Darier disease with disseminated herpes simplex virus type 2 infection

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Abstract

Darier disease (DD), also known as keratosis follicularis or Darier-White disease, is a rare autosomal dominant genodermatosis that presents as hyperkeratotic, warty papules affecting the seborrheic and intertriginous areas. Patients with DD are at risk of secondary infections including the rare complication of Kaposi varicelliform eruption (KVE), a widespread viral infection most commonly caused by herpes simplex virus (HSV). Darier disease with secondary KVE can lead to widespread systemic infection and death. This case report discusses an individual with DD who subsequently developed KVE due to disseminated HSV type 2 infection.

Keywords: Darier disease, keratosis follicularis, herpes simplex virus, Kaposi varicelliform eruption

Introduction

Darier disease (DD), also known as keratosis follicularis, is a rare, autosomal dominant genodermatosis caused by a mutation in the *ATP2A2* gene [1]. Darier disease is characterized by diffuse hyperkeratotic warty papules with scaly plaques in seborrheic regions with associated mucous membrane and nail changes [2]. Owing to their defect in skin barrier function, patients with DD are at risk of secondary infections including the rare complication of Kaposi varicelliform eruption (KVE), a widespread viral infection most commonly caused by herpes simplex virus [3]. This potentially fatal complication is typically caused by herpes simplex virus type 1 (HSV-1). Only two previous cases of KVE caused by herpes simplex virus type 2 (HSV-2) in DD patients exist in the literature. We present a case of KVE caused by HSV-2 in a Darier disease patient who previously had HSV-1 and was diagnosed correctly on initial presentation. The prescribed oral treatment did not suffice in his case, necessitating inpatient intravenous acyclovir treatment.

Case Synopsis

A 52-year-old man with biopsy-proven Darier disease (DD), managed intermittently with acitretin owing to financial issues, presented to clinic for follow-up of his DD with subacute onset of increased tenderness to lesions on his back, arms, and hands for the last two weeks. Three months prior, this patient was previously treated for HSV-1 in his plaques of DD confirmed by positive direct fluorescent antibody. On physical exam, the patient's seborrheic areas, including chest, scalp, face, and superior back, were studded with brown to skin-colored verrucous papules, approximately 12 fissures, and mild hyperkeratosis. Notably, there were grouped vesicles on his back and chest, distinguishable from his typical DD lesions. Another direct fluorescent antibody was performed, which was negative for HSV-1 and -2. However, serum IgG was positive for both HSV-1 and -2 indicating previous infection. The patient was started on acyclovir 800 mg three times a day for clinical presumption of HSV.

The patient returned to clinic for a follow-up after 10 days of acyclovir treatment with worsening tenderness and progressive flare of new vesicules. He reported that the lesions were increasing in number and becoming more painful. On physical exam, he now had more numerous grouped vesicles across his back, abdomen, arms, and legs (**Figure 1**). At this time, a 4mm punch biopsy was performed on a left leg lesion to rule out HSV versus bullous Darier disease flare and a repeat direct fluorescent antibody was ordered.

The microscopic view of the leg lesion biopsy read the next day showed a highly inflamed vesicle with serum and a mixed inflammatory infiltrate comprised of neutrophils, eosinophils, and numerous dyskeratotic keratinocytes, which demonstrated viral cytopathic changes consistent with infection, including margination of nuclear chromatin, nuclear molding, and multinucleate cells (**Figure 2**). There was also a mixed inflammatory infiltrate in the dermis. This represented Darier disease with superimposed herpesvirus infection. This time the direct fluorescent antibody was positive for HSV-2.

Based on these results, the patient's dose of acyclovir was changed to 400mg five times daily for 7 days. When the patient returned to clinic for follow-up the next week, he had erythematous erosions, ulcerations, pustules, and papules with scale and heme-crust, each approximately 3-5mm in diameter and numbering 150 or more generalized across his back, chest, trunk, arms, hands, legs, and feet. Since the oral acyclovir treatment failed to improve his condition, he was admitted to the hospital and started on a maximum does of intravenous acyclovir at 10mg/kg every 8 hours for 10 days. During his hospital follow-up, the patient showed resolution of the eruption. He is currently treated with chronic suppressive acyclovir at a dose of 400mg twice daily and has not had an HSV recurrence for over a year. The patient is continuing to receive treatment for Darier disease and recurrent minor bacterial and fungal infections.

Case Discussion

Darier disease (DD) is a rare, autosomal dominant, keratinizing disorder caused by mutations in the *ATP2A2* gene, which encodes for a calcium pump distributed throughout the endoplasmic reticulum [1]. Mutations in the gene for this pump inevitably disrupt calcium homeostasis, which has been speculated to lead to activation of the endoplasmic reticulum stress response and cell apoptosis [4]. However, it remains unknown exactly how these changes cause the dissociation of epidermal keratinocytes and dyskeratosis typical of DD [5]. The disease manifestations usually begin in childhood or adolescence and can carry on into adulthood. DD is characterized by skin-colored or red-brown hyperkeratotic papules and plaques confluent in both seborrheic and intertriginous areas that commonly crust over and form fissures [2].

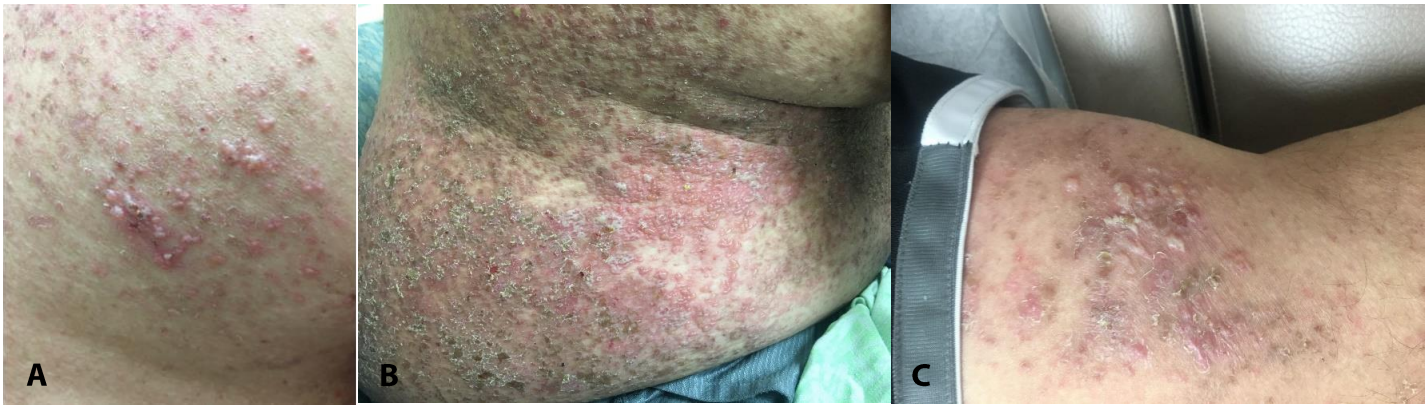

Figure 1. *Darier Disease with disseminated HSV-2. Extensive pustules, vesicles, and papules with scale and heme-crust located on upper back **A)**, abdomen **B)**, and thigh **C)**.*

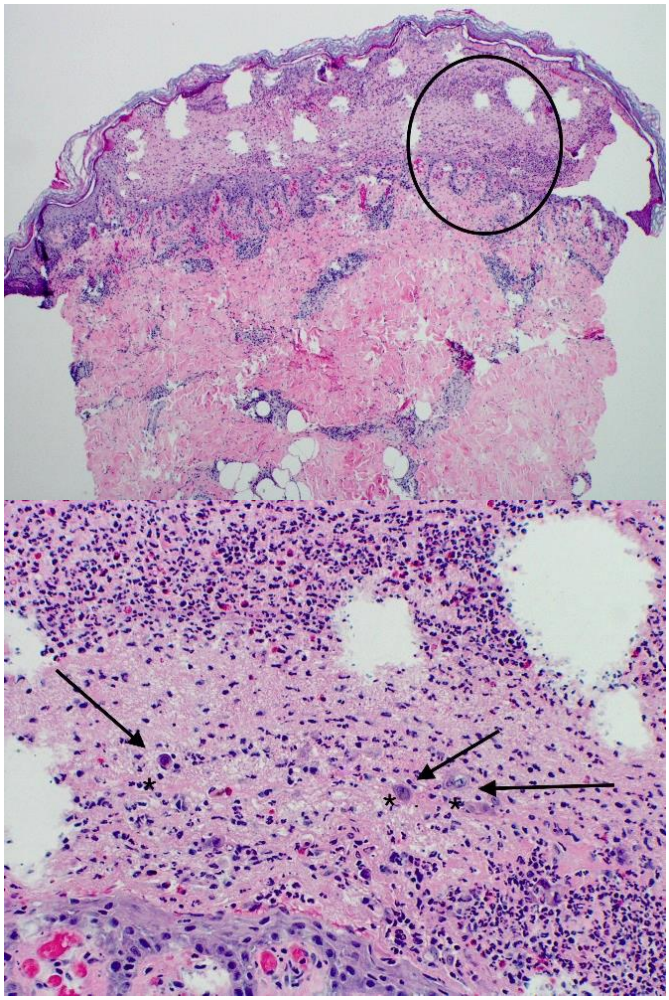

Figure 2. ***A)*** *Intraepidermal vesiculation and acantholysis with a mixed inflammatory infiltrate of lymphocytes and eosinophils. H&E, 10×.* ***B)*** *Viral changes such as multinucleation and margination of chromatin are also present. H&E, 40×.*

Whether active or in remission, DD patients are prone to bacterial and fungal secondary infections. In addition, complications of widespread HSV, varicella-zoster virus, and pox virus infections have been documented in patients with DD [6-8]. The severe complication illustrated by this case is Kaposi varicelliform eruption (KVE), a secondary widespread viral infection most commonly caused by HSV. Kaposi varicelliform eruption concomitantly occurs with pre-existing skin conditions that have disruption in skin-barrier function such as Darier disease, Hailey-Hailey disease, ichthyosis, atopic and contact dermatitis, bullous pemphigoid, psoriasis, burns, and seborrheic dermatitis [3, 9, 10]. Typically, KVE presents as grouped clusters of monomorphic, dome-shaped vesicles or punched out ulcerations that may be accompanied by fever, chills, and regional lymphadenopathy that progress to painful hemorrhagic, crusted, and punched-out ulcers [9].

When DD patients develop KVE, it is most commonly related to HSV-1. There have been two documented cases of DD patients with disseminated HSV-2 [7, 11]. Owing to the lack of initial proper diagnosis, one patient had a morbid outcome [7]. Often DD patients have atypical presentations of HSV infections which cause treatment delays. A direct fluorescent antibody obtained from our patient led to an immediate initiation of oral acyclovir given the high degree of clinical suspicion. Although HSV-2 was found on direct fluorescent antibody, serum IgG was positive for both HSV-1 and -2. It is unclear if the IgG represented a coinfection with HSV-1 and HSV-2 or if the HSV-1 IgG remained elevated from the patient's HSV-1 infection three months prior. Interestingly, our patient had no prior history of HSV-2 genital lesions and did not have any genital involvement of herpetic lesions during his hospitalization or since his recovery, **Table 1**.

In summary, our patient was diagnosed correctly on initial presentation of the onset of his superimposed HSV infection, yet the prescribed oral treatment did not suffice in his case, necessitating inpatient intravenous acyclovir treatment. Expedited hospital admission may have saved the patient from a much more morbid, perhaps even fatal outcome, highlighting the importance of close follow-up with DD patients.

Conclusion

Darier disease patients are susceptible to Kaposi varicelliform eruption, a potentially life-threatening dermatological emergency. This case demonstrates the importance of close follow-up and clinical suspicion for superinfection in patients presenting with increased tenderness and flare of their dermatosis.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Characteristics of patients with Darier disease and superimposed HSV-2 infection.*

Source	Age	Race	Sex	HSV-2 Location	Morphology	Biopsy Results	Antibody Test	Viral Culture	Treatment	Outcome
Nikkels[7]	67	Not Given	Male	Entire trunk, genitals, ears, lips, and palate	Numerous hemorrhagic and oozing bullous skin lesions	Superficial perivascular lymphoid infiltrate with diffuse acantholysis, large keratinocytes and necrotic cells	IHC positive for HSV-2 specific antibody	Negative	IV acyclovir 10 mg/kg/8 hours (until death)	Death
Hazen[11]	26	Not Given	Male	Forehead, neck, trunk, penis, genitocrural folds	Clusters of vesicles on erythematous base and extensive crusting	Suprabasilar separation with corps ronds and grains	Not obtained	Positive for HSV-2	No antiviral medication given	Monthly Recurrence of HSV-2
Our Patient	52	Hispanic	Male	Back, arms, and legs	Numerous grouped vesicles with erythematous base	Vesicle with mixed inflammatory infiltrate of neutrophils, eosinophils, and dyskeratotic multinucleate keratinocytes with nuclear molding and margination of nuclear chromatin	DFA positive for HSV-2	Not obtained	IV acyclovir 10 mg/kg/8 hours for 10 days	Full resolution and remission