



Concurrent development of high-stage cutaneous squamous cell carcinoma during complete response of metastatic cutaneous squamous cell carcinoma to programmed cell death protein 1 blockade with cemiplimab

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Cutaneous squamous cell carcinoma (cSCC) accounts for over 700,000 cases and an estimated 8000 to 10,000 deaths per year in the United States.¹ Although most cSCCs have an excellent prognosis and can be cured with local surgical excision, a subset of cases progress to advanced disease and require additional treatment modalities.² Reported rates of metastasis of cSCC range from 2% to 5%, although the presence of risk factors such as perineural invasion or host immunosuppression increases this risk.³

Metastatic cSCC beyond regional lymph nodes has a poor prognosis and limited therapeutic options. Immune checkpoint blockade with antibodies targeting the programmed cell death protein 1 receptor have emerged as potentially powerful therapies for advanced cSCC. In 2018, the antiprogrammed cell death protein 1 monoclonal antibody cemiplimab was approved in the United States for patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiation. It is possible that immune checkpoint blockade may effectively treat multiple primary cSCCs or premalignant lesions in patients with a high burden of skin cancer, but this has not been adequately studied to date.⁴

We report the case of a patient who developed a high-stage primary cSCC during complete response

Abbreviation used:

cSCC: cutaneous squamous cell carcinoma

of a separate metastatic cSCC to immune checkpoint blockade with cemiplimab therapy.

CASE REPORT

A 76-year-old man with a history of chronic lymphocytic leukemia, prostate cancer, and more than 20 keratinocyte carcinomas (cSCCs and basal cell carcinomas) presented with left temple pain, diplopia, and left-sided ptosis and proptosis for 1 month. Computed tomography and magnetic resonance imaging revealed a heterogeneously enhancing mass in the left orbit, involving the sphenoid bone and the rectus and temporalis muscles, consistent with metastasis. Positron emission tomography with computed tomography showed no other distant metastases. Two years before presentation, he had a cSCC of the left cheek metastatic to the left parotid gland and periparotid lymph nodes. At that time, he was treated with wide excision, left parotidectomy, left neck dissection, and radiotherapy (60 Gy over 30 fractions). One year before presentation, he was diagnosed with cSCC of the

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Fig 1. Primary cutaneous squamous cell carcinoma on the left shoulder presenting as a 2-cm ulcer.

right side of the neck with infiltrative histology and perineural invasion; this was treated with wide excision and radiotherapy (60 Gy over 30 fractions). Five years before presentation, the patient was diagnosed with Rai stage I chronic lymphocytic leukemia. His chronic lymphocytic leukemia had been stable under active surveillance without treatment. Medications included acitretin 10 mg daily for prophylaxis of skin cancer.

The left orbit lesion was diagnosed as metastatic cSCC. The patient was offered treatment by surgical resection with orbital exenteration, radiotherapy with concurrent chemotherapy, or primary immunotherapy with cemiplimab. He was treated with cemiplimab 350 mg intravenously every 3 weeks. After 2 months of therapy, the patient noted complete resolution of his visual symptoms and pain. After 9 weeks, magnetic resonance imaging revealed decreased size of the left orbit lesion. After 2 to 5 months of therapy, the patient complained of mild productive cough and diffuse pruritus; the latter was controlled with triamcinolone 0.1% cream. Nine months after initiation of cemiplimab, positron emission tomography with computed tomography revealed complete resolution of the left orbit lesion as well as interval worsening of grade 1 pneumonitis. Cemiplimab was discontinued. No systemic therapy was given for pneumonitis.

The patient was evaluated by the dermatology department 5 weeks after the last dose of cemiplimab. Skin examination was notable for a 2-cm ulcer with a raised rim on the left shoulder (Fig 1). At that time, the patient reported that the lesion had been growing for approximately 5 months. He first noted

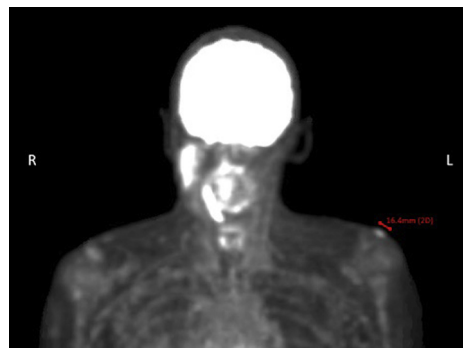


Fig 2. Primary cutaneous squamous cell carcinoma on the left shoulder identified on positron emission tomography-computed tomography performed between cycles 12 and 13 of cemiplimab treatment.



Fig 3. Surgical defect following complete extirpation of primary cutaneous squamous cell carcinoma on the left shoulder by Mohs micrographic surgery.

the lesion 4 months into treatment with cemiplimab. Review of a positron emission tomography-computed tomography scan obtained between cycles 12 and 13 of cemiplimab treatment confirmed the presence of a hypermetabolic, 1.64-cm lesion on the left shoulder (Fig 2). Biopsy of the lesion revealed cSCC. It was treated with Mohs micrographic surgery. The lesion was completely excised in 3 Mohs stages, resulting in a surgical defect measuring 5 × 6 cm (Fig 3). The defect was repaired with a linear closure. Two additional cSCCs on the right temple and the central part of the back (each ≤ 1 cm) were also treated with Mohs micrographic surgery.

Formalin-fixed sections of the left shoulder cSCC showed infiltrative histology and perineural invasion of a nerve measuring 0.2 mm in diameter (Fig 4, A and B), consistent with AJCC 8 T3 cSCC.⁵ Immunohistochemistry of the left shoulder tumor showed positive staining for programmed

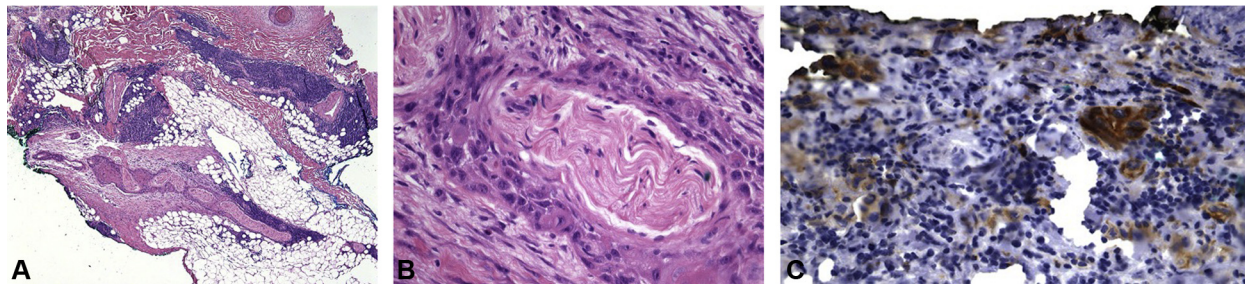


Fig 4. Primary cutaneous squamous cell carcinoma (cSCC) of the left shoulder with infiltrative histology and perineural invasion. **A**, Low-power histology image showing cSCC associated with a nerve in the subcutis. There is a dense lymphocytic infiltrate compatible with the patient's chronic lymphocytic leukemia. **B**, High-power histology image highlighting cSCC circumferentially enveloping a nerve fiber. **C**, Immunohistochemistry stain showing cSCC tumor cells staining positive (*brown*) for programmed death-ligand 1. (**A** and **B**, Hematoxylin-eosin stain; **C**, Immunohistochemistry stain; original magnifications: **A**, $\times 40$; **B**, $\times 400$; **C**, $\times 400$.)

death-ligand 1 (Fig 4, C). Similar staining was seen in the previous metastatic cSCC of the left parotid. Given the high-risk nature of the tumor, the patient was treated with adjuvant radiation therapy, completing 60 Gy in 30 fractions 3 months after surgery. At 7 months after surgery, the patient remains off cemiplimab with no evidence of recurrence of the left shoulder cSCC or the left orbit metastatic lesion.

DISCUSSION

It is well established that the diagnosis of one cSCC confers an increased risk of developing one or multiple subsequent cSCCs.² Moreover, patients with more than 10 previous cSCCs have a markedly increased risk of cSCC metastasis, suggesting that lifetime skin cancer burden is a predictor of cSCC progression and adverse outcome.⁶ The concept of field cancerization provides a framework for understanding the pathophysiology and guiding management of multiple cSCCs.⁷ With multifocal disease, patients harbor many genetically distinct premalignant lesions, each at risk of progressing to cSCC.

In a phase 2 trial of cemiplimab for metastatic cSCC, the overall response rate was 47%.⁸ Response to immunotherapy can likely be attributed both to host factors and to genetic differences within the cancer itself; individual cSCCs can be heterogeneous, with divergent responses to immunotherapy.^{7,9} In our case, there was a dichotomous response to immunotherapy within one patient, with one metastatic lesion exhibiting a complete clinical response, while a second primary cSCC progressed to a high local stage. Additional cSCCs continued to develop after discontinuation of cemiplimab. There are limited data on the response of nontarget cSCCs or new primary cSCCs to immunotherapy. Patients

with advanced cSCC are at high risk of subsequent skin cancers that may significantly impact function and overall survival. Additional research to predict response to immune checkpoint blockade and define the effect of this therapy on subsequent cancers will be invaluable.¹⁰

Conflicts of interest

None disclosed.

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