Spindle Cell Squamous Cell Carcinoma of the Scalp Treated With Pembrolizumab Cisplatin and 5-Fluorouracil

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Abstract
Cutaneous spindle cell squamous cell carcinoma (SpSCC) of the head and neck is a very rare tumor. It is an aggressive variant of squamous cell carcinoma. The usual treatment of the localized disease is surgery with or without radiotherapy. No standard treatment for metastatic disease although some case reports had reported the effectiveness of programmed cell death protein 1 (PD-1) blockade as a possible treatment.

We are reporting a 57-year-old Arabic female who noticed a lesion of the right side of the scalp in July 2019, which was a nodule with a slowly growing trend and no other associated symptoms. On examination, there were two small nodules at the margins of the previous surgical scar. The superior nodule measure 1 cm x 1.5 cm and the other was 1.5 cm x 2 cm at the inferior surgical margin (Figure 1).

Case Presentation
We are reporting a 57-year-old Arabic female who noticed a lesion of the right side of the scalp in July 2019, which was a nodule with a slowly growing trend and no other associated symptoms. On examination, there were two small nodules at the margins of the previous surgical scar. The superior nodule measure 1 cm x 1.5 cm and the other was 1.5 cm x 2 cm at the inferior surgical margin (Figure 1).
She underwent full reevaluation with magnetic resonance imaging (MRI) of the head and neck and computer tomography (CT) of the chest, abdomen, and pelvis. The MRI showed that there was evidence of residual/recurrent soft tissue tumor at the superior and inferior aspects of the surgical bed. The first lesion at the high left parietal area measured 1.2 cm x 2 cm x 2.1 cm, it demonstrated features of internal hemorrhage. The other lesion noted at the left occipital region measured about 1.2 cm x 2.3 cm x 2.5 cm. Both lesions demonstrate post-contrast enhancement. There was no evidence of underlying bony involvement and no intracranial extension was seen. A few small lymph nodes were noted at the posterior neck on the left side (Figures 2, 3). The CT chest showed multiple lung metastases (Figure 4).
FIGURE 2: MRI showing the lower lesion (white arrow).
FIGURE 3: MRI showing the upper lesion (white arrow).

FIGURE 4: CT scan of chest showing multiple lung metastases (black arrows).

The histopathology review has shown malignant spindle cell neoplasm, poorly differentiated/sarcomatoid squamous cell carcinoma with perineural invasion but without lymphovascular invasion (Figure 5). Immunohistochemistry staining showed positive staining of vimentin, desmin, and cluster of differentiation (CD) 10. The cytokeratin staining, cytokeratin (CK)-Pan, CK5/6, P63, and CK7 were focally positive. S100, human melanoma black (HMB)-45, CD117, paired-box gene 8 (PAX-8), estrogen receptors (ER), progesterone receptors (PR), CK20, gross cystic disease fluid protein 15 (GCFP-15), CD34, CD1a, myoblast determination protein 1 (MyoD1), and myogenin were all negative. All of the above were supporting the diagnosis.
FIGURE 5: The image is showing spindle cell carcinoma, small islands and, cords of squamous cell carcinoma and dense proliferation of neoplastic spindle cells.

She was discussed in the tumor board and the decision was to give palliative radiotherapy to the local lesion and to start palliative systemic chemotherapy. She was fit with Eastern Cooperative Oncology Group (ECOG) performance status of one. After a full discussion of the possible benefits and side effects, it was decided to start her on pembrolizumab, cisplatin, and 5-fluorouracil protocol since the main histopathological component was squamous cell carcinoma. Programmed death-ligand 1 (PD-L1) testing was sent abroad since the local laboratories were still not accredited at that time. She received three cycles with good tolerance but the reevaluation CT scan showed progression of the lung metastases. At that time the PD-L1 testing came back as negative. We substituted pembrolizumab with cetuximab. Further three cycles were given but after the third cycle, she started to have shortness of breath. Chest x-ray and CT scan showed further progression with right pleural effusion. She was admitted for pleural drainage and pleurodesis. After stabilization, she was given single-agent doxorubicin. After three cycles of doxorubicin, she had symptomatic improvement with the partial radiological response, but she refused further treatment because she felt more fatigued during chemotherapy. She was kept under follow-up with palliative, symptomatic care at her regional hospital. She progressed further and died after three more months.

Discussion

Most of the SpSCC patients who present with localized head and neck lesions are usually treated with surgery [8]. In the early stages, surgery alone has an excellent outcome. In later stages, the usual treatment is the combination of surgery and radiotherapy although there are some reports indicating radioresistance [9]. Although there are some studies that challenged the concept of radioresistance of spindle cell carcinoma and reported similar responses and outcomes to the classical squamous cell carcinoma [10,11]. Another study had reported the possible detrimental effects of radiotherapy when added to surgery in terms of survival [12].

Two retrospective series showed poor survival outcomes, especially those with oral cavity, sinonasal and oropharyngeal sites, compared to SCCs at similar sites [13,14]. The median overall survival (OS) of 8.9 months was found in a study [14]. For the early-stage group (stages I and II), the three years survival rate of 100% was reported, while those with stages III and IV had one-year survival rate of 9% and three years survival rate was 0%, respectively [14].

Using the surveillance, epidemiology, and end results (SEER) database, one study had compared 4382 cases of classical sinonasal SCCs with 328 cases of other pathological subclassifications. Five-year disease-specific survival (DSS) was as follows: 84.7% for verrucous cell carcinoma, 61.87% for papillary cell carcinoma, 56.2% for basaloid cell carcinoma, 45% for classical squamous, 32% for SpSCC, and 15% for adenosquamous carcinoma. A total of 65.6% of patients with SpSCC were treated with a combination of surgery and...
radiotherapy compared to 40.4% with conventional SCC[10].

Two reported cases with SpSCC of the tongue with locally advanced disease (T4N2M0 and T4aN1M0) were managed with a combined modality treatment, i.e., radical surgery followed by adjuvant chemoradiotherapy. The first case had developed lung metastasis five months after surgery while the second case was disease-free two months after surgery [15].

Although the epidermal growth factor receptor (EGFR) is expressed by >90% of conventional SCC and possibly in 70% of SpSCC, EGFR-specific therapies may not be ideal for SpSCC patients according to some reports [16]. Our case had received anti-EGFR cetuximab with no response.

One case report had suggested that anti-PD-1 therapy with pembrolizumab may be an effective and well-tolerated treatment for patients with SpSCC with metastasis to the CNS [17]. But our case did not show any obvious response when we used pembrolizumab with cisplatin and 5-fluorouracil. Another case report had suggested that 5-fluorouracil is an effective treatment in spindle cell carcinoma of the nasal cavity but our case did not show the same [18].

Recently, pembrolizumab plus platinum and 5-fluorouracil were approved as first-line treatment for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) and pembrolizumab monotherapy for PD-L1-positive recurrent or metastatic HNSCC in a phase 3 trial [7]. We used the same protocol for SpSCC but unfortunately, our patient did not respond. The possible reasons are either because of the negative PD-L1 testing or because of the inherent resistance of this variant to immunotherapy. Our case was showing partial response to doxorubicin single agent as a third line which is well-known chemotherapy for sarcoma, possibly indicating the response of the malignant spindle cells part of the tumor.

**Conclusions**

Our patient with metastatic spindle cell carcinoma of the scalp has shown resistance to pembrolizumab, cisplatin, 5-fluorouracil and cetuximab, cisplatin, 5-fluorouracil regimens which are standard treatments for the classical squamous cell carcinoma of the head and neck. There was a partial response to doxorubicin which is usually effective in sarcoma cases.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained or waived by all participants in this study. King Fahad Medical City IRB issued approval #21-340. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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