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PRURIGO PIGMENTOSA INDUCED BY THE KETOGENIC DIET

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Abstract: ***Introduction****: Prurigo pigmentosa, also called Nagashima disease or "keto-rash", is a rare inflammatory skin condition. The etiology is unknown, but conditions associated with ketosis (fasting, diabetes, post-bariatric surgery) often accompany this rash.*
Clinical case*: A 13-year-old patient with no significant pathological history, overweight, on a ketogenic diet, was consulted for maculo-papular skin lesions and erythematous plaques, discretely pruritic, persistent, confluent, with centrifugal extension, located at the posterior cervical, axillary, laterothoracic, epigastric and lumbar regions. Hematological, biochemical and immunological investigations were normal. Initial therapy with medium-potency topical corticosteroid and anti-H1 antihistamine was ineffective, instead, under treatment with doxycycline and giving up the ketogenic diet, the resolution of the lesions was obtained, residual hyperpigmentation with a reticulated pattern persisting.*
Conclusions*: We present this case to highlight the increasingly common association between prurigo pigmentosa and the ketogenic diet. Dermatologists should identify the relationship between the timing of rash onset and resolution in relation to diet, with a view to early diagnosis and treatment with optimal patient outcomes.*

Key words: *ketogenic diet, prurigo pigmentosa, Nagashima disease.*

1. Introduction

Prurigo pigmentosa (PP), also called Nagashima disease or "keto-rash", is a rare inflammatory skin condition first described in 1971 [1]. PP usually occurs in Asian women of childbearing age, but in recent years it has been increasingly diagnosed in individuals of other non-Asian populations [2-4]. PP is characterized by pruritic papulovesicles and erythematous plaques, usually

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symmetrically distributed on the trunk and neck, confluent and healing with a reticulated hyperpigmentation. The etiology of PP is unknown, but conditions associated with ketosis (fasting, diabetes, post-bariatric surgery) often accompany this rash. We present the case of a 13-year-old Caucasian patient with ketogenic diet-induced PP.

2. Clinical case

A 13-year-old patient, without significant pathological history, without any previous medication, overweight, following a ketogenic diet for 3 months, was consulted for maculo-papular skin lesions and erythematous plaques, mildly pruritic, persistent for 2 weeks, initially with laterothoracic and anterior thoracic localization (fig. 1-2).

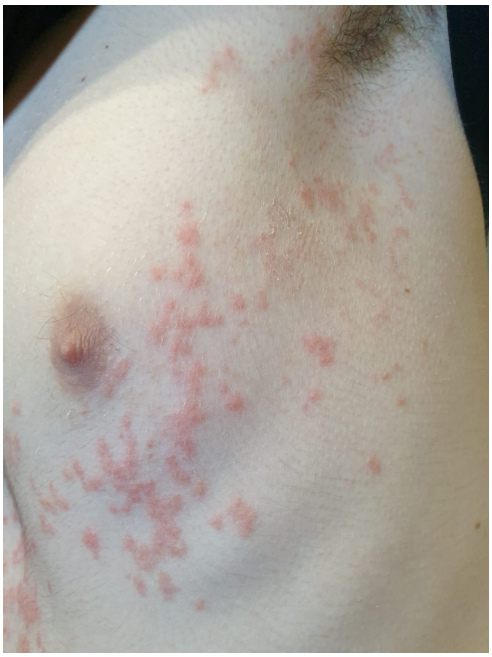

Fig. 1. *Erythematous plaques with laterothoracic and anterior thoracic localization*

At the onset, being interpreted as an allergic contact dermatitis, therapy with a medium-potency topical corticosteroid and anti-H1 antihistamine was ineffective, with existing lesions having a centrifugal extension and a tendency to confluence, and new lesions appearing in the posterior cervical and lumbar areas (fig. 3).

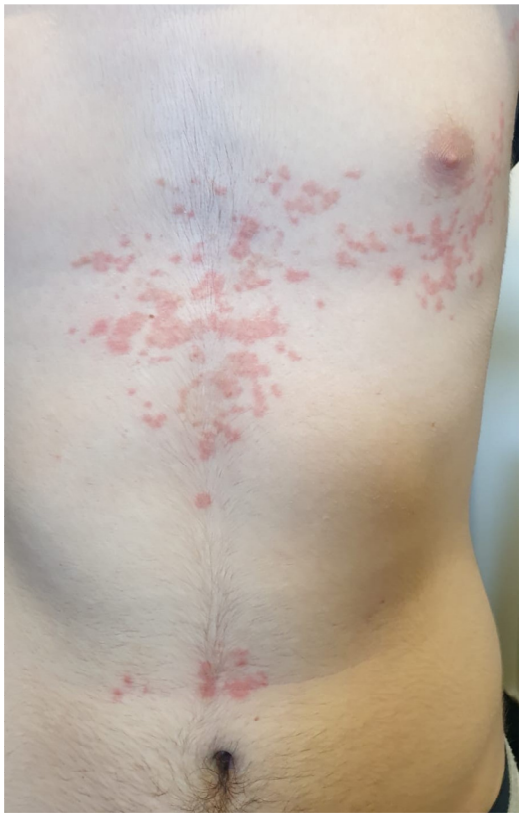

Fig. 2. *Erythematous plaques with anterior thoracic localization*

Hematological, biochemical and immunological investigations (ANA, c3, anti-Ro, anti-La) were normal except for a low blood glucose value (58 mg/dl). Ketone bodies (2+, normal negative) were detected in the urine biochemical examination. The patient refused the skin biopsy. After the clinical elucidation of the diagnosis, under treatment with

doxycycline 100 mg per day for 30 days and giving up the ketogenic diet, the resolution of the lesions was achieved, residual hyperpigmentation with a reticulated pattern persisting (fig. 4-5).

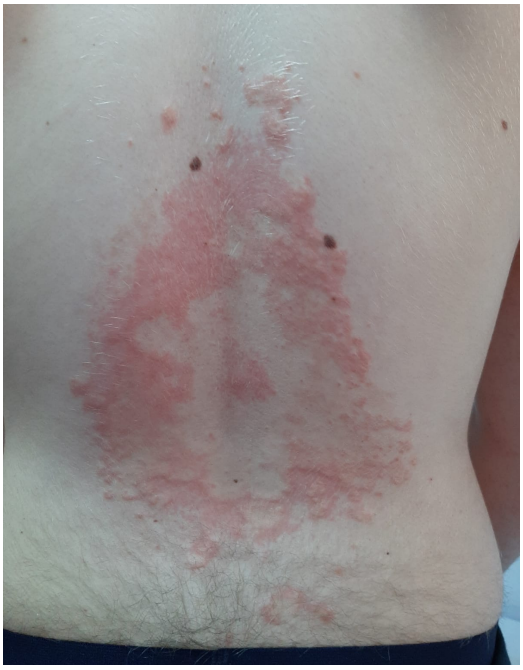

Fig. 3. *Erythematous plaques in lumbar area*

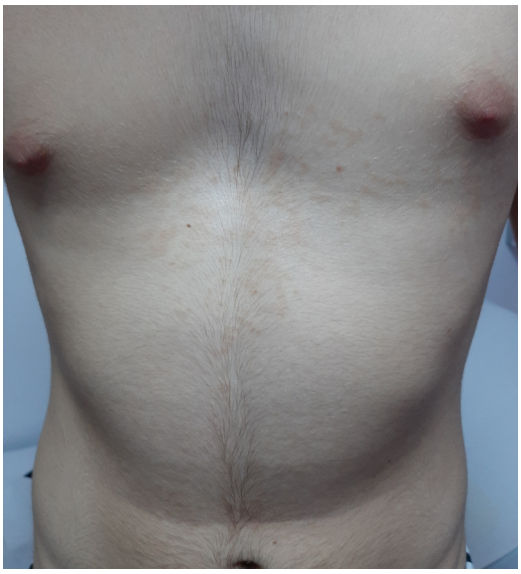

Fig. 4. *Residual hyperpigmentation with a reticulated pattern on anterior thoracic area*

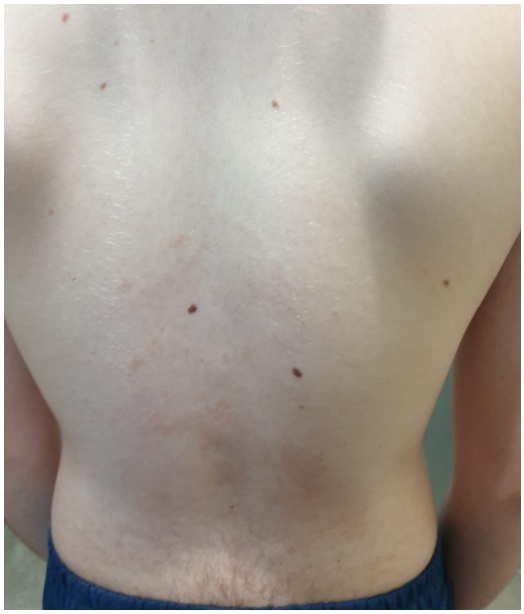

Fig. 5. *Residual hyperpigmentation with a reticulated pattern on lumbar area*

3. Discussions

PP has been reported most often in Japanese patients, and only sporadically in other areas of the world, reflecting underreporting or misdiagnosis rather than a genetic predilection for the Asian populations [5]. PP occurs most commonly in women in their third decade of life, with a female-to-male ratio of 2-4:1. [5] Seasonal clustering of PP cases has been reported, especially in spring and summer. All cases were sporadic, no familial aggregation was observed [6].

PP has a sudden onset, with pruritic erythematous macules and urticaria-like papules and plaques converging in a reticulated pattern. Pustular and bullous variants have also been reported. [6] In the late-stage scales may appear. Although resolution of PP lesions is achieved within one to several weeks, residual post-inflammatory pigmentation with a reticulated pattern may persist for

months [7]. PP usually has a symmetrical distribution, with a predilection for the posterior cervical area, anterior thorax, upper back, lumbosacral region, and abdomen. Asymmetric forms with unilateral or segmental distribution have also been reported [8-9]. Involvement of mucous membranes, nails and hair has not been observed. Recurrences are possible and may occur months or years after the initial presentation [10]. Our patient presented a minor relapse in the axilla after one year.

Although the etiology of PP is unknown, various triggers have been identified: mechanical (friction with clothing, acupuncture), hormonal (pregnancy, menstruation) and metabolic (weight loss, diabetes, anorexia nervosa, bariatric surgery). Other possible aggravating factors include: hypersweating, heat, sunlight and contact allergens [5], [11].

Patients with diabetes, anorexia nervosa, post-bariatric surgery or those following a ketogenic diet for weight loss may be at risk of developing PP. In recent years there has been an increase in PP cases worldwide with the rise in popularity of the ketogenic diet [12]. The ketogenic diet is a very low-carb, moderate-protein, high-fat diet that limits carbohydrate intake to less than 50 grams per day. The goal of ketogenic diet is to induce a metabolic state that mimics starvation and promotes the breakdown of fat into ketone bodies as an alternative source of energy, resulting in the claimed benefits of weight loss and reduced risk of cardiovascular disease and type 2 diabetes [12, 13]. In these metabolic changes, low blood glucose or insulin levels stimulate hepatic synthesis of ketones, leading to increased levels of plasmatic and urine ketone bodies. It is assumed that ketone bodies accumulate around blood vessels, inducing perivascular neutrophilic inflammation. Consequently, treatment with cyclins may be partially effective because they inhibit chemotaxis of neutrophils [14].

A lot of evidence supports a link between the host immunity and intestinal microbiome. Intestinal dysbiosis, because of nutritional and other environmental factors, may play a role in the pathogenesis of PP, and changing the profile of the intestinal microbiome through the use of antibiotics or diet would change the immune response.

The proposed pathogenic mechanism of PP would be a neutrophil-mediated inflammation triggered by environmental and metabolic factors, but the role of ketoacidosis is frequently supported. [15] Ketone bodies are thought to accumulate around blood vessels, leading to a predominantly neutrophilic inflammation. Ketones subsequently enter the cells, leading to changes in intracytoplasmic cellular processes [16]. According to Hartman et al., the increased level of ketone bodies increases the expression of intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen 1 (LFA-1), a phenomenon also observed in lesional keratinocytes of PP, thus linking ketosis with skin inflammation [17]. Resumption of a balanced diet or initiation of insulin therapy reduced ketone levels and resolved lesions, whereas an increase in ketone levels was associated with PP recurrence [18-19].

The histopathological features of PP are nonspecific and depend on the stage of the disease. The early stage is characterized by a perivascular neutrophilic infiltrate and edema of the papillary dermis, mild spongiosis and

neutrophilic exocytosis. Fully developed lesions are characterized by a dense lichenoid dermal infiltrate, with lymphocytic predominance, with varying degrees of epidermal spongiosis and many necrotic keratinocytes in the basal layer. In the final stage of resolution, a poor dermal lymphocytic infiltrate is found, together with melanophages in the upper dermis, a hyperplastic epidermis with focal parakeratosis and few scattered necrotic keratinocytes [5], [16]. The main histological differential diagnoses include spongiotic dermatitis, early psoriatic lesions, lichenoid pityriasis and viral rashes.

Because the clinical features of PP are largely nonspecific, the diagnosis of PP requires a high degree of suspicion as well as clinicopathological correlation. Clinical differential diagnoses include acute/subacute lupus erythematosus, linear IgA dermatitis, dermatitis herpetiformis, pigmented contact dermatitis, Gougerot-Carteaud reticulate and confluent papillomatosis, macular amyloidosis, Dowling-Degos disease, and erythema dyschromicum perstans (ashy dermatosis) [10].

Among the multiple therapeutic options reported in the literature, cyclins remain the option of choice. Their beneficial action is related to their anti-inflammatory effect, particularly in the inhibition of neutrophil migration and function, matrix metalloprotease activity and pro-inflammatory cytokine expression [10]. Other therapeutic options include dapsone, macrolides, sulfamethoxazole, potassium iodide, and isotretinoin [6], [20, 21]/ Antihistamines and systemic or topical corticosteroids have limited effect on PP, helping only to differentiate PP from corticosteroid-sensitive dermatoses such as dermatitis.

4. Conclusions

The diagnosis of PP is based on the recurrent evolution and distinct clinicopathological features, and the first-line therapy is represented by cyclins. Dermatologists should identify the relationship between the timing of rash onset and resolution in relation to diet, with a view to early diagnosis and treatment with optimal patient outcomes.

References

1. Nagashima M. Prurigo pigmentosa - clinical observations of our 14 cases. *J Dermatol*. 1978 Apr;5(2):61-7. doi: 10.1111/j.1346-8138.1978.tb01049.x..
2. Böhler L, Dumann K, Kunz M. Symmetrical pruritic lesions on the trunk in a young woman - a rare case of non-associated Prurigo pigmentosa in Germany. *J Eur Acad Dermatol Venereol.* 2022 Mar 29. doi: 10.1111/jdv.18113
3. Houriet C, Perruchoud DL, Beltraminelli H, Borradori L. Prurigo Pigmentosa in white monozygotic twins. *JAMA Dermatol.* 2017; 153: 353–354. doi: 10.1001/ jamadermatol.2016.4921.
4. Page G, Page B, Beltraminelli H, Borradori L, Schlapbach C. Prurigo Pigmentosa: Demographics and Characteristics in 14 Caucasian Patients. *Dermatology*. 2021; 237(6):878-883. doi: 10.1159/ 000514026.
5. Almaani N, Al-Tarawneh AH, Msallam H. Prurigo Pigmentosa: A Clinicopathological Report of Three Middle Eastern Patients. *Case Rep Dermatol Med.* 2018 Jul 9; 2018:9406797. doi:

10.1155/2018/9406797.
6. Hijazi M, Jessica K, Abdul-Ghani K, Samer G. Prurigo pigmentosa: A clinicopathologic study of 4 cases from the middle east. *Am J Dermatopathol*. 2014; 36(10), 800–6. doi: 10.1097/DAD.0000000000000182.
7. Michaels JD, Hoss E, Dicaudo DJ, Price H. Prurigo pigmentosa after a strict ketogenic diet. *Pediatr Dermatol*. 2015; 32(2), 248–251. doi.org/10.1111/pde.12275
8. Teraki Y, Hitomi K. Unilateral prurigo pigmentosa: A report of two cases. *J Dermatol*. 2016 Jul;43(7):846-7. doi: 10.1111/1346-8138.13289.
9. Torrelo A, Azorín D, Noguera L, Hernández-Martín A, Happle R, Requena L. Segmental prurigo pigmentosa. *Pediatr Dermatol*. 2014; 31(4):523-5. doi: 10.1111/pde.12349.
10. Corley SB, Mauro PM. Erythematous papules evolving into reticulated hyperpigmentation on the trunk: A case of prurigo pigmentosa. *JAAD Case Reports.* 2015;1(2), 60–62. DOI:https://doi.org/10.1016/j.jdcr.2014.12.005
11. Cota C, Donati P, Amantea A. Prurigo pigmentosa associated with an atopic diathesis in a 13-year old girl. *Pediatr Dermatol.* 2007;24:277–279. doi: 10.1111/j.1525-1470.2007.00402.x.
12. Xiao A, Kopelman H, Shitabata P, Nami N. Ketogenic Diet-induced Prurigo Pigmentosa (the "Keto Rash"): A Case Report and Literature Review. *J Clin Aesthet Dermatol.* 2021 Dec;14(12 Suppl 1):S29-S32. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8903224/
13. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr.* 2013 Aug;67(8):789-96. doi: 10.1038/ejcn.2013.116
14. Garrido-Mesa N, Zarzuelo A, Galvez J. Minocycline: far beyond an antibiotic. *Br J Pharmacol*. 2013;169(2):337-352. doi: 10.1111/bph.12139.
15. Beutler BD, Cohen PR, Lee RA. Prurigo Pigmentosa: Literature Review. *Am J Clin Dermatol.* 2015 Dec;16(6):533-43. doi: 10.1007/s40257-015-0154-4.
16. Böer A, Misago N, Wolter M, Kiryu H, Wang XD, Ackerman AB. Prurigo pigmentosa: a distinctive inflammatory disease of the skin. *Am J Dermatopathol.* 2003;25(2):117-129. doi: 10.1097/00000372-200304000-00005.
17. Hartman M, Fuller B, Heaphy MR. Prurigo pigmentosa induced by ketosis: Resolution through dietary modification. *Cutis*. 2019; 103: e10-e13.
18. Teraki Y, Teraki E, Kawashima M, Nagashima M, Shiohara T. Ketosis is involved in the origin of prurigo pigmentosa. *J Am Acad Dermatol.* 1996;34(3):509-511. doi: 10.1016/s0190-9622(96)90460-0.
19. Mufti A, Mirali S, Abduelmula A, McDonald KA, Alabdulrazzaq S, Sachdeva M, Yeung J. Clinical manifestations and treatment outcomes in prurigo pigmentosa (Nagashima disease): A systematic review of the literature. *JAAD Int*. 2021;10;3:79-87. doi: 10.1016/j.jdin.2021.03.003.
20. Abbass M, Abiad F, Abbas O. Prurigo Pigmentosa After Bariatric Surgery. *JAMA Dermatol*. 2015 Jul;151(7):796-7. doi: 10.1001/jamadermatol.2015.0247.
21. Satter E, Rozelle C, Sperling L. Prurigo Pigmentosa: An under-recognized inflammatory dermatosis characterized by an evolution of distinctive clinicopathological features. *J Cutan Pathol.* 2016 Oct;43(10):809-14. doi: 10.1111/cup.12763.