

Pembrolizumab for cutaneous squamous cell carcinoma: Report of a case of inoperable squamous cell carcinoma with complete response to pembrolizumab complicated by granulomatous inflammation



Mireille L. M. van Baar, MD,^{a,b} Alex D. Guminiski, PhD,^{a,c,d} Peter M. Ferguson, PhD,^{a,d,e} and Linda K. Martin, FACP^{a,f}
Sydney, Australia and Nijmegen, The Netherlands

Key words: cutaneous squamous cell carcinoma; granulomatous; immunotherapy; pembrolizumab.

INTRODUCTION

Since initial approval in 2014 for treatment of advanced-stage melanoma, the programmed cell death-1 (PD-1) inhibitor pembrolizumab has been investigated for a wide range of malignancies. Many tumors express the ligand PDL1, which interacts with the PD-1 receptor on activated T cells. Inhibition of the PD-1 receptor results in a potent T-cell activation, causing strong antitumor responses.^{1,2} PD-1 inhibitor therapy can be complicated by immune activation, and autoimmune-like phenomena.³

Recent reports show promising results with pembrolizumab for locally advanced or metastatic cutaneous squamous cell carcinoma (SCC),^{4,5} but clinical responses have not been characterized by histology to date.

Here we report a case of locally advanced inoperable cutaneous SCC with complete clinical and histopathologic resolution after 4 cycles of pembrolizumab, complicated by a granulomatous tissue reaction, mimicking disease progression.

Abbreviations used:

PD-1: programmed cell death 1
SCC: squamous cell carcinoma

CASE REPORT

An 88-year-old woman presented with recurrent inoperable circumferential SCC on her left lower leg. The patient's medical history was notable for mitral valve replacement, ischemic heart disease, permanent pacemaker, and heart failure with lower limb edema. The tumor initially presented 2 years prior and was treated with wide local excision and a graft. Pathology findings confirmed moderately differentiated SCC with intratumoral perineural invasion, with complete excision with the nearest margin of 1.5 mm (Fig 1). Local recurrence occurred within 2 months of the initial excision and rapidly progressed with painful bleeding ulcers and reduced mobility requiring hospitalization. Subsequent wide local excision and grafting of 2 contiguous recurrent

From Melanoma Institute Australia, The University of Sydney^a; Radboud University Medical Center, Nijmegen^b; the Department of Medical Oncology, Royal North Shore and Mater Hospitals, Sydney^c; Sydney Medical School, The University of Sydney^d; the Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital^e; and the School of Women's and Children's Health, University of New South Wales.^f

Funding sources: None.

Conflicts of interest: None disclosed.

Correspondence to: Linda K. Martin, FACP, Melanoma Institute Australia, The Poche Centre, Suite 8, 40 Rocklands Road,

Wollstonecraft, NSW 2065, Australia. E-mail: linda.martin@melanoma.org.au.

JAAD Case Reports 2019;5:491-4.

2352-5126

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jdcrr.2019.04.006>

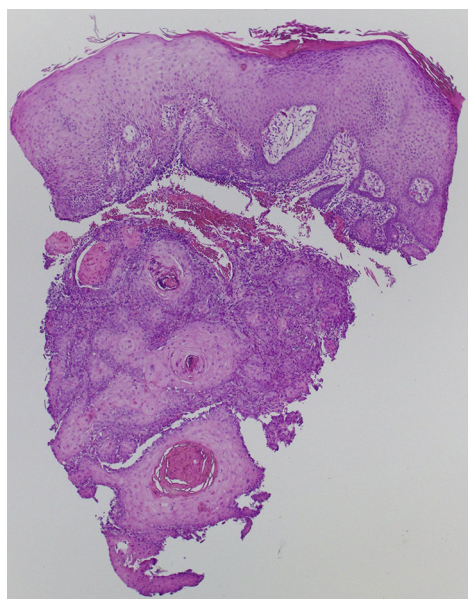


Fig 1. The pretreatment punch biopsy shows a moderately differentiated squamous cell carcinoma.

nodules found subcutaneous infiltration of moderately differentiated SCC involving the deep margins of both excision specimens. During admission, a positron emission tomography scan showed extensive soft tissue fluoro-deoxy-glucose-avid disease in the left leg (Fig 2). There was no evidence of inguinal, pelvic, or distant metastases.

At this point, treatment options were limited to amputation, isolated limb infusion, or systemic drug therapy with immunotherapy. There was no role for radiotherapy given the location and extent of disease.

She received treatment with 4 cycles of pembrolizumab, 95 mg intravenously, 3 weeks apart. Clinically, there was a reduction in the size of the tumors and reduced pain after immunotherapy. She tolerated the immunotherapy course well. She was referred to a dermatologist for the management of residual ulceration 6 months after immunotherapy.

On physical examination, there were multiple deep punched-out ulcers in a circumferential distribution at the site of previous SCC on the left leg (Fig 3). Further biopsy was performed to exclude residual SCC (Fig 4). Pathology findings showed granulomatous inflammation within the dermis with aggregates of multinucleate giant cells surrounding keratinous and calcified debris, with surrounding patchy lymphocytic infiltration. Periodic acid–Schiff and fite stains were negative, and pancytokeratin antibody stained positive. The ulcers were treated with betamethasone dipropionate ointment under occlusion, with good clinical improvement (Fig 3). On follow-up at 12 months, there was no evidence of recurrent disease.

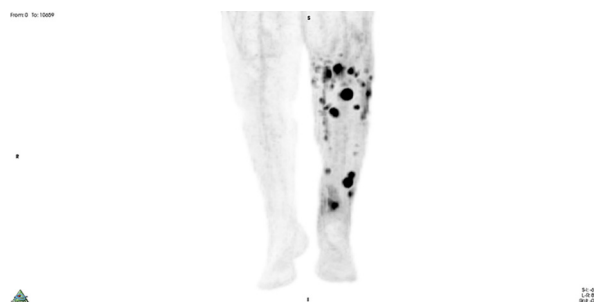


Fig 2. Positron emission tomography scan shows multiple soft-tissue of fluoro-deoxy-glucose-avid deposits on the left leg.

DISCUSSION

Locally advanced cutaneous SCC represents a significant therapeutic challenge. For unresectable SCC not amenable to radiotherapy, the standard systemic treatment options include chemotherapy (usually platinum or fluoropyrimidine based) or targeted therapy with epidermal growth factor receptor inhibitors.⁶ Responses are often of short duration and may be associated with significant side effects in an often elderly and frail population.

Cutaneous SCC is theoretically amenable to checkpoint inhibitor therapy because of tumoral expression of the PD-1 ligand, ultraviolet-induced DNA hypermutation, and correlation with immunosuppression. More recently, there is evidence of sustained responses to immunotherapy with an anti-PD-1 checkpoint inhibitor cemiplimab, with approximately 50% response rates in early-phase trials.⁴ In addition, promising outcomes have been reported in several case reports of patients with advanced SCC treated with pembrolizumab.^{4,7,8}

Immune therapies, in addition to their antitumor effect, can lead to immune dysregulation, resulting in autoimmune-like diseases or chronic inflammation. Both cutaneous and systemic sarcoid-like granulomatous inflammations are described in patients receiving PD-1 inhibitors.^{3,9} In our case, because of the localization of granulomatous inflammation at the site of the treated SCC and the presence of keratinous material within the granulomas, we hypothesize that this may represent an immune response directed against the tumor.

Differentiating between disease progression or recurrence and granulomatous immunotherapy reactions can be difficult, both radiologically and clinically. Awareness of this complication and tissue biopsy are required to prevent misinterpretation of findings.¹⁰

Anti-PD-1 therapy is a promising alternative for treatment for advanced SCC and is currently subject



Fig 3. Clinical photograph immediately post-immunotherapy (left) and 12 months after immunotherapy (right): atrophic scarring 6 months after betamethasone dipropionate ointment under occlusion.

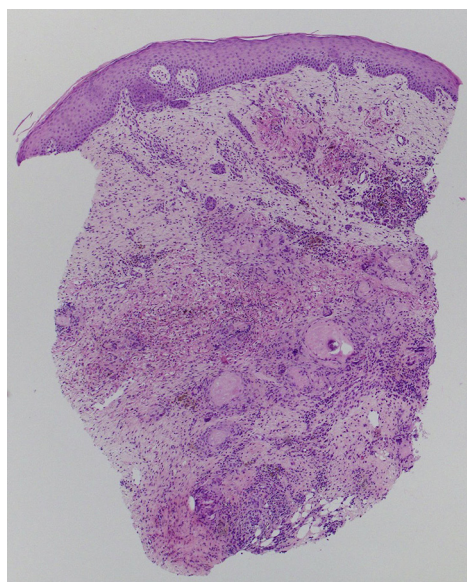


Fig 4. Posttreatment with pembrolizumab. There is granulomatous inflammation in the dermis.

to further investigation in clinical trials. Granulomatous inflammation is a recognized complication of checkpoint inhibitor therapy, which although it may mimic disease progression, appears

to be associated with a favorable prognosis. This case demonstrates the importance of a multidisciplinary approach to correlate the patient's treatment history with the clinical and pathologic findings to guarantee the best standard of care.

REFERENCES

1. Stevenson ML, Wang CQ, Abikhair M, et al. Expression of programmed cell death ligand in cutaneous squamous cell carcinoma and treatment of locally advanced disease with pembrolizumab. *JAMA Dermatol.* 2017;153(4):299-303.
2. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther.* 2015;37(4):764-782.
3. Tetzlaff MT, Nelson KC, Diab A, et al. Granulomatous/sarcoid-like lesions associated with checkpoint inhibitors: a marker of therapy response in a subset of melanoma patients. *J Immunother Cancer.* 2018;6(1):14.
4. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med.* 2018;379:341-351.
5. Papadopoulos KP, Owonikoko TK, Johnson ML, et al. REGN2810: A fully human anti-PD-1 monoclonal antibody, for patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC)—initial safety and efficacy from expansion cohorts (ECs) of phase I study. *J Clin Oncol.* 2017;35(15_suppl):9503.
6. Jarkowski A 3rd, Hare R, Loud P, et al. Systemic therapy in advanced cutaneous squamous cell carcinoma (CSCC): The

- Roswell Park Experience and a review of the literature. *Am J Clin Oncol*. 2016;39(6):545-548.
7. Tran DC, Colevas AD, Chang AL. Follow-up on programmed cell death 1 inhibitor for cutaneous squamous cell carcinoma. *JAMA Dermatol*. 2017;153(1):92-94.
 8. Chang AL, Kim J, Luciano R, Sullivan-Chang L, Colevas AD. A case report of unresectable cutaneous squamous cell carcinoma responsive to pembrolizumab, a programmed cell death protein 1 inhibitor. *JAMA Dermatol*. 2016;152(1):106-108.
 9. Lomax AJ, McGuire HM, McNeil C, et al. Immunotherapy-induced sarcoidosis in patients with melanoma treated with PD-1 checkpoint inhibitors: case series and immunophenotypic analysis. *Int J Rheum Dis*. 2017;20(9):1277-1285.
 10. George S, Motzer RJ, Hammers HJ, et al. Safety and efficacy of nivolumab in patients with metastatic renal cell carcinoma treated beyond progression: a subgroup analysis of a randomized clinical trial. *JAMA Oncol*. 2016;2(9):1179-1186.