CASE REPORT

Skin and coeliac disease, a lot to think about: a case series

Sara O. Vaz,¹ Catarina Franco,¹ Patrícia Santos,² Raquel Amaral¹

¹Pediatric Department, Hospital of Divino Espírito Santo of Ponta Delgada, Ponta Delgada - São Miguel, Azores, Portugal

²Dermatology Department, Hospital of Divino Espírito Santo of Ponta Delgada, Ponta Delgada - São Miguel, Azores, Portugal

Correspondence to

Dr Sara O. Vaz,
sara_vaz@msn.com

Accepted 12 December 2017

SUMMARY

Coeliac disease (CD) is an autoimmune disease, characterised by a permanent sensitivity to gluten. It is being progressively recognised as a multisystemic disease, with multiple extraintestinal manifestations. Skin conditions (eg, dermatitis herpetiformis) are an example of its manifestations; however, its underlying mechanisms are still not well understood. This article presents three cases of uncommon skin conditions in patients with a history of CD. Two of them concern linear IgA bullous dermatosis and erythema nodosum, which have been described in the literature as having potential associations with CD, though only a few cases were reported. The third case corresponds to pityriasis lichenoides—a rare lymphoproliferative disorder of unknown aetiology—, which has no correlation with CD in the literature reviewed. The authors aim to draw attention to the possibility of CD as a potential predisposing factor for the occurrence of these skin diseases.

BACKGROUND

Coeliac disease (CD) is an immune-mediated enteropathy that is characterised by a permanent sensitivity to gluten in genetically predisposed people.¹ It is estimated to affect 1 in every 100 inhabitants of the Western Hemisphere, with a highly variable cluster of symptoms.² The pathophysiology of the disease is still unclear; however, there is a strong association with HLA (Human leukocyte antigen) phenotypes, A1, B8, DR3, DR7 and particularly DQ2 (approximately 95% of the cases) and DQ8 (the remainder).^{3–5} Other autoimmune disorders, such as thyroid disease, type I diabetes and rheumatoid disease, share these alleles with CD, demonstrating that this disease is not an isolated event, but part of a bigger spectrum.^{2 6 7}

Gastrointestinal manifestations are the classic symptoms of this disease. Nonetheless, its presentation can often be misleading and largely variable, which is why it is important to be aware of extraintestinal manifestations.^{8 9} Numerous reports linking skin conditions to CD have been published over the last few years, especially about dermatitis herpetiformis (DH).⁷ For this reason, nowadays, it is well established that DH was not merely associated with CD, but formerly a cutaneous manifestation of this disease.¹⁰ Other skin disorders (eg, linear IgA bullous dermatosis (LABD), vitiligo and dermatomyositis, among others) might have an association with CD (the evidence is very scarce), yet there are

few cases reported and a pathogenic link was not effectively demonstrated.^{9 11–13}

The aim of this article is to draw attention for CD as a multisystemic disease, focusing on extraintestinal manifestations, particularly cutaneous. Therefore, we report three cases of rare conditions—LABD, erythema nodosum (EN) and pityriasis lichenoides (PL)—with a possible association with CD. To our knowledge, this is the first article in which PL and CD occur in the same patient.

CASE PRESENTATION

Case 1

A 10-year-old boy presented to the emergency department with 2–3 days' history of painful skin nodules. He also had a dry cough, but no fever, weight loss, anorexia, decreased activity or other symptoms. The child did not present an infectious context or recent travel history. His immunisations were up-to-date.

His medical history revealed a CD diagnosed at 2 years. His caregivers mentioned that in the past few months, he had been eating gluten. His family history was unremarkable.

On physical examination, the child was well appearing, afebrile and haemodynamically stable. It was possible to identify several nodular, painful, erythematous violaceous lesions over the arms and lower extremities (figure 1). There were no visible any other changes on physical examination.

The patient was admitted to general paediatric service. Laboratory evaluation and chest radiograph were performed, in order to find an aetiology.

Case 2

A 4-year-old girl presented to the emergency department with a 5-day history of a non-pruritic bullous eruption. It had started as a macular skin rash in the upper left limb. Subsequently, it had quickly progressed to a bullous rash and spread to the other members, gluteum and lumbar region. The review of symptoms was otherwise negative.

The mother stated a history of paronychia, 15 days before the beginning of the cutaneous eruption, treated with topic fusidic acid.

Her medical history included hydrocephaly caused by partial stenosis of Sylvius aqueduct (currently stabilised) and CD diagnosed at the age of 2 years. She was fully vaccinated. The child's family history revealed an aunt with an autoimmune disease of unknown aetiology.

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To cite: Vaz SO., Franco C, Santos P, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222797

Figure 1 Multiple erythematous violaceous nodules on the lower leg.

On physical examination, the girl was afebrile, eupneic on room air and haemodynamically stable. Widespread skin blisters were present, more pronounced on the extremities, buttocks and lumbar region ([figure 2](#)). The fourth finger presented inflammatory signs, with purulent exudate. Nikolsky's sign was negative. Her neurological examination yielded unremarkable results. The remainder of the examination was normal.

Bullous impetigo was assumed as the major hypothesis, and she was hospitalised. Laboratory studies, blood cultures and exudate cultures were obtained.

Case 3

A 13-year-old boy presented a 1-year history of an intensely pruritic skin rash located on the trunk, members and face. He denied any type of pain, fever or other symptoms.

There were no sick contacts, and no one else in the family manifested a skin rash. He had a known history of CD with

Figure 2 Linear IgA bullous dermatosis affecting the lumbar region.

sporadic transgression of gluten-free diet. Family history was unremarkable.

On presentation, he appeared well. His skin was diffusely pruritic and presented a macular, erythematous, desquamative rash ([figure 3](#)). Abdomen was soft and tender, without organomegaly. The rest of the physical examination was within normal parameters.

He was then referred to a dermatologist who suspected on lichenoid dermatitis. Therefore, he underwent a routine laboratory evaluation, as well as, a cutaneous biopsy.

INVESTIGATIONS

Case 1

The routine laboratory exams and chest radiographs were normal. Serologies (herpesvirus, viral hepatitis, *Yersinia enterocolitica* and *Mycoplasma pneumoniae*), Mantoux test, faeces culture, *Streptococcus* in oropharynx and rotavirus and adenovirus in faeces came negative. ASCA (Anti-saccharomyces cerevisiae antibodies) and ANCA (Anti-neutrophil cytoplasmic antibodies) were also negative. Nonetheless, the antitransglutaminase antibodies were elevated (IgA antitransglutaminase 36 U/mL and IgG antitransglutaminase 25 U/mL).

Case 2

The child's complete cell count was normal and had negative inflammatory parameters. The blood and exudate cultures were negative. After exclusion of bullous impetigo, a dermatological observation was requested. Regarding the clinical history and findings on physical examination, the suspicion of LABD/DH was raised. Therefore, a cutaneous biopsy of the lesions

Figure 3 Pityriasis lichenoides rash on the abdomen.

was performed, suggesting an LABD. This diagnostic was then confirmed by direct immunofluorescence.

She did not present positive CD antibodies, and the screening for glucose-6-phosphate dehydrogenase deficiency was normal.

Case 3

The results of laboratory screening were normal. Serum coeliac antibodies revealed 51.7 U/mL IgA antitransglutaminase, >200 U/mL IgG antitransglutaminase and positive antiendomysial antibody. The cutaneous biopsy revealed a diagnosis of PL chronica.

DIFFERENTIAL DIAGNOSIS

Case 1

EN could be confounded with other forms of panniculitis, such as subcutaneous infections, nodular vasculitis or superficial thrombophlebitis.

Case 2

The onset and quick widespread of annular blisters is typical of LABD. However, other disorders can mimic and share similar clinical features, such as DH, pemphigoid bullous, bullous impetigo and bullous lupus erythematosus.

Case 3

The differential diagnosis of PL must include other disorders with the same cutaneous characteristics, such as PL et varioliformis acuta, pityriasis rosea, guttate psoriasis, lichen planus, secondary syphilis, lymphomatoid papulosis and hypopigmented mycosis fungoides.

TREATMENT

Case 1

He started an anti-inflammatory medicine (ibuprofen), bed rest and a strict gluten-free diet.

Case 2

She was initially treated with a course of 7 days of intravenous antibiotics (amoxicillin-clavulanic acid). On the fifth day of antibiotic therapy, the girl started a treatment with potassium permanganate 1/10 000 and oral dapsone 1 mg/kg/day, given the normal levels of glucose-6-phosphate dehydrogenase.

Case 3

The boy was treated with a topical corticosteroid and a course of antibiotic (doxycycline, 40 mg). He was advised a strict gluten-free diet.

OUTCOME AND FOLLOW-UP

Case 1

When the treatment was started, the lesions begun to vanish, and after a few weeks, it was not possible to identify any cutaneous lesion. This episode did not occur again. He is currently well and accomplished his diet goals.

Case 2

During the first 5 days of hospitalisation with antibiotic therapy, no improvement was seen. Nonetheless, after initiating treatment with dapsone and potassium permanganate, the lesions started to ameliorate and gradually disappeared.

Presently, she did not manifest recurring episodes of the cutaneous disease. The girl maintains a gluten-free diet.

Case 3

The boy was symptom-free after treatment institution. Although the adolescent had accomplished a gluten-free diet for the first months, he continued to have recurring episodes of cutaneous disease, though in smaller extension. This recrudescence was controlled with topical corticosteroids.

Nowadays, the adolescent continues to have sporadic transgression of gluten-free diet and maintains skin relapses. He is being regularly accompanied in ambulatory care (dermatological and gastroenterological consultations).

DISCUSSION

Cutaneous manifestations of CD, other than DH, are poorly known. Nonetheless, growing evidence supports the link between CD and several skin disorders.¹⁴

EN is a chronic panniculitis and is thought to be a consequence of an allergic reaction to an antigen or a reaction mediated by immune complexes. In CD, there is an altered permeability, thereby this reaction can persist for several weeks or months, depending on antigen stimulation.^{14 15} As it was shown in the first case, removing the implicated antigen (in this case presumably gluten, but we cannot exclude other antigens as possible causes) was the proper treatment for this condition. Therefore, we can hypothesise the causative link between CD and EN, like it was formulated in previous reports.¹⁴⁻¹⁷ It is also important to do a careful assessment and exclude other diseases that could originate this condition (infections, inflammatory bowel disease, sarcoidosis and lymphomas), which was also made in this report.¹⁵⁻¹⁸ Still, the physiopathology of EN remains obscure, and in many situations, it is impossible to find a cause.¹⁶⁻¹⁸

LABD is characterised by the linear deposition of IgA along the lamina lucida or in the sub-basal lamina area of stratified squamous epithelium.¹⁴ This disorder shares common haplotypes (A1, B8 and DR3) with DH, a well-established manifestation of CD.^{3 9 14} It is also known that LABD is often linked to malignancy, particularly lymphoma, a common complication of CD.⁷ LABD was not the first clinical hypothesis on case 2; however, given the personal background of CD, the clinical presentation and the evolution, it made sense to include it in the differential diagnosis. Thereby, even though there are only a few cases reported in the literature, we suggest that these two diseases are probably connected and that CD might be the predisposing factor that triggered this disorder.^{9 11 14 19}

PL is a rare cutaneous disease, with an unknown aetiology.²⁰ The pathogenesis is not well understood, but three theories were created in order to explain it. The first theory implicates infections (Epstein-Barr virus or *Toxoplasma gondii*) as the triggers of PL.^{21 22} The second includes PL as a primary lymphoproliferative

disorder, based on studies with detection of clonal CD4+ T cell populations in patients with the disease.²³ This last concept supports the link between PL and CD, since CD is presumed to be caused by and enhanced reactivity of CD4+ T cells to gluten.⁶ The third theory is based on the hypothesis of a hypersensitivity to immune complexes, which is related to the presence of circulating immune complexes in PL and also occurs in CD.^{6,24} We cannot assume a cause-effect relationship between these two entities, but we can think of a common underlying mechanism that can interfere with each other. Moreover, this report (case 3) opens the door to an eventual link between these two diseases.

Therefore, we aim to highlight CD as a multisystemic disorder, to reflect about its multiple clinical manifestations and about other diseases that can occur in association. An accurate clinical history is the most important weapon, prompting an early recognition of the disease and its potential comorbidities/complications. Even though unclear, the underlying mechanism of CD could also predispose to the manifestation of these cutaneous diseases. Thus, presuming the existence of a causative link, it seems plausible to propose a screening for CD in patients with refractory LABD, EN or, in a lesser degree, with PL. We also reinforce the importance of a strict gluten-free diet in these patients, if CD diagnosis is reached.

Nevertheless, more studies are needed in order to correctly establish this association.

Learning points

- Recognise coeliac disease (CD) as an autoimmune disease and its diverse extraintestinal manifestations, namely cutaneous.
- Highlight the potential association between CD and erythema nodosum and IgA linear bullous dermatosis.
- First known hypothesis of an eventual link between pityriasis lichenoides (PL) and CD in the same patient.
- Reinforce the importance of a strict gluten-free diet in order to prevent the recrudescence of CD and perhaps the manifestation of erythema nodosum, linear IgA bullous dermatosis or PL in patients with a history of CD.

Acknowledgements We are deeply grateful to all of the clinicians from Hospital do Divino Espírito Santo de Ponta Delgada who were involved in the patient care. We are also thankful to Dr Beatriz Fraga for all the support.

Contributors All authors were involved in the patient care and contributed to the conception, design, acquisition, analysis and interpretation of data. SOV drafted and revised the article. CF, PS and RA revised it critically for important intellectual content. All authors read and gave final approval for the version to be published.

Competing interests None declared.

Patient consent Guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Schuppan D. Current concepts of celiac disease pathogenesis. *Gastroenterology* 2000;119:234–42.
- 2 Wijmenga C, Gutierrez-Achury J. Celiac disease genetics: past, present and future challenges. *J Pediatr Gastroenterol Nutr* 2014;59(Suppl 1):S4–7.
- 3 Poon E, Nixon R. Cutaneous spectrum of coeliac disease. *Australas J Dermatol* 2001;42:136–8.
- 4 Koning F. Celiac disease: caught between a rock and a hard place. *Gastroenterology* 2005;129:1294–301.
- 5 Jabri B, Sollid LM. Tissue-mediated control of immunopathology in coeliac disease. *Nat Rev Immunol* 2009;9:858–70.
- 6 Troncone R, Discepolo V. Celiac disease and autoimmunity. *J Pediatr Gastroenterol Nutr* 2014;59(Suppl 1):S9–S11.
- 7 Humbert P, Pelletier F, Dreno B, et al. Gluten intolerance and skin diseases. *Eur J Dermatol* 2006;16:4–11.
- 8 Volta U, Villanacci V. Celiac disease: diagnostic criteria in progress. *Cell Mol Immunol* 2011;8:96–102.
- 9 Caproni M, Bonciolini V, D'Errico A, et al. Celiac disease and dermatologic manifestations: many skin clue to unfold gluten-sensitive enteropathy. *Gastroenterol Res Pract* 2012;2012:1–12.
- 10 Collin P, Reunala T. Recognition and management of the cutaneous manifestations of celiac disease: a guide for dermatologists. *Am J Clin Dermatol* 2003;4:13–20.
- 11 Egan CA, Smith EP, Taylor TB, et al. Linear IgA bullous dermatosis responsive to a gluten-free diet. *Am J Gastroenterol* 2001;96:1927–9.
- 12 Rodríguez-García C, González-Hernández S, Pérez-Robayna N, et al. Repigmentation of vitiligo lesions in a child with celiac disease after a gluten-free diet. *Pediatr Dermatol* 2011;28:209–10.
- 13 Buderus S, Wagner N, Lentze MJ. Concurrence of celiac disease and juvenile dermatomyositis: result of a specific immunogenetic susceptibility? *J Pediatr Gastroenterol Nutr* 1997;25:101–3.
- 14 Abenavoli L, Proietti I, Leggio L, et al. Cutaneous manifestations in celiac disease. *World J Gastroenterol* 2006;12:843–52.
- 15 Zone JJ. Skin manifestations of celiac disease. *Gastroenterology* 2005;128:S87–S91.
- 16 Bohn S, Büchner S, Itin P. [Erythema nodosum: 112 cases. Epidemiology, clinical aspects and histopathology]. *Schweiz Med Wochenschr* 1997;127:1168–76.
- 17 Bartyk K, Várkonyi A, Kirschner A, et al. Erythema nodosum in association with celiac disease. *Pediatr Dermatol* 2004;21:227–30.
- 18 Chowanec M, Starba A, Wiland P. Erythema nodosum - review of the literature. *Reumatologia* 2016;54:79–82.
- 19 Daoud W, El Euch D, Mokni M, et al. [Linear IgA bullous dermatosis associated with celiac disease]. *Ann Dermatol Venerol* 2006;133:588–9.
- 20 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006;55:557–72.
- 21 Nassef NE, Hammam MA. The relation between toxoplasmosis and pityriasis lichenoides chronica. *J Egypt Soc Parasitol* 1997;27:93–9.
- 22 Klein PA, Jones EC, Nelson JL, et al. Infectious causes of pityriasis lichenoides: a case of fulminant infectious mononucleosis. *J Am Acad Dermatol* 2003;49:151–3.
- 23 Vonderheid EC, Kadin ME, Gocke CD. Lymphomatoid papulosis followed by pityriasis lichenoides: a common pathogenesis? *Am J Dermatopathol* 2011;33:835–40.
- 24 Fernandes NF, Rozdeba PJ, Schwartz RA, et al. Pityriasis lichenoides et varioliformis acuta: a disease spectrum. *Int J Dermatol* 2010;49:257–61.

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