Metastatic Spiradenocarcinoma Managed With PD-1 Inhibition
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ABSTRACT

Spiradenomas are rare skin adnexal tumors, usually benign, appearing in early adulthood. The etiology of this tumor is still debated. The tumor suppressor gene CYLD, responsible for the Brooke-Spiegler syndrome, causes spiradenomas, trichoepitheliomas, and cylindromas. With time, spiradenomas can degenerate into aggressive spiradenocarcinomas. With only 117 malignant cases reported, treatment recommendations are based on case reports and expert opinion. There is no standard of care beyond surgical resection for localized disease and no guidelines for management of metastatic disease. With the advent of immunotherapy and PD-1 inhibition, we present the first reported case of a metastatic spiradenocarcinoma managed with pembrolizumab.

Background

Spiradenomas are rare skin adnexal tumors, usually benign, appearing in early adulthood. The etiology of this tumor is still debated. The tumor suppressor gene CYLD, responsible for the Brooke-Spiegler syndrome, causes spiradenomas, trichoepitheliomas, and cylindromas. The cellular matrix interacting proteins claudin-4, cadherin, and β-catenin might be involved in neoplasm formation. With time, spiradenomas can degenerate into aggressive spiradenocarcinomas (SCs). With only 117 malignant cases reported, treatment recommendations are based on case reports and expert opinion. There is no standard of care beyond surgical resection for localized disease and no guidelines for management of metastatic disease. With the advent of immunotherapy and PD-1 inhibition, we present the first reported case of a metastatic SC managed with pembrolizumab.

Case Description

A 64-year-old White woman reported a recent, rapid growth of a nodule on her right upper arm. The growth had been present for 15 years but had only started changing recently. Clinical examination revealed a 10-cm painful subcutaneous nodule. Histopathologic examination disclosed a large tumor in the dermis and subcutaneous tissue with a dense basophilic adnexal proliferation with nuclear pleomorphism, atypia, and mitoses (Figure 1). In other parts of the specimen (not available for photomicrograph), features of classic spiradenoma were seen (blue dermal nodule with larger round islands of blue cells with little cytoplasm, dark and pale nuclei, islands peppered with black lymphocytes, and deeply eosinophilic hyaline droplets in the islands), which aided in diagnosing SC.

PET/CT revealed right-sided lung metastases and lymph node involvement in the right axilla. Based on the large size of the tumor and axillary lymphadenopathy, the outside institution opted to excise the SC with negative margins and perform a radical lymph node dissection to reduce the tumor burden. On final pathology, the tumor was poorly differentiated, measuring 10 cm in maximum diameter, with 8 of 28 nodes positive for metastases and extranodal extension (2.5 cm in greatest dimension). The pathologic stage according to the 8th edition of the AJCC Cancer
Staging Manual was T4N3bM1b. On immunohistochemical analysis, the tumor was negative for estrogen receptor (ER) and progesterone receptor expression but had a high expression of PD-L1. The combination of carboplatin and paclitaxel was administered every 3 weeks for 4 cycles, but the disease progressed in the right lung. She was then referred to Ohio State University, and 200 mg of pembrolizumab was administered intravenously once every 3 weeks based on high PD-L1 expression on immunohistochemistry. After 6 months of pembrolizumab, the lung metastases decreased in size. Four months later, she developed a single frontal brain metastasis treated with Gamma Knife radiation (3 fractions). Paclitaxel was added with continuation of pembrolizumab for 3 cycles. The lung metastases regrew and caused a right-sided pneumothorax. The next treatment consisted of 3 cycles of oral capecitabine, but the disease progressed in the peritoneum. The patient then presented with a bowel obstruction requiring a gastrostomy. Palliative radiation was given on the bulkiest mass. She refused hospice care and requested further therapy. She was offered an alternative regimen of gemcitabine and docetaxel that was well tolerated, but she died of the disease within 1 month.

Discussion
SCs are rare skin adnexal tumors, with 117 such cases described over 41 years in the SEER database. SCs may arise de novo or more commonly from an eccrine spiradenoma in approximately 5% of all spiradenoma cases. SCs are typically found on the trunk and extremities in patients at an average age of 60 years. The latency period when arising from a spiradenoma is 0.5 to 70 years. Our patient had noted a growth in childhood, with malignant transformation at age 64 years, consistent with this timeline. With only 117 cases reported, randomized controlled trials are not available for metastatic disease.

Benign spiradenomas should be fully excised and histologically graded to rule out malignancy, because high-grade SCs have a 50% recurrence and a 38% death rate versus 14% for recurrence and death rates if they are low grade. Tumor-free margin surgical excision is the definitive treatment for patients without lymph node metastasis, with 100% of the 35 patients showing no evidence of disease at a mean follow-up of 33 months. In patients with no distant metastasis but positive lymph nodes, surgical excision with lymphadenectomy yields a good disease-free survival at a mean follow-up of 33 months (6 of 7 patients with no recurrence). In descending order, SC metastasizes to regional lymph nodes, lungs, brain, and liver/gastrointestinal tract. Our patient presented with metastases to the regional lymph nodes and lung, then developed a single brain metastasis and finally gastrointestinal metastases.

Data for optimal management of metastatic SC are lacking. In 1986, a review of adnexal gland tumors (which includes SCs) found them to be radioresistant. Reports of patients receiving 5-FU, epirubicin, and ifosfamide did not show benefit, because the patients had new distant metastases or died within 4 months of treatment. Similarly, our patient did not respond to carboplatin, oral capecitabine, gemcitabine, or docetaxel.

Tamoxifen, a selective ER modulator, has been used successfully to treat ER-positive metastatic SC in a 70-year-old man, who had no progression at 41-month follow-up. We therefore, based on the aforementioned report, recommend ER/progesterone receptor testing, which we also performed in our patient.

Conclusions
With the advent of immune checkpoint inhibitor therapy, we present the first case of metastatic SC managed with a PD-1 inhibitor (pembrolizumab in our case). Because the
tumor displayed high PD-L1 expression, we recommend exploring immunohistochemical expression of PD-L1 in newly diagnosed SCs. However, PD-1 inhibition was not curative in our case. Our patient initially improved with pembrolizumab, but her disease progressed after 10 months of pembrolizumab therapy. The mixed response we observed might offer a glimpse of hope for patients with metastatic SC.

References