CASE REPORT

Eruptive squamous cell carcinomas in metastatic melanoma: An unintended consequence of immunotherapy

Samantha Haraszti, MS,a Samantha Polly, MD,b Harib H. Ezaldein, MD,b Robert Rothbaum, MD,b Gregory R. Delost, DO,b and Mara Beveridge, MDb
Philadelphia, Pennsylvania and Cleveland, Ohio

Key words: checkpoint inhibitor therapy; Dynavax; eruptive squamous cell carcinomas; immune-related adverse events; matrix-metalloproteinase 13; metastatic melanoma; pembrolizumab; SD-101; TLR9 agonist.

INTRODUCTION

With the increasing use of immune-targeted therapy in metastatic melanoma over the last decade and the continued discovery of new targets, it is important to consider not only the efficacy and tolerability of these interventions but also their potential to impact other nontargeted pathways. Currently, in the clinical trial phase, Dynavax (Berkley, CA) is developing SD-101, a TLR9 agonist designed to elicit a potent and focused immune response to solid tumors and hematologic malignancies. Dynavax has been shown to have antitumor activities when used alone and in combination with immune checkpoint inhibitors.1 Here we report a case of the development of 10 invasive cutaneous squamous cell carcinomas (cSCC) after the initiation of SD101 injected peritumorally in combination with pembrolizumab to treat metastatic melanoma.

CASE REPORT

An 84-year-old white man with recently diagnosed ulcerated malignant melanoma (Breslow depth at least 2.5 mm) of his right second toe presented to our dermatology department in 2012 for surgical evaluation and treatment recommendations. The patient underwent amputation of his distal second toe with histopathology showing melanoma within the bone and right ilioinguinal lymph node dissection positive in 1 of 10 nodes resulting in initial stage IIIC (T3b, N1b, M0) designation. Following external beam radiation to the right inguinal region, he was closely monitored clinically along with surveillance positron emission tomography imaging. Over the next 2 years, he had 2 cutaneous melanoma metastases, which were adequately surgically treated with wide local excision.

Beginning in 2017, following development of multiple in-transit melanoma metastases across the right lower extremity, he was started on immune therapy with pembrolizumab. Because of disease progression, the patient was subsequently enrolled in a phase II clinical trial with SD101, a TLR9 agonist, injected peritumorally into a melanoma metastasis on his right anterior thigh, and concomitant pembrolizumab. However, within 4 months of enrolling, 10 pink scaly papules and plaques developed across the body (Fig 1), which were biopsy-proven invasive cSCCs, without signs of viral cytopathic changes (Fig 2). Seven of the 10 cSCCs were located on bilateral distal lower extremities and not localized to TLR9 injection site. The remaining 3 cSCCs were found on photo-exposed sites on left temple and bilateral upper extremities. As cutaneous melanoma metastases continued to develop in addition to cSCCs, he was discontinued from the trial and started on...
nivolumab with acitretin for cSCC prevention. Since initiating acitretin, the patient has not had new nonmelanoma skin cancers.

**DISCUSSION**

The skin continuously interfaces with the external environment and serves as the first line of defense, both as a physical barrier and as a key component of the immune system.° Toll-like receptors (TLRs) expressed by keratinocytes and melanocytes are responsible for inducing an inflammatory response to help eliminate pathogens but, in doing so, can inadvertently contribute to the development of skin cancer.° When TLR9 is activated, it is found to enhance invasion and promote proliferation of malignant cells via COX-2 and NFkB activation.°,3

Although TLR expression on tumor cells may allow tumors to evade immune surveillance, TLRs are also being developed as targets for anticancer interventions that result in the recognition and destruction of tumor cells.° TLR agonists specifically targeting TLR7, 8, and 9, have been developed as treatment options for difficult-to-treat melanoma and basal cell carcinoma, functioning by recruiting dendritic cells and inducing a robust T-cell response.° By stimulating the natural immune response, these TLR agonists have the potential to be broadly effective in multiple tumor types.1

Mouse tumor model studies have found that intratumorally administered SD-101 can increase the quantity and quality of tumor specific CD8+ T cells in patients previously nonresponsive to programmed cell death protein 1 (PD-1) blockade.° SD-101 activates plasmacytoid dendritic cells via TLR9 and is used to stimulate both interferon-γ production and activate tumor-specific cytotoxic CD8+ cells.°,2

In preliminary studies when used in conjunction with PD-1 blockade, an increase in immune cell infiltrates in the tumor microenvironment have been reported.° However, TLRs can potentiate chronic inflammation, which can ultimately contribute to squamous cell carcinoma (SCC) development.°,3 One study found that TLR9 mediated the invasion of in vitro oral SCC, and that its expression was an
independent predictor of poor prognosis. At this time, however, it is currently unknown if any association exists between TLR9 agonists, such as SD-101, and the development of cSCC.

Numerous case reports demonstrate how the PD-1 inhibitors, pembrolizumab and nivolumab, can induce several cutaneous immune-related adverse events including bullous pemphigoid, cutaneous sarcoidosis, vitiligo, and psoriasis. There are also reports of PD-1 inhibitors, particularly pembrolizumab, inducing keratoacanthomas. However, despite these reports, the CARSKIN trial found that pembrolizumab can be used to successfully treat advanced cSCC, and the US Food and Drug Administration recently approved a new PD-1 inhibitor cemiplimab for the treatment of metastatic cSCC. In the presented case, this patient did not have any adverse reactions to pembrolizumab when used as a monotherapy. However, it is possible that combining pembrolizumab with SD-101 may have altered the tumor microenvironment leading to the development of 10 cSCCs.

One proposed mechanism (Fig 3) in this case is that the use of SD-101 led to increased expression of matrix-metalloproteinase 13 as seen in oral SCC and increased invasion and migration of a previously undiagnosed cutaneous SCC. As our understanding of the signaling pathway of melanoma grows, observed cutaneous and systemic
side effects may bring to light the interactions between distinct disease processes. Clinicians must continue to be aware of potential immune-related adverse events as immune checkpoint inhibitors and TLR agonists become more frequently utilized members of our oncology treatment arsenal. Moving forward, it will be imperative to document cases of SCC arising in patients treated with immunotherapy and to develop strategies that do not interfere with antitumor responses.

REFERENCES

1. Dynavax Cancer Immunotherapy. SD101. December 2018. Dynavax website. Available from: http://www.dynavax.com/our-pipeline/cancer-immunotherapy/sd101/.

2. Burns EM, Yusuf N. Toll-like receptors and skin cancer. Front Immunol. 2014;5:135.

3. Kauppila J, Korvala J, Siirila K, et al. Toll-like receptor 9 mediates invasion and predicts prognosis in squamous cell carcinoma of the mobile tongue. J Oral Pathol Med. 2015;44:571-577.

4. Damsky W, Kole L, Tomayko MM. Development of bullous pemphigoid during nivolumab therapy. JAAD Case Rep. 2016;2:442-444.

5. Birnbaum MR, Ma MW, Fleisig S, et al. Nivolumab-related cutaneous sarcoidosis in a patient with lung adenocarcinoma. JAAD Case Rep. 2017;3:208-211.

6. Cotiar J, Querfeld C, Boswell WJ, Raja N, Raz D, Chen R. Pembrolizumab-associated sarcoidosis. JAAD Case Rep. 2016;2:290-293.

7. Suozzi KC, Stahl M, Ko CJ, et al. Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. JAAD Case Rep. 2016;2:264-268.

8. Totonchy MB, Ezaldein HH, Ko CJ, Choi JN. Inverse psoriasiform eruption during pembrolizumab therapy for metastatic melanoma. JAMA Dermatol. 2016;152(5):590-592.

9. Freites-Martinez A, Kwong BY, Rieger KE, Coit DG, Colevas AD, Lacouture ME. Eruptive keratoacanthomas associated with pembrolizumab therapy. JAMA Dermatol. 2017;153(7):694-697.

10. Maubec E, Boubaya M, Petrow P, et al. Pembrolizumab as first line therapy in patients with unresectable squamous cell carcinoma of the skin: Interim results of the phase 2 CARSkin trial. J Clin Oncol. 2018;36(15):9534.