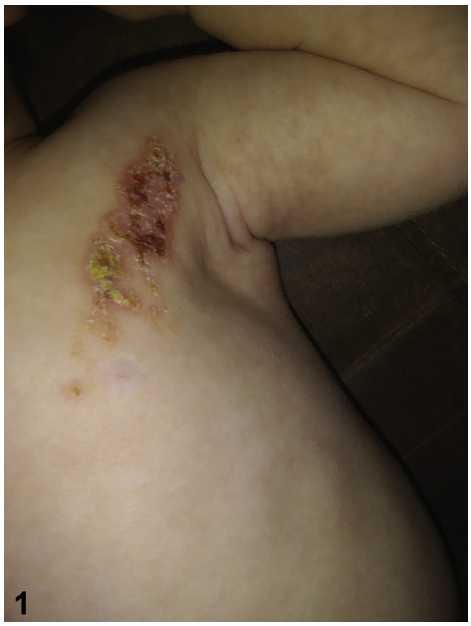
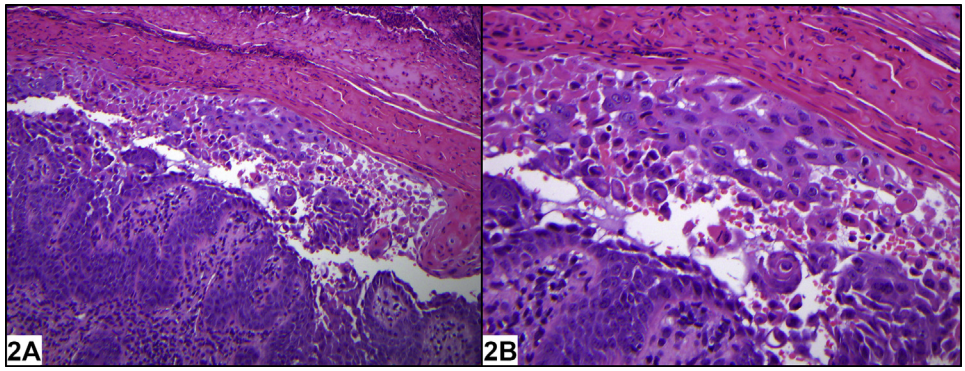
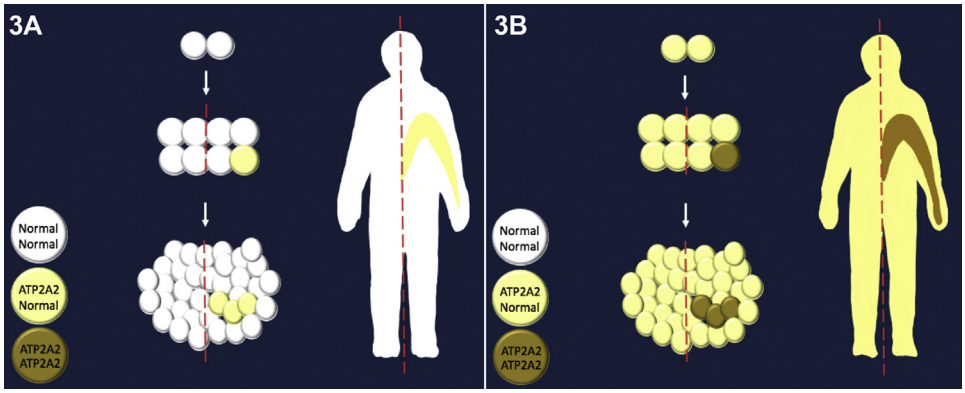
Linear crusted papules in an infant

Lauren Langenderfer, BS,[a] Rachel Giesey, DO,[b] Robert Rothbaum, MD,[b] Luisa Christensen, MD,[b] Ari Konheim, MD,[b] and Gregory Delost, DO[c]
Cleveland and Mayfield Heights, Ohio

Key words: ATP2A2; autosomal dominant; Darier disease; forward mosaicism; incontinentia pigmenti; inflammatory linear verrucous epidermal nevus; linear; linear lichen planus; mosaic neurofibromatosis type 1; segmental Darier disease; SERCA2.







CLINICAL VIGNETTE

An otherwise developmentally normal 3-month-old female infant born at term to a mother with an uncomplicated prenatal history presented with a linear crusted plaque involving the left upper aspect of the chest, which had been present since birth (Fig 1). A punch biopsy of the lesion was obtained (Fig 2). The patient's mother was incidentally found to have small, symmetric, skin-colored to yellow-brown, crusted papules on her face and chest, which she reported had been present since adolescence. Family history was significant for multiple generations of male and female relatives with findings similar to those of the patient's mother.

Question 1: What is the most likely diagnosis?

A. Inflammatory linear verrucous epidermal nevus

B. Incontinentia pigmenti

C. Linear lichen planus

D. Segmental Darier disease

E. Mosaic neurofibromatosis type 1

Answers:

A. Inflammatory linear verrucous epidermal nevus—Incorrect. Although inflammatory linear verrucous epidermal nevus can present in a unilateral distribution along the lines of Blaschko, lesions are typically scaly patches or verrucous papules. In addition, it histologically has a psoriasiform appearance with elongation and thickening of the rete ridges, epidermal hyperplasia, papillomatosis, parakeratosis, and acanthosis.[1]

B. Incontinentia pigmenti—Incorrect. Incontinentia pigmenti may also present at or shortly after birth, following Blaschko lines; however, streaking, whorled papulovesicular lesions with characteristic hyperpigmentation and female predominance (because of lethality in utero in male patients without XXY genotype or mosaicism) clinically distinguishes incontinentia pigmenti.[1]

C. Linear lichen planus—Incorrect. Linear lichen planus classically manifests as flat-topped violaceous papules along lines of Blaschko.[1]

D. Segmental Darier disease—Correct. Histopathology of segmental Darier disease is indistinguishable from that of classic segmental Darier disease, with acantholysis, suprabasal cleavage, and keratin plugs, as well as 2 dyskeratotic cell types, corps ronds and grains. These findings, combined with the clinical presentation of crusted or hyperkeratotic papules or plaques following the lines of Blaschko, sparing nails, palms, soles, and the oral cavity, argue for a diagnosis of segmental Darier disease.[2–4] The differential diagnosis also includes an epidermal nevus with Darier-type acantholysis; however, this was thought to be less likely, given the extensive family history.

E. Mosaic neurofibromatosis type 1—Incorrect. Although the cutaneous distribution described may resemble mosaic neurofibromatosis type 1, analysis of the lesion and histopathology were indicative of segmental Darier disease.[1]

Question 2: Pathogenic variants of which of the following genes are associated with this disease?

A. *ATP2C1*

B. *ATP2A2*

C. *KRT10*

D. *ABCA12*

E. *COL7A1*

Answers:

A. *ATP2C1*—Incorrect. Pathogenic variants of the *ATP2C1* gene result in Hailey-Hailey disease. Like segmental Darier disease, this gene encodes a calcium ATPase pump that, when mutated, results in calcium dysregulation and loss of epidermal cell

From Ohio University Heritage College of Osteopathic Medicine[a]; Department of Dermatology, University Hospitals Cleveland Medical Center[b]; and Apex Dermatology and Skin Surgery Center.[c]

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Rachel Giesey, Department of Dermatology, University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Lakeside 3500, Cleveland, OH 44106. E-mail: rachel.giesey2@uhhospitals.org.

JAAD Case Reports 2020;6:441-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.02.032

adhesion. In contrast to segmental Darier disease, the calcium ATPase pump for Hailey-Hailey disease is located in the Golgi apparatus, not the endoplasmic reticulum.[2,3]

B. *ATP2A2*—Correct. Segmental Darier disease results from pathogenic variants of the *ATP2A2* gene. This gene encodes the sarco/endoplasmic reticulum calcium ATPase pump, which transports calcium into the endoplasmic reticulum and is critical to cellular function. In particular, loss of calcium transport by the sarco/endoplasmic reticulum calcium ATPase-b isoform localized to the epithelium results in the acantholysis and cutaneous manifestations of segmental Darier disease.[2-4]

C. *KRT10*—Incorrect. Pathogenic variants of the *KRT10* gene disrupt keratinocyte differentiation, resulting in epidermolytic hyperkeratosis, not segmental Darier disease.[2]

D. *ABCA12*—Incorrect. Pathogenic variants of the *ABCA12* gene disrupt lipid transporters on epidermal cells, which are critical to cellular structure, resulting in autosomal-recessive congenital ichthyosis, not segmental Darier disease.[3]

E. *COL7A1*—Incorrect. The *COL7A1* gene encodes type VII collagen, the critical component of anchoring fibrils. Therefore, pathogenic variants *COL7A1* gene causes separation of the epidermis from the dermis, resulting in dystrophic epidermolysis bullosa.[2]

Question 3: The cutaneous distribution of these findings is most likely a result of which of the following?

A. Autosomal-dominant inheritance

B. Revertant mosaicism

C. Isodisomy

D. Lyonization

E. Forward mosaicism

Answers:

A. Autosomal-dominant inheritance—Incorrect. Although classic segmental Darier disease follows an autosomal-dominant inheritance pattern, this alone would not account for the linear and segmental findings in this patient.[2-4]

B. Revertant mosaicism—Incorrect. Revertant mosaicism would present with a background of diseased skin with a linear patch of normal skin, the inverse of our patient's presentation.[5]

C. Isodisomy—Incorrect. Inheritance of 2 identical homologous chromosomes, as observed in isodisomy, would not explain the segmental cutaneous distribution described.[2]

D. Lyonization—Incorrect. Although lyonization, or X-chromosome inactivation, can lead to skin disease following the lines of Blaschko, this is not the mechanism thought to cause segmental Darier disease.[2]

E. Forward mosaicism—Correct. Typically, segmental Darier disease is inherited in a type 1 forward mosaic pattern (Fig 3). Although findings of segmental Darier disease usually appear later in life, we postulate that this patient's disease presented at birth because of loss of heterozygosity in a mosaic pattern, and that she may develop more generalized findings of classic segmental Darier disease later in life, thus exemplifying a type 2 forward mosaic pattern of inheritance.[4,5] Cell lines affected in segmental Darier disease with type 2 forward mosaicism will have *ATP2A2* pathogenic variants in both alleles, but neighboring cell lines will have the autosomal dominantly inherited variant in only 1 allele. Clinically, this results in a background of diseased skin with linear areas of more severely diseased skin.

REFERENCES

1. Saraswathy P, Nithya DGD, Sivaranjani J. Study on linear dermatoses. *Int J Res Dermatol*. 2018;4(2):190-196.
2. Destefano GM, Christiano AM. The genetics of human skin disease. *Cold Spring Harb Perspect Med*. 2014;4(10):1-25.
3. Takagi A, Kamijo M, Ikeda S. Darier disease. *J Dermatol*. 2016;43(3):275-279.
4. Reese DA, Paul AY, Davis B. Unilateral segmental Darier disease following Blaschko lines: a case report and review of the literature. *Cutis*. 2005;76(3):197-200.
5. Bolognia JL, Schaffer JV, Cerroni L. Molecular biology. In: DeStefano GM, Christiano AM, eds. *Dermatology*. 4th ed. China: Elsevier; 2017:1004-1020.