associated with allergy). The loss of skin barrier function means that water is lost (xerosis) and irritants (e.g., soap, detergent, solvents, dirt and so on) and allergens (e.g., pollens, dust-mite antigens and microbes) may penetrate it [95].

The specialized immune cells of the epidermis (Langerhan's cells) in AD have an increased response to these antigens and interact with dermal T cells to produce a Th2 response. Food allergies affect approximately a third of children with eczema [96]. These children are most commonly allergic to egg, cows milk, soy, peanuts, fish and wheat. Räsänen *et al.* studied the clinical features, hypersensitivity mechanisms and differential diagnosis of cereal allergy or intolerance in children with AD, and demonstrated that the coexistence of cereal allergy and CD seems to be rare [97]. Intestinal permeability was investigated in patients with atopic eczema by *in vivo* and *in vitro* techniques and the results suggested that altered intestinal permeability is not important in the pathogenesis of eczema [98,99]. In the literature, there is only one report of concomitant Hodgkin's lymphoma and AD in a child with CD [100].

Expert commentary & five-year view

In the past few years, the diagnosis of CD has become more and more frequent owing to the recognition of 'new' symptoms and associated extraintestinal manifestations. Classical CD is dominated by symptoms and sequelae of GI malabsorption. In the 'atypical forms', the extraintestinal features usually predominate, with few or no GI symptoms. Silent CD refers to asymptomatic

patients with a positive serologic test and villous atrophy on biopsy. The recognition of atypical manifestations of CD is very important because many cases can remain undiagnosed with an increased risk of long-term complications.

Many skin diseases are characterized by a dysregulation of the underlying immune system. In addition, CD appears to be associated with other immune diseases, such as Type 1 diabetes mellitus, autoimmune thyroiditis (Graves' and Hashimoto's diseases), Sjögren's syndrome, rheumatoid arthritis, IgA nephropathy and autoimmune hepatitis. Immune system dysregulation is the possible pathogenetic trigger in these associations [101].

In 1973, Jones described the skin as a 'mirror of the gut', underlining the close connection between these two sites [102]. The author identified four subtypes of association between the skin and the gut:

- A primary alimentary disease associated with skin changes
- A primary skin disorder associated with small intestinal dysfunction
- A specific skin disease associated with a particular gut disorder
- A generalized disorder associated with changes both in the skin and in the gut

This association reflects the pathogenic link between the 'gut-skin axis' and should be considered in the clinical management of an intestinal and/or skin disease [21].

In the past few years, several hypotheses have been proposed regarding the possible mechanisms involved in the association between CD and skin diseases. In particular, an abnormal small intestinal permeability appears to be implicated, which may allow the crossing of endogenous or exogenous antigens, and may provoke the immunological response, common immune mechanisms, vascular alterations, and vitamin and amino acid deficiency secondary to malabsorption in patients with CD. However, at present, the data are not homogeneous and most of the evidence for this association is based on case reports, making it difficult to draw definitive conclusions on this topic.

In the near future, controlled studies are needed to verify the real involvement of the skin in CD. In addition, another research step is the analysis of the immunological basis of this association. Nevertheless, despite these limitations, the opportunity to investigate the possible presence of CD in some dermatological patients seems at present to be justified.

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Key issues

- Celiac disease (CD) is an autoimmune gluten-dependent enteropathy characterized by atrophy of the intestinal villi that improves after a gluten-free diet.
- CD is often associated with extraintestinal manifestations.
- In the last few years, growing evidence has documented a number of skin diseases among the extraintestinal manifestations of CD.
- Several hypotheses have been proposed regarding the possible mechanisms involved in these associations.
- An abnormal small intestinal permeability appears to be implicated, which may allow the crossing of endogenous or exogenous antigens, and may provoke an immunological response, common immune mechanisms, vascular alterations and lastly malabsorption.

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