UC Davis
Dermatology Online Journal

Title
BRAF inhibitor and hairy cell leukemia-related transient acantholytic dermatosis

Permalink
https://escholarship.org/uc/item/3ps33564

Journal
Dermatology Online Journal, 26(2)

Authors
Singh, Amy Garcia
Tchanque-Fossuo, Catherine N
Elwood, Hillary
et al.

Publication Date
2020

DOI
10.5070/D3262047420

Copyright Information
Copyright 2020 by the author(s).This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at https://creativecommons.org/licenses/by-nc-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

BRAF inhibitor and hairy cell leukemia-related transient acantholytic dermatosis

Amy Garcia Singh[1*] MD, Catherine N Tchanque-Fossuo[2*] MD MS, Hillary Elwood[2,3] MD, John R Durkin[2] MD

*Authors contributed equally

Affiliations: [1]University of New Mexico, School of Medicine, Albuquerque, New Mexico, USA, [2]Department of Dermatology, University of New Mexico, School of Medicine, Albuquerque, New Mexico, USA, [3]Tricore Reference Laboratories, Albuquerque, New Mexico, USA

Corresponding Author: John R. Durkin MD, Department of Dermatology, University of New Mexico, School of Medicine, 1021 Medical Arts Avenue, NE, Albuquerque, NM 87102 USA, jdurkin@salud.unm.edu

Abstract

Grover disease (GD) is an acquired, nonfamilial, nonimmune mediated, transient or persistent acantholytic dermatosis. Herein, we present a 72-year-old man who had clinical and histopathologic findings of GD following two weeks of treatment with vemurafenib without MEK inhibitor. The patient was successfully treated with topical emollients and a high-potency corticosteroid. Meanwhile, vemurafenib was temporarily discontinued. Drug-induced GD has increasingly been reported in patients on BRAF inhibitor monotherapy as an immune-related adverse event. The cutaneous side effects seem to arise secondary to a paradoxical activation of the mitogen-activated protein kinase signaling of BRAF inhibitor treatment, leading to keratinocyte proliferation. Although the pathogenesis of GD has not been delineated, there is suggestion of activation of T lymphocytes, particularly helper cells under the action of pro-inflammatory cytokines, resulting in proliferation of keratinocytes. Combination therapy with a MEK inhibitor appears to prevent BRAF-induced GD. Given that there is a higher prevalence of GD in patients with hematologic malignancy, a direct causal relationship between the initiation of vemurafenib therapy and development of GD in this case may be difficult to establish.

Keywords: BRAF, transient acantholytic dermatosis, Grover disease, hairy cell leukemia

Introduction

Grover disease (GD) is a transient acantholytic dermatosis that most commonly presents in an older white male as a highly pruritic rash on the upper trunk and proximal extremities with a tendency to wax and wane or spontaneously involute. The associated rash most commonly appears as scattered red-brown or pink papules with variable hyperkeratosis and papulovesicles, but the disease can also rarely present with eczematous plaques. The eruption is usually transient; however, a persistent form is also recognized. The average duration of symptoms is two-to-four weeks. Known precipitating factors include excessive sweating, malignancy, high fever, friction, sun exposure, and being bedridden. Histopathologic characteristics include dyskeratosis and focal acantholysis [1]. The histologic features are often compared to Hailey-Hailey, pemphigus vulgaris, Darier-White disease, pemphigus foliaceous, and spongiotic dermatitis.

Chemotherapeutic drugs are also implicated in the development of GD [1]. It is hypothesized that chemotherapeutic agents may cause GD through excretion in sweat leading to accumulation in the epidermis leading to epidermal toxicity [1]. Recent reports discuss a higher than expected incidence of GD with the administration of BRAF inhibitors, including documented case reports of acantholytic dermatosis after treatment with vemurafenib [2]. Herein, we describe a patient who experienced GD following the administration of vemurafenib.

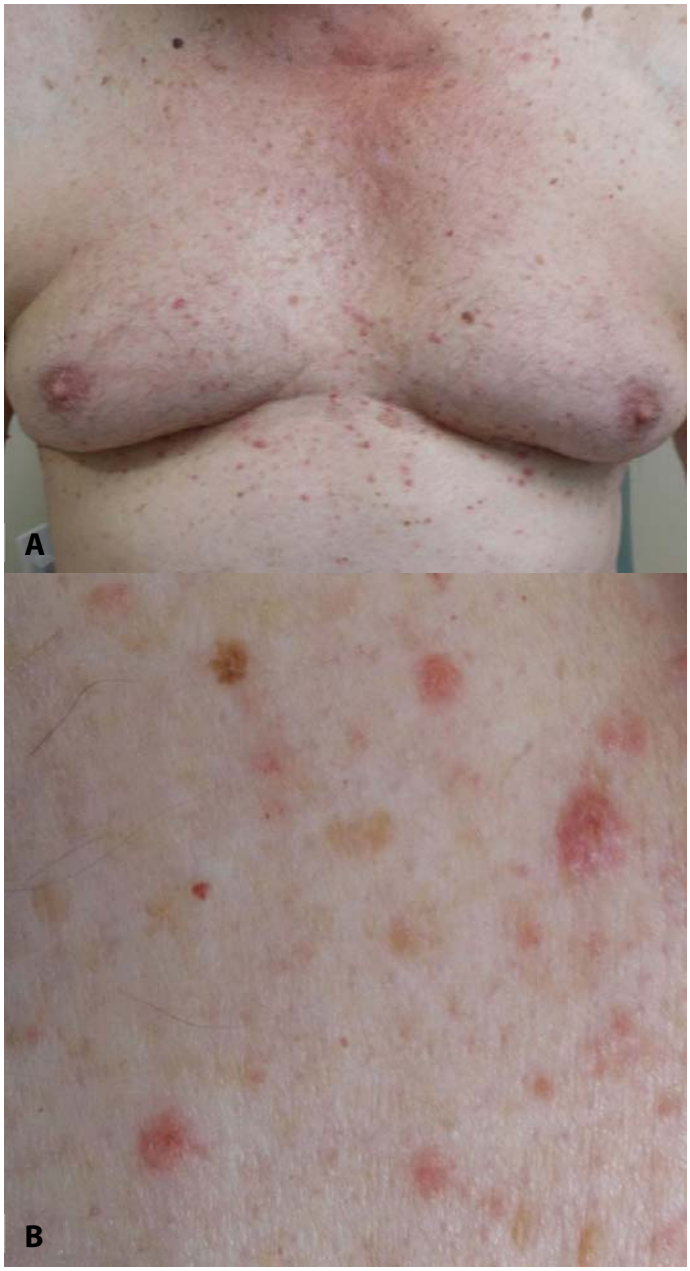

Figure 1. *Clinical photographs of the patient with red papules involving the **A)** arms, chest, and **B)** abdomen.*

Case Synopsis

A 72-year-old man presented with a mildly pruritic erythematous papular rash involving his arms and chest, which is shown in (**Figure 1**). On physical exam, 1-6mm red papules were noted on the involved areas, some with central ulceration and crusting and an atypical vascular pattern on dermoscopy. The skin eruption began two weeks prior to presentation after initiation of vemurafenib monotherapy for treatment of recurrent hairy cell leukemia. The patient was initially diagnosed with hairy cell leukemia 14 years previously and he was in remission after treatment with cladribine purine analog therapy. He denied other symptoms at that time. A shave biopsy was performed of a portion of the eruption on the right upper quadrant abdomen. Pathology results showed prominent suprabasilar acantholysis and dyskeratosis with frond-like villi at the base and associated lymphocytoplasmacytic inflammation (**Figure 2**).

Initially, shave biopsy was performed owing to concern for eruptive squamous cell carcinoma in the setting of vemurafenib use without concurrent MEK inhibitor. However, the pathology findings were compatible with a Darier-like histologic manifestation of GD. Vemurafenib was discontinued after consultation with the oncologist and the patient was treated with clobetasol 0.05% cream twice daily and topical emollients with resolution of the rash. Currently, the patient remains off vemurafenib therapy and he is in remission from his hairy cell leukemia for the past 6 months.

Discussion

The pathogenesis of GD has not yet been fully determined. Risk factors for development of the disease include: acute ultraviolet exposure, excessive sweating, heat, bed confinement, hematologic malignancies, solid tumors, and drugs [3-8]. In fact, drug-induced GD has increasingly been reported in patients on BRAF-inhibitor monotherapy as an immune-related adverse event [6-10]. In one report, the authors described two cases in which patients developed acantholytic dyskeratosis with histological features consistent with a "Grover-like rash." They concluded that BRAF inhibitor-induced rash is related to paradoxical activation of the MAP-kinase pathway resulting in keratinocyte proliferation [2]. In a separate study, patients enrolled in the phase I/II clinical trial for dabrafenib were monitored for the development of new skin lesions [11]. Twenty-seven percent of the participants developed GD. The authors agree that these skin lesions were related to BRAF inhibitor-induced keratinocyte proliferation. This hypothesis is

supported by the results of a retrospective cohort study, which demonstrated that vemurafenib is associated with a variety of other hyperkeratotic cutaneous adverse reactions including plantar hyperkeratosis, verrucal keratosis, squamous cell carcinoma, and keratosis pilaris-like reactions [12]. The most common cutaneous adverse event associated with single agent BRAF inhibitor treatment was GD in 42.9% of the cases. In describing this finding, the authors agreed with the hyperkeratotic mechanism of action described above [12].

Researchers have postulated several theories in the pathogenesis of GD. One theory attributes the development of GD to occlusion of damaged eccrine ducts. This theory is supported by the association with increased seating, heat, and sun exposure [4]. However, GD often spares the palms and soles of the feet which contain a high density of eccrine glands.

In drug-induced GD, one proposed mechanism for the hyperkeratotic reaction postulates that the metabolites generated by the chemotherapeutic agents are concentrated by sweat, leading to accumulation in the epidermis with resultant epidermal toxicity and the subsequent dyskeratosis and acantholysis [13]. However, a second theory hypothesizes that the transient acantholysis might be the result of an off-target effect of the BRAF-inhibitors [14]. Combination therapy with a MEK inhibitor appears to prevent BRAF-induced GD. In a retrospective cohort study of melanoma patients, Carlos et al. found that no patients treated with dabrafenib or vemurafenib combined with trametinib developed GD, in comparison to 38.9% of patients treated with vemurafenib alone [12]. Heidorn et al. propose that selective inhibition of BRAF also drives RAS-dependent BRAF binding to CRAF, leading to the activation of CRAF and MEK-ERK signaling [15]. Therefore, the addition of a MEK inhibitor seems to mitigate such effect.

Owing to the higher occurrence of GD in the patient population to which our patient belongs, in addition to higher prevalence in those with hematologic malignancy, it is difficult to prove direct causal relationship between the initiation of vemurafenib therapy and development of GD in this case. It is important to consider the possibility that this patient may have developed GD coincidentally. However, onset of the rash shortly after initiation of vemurafenib therapy and resolution with discontinuation indicates that this is the most likely cause. If the patient is restarted on vemurafenib therapy in the future with recurrence of GD, this would help to support this theory.

There are previous reports of BRAF therapy induced GD in melanoma patients but cases in other types of malignancies are not well-documented. This is important because hematologic malignancy, specifically hairy cell leukemia, is a known precipitant of GD [3, 5]. Therefore, direct causation is difficult to

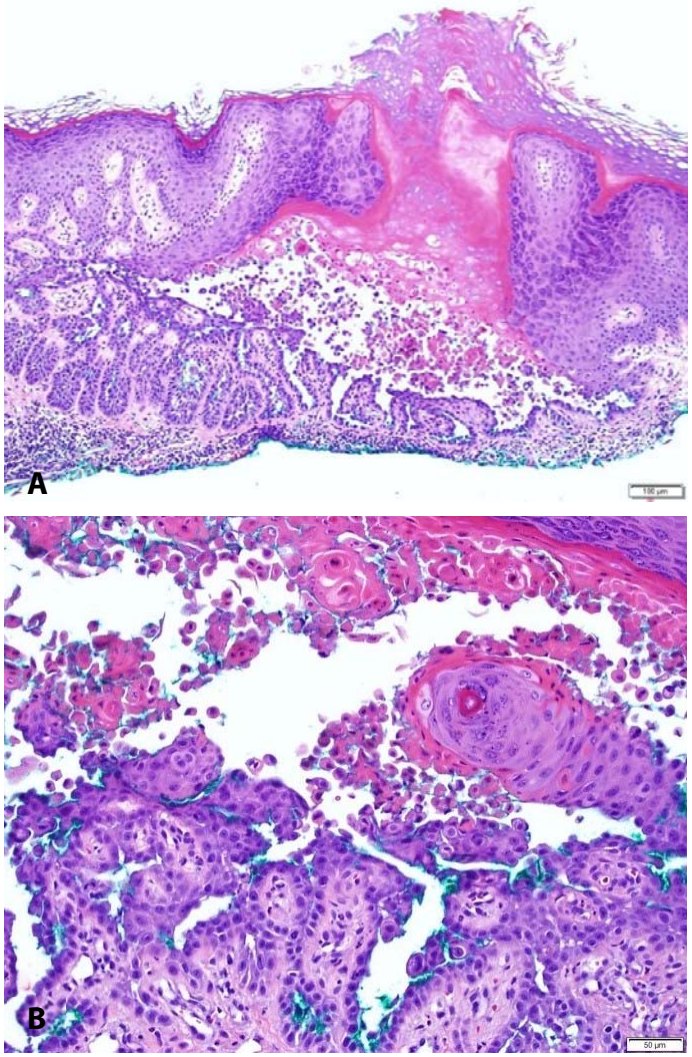

Figure 2. *Hematoxylin-eosin stain with **A)** prominent suprabasilar acantholysis and dyskeratosis with frond-like villi at the base, 10×, and **B)** associated lymphocytoplasmacytic inflammation, 40×.*

establish as hematologic malignancy may be a further confounding factor in this case. The management of the benign skin eruption is based on topical corticosteroids and emollients and the chemotherapeutic agents should not be discontinued but rather temporarily stopped only if required.

Conclusion

Drug-induced Grover disease is increasingly prevalent in the setting of BRAF inhibitor monotherapy. This immune-related adverse event can potentially be prevented with the addition of a MEK inhibitor. Patients on BRAF inhibitors require routine dermatologic evaluations to prevent or recognize cutaneous toxic effects of BRAF inhibitors or provide prompt management.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Weaver J, Bergfeld WF. Grover Disease (Transient Acantholytic Dermatosis). *Arch Pathol Lab Med*. 2009;133:1490-4. [PMID: 19722762].
2. Sabatier-Vincent M, Charles J, Pinel N, et al. Deux cas de dermatose acantholytique sous vémurafénib. *Ann Dermatol Venereol*. 2014;4351:653. [PMID: 25442474].
3. Grover RW, Rosenbaum R. The association of transient acantholytic dermatosis with other skin diseases. *J Am Acad Dermatol*. 1984;11:253–6 [DOI: 10.1016/S0190-9622(84)70160-5].
4. Hu CH, Michel B, Farber EM. Transient acantholytic dermatosis (Grover's disease). A skin disorder related to heat and sweating. *Arch Dermatol*. 1985;121:1439-41. [PMID: 4051530].
5. Davis MDP, Dinneen AM, Landa N, Gibson LE. Grover's disease: clinicopathologic review of 72 cases. *Mayo Clin Proc*. 1999;74:229-34. [PMID: 10089990].
6. Cohen PR, Kurzrock R. Transient acantholytic dermatosis after treatment with 2-chlorodeoxyadenosine. *Acta Derm Venereol*. 1997;77(5):412-3. [PMID: 9298152].
7. Cohen PR, Kurzrock R. 2-chlorodeoxyadenosine-associated transient acantholytic dermatosis in hairy cell leukemia patients. *Am J Dermatopathol*. 1999;21:106-8. [PMID: 10027536].
8. Guana AL, Cohen PR. Transient acantholytic dermatosis in oncology patients. *J Clin Oncol*. 1994;12:1703-9. [PMID: 8040681].
9. Hwang SJE, Anforth R, Carlos G, Fernandez-Peñas P. Cutaneous adverse events of new anti-melanoma therapies: classification and management. *Actas Dermosifiliogr*. 2017;108:6-16. [PMID: 27642030].
10. Curry JL, Tetzlaff MT, Nagarajan P, et al. Diverse types of dermatologic toxicities from immune checkpoint blockade therapy. *J Cutan Pathol*. 2017;44:158-76. [PMID: 27859479].
11. Anforth RM, Blumetti TCMP, Kefford RF, et al. Cutaneous manifestations of dabrafenib (GSK2118436): a selective inhibitor of mutant BRAF in patients with metastatic melanoma. *Br J Dermatol*. 2012;167:1153-60. [PMID: 22804352].
12. Carlos G, Anforth R, Clements A, et al. Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma. *JAMA Dermatol*. 2015;151:1103-9. [PMID: 26200476].
13. Gupta M, Huang V, Linette G, Cornelius L. Unusual complication of vemurafenib treatment of metastatic melanoma: exacerbation of acantholytic dyskeratosis complicated by Kaposi varicelliform eruption. *Arch Dermatol*. 2012;148:966-8. [PMID: 22911209].
14. Cabanillas ME, Patel A, Danysh BP, et al. BRAF inhibitors: experience in thyroid cancer and general review of toxicity. *Horm Cancer*. 2015;6:21-36. [PMID: 25467940].
15. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell*. 2010;140:209-21. [PMID: 20141835].