Title
Transient acantholytic dermatosis in a patient with prostate cancer

Journal
Dermatology Online Journal, 26(2)

Authors
Khan, MS
Khan, M
Aivaz, O

Publication Date
2020

DOI
10.5070/D3262047431

Transient acantholytic dermatosis in a patient with prostate cancer

MS Khan[1] DO, M Khan[2] MD, O Aivaz[3] MD

Affiliations: [1]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA, [2]Foundation University Medical College, Islamabad, Pakistan, [3]Department of Dermatology, Cedars-Sinai Medical Center, Los Angeles, California, USA

Corresponding Author: Mohammad S. Khan, DO, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048, Tel: 407-879-2764, Email: mohammad.khan@cshs.org

Abstract

Transient acantholytic dermatosis (TAD) is a relatively common entity that has been also noted to occur in patients with cancer. Herein, we describe a case of transient acantholytic dermatosis occurring in a patient with a history of prostate cancer status post radiation, now being treated with combination therapy with pembrolizumab and carboplatin-pemetrexed for advanced lung adenocarcinoma. Our case emphasizes the importance of being cognizant of TAD and its associations, particularly in cancer patients.

Keywords: Transient-acantholytic dermatosis, TAD, immune-related adverse events, irAEs

Introduction

Transient-acantholytic dermatosis also known as transient acantholytic dermatosis occurs generally among Caucasian males (male-to-female ratio 2.4:1 with a mean age at diagnosis of 61 years) with an incidence of 0.8%. It presents clinically as a papulovesicular eruption on the trunk and proximal extremities [1]. Histologically, the disease manifests as small well-circumscribed foci of supra-basal acantholysis with dyskeratosis, a spongiotic epidermis, lymphohistiocytic interface dermatitis, and peri-vascular infiltrates [2]. The rash can be exacerbated by exercise, heat, sweat, ultra-violet light, friction, and malignancy.

Particularly in cancer patients, TAD has been reported to occur in four different settings: (1) idiopathic, (2) after antineoplastic therapy, (3) after radiation therapy, and (4) paraneoplastic. Peculiarly, as part of a paraneoplastic syndrome, the appearance of TAD has led to the detection of a co-existing malignancy or the resolution of TAD has coincided with a favorable response to therapy for that malignancy [3]. Predominantly hematological malignancies have been associated with TAD, occurring in 8% of cases [4]; reports of somatic malignancies associated with TAD are fewer in number (see **Box 1**).

On the other hand, in this era of an ever-expanding list of drugs used to treat advanced cancer, it is no

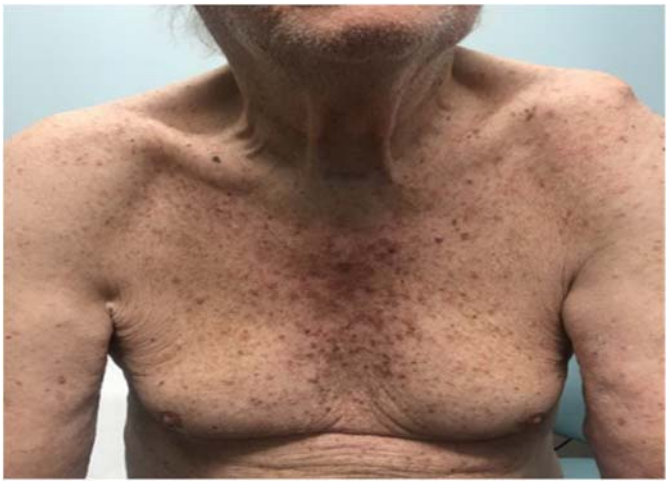

Figure 1. *Dermatologic findings after the first course of pembrolizumab treatment. **A)** Clinical presentation. Overview image showing diffuse eruption of a papulovesicular rash on the patient's upper trunk.*

Box 1. *Malignancies associated with transient-acantholytic dermatosis.*

Hematopoietic malignancies:
Acute myeloid leukemia [25-27]
Non-Hodgkin's lymphoma [28]
Waldenstrom's Macroglobulinemia (ie. lymphoplasmacytic lymphoma) [29]
Angioimmunoblastic lymphadenopathy with dysproteinemia-like T-cell lymphoma [30]
Myeloid sarcoma/ leukemia cutis [27,31]

Solid malignancies:
Carcinoma of the GU organs (prostate, urothelial, renal) [25,32]
Laryngeal carcinoma [33]
Melanoma [34]
Non-small cell lung cancer [35]

surprise that the list of drugs associated with TAD also keeps growing. Drug-induced triggers known to precipitate TAD include interleukin-4 [5], D-penicillamine [5, 6], ribavirin [6], anastrozole [7], and anti-neoplastic drugs, including immunotherapy [2, 8-11], among many others (see **Box 2**). TAD has also been associated with 2-chlordeoxyadenosine in patients being treated for hairy cell leukemia [3]. Given the multifactorial etiology of TAD, it is then important to be cognizant and familiar with this entity and its associations, particularly in managing cancer patients.

Box 2. *Drugs associated with transient-acantholytic dermatosis.*

Anastrozole [7]
Penicillamine [5,6]
CTLA-4 inhibitors (ipilimumab) [2, 10-11]
PD-1/PDL-1 inhibitors (pembrolizumab) [8-9]
Ribavirin [6]
2-chlorodeoxyadenosine [4,36]
BRAF inhibitors (vemurafenib and dabrafenib) [37]

Case Synopsis

We report a case of a 78-year-old man with a history of prostate cancer, status post radiation therapy and currently being treated with pembrolizumab and carboplatin-pemetrexed combination therapy for stage IV lung adenocarcinoma of the left lower lobe. The tumor cells were positive for PDL-1 with 40% expression analyzed via immunohistochemistry. Pertinent laboratory values were unremarkable with peripheral eosinophil counts being normal.

Shortly after initiation of the second cycle of combination therapy, the patient developed a generalized rash. Physical examination revealed a widespread painless polymorphic papulo-vesicular dermatosis on photo-distributed areas to include the upper back, chest, and upper extremities with intense pruritus and mild exfoliation; there was no notable improvement with oral benadryl and topical hydrocortisone (**Figure 1**). The patient reported no history of prolonged sun exposure, fever, infection, abundant sweating, autoimmune disease or a previous episode of TAD-like eruption. Skin biopsy of the lesions on the mid chest revealed focal vacuolar alteration of the dermal/epidermal junction with necrotic keratinocytes, lymphocytes, and rare eosinophils in the dermis (**Figure 2**). The epidermis also demonstrated multiple foci of superficial acantholytic dyskeratosis accompanied by keratinocyte dysmaturation and parakeratosis.

In this clinical context, the differential diagnosis was TAD versus drug eruption, including drug-induced TAD. The lesions were relatively asymptomatic and stable and treatment with combination therapy was continued owing to the mild severity of the rash. The patient was prescribed 0.1% topical triamcinolone cream to relieve pruritus and advised to avoid sun exposure. A close follow-up assessment eight days after initial presentation revealed that the rash was responsive to topical coritcosteroids with complete resolution. No other therapy related adverse events were noted in the patient at that time.

Long term follow-up revealed that the patient had completed four cycles of combination therapy

followed by maintenance pembrolizumab with an initial partial response followed by recent disease progression demonstrated by CT scans. No recurrence of a rash or a dermatologic immune-related adverse event (irAE) have been reported since the initial skin biopsy in 2017. Given that the patient was not a good candidate for aggressive cytotoxic therapy and recent disease progression, hospice care was recommended owing to failure to thrive.

Case Discussion

Given that our patient had multiple cancers and was currently receiving anti-neoplastic therapy, the possibility of drug-induced TAD was clinically raised because a wide range of irAEs have been associated with both anti-CTLA-4 and anti-PD-1/PDL-1 inhibitors [8, 12-24]. In particular, TAD-like irAEs have been previously reported in patients treated with both ipilimumab [2, 10-11] and PD-1/PDL-1 inhibitors [8, 9], but are rare events. In our case however, the fact that the patient's rash resolved despite continuation of combination therapy and the patient did not develop a TAD-like rash despite subsequent cycles of combination therapy followed by maintenance pembrolizumab favors that the eruption was not drug induced. Given that TAD is a known association in multiple different settings in cancer patients, this finding is not surprising, but invariably helpful for patient management.

Conclusion

Our case demonstrates that it is important to be aware of TAD and its association within a variety of cancer settings, particularly with the ever-expanding list of therapies being used to treat advanced cancers. More importantly, the need for active dermatological surveillance and close follow-up has become ever more important in such patients, often requiring clinicopathological correlation to ultimately dictate clinical management.

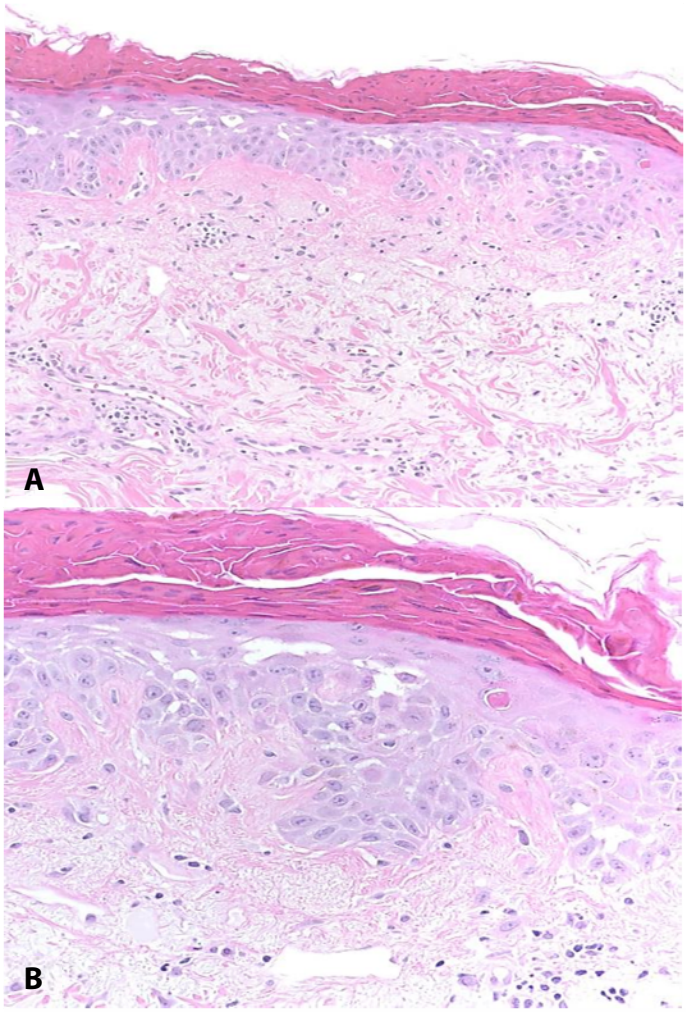

Figure 2- *Histopathological findings of the skin biopsy, hematoxylin-eosin stain.* ***A)*** *Overview image demonstrating circumscript acantholysis of the epidermis accompanied by keratinocyte dysmaturation and parakeratosis, 20×.* ***B)*** *Higher power detail image showing TAD-like features with acantholytic and dyskeratotic keratinocytes present within the epidermis, 40×.*

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2014;372:320. [PMID: 25399552].
2. Viktor H. Koelzer, Toblas Buser, Niels Willi et al. Grover's like drug eruption in a patient with metastatic melanoma under ipilimumab therapy. *J Immunother Cancer*. 2016;4:47. [PMID: 27532022].
3. Cohen PR, Kurzrock R. 2-cholorodeoxyadenosine-associated transient acantholytic dermatosis in hairy cell leukemia patients. *Am J Dermatopathol*. 1999;1:106-8. [PMID: 10027536].

4. Davis, M. D., A. M. Dinneen, N. Landa, and L. E. Gibson. Grover's disease: clinicopathologic review of 72 cases. *Mayo Clin Proc*. 1999;74:229–234. [PMID: 10089990].
5. Zvulunov A, Grunwald MH, Avinoach I, Halevy S. Transient acantholytic dermatosis (Grover's disease) in a patient with progressive systemic sclerosis treated with D-penicillamine. *Int J Dermatol*. 1997;36:476-7. [PMID: 9248901].
6. Antunes I, Azevedo F, Mesquita-Guimaraes J et al. Grover's disease secondary to ribavirin. *Br J Dermatol*. 2000;142:1257-8 [PMID: 10848771].
7. Crockett JS, Burkemper NM. Grover disease (transient acantholytic dermatosis) induced by anastrozole. *Cutis*. 2011;88:175-7. [PMID: 22106724].
8. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. 2016;60:12. [PMID: 27043866].
9. Martina Sanlorenzo, Igor Vujic, Adil Daud, et al. Pembrolizumab cutaneous adverse events and their association with disease progression. *JAMA Dermatol*. 2015;11:1206-1212. [PMID: 26222619].
10. Munoz J. Guillot B, Girard C, Dereure O. Du-Thanh A. First report of ipilimumab-induced Grover disease. *Br J Dermatol*. 2014;171:1236. [PMID: 24749658].
11. Uemura M, Faisal F, Haymaker C, et al. A brief report of Grover's disease- a Th2 immune mediated skin toxicity induced by inhibition of CTLA-4 but not PD-1. *J Immunother Cancer*. 2016;4:55. [PMID: 27660709].
12. Lacouture ME, Wolchok JD, Yosipovitch G, et al. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol*. 2014;71:161-9. [PMID: 24767731].
13. Weber JS, Kahler KC, Hausechild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30:2691-7. [PMID: 22614989].
14. Voskens CJ, Goldinger SM, Loquai C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from ipilimumab network. *PLoS One*. 2013;8:e53745. [PMID: 23341990].
15. Hwang SJ, Carlos G, Wakade D, Sharma R, Fernandez-Penas P. Ipilimumab-induced acute generalized exanthematous pustulosis in a patient with metastatic melanoma. *Melanoma Res*. 2016;26:417. [PMID: 27031538].
16. Sheik Ali S, Goddard AL, Luke JJ, et al. Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphyocyte antigen 4 blockade. *JAMA Dermatol*. 2015;151:195. [PMID: 25321335].
17. Rudolph BM, Staib F, Von Stebut E, Hainz M, Grabbe S, Loquai C. Neutrophilic disease of the skin and intestines after ipilimumab treatment for malignant melanoma- simultaneous occurrence of pyoderma gangrenosum and colitis. *Eur J Dermatol*. 2014;24:268. [PMID: 24721740].
18. Gormley R, Wanat K, Elenitsas R, et al. Ipilimumab-associated Sweet syndrome in a melanoma patient. *J Am Acad Dermatol*. 2014;71:e211. [PMID: 25437997].
19. Kyllo RL, Parker MK, Rosman I, Musiek AC. Ipilimumab-associated Sweet syndrome in a patient with high-risk melanoma. *J Am Acad Dermatol*. 2014;70:e 85. [PMID: 24629370].
20. Pintova S, Sidhu H, Friedlander PA. Holcombe RF. Sweet's syndrome in a patient with metastatic melanoma after ipilimumab therapy. *Melanoma Res*. 2013;23:498. [PMID: 24113862].
21. Libon F. Arrese JE, Rorive A, Nikkels AF. Ipilimumab induces simultaneous regression of melanocytic naevi and melanoma metastases. *Clin Exp Dermatol*. 2013;38:276. [PMID: 23020081].
22. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomized, double-blind,multicenter, phase 2, dose-ranging study. *Lancet Oncol*. 2010;11:155. [PMID: 20004617].
23. Hodi FS, O' Day SJ, McDermott DF, et al. Improved survival with iplimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711. [PMID: 20525992].
24. Staser L. Chen D, Solus J, et al. Extensive tumoral melanosis associated with ipilimumab-treated melanoma. *Br J Dermatol*. 2016;175:301. [PMID: 26877232].
25. Guana AL, Cohen PR. Transient acantholytic dermatosis in oncology patients. *J Clin Oncol*. 1994 8:1703-9. [PMID: 8040681].
26. Zhu HJ, Clark LN, Deloney LA, McDonald JE. Grover disease (transient acantholytic dermatosis) in acute myeloid leukemia on FDG PET/CT. *Clin Nucl Med*. 2014;2:e-173-5. [PMID: 24152615].
27. Sakalosky PE, Fenske N, Morgan MB. A case of acantholytic dermatosis and leukemia cutis: cause or effect? *Am J Dermatopathol*. 2002;3:257-9. [PMID: 12140444].
28. Fujita Y, Sato-Matsumura KC, Ohnishi K. Transient acantholytic dermatosis associated with B symptoms of follicular lymphoma. *Clin Exp Dermatol*. 2007;6:752-4. [PMID: 17868396].
29. Roger M, Valence C, Bressieux JM, Bernard P et al. Grover's disease associated with Waldenstrom's macroglobulinemia and neutrophilic dermatosis. *Acta Derm Venereol*. 2000;2:145-6. [PMID: 10877140].
30. Zelickson BD, Tefferi A, Gertz MA et al. Transient acantholytic dermatosis associated with lymphomatous angioimmunoblastic lymphadenopathy. *Acta Derm Venereol*. 1989;69:445-8. [PMID: 2572118].
31. Joshua W. Wilma FB. Grover Disease (transient acantholytic dermatosis). *Archives of Pathology & Laboratory Medicine*. 2009;133:1490-1494. [PMID: 19722762].
32. McDermott DF, Drake CG. Sznol M, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *J Clin Oncol*. 2015;33:2013. [PMID: 25800770].
33. Aloi FG, Colonna SM, Amasio ME. Grover's disease of cutaneous and laryngeal localization associated with a carcinoma of the larynx. *G Ital Dermatol Venereol*. 1984;119:407-10. [PMID: 6530242].
34. Tognetti L, Nami N, Fimiani M et al. Grover's disease and cutaneous melanoma: a fortuitous association or a paraneoplastic case? *G Ital Dermatol Venereol*. 2015;150:756-8.. [PMID: 26159656].
35. Gettinger SN, Horn L., Gandhi L, et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small cell lung cancer. *J Clin. Oncol*. 2015;33:2004. [PMID: 25897158].
36. Cohen PR, Kurzrock R. Transient acantholytic dermatosis after treatment with 2-cholordeoxyadenosine. *Acta Derm Venereol*. 1997;77:412-3. [PMID: 9298152].
37. Anforth R, Fernandez-Pena P, Long GV. Cutaneous toxicities of RAF inhibitors. *Lancet Oncol*. 2013;14:e11-8. [PMID: 23276366].