Complete pathologic response of metastatic cutaneous squamous cell carcinoma and allograft rejection after treatment with combination immune checkpoint blockade

David M. Miller, MD, PhD,[a,b] Beverly E. Faulkner-Jones, MD, PhD,[c] James R. Stone, MD, PhD,[d] and Reed E. Drews, MD[a]
Boston, Massachusetts

Key words: immune checkpoint blockade; ipilimumab; nivolumab; squamous cell carcinoma.

INTRODUCTION

Roughly 1.1 million cases of cutaneous squamous cell carcinoma (cSCC) occur annually. Although most cases can be cured with local therapy, up to 8,000 deaths from metastatic cSCC (mcSCC) occur each year, a number similar to that of melanoma.[1] With no US Food and Drug Administration–approved options available for mcSCC, common approaches include platinum-based chemotherapy and off-label cetuximab. These strategies lack durability, and overall survival for mcSCC is only 10.9 months.[2] Clinical responses in mcSCC have recently been reported with the use of PD-1 antibodies, pembrolizumab and nivolumab.[3-5] Here we report a complete pathologic response after 4 cycles of nivolumab and the anti–CTLA-4 antibody, ipilimumab, in a patient with mcSCC.

Abbreviations used:

cSCC:	cutaneous squamous cell carcinoma
DICB:	dual immune checkpoint blockade
ICB:	immune checkpoint blockade
ipi/nivo:	ipilimumab and nivolumab
mcSCC:	metastatic cSCC

CASE REPORT

At the age of 68, the patient underwent a renal transplant because of complications from diabetes mellitus, and he was placed on mycophenolate and tacrolimus for immunosuppression. Three years later, a poorly differentiated, spindle-cell cSCC developed on his left frontal scalp, which was treated with 1 stage of Mohs micrographic surgery. Although examined margins were clear, pathologic examination found a lesion infiltrative to the subcutaneous tissues with areas of marked pleomorphism and tumor close to a small nerve (Fig 1).[6] Because of the patient's immunocompromised state and these aggressive histologic features, the lesion was re-excised, and a sentinel lymph node biopsy was performed. The sentinel lymph node biopsy result was normal, but residual tumor was seen in the re-excision; thus, the patient underwent adjuvant radiotherapy. Roughly 1 month after radiotherapy, a localized recurrence developed. Subsequent imaging found locoregional disease and pulmonary metastases. After successful resection of locoregional and metastatic nodules, the dose of mycophenolate was lowered, and he was switched from tacrolimus to sirolimus.

A year later, additional metastases were identified in the lung and intestine. After resection of the small intestinal metastasis, he was started on carboplatin and paclitaxel. After 2 cycles, repeat imaging found

From the Division of Hematology/Oncology[a] and the Department of Pathology,[c] Beth Israel Deaconess Medical Center and the Departments of Dermatology[b] and Pathology,[d] Massachusetts General Hospital.

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: David M. Miller, MD, PhD, Department of Dermatology, Massachusetts General Hospital, 50 Staniford Street, Boston, MA 02114. E-mail: dmiller4@partners.org.

JAAD Case Reports 2017;3:412-5.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.06.005

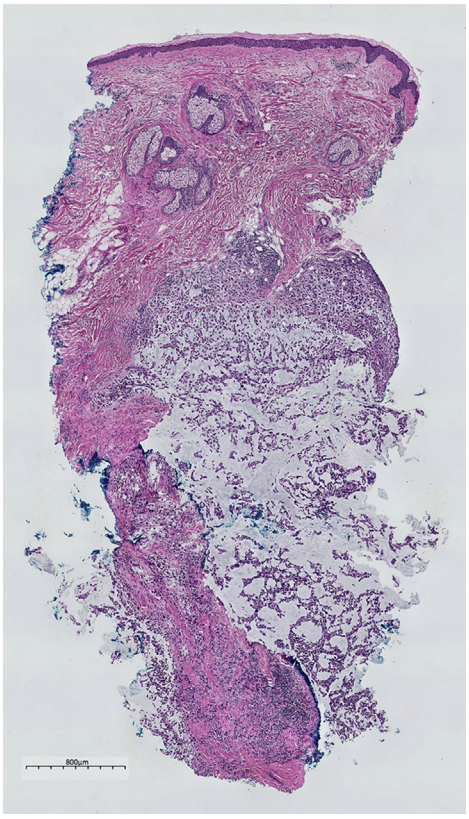

Fig 1. Punch biopsy of scalp recurrence shows myxoid spindle cell SCC. (Hematoxylin-eosin stain; low power). A high-resolution version of the image is available as eSlide: https://slide-atlas.org/link/mx4sax.

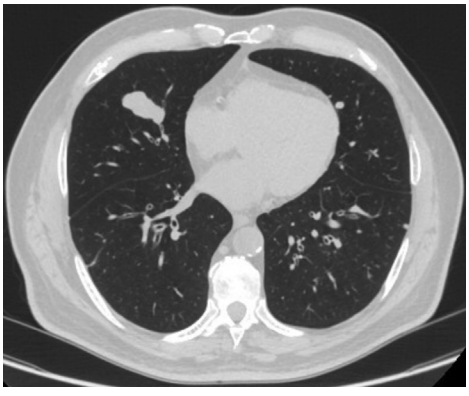

Fig 2. Computed tomography scan of the chest without contrast before starting ipi/nivo. Numerous pulmonary metastases can be seen.

many new and enlarging pulmonary nodules (Fig 2). He was then treated with weekly cetuximab. After 8 doses, repeat imaging found new lesions in the peritoneum and descending colon.

Next-generation sequencing of the resected jejunal lesion found single nucleotide variants in *HRAS, ERBB4, MYCN, APC, FBXW7, CDKN2A,*

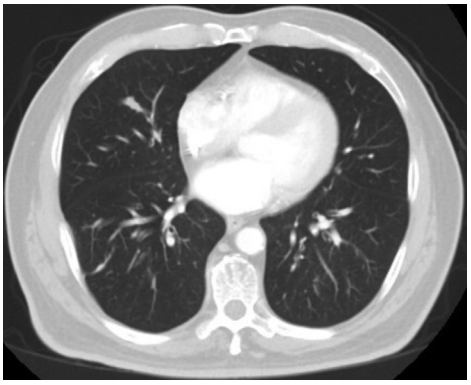

Fig 3. Computed tomography scan of the chest with contrast after 4 cycles of ipi/nivo. Significant decrease in the size and number of pulmonary metastases is noted compared with the pretreatment scan.

DDX3X, BRCA2, CCND2, and *TP53*. Given recent data suggesting a positive correlation between tumor mutational burden and response to immunotherapy,[7,8] we reviewed the risks/benefits of immune checkpoint blockade (ICB) with the patient and his transplant team. Because of his rapidly progressive disease, we decided to stop the immunosuppression and treat with dual ICB (DICB). After endorsement of our multidisciplinary tumor board, he was started on a combination of ipilimumab and nivolumab (ipi/nivo) after a 1-week immunosuppression washout period.

On cycle 1/day 8 of ipi/nivo, he presented complaining of fever, nausea and vomiting, abdominal pain, and oliguria. He was febrile and had hematuria and acute kidney injury. Renal ultrasound scan found abnormal flow. He was started on hemodialysis and methylprednisolone because of concern for acute rejection. He underwent nephrectomy on cycle 1/day 13, and pathologic analysis confirmed allograft rejection. He recovered without complication, and cycle 2 of ipi/nivo was administered with a 1-week delay.

Imaging after cycle 2 found a substantial decrease in the size and number of the pulmonary metastases and complete response of the abdominal lesions. He then completed 2 additional cycles of ipi/nivo to finish induction therapy without significant adverse effects. Imaging after induction found a stable response of the pulmonary nodules with no evidence of new disease (Fig 3), and the decision was made to observe closely with serial imaging.

For the next several months he continued in his usual state of health with few adverse effects aside from fatigue. Nearly 5 months after starting DICB, however, he experienced a sudden cardiac death of unclear etiology during dialysis. No antecedent

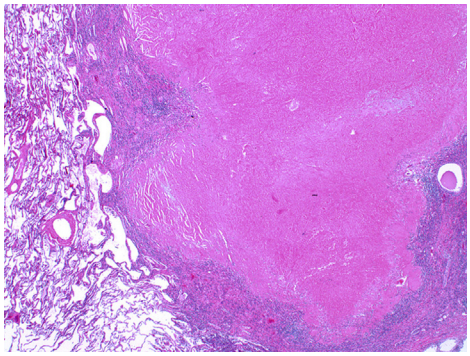

Fig 4. Right upper lobe lung nodule acquired at necropsy. Tissue did not contain any neoplastic cells or organisms and was consistent with treated malignancy. Another 1-cm necrotic lung nodule in the left upper lobe was identified at necropsy and was most consistent with treated mcSCC.

symptoms leading up to the dialysis run were endorsed. At autopsy, the cause of death was cardiac arrest in the setting of aspiration and myocardial fibrosis, presumed secondary to long-standing diabetes. There was no evidence of myocarditis, acute myocardial infarction, or active malignancy. There were 2 necrotic nodules in the lung (Fig 4) that did not contain any organisms or neoplastic cells and was thought to represent treated malignancy.

DISCUSSION

McSCC portends a poor prognosis with few available treatment options outside of palliative chemotherapy. We report a complete pathologic response after 4 cycles of DICB. To our knowledge, this is the first case report of a patient with mcSCC treated with DICB. The decision to start immunotherapy in transplant recipients is fraught with challenges. Our patient's experience highlights the potential benefit of immunotherapy in mcSCC and the possible complications. Goals-of-care conversations and multidisciplinary consultation are necessary before starting ICB, given the uncertainty of response and high likelihood of transplant rejection.

Although there are no definitive predictive biomarkers of immunotherapy activity, neoantigens produced by somatic mutations in tumor cells are thought to drive certain antitumor responses. Consequently, tumors with high mutational counts may have improved clinical outcomes with ICB.[7-9] Therefore, the remarkable antitumor activity seen in our patient may have been a consequence of the high mutational burden seen in the tumor, as evidenced by next-generation sequencing.

The expression of the PD-1 ligand, PD-L1, has also been correlated with response to therapy in several malignancies,[10,11] although its role in mcSCC is unknown. In addition, even tumors with limited PD-L1 expression can respond to anti-PD-1.[11] Therefore, because of the limited treatment options available, we did not assess the patient's tumor for PD-L1 expression, as it was unlikely to change our management. Additional studies of the tumor microenvironment are needed before PD-L1 expression can adequately inform clinical decision making in cutaneous oncology.

Little is known about the discrete roles of PD-1 and CTLA-4 in transplantation tolerance or the kinetics of allorejection in the setting of immunotherapy. Renal allograft rejection has been reported 2 months after initiation of PD-1 blockade for mcSCC,[3] whereas preserved grafts were noted in 2 kidney transplant recipients with melanoma treated with single-agent ipilimumab.[12] These observations suggest the PD-1 pathway may play a greater role than the CTLA-4 pathway in transplantation tolerance. Our patient's sudden rejection may have resulted from the use of DICB in the context of immunosuppression cessation. His rapid rejection raises several questions, including (1) the use of single-agent ICB rather than DICB, (2) the role of preemptive nephrectomy before initiation of DICB, and (3) the concomitant use of glucocorticoids and mTOR inhibitors during induction therapy to minimize transplant rejection. Because of our patient's aggressive disease, we decided to rapidly wean the immunosuppression and treat with DICB, as ipi/nivo has produced higher rates of response in melanoma compared with single-agent anti—PD-1.[13] Interestingly, recent data from a phase I study showed 6 partial responses, but no complete responses in 10 patients with mcSCC treated with single-agent anti—PD-1.[14] Although these data suggest DICB may be more efficacious, we do not know if single-agent ICB would have been equally effective in our patient, while perhaps imparting a lower risk of rejection. Even though our patient ended up safely undergoing urgent nephrectomy, there may be a role of scheduled, preemptive nephrectomy in selected patients. For those patients in whom allograft removal is not appropriate or feasible, weighing a more conservative weaning of immunosuppression with the possible reduction in efficacy of ICB may be advisable. A recent report described the successful preservation of allograft kidney function in a patient with metastatic adenocarcinoma who was treated with nivolumab plus an immunosuppressive regimen consisting of sirolimus and tapering doses of prednisone.[15] These experiences highlight the need to identify ICB and immunosuppressive regimens that can simultaneously maintain allograft preservation and maximize antitumor immunity.

This case also emphasizes the importance of pathologic analysis when deciding on the role of maintenance immunotherapy after induction, as no current guidelines exist. After the initial response seen after cycle 2, subsequent imaging found stable lung nodules that at necropsy showed only necrotic tissue (Fig 4). This finding suggests that a significant antitumor immune response occurred early and that the stable nodules seen on computed tomography scan reflected slow evacuation of killed tumor cells. Thus, acquiring tissue, when feasible, may be helpful in adjudicating the need for additional therapy.

The cause of the patient's aspiration and cardiac death remains unclear. There was no evidence of immune-related adverse effects such as fulminant autoimmune myocarditis, which has been previously reported after treatment with ipi/nivo.[16] The patient had been feeling well up until the time of the aspiration, making a treatment-related effect less likely. This case report underscores the exciting potential of immunotherapy for advanced cSCC but is also a reminder of the challenges of managing allograft transplant patients with metastatic cancer.

REFERENCES

1. Karia PS, Han J, Schmults CD. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. *J Am Acad Dermatol*. 2013;68(6):957-966.
2. 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.
3. Lipson EJ, Bagnasco SM, Moore J Jr, et al. Tumor regression and allograft rejection after administration of anti-PD-1. *N Engl J Med*. 2016;374(9):896-898.
4. 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.
5. Borradori L, Sutton B, Shayesteh P, Daniels GA. Rescue therapy with anti-programmed cell death protein 1 inhibitors of advanced cutaneous squamous cell carcinoma and basosquamous carcinoma: preliminary experience in five cases. *Br J Dermatol*. 2016;175(6):1382-1386.
6. Peters TW, A. Burns, K. Faulkner-Jones, B. Primary cutaneous myxoid spindle cell squamous cell carcinoma: a rare variant of squamous cell carcinoma with stromal mucin deposition. 51st Annual Meeting of the American Society of Dermatopathology; 2015; Singapore.
7. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128.
8. Van Allen EM, Miao D, Schilling B, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science*. 2015;350(6257):207-211.
9. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
10. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823-1833.
11. Daud AI, Wolchok JD, Robert C, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. *J Clin Oncol*. 2016;34(34):4102-4109.
12. Lipson EJ, Bodell MA, Kraus ES, Sharfman WH. Successful administration of ipilimumab to two kidney transplantation patients with metastatic melanoma. *J Clin Oncol*. 2014;32(19):e69-e71.
13. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
14. Papadopoulos K, Owonikoko T, Johnson M, 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. Paper presented at: ASCO; June 4. 2017, 2017; Chicago, Illinois.
15. Barnett R, Barta VS, Jhaveri KD. Preserved renal-allograft function and the PD-1 pathway inhibitor nivolumab. *N Engl J Med*. 2017;376(2):191-192.
16. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.