Darier's Disease - Response to Oral Vitamin A: Report of a Case and Brief Review

Abstract

Darier's disease is an uncommon chronic dermatosis of autosomal dominant inheritance with significant psychosocial morbidity and shows unsatisfactory response to several topical and systemic therapies or various resurfacing or surgical procedure. A 24-year-old woman having characteristic asymptomatic and progressive, hyperkeratotic papular lesions involving the scalp, face, upper trunk, and dorsal hands and feet was diagnosed clinicopathologically as Darier's disease. She was treated successfully with oral Vitamin A 25000 IU given twice daily. The response was apparent within 4 weeks and most lesions cleared in 2 months without any adverse effects. Oral Vitamin A provides an effective and safe low-cost therapeutic alternative in Darier's disease, especially when systemic retinoids, the only effective treatment, remain contraindicated or is not tolerated and for maintenance therapy in the long-term.

Keywords: *Darier-white disease, keratosis follicularis, retinoids, Vitamin A*

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Introduction

Darier's disease (synonyms: Keratosis follicularis, Darier-White disease) is an uncommon chronic dermatosis of autosomal dominant inheritance. It's response to a plethora of therapeutic modalities such as topical keratolytics, steroids, 5-fluorouracil, pimecrolimus or retinoid creams, systemic retinoids or antibiotics, Er:Yag, pulse-dye or CO_2 laser and other fractional resurfacing devices, electron beam therapy, photodynamic therapy, dermabrasion, electrosurgery, and surgical excision vary from inconsistent to complete failure.[1,2] We describe a patient with Darier's disease who showed complete clearance of skin lesions two months after treatment with oral Vitamin A and also briefly review cases described in English literature.

Case Report

A 24-year-old woman, born to otherwise healthy non-consanguineous parents after an uneventful pregnancy, presented with numerous asymptomatic hyperkeratotic papular lesions over scalp, forehead and face [Figure 1a and b], neck, and chest predominantly involving seborrheic areas for more than 2 years with infrequent remissions and relapses. They were progressively increasing in number and had also appeared over dorsal hands [Figure 1c] and feet during last few months. The examination also showed fine punctate pitting over palms [Figure 2a] and soles, and white longitudinal streaks over fingernails and "V" shaped nicks at their free end [Figure 2b]. Hair and mucosae showed no abnormality. Her 21-year-old maternal sister also had similar lesions while her 18-month-old daughter, two younger siblings, and parents were reportedly healthy. Her other medical and obstetric history and systemic examination were unremarkable. Biopsy from the lesion showed features consistent with Darier's disease [Figure 3]. Laboratory investigations including complete hemogram, blood sugar, lipidogram, thyroid, liver and renal function tests, and urinalysis revealed no abnormalities. Treatment with ketoconazole (2%) shampoo for alternate day scalp washing, topical clobetasol propionate 0.05% + salicylic acid 3% lotion for once daily scalp application, and bland emollient for face and body application for two months did not benefit. Oral treatment with water-miscible Vitamin A palmitate 25000 IU twice daily (Aquasol A®,

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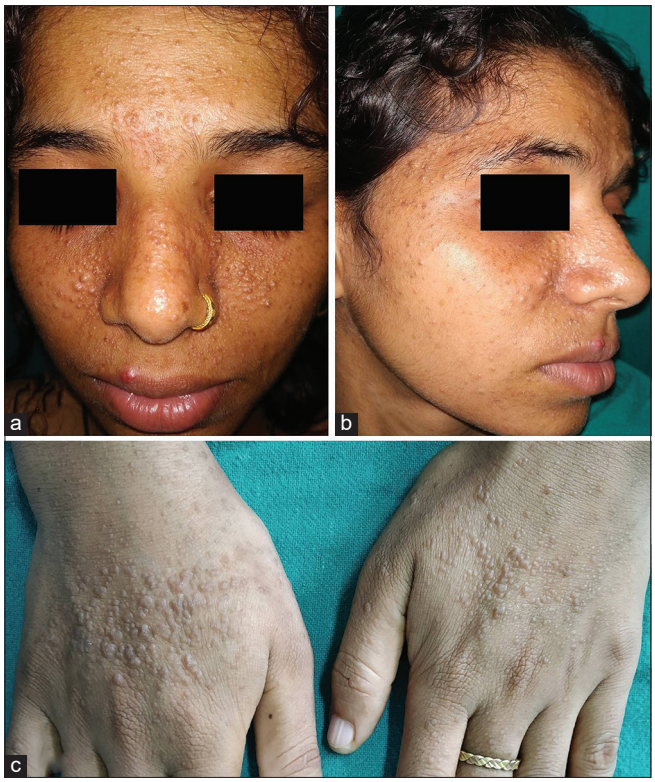

Figure 1: (a and b) Numerous keratotic and comedo-like lesions over forehead, mid face, nasolabial folds, and temple at the hairline. (c) Multiple keratotic papules over dorsal hand. Similar lesions were present over dorsal feet

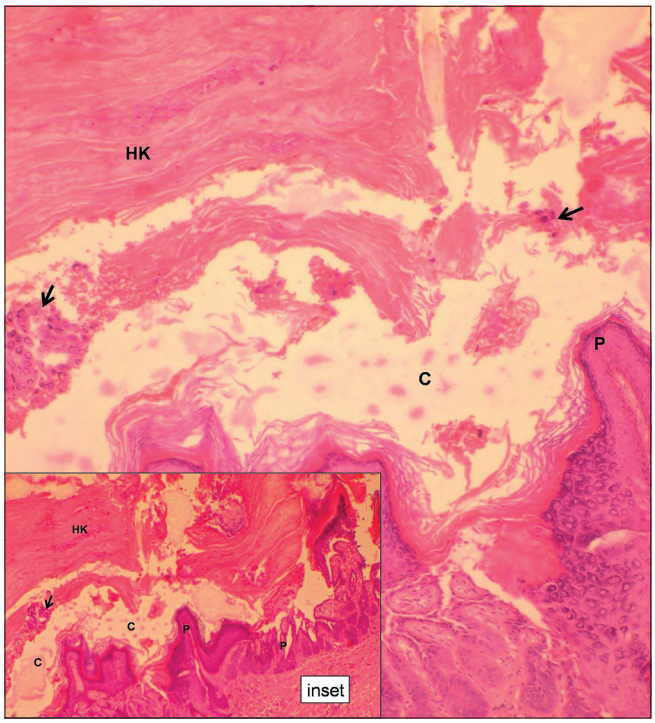

Figure 3: Extensive hyperkeratosis (HK), papillomatosus (P), corp ronds and grains (arrows) in the stratum granulosum, suprabasal acantholytic clefting (C) with villus-like dermal papillae (P) projecting into it, no acantholytic cells, and minimal dermal infiltrate are notable features (stain, H and E, ×40, inset ×10)

USV Pvt Ltd, Mumbai) and bland emollients for face/skin was initiated as she was breastfeeding. Her lesions started improving 4 weeks after treatment and her scalp, face [Figure 4a and b] and dorsal hands [Figure 4c] and body lesions cleared almost completely 2 months after this treatment. At a recent visit, she was highly satisfied with near total clearance of her skin lesions. She did not show any evidence of hepatotoxicity, blurred vision, drowsiness, mild frontal headache, and dryness of lips or nose associated usually with very high cumulated doses of vitamin A. The dose of Vitamin A was reduced to

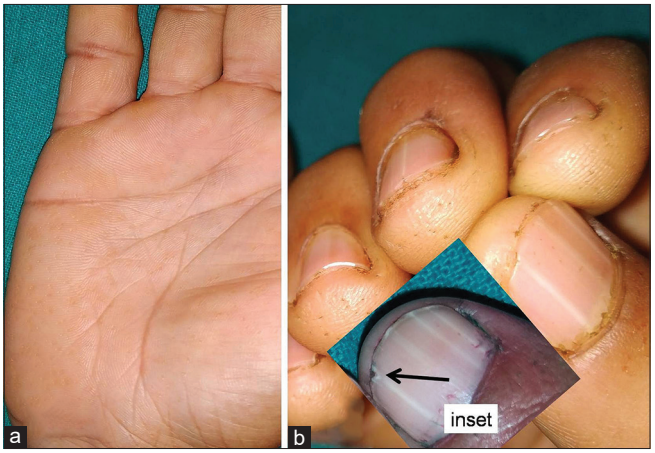

Figure 2: (a) Characteristic multiple palmar pits. (b) Alternating longitudinal white and red streaks over nail plate with V-shape nicking (inset) of free edge of nail plate (arrow)

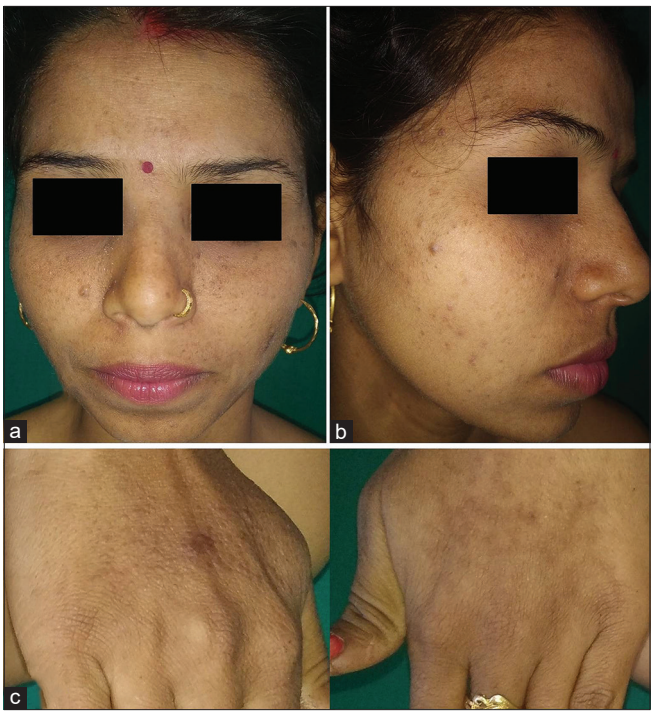

Figure 4: (a and b) Substantial clearance of all facial lesions at 2 months after oral Vitamin A therapy. (c) Substantial clearance of all lesions over dorsal hands at 2 months after oral Vitamin A therapy

25000 IU once daily for maintenance, and she was asked to follow-up regularly.

Discussion

Treatment of Darier's disease mostly remains unsatisfactory, and it tends to persist for life with partial remissions. Exacerbations are frequent from heat, sweat, humidity, and secondary bacterial infections. Although systemic antibiotics help to control flare-ups from bacterial infections, oral retinoids (acitretin, isotretinoin, and alitretinoin) remain the mainstay of treatment as they decrease hyperkeratosis and smoothen keratotic papules in Darier's disease.[1,3] However, significant adverse effects (mucocutaneous dryness, hyperlipidemia, skeletal hyperostosis, transaminits, and pseudotumor cerebri) in general and teratogenicity concerns, in particular, limit their use in practice.[4,5] Moreover, long-term remissions cannot be maintained after stopping retinoids. Oral Vitamin A had been used to treat Darier's disease prior to retinoids became widely acceptable treatment option. A PubMed search for use of oral Vitamin A in Darier's disease on Mar 29, 2019 showed 8 reports comprising 28 cases published in English literature between 1941 and 1987 [Table 1].[6-13] Their review shows that oral Vitamin A had been used safely in doses between 18000 and 240,000 IU/day with significant efficacy in them without obvious hypovitaminosis A. The overall outcome was graded as complete clearance in 4, considerable, great or much improvement in 6,

Table 1: Clinical studies using oral Vitamin A in the treatment of Darier's disease

Reference	Number of cases	Age in years and gender	Duration of disease	Dose of oral Vitamin A	Treatment duration	Clinical outcome	Investigations and Adverse effects	Remarks
Peck, *et al*., 1941	3	NA	NA	200,000 IU/d	NA	Considerable clearance	Pretreatment serum Vitamin A levels were normal, but one patient had problems with dark adaptation. No adverse effects recorded.	Original report could not be retrieved.
Carleton and Steven 1943	4	**49 F***	26 y	18000 IU/d	9 m	Complete clearance	Pretreatment serum Vitamin A levels were low in one patient. Dark adaptation testing was normal. No adverse effects recorded	No previous treatment.
		18 M*	6 y	27000 IU/d	9 m	No response		No previous treatment.
		35 M**	3 y	27000 IU/d	5 m	Complete clearance		Previously treated with topical tar for 8 months with slight benefit. Recurrence 3 month after stopping oral Vitamin A that again responded to same dose of oral Vitamin A.
		34 F**	14 y (approx)	27000 IU/d	4 m	No response		No previous treatment. She had 8 months pregnancy at the initiation of treatment with Vitamin A and delivered a healthy baby.
Porter, *et al*., 1947	7	33 M	Lifelong	3,000,000 IU$	3 m	Much improvement	No adverse effects recorded.	No previous treatment.
		30 F#	Lifelong	25,600,000 IU$	30 m	Slight improvement		No previous treatment.
		9 F	6 y	30,000,000 IU$	10 m	Slight improvement		No previous treatment.

Contd...

Table 1: Contd...

Reference	Number of cases	Age in years and gender	Duration of disease	Dose of oral Vitamin A	Treatment duration	Clinical outcome	Investigations and Adverse effects	Remarks
		42 F[#]	Many years	900,000 IU[$]	1 m	No improvement	Pretreatment serum Vitamin A levels were normal. No adverse effects recorded,	Topical Vitamin A 5000 IU/g for 1 month was ineffective. Improved during pregnancy. Summer exacerbation.
		34 F	3 y	9,200,000 IU[$]	3 m	No improvement	Pretreatment serum Vitamin A levels were normal. No adverse effects recorded	Improved during pregnancy and summers.
		19 F	1 y	21,000,000 IU[$]	7 m	Great improvement	Pretreatment serum Vitamin A levels were normal No adverse effects recorded.	No previous treatment.
		13 F	8 y	12,000,000 IU[$]	4 m	Slight improvement	Pretreatment serum Vitamin A levels were normal. No adverse effects recorded.	No previous treatment.
Leitner *et al*., 1948	6	**16 M**	15 y	240,000 IU	20 m	Complete clearance	Baseline and post treatment dark adaptation test, hemogram, liver function tests, Kahn and Wassermann tests, serum Vitamin A, electrolytes, carotene, urinalysis were normal. No adverse effects noted	Grenz-ray irradiation before oral Vitamin A.
		34 M	27 y	240,000 IU/d	9 m	Complete clearance	Except for some abnormality in LFTs and dark adaptation, all other laboratory tests as above were normal No adverse effects noted	Grenz-ray irradiation before oral Vitamin A. Subsequent relapses also responded to Vitamin A
		57 F	43 y	150,000 - 240,000 IU/d	6 m-17 m	Some improvement. Subsequent relapses did not respond to Vitamin A and were considered treatment failure	Except for some abnormality in LFTs, baseline and post treatment dark adaptation test, hemogram, Kahn and Wassermann tests, serum Vitamin A, electrolytes, carotene, urinalysis were normal. Treatment stopped owing to increased serum Vitamin A levels.	Grenz-ray irradiation before oral Vitamin A.
		63 F	50 y	NA	25 m	No improvement	Except for some abnormality in LFTs, baseline and post treatment hemogram, serum Vitamin A, electrolytes, carotene, urinalysis were normal. Treatment stopped owing to increased serum Vitamin A levels.	Grenz-ray irradiation before oral Vitamin A.

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Table 1: Contd...

Reference	Number of cases	Age in years and gender	Duration of disease	Dose of oral Vitamin A	Treatment duration	Clinical outcome	Investigations and Adverse effects	Remarks
		35 F	6 y	96000 IU/d	36 m	Slight improvement	Baseline and post treatment hemogram, liver function tests, Kahn and Wassermann tests, serum Vitamin A, electrolytes, carotene, urinalysis were normal.	Grenz-ray irradiation before oral Vitamin A.
							No adverse effects noted.	
		19 F	7 y	96000 IU/d	15 m	Slight improvement	Baseline and post treatment hemogram, liver function tests, Kahn and Wassermann tests, serum Vitamin A, electrolytes, carotene, urinalysis were normal.	Grenz-ray irradiation before oral Vitamin A.
							No adverse effects noted.	
Fulton Jr., *et al*., 1968	1	51 M	20 y	Large doses (details not presented)	Not recorded	Improvement	Stopped because of malaise, blurred vision, headache, hepatomegaly.	Methotrexate, oral/topical steroids were ineffective.
Ayres *et al*., 1972	1	**26 M**	13 y	200,000 IU/d	5 y	Improved 7 m onwards after addition of Vitamin E 400 IU thrice/d	No adverse effects recorded.	Exacerbations from summers, sun exposure, and psychological stress.
Thomas *et al*., 1982	3	44 F	13 y	100,000 IU/d	14 d	Skin lesions improved (80%)	Baseline and post treatment hemogram, liver function tests, blood urea, serum lipids, electrolytes, carotene, phospholipid were normal.	Topical steroids and emollients.
							Sleeplessness, dry nose and lips	
		23 M	>15 y	100,000 IU/d	14 d	Skin lesions improved (50%)	Baseline and post treatment hemogram, liver function tests, electrolytes, lipids, chest X-ray, urinalysis were normal.	Photo aggravation. Remission for 1 y after treatment.
							Mild headache relieved after aspirin.	
		30 M	2 y	100,000 IU/d	14 d	Skin lesions improved (50%)	Baseline and post treatment hemogram, liver function tests, electrolytes, lipids, chest X-ray, urinalysis were normal.	Exacerbations from summers and sun exposure.
							Mild headache.	
Mohamed, 1987	2	29 F[##]	15 y	100,000 IU/d	2 y	Improved 2 y onwards after addition of Vitamin E 400 IU thrice/d	Baseline hemogram, liver function tests, blood urea, serum electrolytes, total lipids were normal.	Exacerbations from summers and sun exposure.
							No adverse effects recorded.	

Contd...

Table 1: Contd...

Reference	Number of cases	Age in years and gender	Duration of disease	Dose of oral Vitamin A	Treatment duration	Clinical outcome	Investigations and Adverse effects	Remarks
		29 F[##]	15 y	100,000 IU/d	2 y	Improved 2 y onwards after addition of Vitamin E 400 IU thrice/d		Maintained with Vitamin A 50,000 IU and Vitamin E 800 IU for 1 y and remained in remission for 4 m at last visit without further treatment.

M=Male; F=Female; m=Months; y=Years; d=Day; IU=International units; NA=Not available; *these patients were mother and son; **these patients were brother and sister; [#]these patients were sisters; [##]these patients were twins; cumulative dose[$]. Bold figures indicate histologically proven cases of Darier's disease

80% improvement in one, 50% improvement in 2, and some or slight improvement in 7 patients, respectively. Three patients who did not benefit with Vitamin A alone improved significantly even at reduced dose after addition of Vitamin E (1200 IU/day) given for 7 months to 2 years. Overall, 5 patients did not benefit at all. Porter *et al*.[8] had used a cumulative dose as high as 21,000,000 IU to 30,000,000 IU of Vitamin A in their six patients given over a period of 3 to 30 months with results varying from none to great improvement. They also reviewed 11 additional cases treated successfully with oral Vitamin A between 1941 and 1942 (original reports could not be retrieved). We also observed highly encouraging results in our patient just one month after initiating treatment and substantial clearance of all lesions two months after oral Vitamin A, whereas response to topical therapies for 2 months remained unsatisfactory.

Vitamin A is important for retinal photoreceptor function, epithelial proliferation, and keratinization. However, any attempt to delineate the mechanism of therapeutic efficacy of Vitamin A in Darier's disease will be speculative. Darier's disease results from a mutation in ATP2A2 gene encoding sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATP isoform 2 protein (SERCA2) mapped to chromosome 12q23-24.1 that affects cell adhesion. The defect manifests clinically with characteristic skin lesions, and pathognomic features of suprabasal acantholysis, corps ronds, and grains (dyskeratosis cells) in the stratum corneum as in our patient. The two clinically important and active metabolites of Vitamin A are *retinal*, a key component of rhodopsin generation in retina, and *retinoic acid* that regulates keratinization, cell differentiation, and immune competence.[14,15] Retinoic acid acts on transcriptional regulation of hundreds of genes involved in many processes such as embryogenesis, growth, cell multiplication and differentiation, apoptosis, immunity, hematopoiesis, spermatogenesis, and bone/tissue homeostasis.[14-16] Retinoids, natural or synthetic derivatives of retinol (Vitamin-A alcohol) with activity and a toxicity profile similar to Vitamin A, too have a profound effect on epithelial cell growth, differentiation, cellular tonofilaments-desmosomes adhesiveness, and keratinocyte apoptosis in various hyperproliferative, keratinizing, inflammatory, and malignant dermatoses through diverse biological activity.[17,18] We hypothesize that Vitamin A perhaps exerts its retinoid-like therapeutic effect in Darier's disease by virtue of its retinoic acid metabolite. Because low blood level of Vitamin A is not in itself indicative of deficiency and its high levels have no permanent influence on clinical condition in each case, it has been suggested that a subset of patients respond slowly and might be considered non-responders if treatment is discontinued early.[7-9] This warrants continuation of treatment until maximum benefit is achieved or at least for two months when the dose can be reduced to maintain remission.[8] However, the use of Vitamin A within the recommended dietary intake (1300 µg retinol per day) for lactating women is usually considered safe.

Although we make no recommendations, we feel that oral Vitamin A particularly water-miscible formulation is safe and provides an economical and effective alternative to retinoids for treating Darier's disease, especially in patients who are intolerant or have a contraindication to oral retinoids, or need long-term maintenance therapy as relapses remain a major concern. However, our viewpoints are open to debate.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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