Unilateral Segmental Darier Disease Following Blaschko Lines: A Case Report and Review of the Literature

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GOAL

To understand Darier disease (DD) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical presentation of DD.
2. Explain the genetic causes of DD.
3. Discuss the variants of DD.

CME Test on page 193.

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Darier disease (DD) is an autosomal-dominant skin disorder that is characterized by multiple keratotic papules, loss of epithelial adhesion, and abnormal keratinization. We describe an unusual case of late-onset unilateral segmental DD that follows the lines of Blaschko. Our patient did not exhibit other classic findings of DD. Our case and review of the literature suggest that lesions previously classified as acantholytic dyskeratotic epidermal nevi (ADEN) are actually unilateral segmental presentations of DD.

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Darier disease (DD), or keratosis follicularis, is an uncommon, slowly progressive, autosomal-dominant skin disorder characterized by multiple keratotic papules, loss of adhesion between epidermal cells, and abnormal keratinization. The prevalence of DD in individuals has been estimated

to be from 1 in 55,000[1] to 1 in 100,000.[2] Men and women are affected equally. The first signs of the generalized condition usually appear in patients between the ages of 6 and 20 years. The disease often is exacerbated by sun exposure and perspiration.[3,4]

Persons with DD develop hyperkeratotic papules that can coalesce into warty plaques in seborrheic areas on the central trunk, scalp, forehead, and flexures. The lesions can have a greasy appearance and can be malodorous, especially in intertriginous areas. Persons with DD also usually have keratotic papules and pitting on the palms and soles. Distinctive nail abnormalities include alternating red and white longitudinal bands, often with V-shaped nicking at the distal nail, along with subungual hyperkeratosis. Fine white papules sometimes appear on mucous membranes. The dorsum of the hands may develop verrucous papules (acrokeratosis verruciformis of Hopf). These papules, as well as nail changes, often are the first presenting signs of the generalized condition.[4] Histopathology results demonstrate suprabasilar splitting (acantholysis), with underlying villuslike structures in the dermis. Dyskeratosis is demonstrated by corps ronds and grains with overlying hyperkeratosis. A lymphocytic infiltrate commonly is seen.

It has been estimated that in 10% of DD cases, lesions are distributed following a segmental, linear, or localized pattern, and that they may be unilateral.[5,6] The average age of presentation in cases of unilateral DD has been estimated to be 27 years. The characteristic accompanying features of generalized DD (nail, palm, or mucous membrane changes) may be absent in unilateral DD. We present such a case of unilateral DD, describe the unique distribution of the lesions, and discuss the differential diagnosis.

Case Report

A healthy 48-year-old woman presented to the dermatology clinic with a 15-year history of a mildly pruritic rash on her left abdomen that wrapped around to her mid back (Figure 1). The eruption waxed and waned periodically but never fully resolved. She had tried low-potency topical steroids over the years, with minor improvement in the appearance and pruritus of the rash. She noted that no one else in her family had such a condition, and she did not have children. The only factor that seemed to exacerbate the condition was eating chocolate, which she avoided.

Results of a physical examination revealed scattered, 1- to 3-mm, erythematous to light-brown papules with scale that presented in a swirling distribution along the Blaschko lines beginning at the patient's abdominal midline, continuing over her left flank, and extending partially onto her mid back. Multilinear separate areas delineated by a band of unaffected skin were apparent. She had no nail or oral mucosal abnormalities. Results of a biopsy of mid and left lower abdominal lesions showed foci of suprabasilar acantholysis and dyskeratosis including both corps ronds and grains (Figure 2). The patient was given a midpotency topical steroid to use as needed for the pruritus; she declined any further treatment because the rash usually was covered by clothing and was not bothersome.

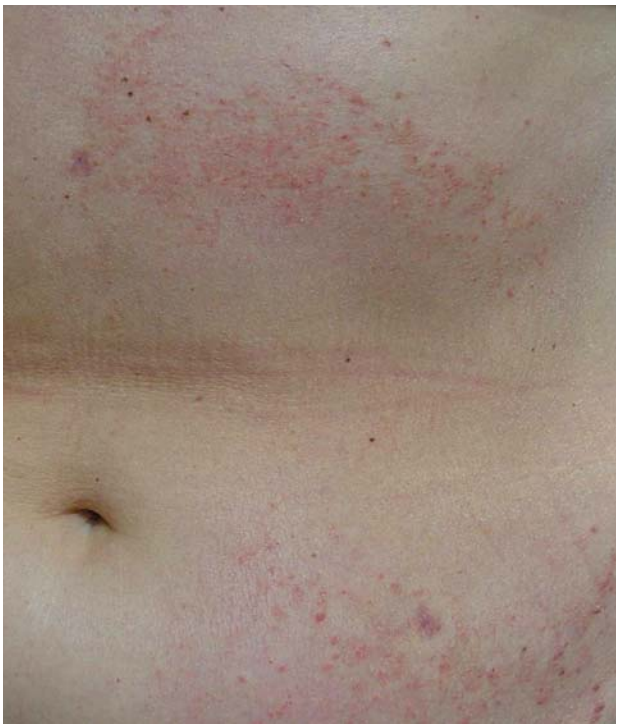

Figure 1. An abrupt midline break in pattern.

Comment

Kreibich[7] described DD in a localized pattern in 1906, and a case of unilateral DD was reported in 1948 by Anderson.[8] Since then, other cases occasionally have been reported. The age of onset of unilateral DD is between the second and fourth decades,[4] with the average age being 27 years, though generalized DD presents at an earlier age.[9] A negative family history is typical in unilateral cases.[7]

DNA testing has elucidated the genetic cause of DD, which is a mutation for the ATP2A2 gene on chromosome 12q23-12q24.[10,11] This gene encodes the sarcoplasmic/endoplasmic reticulum ATPase Ca^{2+} pump.[12,13] A defective pump leads to a deficiency of Ca^{2+} at the membrane, and abnormal expression of P-cadherins in desmosomes results in impaired adhesion between keratinocytes.[14] This

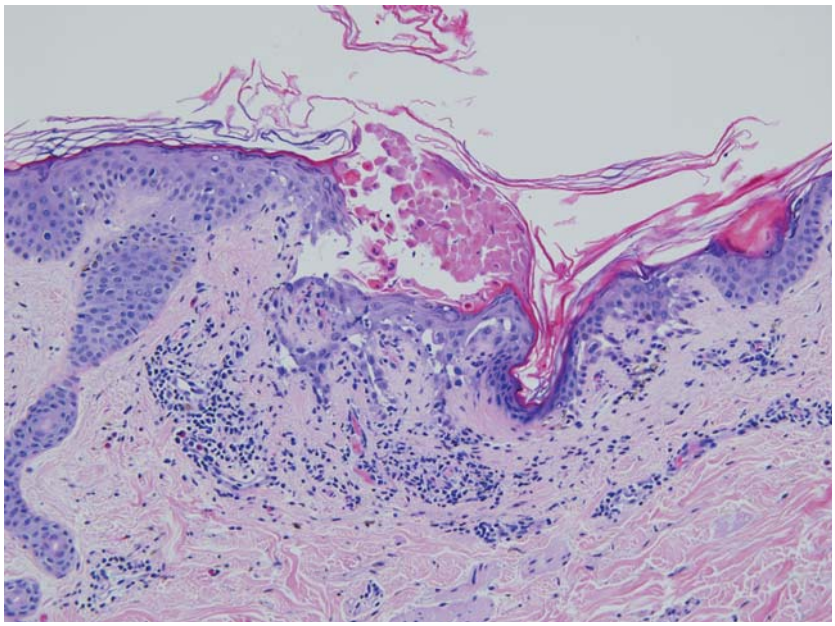

Figure 2. Dyskeratosis and corps ronds (H&E, original magnification ×40).

impaired cell-to-cell adhesion causes acantholysis. In the case of unilateral DD, it is theorized that a genetic mosaicism due to a postzygotic somatic mutation after embryonic lateralization has occurred results in a unilateral presentation along the lines of Blaschko.[15] Genetic studies by Sakuntabhai et al[16] in 2000 and by Wasa et al[17] in 2003 have shown that keratinocytes in lesional skin contain the mutation, whereas the unaffected skin does not.

O'Malley et al[9] suggested that localized DD is a genetic mosaic of generalized DD that results from a postzygotic somatic mutation in early embryogenesis. Blaschko lines are proposed to be embryologic developmental skin patterns that do not follow dermatomal or lymphatic configurations.[15,18] As Moss[19] explained, "Embryonic keratinocytes move outwards from the neural crest by directional proliferation, thus forming a continuous line, the tortuous patterns being created by a complex interplay between cell migration and surface remodeling." Some clinicians have termed the presentation of localized DD as *zosteriform*,[20,21] but it is likely that on closer examination, patients with this form of DD would demonstrate a Blaschkoid—rather than a dermatomal—distribution.

The differential diagnosis of DD includes Hailey-Hailey disease and Grover disease. Although these conditions can be difficult to distinguish histologically, the distribution in Hailey-Hailey disease is primarily intertriginous.[22] Grover disease (transient acantholytic dermatosis) is nonhereditary and usually lasts for months but rarely for years.[23,24]

The terms *segmental* (linear, localized, unilateral) *DD* and *acantholytic dyskeratotic epidermal nevus* (ADEN) have been used to describe the same dermatologic manifestation.[24] Clinicians have been divided on whether to term the eruption *ADEN*[20,24] or *unilateral DD*.[7,16,17,21,25,26] Although our patient showed no other signs of DD, it is our opinion that both clinical and histologic evidence, as well as recent genetic studies of similar lesions, indicate this case should be classified as a unilateral variant of DD rather than as linear ADEN. Patients in the studies by Sakuntabhai et al[16] and Wasa et al[17] also lacked the classic signs of DD, and none of them had a positive family history. This lack of family history of unilateral DD can be explained by the presence of a new postzygotic somatic mutation in the embryonic stages.

Although it is possible that 2 distinct disease entities may have similar histopathology, the results of the aforementioned genetic studies provide strong evidence for calling these lesions *DD* instead of *ADEN*. It has been suggested that genetic testing can better clarify the issue.[7] The genetic testing of ADEN may lead to the finding that all of these lesions are segmental forms of DD.

Differentiating unilateral DD affects treatment considerations and patient outcome. Because it has been found that the turnover rate of cells in DD is 7 times less than that of healthy cells,[27] treatment with retinoids should help speed the process of desquamation. Treatment of DD includes topical and oral retinoids.[7,28] Patients also should use sunscreen and emollients. Oral retinoids have been the most effective therapy; however, significant toxicities limit their long-term use. Additionally, when a patient is no longer taking retinoids, the disease recurs. Hence, topical retinoids should be prescribed for long-term treatment, and oral retinoid supplements should be given for flare-ups.

Conclusion

Recent cases of unilateral DD have been found to contain the same gene mutation as generalized DD. The unilateral presentation is due to a genetic mosaicism that results during embryologic development. Thus, cases of ADEN that are found to

contain the same mutation instead may be called *unilateral DD*, and the term *ADEN* soon may become obsolete.

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