Exacerbation of Darier disease with lithium therapy

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Abstract

Darier disease is an autosomal dominant blistering disorder linked to mutation of the endoplasmic reticulum calcium pump, *SERCA2*, which compromises keratinocyte adhesion and differentiation. Beyond the typical keratotic and eroded skin lesions, patients with Darier disease often present with psychiatric co-morbidities. Herein, we present a biopsy-confirmed case of Darier disease in a patient with bipolar disorder, whose cutaneous disease dramatically worsened upon initiation of lithium therapy. In consultation with the patient's psychiatrist, lithium was tapered, leading to rapid improvement in her skin. This case highlights the potential for lithium to complicate management of Darier disease and underscores the need for dermatologists to collaborate with psychiatrists to optimize both cutaneous and mental health in patients.

Keywords:) ATP2A2, Darier disease, genodermatosis, lithium, SERCA2

Introduction

Darier disease is a rare autosomal dominant genodermatosis usually presenting in adolescence with hyperkeratotic papules and plaques, sometimes with painful erosions and fissuring. Typical skin lesions tend to be concentrated in seborrheic areas including the scalp, face, and trunk [1]. Nail findings can be pathognomonic as the combination of white and red striping of the nailbeds with distal V-shaped nicking of the nail plates is uniquely associated with this disease. Beyond cutaneous findings, this inherited dermatologic condition is associated with neuropsychiatric disease, including bipolar disorder [2]. Herein, we discuss a case in which treatment of co-morbid psychiatric disease exacerbated the skin lesions in a patient with Darier disease and required collaboration with her psychiatrist to optimize her dermatologic care.

Case Synopsis

A 25-year-old woman with bipolar disorder presented with a painful, scaly and fissured eruption on the face, neck, and trunk. The patient had experienced mild recurrent episodes of a similar rash since her teenage years along with brittle nails. She reported no family history of skin issues, though her mother endorsed brittle nails. The patient developed progressive worsening of her eruption three months prior to presentation when admitted for inpatient psychiatric care for depression and lithium therapy was initiated at 1200mg daily. Her other unchanged chronic medications included clonazepam, escitalopram, and quetiapine. The patient's rash continued to worsen despite oral doxycycline and topical hydrocortisone and chlorhexidine.

Physical examination was notable for crusted papules and fissured hyperkeratotic plaques of the nasolabial folds, neck, chest, and back (**Figure 1**). The nailbeds had red and white striping and several nail plates had distal V-shaped nicks. A skin biopsy demonstrated suprabasal epidermal acantholysis with prominent dyskeratosis, confirming a diagnosis of Darier disease (**Figure 2**).

Doxycycline was discontinued and the patient was treated with tretinoin cream and triamcinolone cream with minimal benefit. Given the lack of improvement with topical therapy and prior reports of lithium-induced flaring of Darier disease, lithium

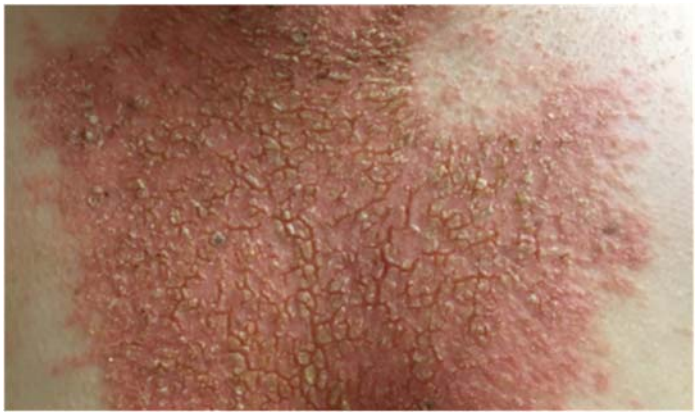

Figure 1. *Skin photograph during lithium therapy: A hyperkeratotic and fissured pink plaque covering much of the chest developed over three months of lithium treatment.*

was tapered in collaboration with the patient's psychiatrist. Two months after lithium cessation, the patient's eruption nearly completely resolved and she has remained in remission off all prescription dermatologic therapies for over a year (**Figure 3**).

Case Discussion

Darier disease has been linked to mutation of *ATP2A2*, which encodes the sarco-endoplasmic reticulum calcium ATPase type two protein (SERCA2), [3]. A membrane-embedded pump, SERCA2 regulates intracellular calcium by transporting the cytosolic ion into the endoplasmic reticulum (ER). In keratinocytes, impaired SERCA2-dependent calcium regulation is thought to cause two primary cellular defects: 1) compromised desmosome assembly and stability [4], leading to impaired intercellular adhesion and acantholysis, and 2) increased ER stress inducing apoptosis of keratinocytes [5], manifesting as dyskeratotic corps ronds and grains. Neurons are also sensitive to SERCA2-regulated calcium flux [6], which may explain the psychiatric co-morbidities of Darier disease.

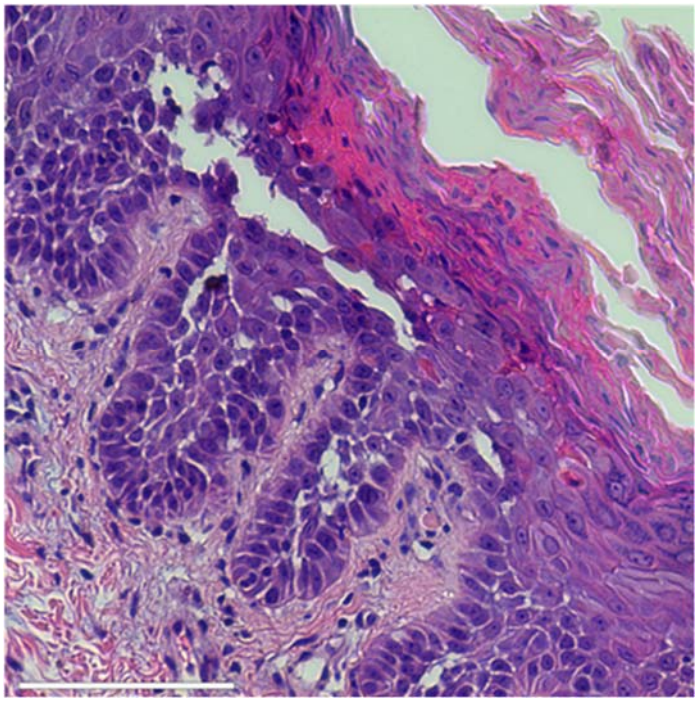

Figure 2. *Punch biopsy of the skin: The epidermis shows acantholysis of keratinocytes with suprabasal clefting and dyskeratosis in the superficial layers. H&E, 40×, scale bar 100μm.*

Interestingly, flaring of Darier disease has been attributed to lithium therapy for co-morbid psychiatric disease in few prior reports [7-10], (**Table 1**). Applying the Naranjo criteria [11] to this case results in a score of 7, which indicates a probable adverse drug reaction (**Table 2**). The mechanism underlying this treatment complication has not been fully explained, but in rodents, lithium impaired epidermal SERCA2 expression [12] and could similarly reduce wild-type SERCA2 levels in heterozygous patients. Further studies of how lithium regulates SERCA2 expression could potentially reveal novel pathways to target in clinical studies. Current treatment of Darier disease is challenging since prospective clinical trial data are lacking for this orphan disorder. Reported therapies include topical and oral retinoids, topical corticosteroids, and topical vitamin D analogues along with behavioral avoidance of exacerbating

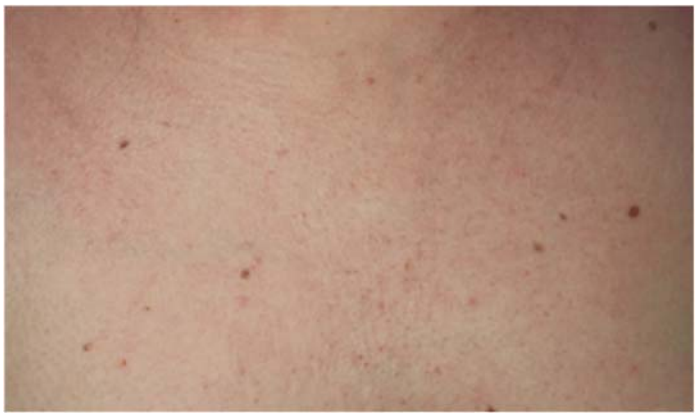

Figure 3. *Skin photograph after lithium cessation: The eruption on the chest completely resolved within two months of stopping lithium treatment.*

Table 1. *Comparison to previously reported cases.*

Case	Age	Sex	Race	Age of Darier disease onset	Psychiatric diagnosis and age at diagnosis	Lithium dose, daily	Time to Darier flare after lithium	Dermatologic treatments	Response after lithium cessation	Reference
1	25	F	White	13 years	Bipolar disorder at 25 years old	1200mg	1 month	Doxycycline 100mg daily; hydrocortisone 1% cream; chlorhexidine 1% gel; tretinoin 0.05% cream; triamcinolone 0.1% cream	Skin disease improved to baseline two months after lithium cessation	Current report
2	31	F	Not reported	Reported "long-standing history"	Bipolar disorder at 31 years old	900mg initial; 1200mg on re-challenge	A few weeks	Unspecified topical preparations	Skin disease improved after patient self-discontinued lithium on two reported occasions.	[7]
3	40	F	White	Reported "since childhood"	Bipolar disorder at 34 years old	Not reported	1 month	Etretinate 1mg/kg/day	Skin disease improved to baseline two weeks after lithium cessation	[8]
4	50	F	Not reported	16 years	Bipolar disorder at 47 years old	1200mg	3 months	None reported	Skin disease improved to baseline two weeks after lithium cessation	[9]
5	18	F	Not reported	18 years	Bipolar disorder at 18 years old	Not reported	2 weeks	Hydrocortisone 1% cream Tretinoin 0.025% cream	Skin disease improved within several weeks after lithium cessation.	[10]

factors including heat, sweating, and skin friction [13].

Conclusion

Herein, we describe a confirmed case of Darier disease in which the patient experienced marked worsening of skin manifestations after initiating lithium treatment for bipolar disorder and had rapid improvement upon lithium cessation. Although lithium remains a mainstay of treatment for bipolar disorder, patients who also suffer from Darier disease should avoid lithium if a safe alternative psychiatric therapy is available given clear reports of lithium-induced exacerbation of this dermatologic condition.

Potential conflicts of interest

The authors declare no conflicts of interest.

Table 2. *Naranjo adverse drug reaction probability scale.*

Question	Yes	No	Unknown	Score
Are there previous *conclusive* reports on this reaction?	+1	0	0	**+1**
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**+2**
Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	**+1**
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	**0**
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**+2**
Did the reaction reappear when a placebo was given?	-1	+1	0	**0**
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	**0**
Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	**0**
Was the adverse event confirmed by any objective evidence?	+1	0	0	**+1**
Total Score				**7**

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