Gluten related disorders: even a dermatological issue

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Summary

“Gluten-related disorders” (GRD) is a term that includes different diseases triggered by the ingestion of gluten-containing food. Because of their high incidence, also linked to the wide consumption of these foods in the world, the scientific community has been intensively studying them. GRD are divided on the basis of their pathogenic mechanism: autoimmune, celiac disease (CD), gluten ataxia (GA) and dermatitis herpetiformis (DE); allergic, wheat allergy (WA, IgE or non-IgE mediated) and unknown as in the case of non-celiac gluten sensitivity (NCGS). Taken together, these disorders can affect at least 3% of the population. However, DH is not the only skin disease associated with CD. In 2012 we published a review article about skin manifestations of CD, underlining that many skin diseases, in particular psoriasis, atopic dermatitis, chronic urticaria, alopecia areata and hereditary angioneurotic edema, are actually more common in the celiacs or show atypical clinical presentation often associated with resistance to standard therapies in those patients. These skin diseases cannot be classified as a GRD, but it is important to consider the possible presence of a GRD in all patients who do not respond to standard therapies. Recently we described cutaneous manifestations of a 17 consecutive patients affected by NCGS, suggesting the existence of a new cutaneous disease, “cutaneous gluten sensitivity”, that might be classified among GRD in the future.

KEY WORDS: gluten related disorders; celiac disease; skin disease; gluten sensitivity; cutaneous gluten sensitivity.

Introduction

“Gluten-related disorders” (GRD) is a term that includes different diseases triggered by the ingestion of gluten-containing food. Because of their high incidence, also linked to the wide consumption of these foods in the world, the scientific community has been intensively studying them (1). In spite of the importance of wheat in the human diet throughout history, the interaction between its components (gliadin, gluten, amylase trypsin inhibitor, etc.) and the human body triggers an increasing variety of symptoms, syndromes, allergic reactions, autoimmune diseases (2). The first description of a patient affected by a disorder related to gluten ingestion (celiac disease, CD) has been ascribed to Areteus of Cappadocia, who in the 2nd century AD reported a case of chronic diarrhea and malabsorption (3). This scenario appears in contrast with the wide diffusion of the genetic background susceptible to immune reactions against gluten, the HLA DQ2 and/or DQ8 haplotypes, which are essential for the development of CD (4). The continuous worldwide diffusion of diseases and syndromes recognizing gluten or other wheat components as the dominant environmental factors, has induced the scientific community to study the mechanisms underpinning the intestinal and systemic damage following their ingestion and to group them into the umbrella definition GRD (5, 6). GRD are divided on the basis of their pathogenic mechanism: autoimmune, CD (7); allergic, wheat allergy (WA, IgE or non-IgE mediated) and unknown as in the case of non-celiac gluten sensitivity (NCGS) (6). Taken together, these disorders can affect at least 3% of the population and probably an even greater proportion of the patients attending gastroenterological outpatient services (2, 8). For these reasons the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) considered it important and necessary to develop a position statement on the nomenclature and diagnosis of GRD in adults, to clarify the clinical issues that gastroenterologists and endoscopists usually face with during their clinical practice (1).

Skin and gluten related disorders

Indeed the above classification is closely gastroenterological and it does not include GRD that affect other organs and systems, such as skin and central nervous system. Previously in fact, Sapone et al. proposed a different classification, which also included dermatitis herpetiformis (DH) and gluten ataxia (GA) between GRD with autoimmune pathogenesis (6) (Figure 1).
Skin manifestations and celiac disease

Currently the only skin disease regularly included in the group of GRD is DH, considered as the cutaneous manifestation of gluten-dependent enteropathy. DH, initially described by Louis Duhring in 1983 (9), is considered an autoimmune skin disease with an estimated prevalence range from 1.2 to 39.2 per 100,000 and an incidence range of 0.4 to 2.6 per 100,000 per year with geographical variability. Males have a higher prevalence of DH (10). In fact, most population-based studies to date have found male-to-female ratios ranging from 1.5:1 to 2:1 (11). Interestingly, the opposite has been shown about gender prevalence of CD, with female-to-male ratios ranging from 2:1 to 4:1. The time of onset of the disease is variable. Cases of childhood DH are currently more often reported than in the past, but the average age at presentation varies from 30 to 40 years old (12, 13). A recent epidemiological study conducted by Salmi et al. (14) in Finland reported some interesting results about the increasingly rarity of DH. Although the rates of incidence and prevalence of DH, in the Finnish population in the thirty years between 1980 and 2009, were higher than those of previous studies conducted elsewhere, in the course of time there was a downward trend especially in the 90s. In particular, the estimated prevalence rate was 75.3 per 100,000, while annual incidence rates were respectively 5.2 per 100,000 in 1980-1989, 2.9 per 100,000 in 1990-1999 and 2.7 per 100,000 in 2000-2009, with a decrease in incidence rate between the first and second 10-year period that was statistically significant. In the study of Salmi et al. (14) emerged a ratio between DH and CD of 1.8, that resulted lower than at the estimated 1:5 showed in previous studies (15). Theoretically, the lower rate of DH can be explained by the underestimation of the criteria for the diagnosis of CD, but also by the possibility of spontaneous remission of DH. However, DIF on perilesional skin should be considered the gold standard for the diagnosis (26, 27). In particular, two different patterns of DIF are possible: (a) granular deposits in the dermal papillae and (b) granular deposition of the lesions on the extensor surfaces of the upper and lower extremities, elbows, knees, scalp, nuchal area, and buttocks is considered a hallmark of the disease. At times, face and groins may be involved. DH is rarely observed in darker-skinned individuals (17, 18); however, there were no significant clinical differences compared to those North European. Since 1971, sporadic cases of DH presenting as palmo-plantar purpura were reported. This uncommon skin manifestation is usually observed in the children, but a number of adult cases has been described (19-21). Clinical presentation of DH is often atypical, especially in early and later stages in which prevailing scratching lesions, therefore DH must be differentiated from atopic dermatitis, scabies, papular urticaria, and impetigo in children, whereas eczema, other autoimmune blistering diseases (especially linear IgA bullous disease and bullous pemphigoid), prurigo nodularis, urticaria, and erythema multiforme should be considered in adults (22).

Diagnosis of DH is based on physical examination, histopathology, immunofluorescence studies, and serologic testing. Routine histopathology of lesional skin of DH, that should ideally contain an intact vesicle or should be taken in the vicinity of early blisters (23), can be evocative, but not diagnostic, and nonspecific. Furthermore, the lesions present characteristic histopathological changes, in fact the initial inflammatory event is variable edema in the papillary dermis with discrete subepidermal vacuolar alteration and neutrophils along the dermal-epidermal junction (DEJ). As the lesion develops, neutrophils, to a lesser extent eosinophils, and fibrin accumulate within the dermal papillae and form microabscesses. These become confluent resulting in a subepidermal blister. In early stages of the disease, the inflammatory infiltrate contains mostly neutrophils, but in later stages, variable numbers of eosinophils can be present (24). A prevalent lymphocytic infiltrate was also reported by Warren et al. (25) probably corresponding to a later stage of the disease. However, DIF on perilesional skin should be considered the gold standard for the diagnosis (26, 27). In particular, two different patterns of DIF are possible: (a) granular deposits in the dermal papillae and (b) granular

![Classification of Gluten Related Disorders adapted by Sapone et al. (6).](image-url)
deposits along the basement membrane. Sometimes, a combination of both patterns, consisting in granular IgA deposition along the basement membrane with accentuation at the tips of the dermal papillae, may be present (28, 29). Recently Ko et al. suggested the existence of a third different pattern of IgA deposition at DIF, the fibrillar pattern, that may be related to a clinical variant of DH (30). Also serologic tests, and in particular IgA anti-tissue transglutaminase antibodies (anti-tTG) and IgA endomysial autoantibodies (EMA), have become relatively sensitive and specific tools for detection of gluten-sensitive diseases and therefore of DH in subjects on a diet free. Other serologic tests for the diagnosis of DH include the detection of antibodies directed to epidermal TG (anti-tTG), that is currently considered the key autoantigen in DH, as well as antideamidated gliadin peptides antibodies (IgA and IgG), that are particularly reliable in children under 2 years old, and antibodies against to the covalent complex ITG-deamidated gliadin peptides, that was coined as neoepitope (31, 32). Currently, the diagnosis of CD in patients also affected by DH not requires further investigation because skin disease is sufficient for diagnosis of CD (33).

To date, the first-line therapy of DH, as well as CD, is gluten free diet (GFD), that should not be considered as a mere symptomatic approach and therefore continue without interruption even after clinical remission (34). Generally, several months are necessary to obtain the control of the skin disease. For this reason, other treatment may be used as symptomatic agents such as dapsone, sulfasalazine and sulphasemethoxypryridazine, topical potent or very potent corticosteroids, and antihistamines. Since 1950, when the first report on successful use of dapsone in the treatment of DH was published (35) dapsone became the best tolerated symptomatic pharmacologic therapy for DH in both adults and children. In particular, the anti-inflammatory properties of this drug are linked to inhibition of neutrophil recruitment and local neutrophil- and eosinophil-mediated tissue injury. Dapsone represents a valid therapeutic option during the 1- to 2-year period until the GFD is effective; dosages of 1/mg/kg/day can control itching and blister development. The commonest side effect of dapsone is haemolysis and patients should be seen within 2 weeks after starting the drug as haemolysis may be acute in some individuals (22). Sulfasalazine and sulfamethoxypryridazine might provide an effective alternative to dapsone especially when it fails to control the disease or the therapy is complicated by adverse events (22). However, even if DH is not the only skin disease associated with CD. In 2012 we published a review article about skin manifestations of CD, underling that many skin diseases, in particular psoriasis, atopic dermatitis, chronic urticaria, alopecia areata and hereditary angioneurotic edema, are actually more common in the celiacs or show atypical clinical presentation often associated with resistance to standard therapies in those patients (36). These skin diseases cannot be classified as a GRD, but it is important to consider the possible presence of a GRD in all patients who do not respond to standard therapies. Furthermore we reported other skin and oral conditions sporadically associated with CD as well as dermatologic manifestation secondary to nutritional deficiencies due to the enteropathy, also adapting the classification proposed by Humbert et al. in 2006 (37) (Tables 1 and 2).

“Cutaneous gluten sensitivity”

Recently we described cutaneous manifestations of 17 consecutive patients affected by NCGS (38). They showed different cutaneous manifestation, that were mainly erythematous, excoriated papular-vesicular and extremely itchy, similar to subacute eczema or DH. Nevertheless, some patients had hyperkeratotic scaly lesions instead overlying mild erythematous infiltrative lesions and they were associated with excoriations similar to chronic psoriasis. In order of frequency, the sites of the lesions were: extensor surfaces of upper limbs [elbows and back of the hands (94% and 6%)], extensor surfaces of lower limbs (knees, 59%), bottom (29%), chest (18%), neck (18%), the palms of the hands (6%), extensor surface of upper limbs (6%) and face (6%). In all enrolled patients skin lesions were sensitive to the gluten free diet (GFD) and the main time of their disappearance after adoption of GFD was one month or so. Histologically, it was not possible to outline a specific pattern, but it is important to point out the similarity with psoriasis, eczema and DH. Finally, we reported the immunohistological features obtained by a direct immunofluorescence (DIF) test on a skin biopsy got from a perilesional skin, as it is usual in suspected DH to preserve immunological deposits. We described the type of reactant that forms the immunological deposit (IgG, IgM, IgA, C3 or C1q) and the site (dermo-epidermal junction, perivascular, fluorescent bodies). The patterns of distribution along the dermo-epidermal junction were microgranular/granular in all patients. For each reactant we calculated (IgG, IgM, IgA, C3 and C1q) in how many patients it appears in different skin sites. The C3 fraction of the complement system is the only reactant percentage in more than a half of the patients (82%) localized in particular along the dermo-epidermal junction. The main aim of our study was to characterized skin manifestations of NCGS patients in order to define a new dermatological disease, as “cutaneous gluten sensitivity”, worthy of inclusion in the group of GRD, but at the moment the result do not allow that. In fact the only data common to most of these patients affected by NCGS associated to non-specific skin manifestations were: 1) itching; 2) the presence of C3 at the dermoepidermal junction; and 3) a rapid resolution of lesions adopting the GFD.

Conclusions

In conclusion gluten may be responsible for the onset of several cutaneous manifestations, some of them already described as DH, other under study, for example probable “cutaneous gluten sensitivity”. Therefore, dermatologists must be familiar with the cutaneous manifestations and symptoms of gastrointestinal disorders.
An appropriate understanding, work-up, consultation and management will help to identify the important cutaneous-gastrointestinal connection and will not be ignored an important gastroenterological disease in patients with skin manifestations. We suggest an accurate follow-up of all patients who report intense itching and gastrointestinal disorders, even when histology and morphology of the skin lesions do not identify a specific skin disease. The exact characterization of new clinical entities such as CGS and NCGS represents an important objective both for diagnostic and therapeutic purposes, since these are patients who benefit actually of GFD and who do not adopt it only for fashion.

Finally we want to stress once again the importance of a close collaboration between gastroenterologists and dermatologists, because the gastrointestinal system and the skin may be considered more and more “the two sides of the same coin” and patients require an interdisciplinary support, especially given the upcoming changes relatively to “standard healthcare provision” classification of CD and DH as chronic disease and no longer as rare diseases.

Table 1 - Skin diseases associated with CD (adapted by Humbert et al.) (37).

<table>
<thead>
<tr>
<th>Category</th>
<th>Proved association</th>
<th>Improvement in skin disease by GFD or/and presence of serologic markers in several data</th>
<th>Fortuitous association (sporadic cases reports)</th>
</tr>
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<tbody>
<tr>
<td>Autoimmune diseases</td>
<td>Dermatitis herpetiformis</td>
<td>Alopecia areata</td>
<td>IgA linear dermatitis</td>
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<td></td>
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<td>Cutaneous vasculitis</td>
<td>Dermatomyositis</td>
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<td>Vitiligo</td>
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<td>Lupus erythematosus</td>
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<td>Lichen sclerosus</td>
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<td>Allergic diseases</td>
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<td>Inflammatory diseases</td>
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<td>Miscellaneous diseases</td>
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Table 2 - Dermatological manifestations secondary to nutritional deficiencies (adapted from Caproni et al.) (36).

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Manifestations</th>
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<tbody>
<tr>
<td>Zinc deficiency</td>
<td>Crusty-erythematous-squamous dermatitis localized to periorificial regions, genitals and flexures, associated with diffuse alopecia, stomatitis, balanitis, vulvar, and procatitis</td>
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<tr>
<td>Iron deficiency</td>
<td>Atrophy and dryness, itching, hair loss, atrophic glossitis, angular stomatitis, and koilonychia</td>
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<tr>
<td>Vitamin A deficiency</td>
<td>Pytiriasis rubra pilaris-like</td>
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<tr>
<td>Vitamin B12 and folic acid deficiency</td>
<td>Angular stomatitis, glossitis, and oral mucosa ulcers, hyperpigmentation</td>
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<td>Vitamin PP deficiency</td>
<td>Pellagra</td>
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</table>

References

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