



Clinicopathologic findings of guttate leukoderma in Darier disease: A helpful diagnostic feature

Jennifer Nicole Harb, MD, and Kiran Motaparathi, MD
Gainesville, Florida

Key words: Darier disease; guttate leukoderma; hypopigmented macules; keratosis follicularis.

INTRODUCTION

Darier disease (DD), also known as keratosis follicularis or Darier-White disease, is a rare autosomal dominant genodermatosis attributed to a mutation in the *ATP2A2* gene. DD affects both males and females worldwide, with high penetrance (95%) and variable expressivity, allowing for varied clinical manifestations and disease severity among affected families and individuals.¹ The characteristic feature of DD is the presence of firm, greasy, skin-colored to yellow-brown, hyperkeratotic papules distributed in seboreic areas, such as the scalp, face, and trunk. Other classic findings include flat, wart-like papules over the dorsal hands and feet (acrodermatitis verruciformis of Hopf); flexural vegetative lesions; palmoplantar pitting; cobblestone appearance of the oral mucosa; and V-shaped scalloping of the distal nail plate.²

Confetti-like hypopigmented macules in association with DD were described by Goodall and Richmond, and this manifestation was termed guttate leukoderma (GL).³ This unique feature is considered distinct from postinflammatory changes that can be seen at sites of healed lesions in darkly pigmented skin. Since the initial description, this manifestation has been sparsely reported and might be infrequently recognized as a diagnostic feature of this genodermatosis.⁴ Herein, we report GL as a helpful identifying clinical finding in a case of previously unrecognized DD and, in addition, describe the histopathology of this dyschromia.

CASE REPORT

A 55-year-old black man requested evaluation of a pruritic, papular eruption on his back of 1-month

Abbreviations used:

DD: Darier disease
GL: guttate leukoderma
IGH: idiopathic guttate hypomelanosis

duration. His condition was aggravated with sweating. He also noted the appearance of asymptomatic hypopigmented macules over his neck, arms, chest, abdomen, and back since the first decade of life. Over the years, the lesions increased in number and became more prominent. Family history revealed that his maternal grandmother, 4 siblings, and daughter had the same leukoderma and onset of findings.

Physical examination revealed widespread involvement of multiple 1-4 mm discrete and coalescing hypopigmented macules scattered over his central chest, abdomen, and back (Fig 1, A; Fig 2, A and B), with less prominent involvement of his neck and 4 extremities. Examination of his fingernails revealed subungual hyperkeratosis and V-shaped scalloping of several of the distal nail plates (Fig 1, B). On the lower back, there were multiple firm, greasy, hyperkeratotic, brown papules (Fig 2, A and B).

Histopathologic evaluation of a biopsy taken from a papular lesion on the back revealed verrucous epidermal hyperplasia with suprabasilar clefting, as well as numerous dyskeratotic cells forming corneoid and grains; follicular involvement was evident (Fig 3, A and B). Examination of a hypopigmented macule demonstrated papillomatosis without acanthosis, thinned epidermis and rete ridges, and

From the Department of Dermatology, University of Florida College of Medicine, Gainesville.

Funding sources: Supported by the open access publishing fund at the University of Florida.

Conflicts of interest: None declared.

Correspondence to: Kiran Motaparathi, MD, Department of Dermatology, University of Florida College of Medicine, 4037 NW 86th Ter, 4th floor, Springhill room 4119, Gainesville, FL 32610. E-mail: kmotaparathi@dermatology.med.ufl.edu.

JAAD Case Reports 2018;4:262-6.
2352-5126

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<https://doi.org/10.1016/j.jdc.2017.09.021>



Fig 1. **A**, Chest and abdomen with multiple 1-4 mm discrete and coalescing hypopigmented macules. **B**, Subungual hyperkeratosis and V-shaped scalloping of the fingernails.

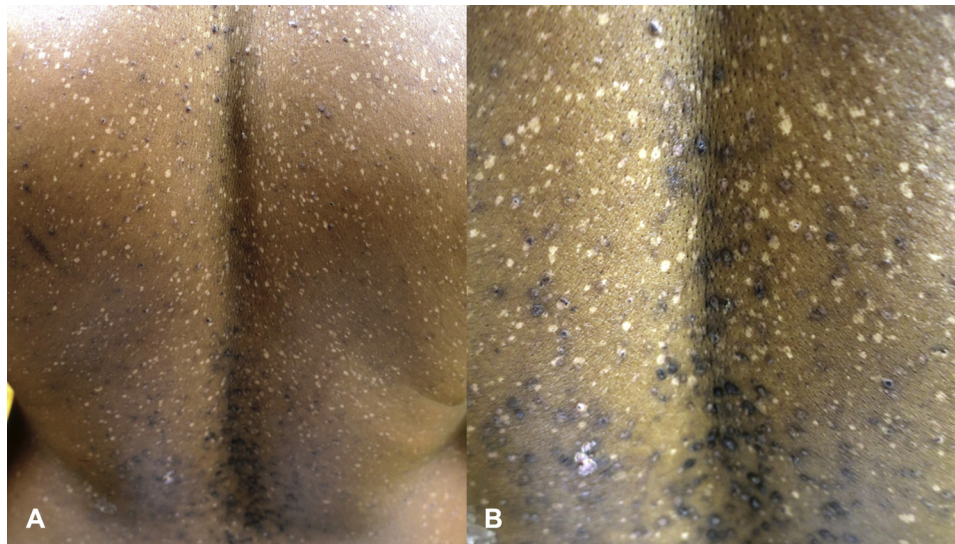


Fig 2. **A** and **B**, Back with multiple hypopigmented macules admixed with multiple hyperkeratotic brown papules.

maintained basilar pigmentation of the rete ridges (Fig 3, A); these features contrasted starkly to the patient's nonlesional skin (Fig 3, D). In addition, immunoperoxidase for SOX-10 and a Fontana Masson special stain highlighted a focal absence of pigmentation and melanocytes, with preservation of melanization at the base of rete ridges. Pigment incontinence and dermal melanophages were absent (Fig 4, A-D).

Given the family history, onychodystrophy, and cutaneous clinical and histologic morphology, a diagnosis of Darier disease was made. Sequencing analysis for *ATP2A2* gene mutations was recommended but was deferred by the patient due to financial constraints.

DISCUSSION

Fewer than 30 cases of GL in DD have been documented in the literature. While the majority of cases have been reported in dark-skinned individuals of African descent, there have been cases reported in fair-skinned Japanese patients as well.⁴

The pathogenesis of GL has not yet been fully elucidated. Several features support GL as a manifestation of the disease itself, rather than secondary postinflammatory change.

In 70% of patients with DD, keratotic or verrucous papules first present during 6-20 years of age, with peak onset during the second decade of life in the peripubertal period.⁵ Given the patient's history of recent onset of keratotic papules, transient

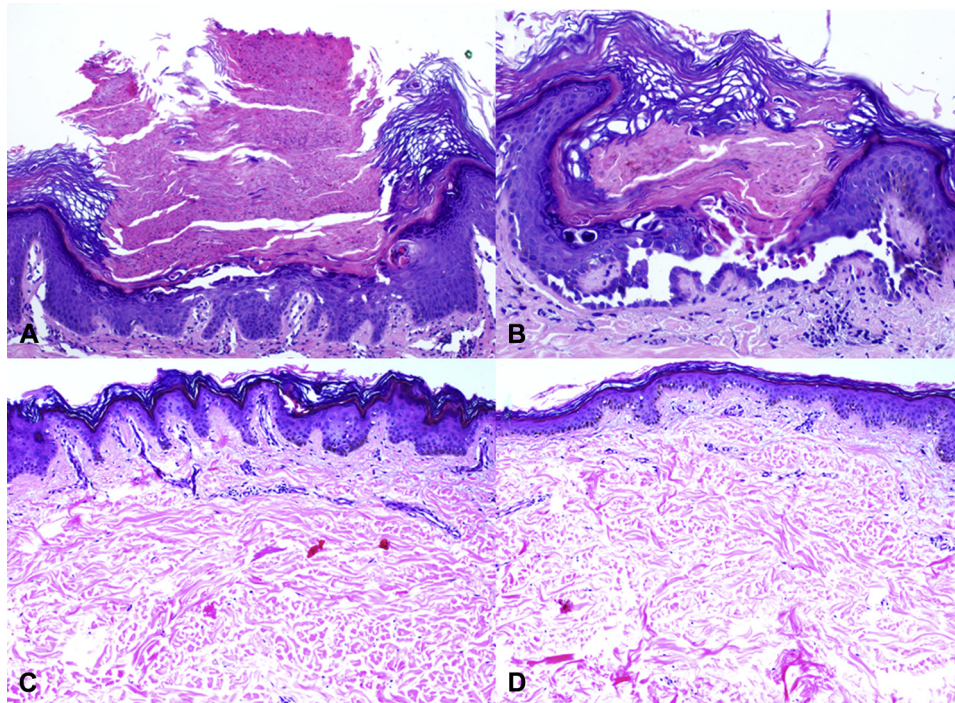


Fig 3. **A** and **B**, Verrucous epidermal hyperplasia, acantholytic dyskeratosis, and relationship to the follicular infundibulum are demonstrated in a keratotic papule from the sacrum. **C**, Basket-weave stratum corneum, papillomatosis without acanthosis, thinned epidermis, and maintained basilar pigmentation at the ends of rete ridges are observed in guttate leukoderma. **D**, Basilar pigmentation is retained within a normal epidermis in the patient's adjacent, nonlesional skin. (**A-D**, Hematoxylin-eosin stain; original magnifications: **A**, **C**, **D**: $\times 100$; **B**: $\times 200$.)

acantholytic dermatosis (Grover disease) was considered. However, transient acantholytic dermatosis is not associated with a family history consistent with a hereditary process, GL, or the characteristic onychodystrophy described herein. Lesions of GL typically appear simultaneously or, more commonly, years before the development of papular lesions; only 1 previously reported case described subsequent onset of macular lesions.⁶ In the patient presented here, the hypopigmented macules developed several decades before the keratotic papules, without evolution into classic lesions of DD. Unlike keratotic papules of DD, GL is not limited to sebaceous areas, but is widespread with involvement of the extremities and sometimes face and scalp.⁴ In addition, while treatment with systemic retinoids typically leads to clinical improvement in keratotic lesions, no effective treatment has been reported for GL.

Previously described histologic features of GL are a decrease in the density of basal epidermal melanocytes, with variable dyskeratosis and acantholysis.^{4,6,7} In the case described here, the histopathologic features are notably similar to that

of confluent and reticulated papillomatosis, with an attenuated epidermis, slender rete ridges, and absence of acanthosis.⁸ Furthermore, the skip melanization observed here is similar to that described in idiopathic guttate hypomelanosis (IGH), but this pattern has not been reported previously for GL of DD. Distinction from IGH is supported by the epidermal changes observed; epidermal atrophy is typical of IGH.⁹ Evidence of postinflammatory pigment alteration (pigment incontinence and melanophages) was absent. Taken together with the unique histologic findings, the historical and clinical findings of GL support this manifestation as a distinct clinicopathologic feature of DD.

Several proposed mechanisms exist regarding the underlying pathogenesis of GL. Goh et al proposed that mutations in *ATP2A2* are directly responsible. In DD, mutations in the *ATP2A2* gene lead to the dysfunction of SERCA-2, a calcium pump of the sarcoplasmic endoplasmic reticulum. This results in disruption of intracellular calcium levels, ultimately leading to loss of cell-cell adhesion (acantholysis) and induction of apoptosis (dyskeratosis).^{2,4}

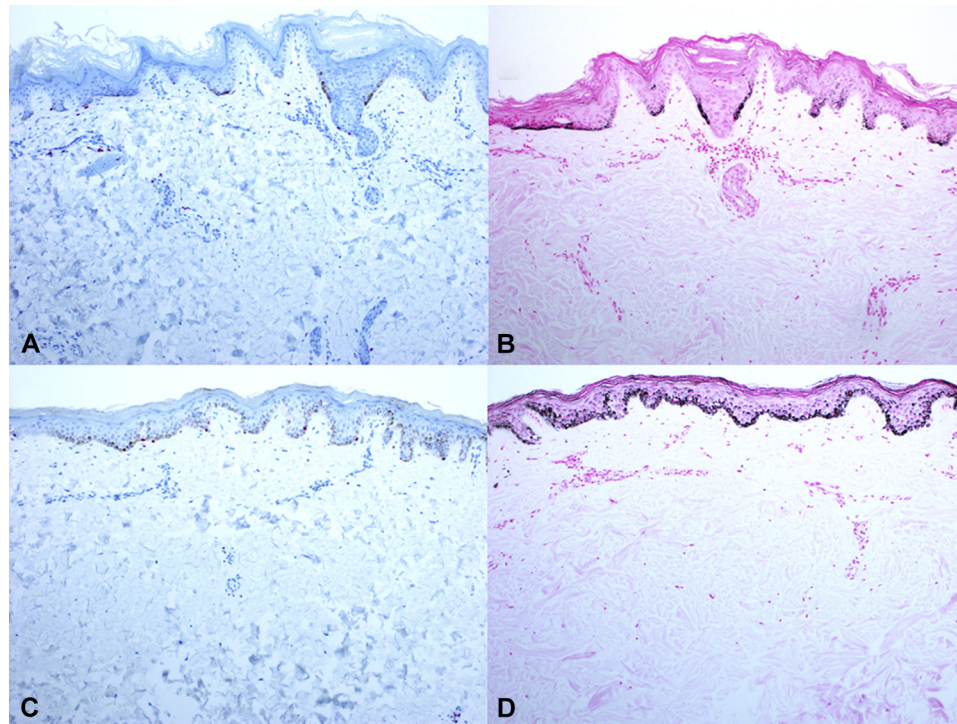


Fig 4. **A**, Immunostaining for SOX-10 within a hypopigmented macule demonstrates an overall reduction in the number of melanocytes at the dermoepidermal junction, with preservation of melanocytes at the base of rete ridges and acrosyringium and absence within the epidermis overlying dermal papillae. **B**, A corresponding near absence of melanization is also demonstrated between rete ridges, while basilar pigment is preserved at the ends of rete ridges and the acrosyringium. Pigment incontinence is absent. **C** and **D**, For comparison, the patient's adjacent nonlesional skin features a normal complement of melanocytes and complete melanization. (**A** and **C**, SOX-10 stain; **B** and **D**, Fontana Masson stain; original magnification: $\times 100$.)

E-cadherin is a calcium-dependent transmembrane glycoprotein that functions within adherens junctions to mediate epithelial intercellular adhesion. E-cadherins also play a pivotal role in the adhesion of melanocytes to keratinocytes, and formation of melanocyte dendrites requires this direct keratinocyte contact. Defective E-cadherins disrupt melanocyte-keratinocyte adhesion, resulting in impaired dendrite formation and melanin transfer. Melanocyte apoptosis consequently follows, suggesting the underlying pathophysiology of GL in DD.⁷

Given the rarity of GL in DD, dermatologists and dermatopathologists might be unaware of this unique feature. However, it is both important and helpful to recognize this manifestation: GL often precedes the onset of keratotic papules, thereby serving as an early marker of DD. This finding might also be useful in dark-skinned patients without classic keratotic papules in a seborrheic distribution. In addition, the histology of GL, including findings that might simulate confluent and reticulate papillomatosis and the skip melanization of IGH, may

prompt consideration of DD when evaluating a leukoderma. Awareness of the clinicopathologic features of this unusual manifestation could allow earlier diagnosis and appropriate counseling to patients and family members with this genodermatosis.

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