# DARIER DISEASE: CLINICAL, HISTOPATHOLOGICAL AND THERAPEUTIC PERSPECTIVES

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**Summary**

*Darier's disease (DD), also referred to as keratosis follicularis, is a rare autosomal dominant genodermatosis caused by mutations in the ATP2A2 gene. Clinically, DD typically appears during the first or second decade of life, presenting with greasy, hyperkeratotic papules and plaques that predominantly affect seborrheic regions such as the scalp, face, neck, and trunk and occasionally the oral mucosa. Histological examination shows suprabasal clefts with acantholysis, alongside dyskeratotic cells. Current management primarily focuses on symptomatic relief and avoidance of exacerbating factors as available treatments, including retinoids, corticosteroids, vitamin D analogs, photodynamic therapy, and surgical methods, often provide only partial short-term benefits. The following clinical case presented underscores the significance of an accurate diagnosis achieved through the integration of clinical and histopathological findings. Enhanced recognition of this disorder is essential for therapeutic management.*

***Keywords**: rare disease, genodermatosis, Darier's disease, management.*

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## Introduction

Darier's disease (DD), with a prevalence estimated between 1 in 30,000 and 1 in 100,000, is an autosomal dominant genodermatosis characterized by keratotic papules and plaques with highly variable distribution and appearance. [1,2] Histologically, lesions reveal suprabasal clefts accompanied by acantholysis and dyskeratotic cells termed corps ronds and grains.[3,4]

Classical lesions consist of skin-colored or reddish-brown papules that typically affect seborrheic regions such as the scalp, face, chest, and back, while acral areas may show wart-like lesions on the hands and feet. [5-7] Nail changes, such as subungual hyperkeratosis, longitudinal red and white streaks, and V-shaped distal notches represent key diagnostic indicators. Less frequent forms may feature acral keratoderma, leukodermic macules, giant comedones, keloid-like vegetations, or hemorrhagic blisters. [6-8]

Mucosal and genital involvement can also occur, presenting as whitish or hyperkeratotic papules, erosions, or plaques, sometimes accompanied by pruritus, discomfort, or secondary infection. Ocular findings, though rare, include eyelid papules, conjunctival keratosis, blepharitis, and corneal ulceration.

DD is associated with an increased risk of skin infections, particularly by Staphylococcus aureus and herpes simplex virus. [3,6,7] Individuals with DD often experience itching, burning, and pain. Lesions in intertriginous areas frequently produce a fetid odor, contributing to social discomfort. [3,8] Secondary complications such as impetiginization, eczematization, and

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colonization by bacteria, yeast, or dermatophytes are common. These changes can result in vegetating plaques and may predispose patients to widespread viral infections, including eczema herpeticum. [8,9] Occasionally, salivary gland obstruction is observed. Rarely, squamous cell carcinoma arises in the scalp, vulva, scrotum, thigh, or subungual regions, sometimes linked to human papillomavirus (HPV) infection. [7-9]

Management of DD requires careful infection control and monitoring for secondary complications to reduce morbidity. Overall, these clinical and histological features reflect the heterogeneous and multisystemic nature of DD. Other extracutaneous manifestations include learning difficulties and neuropsychiatric features such as seizures, mild intellectual disability, schizophrenia, and bipolar disorder. [6,7,10]

Its clinical features can resemble several other disorders, such as Hailey–Hailey disease, seborrheic dermatitis, Grover's disease, pemphigus vegetans, acanthosis nigricans, and palmar warts. [3,7] Distinguishing DD from these conditions is crucial for correct diagnosis and effective management. [1,3]

## Case Presentation

### Anamnesis and Medical Context

We present the case of a 32-year-old patient who was evaluated for the first time in the dermatovenerology outpatient clinic for keratotic, brownish-red papules with a rough surface on palpation, distributed generally but predominantly in seborrheic areas.

The patient reports intense pruritus and a fetid odor, exacerbated by physical exertion and heat exposure.

From the medical history, the patient stated that during adolescence, he presented with multiple, polymorphic acneiform eruptions on the face and trunk, for which he underwent systemic retinoid therapy.

Although the clinical evolution was favorable, the treatment was discontinued due to the onset of persistent headaches and the development of tendinitis in the lower limbs.

The current lesions began approximately two years ago, initially on the trunk, with extension to the scapular, deltoid regions, and upper limbs. No relevant family history was identified. At presentation, the patient was afebrile, conscious, and cooperative, with normal hemodynamic parameters and no signs of visceral involvement.

### Clinical Examination and Paraclinical Investigations

Dermatologic examination revealed multiple keratotic papules, brown reddish in color, approximately 1-3 mm in size, with a rough surface on palpation, some partially crusted, with slight tendency to coalescence, distributed generally, predominantly in seborrheic areas. Subjectively, the patient reports intense pruritus and a foul odor, with a significant impact on quality of life. He also describes depressive episodes attributed to the disease and its physical appearance, noting that he feels inhibited in carrying out daily and social activities that he previously engaged in. The clinical appearance, lesion evolution, and patient age raise suspicion for a genodermatosis.

Paraclinical investigations were within normal limits complete blood count, liver and kidney function tests were normal, with no signs of systemic inflammation. Skin biopsy revealed a thin epidermis with parakeratosis and acanthosis, acantholytic dyskeratosis, multiple granular and round bodies, suprabasal clefting, and dermal papillae lined by a single layer of basal cells in acantholytic areas. In the dermis, a mild lymphoplasmacytic inflammatory infiltrate was observed, without eosinophils. Morphological findings support a diagnosis of Darier disease, with confirmation requiring genetic testing for ATP2A2 mutation. Although genetic testing is strongly recommended, considering the fertile age and the autosomal-dominant inheritance of the disease, the patient has deferred it due to financial constraints.

### Therapeutic Management and Outcome

Considering the current psychological impact and previous complications associated with systemic retinoid therapy, an individualized therapeutic plan was instituted.

Topically, 0,1% tretinoin in emollient lotion was applied in the evening every other day for 30 days, while in the morning, an 8% calamine topical preparation was applied to reduce

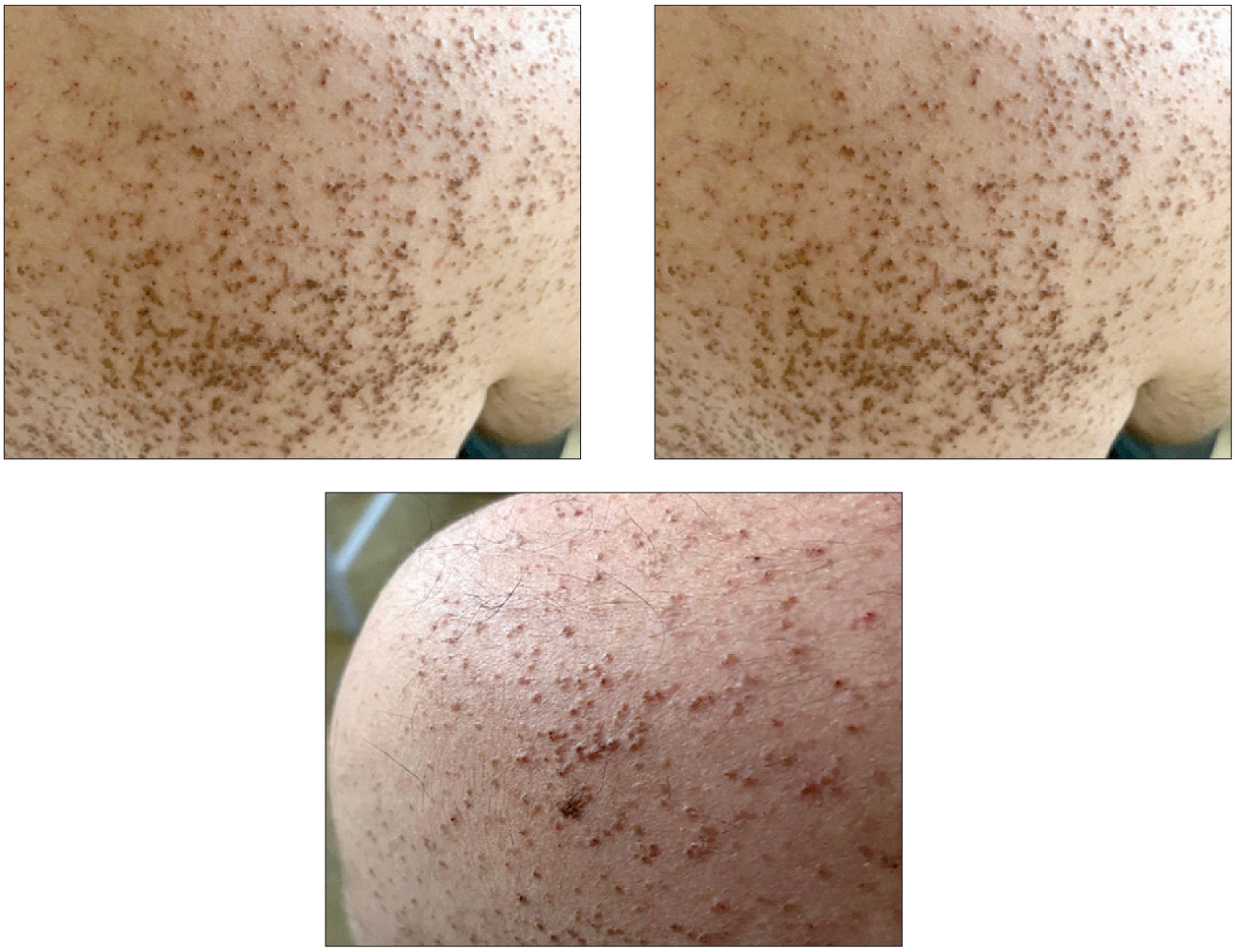

*Figure 1-3. Patient appearance at presentation*

pruritus. Systemically, the patient received cyclosporine 175 mg/day (4 tablets of 25 mg in the morning, 3 tablets of 25 mg in the evening). The treatment was well tolerated, and the clinical course was favorable, with improvement of pruritus and progressive regression of skin lesions and their pigmentation.

## Discussions

Although inherited in an autosomal dominant pattern, nearly half of DD cases present without a positive family history, likely due to unrecognized mild forms among relatives. [8] The disease follows a chronic, relapsing course, and, management is primarily symptomatic focusing on minimizing triggers, controlling hyperkeratosis, reducing malodour, and preventing secondary infections. [1,3,8]

General measures include sun protection, lightweight clothing, and daily skin care using antimicrobial cleansers and keratolytic emollients to limit bacterial colonization. [8,9]

Topical therapies such as retinoids are most effective for localized lesions, although irritation is common; low to mid potency corticosteroid, vitamin D analogues, or diclofenac gels may be used. [1,8]

Systemic retinoids (isotretinoin, acitretin, and alitretinoin) demonstrate significant improvement in extensive disease, reducing hyperkeratosis and odor.The treatment requires close monitoring, as discontinuation may lead to relapse, while continued administration can

cause adverse effects such as mucosal dryness, photosensitivity, osteoarticular and metabolic disturbances, as well as a possible exacerbation of neuropsychiatric and neurological symptoms. [1,3,8] In patients intolerant or unresponsive to retinoids, cyclosporine or doxycycline may be considered, and procedural interventions (laser therapy, dermabrasion, photodynamic therapy, or surgical excision) can be employed for refractory, localized lesions. [1,3,8] In severe, therapy-resistant cases, emerging immuno modulatory strategies targeting the IL-23/IL-17 axis represent a promising avenue. [3,11]

## Conclusions

DD is a rare autosomal dominant genodermatosis. It presents with chronic, relapsing skin lesions and variable systemic involvement. The condition shows significant clinical and genetic heterogenity. Accurate diagnos requires clinical and histopathological, genetical correlation. Treatment is mainly symptomatic, including topical and systemic therapies, general care measures, and procedural interventions. A personalized, multidisciplinary appriach is essential to optimize patient outcomes.

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Conflict of interest
NONE DECLARED

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