CLINICAL VIGNETTE

A Case of Locally Advanced Conjunctival Squamous Cell Carcinoma

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Case Presentation

An 81-year-old man with a history of multiple non-melanoma skin cancers initially presented with a bump in the medial corner of the left eye. An ophthalmologist performed a biopsy of the left conjunctival lesion, which showed fragments of poorly differentiated squamous cell carcinoma (SCC). The ophthalmologist noted, diffuse ocular surface and eyelid involvement by the SCC. He was treated with topical 5-fluorouracil and bleomycin injections with disease control reported.

He established care with UCLA Head & Neck Surgery three years after his initial diagnosis because of increasing pain in his left eye and vision changes. ENT's exam, noted an inferomedial mass in the left orbit, left eye proptosis, inflamed conjunctiva, impaired extraocular movement, and palpable left-sided cervical lymphadenopathy. The MRI of the face and neck showed a left medial orbital mass invading into the anterior left ethmoid sinus and the nasolacrimal duct as well as level I and II left-sided cervical lymphadenopathy measuring up to 22 x 13 mm. Staging FDG-PET/CT showed a hypermetabolic left nasal bridge/medial orbit mass measuring 3.1 cm (SUV max 9.7) with invasion into the left anterior ethmoid sinus and lateral displacement of the left orbit, a soft tissue mass along the left alveolar ridge with extension into the left maxillary sinus, and multiple abnormal left cervical lymph nodes. There was no evidence of distant metastatic disease.

The patient underwent exenteration of the left orbit without additional surgical resection. The reason for the limited surgery was planned definitive radiation therapy. Removal of the eye was necessary due to concerns that radiation would cause not only blindness but also severe pain in the eye. The orbital content was negative for malignancy on final pathology, but a biopsy of the left nasal floor during intraoperative endoscopy showed moderately differentiated squamous cell carcinoma. The patient changed his mind about proceeding to radiation therapy and chose instead to start systemic therapy with immune checkpoint inhibitor (ICI) cemiplimab.

Pre-treatment CT scans showed continued growth of the soft tissue mass in the left medial orbit invading the frontal, ethmoid, maxillary sinuses as well as cervical lymphadenopathy. After 3 cycles of cemiplimab, a restaging scan showed marked improvement in the left orbital mass and resolution of cervical lymphadenopathy. This was apparent on physical exam with shrinkage of the left medial orbital mass and cervical lymph nodes no longer being palpable. Repeat CT scans after 7 cycles of cemiplimab showed only soft tissue thickening along the border of left orbital cavity. On exam, there was complete flattening of the left medial orbit where there used to be a bulky soft tissue mass.

Discussion

Conjunctival SCC (cSCC) belongs to a group of diseases referred to as ocular surface squamous neoplasia (OSSN). OSSNs are the most common non-pigmented neoplasms of the ocular surface, although they are relatively uncommon diseases in general. For example, cSCCs have an incidence of 0.02 to 3.5 per 100,000. In the western hemisphere, they are more likely to be found in white men in their 60s who live near the equator. cSCCs almost always arise in the sun damaged conjunctiva, with the best-known risk factor being UV radiation exposure. Other proposed risk factors include HIV, HPV, cigarette smoking, chronic inflammation, and chronic infection. Patients may present with a sensation of irritation in the eye, redness of the eye, plaque-like lesions, or nodular lesions. These tumors are most often localized at initial presentation and are typically treated with surgical excision. Recurrences are common and can occur in as many as half of the cases after surgery. They are usually local recurrences that may be treated with repeat excision.

Eye-sparing surgery is preferred for localized disease whenever possible. With more locally advanced disease, such as with invasion of the periorbital structures, extensive conjunctival involvement, or invasion into the inner structures of the eye, orbital exenteration may be necessary. Because recurrences are common despite aggressive surgical resection, adjuvant topical therapy or adjuvant radiation therapy may be considered. Up to a quarter of patients may develop metastasis in the regional lymph nodes (most commonly in the parotid and submandibular nodes), and as many as 7% of patients may eventually develop distant metastases.

Due to the rarity of cSCCs, especially those with regional or distant metastatic disease, there are no prospective randomized controlled trial data to guide the optimal management of locoregional disease. While this type of malignancy is pathologically distinct from both head and neck mucosal SCCs and

cutaneous SCCs, extrapolation from data or guidelines for the two more common disease sites may be unavoidable. As an example, locally advanced head and neck SCCs are often treated with concurrent systemic therapy/radiation therapy (RT) using chemotherapy agents such as cisplatin, and this combined modality approach may be considered in locally advanced cSCC. Radiotherapy alone has also been used successfully for tumor control in cSCCs.

PD-L1 expression has been reported in cSCCs, which presents an appealing target for ICIs, since these agents have demonstrated efficacy in multiple other tumor types.[1] Additionally, a study that evaluated molecular genomic alterations of cutaneous and ocular SCCs using next-generation sequencing discovered that the two tumor histologies shared many so-called UV-signature mutations.[2] The similarity of the somatic genomic landscapes suggests potential overlap in responsiveness to anti-PD1 therapy. This is a salient point, as landmark trials have established the efficacy of cemiplimab, an anti-PD1 inhibitor, in both first-line and neoadjuvant settings for cutaneous SCCs.[3] One could then reasonably extrapolate this data to cSCCs. In fact, one case series described off-label use of ICIs in five patients with advanced cSCC with orbital extension.[4] In this report, 3 patients received cemiplimab with complete response (CR); 1 patient received pembrolizumab with CR; and 1 patient received pembrolizumab along with 5-fluorouracil and carboplatin with progressive disease as the best response. The four tumors that had CR also had a high tumor mutational burden, in contrast to the one tumor that did not respond. The patients who had CR had no evidence of relapse after 2-11 months of follow-up. There are no larger studies with cSCC patients treated in this manner.

For the patient in this case, the initial focus was deciding on the appropriate local therapy. Given the significant local invasion of cSCC into nearby sinuses and cavities, head and neck surgery felt that the likelihood of cure even with the most aggressive treatments was quite low. The patient was presented with the options of aggressive surgical resection/debulking followed by adjuvant radiation +/- concurrent systemic therapy vs primary radiation therapy +/- concurrent systemic therapy.

The patient was not interested in a major surgery, so he initially planned to undergo radiation therapy after undergoing exenteration of the left orbit. After his limited surgery, he expressed hesitation about radiation because of its intensive schedule and potential side effects. After consultation with radiation oncology and medical oncology, his options were to undergo concurrent systemic therapy/radiation therapy (RT), RT followed by consolidation systemic therapy, or upfront systemic therapy followed by possible consolidative RT. He was not a cisplatin candidate and was a poor candidate for cytotoxic chemotherapy in general, so ICIs were one of the few remaining feasible systemic therapy agents. He decided to start with cemiplimab because he found it appealing that there was a possibility of deferring radiation therapy if he had a complete clinical response.

Of note, the tumor was not tested for PD-L1 or TMB prior to starting cemiplimab since there was very little data to confirm their predictive value specifically in cSCC. The cutaneous SCC neoadjuvant cemiplimab trial, response was also seen in PD-L1 negative patients, and there appeared to be a poor correlation between TMB and pathologic response. Moreover, the patient had very limited systemic therapy options, and the results of such biomarker testing were not likely to change management.

The patient responded very well to cemiplimab. Palpable masses in the left orbit and the neck resolved, and there was minimal measurable disease remaining on the restaging CT scans after 7 cycles of cemiplimab. He continues to tolerate cemiplimab with no significant immune-related adverse effects. He was able to avoid surgery or radiation as the initial treatment, which would have been associated with significant morbidity and/or disfigurement. This case illustrates that for a patient with cSCC who is not a candidate for or refuses local therapy, single agent ICIs such as cemiplimab may be considered and can induce a dramatic response.

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