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Response to PD-1 Immunotherapy in Metastatic Spiradenocarcinoma

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INTRODUCTION

Spiradenocarcinoma is a rare skin adnexal malignancy. Although spiradenocarcinomas can grow de novo, most arise from a malignant transformation of a solitary pre-existing benign spiradenoma. Pathologically, spiradenoma is usually characterized by the loss of pleomorphic nuclei with basaloid cells and an infiltrative border.[1] Most appear to originate as ventral cutaneous lesions of the head, neck, and upper extremities,[2-4] although primary sites in perineum, breast, toe, and vulva have also been documented in isolated case studies.[5-8] Sex (48% female *v* 36% male) and age (ranging from 8 to 92 years) are not suggestive of a predisposition, although Whites (about 57%) appear to have had a higher prevalence compared with other ethnicities.[9,10]

Genetically, loss of the *CYLD* gene, as seen in the Brooke-Spiegler syndrome, is associated with spiradenoma.[10] The product of the *CYLD* protein regulates the levels of *NF-κB*, and subjected patients with this syndrome develop a variety of skin appendage tumors. In sporadic spiradenoma, the genetic drivers have not yet been identified.

On the basis of available case reports, it appears that surgical resection of nonmetastatic spiradenoma is associated with prolonged survival. In a previous study by Andreoli and Itani,[11] 35 of the 36 patients who had surgery for their localized disease exhibited a 100% disease-free survival at a mean follow-up period of 33 months. Additionally, a study by Tanese et al[12] noted that, of the 15 patients, 10 patients presented with locoregional disease and successfully underwent lymphadenectomy—of whom six were classified as disease-free. Although curative surgery is often used, incomplete clearance of residual tumor necessitates adjuvant treatment, usually including a combination of cytotoxic chemotherapy and/or radiosurgery. Disappointingly, most did not respond to treatment and subsequently developed fatal systemic progression.[8] Furthermore, patients who developed metastatic disease died soon after despite aggressive chemotherapy combinations.[10]

Immune checkpoint inhibition for spiradenocarcinoma is an alternative systemic modality that has yet to be explored. Here, we report a case of a patient with metastatic spiradenocarcinoma exhibiting a promising treatment response to antiprogrammed death-1 (PD-1) monotherapy with the PD-1 antibody pembrolizumab.

Case Presentation

A 56-year-old White male presented to the University of California, San Francisco (UCSF), to discuss treatment options for his newly diagnosed metastatic spiradenocarcinoma. During the 1980s, he first noticed a callus-like solitary lesion on the ventral aspect of his right ring finger. In 2016, the tumor began to grow at an unmanageable rate after being physically struck by a baseball, and in 2017, the lesion was resected (Fig 1A).

The pathology revealed the presence of spiradenocarcinoma that extended to surgical margins. There were large lobular areas of atypical epithelial cells with obvious glandular differentiation and an increased mitotic index. The encompassing stroma contained fibrotic and edematous elements with multiple central areas of pleomorphic fusiform epithelial cells. Also visualized were small adnexal keratinocytes suggestive of a contiguous spiradenocylindroma.

A staging positron emission tomography-computed tomography (PET-CT) scan revealed multiple bilateral pulmonary nodules with the largest mass measuring approximately 1.2 cm in the longest dimension. Significant FDG avidity was also appreciated in the rectum and small bowel, although malignancy was formally excluded after a colonoscopy and biopsy of the rectum, sigmoid, and transverse colon revealed hyperplastic and adenoma fragments. A right upper lobe biopsy was attempted, but the pathology was nondiagnostic. The patient underwent right-sided thoracotomy with wedge resections of numerous lesions in the upper, middle, and lower lobes. Although negative margins were appreciated for all the resected tumors, the pathology report revealed lobular arrangements of atypical basaloid epithelial cells with a basement membrane and focal glandular differentiation, consistent with metastatic spiradenocarcinoma (Fig 1B). The diagnosis was confirmed by a secondary external pathological review at MD Anderson Cancer Center.

Further immune profiling evaluating programmed death-ligand 1 (PD-L1) expression was done to seek a viable therapeutic option. A tumor sample was submitted to NeoGenomics for further analysis. A PD-L1

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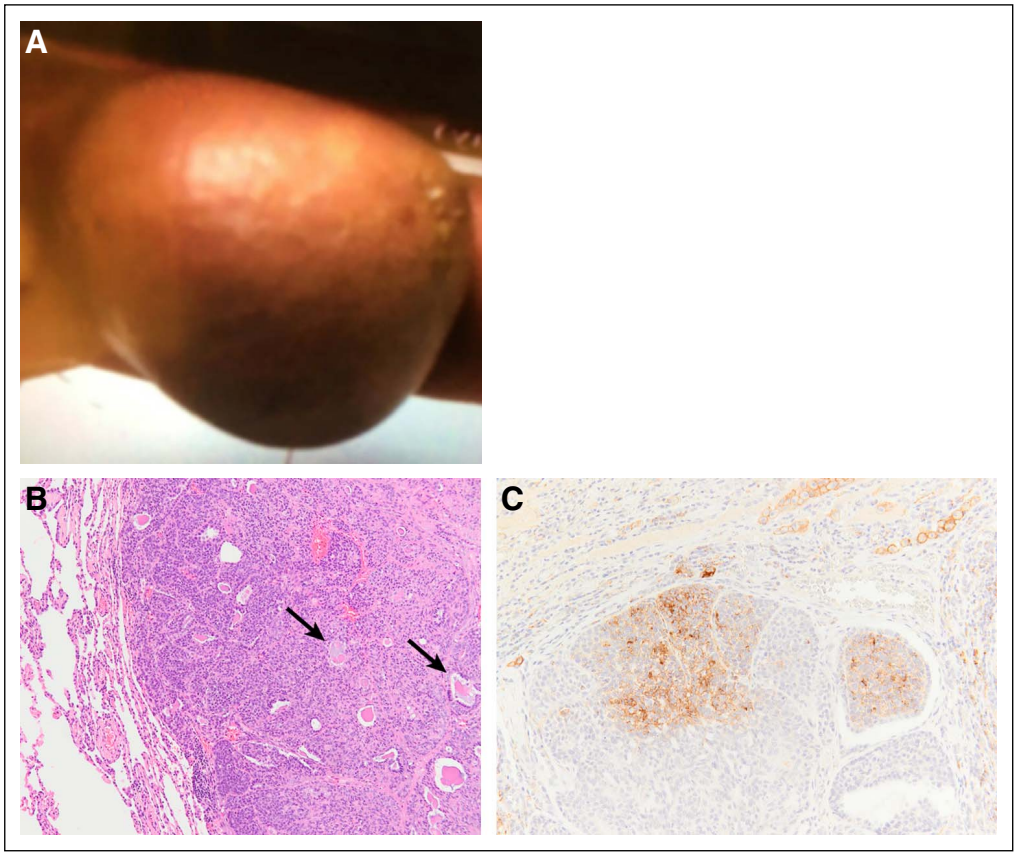

FIG 1. Photodocumentation revealing a rapidly proliferating mass (A) of the ventral right ring finger. Hematoxylin and eosin stain (B) of the lesion demonstrating the presence of metastatic spiradenocarcinoma embedded within the pulmonary parenchyma, with prominent basaloid features, and an increased mitotic index; immunohistochemistry staining (C) demonstrating weak focally prominent PD-L1 expression within tumor cells. Original magnification 200×. PD-L1, programmed death-ligand 1.

IHC 28-8 assay showed 5% PD-L1–positive cells. Additionally, a genomic sequencing test, the UCSF 500 Test, was conducted at UCSF. This test uses next-generation sequencing to analyze 479 cancer genes. The somatic genomic alterations found were a *CDKN2A/B* deep deletion, *CYLD* deletion, and *TERT.c-146C>T* mutation. There were no germline genomic alterations found. Interestingly, the microsatellite instability index of the tumor was negative (0%). Six hundred fifty-one microsatellites were tested. Concurrently, baseline restaging scans were done, which showed continued progression of multiple bilateral pulmonary nodules and a new 1.4-cm subcarinal lymph node. A 1-cm right axillary lymph node enlargement was also reported (Fig 2A). Given the disease progression, it was imperative to initiate systemic treatment, and the patient was treated with PD-1 blockade therapy in the compassionate use setting. As a result, he received his first dose of pembrolizumab at a dose of 200 mg in March 2018. The patient understood and provided the appropriate consent to pursue off-label immunotherapy. No ethical approval was necessary. We obtained formal written consent from the patient to use their individualized health information and the accompanying images for this case study.

Thus far, the patient has received a total of 22 doses of pembrolizumab, one dose of pembrolizumab 200 mg every 3 weeks. Associated symptoms have been relatively tolerable with primary complaints of fatigue likely related to autoimmune thyroiditis, for which he was started on Synthroid 88 mcg P.O. daily. Mild rash and diarrhea were also reported, although the diarrhea episodes did not appear to be treatment related. A routine contrast CT chest scan after four cycles of immunotherapy demonstrated interval improvement of multiple bilateral pulmonary nodules (Fig 2B). Of note, the indeterminate right axillary lymph node did exhibit a slight increase in size (now approximately 1.3 cm), whereas the subcarinal lymphadenopathy was grossly unchanged. The patient has been responding well to the PD-1 checkpoint inhibitor and continues to remain stable assessed by serial CT scans every 3 months. He continues to receive treatment without any dose-limiting toxicities.

DISCUSSION

Currently, there is no widely accepted therapeutic option for the management of metastatic spiradenocarcinoma. Without an established guideline and limited options, many have defaulted to the use of various cytotoxic chemotherapy combinations with limited success.

Immunotherapy with PD-1 checkpoint inhibition has recently emerged as an exciting therapeutic modality. In 2014, the FDA first approved the use of PD-1 inhibitors in patients with metastatic melanoma after demonstrating significant response rates with improved progression-free survival.[13] Since then, these agents have been experimented on other metastatic cancers including of the

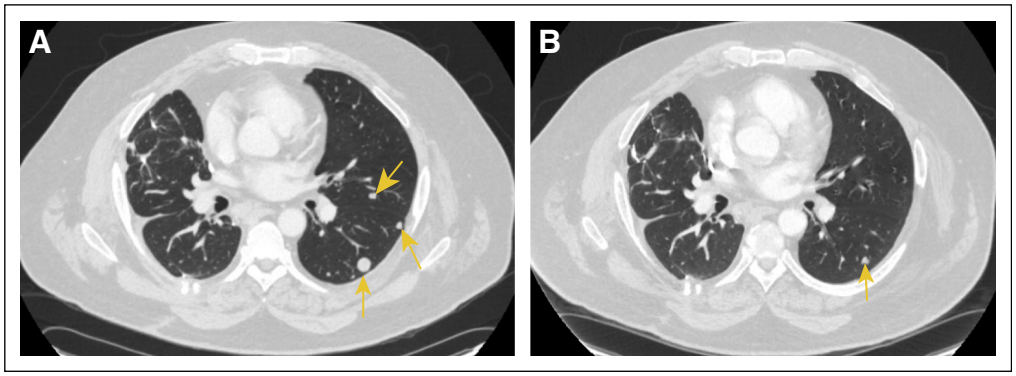

FIG 2. Axial section of a pretreatment CT chest scan (A). Arrows indicate at least three pulmonary nodules in the left upper and lower lobe segments. Postsurgical changes were observed in the right lung. Axial section of a CT chest scan after completing four cycles of pembrolizumab administered every 3 weeks (B). By comparison with pretreatment scan, two nodules have completely regressed. The largest pulmonary nodule in the left lower lobe has also demonstrated significant regression. The overall tumor burden was drastically improved. Once again, postsurgical changes were observed in the right lung. CT, computed tomography.

pancreas, breast, colon, and kidney with varied success. Interestingly, cancers that originate from cutaneous tissue such as Merkel cell carcinoma and squamous cell carcinoma of the skin were highly sensitive to PD-1 inhibitors, resulting in their FDA approval.[14,15] With the primary origin of this patient's disease, we surmised that compassionate use of this PD-1 checkpoint inhibitors could potentially provide some clinical benefit.

Additionally, a positive PD-L1 test as in this case signifies a tumor microenvironment is immune infiltrated.[16] PD-L1 testing is a common diagnostic biomarker that can predict response to PD-1 checkpoint inhibitors to a variety of cancers.[17]

For rare cutaneous malignancies, it is unlikely that a critical threshold of data will be reached to permit prospective clinical trials for use of PD-1 inhibition. Here, we reviewed a patient with metastatic spiradenocarcinoma, in the context of a rapid recurrence, who responded well to PD-1 checkpoint inhibition. This case highlights the potential benefit of PD-1 checkpoint inhibition in patients with rare cutaneous malignancies such as spiradenocarcinoma.

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Provision of study materials or patients: Adil Daud
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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