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BRIEF REPORT

Disseminated superficial actinic porokeratosis following hydroxyurea treatment: A case report

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Abstract

Porokeratosis encompass a group of acquired and familial, preneoplastic, keratinization disorders, clinically characterized by atrophic macules or patches with a peripheral keratotic rim, the cornoid lamella. Genetic background is recognized as crucial in its pathophysiology, while immunosuppression and ultraviolet radiation represent triggering factors. We report the case of a woman who developed disseminate superficial actinic porokeratosis following the intake of hydroxyurea for a polycythaemia vera. Clinical, dermoscopic and histopathology data are showed, and the role of drug as a second-hit mutation trigger is discussed.

KEYWORDS

adverse effect, genetic analysis, hydroxyurea, Porokeratosis, squamous cells neoplasm mevalonate kinase deficiency

INTRODUCTION

Porokeratosis (PK) represents a group of rare, preneoplastic diseases characterized by the clonal expansion of keratinocytes and hallmarked by the presence of a cornoid lamella of parakeratosis. Its pathophysiology remains elusive but predisposing and/or precipitating factors seems to play a crucial role, such as genetic background, ultraviolet radiation (UVR), immunosuppression and some drugs.[1]

Herein, we report the case of a patient who developed disseminated superficial actinic porokeratosis (DSAP) following hydroxyurea administration.

MAIN TEXT

A 56-years-old Filipino woman came to our department for the presence of erythematous and scaling lesions on the lower legs, which onset approximately 2 months after hydroxyurea (HU) administration (500 mg per day) for a polycythaemia vera (PV), which was diagnosed following whole blood count (WBC) abnormalities – haematocrit (HCT) 51% and haemoglobin (Hb) 19.8 g/dl – and confirmed by the presence of the pathogenic variant V617F in *JAK2* among haematopoietic cells. In addition to HU, ticlopidine and phlebotomies were prescribed by haematology. Clinical examination revealed multiple, slightly depressed, erythematous-to-brown roundish lesions, some surmounted with a central adherent scale while some others presented a peripheral keratotic rim (Figure 1a–d). The lesions appeared after summertime (UV exposure), were referred as occasionally itching, and persisted despite the application of a daily emollient cream. Dermoscopy of the lesion corroborated the clinical findings showing a central and peripheric scaling on an erythematous background (Figure 2a–b). Routine laboratory examination, including

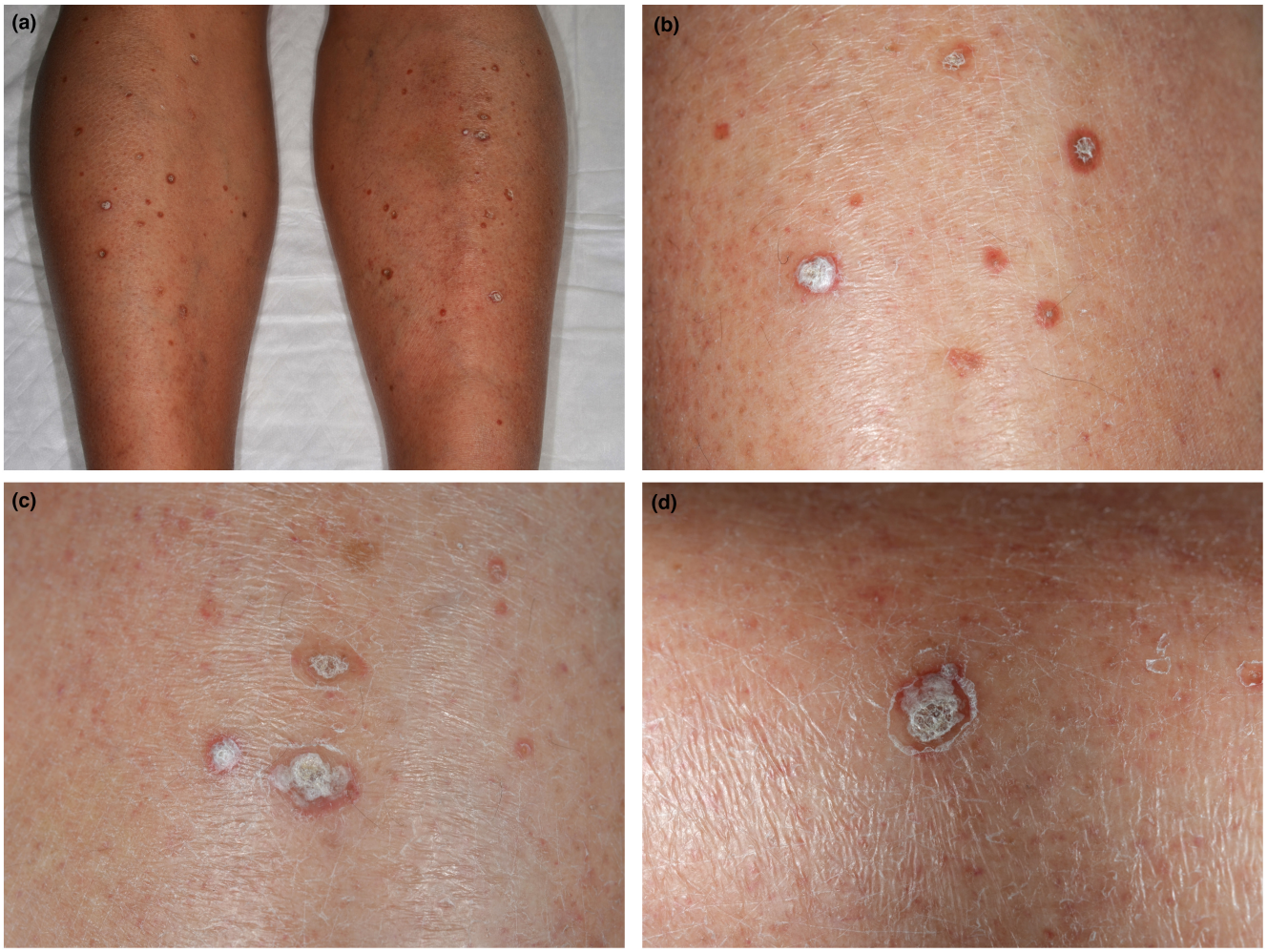

FIGURE 1 Clinical images showing (a) polymorphic erythematous to-brown round lesions on the lower legs of the patient; (b) a detail of erythematous lesion without scaling and one presenting with a central adherent scale; (c) slight depression of the lesional skin; (d) a lesion with well-represented peripheral keratotic rim suggestive for porokeratosis.

WBC, was within the normal range (Hb 11.7 g/dl, HCT 40%). Apart from PV and autoimmune hypothyroidism, patient's past medical history was unremarkable. No history of previous UV-therapy was reported. Basing on the clinical and dermoscopic features, DSAP and pityriasis lichenoides chronica were the two main differential diagnoses. A 4 mm punch biopsy on the central area of a lesion was performed to confirm the diagnosis. Histopathological examination revealed diffuse parakeratosis with only a hint of cornoid lamella, acanthosis and dyskeratotic cells in epidermis, accompanied by a band-like lymphocytic infiltrate at the dermo-epidermal junction (Figure 2c–d).

These findings were consistent with a diagnosis of DSAP. Topical diclofenac cream 3% bid was prescribed for 3 months and strict photoprotection was recommended. Considering PV response, HU was tapered to 500 mg 3 days per week by the haematology colleagues. At 3 months follow-up the patients referred a marked improvement of the lesions.

Porokeratosis encompass a group of keratinization disorders hallmarked by the presence of dysplastic keratinocytes with the formation of a thin column of parakeratotic cells which invaginates into the epidermis – the cornoid lamella – representing the thread-like active border of the lesions, pathognomonic in all PK forms.[1]

Genetic predisposition seems to play a pivotal role in all clinical variants of PK; to date, heterozygous germline mutations of four mevalonate kinase (MVK) pathway genes (*MVK*, *MVD*, *PMVK* and *FDPS*) have been reported as causative of PK.[2] In DSAP, it has been hypothesized that mitochondrial dysfunction induced by MVK pathway mutations could be an important contributory mechanism, since MVK pathway play a role in regulating calcium-induced keratinocyte differentiation and could have a protective effect on apoptosis of keratinocytes induced by UV-A spectrum light.[2,3] DSAP can be regarded as a benign intraepidermal neoplastic process that could be explained by Knudson's two-hit hypothesis: it has been demonstrated that PK lesions

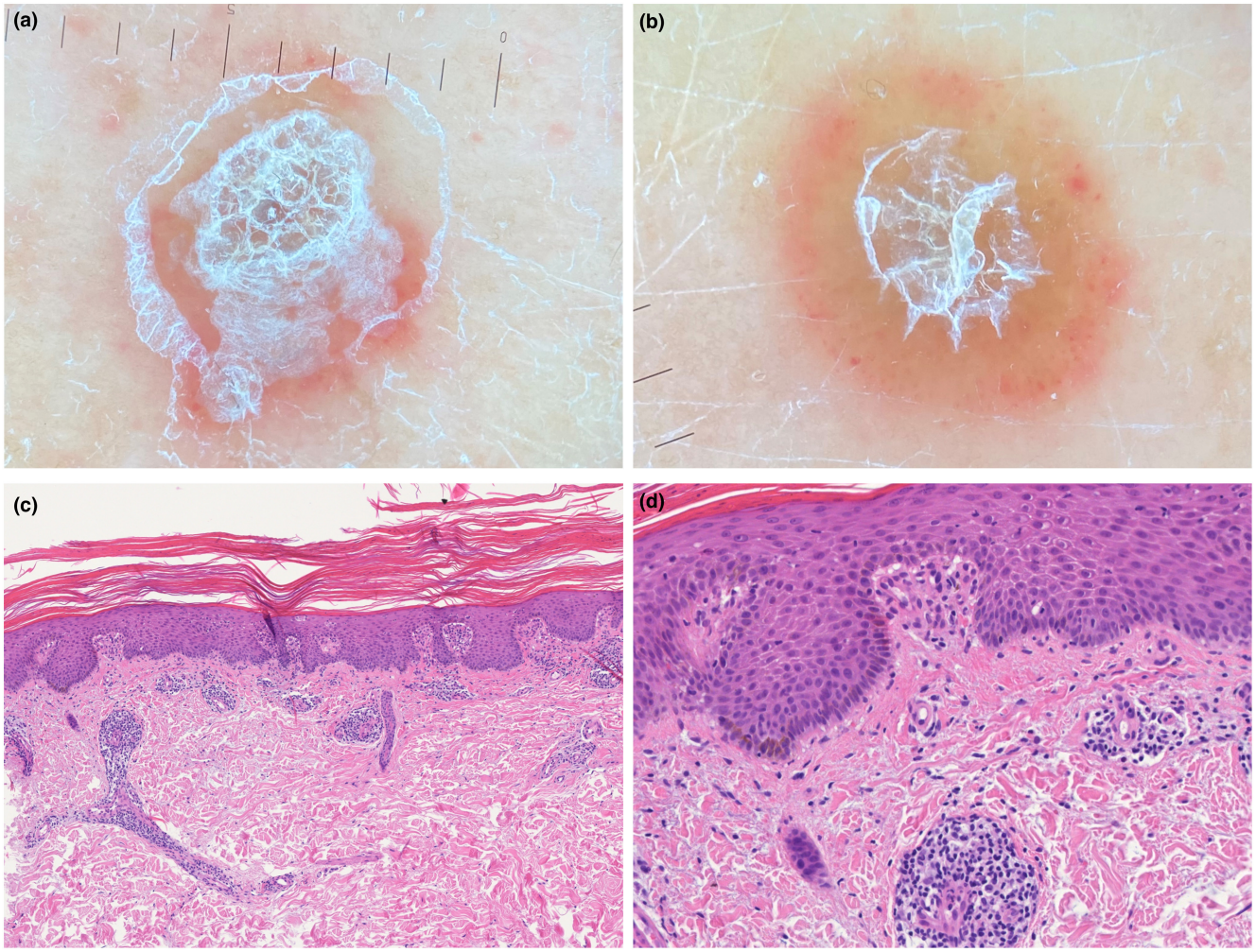

FIGURE 2 Dermoscopic images of the lesions showing (a) central scale with the peripheral keratotic rim; (b) a central scale on an erythematous-to-orange inflammatory background, with dotted vessels at the periphery of the lesion. Histological images showing (c) large area of parakeratosis accompanied by a band-like and perivascular lymphocytic infiltrate (haematoxylin and eosin staining, magnification 4x); (d) a detail showing moderate acanthosis, dyskeratotic cells and a lichenoid infiltrate at the dermo-epidermal junction (haematoxylin and eosin staining, 40x).

can result from second-hit somatic mitotic recombination and/or post-zygotic point-mutations in MVK genes induced by trigger factors such as UVR and immunosuppression, thus leading to a loss of heterozygosity in the skin.[4,5]

The relationship between PK onset and drugs has been recently evaluated in a systematic review, which mentioned HU as a possible trigger drug (mean Naranjo score of 3.3).[1] HU is an anti-metabolite drug which inhibits ribonucleotide reductase, thus affecting the production of deoxyribonucleotides and finally altering DNA repair.[6] Long-term exposure to HU has been linked with variable mucocutaneous side effects[6,7] but notably with an increased risk of actinic keratoses (AK) and squamous cell carcinomas.[8] The synergistic effect of HU-related immunosuppression – via the inhibition of DNA repair in mitotically active cells like keratinocytes – and the UVR photodamage has been demonstrated both in vitro than in vivo to induce squamous dysplasia.[8,9]

Surprisingly, only a report by Kanitakis et al. described the association between HU and PK in two elderly male patients affected by PV, following a long-term drug exposure (7–9 years), and with a previous history of multiple non-melanoma skin cancers (NMSC).[10] Differently from the previous report, in our case porokeratosis onset was abrupt, accompanied by inflammatory signs – clearly seen by dermoscopy (erythematous background and dotted vessels) and histopathology (lichenoid infiltrate) – and the absence of other signs of photodamage and/or dysplastic squamous lesions.

CONCLUSION

Based on the current knowledge of the PK pathogenesis, we speculate that in genetically predisposed individuals, HU could act as a trigger factor for a "second-hit"

mechanism that underlies the onset of PK, but further clinical, molecular and genetic studies are needed to confirm this hypothesis.

However, PK should be considered as a side-effect of HU therapy in predisposed individuals, periodic dermatological evaluation and strict photoprotection should be strongly recommended in this group of patients, to minimize the possible squamous dysplasia and the evolution to aggressive skin cancers.

AUTHOR CONTRIBUTIONS

MR: concept and design, drafting. DR, ADB, FB: acquisition and analysis of the data. SAV: critical revision. CM: concept and design, drafting. All the authors approved the final version of the manuscript.

FUNDING INFORMATION

None to declare.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PATIENT CONSENT

Written informed consent was obtained from the patient to publish his/her case details.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki.

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