Ipilimumab-associated halo-like inflammatory reactions around nevi during therapy for metastatic melanoma

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Abstract

Ipilimumab is an immune-modulating drug that is being used today for various cancers including metastatic malignant melanoma. Owing to its mechanism of action, several adverse events have been reported, including some affecting skin. In this work, we report a novel display of multiple ipilimumab-associated halo lichenoid reactions surrounding benign nevi during treatment of metastatic melanoma. A patient underwent treatment with ipilimumab for treatment of stage IIIC melanoma at our center and was monitored for progress and adverse events throughout treatment. During treatment with ipilimumab, the patient clinically developed multiple halo lichenoid reactions surrounding previously present nevi, which histopathologically showed a lichenoid interface dermatitis associated with the mildly atypical nevi and ill-formed granulomata within the infiltrate. Therefore, ipilimumab may be associated with halo lichenoid reactions surrounding benign nevi and this adverse effect should be added to the various dermatologic reactions that patients can develop while being treated with this agent.

Keywords: ipilimumab, immune-modulating drug, dermatologic adverse event, lichenoid reaction, metastatic melanoma

Introduction

Ipilimumab is a drug that inhibits the CTLA-4 pathway, which in recent years has been approved for use in various cancers including metastatic melanoma. Likely secondary to its mechanism of action on immune cells, several drug reactions or adverse events have occurred with ipilimumab, reflecting its immunomodulating effects on the

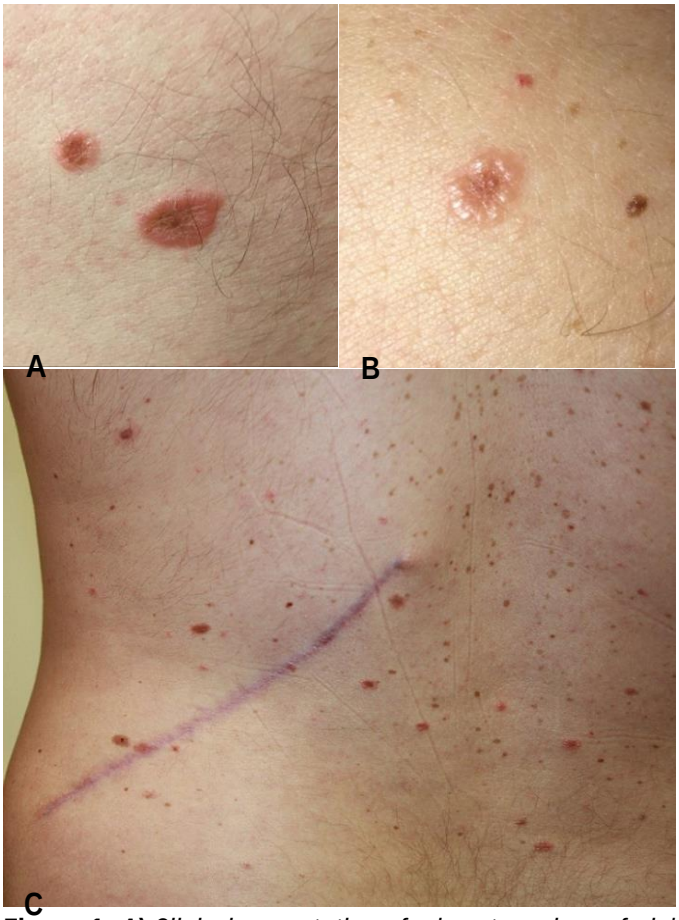

Figure 1. ***A)*** *Clinical presentation of edematous rings of pink papules surrounding benign-appearing macular nevi after starting ipilimumab therapy.* ***B)*** *Clinical presentation of edematous rings of pink papules surrounding benign-appearing macular nevi after starting ipilimumab therapy.* ***C)*** *Clinical image of the patient status post wide local excision for malignant melanoma of the left lower back. The pink, edematous, papular halo reaction around several of the nevi after starting ipilimumab therapy can be seen from a distance here.*

body. The literature reports a range of dermatologic adverse events occurring in 3-68% of patients receiving ipilimumab therapy [1-7]. We report a novel clinical presentation of ipilmumab-associated halo-like nevus reaction to multiple nevi in a patient with metastatic melanoma.

Case Synopsis

A 32 year-old man presented with a 6mm pink-brown papule on the left lower back. After initial biopsy showing a malignant melanoma, a wide local excision, sentinel inguinal node biopsy, and subsequent lymph node dissection of the left inguinal and axillary regions were performed. Workup revealed a 2.23mm deep, stage IIIC melanoma with three total positive lymph node metastases (two in the groin and one in the axilla). Ipilimumab was started thereafter. After three treatment cycles, each three weeks' apart, the patient developed edematous skin colored and slightly erythematous rings around multiple pink/light brown macular nevi (**Figure 1**). A biopsy showed a lichenoid interface dermatitis associated with a mildly atypical nevus. In addition, ill-formed granulomata were present within the infiltrate (**Figure 2**).

At this point in time, the patient was also noted to have elevated liver function tests, which were previously normal. The fourth ipilimumab treatment cycle was held secondary to worsening drug eruption, headaches, and liver dysfunction. A repeat brain MRI was stable with no concern for melanoma metastases. The patient was started on oral prednisone 60mg daily tapered over several weeks and the skin lesions, headaches, and liver dysfunction resolved.

Case Discussion

Dermatologic reactions to ipilimumab have been reported as a dose-dependent phenomenon, typically occurring 2-12 weeks after ipilimumab treatment initiation [1-3, 8-10]. Common dermatologic adverse events (DAEs) to ipilimumab include pruritus, morbilliform dermatitis, vitiligo-like melanoma-associated hypopigmentation, sarcoidosis, and psoriasis [1-4, 6, 11, 12]. Other rare patterns of drug-related eruption have been reported including lichenoid drug eruptions, DRESS, and SJS/TEN [13]. Although lichenoid drug eruptions are typically

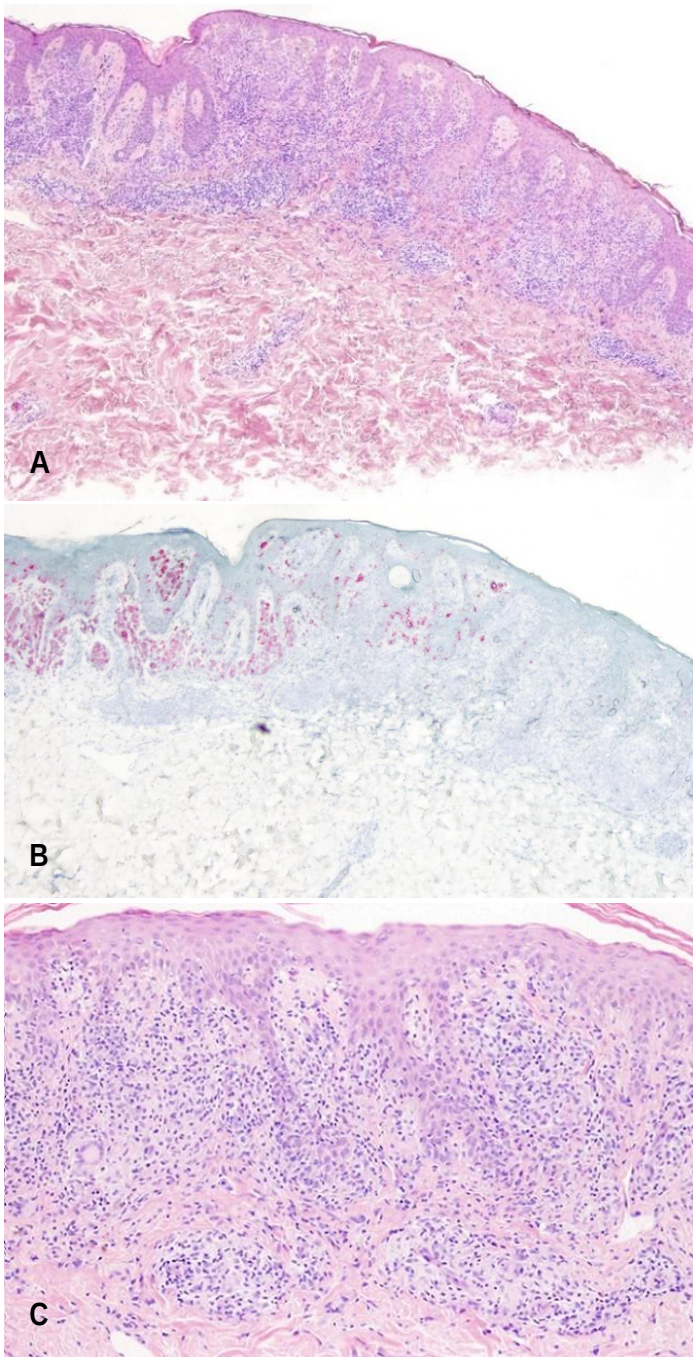

Figure 2. ***A)*** *Mildly atypical nevus with an associated dense lichenoid inflammatory infiltrate. H&E, 4x.* ***B)*** *MART-1 stain highlighting the melanocytic nevus with associated halo-like inflammatory reaction including a dense lymphomononuclear infiltrate with diminished density of melanocytes. MART-1 (Melan-A) ALK PHOS (A103, Ventana), 4x.* ***C)*** *Mildly atypical nevus with associated ill-formed granulomata within the lichenoid inflammatory infiltrate. H&E, 10x.*

reported with drug classes such as antibiotics, NSAIDs, ACE-inhibitors, antihistamines, lipid lowering drugs, and hydroxychloroquine sulfate [12], these reactions are more rare with immune-modulating drugs such as the anti-PD-1 and anti-PD-L1 drug classes [14-16]. Similar to our case, Libon et al. reported a lichenoid lymphohistiocytic infiltrate associated with regressing "bystander" atypical nevi in a patient receiving ipilimumab for metastatic melanoma. However, in contrast to our current case, the skin surrounding the regressed nevi appeared entirely normal clinically [17].

To our knowledge, this is the first case of a patient treated with ipilimumab for metastatic melanoma who presented with clinically apparent skin changes surrounding nevi that yielded a lichenoid infiltrate associated with the atypical nevus on biopsy, consistent with the halo nevus phenomenon. The distribution of the halo reaction around nevi may represent a form of immunologic or inflammatory regression of the nevi by activation of the immune system [13, 18]. Interestingly, the presence of immunologic regression elsewhere may indicate regression of the cancer. According to Downey et al. [19], an increased efficacy of ipilimumab was found in patients that developed immune-related adverse effects (26% responded) as compared to those without immune-related adverse effects (2% responded). Further, a higher-grade severity of the immune-related adverse effects corresponded to higher overall response rates to ipilimumab therapy. Thus, in a patient being treated with ipilimumab, the presence of the halo nevus phenomenon could be a strong indicator that treatment is working and that the patient could have a successful response to the melanoma.

Conclusion

As the era of immune-modulating drugs for use in the setting of oncology expands, clinicians must be aware of the adverse reactions that can occur. Dermatologists have a critical role in monitoring for these reactions as DAE have a shorter time to onset as compared to those of other organ systems [13]. It is also worthwhile to note that for the majority of patients, DAEs are relatively mild and are successfully treated with supportive care or a short course of topical steroids without the need to halt treatment. Our patient required oral steroids and a brief reprieve from ipilimumab treatment owing to liver function abnormalities. A clinically apparent halo-like inflammatory reaction to ipilimumab may represent a new clinical presentation to the growing list of adverse events. Reporting is imperative so that dermatologists, oncologists, and primary-care physicians can be made aware.

References

1. deGolian E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous Complications of Targeted Melanoma Therapy. *Curr Treat Options Oncol.* 2016;17(11):57. [PMID: 27645330].
2. Kahler KC, Hauschild A. Treatment and side effect management of CTLA-4 antibody therapy in metastatic melanoma. *J Dtsch Dermatol Ges.* 2011;9(4):277-86. [PMID: 21083648].
3. Minkis K, Garden BC, Wu S, Pulitzer MP, Lacouture ME. The risk of rash associated with ipilimumab in patients with cancer; a systematic review of the literature and meta-analysis. *J Am Acad Dermatol.* 2013;69(3);e121-28. [PMID: 23357570].
4. Ibrahim RA, Berman DM, DePril V, et al. Ipilimumab safety profile: summary of findings from coompleted trials in advanced melanoma [abstract 8583]. *J Clin Oncol.* 2011;29(15 suppl). DOI: 10.1200/jco.2011.29.15_suppl.8583.
5. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* 2012;30(21):2691-97. [PMID: 22614989].
6. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364(26):2517-26. [PMID: 21639810].
7. Wolchok JD, Hodi FS, Weber JS, et al. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. *Ann N Y Acad Sci.* 2013;1291:1-13. [PMID: 23772560].
8. 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 the ipilimumab network. *PLoS ONE.* 2013;8(1): e53745. [PMID: 23341990].
9. Dummer R, Maoi M, Hamid O, et al. Time to onset and resolution of immune-related adverse events associated with ipilimumab therapy in patients with advanced melanoma. *Proceedings of the 14th Perspectives in Melanoma.* 2010; Amsterdam, the Netherlands.
10. 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-lymphocyte antigen 4 blockade. *JAMA Dermatol.* 2015;151(2);195-99. [PMID: 25321335].
11. Reyes-Habito CM, Roh EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer: Part II. Targeted therapy. *J Am Acad Dermatol.* 2014;71(2): 217.e1-11. [PMID: 25037801].

12. Magro CM, Crowson AN. Lichenoid and granulomatous dermatitis. *Int J Dermatol.* 2000;39(2);126-33. [PMID: 10692062].
13. Lacouture ME, Wolchok JK, Yosipovitch G, Kahler CK, Busam KJ, Hauschild A. Ipilimumab in patients with cancer and the management of dermatologic adverse events. *J Am Acad Dermatol.* 2014;71;161-9. [PMID: 24767731].
14. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol.* 2016;43;339-46. [PMID: 26762844].
15. Belum VR, Sibaud V, Lamant L, et al. Oral lichenoid mucositis in cancer patients during nivolumab therapy: a case-series. *Cancer Immunol Res (in press).*
16. Joseph RW, Cappel M, Goedjen B, et al. Lichenoid dermatitis in three patients with metastatic melanoma treated with anti-PD-1 therapy. *Cancer immunol Res.* 2015;3:18-22. [PMID: 25287118].
17. Libon F, Arrese JE, Rorive A, Nikkels AF. Ipilimumab induces simultaneous regression of melanocytic naevi and melanoma metastases. *Clin Exp Dermatol.* 2013;38(3);276-9. [PMID: 23020081].
18. Dalton SR, Baptista MA, Libow LF, Elston DM. Lichnoid tissue reaction in malignant melanoma. *Am J Clin Pathol.* 2002;117:766-70. [PMID: 12090426].
19. Downey SG, Klapper JA, Smith FO, et al. Prognositc factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin Cancer Res.* 2007;13:6681-88. [PMID: 17982122].