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

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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

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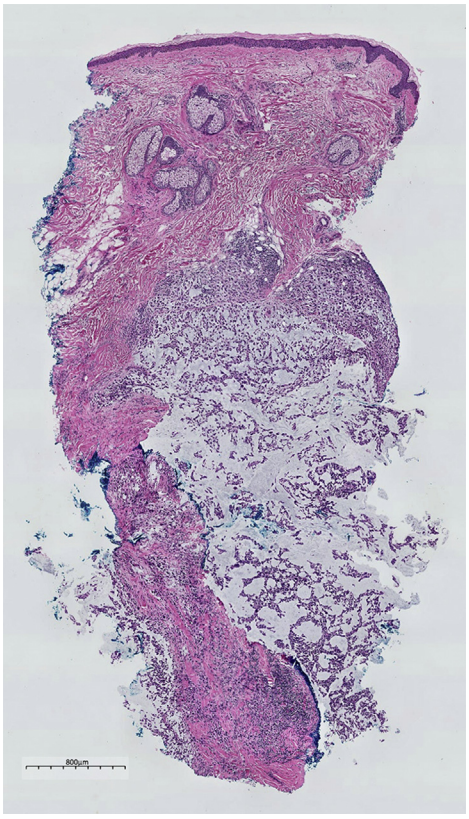

Fig 1. Punch biopsy of scalp recurrence shows myxoid spindle cell SCC. (Hematoxylin-eosin stain; low power). A high-resolution version of the image is available as eSlide: https://slide-atlas.org/link/mx4sax.

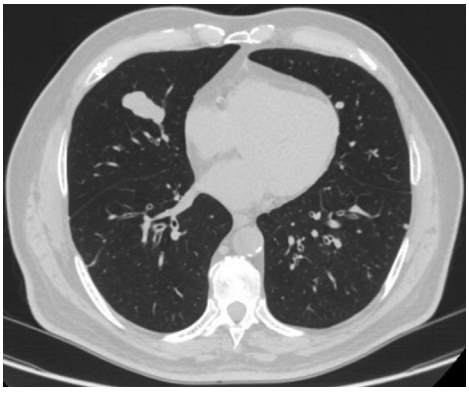

Fig 2. Computed tomography scan of the chest without contrast before starting ipi/nivo. Numerous pulmonary metastases can be seen.

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,*

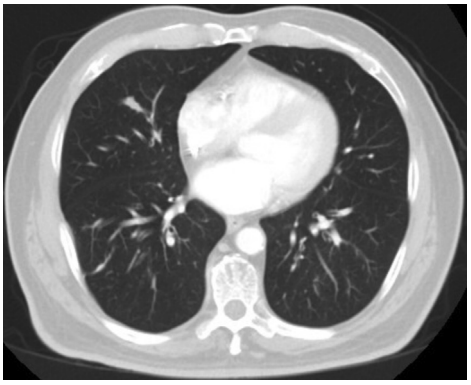

Fig 3. Computed tomography scan of the chest with contrast after 4 cycles of ipi/nivo. Significant decrease in the size and number of pulmonary metastases is noted compared with the pretreatment scan.

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