Guttate leukoderma and acrokeratosis verruciformis of Hopf: a rare combination in Darier disease

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Abstract

A distinct Darier phenotype presenting with confetti-like hypopigmented macules was first described in 1965. Designated as "guttate leukoderma," this skin finding is a rarely-reported presentation of Darier disease. It has been theorized that the mutation in *ATP2A2* causes defective E-cadherin, which in turn disrupts the adhesion of melanocytes to keratinocytes, thus leading to impaired dendrite formation, hindered melanin transfer, and ultimately to melanocyte apoptosis. Herein, we contribute a case of a 56-year old woman who presented with the rarely-described guttate leukoderma of Darier disease and acrokeratosis verruciformis of Hopf.

Keywords: Darier disease, acrokeratosis verruciformis of Hopf, genodermatosis, calcium, guttate leukoderma

Introduction

Darier disease (DD) is a rare autosomal dominant dermatosis caused by a mutation in the ATP2A2 gene encoding the sarcoplasmic and endoplasmic reticulum Ca2+ ATPase. High levels of calcium in the endoplasmic reticulum are required for proper trafficking of junctional proteins (desmoglein and desmoplakin). When these are depleted, impaired intercellular adhesion strength occurs [1].

Clinically, skin manifestations include hyperkeratotic papules and plaques that often develop in seborrheic and intertriginous areas. These crusted lesions develop around late childhood to early adulthood and can be described as red to brown in color, firm, and greasy; they are often macerated and malodorous. Nail abnormalities include increased fragility, red and white longitudinal bands, and V-shaped notches at the distal nail plate [2].

Additional cutaneous findings include "acrokeratosis verruciformis of Hopf" (AKV), which is commonly described as skin-colored to brown, flat-topped papules of the dorsal hands and feet with an appearance similar to that of verruca planae. These keratotic papules have a distinct histopathologic appearance from that of Darier disease. Thus far, five families with pure AKV phenotypes have carried the specific *ATP2A2* p.(Pro602Leu) mutation that is not seen in Darier disease [3]. This mutation has also been associated with long QT syndrome and dilated cardiomyopathy [3, 4].

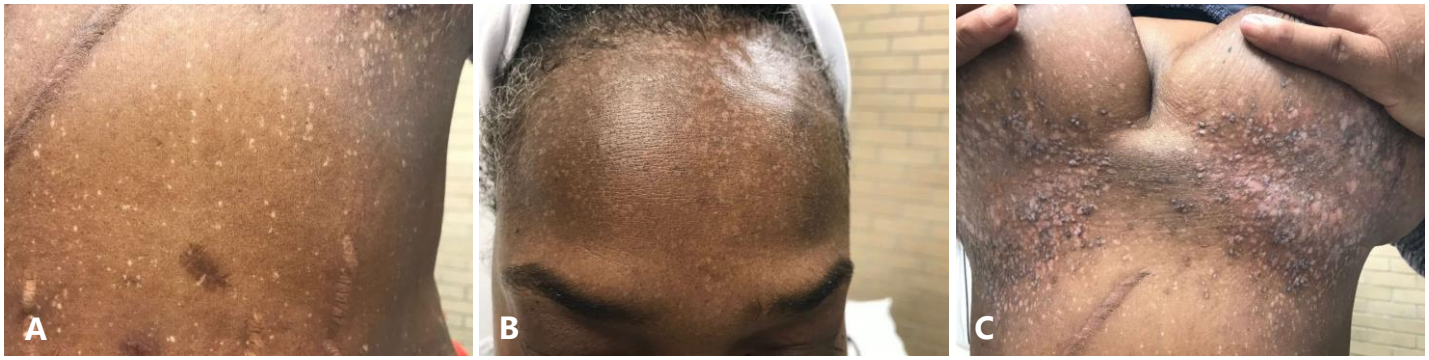

Figure 1A. *Hypopigmented macules scattered over the abdomen.* ***B)*** *Hypopigmented macules on the forehead.* ***C)*** *Hyperkeratotic plaques and hypopigmented macules under the inframammary folds.*

A rare Darier phenotype presenting with confetti-like hypopigmented macules is designated as "guttate leukoderma" (GL). Fewer than 30 cases of DD with GL have been reported in the literature and mostly in patients with higher skin phototype such as Fitzpatrick 4-6 [5]. Hypopigmented macules tend to precede the development of the more classic hyperkeratotic plaques, sometimes by decades [5]. Although the exact pathophysiology of GL is unknown, it has been theorized that the mutation in *ATP2A2* causes defective E-cadherins, which in turn disrupt the adhesion of melanocytes to keratinocytes leading to impaired dendrite formation, hindered melanin transfer, and ultimately to melanocyte apoptosis [6]. This mechanism is further supported by the presence of GL in patients with AKV without Darier disease, as both are due to mutations in the *ATP2A2* pathway affecting intracellular calcium storage [7].

Case Synopsis

We report the case of a 56-year-old woman who presented with a 40-year history of a pruritic eruption in the inframammary area. Although the patient could not identify any inciting events, she noted that weight gain and sweating seemed to worsen her skin findings. She denied any constitutional symptoms. She denied similar cutaneous findings in her parents and her children.

On physical examination, the patient was noted to have hypopigmented macules over her abdomen (**Figure 1A)**, back, arms, legs, and face (**Figure 1B)**. Thickened and hyperpigmented punched-out papules that coalesced into plaques were found on the palms and soles. The inframammary folds and abdominal pannus were significant for erythematous, hyperkeratotic, and macerated plaques (**Figure 1C)**. Multiple fingernails and toenails displayed V-shaped notching and dystrophy. In addition, she exhibited multiple flat-

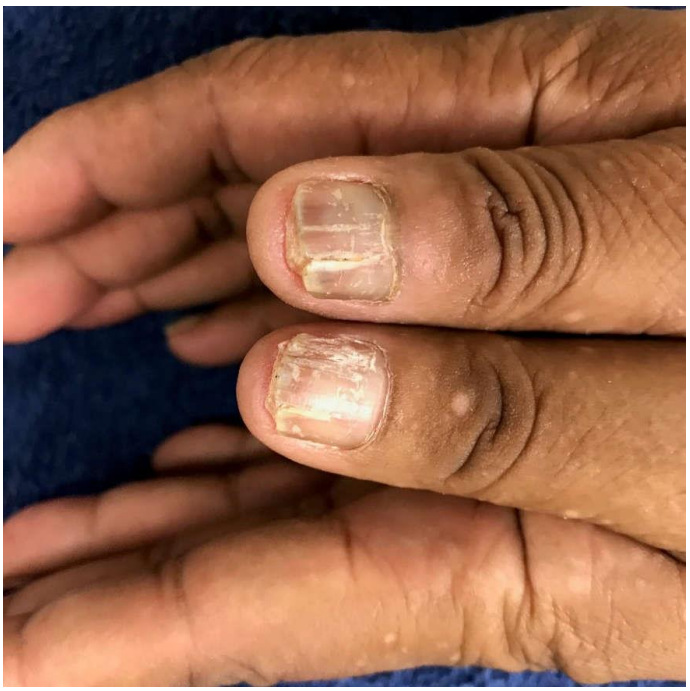

Figure 2. *V-shaped notching and dystrophy of bilateral thumbnails as well as multiple hypopigmented flat topped papules.*

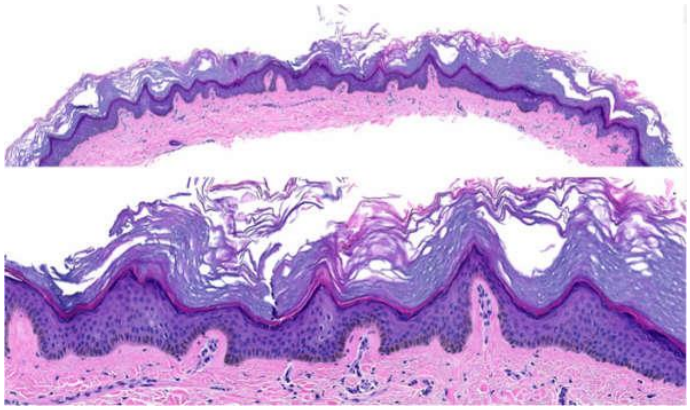

Figure 3 *Hematoxylin and eosin stain at 40× (top) and 100× (bottom) magnification showing basket-weave stratum corneum in acrokeratosis verruciformis of Hopf from patient's left dorsal hand.*

topped, hypopigmented papules on the dorsal hands and feet (**Figure 2**).

To aid in the diagnosis four shave biopsies were performed. A shave biopsy from the left dorsal hand showed basket-weave stratum corneum, church spire-like papillomatosis, and mild acanthosis consistent with acrokeratosis verruciformis of Hopf (**Figure 3**). An additional shave biopsy of a hypopigmented macule from the abdomen demonstrated a patchy decrease in pigmentation within the basal layer of the epidermis, representing a leukodermic macule of Darier (**Figure 4**). Melan-A immunostaining of this hypopigmented macule showed a reduction in the number of melanocytes at the dermoepidermal junction, consistent with the guttate leukoderma described in Darier disease (**Figure 5**). Two further shave biopsies of the inframammary folds revealed verrucous epidermal hyperplasia with multiple foci of acantholytic dyskeratosis (**Figure 6A)** along with the classic corps ronds and corps grains (**Figure 6B)**, characteristic of Darier disease.

At a follow-up visit, our patient noted some improvement of the papules in her inframammary folds with triamcinolone 0.1% ointment used twice daily for several weeks. Finally, our patient's most recent EKG showed a borderline QT-interval of 446ms.

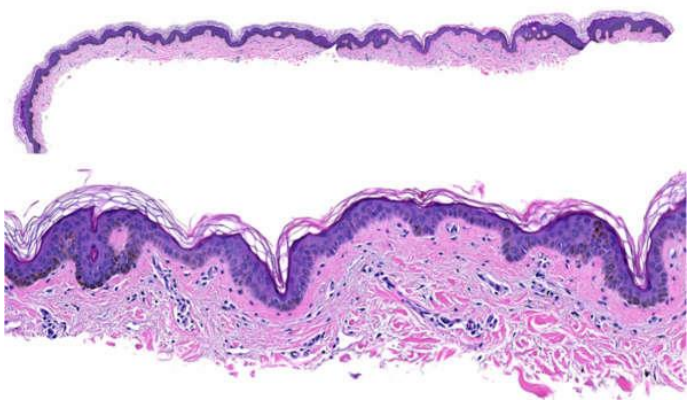

Figure 4. *Hematoxylin and eosin stain at 40× (top) and 100× (bottom) magnification showing decrease in pigmentation in basal epidermis of idiopathic guttate hypomelanosis from patient's mid abdomen.*

Case Discussion

Biopsies of leukodermic macules in patients with GL related to Darier disease show the classic histology of acantholytic dyskeratosis and additionally feature decreased number of melanocytes in the perifollicular basal layer of the epidermis [8, 9]. A biopsy taken from our patient's abdomen was consistent with these features.

Although leukodermic macules most often precede hyperkeratotic papules, concurrent eruptions of the two findings have been reported [8, 9]. A comprehensive review of the literature reveals that the GL leukoderma in DD is mostly found in darker skinned individuals, often begins

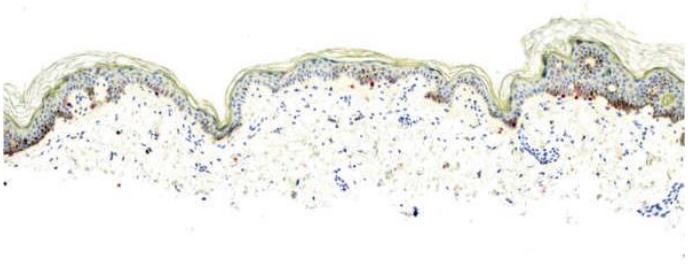

Figure 5. *Melan A immunostaining from a hypopigmented macule at 100× magnification showing reduction in the number of melanocytes at the dermoepidermal junction.*

in childhood or early adulthood, and is prevalent on sun-protected skin such as the trunk (**Table 1**). Taken together, the clinical morphology, natural history, patient demographics, and histopathology support a separate disease process for leukodermic macules, rather than the more common phenomena of post-inflammatory hypopigmentation and idiopathic guttate hypomelanosis. Thus, it may be reasonable to screen for DD in patients who present with forms of leukoderma. Indeed, guttate leukoderma is often characterized by an absence or reduction in melanocytes owing to apoptosis; post-inflammatory hypopigmentation differs by a defect in the transfer of melanosomes from melanocytes to keratinocytes. The absence of melanosomes with normal melanocytes is seen after prolonged freezing of the skin [10].

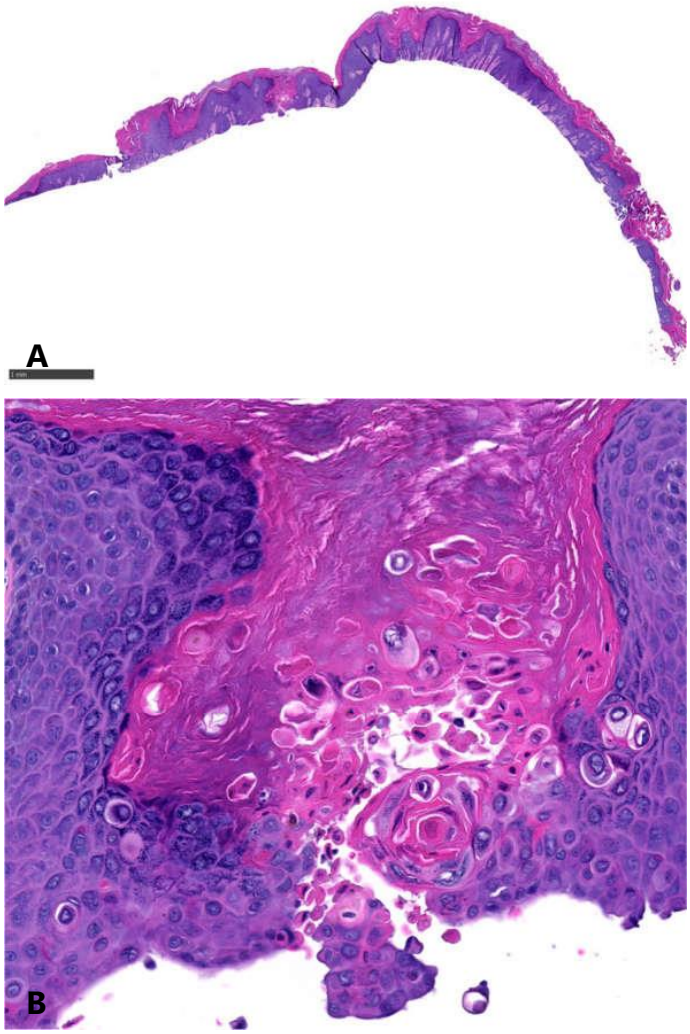

Figure 6. ***A)*** *Hematoxylin and eosin stain at 20× magnification showing verrucous epidermal hyperplasia with multiple foci of acantholytic dyskeratosis.* ***B)*** *Hematoxylin and eosin stain at 200× magnification showing acantholysis and classic corps ronds and corps grains characteristic of Darier disease.*

It is also interesting to note the variable expressivity of DD despite known autosomal dominant inheritance. Our patient was the only person in her immediate family who experienced symptoms of DD. However, a few cases provide evidence of vertical transmission and similar appearance of leukodermic macules between siblings [9]. This suggests that the leukodermic variant may also be an inheritable form of DD with variable penetrance.

In terms of management, our patient may be given further therapy with an oral retinoid, such as acitretin or isotretinoin, if she is interested. If the lesions of AKV do not clear with acitretin therapy, superficial ablative methods may be required.

Conclusion

Overall, guttate leukoderma is a rare phenotype in Darier disease with still unknown pathophysiology. It is possible that leukodermic macules have a similar prevalence in lighter-skinned patients with Darier disease, but are simply less apparent. Thus, we recommend looking for hypopigmentation in all patients presenting with symptoms of Darier disease. Unlike guttate leukoderma, there is no known association of acrokeratosis verruciformis of Hopf with higher phototype, Fitzpatrick 4-6, skin.

Potential conflicts of interest

Sylvia Hsu MD was recipient of the following. Lilly Pharma: Advisory Board Member, Honoraria;

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References

1. Savignac M, Simon M, Edir A, Guibbal L, Hovnanian A. SERCA2 Dysfunction in Darier disease causes endoplasmic reticulum stress and impaired cell-to-cell adhesion strength: rescue by Miglustat. *J Invest Dermatol.* 2014;134:1961–1970. [PMID: 2439139].
2. Schmieder SJ, Rosario-Collazo JA. Keratosis Follicularis (Darier Disease), [Updated 2018 Oct 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan. https://www.ncbi.nlm.nih.gov/books/NBK519557. Accessed on May 20, 2019.
3. Ronan A, Ingrey A, Murray N, Chee P. Recurrent ATP2A2 p.(Pro602Leu) mutation differentiates Acrokeratosis verruciformis of Hopf from the allelic condition Darier disease. *Am J Med Genet Part A*. 2017;173A:1975–1978. [PMID: 28498512].
4. Kaliyadan F, Manoj J, Venkitakrishnan S. Acrokeratosis verruciformis of Hopf associated with dilated cardiomyopathy. *Indian J Dermatol*. 2009;54:296–297. [PMID: 20161869].
5. Terrom M, Dhaille F, Baltazard T. Guttate leukoderma in Darier disease: case report and review. *J Eur Acad Dermatol Venereol*. 2016;30:e205–e209. [PMID: 26853929].
6. Goh BK, Kumarasinghe SP, Ng SK. Two Singaporean cases of guttate leucoderma in Darier's disease. *Clin Exp Dermatol*. 2004;29:313–314. [PMID: 15115521].
7. Damarla SV, Arakkal GK, Chintagunta SR, Vasavi Latha CH. Acrokeratosis verruciformis: An unusual presentation. *J NTR Univ Health Sci.* 2016;5:303-5.
8. Sornakumar L, Srinivas CR. Darier's disease with perifollicular hypopigmentation. *Indian J Dermatol*. 2010;55:299–300. [PMID: 21063534].
9. Levine A, Glick S. An unusual leukodermic variant of Dariers disease in 3 siblings. *J Am Acad Dermatol*. 2007;56:AB109.
10. Burge SM, Bristol M, Millard PR, Dawber RP. Pigment changes in human skin after cryotherapy. *Cryobiology*. 1986;23:422–32. [PMID: 3769517].

Table 1. *Published cases and characteristics of guttate leukoderma in Darier disease.*

Reference	Patient Sex, Race	Family History of Guttate Leukoderma	Clinical Features of Guttate Leukoderma	Histology of Leukodermic Macules
Goddal et al. 1965 [10]	F, Black	No	Tiny, in bran-like pattern over trunk and upper extremities Onset at the same time as DD lesions	Not done
Cattano et al. 1968 [11]	M, Black	No	Not reported	Epidermal thinning with decrease in number of melanocytes
Cornelison et al. 1970 [12[	Patient 1: F, Black Patient 2: M, Black Patient 3: M, Latin-American	Not reported for any patient	Patient 1: Peri and interfollicular, on trunk and extremities Patient 2 & 3: Proximal trunk and extremities Onset at the same time as classic DD lesions	Patients 1 & 2: Marked decrease in melanin in the basal layer Patient 3: Not done
Berth-Jones et al. 1989 [13]	M, Asian	Not reported	Trunk and proximal limbs	Supbrabasal clefting, acantholysis, corps ronds and corps grains
Jacyk et al. 1992 [14]	Patient 1: M, Black Patient 2: M, Black Patient 3: F, Black Patient 4: F, Black	Positive family history of Darier disease in one patient only	Patient 1: Abdomen, chest, lower extremities Patient 2: Chest, lower extremities. Coalescing into thin strands in some areas Patient 3: Abdomen Patient 4: Abdomen, chest, thighs, legs	Patient 1: Decrease in melanin in basal layer of epidermis Patient 2: Decrease in melanin in basal layer of epidermis Patient 3:Decrease in melanin in basal layer of epidermis Patient 4: Suprabasal clefting and decrease in melanin
Ohtake et al. 1994 [15[	M, Japanese	No	Neck, trunk, and hands which erupted five years before hyperkeratotic papules	Typical DD and thinned out corneal layer

Tolat et al. 1994 [16]	M, Indian	Several family members spanning 3 generations	Discrete, depigmented macules scattered over his chest, abdomen, back, buttocks and thighs Erupted in early childhood	Lacuna or fissure, few dyskeratotic corps ronds Absence of acanthosis, hyperkeratosis and parakeratosis Decreased number of melanocytes in basal cells beneath the clefts
Rowley et al. 1995 [17]	Patient 1: M, Black Patient 2: M, Black	Patient 1: Not reported Patient 2: None	Patient 1: Small hypopigmented macules on trunk Small papules and vesicles on chest, back groin, intergluteal cleft Patient 2: Guttate hypopigmented macules over body, sparing hair, teeth, and nails	Patient 1: Acantholysis Patient 2: Decreased melanin in the epidermis, one biopsy with acantholysis
Bleiker et al. 1998 [18]	F, Asian	No	Onset at age 2, affecting inner aspect of neck, trunk, thighs, and trunk	Acantholysis, dyskeratosis, absence of melanin
Peterson et al. 2001 [19]	F, Black	Yes, classic DD and GL lesions in sister and daughters	Hypopigmented macules on jawline, lateral neck, upper chest, and thighs that developed a few years after classic DD lesions	Not performed
Gupta et al. 2003 [20]	M, Black	No	Hypopigmented macules only on right trunk and extremities	Acantholysis, parakeratosis, focal decrease in pigment
Goh et al. 2004 [6]	Patient 1: M, Malaysian Patient 2: M, Chinese	No	Onset of hypopigmented macules on chest, abdomen, back, and buttocks five years before classic DD lesions	Patient 1: Decreased melanin, acantholysis in basal cell layer Patient 2: Low melanin and decreased melanocytes
Fangman et al. 2006 [21]	F, Black	Not reported	Asymptomatic hypopigmented macules on abdomen, 18 years after hyperkeratitic papules appeared	Decreased number of melanocytes, dermal infiltrate of lymphocytes and melanophages

Levine et al. 2007 [9]	3 female siblings from the US	Not reported	White macules over neck, collar, and upper neck region	Irregular distribution of melanin pigment within basal keratinocytes and decreased melanin in the basement zone.
Sornakumar et al. 2010 [8]	M, Indian	Father with hypopigmented macules since childhood	Asymptomatic perifollicular hypopigmented white lesions over forehead, chest, back, and extremities Acneiform lesions over chest and back	Epidermal hyperkeratosis with cup-shaped invagination over sebaceous unit showing focal subrabasal acantholysis and corps ronds and grains
Mouhari Toure et al. 2011 [22]	F, Togo	No	Hypopigmented macules on trunk, limbs, and mandible starting at age 6 - 9 years before DD lesions	Hyperkeratosis, acantholysis, decrease in melanin
Terrom et al. 2015 [5]	F, Angola	Positive history of squamous papules and leukoderma	Hypopigmented macules on upper and lower limbs, trunk, and neck	No acantholysis or dyskeratosis Evenly pigmented epidermis on Fontana-Masson staining
Sharma et al. 2016 [23]	M, Indian	Classic DD in grandfather, father, paternal uncle, and sister	1-5mm perifollicular, hypopigmented macules in bilaterally symmetrical fashion over chest and abdomen	Normal epidermis with decreased melanocytes
Sakhiya et al. 2017 [24]	F, Indian	None	5mm-1cm sized hypopigmented macules and papules, confined to the left side of the body	Hyperkeratosis, parakeratosis, suprabasilar separation, acantholytic dyskeratosis and corp ronds with grains. Decreased number of melanocytes in epidermal basal layer
Kansal et al. 2018 [25]	Patient 1: M, Indian Patient 2: F, Indian Patients are siblings	Classic DD in father, sister, and paternal grandfather	Patient 1: Leukodermic macules on the back Patient 2: Leukodermic macules on trunk since age 4	Not done

Harb et al. 2018 [26]	M, Black	Maternal grandmother, 4 siblings, and daughter had the same leukoderma and onset of findings	Hypopigmented macules scattered over his central chest, abdomen, and back with less prominent involvement of his neck and 4 extremities.	Papillomatosis without acanthosis, thinned epidermis and rete ridges, maintained basilar pigmentation of the rete ridges. Immunoperoxidase for SOX-10 and a Fontana Masson special stain showed focal absence of pigmentation and melanocytes, with preservation of melanization at the base of rete ridges
Gupta et al. 2019 [27]	F, Indian	History of similar lesions in mother	Multiple hypopigmented to depigmented perifollicular macules of size varying from 2 to 5 mm on chest, abdomen, back, and anterior aspect of bilateral thighs	Thinned out epidermis with mild spongiosis. Dermis reveals dense collagen bundles and sparse lymphomononuclear infiltrate
Sun et al. 2020 (this case)	F, Black	None	Hypopigmented macules over her abdomen, back, arms, legs, and face	Patchy decrease in pigmentation within the basal layer of the epidermis. Melan-A immunostaining showed decreased number of melanocytes at the dermoepidermal junction