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Case Study

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Small Bowel and Skin: Celiac Disease and Dermatitis Herpetiformis

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Abstract

Dermatitis herpetiformis, also known as Dühring-Brocq disease, is a chronic autoimmune dermatosis that evolves in outbreaks. It is characterized by the presence of small blisters that tend to cluster on the elbows, knees, and buttocks, with a symmetrical distribution and intense itching. It is considered a cutaneous manifestation of celiac disease. It affects young adults (20 to 50 years old). Histopathological examination reveals subepidermal blisters. Direct immunofluorescence is characteristic, showing granular deposits of IgA at the tips of the dermal papillae. Even in the absence of digestive symptoms, celiac disease should be investigated in all patients. A gluten-free diet is the key to treatment. In patients with intense itching or extensive dermatosis, oral dapsone can be used to quickly relieve cutaneous manifestations, but it does not alter the course of the digestive disease. We present a patient in whom the diagnosis of dermatitis herpetiformis was made initially, followed by a diagnosis of celiac disease based on the skin lesions.

Keywords: Dermatitis herpetiformis; Dühring-Brocq disease; Celiac disease; Gluten

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Introduction

Dermatitis herpetiformis (DH) or Dühring-Brocq disease is an autoimmune ampoule disease described by Louis Dühring in 1884. It affects both men and women, with a peak of incidence between 20 and 50 years. It is more common in Caucasian people and very rare among African and Asian populations [1]. In its pathogenesis, genetic, immunological, and environmental factors are involved.

It is considered an expression in the skin of celiac disease (EC). In all patients with DH, EC should be investigated, although most of them do not have digestive symptoms: 75 to 90% are with silent EC, with anti-transglutaminase antibody dosage positive transglutaminase and intestinal biopsy with typical EC injury, in the absence of symptoms [2-4].

The DH-E-E prevail ratio is 1:8. The incidence of DH is in descent, while that of EC, on the rise, probably due to the greater knowledge and recognition of the latter, which allows an early diagnosis and adequate treatment, which determines a lower probability of skin condition [2,3]. This work presents a patient who from the skin lesions was made diagnosis of DH first and subsequently, of celiac disease.

Case Report

A 43-year-old man, without personal history of relevance. He consulted for pruriginous dermatosis of 7 months of evolution, for which he had performed oral treatment with various antihistamines and with corticosteroids at different doses, without response. I did not refer to any other associated symptoms. The dermatological physical examination observed small blisters, erosions, hematical scabs, excoriations and hyperpigmented macules in elbows, scrotum, buttocks, back face of thighs, knees, front and neck (Figure 1 and figure 2). He did not present mucous commitment, palms, plants, or the rest of the tegument. The patient said that dermatosis evolved in outbreaks, with moments of improvement and moments of appearance of new injuries, with a pruritus so intense that the dream made it difficult.

The histopathological study evidenced dermo-epidermal takeoff forming a subepidermal blister, with neutrophil polymorphonuclear leukocytes inside; superficial papillary and reticular dermis with moderate inflammatory infiltrate constituted by neutrophil, eosinophilic and lymphocyte polymorphonuclear, predominantly perivascular disposition.

Direct immunofluorescence was positive for IgA granular deposits in the dermal paps of intensity +++/+++; IgG, IGM and C3 negative. With a diagnosis of DH, laboratory was requested: hemogram, IgA dosage, thyroid profile, and rest of the routine within normal limits; glucose 6 phosphate dehydrogenase 9.4 (VN: 7-20.4); Anti-transglutaminase antibodies IgA 43 (negative: <20), antigliadin antibodies 31 (negative: <20).

In spite of the absence of digestive symptomatology, taking into account dermatosis and the positive result of antigliadin and anti-transglutaminase antibodies, the patient was derived at the gastroenterology service, where ban village was performed: duodenal mucosa with subtotal vill velositarian atrophy and deepening of the crypts (Figure 3 and figure 4); Increase in intraepithelial lymphocytes

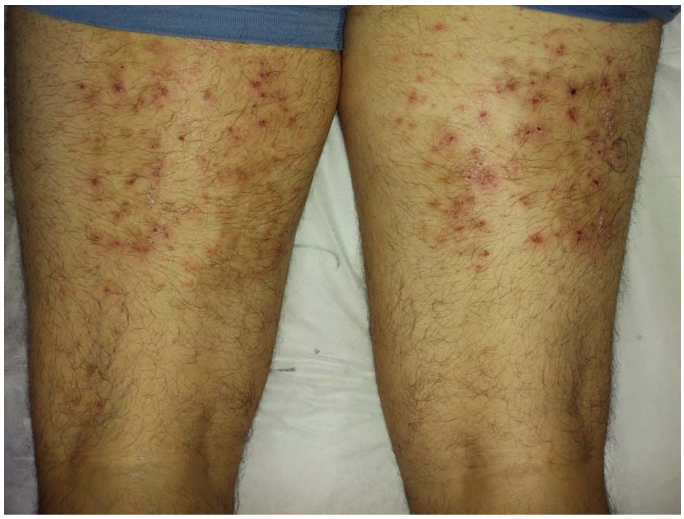

Figure 1: Blisters, erosions, scabs, and excoriations on the back of the thighs.

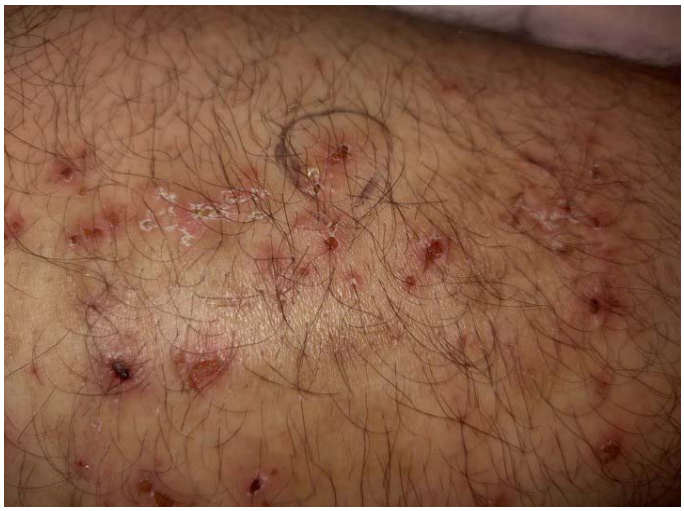

Figure 2: Small blisters, erosions, scabs, excoriations, and hyperpigmented macules.

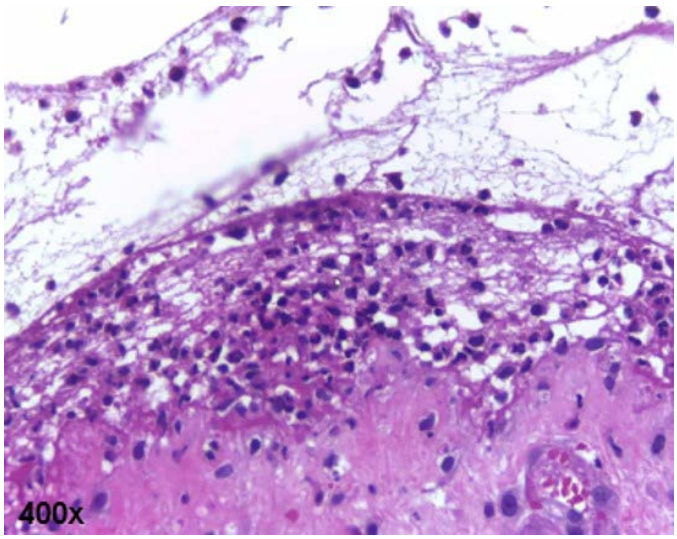

Figure 3: HyE 400 x. Subepidermal blister with neutrophilic polymorphonuclear leukocytes inside; dermis with moderate inflammatory infiltrate filled with polymorphonuclear neutrophils, eosinophils, and lymphocytes.

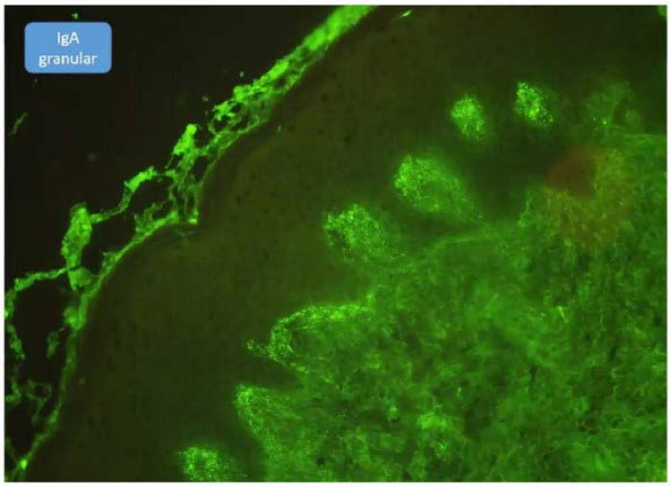

Figure 4: Positive DFI for granular IgA deposits in dermal papillae.

(> 30 lymphocytes every 300 enterocytes); Chorion with vasocony and moderate lymphoplasmocyte infiltrate with eosinophils isolated.

With final diagnosis of DH + celiac disease, gluten-free diet, and treatment with Dapsona 50 mg/day VO was indicated. At 48 h the patient referred to Franco's pruritus. At 3 months, already with the suspended dapsona, complete remission of dermatosis was found.

Discussion

DH is an autoimmune disease triggered by gluten intake. Gluten are proteins present in wheat, oatmeal, barley, and rye, which are transformed into peptides when they are degraded by the action of gastric, pancreatic peptidases and the brush edge of the intestine. There they are de-amined by the action of tissue transglutaminase generating gliadin fragments. These are bound to antigens presenting cells that express the HLA-DQ2 or DQ8 molecules, with the activation of T lymphocytes and cytokine production. It produces tissue damage at the intestinal level, with villi atrophy, inflammation of the mucosa and decreased nutrient absorption.

In addition, B lymphocytes are activated, with the generation of autoantibodies against transglutaminase, known as anti-transglutaminase antibodies Tissular 2 and anti-peptide antibodies of giadin of amazada and anti-endomisio antibodies.

Tissue transglutaminase (TTG2) is autoantigen in EC, while epidermal transglutaminase (ETG or TTG3) is in DH. TTG3 is an enzyme that is expressed physiologically in the epidermis spiny layer and contributes to the terminal epidermal differentiation. Although the main autoantigens differ between both diseases, they have shared epitopes that allow a cross reaction: amino acid conservation is 38% between TTG2 and TTG3, with up to 64% homology in certain regions. After prolonged exposure to gliadin, IgA antibodies are also developed that have low avidity by TTG2 and very high by TTG3 (ANTI TTG3). IgA-TTG3 circulating immune complexes are deposited in the skin, in the dermal papillae. The IGA-TTG3 tank activates the complement and causes infiltration of papillae by activated neutrophils from circulation. Its degranulation releases proinflammatory cytokines (IL-17, IL-36), elastases and granzima B, which increase inflammation and lead to the destruction of the basal membrane, which translates into the formation of ampoules [1,3,4].

Both EC and DH have an important genetic component. Both diseases are strongly related to HLA-DQ2 (86%) and DQ8 (5-10%). However, their presence is considered necessary but not sufficient to develop the disease, since most people HLA-DQ2 or DQ8 positive do not present dermatosis [1,3,4].

In summary, in genetically predisposed individuals (HLA DQ2 and DQ8), gluten intake would stimulate the immune system, with the production of l own skin (DH). From the clinical point of view, DH is characterized by small, intensely pruriginous ampoules, which are distributed symmetrically in the elbows, knees, sacral region and buttocks. These injuries tend to group, acquiring a "herpetiform" appearance. In the most severe cases, the scalp, the neck, the face, and the upper back can also be affected. Intense pruritus is characteristic and can precede the appearance of injuries. Excoriations coexist (scratching lesions), erosions, scabs and hyper or residual hypopigmented macules, which gives the cutaneous picture a polymorphic appearance. Oral manifestations are rare and consist of erosions of the oral and tongue mucosa, associated with pain and ardor. Dermatosis evolves by outbreaks, with remissions and relapses, which resolve without leaving scar [1,2,4].

There is a broad spectrum of pathologies associated with DH: Due to the jugorion linked to the intestinal process, patients with DH are at risk of ferropenic anemia, megaloblastic anemia, osteopenia, and osteoporosis. And due to the alteration of the immune system, patients with DH are at risk of association with other autoimmune diseases, such as Hashimoto thyroiditis, DBT type 1, Sjögren syndrome, pernicious anemia, dermatomyositis, polymiositis, vitiligo, and rheumatoid arthritis.

The association with EC makes patients with DH susceptible to developing neoplasms of the digestive tract, such as intestinal T lymphoma, thin intestine adenocarcinoma and carcinomas of the upper third of the esophagus and pharynx [4,5].

The diagnosis of DH is based on the triad clinical presentation-histopathology-direct directness. The histological findings show edema in the papillary dermis, AME of neutrophils at the tip of the dermal papillae and subepidermal ampoules with neutrophilic content. The IFD is positive for IgA granular deposits in the dermal papillae, in the basal membrane or both, and is pathognomonic and indispensable for diagnostic confirmation [2,5].

The diagnosis of EC is based on serological tests and duodenal biopsy. The measurement of anti-TTG2 antibodies has a high sensitivity (98%) and a good negative predictive value (99%), therefore, the first-line exam for diagnosis is considered. Antindomisio antibodies have a sensitivity close to 100% and a specificity of between 52 and 100%. Both antibodies are IgA type and decrease dramatically with gluten-free diet, so they are very useful not only for diagnosis but also for follow-up [1,3,5].

Due to the possible association with other autoimmune diseases, the determination of antithyroid and antinuclear antibodies, hemogram, blood glucose and thyroid function in the evaluation of patients with DH5 is suggested.

Due to the little knowledge and recognition of the DH, the average time between the appearance of the symptoms and the diagnosis of the entity ranges between 2 and 10 years, with an average of 3.2 years. The main clinical differential diagnoses of DH are atopic dermatitis, scabiosis, eczema, and prurigo [2,5].

The treatment of DH is based on gluten-free diet (DLG) and the use of Dapsona. DLG is the first-line treatment, with which both cutaneous and digestive manifestations are controlled. Despite this, the remission of dermatosis can take between 1 - 2 years. It must be maintained for life, since skin lesions invariably resort within 12 weeks after gluten reintroduction. Only 10 to 20% of patients develop immune tolerance and can consume foods with gluten content without presenting skin lesions or intestinal damage [3-5].

Dapsona is a bacteriostatic that inhibits chemotaxis and reduces tissue damage mediated by neutrophils in lesional sites. It is the drug of choice for the suppression of the symptoms of DH. It is used for 6 to 24 months, until the DLG is effective. It only controls dermatosis but has no effect on enteropathy. Its action is rapid: it relieves the pruritus within 48 - 72 h and resolves skin lesions in days, but they resort 24 - 48 h after treatment interruption. It starts with a low dose (25 - 50 mg/day) to minimize side effects and, if necessary, can be gradually increased to 100 - 200 mg/day. The main adverse effects, hemolytic anemia and methemoglobinemia depend on the dose and are more frequent in patients with comorbidities (anemia, cardiopulmonary disease, and serious hepatopathies) and in patients with glucose-6-phosphate dehydrogenase deficiency. This is why prior to its start; dosing of this enzyme must be requested (the dapsona is contraindicated in individuals with low basal values) [4].

Sulfasalazine, in doses of 1 - 2 g/day, and sulfametoxipiridazine, in doses of 0.25 - 1.5 g/day, are alternatives for the treatment of DH in those patients in whom dapsona is contraindicated. In both, the most common adverse effects are gastrointestinal (nausea, vomiting, and anorexia). Hemolytic anemia and hypersensitivity reactions are less frequent.

It has been described the use of immunosuppressants, such as azathioprine, mofetyl mycophenolate and cyclosporine, and rituximab for the treatment of patients with refractory DH or with contraindication to traditional drugs [4]. Antihistamines and oral corticosteroids are not effective [3].

Conclusion

DH is a chronic autoimmune blister disease, characterized by the presence of intensely prurigine, symmetrical distribution lesions, on members of members (elbows and knees) and buttocks.

It constitutes a cutaneous manifestation of gluten intolerance. 75 - 90% of patients with DH have EC, which is usually asymptomatic. 5 - 10% of patients with poorly controlled EC will develop DH throughout their lives. Gluten-free diet is the treatment pillar for both entities. The oral dapsona collaborates with the resolution of the DH but does not modify the course of the intestinal disease. The recognition of the DH allows us to arrive promptly to the diagnosis of EC and establish a gluten-free diet that modifies the course of the disease and decreases the risk of intestinal neoplasms and other autoimmune diseases.

Acknowledgments

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethics Statement

The work has been approved by the ethics committee responsible in the workplace.

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