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Review

Cutaneous and Mucosal Manifestations Associated to Celiac Disease

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Abstract: Celiac disease (CD) is an immune-mediated gluten-induced enteropathy that affects predisposed individuals of all ages. Many patients with CD do not report gastrointestinal symptoms making it difficult to reach an early diagnosis. On the other hand, CD is related to a wide spectrum of extra-intestinal manifestations, being dermatitis herpetiformis (DH) the best characterized. These associated conditions may be the clue for reaching the diagnosis of CD. Over the last years, there have been multiple reports of the association between CD and several cutaneous manifestations that may improve with a gluten-free diet (GFD). The presence of some of these skin diseases, even in absence of gastrointestinal symptoms, should give rise to an appropriate screening for CD. The aim of this paper is to describe the different cutaneous manifestations that have been associated to CD and the possible mechanisms involved.

Keywords: Celiac disease; Dermatitis herpetiformis; Alopecia areata; Cutaneous vasculitis; Urticaria; Atopic dermatitis; Psoriasis; Recurrent aphtous ulceration; Chronic ulcerative stomatitis; Gluten-free diet

1. Introduction

Celiac disease (CD) is a chronic immune-mediated enteropathy triggered by gluten intake in genetically predisposed individuals. Gluten and its major protein fractions, gliadin and glutenin, are present in wheat, rye, barley and processed foods [1]. Almost all patients with celiac disease possess human leukocyte antigen (HLA) DQ2 (>90%) or HLA DQ8 (5-10%); nevertheless, up to 40% of people in the Americas, Europe, and Southeast Asia also carry these alleles, indicating that these genes are necessary but not sufficient for celiac disease development [2]. An intestinal biopsy showing atrophy of intestinal villi together with positive CD-specific serology represents the gold

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standard in diagnosing CD. IgA anti-tissue transglutaminase are the most sensitive and cost-effective antibodies to diagnose CD, although deamidated gliadin peptide IgG antibodies might be useful in seronegative patients with innate IgA deficiency. A life-long gluten-free diet (GFD) is mandatory, achieving clinical and histological recovery in most patients [1,3].

In past decades CD was considered to be an uncommon disease affecting mainly children and limited to individuals of European ancestry. In the present we know that this disorder may be detected at any age, and is regarded as one of the most common chronic diseases encountered worldwide with a prevalence of about 1%-2% [4]. Mean age of adult CD diagnosis is 45 years, although up to 20% of patients are diagnosed at the age of 60 years or above. CD is probably an under-diagnosed entity in adulthood partly because many patients in this age group lack of the classical symptoms such as diarrhea or signs of malabsorption. In fact, in most adult patients gastrointestinal symptoms are subtle or even absent and clinical suspicion arise from extra-intestinal manifestations (non-classic or atypical CD), such as anemia, cutaneous disorders, neurological disease, osteoporosis, and abnormal liver function tests [3,5]. We emphasize the importance of considering non-typical symptoms to diagnose adult CD and to do an active search of extra-intestinal associated manifestations in order to start an early GFD and prevent the onset of long-term complications.

CD patients are more frequently affected by other immune-mediated disorders (ID) compared to the general population, as reported in previous studies, mainly thyroid and skin diseases. This observation may be partially explained by a possible spread of the adaptive immune response, initially triggered in the gastrointestinal tract, to other tissues [5,6]. Hashimoto's thyroiditis is the most frequently associated ID, followed by several skin disorders such as alopecia areata, atopic and spongiotic dermatitis, erythema nodosum, lichen planus, lupus erythematosus, psoriasis, scleroderma and vitiligo. Interestingly, 60% of CD patients with associated thyroid disease that develop a third ID are skin related. These data suggest an axis between the immunological system of the thyroid, skin and small bowel, which seems more susceptible to develop an aberrant immunological response against auto-antigens. [6-12].

Cutaneous manifestations associated with CD, other than dermatitis herpetiformis, are poorly known. Nevertheless, there is growing evidence that supports the link between CD and several skin disorders. In 2006, Humbert et al. proposed a classification of skin diseases associated with CD, dividing them into four categories: autoimmune, allergic, inflammatory, and miscellaneous (Table 1) [10-12]. Recently, Bonciolini et al. described 17 patients affected by non-celiac gluten sensitivity with skin manifestations similar to eczema, psoriasis and dermatitis herpetiformis that did not show a specific histological pattern. The only common findings in most of these patients were the severe itching, the presence of C3 at the dermo-epidermal junction and a rapid resolution after adopting a GFD. The authors emphasized the importance of a close collaboration between gastroenterologists and dermatologists due to the multiple associations between gastrointestinal and skin disorders [13]. In the present paper we aim to describe the multiple skin disorders associated to CD and the possible mechanisms involved.

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Table 1. Strength of evidence for the association between gluten intolerance and skin diseases. (Adapted from Humbert et al, Caproni et al). [8,9]

	Proved association	**Improvement in skin disease by gluten-free diets or/and presence of serologic markers in several data**	**Fortuitous association (Sporadic cases reports)**
Autoimmune diseases	Dermatitis herpetiformis	Alopecia Areata Cutaneous vasculitis	Ig A linear dermatosis Dermatomyositis Vitiligo Lupus erythematous Lichen sclerosus
Allergic diseases		Urticaria Atopic Dermatitis	Prurigo nodularis
Inflammatory diseases		Psoriasis	Pityriasis rubra pilaris Erythroderma Erythema elevatum diutinum Necrolytic migratory erythema Pityriasis lichenoides Erythema nodosum
Miscellaneous diseases		Oral mucosa Chronic ulcerative stomatitis	Cutaneous amyloidosis Annular erythema Partial lipodystrophy Generalized acquired cutis laxa Icthyosis Transverse leukonychia Porphyria Rosacea Hypertricosis lanuginosa

2. Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is a well-known autoimmune cutaneous disease that represents one of the oldest well-established extraintestinal manifestations of CD. DH was initially described in 1883 by the French dermatologist Louis Duhring. In some countries it is still known as Duhring's disease [14]. In 1966, Marks et al. identified the presence of histological lesions in the small intestine of these patients, which were identical to those observed in individuals diagnosed with celiac disease (CD) [15]. DH is considered the main cutaneous manifestation of gluten intolerance [16,17]. Its etiology is multifactorial and has a polygenetic foundation. The association with HLA class II genetic markers, mainly HLA-DQ2 and/or HLA-DQ8, is equal to that observed in CD. DH is characterized by the presence of IgA-type autoantibodies, induced by gluten, against tissue transglutaminases-2 (tTG-2) and tTG-3 [18]. Furthermore, DH has other autoimmune disease associations besides CD, including IgA deficiency, diabetes mellitus type 1, autoimmune thyroid disorders, Addison's disease and Sjögren's syndrome [19-24].

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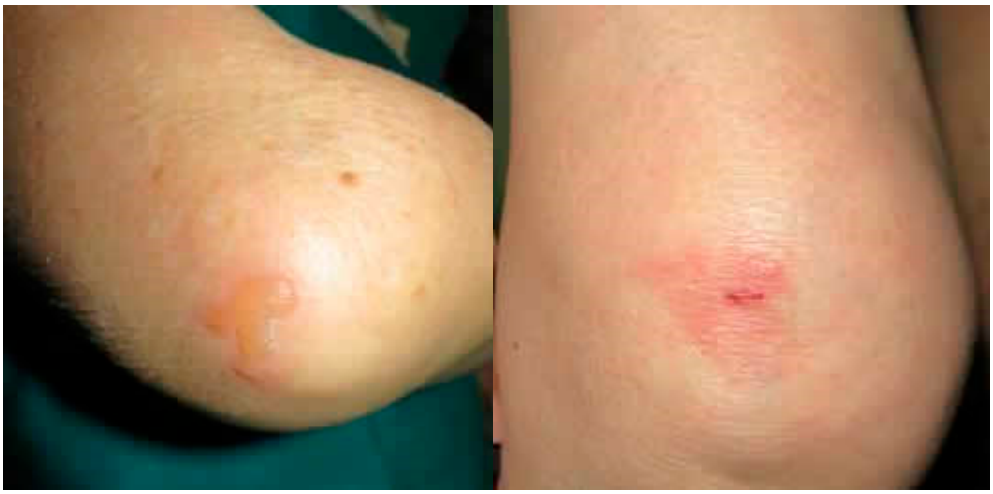
Onset is commonly in adult life, typically in the fourth decade, but it can also start in children and elderly people. Males are more affected than women (1.5-2/ 1) in contrast to celiac disease without DH, which is clearly predominant in females (2-3/ 1) [20-22]. Frequently, DH patients relate the onset of the cutaneous symptoms during warm months, from the beginning of spring to the end of summer [25-26]. Around 25 % of CD patients may present DH along their lives. The coexistence of DH with CD is very characteristic, although in some cases CD has not been previously diagnosed and an active search for reaching this diagnosis must be made. Most patients do not report digestive symptoms. Sometimes, they only show ferropenic anemia secondary to iron malabsorption [10-12].

The primary cutaneous lesions appear as erythematous papules, associated with fluid-filled vesicles [19]. Since the vesicles induce pruritus, patients often scratch themselves and burst the lesions, releasing their liquid content and causing crusted an eroded lesion (Figure 1). These lesions may heal leaving hypopigmentation or hyperpigmentation. A hallmark of the disorder is the intense pruritus that these patients experience and that often describe as burning or stinging. This symptomatology may precede the appearance of the cutaneous eruption. The lesions usually have a symmetrical distribution, affecting different parts of the body, mainly extension surfaces such as elbows, knees and buttocks or the lower back. Lesions can be limited to small areas or affect the whole body. Purpuric lesions in palms and soles have been described predominantly in children [21]) (Figs. 1–6).



Figures 1 and 2. Dermatitis herpetiformis. Intact tense symmetrical bullae in both elbows.

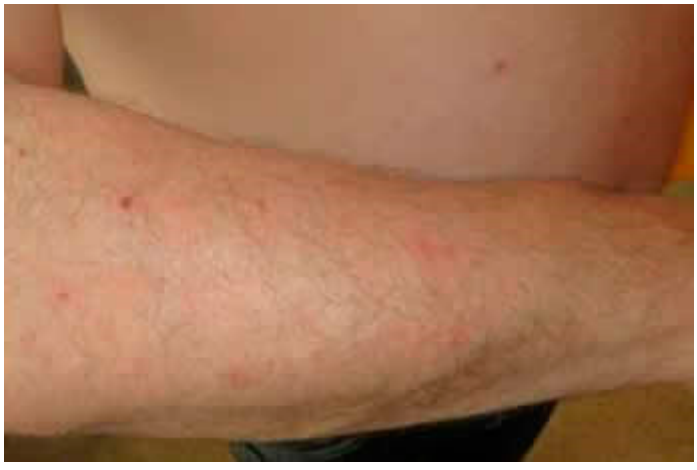


Figure 3. Dermatitis herpetiformis. Several crusted lesions at the right forearm.

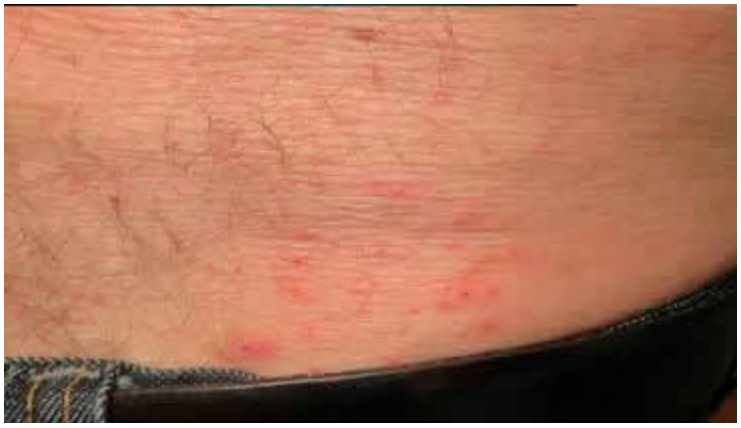


Figure 4. Dermatitis herpetiformis. Isolated crusted lesions at the abdominal wall.

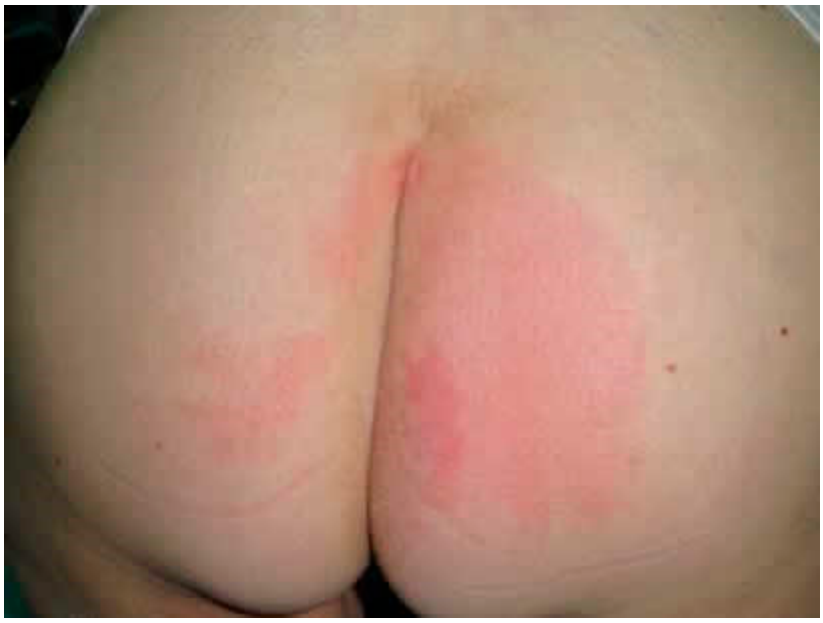


Figure 5. Pruritic bilateral erythema on the both buttocks.

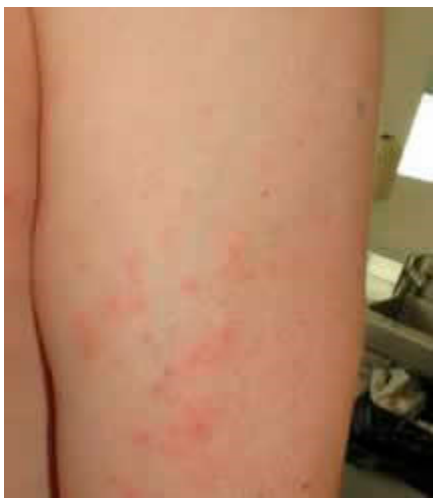


Figure 6. Dermatitis herpetiformis. Several papullous lesions on the right arm.

The diagnosis of DH is made by the presence of characteristic clinical features, serology, histopathology and direct immunofluorescence testing. Histopathologic findings of DH depend on timing of the biopsy. Early lesions show edema with the accumulation of neutrophils and occasional

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eosinophils in the dermal papilla. Subepidermal vesicles between rete ridges become more apparent as lesions age. There is frequently perivascular inflammatory cell infiltrate. Because vesicles may not survive the pruritis, clefting within the lamina lucida may not be seen. Direct immunofluorescence typically shows deposits of granular IgA placed in the tips of the dermal papillae or along the basement membrane; these findings represent the most characteristic features for the diagnosis of DH (Figure 7). Biopsy samples for direct immunofluorescence should be taken from the perilesional skin [27,28].

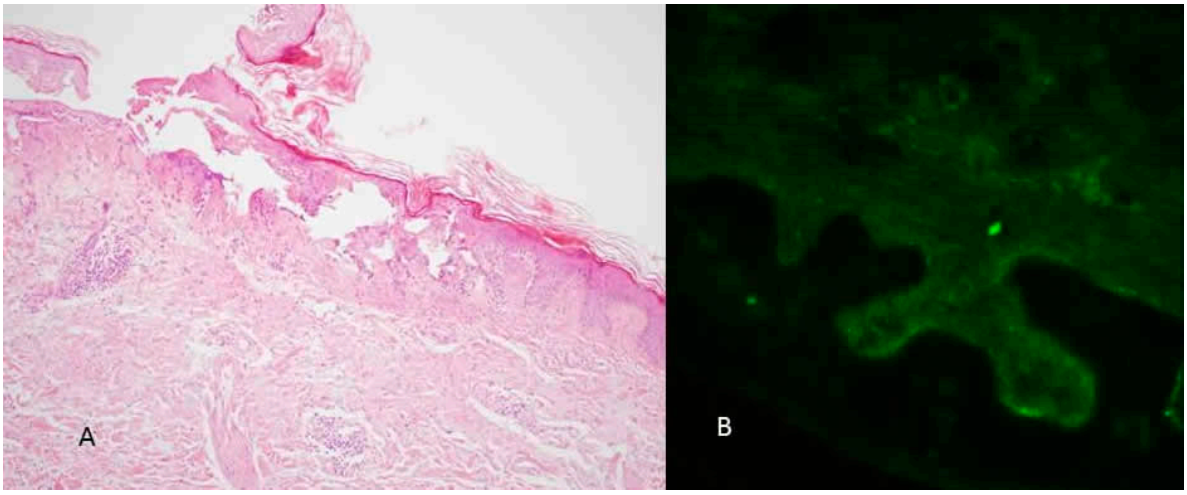

Figure 7. Dermatitis herpetiformis. A) Subepidermal blister; one microabscess is present in a dermal papilla. B) Granular IgA deposist in dermal papillae. (Direct Immuno-Fluorescence).

Differential diagnosis of DH must be made with scabies, atopic dermatitis, contact eczema, and other autoimmune bullous diseases, such as linear IgA dermatosis and bullous pemphigoid. The histopathological and direct immunofluorescence findings are usually definitive to reach the final diagnosis.

The main treatment for DH is a GFD, which must be strictly and continuously maintained throughout life. Resolution of skin lesions can take months or longer on a GFD and pharmacological therapy with dapsone may be required to rapidly improve symptoms. This drug inhibits the migration of neutrophils and is used temporarily until the complete disappearance of skin lesions [29]. Other sulphonamide drugs, such as sulphapyridine, and sulphasalazine, may be of utility in patients intolerant to dapsone.

A Finnish study, carried out between 1971 and 2010, on the death rate and causes of death in 476 consecutive patients with DH documented a significant reduction in mortality for all causes and also for cerebrovascular disease. The authors suggested that a strict adherence to the GFD, a reduction in tobacco consumption and a strict control of the hypercholesterolemia, had also an important role in the observed final health benefit [30].

3. Alopecia Areata

Alopecia Areata (AA) is an autoimmune disease that presents as a non-scarring type of hair loss. AA affects both sexes equally, affects patients of all ages, and is found in approximately 0.1% to 0.2% of the general population. Clinical presentation of AA is very heterogeneous, ranging from small and well-circumscribed patches of hair loss to a complete absence of body and scalp hair

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(Figure 8). Exclamation point hairs, dystrophic hairs, and yellow dots are features of AA that can be identified with trichoscopy. Nail abnormalities, such as pitting, brittleness, or striations, are seen in 10% to 20% of patients. The main factors affecting prognosis include age at onset and disease extent; younger age at initial presentation and severity at onset are the most important prognostic indicators. The etiology of AA remains unclear, though it is believed to result from a loss of immune privilege in the hair follicle, autoimmune-mediated hair follicle destruction, and the upregulation of inflammatory pathways [31].

AA is associated to other autoimmune disorders, such as Addison´s disease, autoimmune thyroiditis, atrophic gastritis, systemic lupus erythematous, rheumatoid arthritis, myasthenia gravis and vitiligo [32]. In 1995, Corazza et al described for the first time the association between AA and CD [39]. Since then, there have been other reports of this association. The estimated prevalence rate of CD in patients with AA is from1:85 [33] to 1:116 [34]. In addition, the prevalence of anti-gliadin antibodies in patients with AA was 18:100 in a study conducted in 2011, being more often in severe variants of AA, in particular alopecia universalis [35]. Furthermore, genome-wide association studies have also revealed shared risk loci between AA and CD [31]. It has been recommended an active search for CD using serological screening tests to diagnose the numerous cases of subclinical CD [9] but a recent study stated that the biological tests to search for CD do not bring information and proof enough, and recommended another approach to disclose gluten intolerance in AA patients [35].

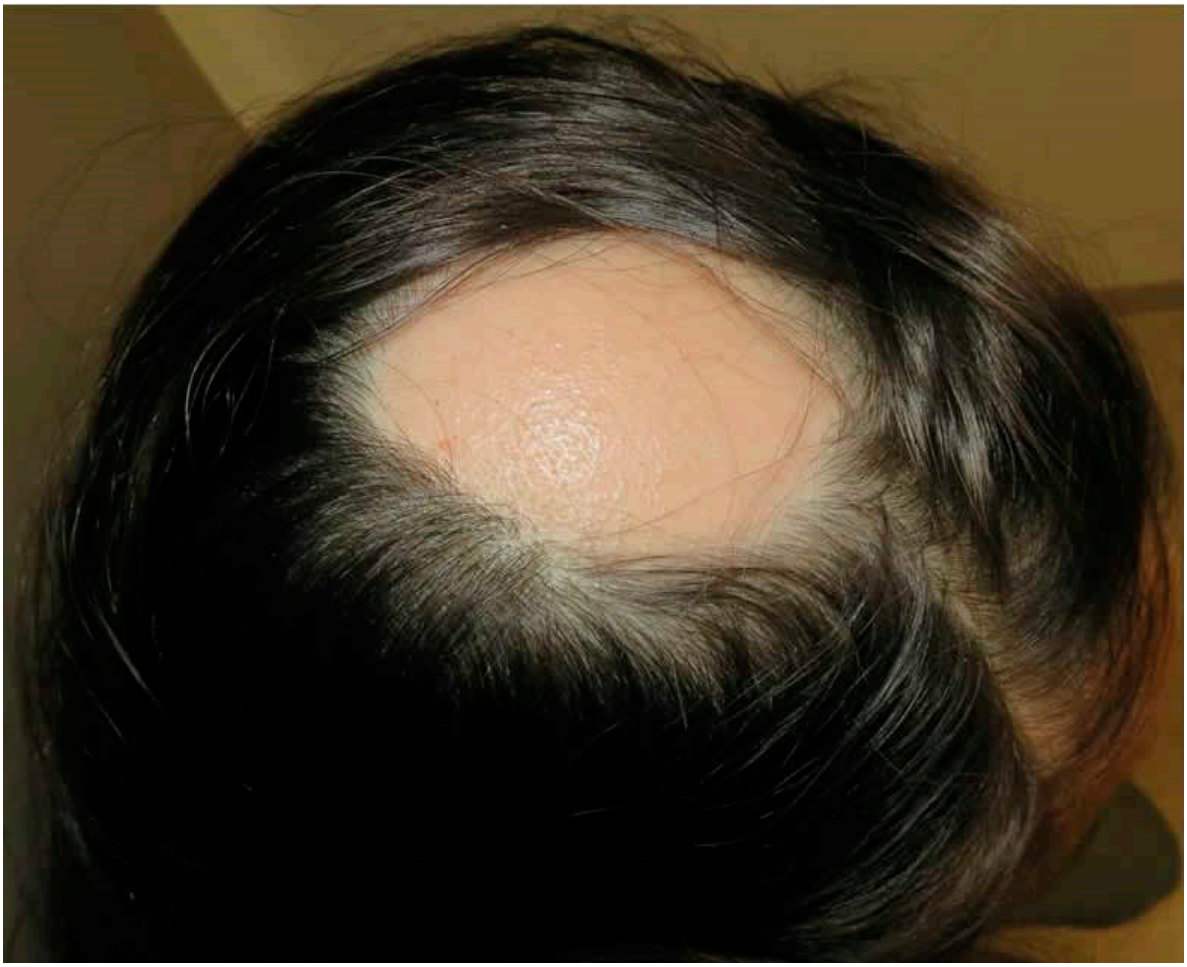
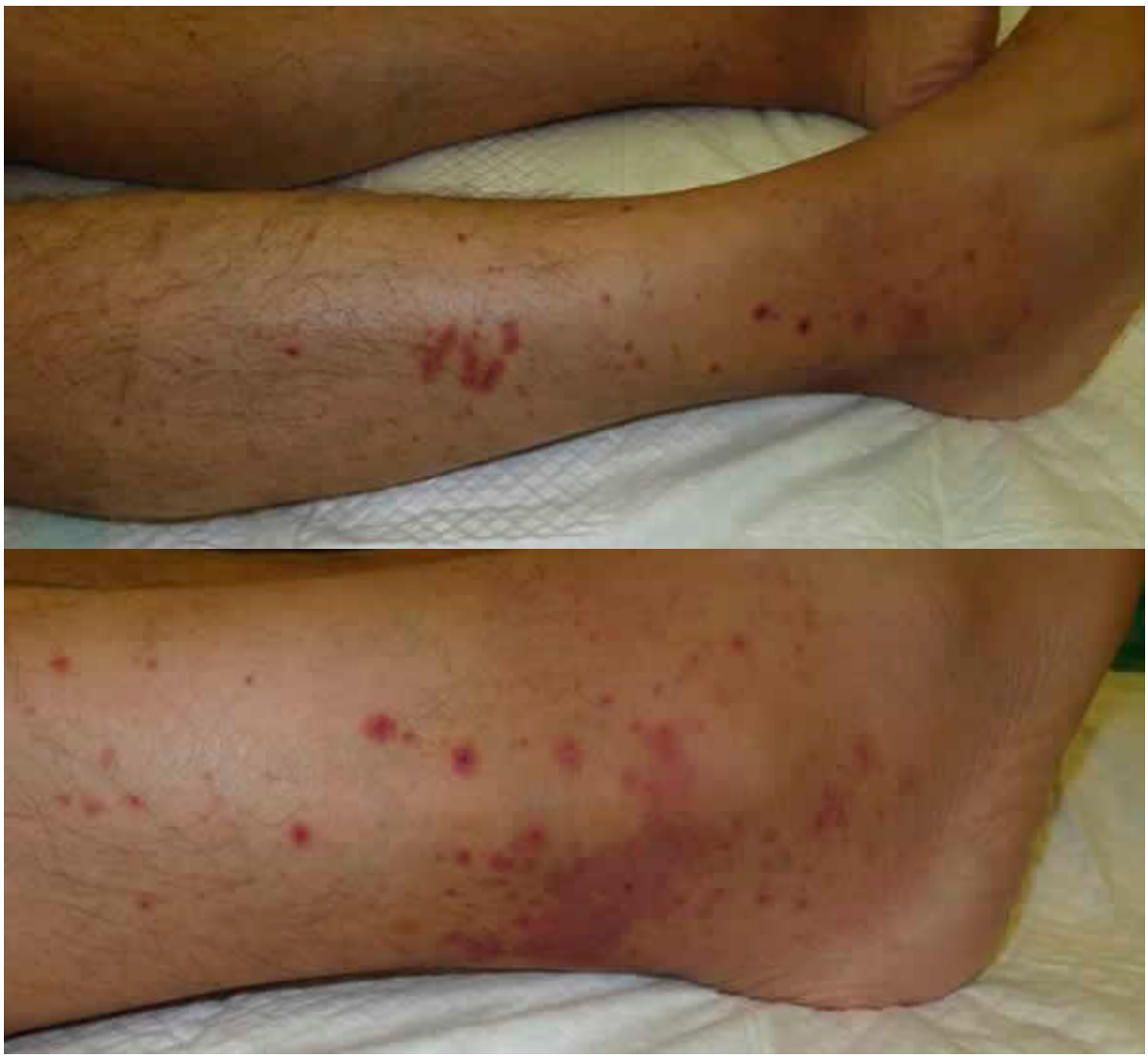


Figure 8. Alopecia Areata. Patchy head hair loss.

The positive effects of a GFD on the pattern of autoimmune conditions, such as AA, associated with CD have been attributed to a normalization of the immune response [37]. Although remission and recurrence may be observed during the clinical course of AA, many patients on a GFD showed complete regrowth of scalp and other body hair and no further recurrence of AA at follow-up [32].

4. Cutaneous vasculitis

Leukocytoclastic vasculitis, also known as "hypersensitivity vasculitis" is a histopathologic diagnosis given to cutaneous, small vessel vasculitis, characterized by the inflammation of the walls of postcapillary venules. Clinical features of leukocitoclastic vasculitis include palpable purpura, nodules, hemorrhagic vesicles, bullae and livedo reticularis, mainy distributed in lower extremities (Figures 9, 10). Extracutaneous involvement is seen in approximately 30% of patients. Systemic vasculitis shows a predilection for certain organs, such as the kidney or lungs. In most cases, leucocytoclastic vasculitis is mediated by immunocomplex deposition, being the antigen either exogenous or endogenous [38-44].



Figures 9 and 10. Vasculitis. Palpable purpuric papules on the lower extremities mainly in the right leg.

When leukocytoclastic vasculitis is suspected, a biopsy should be performed preferably in the first 24 to 48 hours of lesion onset. Additionally, direct immunofluorescence should be performed to evaluate for the presence of immunoglobulins. If no systemic symptoms are present, laboratory testing including complete blood count, erythrocyte sedimentation rate, basic metabolic panel, liver function tests, and urinalysis should be done as well. If there is concern for systemic involvement, a more extensive workup can be fulfilled. Around 90% of leukocytoclastic vasculitis cases are self-limited, showing spontaneous resolution within weeks to months. Treatment depends on the severity of disease and can range from an oral corticosteroid course to various steroid-sparing agents [38-39].

There are sporadic reports about the association between CD and cutaneous vasculitis [40-4]. The coexistence of these two entities might be related to increased intestinal permeability [45], 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. As seen in inflammatory bowel disease (IBD), exogenous antigens may permeate the damaged CD mucous in larger quantities than normal. This is reflected by significant serum milk and gluten fraction antibody titers. Moreover, an autoimmune sensitization may result because of the release of endogenous antigens from damaged small bowel mucosa. Meyers et al [48] described a case of cutaneous vasculitis complicating CD and the remission of skin lesions after the treatment with a strict GFD. Treatment with a GFD may improve cutaneous vasculitis lesions in cases associated with CD [10-12].

5. Urticaria

Urticaria is characterized by the onset of wheals, angioedema, or both (Figure 11) [46,47]. Urticaria is a common disorder, occurring in 15–25% of individuals at some point in life [48]. Chronic urticaria (CU) (duration ≥6 weeks) is seen in about 0.5–1% of the general population [49,50]. CU is associated with a substantial decrease in quality of life [51]. The etiopathogenesis of CU is thought to be associated with autoimmune mechanisms [52-54]. CU has been shown to have a genetic association to the human leukocyte antigen HLA-DQ8 alleles (55). Interestingly, HLADQ8 holds associations with celiac disease [52,56].

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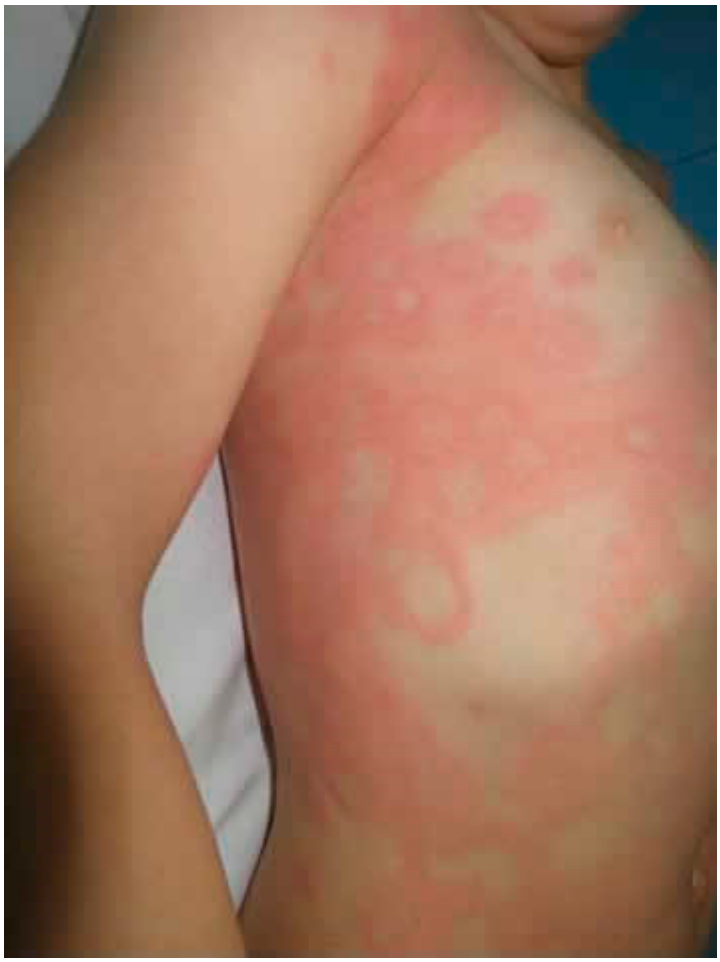


Figure 11. Urticaria. Pale to red, well-demarcated, transient swellings, involving the dermis at the thoracic and abdominal right wall

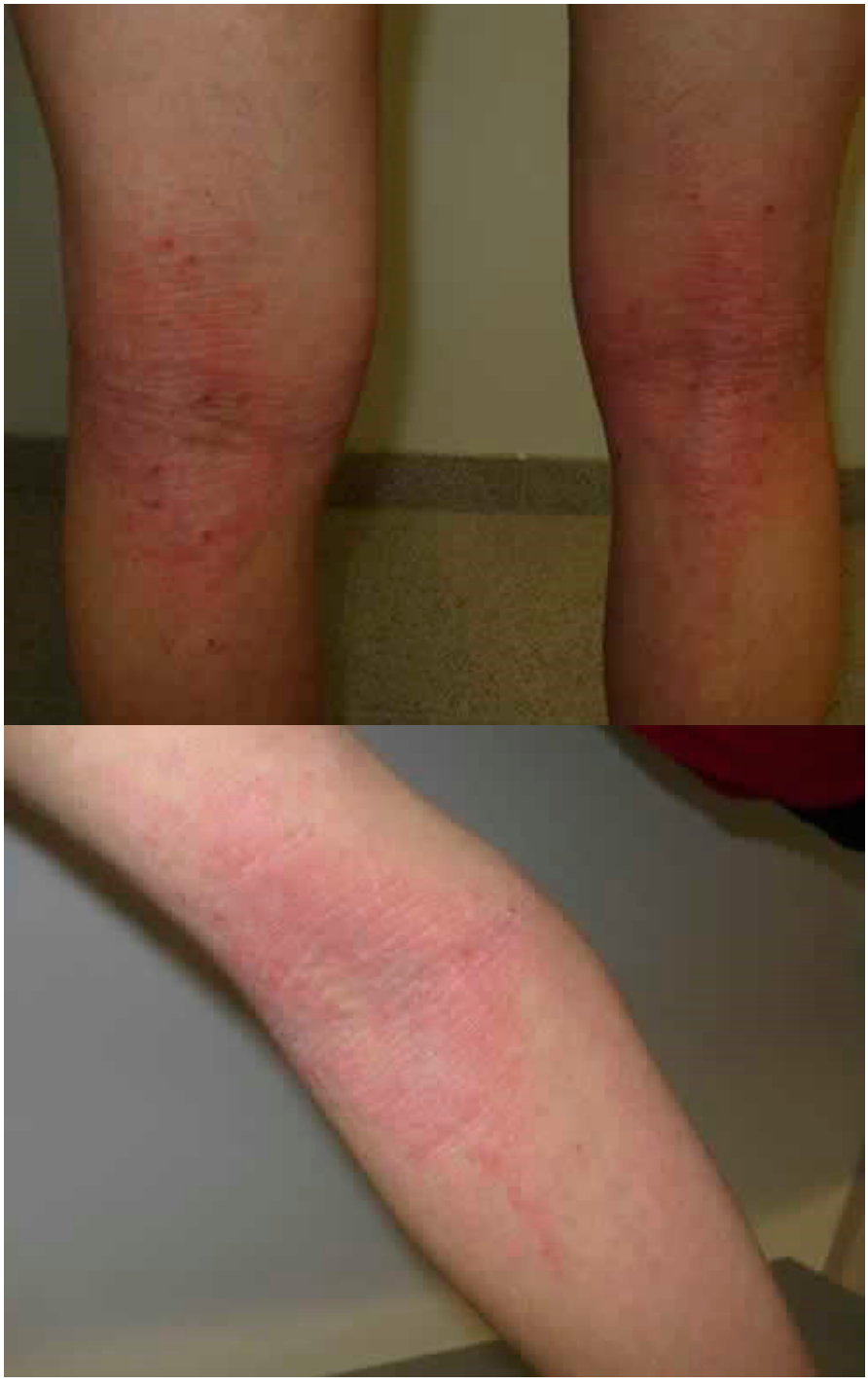
In 1987, Hauteke et al first described the association between CD and chronic urticaria [57], although the relationship between these two diseases is not fully clear. Recently Kolkir et al stated that chronic spontaneous urticaria is strongly linked to various autoimmune diseases, including Hashimoto´s thyroiditis, pernicious anemia, vitiligo, diabetes mellitus type 1, Grave´s disease, rheumatoid arthritis and CD [54]. In a large population study, 453 patients with CD and no previous diagnosis of urticaria developed urticaria and 79 of these 453 patients had chronic urticaria. The corresponding hazard ratios were 1.51 for any urticaria (95%CI=1.36–1.68) and 1.92 for chronic urticaria (95%CI=1.48–2.48). These data supports an increased prevalence of urticaria and chronic urticaria in patients with CD [58].

In some cases of CU the adoption of a GFD has proven effectiveness in controlling the skin flares [59,60], further sustaining that CU may be a cutaneous manifestation of CD and not only a fortuitous association [12].

6. Atopic Dermatitis

Atopic Dermatitis (AD) is a chronic inflammatory skin disease that is associated with a heterogeneous group of symptoms and signs. The cutaneous signs of AD include erythema, lichenification, scaling and prurigo nodules (Figures 12,13).The symptoms of AD include cutaneous itch and pain [61], sleep disturbance and fatigue [62,63], and mental health symptoms [64-66]. All of these manifestations contribute to diminish quality of life, limiting the ability to perform activities of daily life and causing psychosocial distress and stigma [67]. AD affects 40 million individuals

worldwide [68] and its prevalence is still increasing. Notably, AD appears more prevalent among children under five years of age, and its prevalence decreases with advancing age [69]. The onset of AD occurs primarily in childhood and is thought to precede allergic disorders mediated by an immunoglobulin E (IgE) sensitization to environmental antigens, namely, asthma and allergic rhinoconjunctivitis, the so-called atopic march [70-73]. Though extensive recent studies have shed light on the understanding of AD, the exact pathogenesis of the disease is still unknown. The complex interaction between genetics, environmental factors, microbiota, skin barrier deficiency, immunological derangement, and possibly autoimmunity contributes to the development of the disease [74-77].



Figures 12 and 13. Atopic Dermatitis. Excoriated bilateral erythematous scalling papules and plaques on the antecubital and popliteal fossae.

AD has also been linked with CD. Ress et al. analyzed the prevalence of CD in 351 children with AD compared with a general pediatric population and showed a four-times greater risk of developing celiac disease in patients with AD (OR, 4.18; 95% CI, 1.12–15.64). This study also emphasizes the need for evaluating the cost-effectiveness of screening patients with AD for CD in time to prevent long-term complications [77]. Moreover, Ciacci et al. conducted a case–control study involving 4114 adult patients with and without CD and observed that AD was three-times more frequent in patients with CD and two-times more frequent in their relatives than in their spouses (OR, 3.17; 95% CI, 1.02–9.82) [78].

7. Psoriasis

Psoriasis (Ps) is an autoimmune, chronic inflammatory skin disease with an estimated prevalence of 2%–4% in the adult population [79,80]. It affects over 7.5 million people in the United States and approximately 125 million people worldwide [81]. Ps is considered to be a multifactorial disease, in which the genetic background interacts with environmental factors to define the individual's risk [82]. The classical clinical manifestations of Ps consist in the presence of red, infiltrated plaques, covered with a coarse silvery scaling (Figures 14,15). Predilection sites include elbows and knees, scalp, and periumbilical and lumbar regions, although any anatomical site might be affected [83]. The clinical course of Ps is marked by frequent relapses with very fluctuating rates [80].

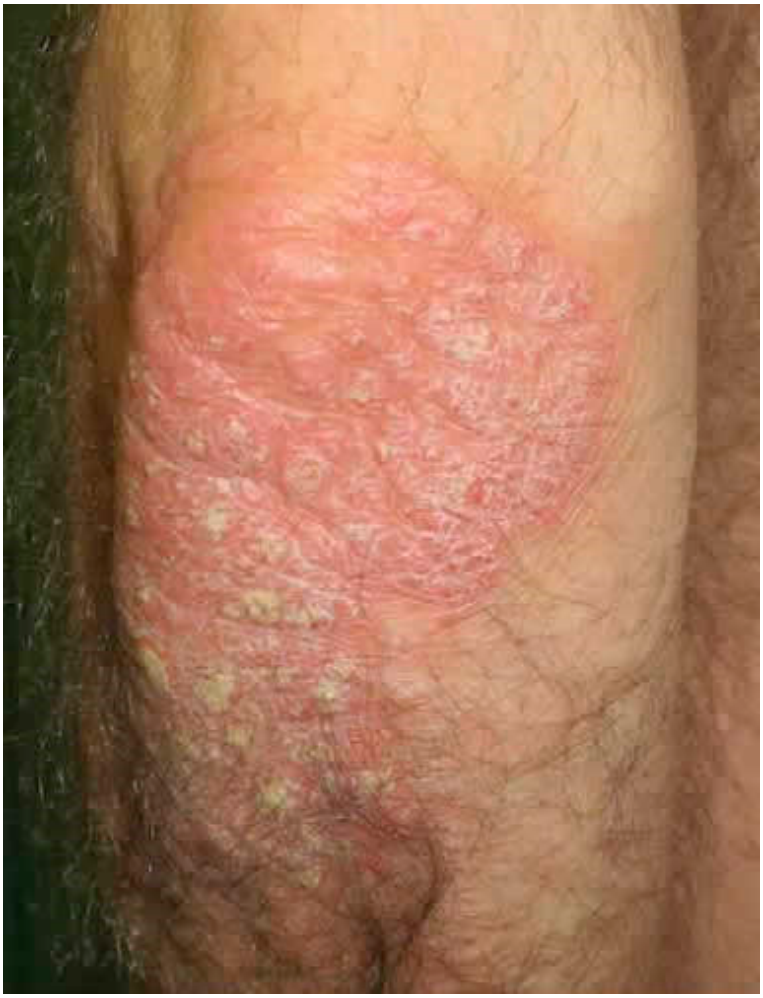


Figure 14. Extense plaque of psoriasis at the left elbow extensor side.

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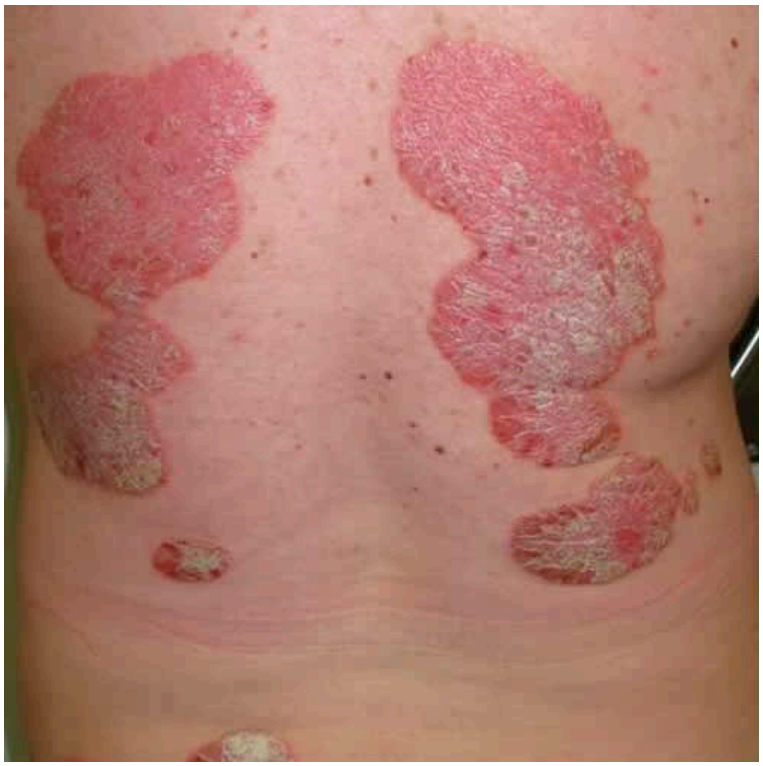

Figures 15. Psoriasis. Well demarcated, erythematous scaly plaques relatively symmetrical on the back.

Ps is known to be associated with an increased risk of several comorbidities including inflammatory arthritis, metabolic syndrome, and atherosclerotic disease. The association between psoriasis and CD has been of recent interest but its first recognition was in 1971 by Marks and Shuster [84]. They described for the first time a "psoriatic enteropathy" in a small group of patients with severe Ps. For many years, the relationship between Ps and CD remained controversial since the few available data were inconclusive. A recent meta-analysis has demonstrated a significantly higher risk of CD among patients with psoriasis compared with participants without psoriasis with the OR of 3.09 (95%CI= 1.92-4.97) [82]. Furthermore, there are seven studies that have reported a positive association between psoriasis and CD markers [85-92]. In contrast, other studies did not find evidence of association between psoriasis and CD markers. However, these studies were of smaller size and some did not employ control groups [93-97]. To resume the evidence for celiac disease antibody positivity in psoriasis, Bhatia et al performed a meta-analysis of nine studies that reported the frequency of IgA antigliadin antibody (IgA AGA) positivity in psoriasis cases and controls. They found a statistically significant higher relative risk of having positive IgA AGA in patients with psoriasis compared to controls (OR=2.36, 95% CI 1.15-4.83) [92]. Other two studies suggested that levels of CD antibodies correlate with Ps or psoriatic arthritis severity [98,99].

The pathophysiologic mechanisms behind the increased risk of CD among patients with Ps are not known but there are different hypothesis that try to explain it [82,100]. The association between CD and several autoimmune diseases, such as type I diabetes mellitus and autoimmune thyroid disease, is well-documented [101,102]. It is believed that shared genes (at-risk HLA haplotypes) might be responsible for this association. The shared genes might play a similar role in the association between psoriasis and CD. Genetic-wide association studies of these two conditions identified genetic susceptibility loci at eight genes regulating innate and adaptive immune response: TNFAIP3, RUNX3, ELMO1, ZMIZ1, ETS1, SH2B3, SOCS1 and UBE2L3 [100, 103-105]. Another possible explanation is that the increased proliferation rate of keratinocytes found in patients with

psoriasis are known to produce an excessive amount of interleukin (IL)-1 and IL-18, the essential signals for the induction of Th1 response. Interestingly, mucosal inflammation in patients with CD is also caused by activation of Th1 in response to dietary gluten [106]. Therefore, it is possible that those ILs might predispose patients to CD. On the other hand, it is possible that intestinal barrier dysfunction associated with undiagnosed or untreated CD may allow increased passage of immune triggers resulting in increased risk of autoimmune diseases including Ps [107,108]. Finally, CD-related malabsorption may affect Ps by causing a vitamin D deficiency status [10, 109]. It is well known that low levels of vitamin D predispose to Ps, and that exposure to sun light and topical administration of vitamin D analogues improve psoriatic lesions, probably due to its immunoregulatory properties [110].

Although available data regarding coexistence of CD and Ps are still inconclusive, there is a considerable amount of evidence that suggests that psoriatic patients either with concomitant CD or asymptomatic gluten intolerance may benefit from a GFD (98,106,116). Furthermore, prevalence of antigliadin IgA antibody is significant higher among patients with PS without a diagnosis of gluten related disorders. For this reason, antigliadin IgA testing can identify patients likely to benefit from GFDs [111].

To summarize, relatively frequent coexistence of CD and Ps justifies monitoring of patients with either condition for clinical evidence of the other. Even more important, implementation of a gluten-free diet should be considered in psoriatic patients presenting with serological evidence of gluten intolerance or clinical signs of CD, including diarrhea, flatulence, fatigue, and history of iron-deficiency anemia.

8. Oral cavity disorders

Numerous authors have described a wide variety of oral cavity disorders in patients with CD and some of these manifestations may be considered a diagnostic clue in silent-atypical forms of CD [112].

Recurrent aphthous stomatitis (RAS) is a common clinical condition producing painful ulcerations in the oral cavity. RAS is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes and yellow or gray floors typically first presenting in childhood or adolescence [113,114] RAS has been recognized for many years as a symptom of celiac disease (CD) [116-118]. A recent meta-analysis showed that celiac patients had greater frequency of aphtous stomatitis (OR=3.79, 95% CI=2.67-5.39); considering only the children, the OR was 4.31 (95%CI= 3.03-6.13), while in the adults the OR of only one study was 47.90 (95%CI6.29-364.57) [119]. RAS patients should be considered at-risk subjetcs even in the absence of any gastrointestinal symptom and should therefore undergo diagnostic procedure for CD [120]. RAS may also be present in patients with DH. A study reported nonspecific mucosal ulcers in up to 40% of patients with DH [121]. Etiopathology of RAS is obscure; it is not known whether RAS lesions are directly influenced by the gluten sensivity disorder, or if these are related to hematinic deficiency with low serum iron, folic acid and vitamin B12 or trace element deficiencies due to malabsorption in patients with untreated CD [118].

Other oral cavity manifestations among patients with CD have also been described [119-122]. Rashid et al. described oral and dental manifestations of CD, consisting in enamel defects, delayed eruption, recurrent aphthous ulcers, cheilitis, and atrophic glossitis [114] Bramanti et al found atrophic glossitis, angular cheilitis and burning tongue more frequent in DC patients

than in control patients [125].

9. Other CD-associated skin conditions.

As reported by Humbert et al and Caprioni et al, in addition to skin diseases with proven association with CD and those improved by a GFD and/or with positivity of celiac serological markers, there are also fortuitous associations with other skin conditions [10-12]. Some of these associations are more common than others.

Dermatomyositis.

Juvenile dermatomyositis, as well as dermatomyositis in adult patients, have been reported in association with CD. Especially when patients are newly diagnosed with these conditions, even in absence of gastrointestinal symptoms, screening for CD should be performed. Clinical manifestations of dermatomyositis may respond to a GFD [126-129].

Vitiligo.

The possible association between CD and vitiligo is controversial. There are few cases that report improvement of vitiligo in patients that started a GFD. A common basic autoimmune mechanism has been hypothesized [130,131].

Lupus erythematosus.

Many similarities exist between the pathogenesis of CD and systemic lupus erythematosus but it is still unknown whether there is a truly association or not [132-134].

Rosacea.

Rosacea is a common inflammatory skin condition that shares genetic risk loci with autoimmune diseases such as type 1 diabetes mellitus and CD. One study showed that women with rosacea had a significantly increased risk for celiac disease (OR=2.03, 95%CI 1.35-3.07) [135].

Other reported and less frequent associations include: lichen planus and lichen sclerosus [136-144], linear IgA bullous dermatosis [145,146], prurigo nodularis [147], pityriasis rubra pilaris and erythroderma [148], erythema elevatum diutinum [149-151], necrolytic migratory erythema [152-154], pityriasis lichenoides [146], erythema nodosum [146,155-157], porphyria [158-159], cutaneous amyloidosis [160], generalized acquired cutis laxa [161-163], acquired hypertrichosis lanuginose [164], ichthyosis [165], partial lipodystrophy [166], transverse leukonychia [167], atypical mole syndrome, and congenital giant nevus [168]. Finally, we want to mention that earlier studies reported an increased risk of malignant melanoma in patients with CD, but a recent study has refuted this relation [169].

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