Formation of eruptive cutaneous squamous cell carcinomas after programmed cell death protein-1 blockade

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INTRODUCTION

The programmed cell death-1 pathway is a key regulatory immune checkpoint that promotes self-tolerance by suppressing Th1 lymphocytes. Pembrolizumab and nivolumab are anti–programmed cell death-1 monoclonal antibodies that mediate anti-tumor responses by reversing tumor suppression of T cells.[1] Heterogeneous dermatologic immune-related adverse effects have been reported in patients receiving programmed cell death-1 inhibitors, including lichenoid, maculopapular, and immunobullous reactions.[2] Toxicity of programmed cell death-1 inhibition is attributed to autoimmunity through reversal of self-protective programmed cell death-1 inhibitory mechanisms. Cutaneous immune adverse effects may be associated with improved prognosis.[3] Recently, eruptive skin neoplasms in sun-exposed areas have been associated with anti–programmed cell death-1 therapy; however, the clinical significance remains unclear.[4,5] We report 2 patients receiving programmed cell death-1 inhibitor monotherapy who developed eruptive cutaneous squamous cell carcinomas (SCCs).

CASE REPORT

A 77-year-old white man with Lynch syndrome underwent pembrolizumab immunotherapy for simultaneous recurrent rectal and gastric adenocarcinomas. His dermatologic history was significant for multiple actinic keratoses, 2 cutaneous SCCs, and a keratoacanthoma. After the third cycle of pembrolizumab, he presented with multiple pruritic verrucous papules with surrounding erythema on the forearms and lower extremities. Biopsy revealed inflamed seborrheic keratoses with an underlying lichenoid infiltrate containing $CD3^+$, $CD4^+$, and programmed cell death-1–positive lymphocytes. The patient was treated with topical steroids and many of the lesions desquamated. After 5 months of pembrolizumab, the patient developed 5 new keratotic lesions located on the bilateral aspect of the forearms, dorsal aspect of the left hand, and scalp. Biopsies revealed cutaneous SCC with programmed cell death-1–positive lymphocytic tumor infiltrates (Fig 1). These tumors were excised by an unaffiliated dermatologist and the patient did not develop additional cutaneous SCCs in a year of follow-up. A similar presentation occurred in an 82-year-old woman receiving nivolumab every 3 weeks for metastatic melanoma. This patient had no history of skin cancer other than the melanoma. After 1 month of immunotherapy, she developed vitiligo on her forearms (Fig 2, *A*). After 8 months of nivolumab, she suddenly developed 6 similar keratotic tumors on the bilateral aspect of her lower extremities (Fig 2, *B*). Biopsies of 3 lesions revealed cutaneous SCCs. Histology revealed tumor surrounded and infiltrated with programmed cell death-1–positive lymphocytes. The patient continued receiving

Abbreviation used:
SCC: squamous cell carcinoma

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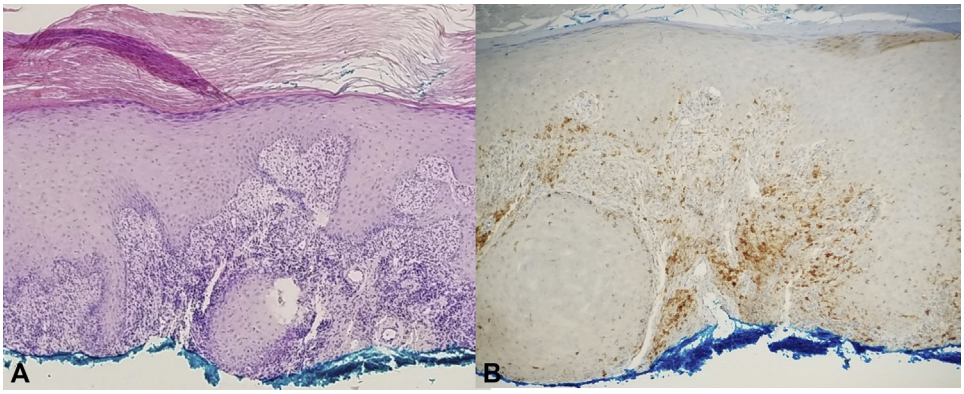

Fig 1. Histology of eruptive squamous cell carcinoma. Shave biopsy of keratotic lesion on arm in patient with Lynch syndrome, demonstrating (**A**) squamous cell carcinoma with numerous horn pearls (eosinophilic parakeratotic keratinization) and (**B**) programmed cell death-1–positive tumor-infiltrating lymphocytes surrounding and infiltrating the tumor periphery. Similar histologic findings were observed in the second patient with metastatic melanoma. (Hematoxylin-eosin stain; original magnification: ×10.)

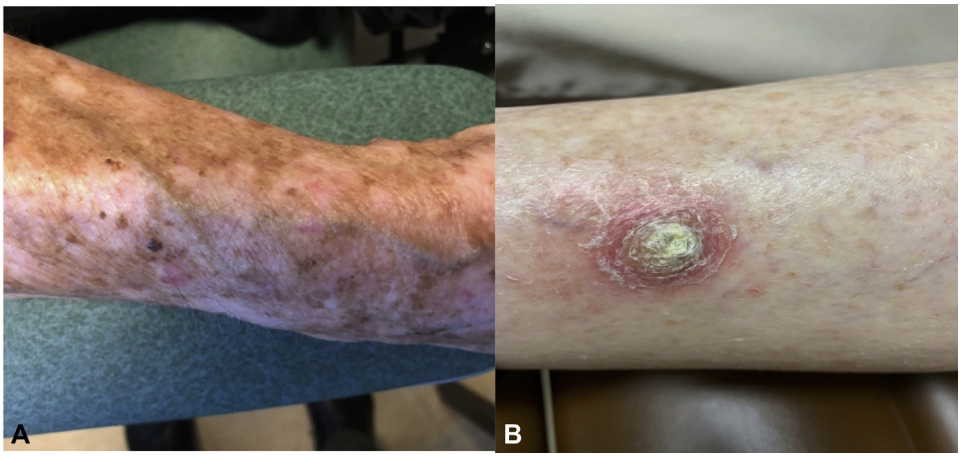

Fig 2. Vitiligo and eruptive squamous cell carcinoma in an 82-year-old woman with metastatic melanoma. **A**, Vitiligo on the upper extremity of patient 2 after 1 month of treatment with nivolumab. **B**, Eruption of keratotic tumor on her lower extremity after 8 months of immunotherapy.

nivolumab, and cutaneous SCCs were treated with topical clobetasol. Three of the cutaneous SCCs resolved after 2 months and the remaining tumors appeared inflamed and decreased in size. Both patients' internal malignancies demonstrated excellent responses to anti–programmed cell death-1 therapy.

DISCUSSION

Programmed cell death ligand-1 is overexpressed in cutaneous SCCs, and programmed cell death-1 inhibitors have demonstrated efficacy in patients with unresectable or recurrent cutaneous SCCs.[6] Eruption of cutaneous SCCs in the setting of programmed cell death-1 inhibition is therefore paradoxic. Two previous cases of programmed cell death-1 inhibitor–associated eruptive cutaneous SCCs have been described. Lee et al[5] reported cutaneous SCCs on the dorsal aspect of the forearms and hands after 4 months of nivolumab and ipilimumab therapy in a patient with metastatic melanoma. Histopathology revealed a lymphocytic lichenoid infiltrate and the lesions were largely responsive to topical corticosteroids. Immunotherapy was not resumed because metastatic lesions remained stable or improved after the eruptive cutaneous lesions. Similarly, Haraszti et al[4] reported 10 invasive cutaneous SCCs on the temple, upper extremities, and lower extremities after 4 months of therapy with pembrolizumab and SD-101 injections peritumorally for metastatic melanoma. No adverse cutaneous

effects occurred when pembrolizumab therapy was used alone. To our knowledge, we are the first to report cutaneous SCC eruptions associated with programmed cell death-1 inhibitor monotherapy.

Eruptive keratoacanthomas have also been documented as rare cutaneous adverse events of programmed cell death-1 inhibition. Similar to reported eruptive cutaneous SCCs, keratoacanthomas occurred in photodamaged regions after 1 to 18 months of anti–programmed cell death-1 therapy. Effective treatment modalities included intralesional and topical corticosteroids, 5-fluorouracil, imiquimod, cryotherapy, and curettage.[5,7,8] In some cases, keratoacanthomas resolved without intervention within 6 to 8 weeks despite continuation of programmed cell death-1 inhibitors.[7] Lichenoid infiltration patterns occurred in eruptive cutaneous SCCs and keratoacanthomas, suggesting that immunoactivating anti–programmed cell death-1 antibodies may induce inflammatory responses potentiating aberrant keratinocyte proliferation in predisposed individuals. Tumor and tumor-infiltrating cells of both keratoacanthomas and cutaneous SCCs exhibit similar programmed cell death ligand-1 expression profiles, with high densities of cytotoxic T cells.[9] Therefore, eruptions of keratoacanthomas and cutaneous SCCs in the setting of programmed cell death-1 inhibition may occur through shared immunomediated mechanisms, but additional studies are needed to elucidate this phenomenon.

Although many documented eruptions of cutaneous SCCs or keratoacanthomas associated with programmed cell death-1 inhibitors occurred in patients with metastatic melanoma, to our knowledge we are the first to report this association in the context of Lynch syndrome. Anti–programmed cell death-1 agents are efficacious in Lynch syndrome because tumors with aberrant mismatch-repair function are more sensitive to programmed cell death-1 blockade than mismatch-repair–proficient tumors.[10] Mismatch-repair–deficient tumors express programmed cell death-1 in the microenvironment, presumably inducing programmed cell death-1–dependent immunoevasion to facilitate tumor survival.[10] Genomic instability yields mutation-associated neoantigens in mismatch-repair deficiency, and higher mutational loads have been correlated with potent anti–programmed cell death-1 responses.[10] Additionally, deficient mismatch-repair tumors have dense infiltrates of $CD8^+$ T cells, enabling durable immunoresponses to anti–programmed cell death-1 therapy.[10] Because programmed cell death-1 inhibitors are efficacious through immunomodulation, tumors with mismatch-repair deficiencies and high mutational burdens may predispose individuals to immunorelated dermatologic toxicities associated with programmed cell death-1 inhibitors, although further study is necessary to substantiate this association.

Additional immunorelated cutaneous effects have been reported in patients receiving programmed cell death-1 inhibitors with various latency periods, indicating a role for both acute and delayed immunoreactions.[2] Programmed cell death-1–associated immunorelated cutaneous lesions tend to occur in combination, consistent with clinical courses observed in this report.[2] After programmed cell death-1 inhibitors were initiated, eruptive inflammatory seborrheic keratoses with rapid resolution preceded the onset of cutaneous SCCs in the first patient, and vitiligo developed before cutaneous SCC onset in the second patient. These events may be attributed to autoimmunity through reversal of programmed cell death-1 inhibitory mechanisms. Both patients' internal malignancies were particularly responsive to anti–programmed cell death-1 therapy. Increased progression-free intervals have been associated with immunorelated cutaneous adverse effects of programmed cell death-1 inhibitors, including hypopigmentation and keratoses.[3]

In summary, we report 2 cases of eruptive cutaneous SCCs as immunorelated dermatologic events associated with programmed cell death-1 inhibitor monotherapy. The cutaneous SCCs were preceded by skin reactions (to seborrheic keratoses in one patient and to melanocytes in the other) several months before the SCCs. Additional studies analyzing the relative contribution of epigenetics, immunomicroenvironments, and antigen-specific immunoresponses may further elucidate the pathogenesis and clinical significance of immunorelated dermatologic lesions in patients receiving programmed cell death-1 inhibitors.

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