Greither's disease: a late-diagnosed case successfully treated with acitretin

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We report a 19-year-old woman, born of a consanguineous marriage but without a positive history in the family, diagnosed histologically and clinically with this disease. All the previous treatments were unsuccessful; we started acitretin, and she responded excellently to treatment. Although the improvement in thickness and hyperhidrosis was noteworthy, and the patient was satisfied with the treatment, as we expected, there was not an acceptable result with the erythema.

Keywords: greither, keratoderma, palmoplantar, acitretin

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INTRODUCTION

Greither disease, also known as transgressions keratoderma, is an autosomal dominant hereditary disease that usually manifests in the second year of life and ends spontaneously after the fifth decade of life. So far, mutations in KRT1 have been reported in this disease [1,2]. The disease is characterized by non-epidermolytic palmoplantar keratoderma (PPK) with erythematous margins extending to the dorsal aspect ('transgrediens') and involvement of the wrist ('progrediens') and Achilles tendon [3]. Histological findings are not specific to the disease and mostly include acanthosis and ortho-hyperkeratosis.

CASE PRESENTATION

In July 2021, a 19-year-old female, born of a consanguineous marriage, presented to the Dermatology Clinic of Sina Hospital (Tabriz) with the chief complaint of redness in the palms and soles since infancy, which had gradually spread over the dorsal surfaces of her hands and feet. During the last four years, hyperhidrosis and scaling of these areas have been added to the patient's clinical complaints. In addition, the patient complained of increased erythema with exposure to heat, which decreased if the hand or leg was raised. During the last four years, the patient had received several topical medications, including emollients and corticosteroids, which did not respond well. Also, the patient had no exact information regarding past treatment types and durations. Last year, micro-Botox was injected into the patient's palms, which reduced the hyperhidrosis for several months, but once again, a return of symptoms was observed. No similar cases were reported in the patient's close relatives. However, the patient's brother had an

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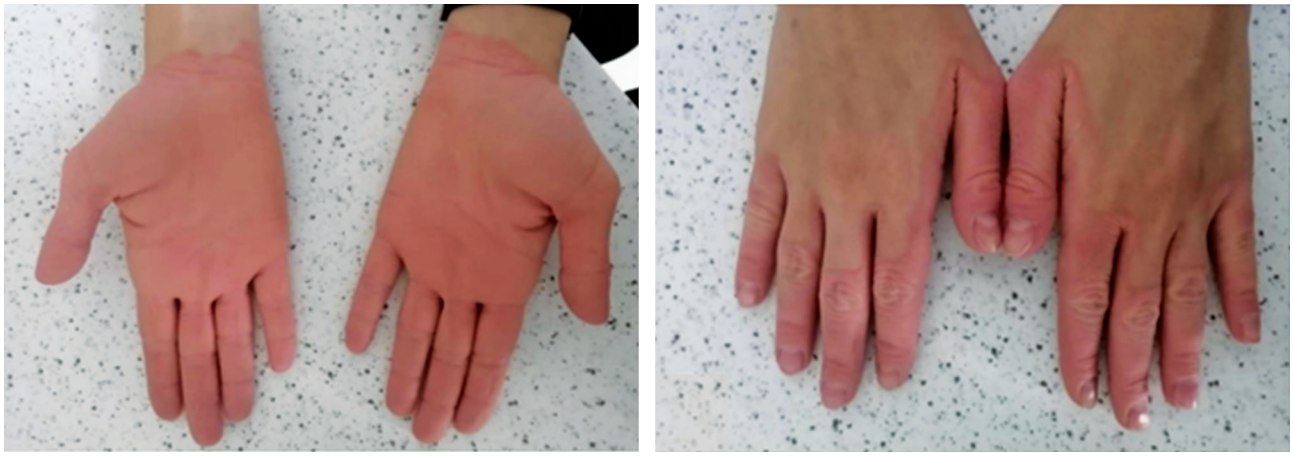


Figure 1. Images before acitretin treatment (palmar keratoderma).

atopic dry skin disease that cutaneous examination revealed diffuse palmoplantar keratoderma with sharp and erythematous margins spreading to the dorsal aspect of the hands and feet with mild to moderate hyperkeratosis. Knuckles ' involvement was evident on the dorsum of the hands, and hyperkeratosis of the plantar surface was less severe than in the upper extremities.

Nails, hair, teeth, and eyes were normal in the physical examination, and the patient had normal psychological condition and mental development (Figure 1). The palmar skin biopsy revealed compact orthokeratosis and focal parakeratosis between the granular layer and hyperkeratotic stratum without the checkerboard pattern. In addition, acanthosis and hypergranulosis were evident. Furthermore, perivascular lymphocytic infiltration was seen (Figure 2). According to the history, clinical examination, and histology, we diagnosed Greither's disease. Before starting treatment, complete blood count, lipid profile, and liver function tests were requested; no abnormalities were observed in the test results. Then, we started to treat the patient with acitretin 10 mg (produced by Aurovitas company) every other day for two months, reduced to one capsule every five days in the third month. An excellent response to treatment with improved scaling and perspiration was observed after six months of therapy (Figure 3).

DISCUSION

Greither's disease was first introduced in 1952 as "keratosis extremitatum hereditaria progrediens" [4]. Then, some similar cases were reported over several years, known as "transgrediens et progrediens keratoderma" [3-5]. Morphological features of the disease include non-epidermolytic palmoplantar keratoderma (PPK) with erythematous margins extending to the dorsal aspect ('transgrediens') and involvement of the wrist ('progrediens') and Achilles tendon [6]. In rare cases, hyperkeratotic plaques were reported in the knees and elbows, some associated with hyperhidrosis [7]. Nail changes and finger amputation have also rarely been reported [8]. Histological findings are not specific to the disease and mostly include acanthosis and ortho-hyperkeratosis.

Regarding histological findings, Grilli *et al.* also described cases with round and focal ortho-keratosis in sunken areas of the dermis [1]. Electron microscope studies have reported tangled tonofilaments around the nucleus with desmosomes and cell-cell junctions representing an imbricated pattern [9]. Although Greither's disease has a determinate phenotype, the patient's symptoms may appear in different body parts over time. The closest differential diagnosis of this disease is Mal de Melinda syndrome (keratosis palmoplantaris transgradiens of Siemens), which is an autosomal recessive PPK disease whose features include yellow waxy PPK with persistent erythema, palmoplantar hyperhidrosis, koilonychia, nail changes, lingua plicata, syndactyly, decreased range of motion of hands and feet, nose erythema, and corneal lesions [10].

The treatment of Greither's disease is the same as other PPKs and includes saline solutions, topical keratolytics, and systemic retinoids [11]. Therapeutic

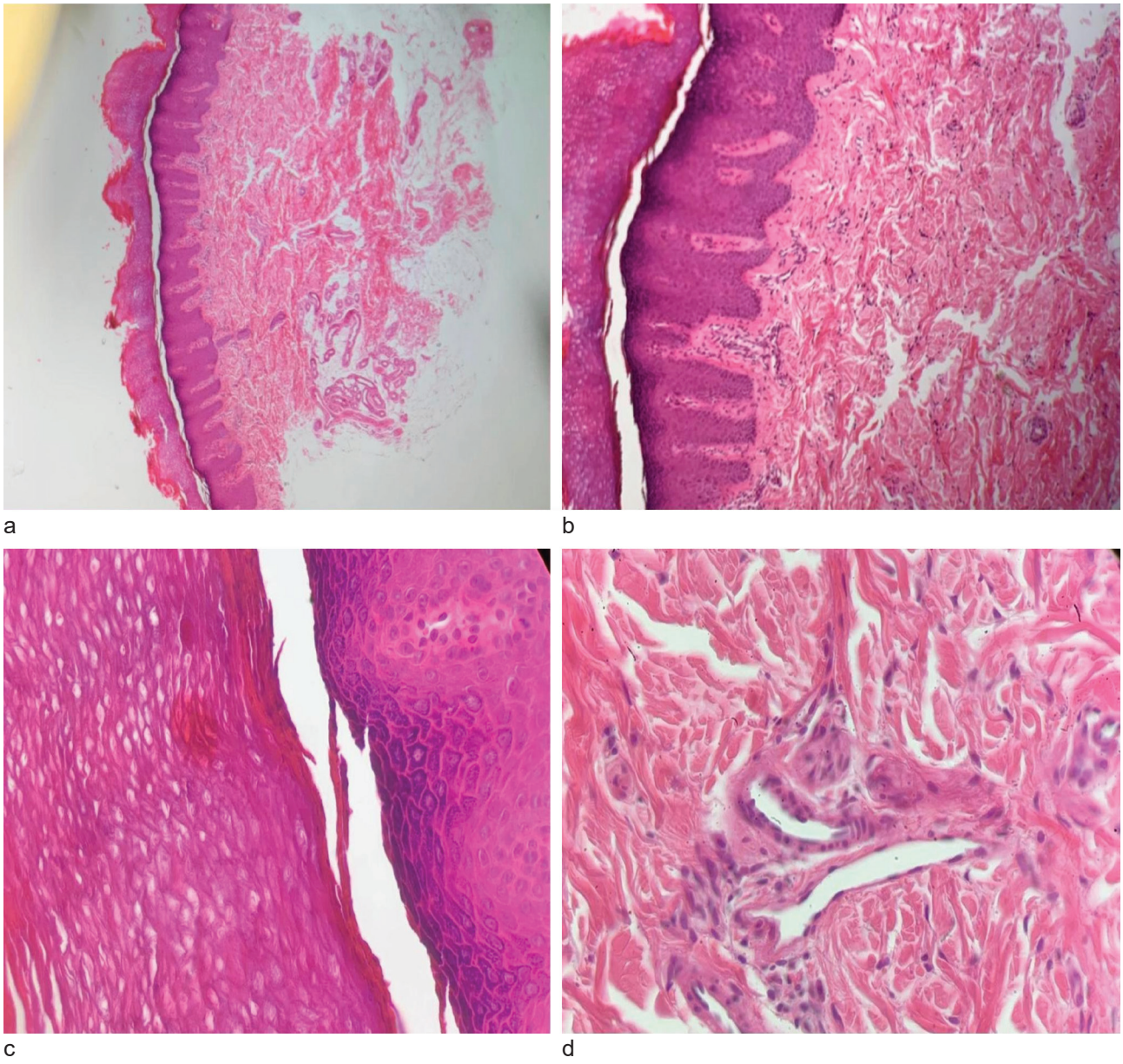
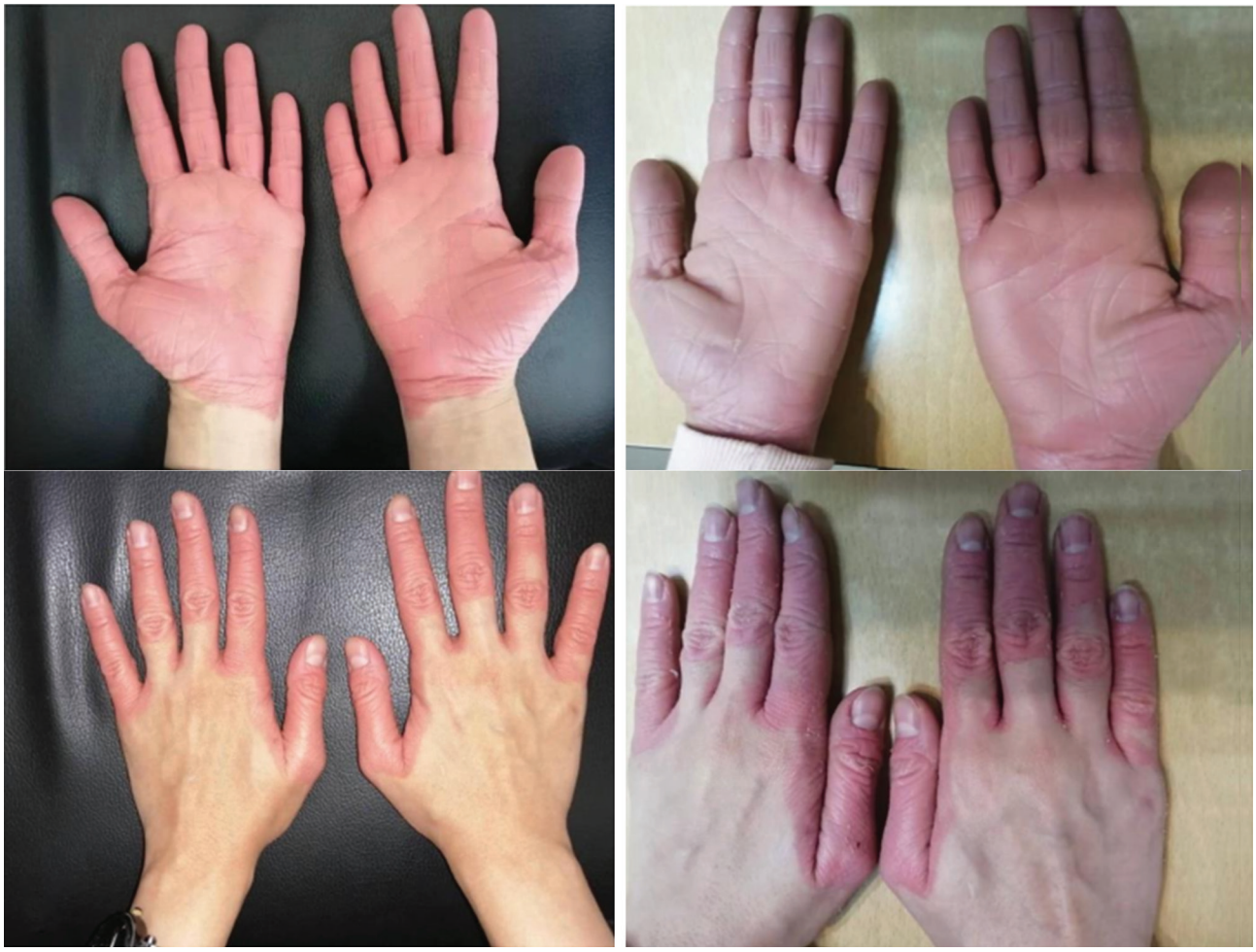


Figure 2. Acanthosis, hypergranulosis, and perivascular lymphocytic infiltration in the upper dermis (H&E stain). a) Hyperkeratosis and acanthosis (× 40). b) Hyperkeratosis and acanthosis (× 100). c) Hypergranulosis (× 400). d) perivascular lymphocytic infiltration in the upper dermis(× 400).

modalities used to treat Greither's disease include keratolytic agents like salicylic acid, topical steroids (in combination with keratolytics), propylene glycol, and systemic retinoids like acitretin. Acitretin is a synthetic retinoid that acts on intranuclear receptors and cytoplasmic proteins. Metabolites of the drug activate retinoic acid nuclear receptors without binding to them, leading to increased gene expression responsible for anti-inflammatory and anti-proliferative activities. In addition, acitretin balances the proliferation and differentiation of keratinocytes in the epidermal layer [12]. The standard dose of this drug is between 25 to 35 mg per day. For the patient introduced in this study, 10 mg of acitretin was used every other day, and the desired result was achieved.

CONCLUSION

In this study, a 19-year-old female patient with Greither's disease achieved excellent results with three months of oral acitretin; scaling and perspiration were significantly reduced, though the improvement



a b

Figure 3. Images after acitretin treatment (a: after receiving 30 doses of medicine; b: after receiving 50 doses of medicine).

in erythema was unsatisfactory.

Authors contributions

A. Gharehaghaji Zare diagnosed and treated the patient. S. Rahimi followed the treatment process and reported the procedure. S. Mohajeri reported the pathological skin biopsy.

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Conflict of Interest: None declared.

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