Cemiplimab-Associated Eruption of Generalized Eruptive Keratoacanthoma of Grzybowski

Bianca Y. Kang, MD; Raveena Khanna, MD; Meera H. Patel, MD; David J. Glembocki, MD; Brooke G. Jeffy, MD; Maya K. Thosani, MD; Neel B. Patel, MD

PRACTICE **POINTS**

- Immunotherapy, including immune checkpoint inhibitors such as programmed cell-death protein 1 (PD-1) inhibitors, is associated with an array of immune-related adverse events that often manifest in a delayed and prolonged manner. They most commonly affect the gastrointestinal tract as well as the endocrine and dermatologic systems.
- Dermatologic adverse effects associated with PD-1 inhibitors include lichenoid reactions, pruritus, morbilliform eruptions, vitiligo, and bullous pemphigoid.
- Eruptions of keratoacanthoma rarely have been reported following treatment with PD-1 inhibitors such as cemiplimab, nivolumab, and pembrolizumab.

To the Editor:

Treatment of cancer, including cutaneous malignancy, has been transformed by the use of immunotherapeutic agents such as immune checkpoint inhibitors (ICIs) that target cytotoxic T lymphocyte-associated antigen 4, programmed cell-death protein 1 (PD-1), or programmed cell-death ligand 1 (PD-L1). However, these drugs are associated with a distinct set of immune-related adverse events (IRAEs). We present a case of generalized eruptive keratoacanthoma of Grzybowski associated with the ICI cemiplimab.

A 94-year-old White woman presented to the dermatology clinic with acute onset of extensive, locally advanced cutaneous squamous cell carcinoma (cSCC) of the upper right posterolateral calf as well as multiple noninvasive cSCCs of the arms and legs. Her medical history was remarkable for widespread actinic keratoses and numerous cSCCs. The patient had no personal or family history of melanoma. Various cSCCs had required treatment with electrodesiccation and curettage, topical or intralesional 5-fluorouracil, and Mohs micrographic surgery. Approximately 1 year prior to presentation, oral acitretin was initiated to help control the cSCC. Given the extent of locally advanced disease, which was considered unresectable, she was referred to oncology but continued to follow up with dermatology. Positron emission tomography was remarkable for hypermetabolic cutaneous thickening in the upper right posterolateral calf with no evidence of visceral disease.

The patient was started on cemiplimab, an anti-PD-1 monoclonal antibody ICI indicated for the treatment of both metastatic and advanced cSCC. After 4 cycles of intravenous cemiplimab, the patient developed widespread nodules covering the arms and legs (Figure 1) as well as associated tenderness and pruritus. Biopsies of nodules revealed superficially invasive, well-differentiated cSCC consistent with keratoacanthoma. Although a lymphocytic infiltrate was present, no other specific reaction pattern, such as a lichenoid infiltrate, was present (Figure 2).

Drs. Kang, Khanna, M.H. Patel, and N.B. Patel are from Creighton University School of Medicine, Phoenix Regional Campus, Arizona. Drs. Glembocki and N.B. Patel are from Southwest Skin Specialists, Phoenix. Drs. Jeffy and Thosani are from Spectrum Dermatology, Phoenix.

The authors report no conflict of interest.

Correspondence: Bianca Y. Kang, MD, Creighton University School of Medicine, Phoenix Regional Campus, 350 W Thomas Rd, Phoenix, AZ 85013 (biancakang94@gmail.com).

doi:10.12788/cutis.0935

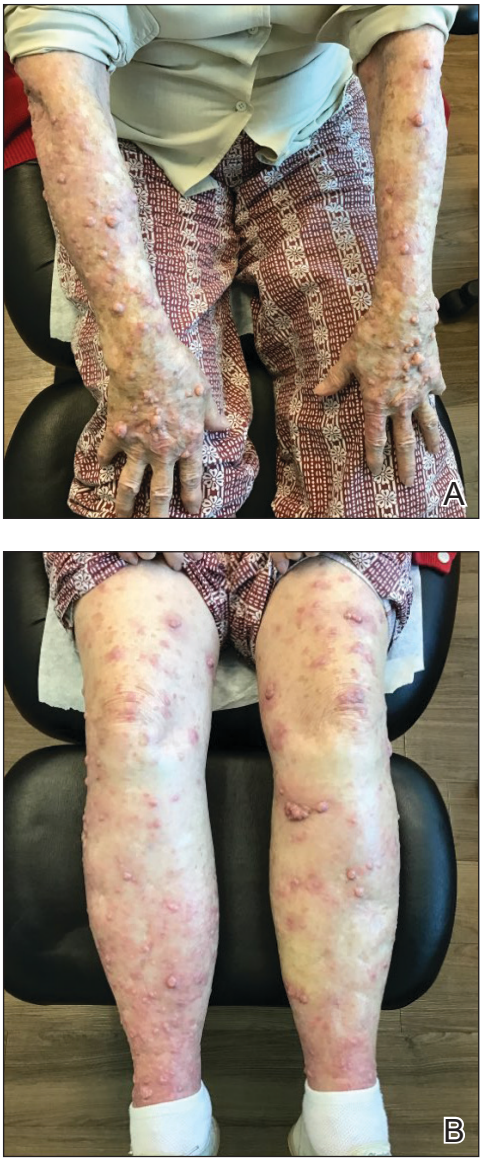

FIGURE 1. A and B, Clinical presentation of well-differentiated cutaneous squamous cell carcinoma, keratoacanthoma type, on the arms and legs, respectively, with widespread red, tender, scaly papules and nodules.

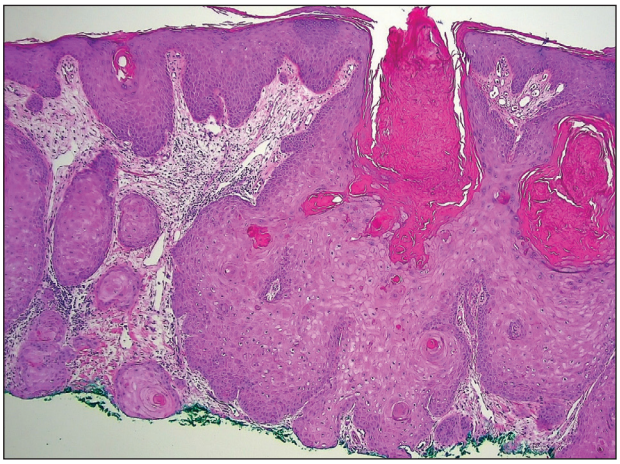

FIGURE 2. Well-differentiated cutaneous squamous cell carcinoma, keratoacanthoma type. Histopathology of a biopsy specimen from the right proximal lateral calf lesion revealed nests of well-differentiated tumor cells with low-grade nuclei and abundant, glassy, eosinophilic cytoplasm, as well as abundant accumulation of keratin (H&E, original magnification ×40).

Positron emission tomography was repeated, demonstrating resolution of the right calf lesion; however, new diffuse cutaneous lesions and inguinal lymph node involvement were present, again without evidence of visceral disease. Given the clinical and histologic findings, a diagnosis of generalized eruptive keratoacanthoma of Grzybowski was made. Cemiplimab was discontinued after the fifth cycle. The patient declined further systemic treatment, instead choosing a regimen of topical steroids and an emollient.

Immunotherapeutics have transformed cancer therapy, which includes ICIs that target cytotoxic T lymphocyte-associated antigen 4, PD-1, or PD-L1. Increased activity of these checkpoints allows tumor cells to downregulate T-cell activation, thereby evading immune destruction. When PD-1 on T cells binds PD-L1 on tumor cells, T lymphocytes are inhibited from cytotoxic-mediated killing. Therefore, anti-PD-1 ICIs such as cemiplimab permit T-lymphocyte activation and destruction of malignant cells. However, this unique mechanism of immunotherapy is associated with an array of IRAEs, which often manifest in a delayed and prolonged fashion.[1] Immune-related adverse events most commonly affect the gastrointestinal tract as well as the endocrine and dermatologic systems.[2] Notably, patients with certain tumors who experience these adverse effects might be more likely to have superior overall survival; therefore, IRAEs are sometimes used as an indicator of favorable treatment response.[2,3]

Dermatologic IRAEs associated with the use of a PD-1 inhibitor include lichenoid reactions, pruritus, morbilliform eruptions, vitiligo, and bullous pemphigoid.[4,5] Eruptions of keratoacanthoma rarely have been reported following treatment with the PD-1 inhibitors nivolumab and pembrolizumab.[3,6,7] In our patient, we believe the profound and generalized eruptive keratoacanthoma—a well-differentiated cSCC variant—was related to treatment of locally advanced cSCC with cemiplimab. The mechanism underlying the formation of anti-PD-1 eruptive keratoacanthoma is not well understood. In susceptible patients, it is plausible that the inflammatory environment permitted by ICIs paradoxically induces regression of tumors such as locally invasive cSCC and simultaneously promotes formation of keratoacanthoma.

The role of inflammation in the pathogenesis and progression of cSCC is complex and possibly involves contrasting roles of leukocyte subpopulations.[8] The increased

incidence of cSCC in the immunocompromised population,[8] PD-L1 overexpression in cSCC,[9,10] and successful treatment of cSCC with PD-1 inhibition[10] all suggest that inhibition of specific inflammatory pathways is pivotal in tumor pathogenesis. However, increased inflammation, particularly inflammation driven by T lymphocytes and Langerhans cells, also is believed to play a key role in the formation of cSCCs, including the degeneration of actinic keratosis into cSCC. Moreover, because keratoacanthomas are believed to be a cSCC variant and also are associated with PD-L1 overexpression,[9] it is perplexing that PD-1 blockade may result in eruptive keratoacanthoma in some patients while also treating locally advanced cSCC, as seen in our patient. Successful treatment of keratoacanthoma with anti-inflammatory intralesional or topical corticosteroids adds to this complicated picture.[3]

We hypothesize that the pathogenesis of invasive cSCC and keratoacanthoma shares certain immune-mediated mechanisms but also differs in distinct manners. To understand the relationship between systemic treatment of cSCC and eruptive keratoacanthoma, further research is required.

In addition, the RAS/BRAF/MEK oncogenic pathway may be involved in the development of cSCCs associated with anti-PD-1. It is hypothesized that BRAF and MEK inhibition increases T-cell infiltration and increases PD-L1 expression on tumor cells,[11] thus increasing the susceptibility of those cells to PD-1 blockade. Further supporting a relationship between the RAS/BRAF/MEK and PD-1 pathways, BRAF inhibitors are associated with development of SCCs and verrucal keratosis by upregulation of the RAS pathway.[12,13] Perhaps a common mechanism underlying these pathways results in their shared association for an increased risk for cSCC upon blockade. More research is needed to fully elucidate the underlying biochemical mechanism of immunotherapy and formation of SCCs, such as keratoacanthoma.

Treatment of solitary keratoacanthoma often involves surgical excision; however, the sheer number of lesions in eruptive keratoacanthoma presents a larger dilemma. Because oral systemic retinoids have been shown to be most effective for treating eruptive keratoacanthoma, they are considered first-line therapy as monotherapy or in combination with surgical excision.[3] Other treatment options include intralesional or topical corticosteroids, cyclosporine, 5-fluorouracil, imiquimod, and cryotherapy.[3,6]

The development of ICIs has revolutionized the treatment of cutaneous malignancy, yet we have a great deal more to comprehend on the systemic effects of these medications. Although IRAEs may signal a better response to therapy, some of these effects regrettably can be dose limiting. In our patient, cemiplimab was successful in treating locally advanced cSCC, but treatment also resulted in devastating widespread eruptive keratoacanthoma. The mechanism of this kind of eruption has yet to be understood; we hypothesize that it likely involves T lymphocyte–driven inflammation and the interplay of molecular and immune-mediated pathways.

REFERENCES

1. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. 2020;6:38. doi:10.1038/s41572-020-0160-6
2. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer*. 2019;7:306. doi:10.1186/s40425-019-0805-8
3. Freites-Martinez A, Kwong BY, Rieger KE, et al. Eruptive keratoacanthomas associated with pembrolizumab therapy. *JAMA Dermatol*. 2017;153:694-697. doi:10.1001/jamadermatol.2017.0989
4. Shen J, Chang J, Mendenhall M, et al. Diverse cutaneous adverse eruptions caused by anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1) immunotherapies: clinical features and management. *Ther Adv Med Oncol*. 2018;10:1758834017751634. doi:10.1177/1758834017751634
5. Bandino JP, Perry DM, Clarke CE, et al. Two cases of anti-programmed cell death 1-associated bullous pemphigoid-like disease and eruptive keratoacanthomas featuring combined histopathology. *J Eur Acad Dermatol Venereol*. 2017;31:E378-E380. doi:10.1111/jdv.14179
6. Marsh RL, Kolodney JA, Iyengar S, et al. Formation of eruptive cutaneous squamous cell carcinomas after programmed cell death protein-1 blockade. *JAAD Case Rep*. 2020;6:390-393. doi:10.1016/j.jdcr.2020.02.024
7. Antonov NK, Nair KG, Halasz CL. Transient eruptive keratoacanthomas associated with nivolumab. *JAAD Case Rep*. 2019;5:342-345. doi:10.1016/j.jdcr.2019.01.025
8. Bottomley MJ, Thomson J, Harwood C, et al. The role of the immune system in cutaneous squamous cell carcinoma. *Int J Mol Sci*. 2019;20:2009. doi:10.3390/ijms20082009
9. Gambichler T, Gnielka M, Rüddel I, et al. Expression of PD-L1 in keratoacanthoma and different stages of progression in cutaneous squamous cell carcinoma. *Cancer Immunol Immunother*. 2017;66:1199-1204. doi:10.1007/s00262-017-2015-x
10. Patel R, Chang ALS. Immune checkpoint inhibitors for treating advanced cutaneous squamous cell carcinoma. *Am J Clin Dermatol*. 2019;20:477-482. doi:10.1007/s40257-019-00426-w
11. Rozeman EA, Blank CU. Combining checkpoint inhibition and targeted therapy in melanoma. *Nat Med*. 2019;25:879-882. doi:10.1038/s41591-019-0482-7
12. Dubauskas Z, Kunishige J, Prieto VG, Jonasch E, Hwu P, Tannir NM. Cutaneous squamous cell carcinoma and inflammation of actinic keratoses associated with sorafenib. *Clin Genitourin Cancer*. 2009;7:20-23. doi:10.3816/CGC.2009.n.003
13. Chen P, Chen F, Zhou B. Systematic review and meta-analysis of prevalence of dermatological toxicities associated with vemurafenib treatment in patients with melanoma. *Clin Exp Dermatol*. 2019;44:243-251. doi:10.1111/ced.13751