Dimethyl fumarate for treating Papillon–Lèfèvre syndrome

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INTRODUCTION

Papillon–Lèfèvre syndrome (PLS) is a rare genetic disorder caused by a mutation in the cathepsin C gene, with over 250 cases reported worldwide, mainly among Caucasians in Saudi Arabia.1

PLS is characterized mainly by oral and cutaneous manifestations that occur simultaneously between 6 months and 4 years of age. It presents as a transgradient appearance of palmoplantar hyperkeratosis.2 Other regions on the skin can also be involved, including the eyelids, cheeks, knees, elbows, thighs, external malleolus, toes, and dorsal fingers.1

As for oral involvement, the periodontal lesions may appear shortly after the development of deciduous dental elements in the arch.3 Evident signs include gingival bleeding, infection, and alveolar bone resorption.4

The current management options for keratoderma include topicals such as steroids, salicylic acid, and emollients. Meanwhile, systemic options include etretinate, isotretinoin, and low-dose acitretin, all of which have been the most important therapeutic options for PLS cutaneous lesions.2 New drug therapies targeting cathepsin C are currently under development by pharmaceutical companies in clinical trials, with evidence still lacking.5

Dimethyl fumarate is a fumaric acid ester derivative approved for the treatment of relapsing forms of multiple sclerosis6; its usage is currently limited in dermatology practice; it obtained European approval in 2017 for treating moderate-to-severe plaque psoriasis as the first-line systemic therapy, and since then, an increasing number of patients have been treated with this medication.7

We report a rare case of a 29-year-old woman with PLS and multiple sclerosis, whose cutaneous lesion was managed incidentally with dimethyl fumarate in the neurology department. This study aimed to explore the use of dimethyl fumarate for treating palmoplantar keratoderma, which can be a new valid option for resistant cases.

CASE REPORT

A 29-year-old woman with a long history of severe hyperkeratosis of the palmar and plantar surfaces since her first few years of life was diagnosed with PLS. She also presented with recurrent dental caries and loss of primary teeth since childhood, treated by flap surgical procedures with the prosthetic approach at a younger age.

The patient’s parents are first-degree cousins, and her 2 brothers present with the similar conditions, all of whom were diagnosed by genetic testing that revealed a mutation in the cathepsin C gene. PLS was confirmed accordingly. Regarding previous treatment history, the patient was started with multiple keratolytic agents, such as urea with a lactic acid ointment of 30% daily, and she took a course of 20 mg daily acitretin for 2 months, which she stopped in January 2022 for reasons related to...
childbearing. All previous treatments demonstrated moderate improvement in her palmoplantar lesions; however, no total clearing was achieved.

Five years prior to consultation, the patient noticed weakness in the upper limbs and lower limbs associated with numbness. During the last 9 months, she presented to the Neurology Department in King Fahad Medical City with worsening spasticity, and she was diagnosed with multiple sclerosis as confirmed by clinical examination and imaging.

The patient was initially treated in the neurology department with baclofen 10 mg once daily for her spasticity and Rebif (interferon beta-1a), which were stopped in February 2022. The patient was then started on dimethyl fumarate 240 mg twice daily and urea with the concurrent usage of lactic acid ointment 30%.

At baseline before starting the new treatment, the palmar surface well-demarcated plaques extended to the margins of the palms and spanned over the thenar eminence extending to the dorsum of the hands (Fig 1, A and B).

After 2 months of treatment, the patient observed improvement on the palmar area. On examination after treatment with dimethyl fumarate, both palmar surfaces demonstrated significant improvement, with very faint erythema and scales on both thenar and hypothenar eminences (Fig 2).

After 5 months of treatment, the patient observed near total clearing of the erythema (Fig 3, A and B).

The plantar surface also demonstrated well-demarcated keratotic scaly plaques that extended from the sole of the foot to the margins of the Achilles tendon, in comparison to the palmar surface it only showed mild improvement after 5 months of treatment (Fig 4, A and B).

At 5 months follow-up, their no alterations in her white blood cells, and she reported no medication side effects.

DISCUSSION

The current treatment guidelines for patients with palmoplantar keratoderma remain difficult and unsatisfactory. Oral retinoids are commonly used as a treatment option for patients with severe PLS when topical treatment has failed. They can be beneficial for both the dermatological and dental manifestations.2

The current recommended initial dose of isotretinoin is 0.5 mg/kg/d. After 16 weeks, the average dose can be increased to 1.95 mg/kg/d. The long-term side effect of using oral retinoids especially during childhood is the risk of bone toxicity, including premature closure of the epiphysis and risk of fractures. Moreover, oral retinoids have a risk of teratogenic effects and cannot be used in female patients of childbearing age.8

In dermatological practice, the use of dimethyl fumarate remains limited in adults with moderate-to-severe psoriasis only. Dimethyl fumarate has anti-inflammatory and immune-modulatory effects, which work by reducing the inflammation and depleting glutathione, thereby shifting the immunological response from Th1/Th17 to Th2.7
The other mechanism, which, in theory, can manage cases with palmoplantar keratoderma, works by inhibiting the activation and proliferation of keratinocytes in response to stimulation due to external oxidative effects.6

A retrospective study has reported that 61% of patients with moderate-to-severe plaque psoriasis experienced side effects from dimethyl fumarate with a daily dosage of 120-360 mg. The most common side effects included gastrointestinal symptoms, transient alteration in complete blood count, with reduced white blood cell count, and hyper eosinophilia, which was reported in <10% of the cases.7

Fig 3. A, Papillon–Lefèvre syndrome (hands palmar surface 5 months post treatment). B, Papillon–Lefèvre syndrome (hands dorsal surface 5 months post treatment).

Fig 4. A, Papillon–Lefèvre syndrome (left plantar surface at baseline). B, Papillon–Lefèvre syndrome (left plantar surface 5 months post treatment).
In a previous case report, dimethyl fumarate 240 mg was used as monotherapy in a patient with hyperkeratotic palmoplantar psoriasis, who had hepatitis B virus and could not receive biological treatment. The skin-related symptoms of the patient resolved after 12 weeks. The physician’s global assessment for palmoplantar psoriasis decreased from 4 at baseline to 1 after 12 weeks of the treatment.9

Another case report involved a 53-year-old woman with a recalcitrant case of palmoplantar psoriasis with a Psoriasis Area Severity Index score of 7.8, for whom multiple treatments failed, including conventional and biological therapy. Dimethyl fumarate 240 mg was started once daily with clinical improvement noted after 1 week. However, adverse effects, including abdominal pain, diarrhea, and flushing were reported. Thus, the dose was modified to 120 mg once daily. The Psoriasis Area Severity IndexPASI score was 5.7 at 12 weeks following administration of dimethyl fumarate and 1.8 after 24 weeks.10

Palmoplantar keratoderma can significantly improve after treatment with dimethyl fumarate. Further large-scale studies should determine the efficacy, long-term effects, and appropriate dosage of dimethyl fumarate for treating palmoplantar keratoderma.

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Conflicts of interest
None disclosed.

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