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EDITORIAL

Cutaneous manifestations in celiac disease

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Abstract

Celiac disease (CD) is an autoimmune gluten-dependent enteropathy characterized by atrophy of intestinal villi that improves after gluten-free diet (GFD). CD is often associated with extra-intestinal manifestations; among them, several skin diseases are described in CD patients. The present review reports all CD-associated skin manifestations described in the literature and tries 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.

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Key words: Celiac disease; Dermatological disease; AGA; EmA; TTG

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INTRODUCTION

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]. Epidemiological studies have shown that CD is very common and affects about 1 in 250 people^[2]. CD is a multigenic disorder associated with HLA-DQ2 (DQA1*/DQB1*2) expressed in more than 90% of patients, or HLA-DQ8 (DQA1*0301/DQB1*0302)^[3]. The expression of these molecules is necessary, but not sufficient, to develop the disease^[4]. The immune response to gluten

takes place in two compartments: the lamina propria and the epithelium. While lamina propria CD4 T cells have a recognized role in the pathogenesis of CD, the role of CD8 T cells in the intestinal epithelium is controversial^[5].

CD is characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi which improves after gluten-free diet (GFD)^[6]. The classic form of CD presents several symptoms such as diarrhea, abdominal pain, weight loss and nutritional deficiencies, particularly of iron, folate, calcium, and vitamin D^[7]. However, there is a large variety of clinical presentations characterized by the presence of extra-intestinal manifestations, including anemia^[8], persistent hypertransaminasemia^[9], osteopenia^[10], neurological^[11], psychiatric and affective disorders^[12-14], features of hyposplenism (Howell-Jolly bodies and thrombocytosis)^[15] and autoimmune diseases^[6]. In the last years, growing evidence has documented the involvement of skin diseases among the extra-intestinal manifestations of CD^[17]. The aim of this review is to report all CD associated skin manifestations described in the English literature and to analyze the possible mechanisms involved in this association.

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a well-described entity, presenting as an itchy, chronic, papulovesicular eruption which may leave pigmentation and scarring^[18]. Classically, skin lesions are characterized by a symmetrical eruption on the extensor surfaces of the body such as the knees, elbows, buttocks, and back. DH tends to occur more in the adult male (M/F ratio 2:1) who may also present with the involvement of oral and genital membranes. However this pattern is reversed in children who may simply have purpura over the palmar surfaces. The age of onset varies with geographical location and the incidence is highest in Ireland and Sweden and rare in Asia^[19]. Histology of lesional skin shows micro abscesses consisting of neutrophils and eosinophils within the dermal papillae. Sub-epidermal vesicles and bullae are produced within the lamina lucida as a result of collagen degradation. Furthermore there is an increased number of activated T cells. Direct immunofluorescence of the normal skin shows the pathogenomic granular IgA deposits in the papillary dermis but the exact target antigen is still unknown^[19-21]. These deposits are often associated with C3 to support the suggestion that the complement is activated via the alternative pathway and C5^[22,23]. 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. Interestingly, patients with a GSE without DH show a similar high incidence of these antigens^[24]. Specific B cell/macrophage antigens have been noted in patients with DH and the gluten-sensitive enteropathy^[25]. Family studies have shown that these B cell antigens segregated independently of HLA antigens^[26]. One hypothesis is that both HLA and non-HLA disease genes are necessary for the development of lymphoid cell surface receptors that recognize gluten.

Antigluten, antiendomysium, antigliadin and tissue transglutaminase antibodies have been detected in patients with DH^[27-29]. These gluten-specific cells migrate to the gut mucosa where they mediate cytotoxic reactions involving the epithelial cells^[30]. There is an immunogenetic association with HLA DR3 DQW2 (HLA class II alleles DQAI 0501 and DQBI 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. Gluten must be present in the diet for the development of DH; however, a genetic susceptibility to gluten has been proposed as an etiological mechanism. This observation could explain why DH is very common in some Asian populations, which have a low daily gluten intake (e.g., 7-8 g/d in Korea) compared with Western populations which have higher daily gluten intake (e.g., 15-20 g/d in Scandinavia)^[19].

As CD and DH may seem 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 the auto antigen tissue transglutaminase resident in the gut and the skin derived epidermal transglutaminase.

Although patients with DH are unlikely to have gastrointestinal 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 a suspicion of DH with a negative skin biopsy but 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^[31,32].

The DH rash is often treated with dapsone in conjunction with the gluten withdrawal. In addition to improving the histological changes of the small intestine, the gluten-free diet may also allow a reduction of suppressive medication^[32]. Just as patients with CD are at a higher risk of malignancies such as lymphomas, so are those patients with DH not compliant with GFD, which should motivate patients with DH to follow the diet regardless of the absence of other symptoms^[31].

Linear IgA bullous dermatosis

Linear IgA bullous dermatosis (LABD) is a rare disease

characterized by erythematous papules or groups of small vesicles. The onset may be acute or gradual and the predominant symptom is usually pruritus. Immunoelectron microscopic studies have shown a linear deposition of IgA along the lamina lucida or in the sub-basal lamina area of stratified squamous epithelium^[32]. At the moment, it is considered as a distinct entity from DH and Bullous pemphigoid^[32,33]. The incidence of gluten sensitivity enteropathy (GSE) in LABD has been described in the literature to range from 0% to 24%^[33-36]. The HLA haplotype (A1, B8, DR3) of LABD patients is often that found in classic DH which is in >85% of CD patients^[37,38]. Although the prevalence of CD is low in LABD, some authors have suggested a diagnosis of GSE in these patients^[34-36,39].

Urticaria

Urticaria is an eruption of transient erythematous or edematous swellings of the dermis or sub-cutaneous tissue and is due to a local increase of permeability of capillaries and small venules. Hautekeete *et al*^[40] first described the association between CD and chronic urticaria, although this association is still debated^[41]. Adults with CD also often have an increase of atopic or immunologic disorders^[42,43]. Scala *et al* reported that a GFD eliminated both skin and intestinal symptoms in patients with concomitant CD and chronic urticaria^[44]. The passage of antigens and immune-complex formation may be facilitated by an increased mucosal permeability. Theoretically, this mechanism might cause urticarial lesions and so, by restoring the integrity of the mucosa, a gluten-free diet might resolve skin symptomatology.

Hereditary angioneurotic edema

Hereditary angioneurotic edema (HANE) is characterized by recurrent edematous attacks in the sub-cutis and sub-mucous due to C1-esterase inhibitor (C1-INH) deficiency^[45]. Brickman *et al*^[46,47] described HANE in association with inflammatory bowel diseases (IBD). In 2002, Farkas *et al*^[48] first described the simultaneous occurrence of HANE and CD. 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^[49]. There might also be a genetically determined etiology of both diseases^[50]. Complement testing is justified whenever the GI symptoms of CD persist despite restoration of damaged mucous. Conversely HANE unresponsive to adequate prophylaxis should prompt for complete GI group tests^[48].

Cutaneous vasculitis

CD may give rise to many skin manifestations but vasculitic skin lesions have rarely been encountered^[51,52]. 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^[53]. The coexistence of cutaneous vasculitis and CD might be related to in-

creased intestinal permeability^[54], and immune complexes, originating from exogenous or endogenous antigens, might circulate because of the impaired phagocytic function of reticular endothelium system and be deposited in the skin^[55]. As in inflammatory bowel disease (IBD), exogenous antigens may permeate the damaged CD mucosa in larger quantities than normal^[54,56]. This is reflected by significant serum milk and gluten fraction antibody titers^[57,58]. Alternatively, an autoimmune sensitization may result because of the release of endogenous antigens from damaged small bowel mucosa^[59]. Meyers *et al.*^[60] described a case of cutaneous vasculitis complicating CD and the remission of skin lesions after the treatment with a strict GFD. Treatment of leucocytoclastic vasculitis has generally been difficult, but corticosteroids and a gluten-free diet may improve the dermatosis in cases associated with CD^[52].

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. Triggers include infections, sarcoidosis, adverse drug reaction, IBD, and lymphomas^[61]. EN generally resolves in 5-8 weeks but if antigenic stimulus persists, the disease may last for a long period^[62]. In 1991, Durand *et al.* first observed a causal linkage between CD and EN^[63]. CD can be a triggering factor of EN because an altered intestinal permeability to endogenous or exogenous antigens may provoke the immunologic response. EN is also a common finding in sarcoidosis which frequently coincides with CD^[62,65]. When EN skin lesions are chronically recurrent or persistent, it is advisable to search for an 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^[66]. Its lesions appear as soft erythematous papule-plaques and become hard nodules mainly symmetrically affecting the backs of the hands and other extensor surfaces overlying the joints^[67]. Ulceration, arthralgia and pain can be other features of this disease^[67,68]. Even if it is presumed to be an immune reaction by bacterial antigens, the etiology of EED is unknown^[69]. EED has been described in association with several other immunological diseases, especially paraproteinemias (i.e., monoclonal IgA gammopathy)^[70]. Tasanen *et al.*^[70] detected dermo-epidermal IgA and complement deposits in lesional skin of a patient affected by CD; the histopathology was suggestive of EED^[71]. 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^[72]. Some authors have therefore suggested that it is important to warrant consideration of underlying CD in at least some patients with EED^[71-73].

Necrolytic migratory erythema

The features of necrolytic migratory erythema (NME) have been reviewed by several authors. Becker *et al.*^[74] first described a cutaneous reaction pattern with specific histopathologic features in association with a pancreatic islet cell carcinoma. NME is a term used by Wilkinson^[75] to describe the characteristic skin disease related with glucagonoma. Typically lesions 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^[76]. Most patients have angular cheilitis, stomatitis, glossitis, diffuse alopecia and brittle nails. Gastrointestinal symptoms such as weight loss and diarrhea are common^[77]. Most cases of NME were part of the glucagonoma syndrome^[76-77]. NME occasionally occurs with chronic liver disease or malabsorption with villous atrophy^[78,79]. Kelly *et al.*^[80], Goodenberg *et al.*^[79] and Thorisdottir *et al.*^[81] described the association between CD and NME. The etiology of NME is uncertain, although deficiencies of zinc, amino acids, or essentially fatty acids could play an important role^[77,78,82,83]. It must be stressed that in CD patients with NME, this latter disorder seems to have an excellent response to GFD^[79,81].

Psoriasis

Psoriasis is a chronic, relapsing dermatosis characterized by scaling, erythema, and less commonly pustulation^[84]. It has been demonstrated that psoriasis is an immunological disease with hyperproliferation of T-cell mediated keratinocytes^[85]. Recent data indicate that HLA-Cw*0602 may play an important pathogenetic role in the majority of psoriasis patients^[86]. Immune mechanisms have an important role in the pathogenesis of this disease. In particular, an overexpression of T helper cell type 1 (Th1) cytokines and a relative under-expression of Th 2 cytokines have been shown in psoriatic patients^[87]. The treatment is often difficult; all currently available effective remedies are retinoids or immunosuppressant drugs such as steroids or cyclosporin^[84], other than topical treatment^[88], photochemotherapy (PUVA)^[89] and biological treatment such as infliximab or etanercept^[90]. Recent studies have showed an association between CD and psoriasis^[91,92,93] and an improvement of skin lesions after 3-6 mo of GFD, without other pharmacological approaches, was described^[91]. However at present the relationship between CD and psoriasis remains controversial since there are few data on this topic and other authors sustain that this association seems to be coincidental^[94].

In one study, 10 out of 32 (31%) subjects affected by different clinical forms of psoriasis had positive antireticulin antibodies with a variability of titers, related to the extent of the disease^[95]. Subsequently, in a first screening study conducted by Michaelsson *et al.*^[96] 16% of 302 subjects with psoriasis had IgA and/or IgG AGA. Only in 1 of 11 IgA AGA-positive patients from this group screened for antibodies to reticulin/EMA was this positive. An increase of EG2-positive eosinophils in duodenal mucosa associated with elevated serum levels of eosinophil cation protein (ECP) has been documented in psoriatic subjects with AGA, but no tendency to higher

ECP values has been detected in those with AGA^[97]. The same authors reported that the increase in the number of eosinophils in the gastrointestinal tract is explained as being part of some unknown process that may be related to the development of skin psoriatic lesions. Cardinali and co-workers^[92] performed a study to verify whether gluten intolerance is more frequent in Mediterranean subjects with psoriasis than in healthy controls. The sera of 39 psoriatic patients and 39 controls were screened for AGA, EMA, antibodies anti-transglutaminase (TgA), ECP, serum total IgE levels and number of eosinophils. The results showed positivity for IgG AGA in two psoriatic patients, one borderline for TgA, and none was positive for EMA or IgA AGA. In these subjects the authors found high serum levels of ECP and IgE, but a normal number of eosinophils; on the contrary eosinophil count and serum IgE levels were within the normal range in the controls. Michaelsson *et al*^[91] evaluated the effect of GFD in 33 AGA positive patients and six AGA negative patients with psoriasis in an open study. Of the 33 AGA-positive patients, 2 had IgA EMA, and at the duodenal biopsy 15 showed an increased number of lymphocytes in the epithelium, but in some this increase was only slight. GFD was for 3 mo. Thirty out of thirty-three patients strictly complied with GFD, after which they showed a significant decrease of psoriatic lesions. This included a significant decrease in the 16 AGA positive patients with normal routine histology in duodenal biopsy. The AGA negative patients did not improve. There was also a significant decrease in the serum of eosinophil cation protein in patients with elevated AGA. In conclusion, the positive effects of GFD were observed not only in patients with an increased number of lymphocytes in the duodenal epithelium, but also in some patients with seemingly normal epithelium^[91,98].

Our group recently reported a case of severe psoriasis in a CD patient, not responding to specific therapies for psoriasis and in whom the regression of skin lesions after GFD was very rapid^[99,100]. The association between psoriasis and CD was subsequently confirmed by Ojetti *et al*^[101]. The authors evaluated the prevalence of CD in patients affected by psoriasis, showing a high frequency of CD (4.34%) in psoriatic patients.

At present the mechanisms implicated in the possible association between CD and psoriasis, and the effect of GFD on psoriatic skin lesions are not known. There are some hypotheses:

Hypothesis 1: Abnormal small intestinal permeability, frequently present both in psoriasis^[102] and in CD patients^[103], could be a triggering factor between CD and psoriasis.

Hypothesis 2: T cells play an important role in the pathogenesis of both psoriasis and CD. An increased number of T cells in the blood, in the dermis and in the epidermis of psoriatic patients has been documented^[87]. In CD patients, gliadin induces a sensitization of T cells^[104] and this may play a role in the pathogenesis of psoriatic skin lesions^[99].

Hypothesis 3: Psoriatic lesions in CD patients could be related to vitamin D deficiency, which is present both in CD^[105] and in psoriasis^[106-107].

Vitiligo disease

Vitiligo is a specific, common, often heritable acquired disorder characterized by well-circumscribed milky white cutaneous macules devoid of identifiable melanocytes^[108]. 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, etc.). Numerous attempts to identify HLA markers have revealed certain ethnic-specific markers: HLA-DR4 (blacks), B13 (Jews) and BW-35 (Yemenites). Theiligore^[108] has proposed three prevailing theories to explain vitiligo: the neural hypothesis, the self-destruct hypothesis and the immune hypothesis. It carries 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^[109,110], a serological screening study for CD in patients with vitiligo did not show any correlation between these two immunological disorders^[111]. This implies that the sporadic associated cases must be considered as coincidental.

Behçet's disease

A history of oral ulceration has been described in 25% of patients with CD and about 2-4% of patients with recurrent oral ulceration also have CD^[112]. Behçet's disease (BD) is characterized by recurrent ulceration of the mouth and genitalia associated with iritis. Males are affected 5-10 times more frequently than females and the onset is usually between the ages of 10 and 30. The oral ulcers usually show only non-specific inflammatory changes, although there may be infiltration of the grossly thickened walls of thrombosed arterioles. Some authors have suggested that BD may be caused by a virus^[113] and antibodies against mucous membrane were demonstrated in 17 of 40 patients^[114] but their significance has not yet been evaluated. Triolo and co-workers^[115] described 3 cases of coexistence of BD and symptomless CD in 11 patients with BD (defined according to International Study Group-ISG criteria). 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 auto antigens or virus trigger action. In patients affected by BD, it may therefore be important to search for underlying undiagnosed CD, but future studies are needed to shed light on this point.

Oral lichen planus

The associations between CD and recurrent oral ulceration, glossitis, angular cheilitis and burning mouth are common^[112]. Three to six percent of patients with these oral manifestations may have underlying undiagnosed CD^[112,116]. Fortune *et al*^[117] described the erosive type

of oral lichen planus (OLP) in a patient with gluten enteropathy. OLP is not rare and frequently involves the buccal mucosa, gingiva and tongue. In both the diseases, the lesions had a mucosal T-cell infiltrate and the relief from eating a gluten-free diet was surprising. It is not clear whether the oral lesions are a direct manifestation of CD or due to the effect of malabsorption on the rapidly dividing mucosal cells already predisposed to soreness by a pre-existing disease; because palliative medication of chronic ulcerative stomatitis is often ineffective, it is important to detect the underlying nutritional deficiencies for the patient's general well-being also.

Dermatomyositis

Dermatomyositis 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. An underlying carcinoma is commonly described in adults. Juvenile dermatomyositis (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^[118].

Some authors have described an association with CD^[119-122]. Both diseases have a strong association with DQA1 0501 heterodimer because a linkage disequilibrium with HLA-DR3 haplotype or alternatively DR5/DR7 heterozygosity in CD^[123,124] DQA1 0501 may lead to the activation of CD4-positive T cells by presentation of a still unidentified peptide that may induce CD or JDM. Evron *et al*^[125] and Marie *et al*^[121] have also described the association between dermatomyositis (DM) and polymyositis (PM) and CD in adults. For these authors CD may be included within the spectrum of gastrointestinal manifestations of DM/PM and they showed that GFD may resolve clinical and laboratory abnormalities.

Porphyria

Mustajoki *et al*^[126] and subsequently Twaddle *et al*^[127] reported the coincidental diagnosis of CD in porphyrics. Patients with CD and porphyria present particular problems in terms of management^[128]. The porphyrias are a group of rare diseases affecting the enzymes of the heme biosynthetic pathway with 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), accumulation of porphobilinogen and 5-aminolevulinic acid is associated with gastrointestinal symptoms and an acute neuropsychiatric syndrome. Some drugs such as dapsone are precipitants of these acute attacks^[128]. It is essential that patients with bullous skin lesions are adequately investigated to distinguish VP from DH because the administration of dapsone could have a potentially fatal outcome. Furthermore, symptomatic control of CD (e.g.,

malabsorption, anorexia, calorie restriction) can prevent precipitation of acute attacks of VP and because gluten sensitivity itself may be associated with neurological and psychiatric disorders^[12,15], neuropsychiatric porphyria could be one of the differential diagnoses^[129].

Alopecia areata

Alopecia areata (AA) is a chronic autoimmune disease characterized by non-scarring alopecia. Histologically it is possible to find perifollicular lymphocyte infiltration, pointing to an immunologic etiology such as CD. In both the diseases there is the presence of organ-specific autoantibodies^[110,130-132], T-lymphocyte infiltration at the site of lesion^[133,134], association with HLA genes^[135,136] and possible etiologic importance of viral co-factors^[137,138].

In the general population the prevalence of CD is 1 in 305^[139] and of AA is 1 in 819^[140]. Corazza and co-workers^[141] found that the prevalence of CD in patients with AA was 1 in 85. Although remission and recurrence may be observed during the clinical course of AA^[142], many patients on gluten-free diet showed complete regrowth of scalp and other body hair and no further recurrence of AA at follow-up^[141,143]. The positive effects of gluten-free diet on the pattern of autoimmune conditions, such as AA, associated with CD have been attributed to a normalization of the immune response. This study suggests that AA patients constitute a novel risk group of CD. Because AA may be the only clinical manifestation of CD, some authors suggest GSE serological screening tests in alopecia universalis^[141].

Acquired hypertrichosis lanuginosa

Acquired hypertrichosis lanuginosa (AHL) is a rare disease and there are less than 40 cases in the literature^[144,145]. 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 most commonly associated with malignancy^[146]. Lymphomas, carcinoid tumors, and the Zollinger-Ellison syndrome have also been associated with this pathology^[146,147].

In 1988, Corazza *et al*^[148] described the only case reported in the literature of acquired hypertrichosis lanuginosa associated with CD. This case report confirms the paraneoplastic features of AHL. CD is often reported as being associated with tumors and can precede clinical presentation of the tumors^[149].

Pyoderma gangrenosum

The pyoderma gangrenosum (PG) is a neutrophilic dermatosis, with destructive, necrotizing and non infectious ulcers, involving face and inferior limbs. The association between PG and CD has been described in some case reports and the importance of GFD in the resolution of PG has been suggested^[150].

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. The earliest reports of ichthyosis have been traced to the Indian and Chinese literatures several hundred years B.C. and a dermatology text by William first discussed the problem. Kinetic studies of the epidermis in the major forms of ichthyosis have shown increased germinative cell hyperplasia and increased transit rate through the epidermis in lamellar ichthyosis^[151]. Menni *et al*^[152] first reported a case of ichthyosis revealing CD 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 digestive and nervous systems. The dermatosis begins as erythema and edema on the back of the hands, with pruritus and burnings, determined especially by exposure to the sun and by localized pressure. In some patients, several days after the onset of erythema, blisters appear; these run together to form bullae and then break. In the second stage, the dermatosis becomes hard and brittle. The skin may look like a goose. 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 both, and aminoacid imbalance may also play a part^[153]. In 1999, Schattner^[153] described a case of a man with a pellagra-like syndrome due to CD.

Generalized acquired cutis laxa

Cutis laxa (CL) is a heterogeneous group of inherited and acquired (generalized or localized) diseases characterized by looseness of the skin with the development of inelastic folds that gives the affected person a prematurely senile appearance^[154-156]. CL presents a destructive phenomenon of previously apparently normal elastic fibers, with cephalocaudal progression^[157]. It occurs mainly in adults and the etiology is unknown. Immunological abnormality has been postulated to explain the destruction of elastic tissue^[158]. Generalized acquired cutis laxa (GACL) has been reported in association with infectious disorders, drugs and autoimmune diseases^[154,158,160-164]. Many authors have described a dermal deposit of immunoglobulins (IgA) in various diseases, suggesting that destruction of elastic tissue may be immunologically mediated^[160]. Cases of association between GACL and CD have been reported^[160,165]. Bodvarsson *et al*^[166] proposed that dietary intake of gluten may induce the production of antibodies to elastin and mediate adherence of neutrophils^[167,168]. A cross-reaction is possible between gluten and some components of elastic fibers, since glutenin presents a 22.3% amino acid sequence similar to elastin^[166,169]. Garcia-Patos and co-workers^[165] described a case of GACL associated with CD, evidence of IgA deposits on the dermal elastic fibers and moderate improvement of eruption after treatment with GFD.

Atypical mole syndrome and congenital giant naevus

Montalto *et al*^[170] first described the association between CD, atypical mole syndrome and congenital giant naevus.

Table 1 Skin disorders in celiac disease

Dermatitis herpetiformis	Seah <i>et al</i> ^[20] Mann <i>et al</i> ^[25] Katz <i>et al</i> ^[22] Porter <i>et al</i> ^[28]
Linear IgA bullous dermatosis	Leonard <i>et al</i> ^[36] Egan <i>et al</i> ^[39]
Urticaria	Hautekeete <i>et al</i> ^[40] Scala <i>et al</i> ^[44]
Hereditary angioneurotic edema	Farkas <i>et al</i> ^[48]
Cutaneous vasculitis	Holdstock and Oleesky ^[52] Jones ^[51] Meyers <i>et al</i> ^[60]
Erythema nodosum	Durand <i>et al</i> ^[63] Crieber <i>et al</i> ^[61] Bartyik <i>et al</i> ^[64]
Erythema elevatum diutinum	Collin <i>et al</i> ^[72] Rodriguez-Serna <i>et al</i> ^[73] Tasanen <i>et al</i> ^[71]
Necrolytic migratory erythema	Goodenberger <i>et al</i> ^[79] Kelly <i>et al</i> ^[80]
Psoriasis	Thorisdottir <i>et al</i> ^[81] Michaelsson <i>et al</i> ^[96] Cardinali <i>et al</i> ^[92] Addolorato <i>et al</i> ^[99] Ojetti <i>et al</i> ^[101] Woo <i>et al</i> ^[93]
Vitiligo disease	Reunala and Collin ^[110] Collin and Reunala ^[109]
Behçet's disease	Triolo <i>et al</i> ^[115]
Oral lichen planus	Fortune and Buchanan ^[117]
Dermatomyositis	Evron <i>et al</i> ^[125] Buderus <i>et al</i> ^[119] Falcini <i>et al</i> ^[120] Marie <i>et al</i> ^[121] Iannone and Lapadula ^[122]
Porphyria	Mustajoki <i>et al</i> ^[126] Twaddle <i>et al</i> ^[127]
Alopecia areata	Corazza <i>et al</i> ^[141] Naveh <i>et al</i> ^[143]
Acquired hypertrichosis lanuginosa	Corazza <i>et al</i> ^[148]
Ichthyosiform dermatoses	Menni <i>et al</i> ^[152]
Pellagra	Schattner ^[153]
Generalized acquired cutis laxa	Lewis <i>et al</i> ^[160] Garcia-Patos <i>et al</i> ^[165]
Atypical mole syndrome and congenital giant nevus	Montalto <i>et al</i> ^[170]
Pyoderma gangrenosum	Gasbarrini and Corazza ^[150]

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^[171-174]. Some authors have therefore suggested a more careful objective examination in all the patients with CD^[170].

CONCLUSION

CD is an enteropathy associated with various extra-intestinal manifestations, including several skin diseases. Several hypotheses have been proposed regarding the possible mechanisms involved in this association. 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, lastly, vitamin and aminoacid deficiency secondary to malabsorption in patients with CD. 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; future controlled studies are consequently needed to verify the real involvement of the cutaneous district in CD (Table 1). Nevertheless, despite these limitations, the opportunity to investigate the possible presence of CD in some dermatological patients seems at present justified.

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