The metastatic dissemination of a squamous cell carcinoma arising from an epidermal cyst and subsequent failure to respond to programmed death 1 inhibition

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INTRODUCTION

Squamous cell carcinoma (SCC) arising from an epidermal cyst is a rare clinical entity, with reported rates of malignant transformation ranging from 0.011% to 0.045%.[1-5] Clinical presentation varies from a rapidly growing symptomatic lesion to an innocuous solitary cyst.[5-7] Diagnosis is often made on pathologic review of a surgical specimen. In these unusual cases, the mainstay of treatment is complete surgical excision of the cyst and its malignant component. Surgery is curative in most cases; however, a subset will display a more aggressive phenotype, including metastatic recurrence.[5,8-10] The rates of locoregional and metastatic recurrence are unknown, and data regarding the optimal treatment of recurrent disease is lacking. Here we present a case of a SCC arising within a rapidly enlarging epidermal inclusion cyst complicated by local recurrence and distant metastasis with failure to respond to immunotherapy.

CASE REPORT

A 71-year-old never-smoking woman with a history of Hashimoto thyroiditis presented with a rapidly enlarging painless mass over the anterolateral aspect of her left knee (Fig 1). Although a small cystic lesion had been present in this area for approximately 8 years, after a fall, the lesion dramatically increased in size over a 4-week period.

Abbreviations used:

CT:	computed tomography
MRI:	magnetic resonance imaging
PD-1:	programmed death 1
SCC:	squamous cell carcinoma
TMB:	tumor mutation burden

Initial magnetic resonance imaging (MRI) of the left knee found a well-circumscribed 5- × 5- × 4-cm mass at the anteromedial aspect of the knee, superficial to the fascia of the vastus medialis (Fig 2). The rim-enhancing mass was fluid filled with an associated 2-cm solid component.

She was evaluated by the orthopedic surgery department and underwent complete resection of the mass with pathology findings consistent with a 2.5-cm SCC arising within the walls of a ruptured epidermal inclusion cyst (Fig 3). Immunohistochemistry found that the carcinoma was negative for androgen receptor, CK7, CEA, and EMA. All margins were negative, and there was no evidence of lymphovascular invasion. Her postoperative course was uncomplicated, and she proceeded with active surveillance to monitor for recurrence.

Five months postoperatively, she had worsening left knee pain and inability to bear weight. MRI found a marrow-replacing process in the left tibial plateau, concerning for recurrent disease. She

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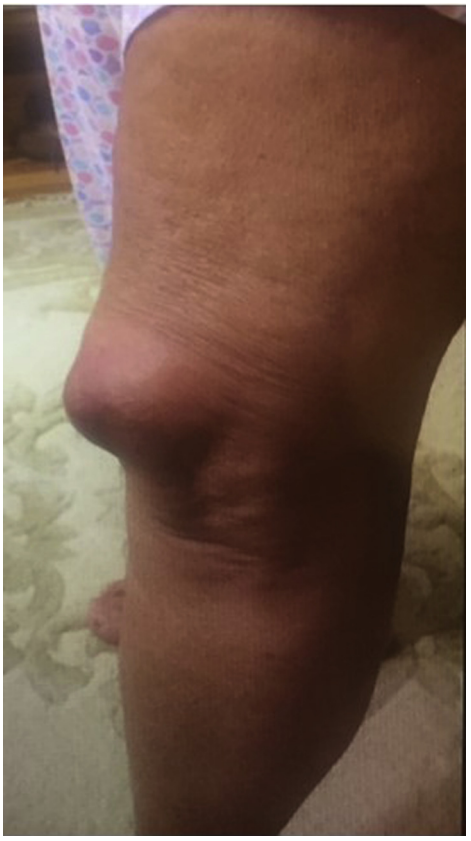

Fig 1. Preoperative photographs of the 5- × 5- × 4-cm mass at the anteromedial aspect of the left knee.

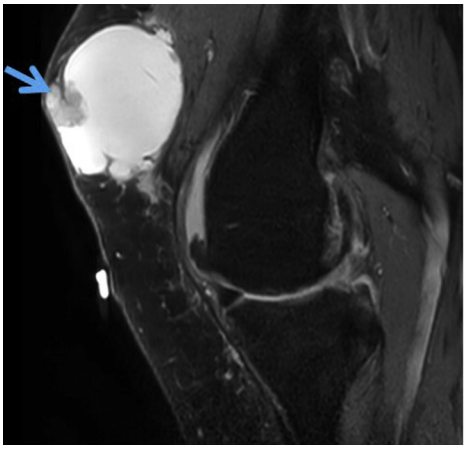

Fig 2. Sagittal MRI (T2-weighted with fat saturation) through the left knee; blue arrow indicates the cystic lesion with an irregular, enhancing mural nodule along its anterior wall (*arrow*).

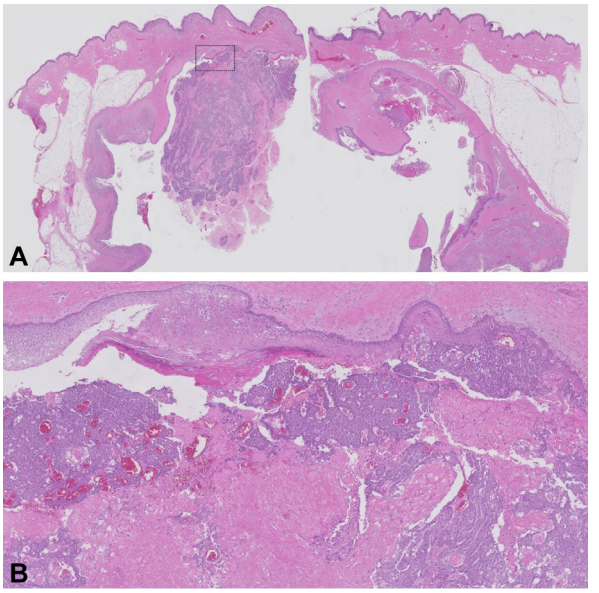

Fig 3. Pathologic findings of completely resected left knee mass. **A**, Low-power image of adjoining sections of a dermal and subcutaneous epidermal inclusion cyst. The cyst wall is composed of nonneoplastic keratinizing squamous epithelium with a granulomatous inflammatory response to cyst wall rupture laterally and a large central nodule of basaloid epithelial proliferation with areas of necrosis. **B**, Medium-power image is demarcated by the hash-box in **A**, showing the cyst wall transition from well-differentiated squamous-lined cyst with orderly keratinocyte maturation (left) to an area of high-grade malignant transformation (right). **A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×12.5; **B**, ×100.

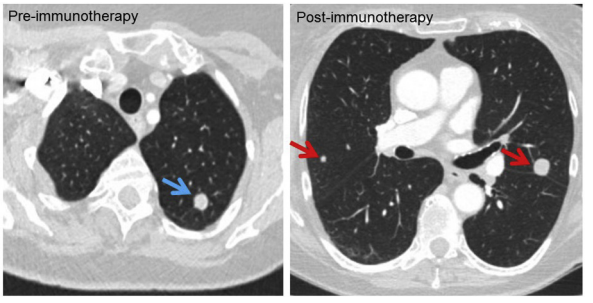

Fig 4. CT scan of the chest with contrast pretreatment. Blue arrow shows original rounded metastatic lesion. Postimmunotherapy CT imaging after 4 cycles of pembrolizumab. Red arrows show new pulmonary metastases.

underwent left proximal tibial lesion curettage with cementing and plating, with pathology findings showing dedifferentiated carcinoma—similar in appearance to the original SCC—heralding a local recurrence. Subsequent Positron emission tomography/computed tomography (PET-CT) found suspicious left inguinal adenopathy and scattered, enlarged pulmonary nodules, including one dominant 1.2-cm solid, rounded nodule in the apical left upper lobe (Fig 4). A percutaneous biopsy of a left upper lobe nodule was performed with pathology findings consistent with SCC, which was felt to represent metastatic disease from cutaneous SCC,

rather than a separate thoracic primary tumor, based on the radiographic and histologic appearance. Immunohistochemical stains were performed on the cell block with tumor cells positive for p63, P40 and CK7 and negative for MOC31, BerEP4, TTF-1, and CK20. PD-L1 immunohistochemistry was negative. Next-generation molecular testing was performed on the pulmonary nodule, and the results demonstrated a solitary *TP53* mutation; no single nucleotide variants, copy number variants, or fusion transcripts were identified. She was subsequently started on the programmed death 1 (PD-1) inhibitor pembrolizumab for treatment of unresectable cutaneous SCC. After 4 cycles of therapy, there was evidence of progressive disease with increasing mediastinal adenopathy and new bilateral pulmonary nodules. She then began treatment on second-line chemotherapy with carboplatin and paclitaxel. She tolerated 4 cycles of therapy well with scans showing improvement in disease burden with decrease in size and number of pulmonary nodules. She is currently in active observation.

DISCUSSION

This case demonstrates the rare clinical, radiologic, and pathologic findings of an aggressive SCC arising from a ruptured epidermal inclusion cyst, and it is the first report, to our knowledge, documenting the use of PD-1 inhibition in this unusual disease state.

The pathologic findings of these cases often depict carcinoma arising within the chronic inflammatory environment of an inclusion cyst. This inflammatory, immunosuppressive environment likely creates a favorable milieu for malignant growth.[1] Although complete surgical resection is often curative, this case highlights the potential for rapid local progression of these lesions as well as distant metastasis. Currently, there are no US Food and Drug Administration–approved regimens for unresectable cutaneous SCC, including those arising from an epidermoid cyst. However, recent data demonstrates the efficacy of immune checkpoint inhibition in the treatment of unresectable or metastatic cutaneous SCC.[11] In this phase I/II study, patients with locally advanced or metastatic SCC received intravenous cemiplimab, a human monoclonal antibody directed against PD-1. The duration of treatment was up to 48 weeks in the phase I study and up to 96 weeks in the phase II study or until unacceptable toxicity or disease progression. In the metastatic disease cohort of the phase II study, a response was observed in 28 of 59 patients (47%; 95% confidence interval, 34 to 61) with 57% of patients experiencing a durable response of $\geq$6 months. Based on these data, and lack of alternative approved treatment options, this patient was started on first-line off-label PD-1 inhibition with pembrolizumab. However, after 4 cycles of therapy, scans found disease progression.

One hypothesis for this lack of response is the likely low mutational burden of a SCC arising from a cyst. Tumor mutation burden (TMB) is an emerging biomarker of response to immune checkpoint inhibition with several studies illustrating that high mutation burden and increased neoantigen expression correlate with response to PD-1 inhibition.[12,13] Because classic cutaneous SCC is a disease driven by chronic ultraviolet exposure with a resultant ultraviolet-induced high mutational burden, it is an ideal target for checkpoint blockade.[11,14] However, because the pathogenesis of carcinoma arising from an enclosed cyst is unlikely to be related to ultraviolet exposure, the mutational landscape is presumably bland rendering a lower probability of durable treatment response to immunotherapy. Although TMB data on our patient is unavailable, molecular analysis found only a single *TP53* mutation. This finding contrasts to the multiple, high-frequency mutations reported in cases of aggressive cutaneous SCC.[14] After progression on immunotherapy, the patient was initiated on second-line cytotoxic chemotherapy with evidence of disease response. She is now in active observation with stable disease.

This unusual case adds to the body of literature on the rare clinical phenomenon of SCC arising from an epidermal cyst. A better understanding of the clinical presentation, histopathologic features, and treatment of this unusual malignant process is necessary to improve management and identify patients at high risk for locoregional and metastatic recurrence. Furthermore, investigation of molecular phenotype, TMB, and tumor microenvironment of this condition will be necessary to refine treatment options in the unresectable and metastatic setting.

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