Dermatitis herpetiformis as the only manifestation of celiac disease: case report and literature review

Dermatite herpetiforme como única manifestação de doença celíaca: relato de caso e revisão da literatura

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ABSTRACT

Aims: To present a case of dermatitis herpetiformis, a papulovesicular rash due to deposits of immunoglobulin A in the papillary dermis. This is a common extraintestinal manifestation of celiac disease, although rare in childhood.

Case description: A 10-year-old girl was diagnosed with celiac disease, suspected only due to the occurrence of typical lesions of dermatitis herpetiformis. Intestinal biopsy demonstrated total atrophy of duodenal villi in spite of the lack of clinical digestive manifestations. Under a gluten-free diet the patient presented favorable evolution, with regression of cutaneous lesions.

Conclusions: Dermatitis herpetiformis is a common manifestation of celiac disease, but is not frequent in infants. Therefore, is very important to investigate any child that presents a chronic papulovesicular cutaneous eruption non-responsive to usual treatments in order to perform a precocious diagnosis of celiac disease, avoiding its serious repercussions.

KEY WORDS: DERMATITIS HERPETIFORMIS; CELIAC DISEASE; GLUTENS; CHILD.

RESUMO

Objetivos: Apresentar um caso de dermatite herpetiforme, uma erupção cutânea papulovesicular pruriginosa devida ao depósito de imunoglobulina A na derme papilar. Esta é uma manifestação extraintestinal comum da doença celíaca, embora rara na infância.

Descrição do caso: Uma paciente com 10 anos de idade foi diagnosticada com doença celíaca, cuja suspeita surgiu unicamente em decorrência de lesões típicas de dermatite herpetiforme. A biópsia intestinal demonstrou atrofia total das vilosidades duodenais, apesar da ausência de manifestações clínicas digestivas. Com dieta livre de glúten a paciente apresentou evolução favorável, com regressão das lesões cutâneas.

Conclusões: A dermatite herpetiforme é uma manifestação comum da doença celíaca que, no entanto, é infrequente na infância. Por isso, é fundamental alto grau de suspeição em qualquer criança que apresentar uma erupção cutânea papulovesicular crônica não responsiva a medidas simples, a fim de realizar o diagnóstico precoce da doença celíaca, evitando suas graves repercussões.

DESCRITORES: DERMATITE HERPETIFORME; DOENÇA CELÍACA; GLÚTEN; CRIANÇA.

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INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy triggered in genetically susceptible individuals by gluten ingestion. Individuals with this disease have permanent intolerance to the gliadin in fraction of wheat, barley and rye proteins.[1-4] It is the most common feeding intolerance in the occidental population and its estimated prevalence is 0.5% to 1% in the general population and 3 to 13 cases per 1000 children.[1,2,5-9] The CD affects usually Caucasian individuals and women in a 2:1 proportion.[6]

In its classical presentation the beginning of CD symptoms occurs generally in 6 to 24 months old children and is characterized by chronic diarrhea, abdominal pain, abdominal distension, insufficient growth, anorexia and vomiting.[4,6,10] However, many individuals can be asymptomatic and are diagnosed only after years of silent disease.[2,10] Atypical manifestation of CD include extraintestinal changes as iron-deficient anemia, osteoporosis, and cutaneous and neurological manifestations.[2,4,6,11,12] Moreover, patients with diagnosed CD have an increased risk of malignancy, in particular of non-Hodgkin's lymphoma.[13-15]

An occurrence of the association between alterations in the jejune mucosa and the deposit of immunoglobulin A (IgA) in the papillary dermis was described in 1966.[16,17] This pathology was the dermatitis herpetiformis (DH), which is characterized by urticarial bullous lesions (often excoriated by pruritus) associated to gluten-sensitive enteropathy, being symptomatic or asymptomatic.[4,18]

The present study describes the case of a patient with CD diagnosis, suspected due to typical lesions of DH, with favorable evolution with a gluten-free diet, showing regression of cutaneous lesions.

CASE REPORT

A 10 years-old, female patient presented pruritic lesions on the skin with six months of evolution and without response to treatment with corticosteroids and antifungals. Biopsy was performed by a dermatologist with the result compatible with DH, being referred to the pediatric gastroenterologist to rule out a diagnosis of CD. There were no clinical signs and associated symptoms such as weight loss, pain, restricted growth and gastrointestinal manifestations. Family history was negative for CD and previous medical history had no particularities. On physical examination, the patient was in good general condition, afebrile, with height and weight appropriate for age. She presented erythematous lesions on the extensor region of elbows and knees bilaterally (**Figure 1**). No other changes were observed in the physical analysis. Antitransglutaminase IgA value was 80U (referential value 18U). Blood count, hepatic, renal and pancreatic functions had no changes. The patient underwent endoscopy with biopsies taken. Histopathological examination revealed mild chronic esophagitis with intraepithelial eosinophils, mild antral chronic gastritis with negative *Helicobacter pylori* research. Duodenal biopsy revealed increased intraepithelial lymphocyte population, crypts hyperplasia and villi shortening (**Figure 2**).

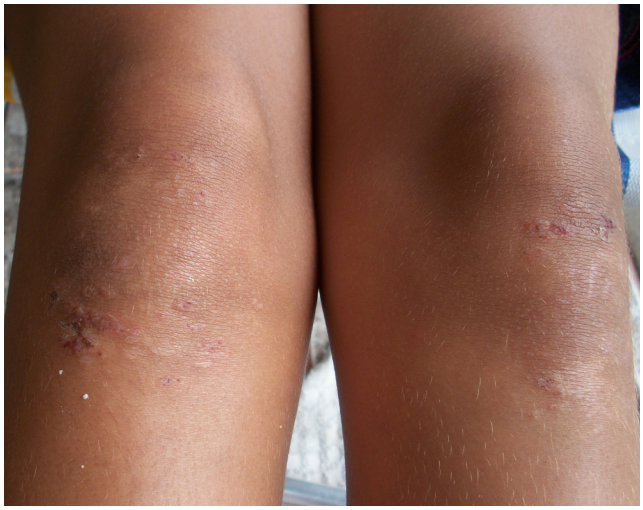

Figure 1. Erythematous and papular lesions with hematic crusts and hypopigmented scars on knees, characteristic of dermatitis herpetiformis.

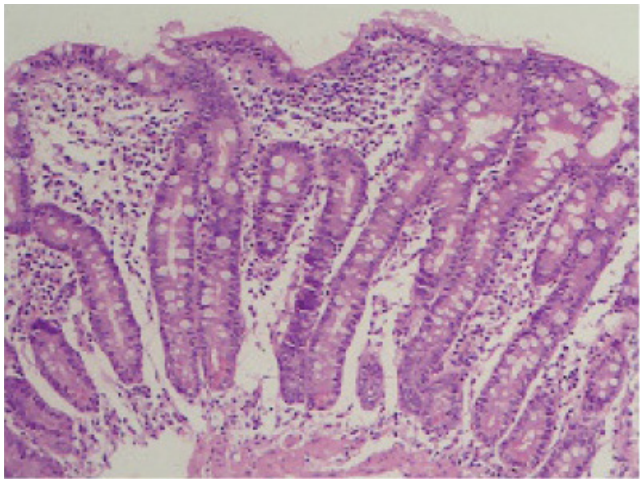

Figure 2. Results of duodenal biopsy showing short villi and long crypts characteristic of celiac disease.

The histopathological and clinical aspects of duodenal biopsy were identified as a category 3B of Marsh-Oberhuber classification for CD. A gluten-free diet was introduced with the confirmed diagnosis. The patient presented favorable clinical evolution with total regression of lesions.

DISCUSSION

DH, also known as Duhring's disease, is a chronic, polymorphous, pruritic skin disease characterized by papulovesicular rash, affecting mainly the extensor surfaces of the body, that may leave areas of hyperpigmentation and scarring.[4,18-21] Certainly variations exist, and bullous, pustular or eczematous lesions can be found sometimes.[22] Lesions are symmetrically distributed and commonly found on elbows, knees and buttocks, but may also occur in the upper back, leather scalp, abdomen, groin and face.[4,9] The average age of diagnosis of DH is 30 to 40 years, with unusual appearance of lesions before puberty. DH affects most commonly males and caucasians.[4,9,19,23-25]

The association of DH with CD was initially described by Marks et al.[16] in 1966, and nowadays the rash of DH appears to represent an external marker of intestinal sensitivity, defined as an extraintestinal manifestation of CD.[4,9,10] Approximately 10% of individuals who have CD manifest lesions of DH, and among individuals with DH, the prevalence of changes compatible with CD by biopsy of the small intestine is 60% to 80%,[9] reaching 93% if the increase of intraepithelial lymphocyte count in intestinal microvilli is considered a diagnostic criteria.[19] However, only 10-20% have classic symptoms of malabsorption.[4,18,21]

The pathogenesis of DH is still unclear, but as in CD, there is an immune response induced by gluten sensitivity.[22,23,26] DH and CD are closely related diseases, in which the main autoantigens are distinct, but share common epitopes.[26] The tissue transglutaminase (tTG) was identified as the autoantigen prevalent in CD,[27] while in the DH, the predominant autoantigen is the epidermal transglutaminase (eTG).[26,28,29] Sardy et al.[26] proposed that the DH pathogenesis consists of immune response of low avidity for tTG, resulting initially in silent CD, that with continued exposure to gliadin, leads to the development of populations of antibodies with high affinity to eTG for cross-reactivity, which manifests as DH. Moreover, as in CD, in which genetic predisposition is associated with the HLADQ2 (allelesDQA1 * 0501 and DQB1 *020) and HLA-DQ8 (DQA1 * 03 alleles and DQB1* 0302), DH presents similar genetic alterations.[30-33]

DH is diagnosed through biopsy of the lesions showing a subepidermal blister with a predominantly neutrophilic infiltrate in the dermal papillary tips, although a mixed or even predominantly lymphocytic dermal infiltrate may also be found.[22] Direct immunofluorescence reveals granular deposition of IgA at the dermo-epidermal junction in both involved and uninvolved skin as well as the oral mucosa.[4,18,19,26] Serologic testing is a useful adjunct for diagnosis and may be used to monitor the therapy response.[29,34] Antigluten, antiendomysium, antigliadin and tTG antibodies have been detected in patients with DH, however, tTG and eTG are considered the target autoantigens in DH.[35] Heil et al.[34] demonstrated that anti-tTG IgA can be useful for screening, because it is very disease-specific (100%) and sensitive (95% CD/96.6% DH) for the diagnosis of gluten sensitivity, while anti-eTG IgA was also very specific (100%), but was present in only 15% of CD cases and 44.8% of DH cases. After the diagnosis of DH, it is necessary to determine who has associated CD. The gold standard for CD diagnosis is biopsy of the intestine, which is recommended for all individuals with DH.[9,10,23]

Treatment for DH, as well as for CD, consists in removing gluten from the diet.[6,8,9,11] Associated with this therapy, suppressive treatments can be used, such as dapsone at a dose of 25-100 mg per day for a short period of time to control local symptoms and reduce the number and severity of skin injuries.[4,9,18,20,23,36]

Table 1. Systematic review of the literature performed on September, 2013

Electronic databases	Key words (MeSH/DeCS)	Results	
		Found	Related
PubMed	"Dermatitis herpetiformis"AND "celiac disease"	669	30
Embase	"Dermatitis herpetiformis" AND "celiac disease"	66	4
Cochrane Library	"Dermatitis herpetiformis" AND "celiac disease"	6	1
Lilacs	"Dermatitis herpetiformis" AND "celiac disease"	12	2
SciELO	"Dermatitis herpetiformis" OR "celiac disease"	70	4

MeSH = Medical Subject Headings; DeCS = Descritores em Ciências da Saúde.

In this patient, diagnosis was suspected due to the typical pattern of injury, being established the gluten-free diet with favorable evolution of skin lesions. DH should be considered in any child who presents chronic papulovesicular rash of unknown origin which is not responsive to simple measures. Its recognition leads to early diagnosis of CD, which is very important considering the great impact that this disease may present.

REFERENCES

1. Cataldo F, Pitarresi N, Accomando S, Greco L. Epidemiological and clinical features in immigrant children with coeliac disease: an Italian multicentre study. Dig Liver Dis. 2004;36(11):722-9.
2. Imanzadeh F, Sayyari AA, Yaghoobi M, Akbari MR, Shafagh H, Farsar AR. Celiac disease in children with diarrhea is more frequent than previously suspected. J Pediatr Gastroenterol Nutr. 2005;40(3):309-11.
3. McGough N, Cummings JH. Coeliac disease: a diverse clinical syndrome caused by intolerance of wheat, barley and rye. Proc Nutr Soc. 2005;64(4):434-50.
4. Abenavoli L, Proietti I, Leggio L, Ferrulli A, Vonghia L, Capizzi R, Rotoli M, Amerio PL, Gasbarrini G, Addolorato G. Cutaneous manifestations in celiac disease. World J Gastroenterol. 2006;12(6):843-52.
5. Gandolfi L, Pratesi R, Cordoba JC, Tauil PL, Gasparin M, Catassi C. Prevalence of celiac disease among blood donors in Brazil. Am J Gastroenterol. 2000;95(3):689-92.
6. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2005;40(1):1-19.
7. Schippa S, Iebba V, Barbato M, Di Nardo G, Totino V, Checchi MP, Longhi C, Maiella G, Cucchiara S, Conte MP. A distinctive 'microbial signature' in celiac pediatric patients. BMC Microbiology. 2010;10:175.
8. Tack GJ, Verbeek WH, Schreurs MW, Mulder CJ. The spectrum of celiac disease: epidemiology, clinical aspects and treatment. Nat Rev Gastroenterol Hepatol. 2010;7(4):204-13.
9. Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. Am J Clin Dermatol. 2003;4(1):13-20.
10. Dahlbom I, Korponay-Szabó IR, Kovács JB, Szalai Z, Mäki M, Hansson T. Prediction of clinical and mucosal severity of coeliac disease and dermatitis herpetiformis by quantification of IgA/IgG serum antibodies to tissue transglutaminase. J Pediatr Gastroenterol Nutr. 2010;50(2):140-6.
11. Presutti RJ, Cangemi JR, Cassidy HD, Hill DA. Celiac disease. Am Fam Physician. 2007;76(12):1795-802.
12. Brar P, Kwon GY, Egbuna II, Holleran S, Ramakrishnan R, Bhagat G, Green PH. Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. Dig Liver Dis. 2007;39(1):26-9.
13. Anderson LA, McMillan SA, Watson RG, Monaghan P, Gavin AT, Fox C, Murray LJ. Malignancy and mortality in a population-based cohort of patients with celiac disease or 'gluten sensitivity'. World J Gastroenterol. 2007;13:146-51.
14. Askling J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology. 2002;123:1428-35.
15. Grainge MJ, West J, Solaymani-Dodaran M, Card TR, Logan RFA. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: a cohort study. Aliment Pharmacol Ther. 2012;35:730-9.
16. Marks J, Shuster S, Watson AJ. Small-bowel changes in dermatitis herpetiformis. Lancet. 1966;2(7476):1280-2.
17. Shuster S, Watson AJ, Marks J. Coeliac syndrome in dermatitis herpetiformis. Lancet. 1968;1(7552):1101-6.
18. Oxentenko AS, Murray AJ. Celiac disease and dermatitis herpetiformis: the spectrum of gluten-sensitive enteropathy. Int J Dermatol. 2003;42(8):585-7.
19. Alonso-Llamazares J, Gibson LE, Rogers RS 3rd. Clinical, pathologic, and immunopathologic features of dermatitis herpetiformis: review of the Mayo Clinic experience. Int J Dermatol. 2007;46(9):910-9.
20. Mendes FBR, Hissa-Elian A, Abreu MAMM, Gonçalves VS. Review: dermatitis herpetiformis. An Bras Dermatol. 2013;88(4):594-9.
21. Zone JJ. Skin manifestations of celiac disease. Gastroenterology. 2005;128:S87-91.
22. Cardones AR, Hall RP 3rd. Pathophysiology of Dermatitis Herpetiformis: A Model for Cutaneous Manifestations of Gastrointestinal Inflammation. Immunol Allergy Clin N Am. 2012;32:263-74.
23. Lemberg D, Day AS, Bohane T. Coeliac disease presenting as dermatitis herpetiformis in infancy. J Paediatr Child Health. 2005;41(5-6):294-6.
24. Weston WL, Morelli JG, Huff JC. Misdiagnosis, treatments, and outcomes in the immunobullous diseases in children. Pediatr Dermatol. 1997;14(4):264-72.
25. Salmi TT, Hervonen K, Kautiainen H, Collin P, Reunala T. Prevalence and incidence of dermatitis herpetiformis: a 40-year prospective study from Finland. Br J Dermatol. 2011;165(2):354-9.
26. Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. J Exp Med. 2002;195(6):747-57.
27. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, Schuppan D. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3(7):797-801.
28. Jaskowski TD, Donaldson MR, Hull CM, Wilson AR, Hill HR, Zone JJ, Book LS. Novel screening assay performance in pediatric celiac disease and adult dermatitis herpetiformis. J Pediatr Gastroenterol Nutr. 2010;51(1):19-23.
29. Jaskowski TD, Hamblin T, Wilson AR, Hill HR, Book LS, Meyer LJ, Zone JJ, Hull CM. IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis and pediatric celiac disease. J Invest Dermatol. 2009;129(11):2728-30.

30. Karell K, Korponay-Szabo I, Szalai Z, Holopainen P, Mustalahti K, Collin P, Mäki M, Partanen J. Genetic dissection between coeliac disease and dermatitis herpetiformis in sib pairs. Ann Hum Genet. 2002;66(5-6): 387-92.
31. Mowat AM. Coeliac disease: a meeting point for genetics, immunology, and protein chemistry. Lancet. 2003;361(9365):1290-2.
32. Hervonen K, Karell K, Holopainen P, Collin P, Partanen J, Reunala T. Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. J Invest Dermatol. 2000;115(6):990-3.
33. Koop I, Ilchmann R, Izzi L, Adragna A, Koop H, Barthelmes H. Detection of autoantibodies against tissue transglutaminase in patients with celiac disease and dermatitis herpetiformis. Am J Gastroenterol. 2000;95(8):2009-14.
34. Marietta EV, Camilleri MJ, Castro LA, Krause PK, Pittelkow MR, Murray JA. Transglutaminase Autoantibodies in Dermatitis Herpetiformis and Celiac Sprue. J Invest Dermatol. 2008;128(2):332-5.
35. Heil PM, Volc-Platzer B, Karlhofer F, Gebhart W, Huber WD, Benesch T, Vogelsang H, Stingl G. Transglutaminases as diagnostically relevant autoantigens in patients with gluten sensitivity. J Dtsch Dermatol Ges. 2005;3(12):974-8.