

## Case Report

# Type 1 segmental Darier's disease: report of two cases with favourable response to topical retinoids

## 第一型節段性毛囊角化病：兩個對外用維甲酸有良好效果的病例報告

Ö Bakar, EÖ Durmaz, E Sezer, ED Çetin

Darier's disease is a rare late-onset genetic disorder of keratinisation. Mosaic forms of the disease characterised by localised and unilateral keratotic papules carrying post-zygotic *ATP2A2* mutation in affected areas have been documented. Segmental forms of Darier's disease are classified into two clinical subtypes: type 1 manifesting with distinct lesions on a background of normal appearing skin and type 2 with well-defined areas of Darier's disease occurring on a background of less severe non-mosaic phenotype. Herein we describe two cases of type 1 segmental Darier's disease with favourable response to topical retinoids.

毛囊角化病是一種罕見的遲發性角質化遺傳病。基因鑲嵌型病例的特點是局部單側的角化性丘疹，患處組織有合子後 *ATP2A2* 基因的突變已有記載。毛囊角化病的節段性病例分為兩種臨床亞型：第一型是除明顯的病灶外，患者其他皮膚並無異樣；第二型則是明顯的局部毛囊角化病患處以外，其他皮膚都有相對輕微的非鑲嵌型表型病徵。本文介紹的兩個第一型節段性毛囊角化病個案，患者都對外用維甲酸有良好的治療效果。

**Keywords:** Darier's disease, segmental, therapy, topical retinoids

**關鍵詞：**毛囊角化病、節段性、治療、外用維甲酸

**Department of Dermatology, Aabadem University  
School of Medicine, Istanbul, Turkey**

Ö Bakar, MD  
EÖ Durmaz, MD  
E Sezer, MD

**Department of Pathology, Aabadem University  
School of Medicine, Istanbul, Turkey**

ED Çetin, MD

Correspondence to: Dr. EÖ Durmaz

Acibadem Maslak Hospital, Büyükdere Caddesi 40, Maslak  
34457, Istanbul/Turkey

## Introduction

Darier's disease (DD) is a rare autosomal dominant genodermatosis caused by loss-of-function mutations in the *ATP2A2* gene. This gene is located on chromosome 12q23-24 and encodes sarco/endoplasmic reticulum calcium adenosine triphosphate isoform 2 (SERCA2). Mutations in the gene impair intracellular  $Ca^{2+}$  signalling and disturb keratinocyte adhesion resulting in acantholysis and dyskeratosis. The disorder presents with disseminated brownish and

pruritic papules showing a predilection for the seborrhoeic areas, along with palmoplantar pits, nail dystrophies (V-shaped nicking and ridging) and keratotic papules on the dorsal aspects of the hands and feet.<sup>1</sup>

Post-zygotic mutations may result in localised or segmental forms of the disease, which are examples of genetic mosaicism.<sup>1,2</sup> Zosteriform, unilateral and linear variants represent the phenotypical forme fruste of segmental forms of DD.<sup>3-5</sup> The term "acantholytic dyskeratotic epidermal naevus" denotes localised or unilateral lesions of DD distributed in a linear fashion and conforming to Blaschko's lines.<sup>1,3</sup>

Herein, we report two cases of segmental DD with favourable response to two different topical retinoid preparations.

### Case 1

A 29-year-old female patient presented with a few month history of itchy pink-brown papules located on the right side of the neck. The patient could recall carrying her bag on her right shoulder as a source of trauma. Previously prescribed topical steroids were of no benefit.

Dermatological evaluation revealed linearly arranged, slightly pink, keratotic, 2-3 mm sized, 10-12 papules on the right side of the neck (Figure 1a). Histology of a punch biopsy sample displayed hyperkeratosis, elongation of rete ridges, suprabasal acantholysis and marked dyskeratosis in the form of corps ronds and grains; the findings were consistent with DD. The patient was advised to avoid friction and use sunblock during the daytime. A trial of tretinoin cream 0.01% (Tretin<sup>®</sup> cream 0.01%) every other night resulted in complete clinical clearance within one month (Figure 1b). The patient has been followed up for four years without any recurrence.

### Case 2

An otherwise healthy, 28-year-old male patient presented with a four month history of asymptomatic tiny papules on the chest. The papules tended to increase in number with sweating. Dermatological evaluation revealed multiple, 2-3 mm sized erythematous, hyperkeratotic papules arranged in a band-like fashion on the left side of the chest (Figure 2). The papules were noted to involve the skin area that came into contact with the seat belt while driving. A skin biopsy portrayed findings suggestive of DD

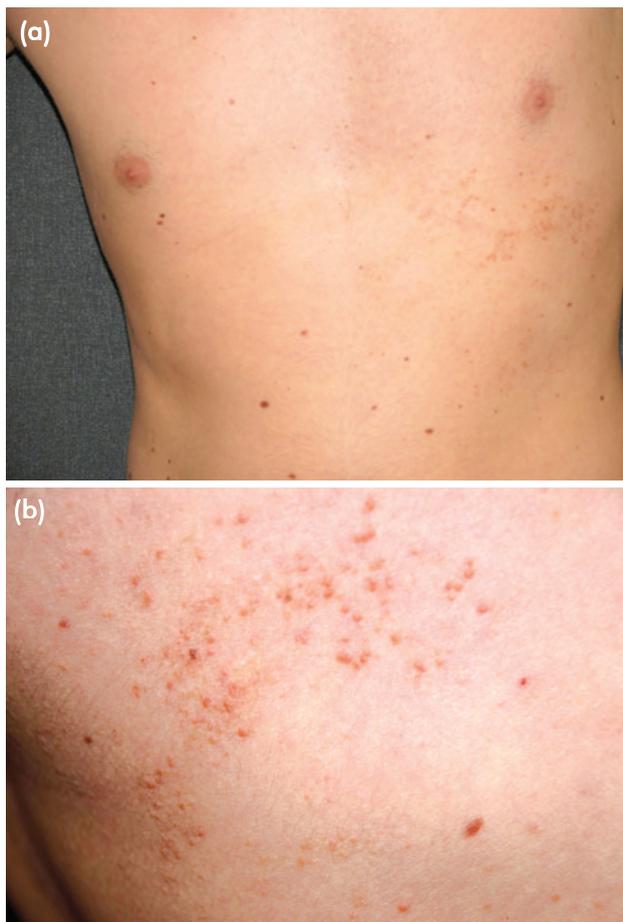


**Figure 1.** (a) Unilaterally localised hyperkeratotic tiny papules on the neck. (b) Complete clearance of the lesions after one-month treatment of topical tretinoin cream.

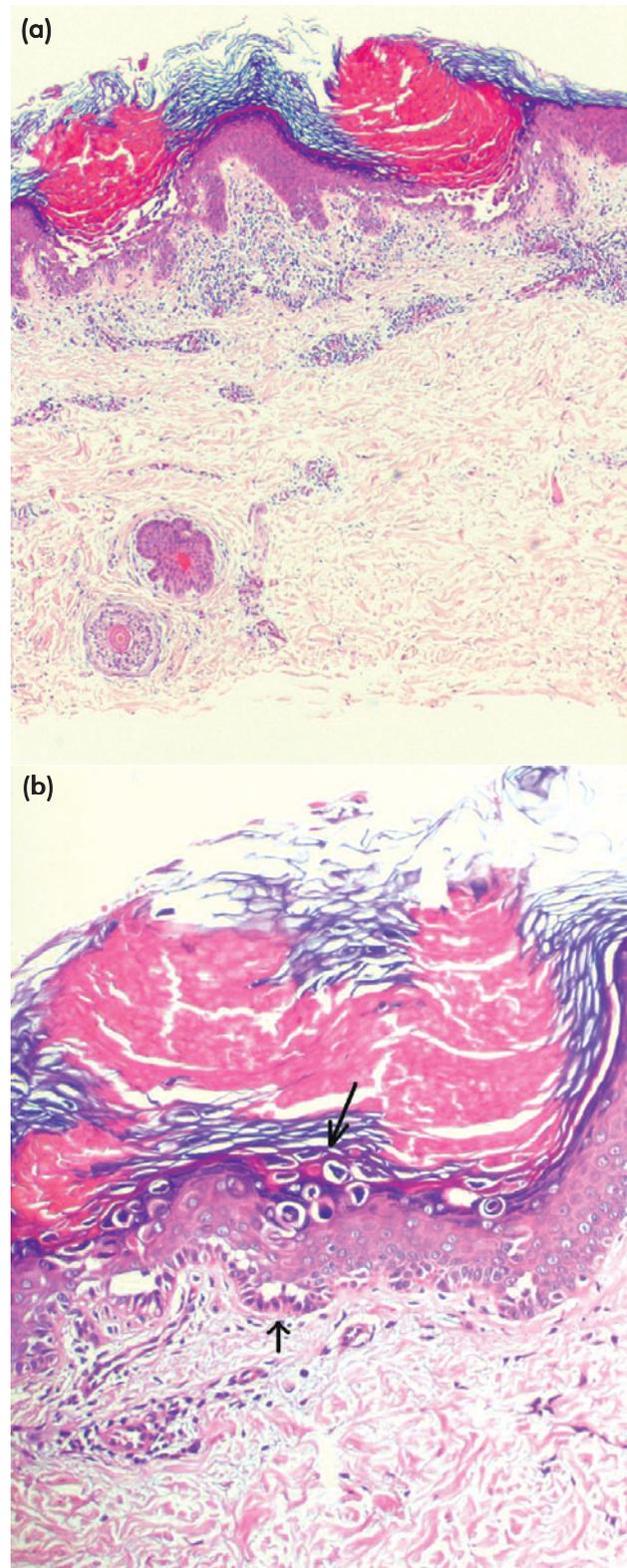
(Figure 3). The patient was advised to avoid friction and use of topical tazarotene gel 0.05% (Tazorac® gel 0.05%) once at bedtime was recommended. Significant improvement was attained after four weeks of treatment.

## Discussion

Localised forms of DD, characterised by hyperkeratotic papules distributed in a linear array, were initially described by Kreibich in 1906.<sup>6</sup> More than 50 cases have been described since then.<sup>4</sup> The prevalence of this variant is estimated as 10% of cases with DD.<sup>7</sup> In 1997, Happle proposed a classification of segmental DD into two forms: Type 1 manifesting with distinct lesions of equal severity on a background of normal appearing



**Figure 2.** (a) Hyperkeratotic papules distributed in a band-like fashion on the chest. (b) Closer view of 2-3 mm sized hyperkeratotic papules.



**Figure 3.** (a) Suprabasal acantholytic clefting and thickened stratum corneum with parakeratosis in two adjacent foci (H&E x 40). (b) Close up. Suprabasal acantholytic clefting (short arrow) and dyskeratotic cells (corps ronds and grains) (long arrow) (H&E x 100).

skin in a non-mosaic presentation and type 2 with well-defined areas of segmental DD occurring on a background of less severe classic (non-mosaic) DD phenotype.<sup>8</sup> It is postulated that type 1 segmental DD represents an early post-zygotic mutation resulting in heterozygosity, whereas type 2 segmental DD is a result of twin spotting (a particular form of loss of heterozygosity).<sup>9</sup> Our cases are illustrative of type 1 segmental DD as the surrounding skin is entirely normal (i.e. does not comprise stigmata of classical DD).

The average age at onset of reported cases is in the late twenties, but years may lapse before the correct diagnosis is established, particularly in subtle type 1 form of the disease. Localised keratotic papules should arouse suspicion for this rare mosaic form of DD.

Lesions can be triggered and exacerbated by sunlight, heat, radiotherapy, ultraviolet radiation, sweating, occlusion and mechanical irritation and can spontaneously disappear in winter.<sup>1</sup> Both of our patients could recall a frictional triggering factor to some extent. Although the pathophysiological effect of ultraviolet light is somewhat understood, the exact mechanism of frictional factors is unknown.<sup>1</sup> There are also some controversial reports regarding the role of sex hormones.<sup>4,6</sup> Exacerbations during pregnancy have been reported.<sup>4</sup> However, the responsible hormones have yet to be identified.

There are no guidelines or evidence based treatment protocols for DD. Systemic and topical retinoids, calcineurin inhibitors, tacalcitol, ciclosporin, 5-fluorouracil, oral contraceptives, electron beam therapy, photodynamic therapy, laser therapy and surgery have all been described as treatment options in the literature.<sup>1,7</sup>

Systemic retinoids have been the most effective treatment modalities for generalised forms, but the side-effect profile limits their use.<sup>1,7</sup> Although topical form of retinoids are more convenient for

use in localised forms of DD, the side effect of irritation should be kept in mind.<sup>10,11</sup> Isomorphic response with lesions appearing on the irritated area can be observed in DD. Short contact application of retinoids has been preferred in some of the reported cases to avoid this adverse effect.<sup>10</sup> We observed favourable outcomes with both topical tretinoin and topical tazarotene in our patients. The treatment was well-tolerated in both cases and once a day or every other day application sufficed for excellent control of the disease.

Both the synthetic retinoid tazarotene and naturally occurring tretinoin selectively bind to the retinoic acid nuclear receptor and act as modulators of keratinisation and cellular differentiation. They have strong anti-inflammatory activity and down-regulate epidermal growth factor receptors and hyperproliferative keratins.<sup>11</sup> Their anti-neoplastic properties may also confer a therapeutic advantage, since there have been reports of non-melanoma skin cancers arising from DD skin areas.<sup>9</sup> We believe that retinoids represent the treatment of choice for patients with localised DD and are worth trying before commencing on immunosuppressive agents.<sup>7</sup> Short contact application may reduce the risk of irritation.<sup>10</sup> We recommend switching to an alternative retinoid when one form fails.

## Conclusion

Although rare, localised forms of Darier's disease may be encountered in clinical dermatology practice. Biopsy is usually required to establish the diagnosis and the list of differential diagnostic considerations include Hailey-Hailey disease (familial benign pemphigus), Grover's disease (transient acantholytic dermatosis) and acrokeratosis verruciformis of Hopf. Topical retinoids might be considered as the initial treatment option in any patient with a confirmed diagnosis of segmental Darier's disease.

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