Utilization of Nivolumab in Adenoid Cystic Carcinoma After Progression on Platinum-Based Chemotherapy

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ABSTRACT

Introduction: Adenoid cystic carcinoma (ACC) is a rare malignant neoplasm within the secretory glands of the head and neck. Clinical findings include a lump on the palate, tongue, or bottom of the mouth. Because symptoms can be mild, patients go for long periods of time without investigation. ACC is diagnosed using histology. Treatment is by surgical resection because there is no effective chemotherapy. Radiation can be effective adjuvant therapy, and proton therapy and stereotactic irradiation can be used for those who are ineligible for surgery. Immunotherapy has clinical activity for those with metastatic head and neck cancers who progress on proton therapy. This case reviews the use of immunotherapy in a patient with ACC.

Case Presentation: A man in his 20s presented with a 6-month history of nasal congestion, epistaxis, and sinus tenderness. Noncontrast computed tomography of the sinuses revealed a mass of the lateral wall of the nasal cavity, lateral wall of the maxillary sinus, and pterygoid plates. Positron emission tomography confirmed metastatic disease in the right iliac crest and right cervical lymph node; biopsy of the nasopharynx confirmed ACC. The patient received proton therapy and intensity-modulated radiotherapy and completed 2 Phase 1 trials but continued to have progressive disease. The patient started nivolumab and died 12 weeks later.

Conclusion: The patient recently received proton therapy, intensity-modulated radiotherapy, and completed 2 Phase 1 trials but continued to have progressive disease.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a malignant neoplasm within the secretory glands of the head and neck. It represents 10% of all neoplasms of the salivary glands. This can occur in the breast, bone, lung, and liver but is most often a metastasis from the head and neck. It very rarely infiltrates the lymphatic system. The cause of ACC is unknown, but it develops from noninherited genetic changes over one’s life. Most patients diagnosed are in their 40s-60s, with a female: male ratio of 3:2.

Clinical findings associated with ACC of the head and neck include a lump on the palate, under the tongue, or in the bottom of the mouth. There can be numbness of the upper jaw, palate, face, or tongue. One can have difficulty swallowing, hoarseness, and paralysis of the facial nerve. Because many of these symptoms can be mild, many patients will go for long periods of time without investigation.

The diagnosis of ACC is made using histology. There are 3 different forms: cribriform, tubular, and solid; solid is the most aggressive. Imaging is used to measure the tumor as well as to identify recurrence. This can be done using computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET).

Optimal treatment of ACC is surgical resection, and radiation may be effective as adjuvant therapy. Unfortunately, the mortality rate in those with ACC is high due to local recurrences and late distant metastases. Treatment of advanced disease is considered palliative because there is no effective chemotherapy; however, proton beam therapy and stereotactic irradiation can be used for those who are ineligible for surgery.

Immunotherapy has been used in the treatment of metastatic head and neck cancers. Immunotherapy inhibits the PD-L1 pathway, which prevents activation of cytotoxic T cells in lymph nodes and deactivates cytotoxic T cells in dendritic cells. PD-L1 also helps cancer cells adjust to the body’s environment and continue to proliferate. Inhibition of the PD-L1 pathway allows tumor-invading cells to be recognized and destroyed by cytotoxic T cells. PD-1/PD-L1 inhibitor therapy includes nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab. Immunotherapy has been shown to have significant clinical activity for those who have progressed on proton therapy. Although the relationship between immunotherapy and ACC has not been well investigated, it has been shown that an estimated 11% of ACCs express PD-L1 on their cell membranes. Also, 70% of tumor-infiltrating monocytes are PD-L1 positive, giving immunotherapy a target for ACC cancer cells. This case study reviews the use of immunotherapy, commonly used in squamous head and neck cancers, implemented in a patient with ACC.
CASE PRESENTATION

A white man in his 20s with a past medical history of attention deficit hyperactive disorder and multiple treatments for serous otitis media and sinusitis presented with a 6-month history of nasal congestion, jaw pain, epistaxis, and rhinorrhea. The patient was a former smoker of 0.5 pack-years. His mother had hypertension and paternal grandmother had breast cancer. Vitals revealed high blood pressure of 141/86 and pulse of 99. On physical examination, the patient had normal ears, normal oral cavity, and no lymphadenopathy or thyroid nodules but had sinus tenderness. On flexible nasal endoscopy, the nasal cavity contained pooled mucous in the choana on the left side and a polyp on the posterior aspect of the left inferior turbinate.

Magnetic resonance imaging of the temporomandibular joint showed degenerative changes bilaterally. Noncontrast CT of the sinuses revealed an abnormal soft tissue lesion within the left maxillary antra with bony erosion extending to the lateral wall, pterygoid plates with extension into the lateral left sphenoid sinus, and erosion of that left lateral sphenoid body (Figure 1). Nuclear medicine positron emission tomography CT skull to mid-thigh confirmed the mass in the left nasopharynx as well as a metastatic right cervical lymph node and hypermetabolic activity in the posterior aspect of the right iliac bone (Figure 2).

Biopsies of the last nasal mass and the right iliac bone were consistent with cribriform ACC and metastatic ACC (Figure 3). Due to the location of the tumor, he was deemed to not be a good surgical candidate. The patient began concurrent chemoradiation with weekly cisplatin using intensity-modulated proton therapy to the primary lesion and later to the iliac bone. Four months later, a new metastasis appeared to the right ischium. Stereotactic irradiation was initiated.

The patient underwent genetic profiling, and it was found that he had a MDM2 mutation;
he began a phase I trial against this mutation. The patient continued to progress, however, and metastases were found in the lung. He began a second trial using milademetan but continued to progress. Immunotherapy is commonly used after proton therapy in head and neck squamous cell cancers, so the patient began the immune check-point inhibitor nivolumab. However, the patient continued to have progressive disease and died 12 weeks after nivolumab initiation.

**DISCUSSION AND CONCLUSIONS**

Immunotherapy is a new method of treatment that enhances one’s own immune system to attack malignant cells.
There are 2 major types of commercially available immunotherapy: PD-1/PD-L1 inhibitors and CTLA-4 immune checkpoint inhibitors. These work to promote activation of antineoplastic T-cells, to reduce tumor size, and to increase progression-free survival as well as overall survival. In 2016, the United States Food and Drug Administration (FDA) approved of the PD-1 immune checkpoint inhibitors nivolumab and pembrolizumab in the treatment of patients with squamous cell carcinoma (SCC) of the head and neck and in those refractory to platinum-based regimens. The European Commission followed with approval of nivolumab and pembrolizumab in those with an expression PD-L1 > 50% and progressed on platinum therapy. In 2019, the FDA granted these treatments as first line in those with metastatic or unresectable, recurrent head and neck SCC as single agents or as a combination with platinum and fouroruracil.

Commonly, head and neck cancers are SCCs; however, rare cancers of the head and neck, such as ACCs, may occur. These rare tumors have not shown to be particularly susceptible to systemic therapies targeted at head and neck SCC. Treatment paradigms have been confined to small study designs owing to the rarity of this tumor. In this case, our patient with a rare cancer of the head and neck progressed after using platinum-based therapy. Because immunotherapy is approved to be used in SCC of head and neck, data from these studies were extrapolated, and it was decided by the treatment team to initiate nivolumab in this patient with ACC of the head and neck given the limited options and progression on 2 early-phase trials. In addition, a small, single-institution study examined the use of nivolumab in 4 patients with ACC who had progressed on platinum-based chemotherapy. The results showed a promising progression-free survival in 2 of the patients (8 and 12 months) and an overall survival of 24 months in 1 patient. Another study implemented a phase 2 trial of using single-agent pembrolizumab (another PD-1/PD-L1 inhibitor) as salvage therapy in ACC. Five of their 14 patients were alive and progression free at 27 weeks. Of the 14 patients who were medically stable for imaging, response to the treatment was measured using RECIST criteria. There was an objective response rate of 14%. Unfortunately, our patient’s course was not as impressive as these aforementioned studies. He lived 3 months following immunotherapy treatments.

Immunotherapy has been used in the treatment of metastatic and recurrent head and neck cancers and has shown clinically significant activity in those who have progressed on platinum-based chemotherapy. To date, no study has evaluated the efficacy of immunotherapy in ACC specifically. Our patient demonstrated a survival of 3 months following the administration of nivolumab after progressing on 2 early-phase trials. There are many phase II clinical trials studying drug efficacy in those with ACC including but not limited to axitinib and avelumab, lenvatinib and pembrolizumab, MYB DNA vaccine and tislelizumab, pembrolizumab and 4L Nasal Mass R ili ac mass

Figure 3. (A and B) Both biopsies consistent with cribriform ACC and metastatic ACC.
docetaxel, and recently, nivolumab with ipilimumab and radiation therapy. However, limited data exist regarding the optimal treatment regimens for patients with ACC. Given the general poor response to cytotoxic chemotherapy used in HNSCC and the favorable toxicity profile of immunotherapy, this therapy may play a role in ACC treatment. Further research is needed to elucidate the role that immunotherapy plays in the treatment of this rare cancer.

Informed Consent
Because the patient expired, informed consent was not able to be obtained. An effort has been made to anonymize patient information.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Authors’ Contributions
Diana V Maslov, MD, MS, and Katharine Thomas, MD, MS, wrote this manuscript. Marc Matrana, MD, MS, FACP, edited this manuscript.

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