Cutaneous Disorders Masking Celiac Disease

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Celiac disease (CD) is an immune-mediated systemic gluten-related disorder characterized by a wide spectrum of intestinal and extra-intestinal manifestations, including damage to cutaneous and connective tissue.

Keywords: celiac disease ; dermatitis herpetiformis ; skin ; gluten-free diet

1. Introduction

The term gluten-related disorders (GRD) refers to a spectrum of chronic disorders triggered by the ingestion of gluten, including celiac disease (CD), wheat allergy, and non-celiac gluten sensitivity (NCGS).

Celiac disease is a chronic inflammatory disorder of the small bowel that occurs in genetically susceptible individuals [1]. The diagnosis of CD is based on clinical and serological data; however, in adults, histological diagnosis is mandatory according to current guidelines [2][3]. Multiple biopsies of distal duodenum (at least four) and biopsies of the duodenal bulb (at least one, more in case of endoscopic evidence of CD) should be performed due to the possibility of patchy lesions [4] and ultra-short disease [5][6]. The HLA determination is not mandatory but might help doctors exclude CD in atypical cases due to its high negative prognostic value [2]. Less than 5% of CD patients are seronegative, i.e., present the impossibility of identifying classic serological biomarkers of CD [7]. Celiac disease has a wide spectrum of clinical manifestations: in addition to the classic gastrointestinal symptoms, it can affect a wide range of extraintestinal organs, including the skin [8]. Dermatitis herpetiformis (DH) is a gluten disorder characterized by a pruritic vesicular rash triggered by dietary gluten and characterized by deposits of immunoglobulin A (IgA) at the tips of the dermal papilla, which affects the extensor surfaces of elbows, knees, buttocks, and scalp [8]. DH is the dermatological disease most frequently associated with CD, and its treatment is a strict gluten-free diet (GFD). However, in the literature, an increased risk of other skin disorders is reported in CD, including psoriasis [9][10][11][12][13][14], alopecia areata (AA), urticaria [15][16], and vitiligo [17][18][19]. CD can also present with cutaneous signs overlapping with connective tissue disease (CTD), cutaneous vasculitis (CV), or other rare dermatological signs of malabsorption, making it more difficult to diagnose.

2. CD Skin Manifestations Overlapping with CTD

Celiac disease is a chameleonic disease [20]. It may be associated with various cutaneous disorders, ranging from the most common DH to rare cases of severe chronic dermatitis which may hide CD.

Skin diseases represent a common extra-intestinal manifestation of CD. Gluten disorders are still a diagnostic and therapeutic dilemma. Individuals with a suspected skin manifestation of SNCD should not be prescribed a GFD before concluding the mandatory investigation to rule out seronegative non-celiac diseases.

The association of CTD and CD has been reported in the literature [21][22][23], and genetic predisposition seems to play an important role. Among CTD, dermatomyositis, a rare autoimmune disease which typically affects the skin, the muscles, and the blood vessels, is the most common CTD described in association with CD [24][25][26][27]. In patients with coexisting CD and DM, a GFD may improve the cutaneous signs of DM [28].

As for systemic lupus erythematosus (SLE), Ludvigsson et al. suggested that individuals with CD have a 3-fold risk of SLE compared to the general population [29]. A recent study by Soltani et al. reported a prevalence of 3% for biopsy-proven CD in patients with SLE [30], while Shamseya et al. found biopsy-confirmed CD in 6% of juvenile SLE population [31]. Another cutaneous disorder in SLE is chilblain, also known as lupus pernio. It is usually characterized by painful papuloerythematosus plaques on the fingers due to superficial and localized inflammation resulting from a maladaptive vascular response to non-freezing cold. To the best of our knowledge, there are only three reported cases in children, all characterized by a significant improvement after adopting a GFD [32][33][34].

The association between Sjogren's syndrome (SS) and CD has been reported in several case reports [35][36][37]. However, the prevalence of CD in patients with SS is not clear, ranging from 1% to 15% [38][39][40][41], and, in recent research, SS occurrence in CD patients varies from 1.2% to 6.5% [42][43][44][45]; this discrepancy may be due to a gap in the diagnosis of CD in SS patients. The link between CD and SS is supported by research studies that demonstrate GFD effectiveness in the control of SS symptoms in patients affected by both diseases [46].

A few publications have reported the coexistence of CD and systemic sclerosis (SSc) [47][48] with a prevalence from 4% to 8% [49][50][51], though the association between these two conditions remains controversial [52]. There is also a study that suggests a higher prevalence of CD in UCTD compared to the general population [53].

Among the overlapping symptoms, AA is an autoimmune disease common in both CD and CTD, especially SLE. The risk of alopecia is three times greater in patients with CD than in the general population [54]. Although its etiopathogenesis is still unclear, a T-cell-mediated reaction has been recognized [55], and AA may improve after starting a GFD in CD patients [56][57]. Moreover, both chronic urticaria (CU) and sclerodactily have been identified as dermatological manifestations of CD [15][16][58][59]. In a study, the odds ratio of having CD was 26.9 in patients with CU (95% CI, 6.6–110.17; $p < 0.0005$), compared to the control subjects [60]. Therefore, in cases of CU, CD screening should be suggested [61][62].

3. CD Skin Manifestation Overlapping with Cutaneous Vasculitis

Cutaneous vasculitis is an inflammatory process affecting the dermal blood vessel wall and leading to its destruction with subsequent ischemic and hemorrhagic events. CV is generally characterized by petechiae, palpable purpura, and infiltrated erythema [63]. The association between CD and CV has been reported in several studies [64], and the literature suggests that CV is more likely to occur in patients with poorly controlled CD and that a GFD may improve CV lesions in such cases [65][66].

4. Acrodermatitis Entheropatica Secondary to CD

A typical feature of CD is the malabsorption and subsequent deficiency of micronutrients. Among these, zinc deficiency is the most common, and it causes alopecia as well as erythematous-squamous dermatitis in the periorificial regions, genitals, and arm flexures. However, a few cases of acrodermatitis entheropatica (AE) secondary to CD have been described in the literature [67]. In these patients, cutaneous manifestations improve with a GFD and oral zinc supplement.

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