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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Jamir Pitton Rissardo, MD, Academic Research, Adjunct Associate Professor, Research Associate, Department of Medicine, Federal University of Santa Maria, Santa Maria 97105110, Brazil. jamirrissardo@gmail.com

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Mixed porokeratosis with a novel mevalonate kinase gene mutation: A case report

Hong-Jun Xu, Guang-Dong Wen

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Hong-Jun Xu, Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Guang-Dong Wen, Department of Dermatology, Peking University People's Hospital, Peking University, Beijing 100044, China

Corresponding author: Hong-Jun Xu, MD, Chief Doctor, Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing 100050, China. ink-008@163.com

Abstract

BACKGROUND

Porokeratosis is a rare, acquired, or inherited disorder of keratinization. There are numerous clinical types of porokeratosis and they can coexist in one patient and multiple members of an affected family. However, coexistence of disseminated superficial actinic porokeratosis (DSAP) and porokeratosis ptychotropica (Ppt) is rare.

CASE SUMMARY

A 45-year-old man presented with long-standing skin lesions. Physical examination identified numerous small, brown 2-mm to 4-mm patches on his face and several hyperkeratotic, verrucous plaques on his trunk and extremities. His father and one of his brothers also had similar lesions for years. Skin biopsies indicated a cornoid lamella in the epidermis. We identified c.155G>A mutation in the mevalonate kinase (MVK) gene, which converted a serine residue to asparagine (p.Ser52Asn) and was causative for porokeratosis in this family. A clinicopathologic diagnosis of DSAP and Ppt with a novel MVK gene mutation was made. The hyperkeratotic plaques on the patient's scrotum were completely removed more than 10 times using a microwave knife.

CONCLUSION

An unusual case of DSAP coexisting with Ppt harbored a novel MVK gene mutation also present in the patient's family.

Key Words: Disseminated superficial actinic porokeratosis; Porokeratosis ptychotropica; Mevalonate kinase gene; Gene mutation; Microwave knife; Case report

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Core Tip: Porokeratosis is a rare, acquired, or inherited disorder of keratinization. The coexistence of disseminated superficial actinic porokeratosis (DSAP) and porokeratosis ptychotropica (Ppt) is rare. We present an unusual case of DSAP coexisting with Ppt and identified a novel mevalonate kinase (MVK) gene mutation in this patient's family. To date, only four cases of DSAP coexisting with Ppt have been reported in the English literature. One case also had an MVK gene mutation. Thus, mutation of phosphomevalonate kinase pathway genes, especially the MVK gene, may have an important role in the pathogenesis of DSAP coexisting with Ppt.

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INTRODUCTION

Porokeratosis is a rare, acquired, or inherited disorder of keratinization, which presents as a keratotic papule or plaque with an annular ridge-like border[1]. Its main histological characteristic is a cornoid lamella, a thin column of parakeratosis leading to a ridge-like hyperkeratotic border. Numerous types of porokeratosis have been described and there are reports of more than one type of porokeratosis developing in the same patient and in multiple members of an affected family[2]. Inherited or sporadic genetic defects have an important role in porokeratosis. Correlations between gene mutations and clinical phenotypes of porokeratosis have been reported previously[3]. Porokeratosis lesions may alter a patient's appearance or function. Furthermore, some cases develop squamous cell carcinoma within the porokeratosis lesions. Currently, no therapeutic interventions with good efficacy are available although various topical, surgical, destructive, and systemic therapies appear to be effective in some patients. Here, we report a rare case of disseminated superficial actinic porokeratosis (DSAP) and porokeratosis ptychotropica (Ppt) associated with a mevalonate kinase (MVK) gene mutation which was successfully treated by surgery.

CASE PRESENTATION

Chief complaints

A 45-year-old man complained of long-standing skin lesions.

History of present illness

The lesions started as brown patches on his face and gradually spread to the trunk and extremities with verrucous plaques 30 years ago. Involvement of the scrotum occurred 20 years ago.

History of past illness

The patient had no medical history and reported no history of ultraviolet exposure, immunosuppression, or immunodeficiency caused by human immunodeficiency virus (HIV) infection, tumors, or drugs.

Personal and family history

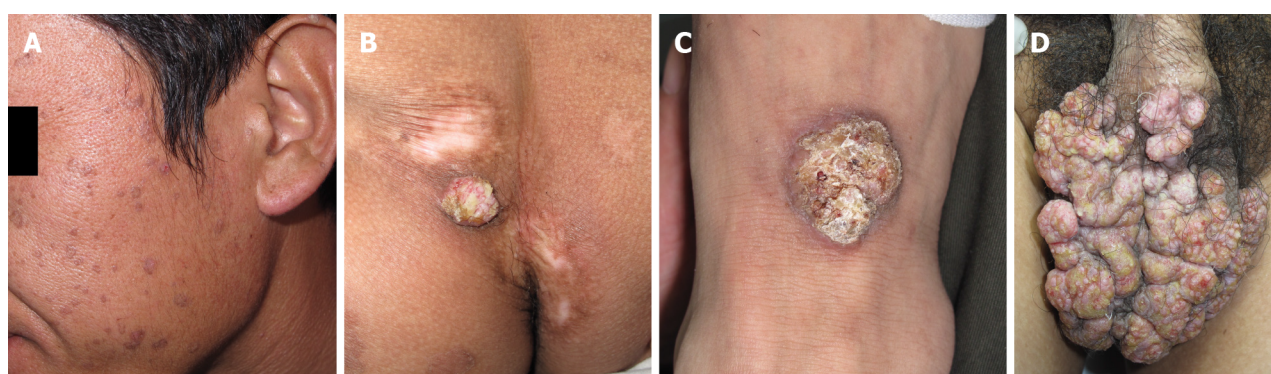
The patient's father and one of his brothers had similar lesions for years.

Physical examination

Physical examination identified numerous small, brown 2-mm to 4-mm patches on his face (Figure 1A) and several hyperkeratotic, verrucous plaques on his trunk (Figure 1B) and extremities (Figure 1C). The widespread verrucous plaques with erosions and crust on his scrotum (Figure 1D) affected his normal life.

Laboratory examinations

Laboratory investigations including routine blood examination, hepatic and renal function, HIV antibody, *Treponema pallidum* hemagglutination test, rapid plasma reagin test, human papillomavirus, hepatitis B and C, tumor markers, and autoimmune screens were all negative.



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Figure 1 Skin lesions of the patient. A: Small, brown patches on the face. B-D: Hyperkeratotic, verrucous plaques on the trunk and extremities and widespread verrucous plaques with erosions and crust on the scrotum.

Imaging examinations

Skin biopsies taken from the hyperkeratotic plaques of lesions on his scrotum showed irregular acanthosis and papillomatosis as well as a cornoid lamella in the epidermis and the absence of the granular layer beneath it (Figure 2).

Gene testing

After obtaining informed consent, genomic DNA was extracted from the proband and his affected and unaffected family members, and all exons of four mevalonate pathway genes including MVK, mevalonate decarboxylase (MVD), phosphomevalonate kinase (PMVK), and farnesyl diphosphate synthase (FDPS) with intronic flanking sequences were amplified by PCR. In addition, genomic DNA from 100 normal healthy Chinese individuals was extracted as controls. Bidirectional sequencing identified a heterozygous synonymous mutation c.155G>A in exon 18 of the MVK gene, which was not present in the unaffected family members and controls (Figure 3). This c.155 G>A mutation in the MVK gene converted a serine residue to asparagine (p.Ser52Asn) and was the causative mutation for porokeratosis in this family.

FINAL DIAGNOSIS

A clinicopathologic diagnosis of DSAP and Ppt with MVK gene mutation was made.

TREATMENT

The hyperkeratotic plaques on the patient's scrotum were completely removed more than 10 times using a microwave knife (Figure 4).

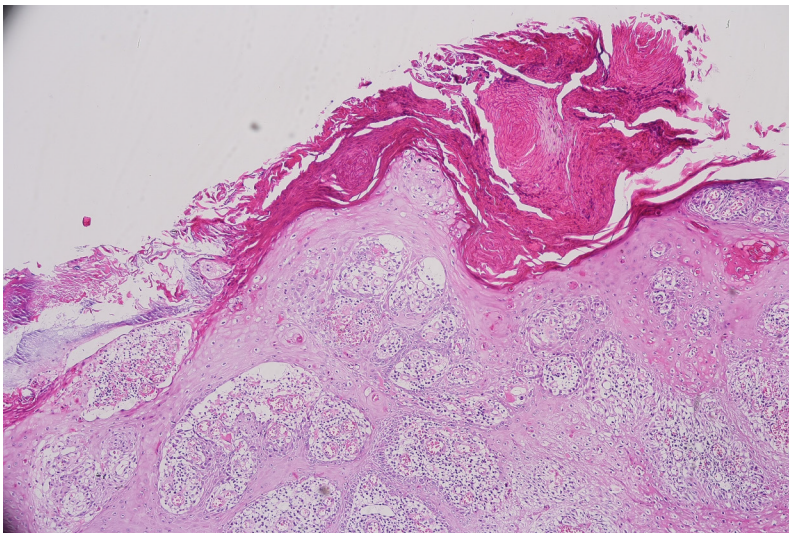
OUTCOME AND FOLLOW-UP

The patient has had no recurrence during 6-years of follow-up.

DISCUSSION

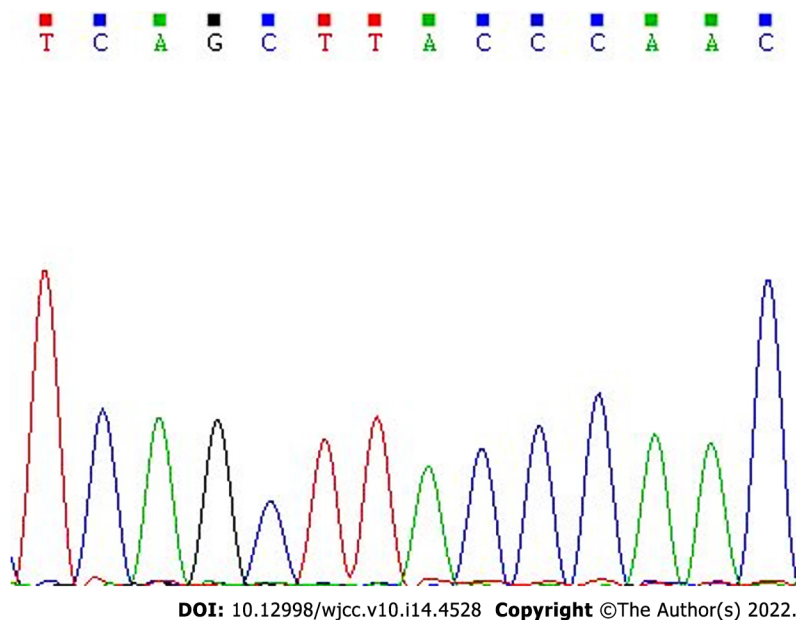
Porokeratosis represents a heterogeneous group of hereditary and acquired disorders of the clonal hyperproliferation of keratinocytes[4]. The characteristic ridge-like, keratotic border termed the "cornoid lamella" confirms the diagnosis of porokeratosis. Several clinical variants of porokeratosis have been described, all of which share this distinctive feature.

DSAP is the most common type of porokeratosis. It presents as keratotic papules with a well-demarcated elevated border, usually ranging from 3 mm to 10 mm in diameter. They are typically skin-colored to tan-brown to pink-red in color. DSAP usually occurs in the third or fourth decade of life, and patients frequently report a history of extensive exposure to ultraviolet radiation. For this reason, it usually occurs in body areas exposed to the sun, especially the shins and extensor forearms. Lesions on



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Figure 2 Histopathological examination shows a cornoid lamella in the epidermis (hematoxylin-eosin staining, original magnification: ×100).



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Figure 3 Analysis of the mutation in the mevalonate kinase gene. A novel mevalonate kinase missense mutation (c.155G>A) was present in the patient's family.

our patient's face were typical of DSAP. Although 15% of DSAP patients have facial lesions, exclusively facial DSAP is an unusual clinical presentation[5]. Ppt is an unusual psoriasiform variant of porokeratosis[6-8], which typically presents with pruritic, red to brown, keratotic, or verrucous papules and plaques on the buttocks or genital skin[8]. Sometimes, these lesions can coalesce. Due to their clinical similarities, Ppt is often mistaken for psoriasis[9] and chronic eczema. Therefore, a skin biopsy is a useful method for differential diagnosis. The verrucous plaques on our patient's scrotum, buttocks, and limbs were diagnosed as Ppt according to the pathologic findings.

Previous studies have reported the coexistence of multiple types of porokeratosis in the same individual[10-20]; however, the co-occurrence of DSAP with Ppt is rare. To the best of our knowledge, this is the fifth case reported in the English literature to date[7,21-23] (Table 1).

The pathogenesis of porokeratosis is poorly understood. Risk factors include genetic susceptibility, exposure to ultraviolet radiation, and immunosuppression. Previous studies reported mutations in the phosphomevalonate kinase pathway genes, including MVD, MVK, PMVK, and FDPS in patients with porokeratosis[24,25]. At least one mutation in a mevalonate pathway gene was found in 98% of familial cases and in > 70% of sporadic porokeratosis cases[3]. Among the above five patients previously

Table 1 Clinical features of patients with coexisting disseminated superficial actinic porokeratosis and porokeratosis ptychotropica

Ref.	Gender	Age	Ethnicity	Nationality	Clinical variants	Genetics	Risk factors	Treatment
Thomas <i>et al</i> [21]	Female	78 yr	NA	United Kingdom	DSAP, Ppt	NA	None	NA
McGuigan <i>et al</i> [7]	Male	84 yr	NA	United States	DSAP, Ppt	NA	Sun exposure, non-melanoma skin cancer	0.025% tretinoin cream, 0.05% tazarotene cream.
Murase <i>et al</i> [22]	Female	73 yr	Korean	Korea	DSAP, Ppt linear porokeratosis	NA	Family history	NA
Peng <i>et al</i> [23]	Male	70 yr	Chinese	China	DSAP, Ppt	MVK missense mutation (c.1039G>C, p.Gly347Arg)	Family history	Oral acitretin (20 mg daily)
Our patient	Male	45 yr	Chinese	China	DSAP, Ppt	MVK missense mutation (c.155G>A, p.Ser52Asn)	Family history	Microwave knife

DSAP: Disseminated superficial actinic porokeratosis; Ppt: Porokeratosis ptychotropica; MVK: mevalonate kinase; NA: Not available.



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Figure 4 The lesions on the patient's scrotum were completely removed after microwave knife treatment.

reported, two had genetic results. Peng *et al* [23] identified a novel MVK missense mutation (c.1039G>C, p.Gly347Arg) in a family with coexisting DSAP and Ppt. In our patient's family, another MVK missense mutation (c.155G>A, p.Ser52Asn) was found. Although this mutation was previously reported as benign, we suggest it is a novel mutation associated with porokeratosis. Functional analysis of this mutation *in vitro* and *in vivo* should be performed in future studies. The findings in these two cases suggest that the mutation of phosphomevalonate kinase pathway genes, especially the MVK gene, might have an important role in the pathogenesis of DSAP coexisting with Ppt. Genetic analysis is useful in affected families to predict the occurrence of these lesions in other individuals of the same family.

Patients with porokeratosis have a 7.5%-10% risk of malignant transformation to squamous cell carcinoma or basal cell carcinoma [26]. Thus, clinical surveillance with regular skin examinations and patient education regarding the warning signs of skin cancer and sun protection are necessary aspects of the management in all patients with porokeratosis. However, some patients with functional impairments or appearance requirements want to have their porokeratosis lesions removed. There are five main types of treatment for porokeratosis: Topical or systemic drug therapy, surgical excision, cryotherapy, laser ablation, and photodynamic therapy. However, the disease commonly reoccurs. We used a microwave knife to remove the hyperkeratotic plaques on the patient's scrotum. The patient did not show any functional impairment related to this treatment and did not develop disease aggravation or recurrence during 6-years of follow-up. This indicates that the microwave knife is an effective and

safe therapy for porokeratosis.

CONCLUSION

In conclusion, we report an unusual case of DSAP coexisting with Ppt and identified a novel MVK gene mutation in this patient's family. The microwave knife is an effective and safe therapy for porokeratosis and clinical surveillance for malignant transformation is necessary for all patients with porokeratosis.

FOOTNOTES

Author contributions: Xu HJ collected all the clinical data and wrote the draft manuscript. Wen GD completed the gene analysis; all authors read and approved the final manuscript.

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ORCID number: Hong-Jun Xu 0000-0002-4002-1549; Guang-Dong Wen 0000-0002-9221-7033.

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