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

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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.

Abbreviations used:

cSCC:	cutaneous squamous cell carcinoma
PD-1:	programmed cell death protein 1
SCC:	squamous cell carcinoma
TLRs:	toll-like receptors

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

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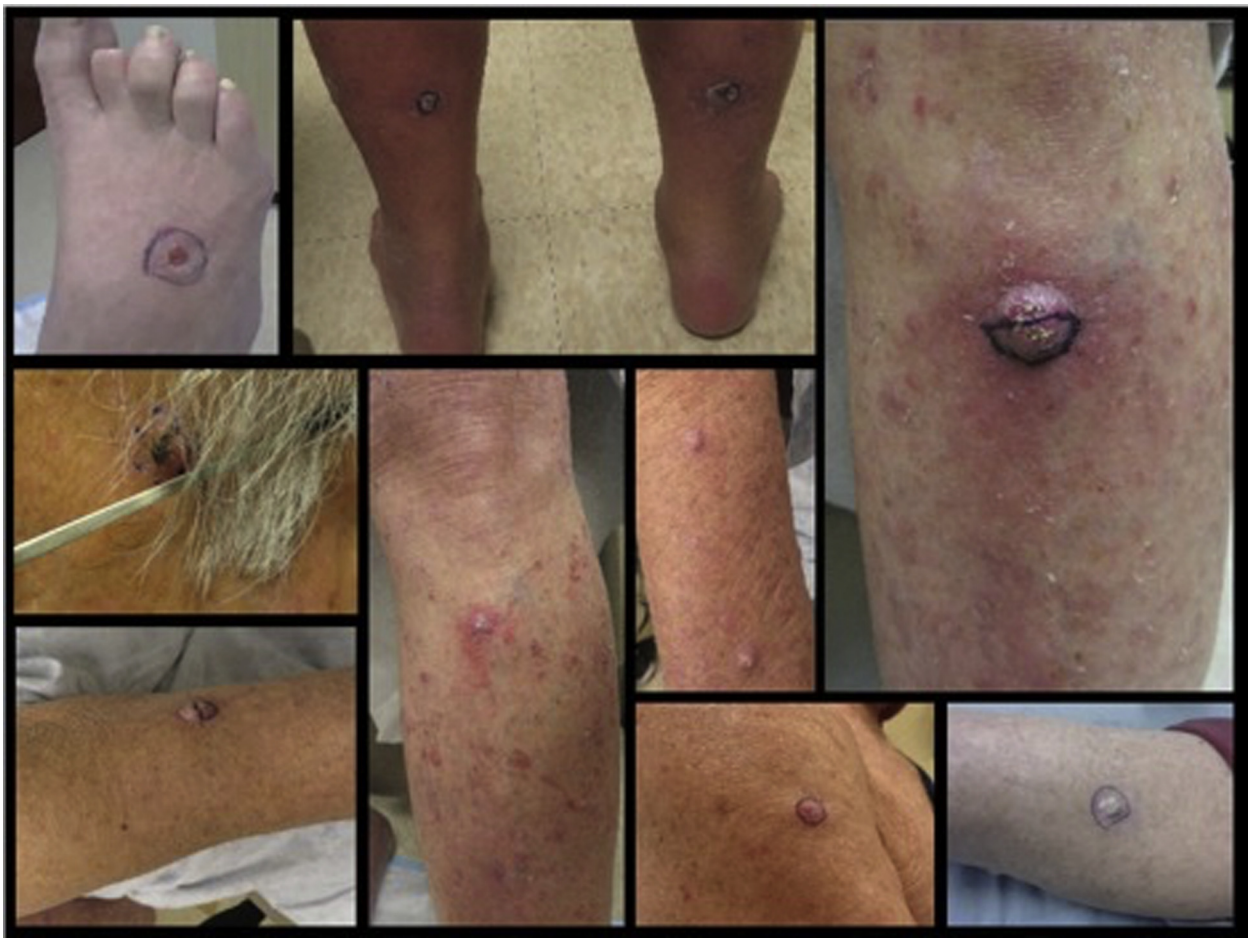

Fig 1. Clinical presentation. Multiple pink scaly papules and plaques across the body, which were biopsy-proven invasive SCCs.

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.[2] 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.[2] When TLR9 is activated, it is found to enhance invasion and promote proliferation of malignant cells via COX-2 and NFkB activation.[2,3]

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.[2] 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.[2] 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.[1] SD-101 activates plasmacytoid dendritic cells via TLR9 and is used to stimulate both interferon-γ production and activate tumor-specific cytotoxic $CD8^+$ cells.[1,2] In preliminary studies when used in conjunction with PD-1 blockade, an increase in immune cell infiltrates in the tumor microenvironment have been reported.[1] However, TLRs can potentiate chronic inflammation, which can ultimately contribute to squamous cell carcinoma (SCC) development.[1,3] One study found that TLR9 mediated the invasion of in vitro oral SCC, and that its expression was an

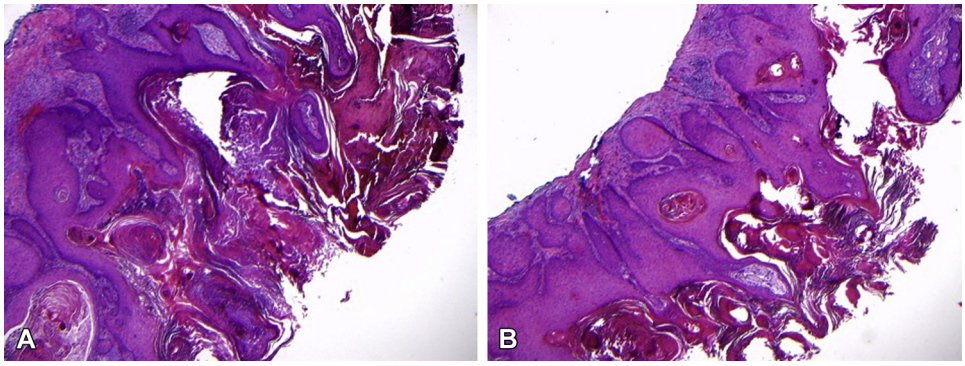

Fig 2. A, Histopathology. Skin, left temple, shave biopsy. Invasive SCC, well differentiated, presented on the deep margin. The tumor is at least 3.5 mm in thickness and extends into the mid reticular dermis. No perineural or lymphovascular invasion is seen. (Original magnification: ×4.) **B**, Histopathology. Skin, right dorsal foot, shave biopsy. Invasive SCC, well differentiated, presented on the deep margin. The tumor is at least 2.5 mm in thickness and extends into at least the mid reticular dermis. No perineural or lymphovascular invasion is seen. (Original magnification: ×4.)

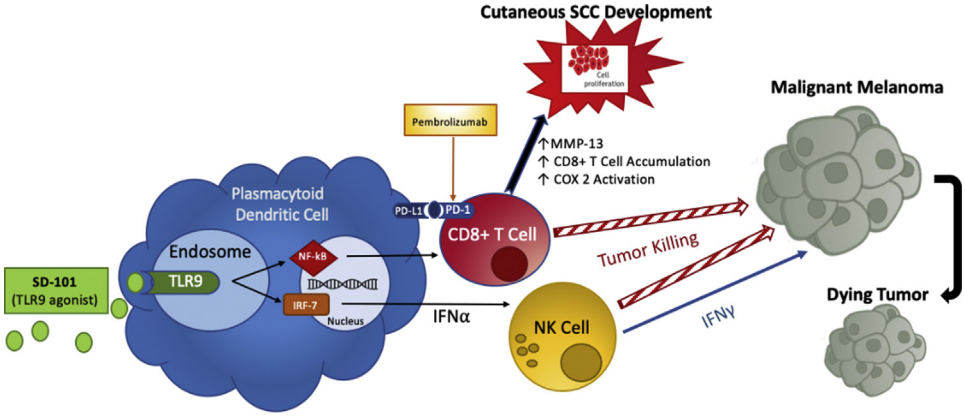

Fig 3. Proposed mechanism leading to cutaneous SCC development. The use of SD-101 led to increased expression of matrix-metalloproteinase 13 as seen in oral SCC and increased invasion and migration of a previously undiagnosed cutaneous SCC.[3]

independent predictor of poor prognosis.[3] 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.[4-8] There are also reports of PD-1 inhibitors, particularly pembrolizumab, inducing keratoacanthomas.[9] However, despite these reports, the CARSKIN trial found that pembrolizumab can be used to successfully treat advanced cSCC,[10] 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 cSCC.[3] We cannot completely rule out that the SCC development in this patient was related to either another medication or idiopathic disease. However, because SCC did not develop while treated solely with pembrolizumab therapy, we hypothesize that the TLR9 agonist activity of SD-101 either alone or in combination with pembrolizumab may have contributed to his disease progression.

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.

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