Treatment of *TRPV3* mutation-associated Olmsted syndrome with erlotinib

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INTRODUCTION

Olmsted syndrome (OS) is a rare keratinizing skin disorder characterized by painful and mutilating palmoplantar keratoderma (PPK) and periorificial keratotic plaques that gradually progress over time.[1,2] Mutations in the transient receptor potential vanilloid-3 (*TRPV3*) gene, and less commonly, the membrane-bound transcription factor site-2 protease gene, have been implicated in OS.[1] The *TRPV3* gene encodes a Ca^{2+} entry pathway in keratinocytes that is tightly associated with the transforming growth factor-α/epidermal growth factor receptor (EGFR)-signaling complex involved in keratinocyte differentiation.[3] A gain-of-function mutation in the *TRPV3* gene is responsible for the increased keratinocyte apoptosis and skin hyperkeratosis seen in affected individuals.[4]

Current treatment options for OS are largely ineffective and may offer only temporary relief. In 2020, Greco et al[1] demonstrated remission of *TRPV3* mutation-associated PPK in 3 patients with OS using erlotinib hydrochloride therapy, an *EGFR* inhibitor. Herein, we report an additional case of erlotinib-induced remission of pain and PPK in a patient with *TRPV3* mutation-associated OS.

Abbreviations used:

EGFR:	epidermal growth factor receptor
OS:	Olmsted syndrome
PPK:	palmoplantar keratoderma
TRPV3:	transient receptor potential vanilloid-3

CASE REPORT

A 12-year-old boy with normal growth and development presented to clinic for painful thickening of the soles. His symptoms initially began after he scraped the undersurface of his right great toe. A small yellow plaque then formed in the same area and fell off without intervention about 4 months later. Subsequently, he experienced several episodes of recurring painful plaques on his feet that occurred following trauma (Fig 1). Each episode was characterized by severe, incapacitating pain unresponsive to multiple pain medications. The patient was unable to walk, play sports, or attend school due to severe pain. His caregivers reported that other family members experienced painful lesions on the feet as well. The plaques in our patient were initially treated with topical keratolytics, topical clobetasol, and oral acitretin without improvement.

On examination, thick hyperkeratotic plaques with central keratinaceous cores were noted on the plantar surface of the right heel and the plantar surface of the first toe (Fig 2). A biopsy of the plaque on the plantar surface of his right heel showed epidermal filiform acanthosis and hyperkeratosis with dilated superficial dermal vessels (Fig 3). Given the overall nonspecific findings on biopsy, the patient was referred to genetics for further evaluation. Testing revealed a heterozygous gain-of-function mutation in the *TPRV3* gene, consistent with a diagnosis of OS.

In a recent case report by Greco et al,[1] 3 patients who had *TRPV3* mutation-associated PPK were treated with erlotinib. Within 3 months of initiating therapy, the patients' hyperkeratosis and pain disappeared. Given this report and the severity of our patient's pain despite treatment with clobetasol and acitretin, erlotinib was initiated at 50 mg in

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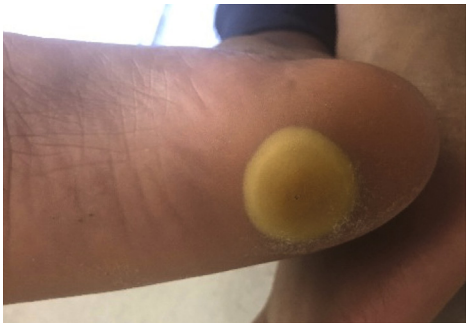

Fig 1. Trauma-related plaques on the plantar surface of the right heel. Injury preceded thick hyperkeratotic plaques growing and forming in the same area.

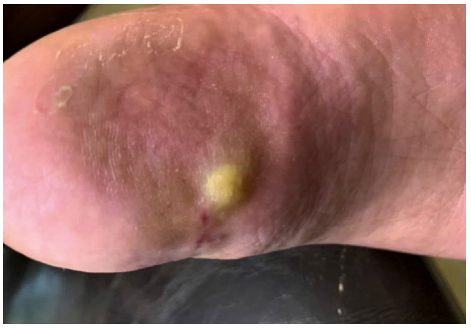

Fig 2. Solitary, dome-shaped, yellowish, firm plaque with surrounding subtle erythema on the plantar surface of the right heel that formed after a splinter was removed.

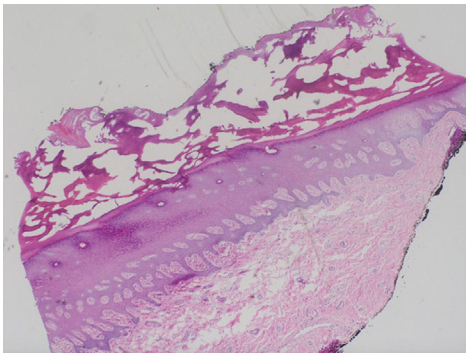

Fig 3. Histologic preperation from a biopsy of a keratotic plaque of the plantar surface of the right heel demonstrating epidermal filliform acanthosis and hyperkeratosis with dilated superficial dermal vessels (H&E stained section at 4× magnification).

conjunction with continuing oral acitretin at 25 mg daily. His weight was 65 kg. Within 3 months, he experienced improvement, and follow-up examination revealed only mild erythema and subtle hyperkeratosis on the bilateral plantar surfaces (Fig 4). After 6 months of treatment with erlotinib 50 mg daily, he still had ongoing pain impacting activities, and his dose was increased to 75 mg daily. He tolerated the medication well aside from nausea that was controlled with ondansetron, and his pain nearly resolved, with only intermittent flares.

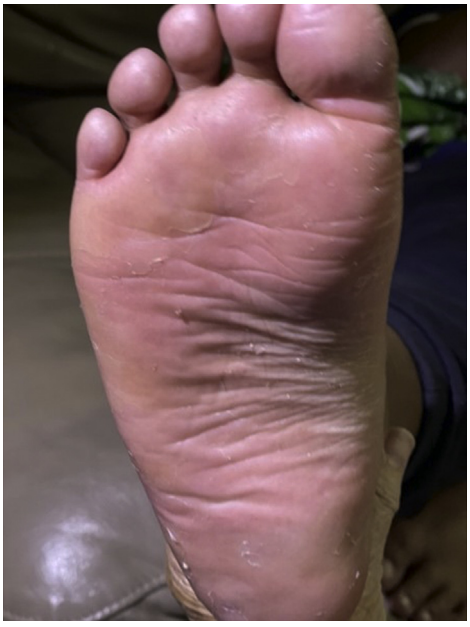

Fig 4. Plantar surface of the right foot showing mild erythema and subtle hyperkeratosis following therapy with erlotinib 50 mg for 3 months.

DISCUSSION

We present a case report of a patient with *TRPV3* mutation-associated OS, who responded well to a novel use of erlotinib to treat pain and PPK. Erlotinib is an *EGFR* inhibitor hypothesized to target the cycle of *TRPV3/EGFR* activation initiated by *TRPV3* gain-of-function mutations commonly seen in OS.[1] Greco et al[1] recently demonstrated that administering erlotinib to patients with OS and *TRPV3* mutations resulted in improvement in pain and disappearance of PPK. Our patient exhibited a similar response with significant improvement in his symptoms within 3 months of initiating erlotinib 50 mg, with nausea as his only notable side effect. His dose was increased to 75 mg for better control of his symptoms, and he has since experienced continued improvement in his skin lesions and pain. He has been able to attend school again and plans to sign up for a recreational basketball team.

Patients with OS have also been treated with up to 100 mg erlotinib with documented adverse effects limited to mild acneiform eruptions and moderate hair loss.[1]

The erlotinib-induced remission of OS symptoms has been shown to persist through 12 months of treatment, and resistance to treatment is not

anticipated.[1] This case emphasizes that erlotinib may represent an effective and novel treatment for pain and PPK in patients with OS and *TRPV3* mutations.

Conflicts of interest

None disclosed.

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