Prolonged response to checkpoint inhibitor therapy in two metastatic mucoepidermoid salivary gland carcinoma cases: a research report

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Abstract

Salivary gland tumors (SGTs) are heterogeneous tumors that range from benign masses to aggressive high-grade carcinomas with distant metastatic potential and limited response to chemotherapy. Mucoepidermoid carcinoma (MEC) accounts for 10% of SGTs and has a poor prognosis. In this research report, we describe two cases of metastatic high-grade MECs with prolonged response to immune checkpoint inhibitor pembrolizumab. Case 1 presented with a left neck mass, and biopsy of the parotid mass revealed MEC. The patient underwent surgical resection and adjuvant chemoradiation therapy for stage IVB disease. Post-treatment, she was found to have brain and spinal metastases and was placed on pembrolizumab. Case 2 presented with a left neck mass, and biopsy of the right parotid gland revealed MEC. Further staging demonstrated metastatic disease in the lungs, and he was placed on pembrolizumab. Both cases of MEC demonstrated prolonged extracranial responses to pembrolizumab. Although both cases reported little to no PD-L1 expression, these results demonstrate immunotherapy efficacy in advanced/metastatic MEC.

INTRODUCTION

Salivary gland carcinoma (SGC), a rare cancer, accounts for roughly 6% of all head and neck cancers in the United States (Barnes et al. 2005). Although rare, the incidence of salivary gland carcinomas has been steadily rising in the United States in the last four decades according to a Surveillance, Epidemiology, and End Results (SEER) analysis study (Del Signore and Megwalu 2017). Within all salivary gland tumors, there exists a large heterogeneity of histologies and topographies with both benign and malignant tumors (Barnes et al. 2005). SGCs are characterized by several local recurrences and prolonged metastasis to distant sites. The most common malignant SGCs in order are mucoepidermoid carcinomas,
adenoid cystic carcinomas, acinic cell carcinomas, and carcinoma ex pleomorphic adenomas (e.g., salivary duct or myoepithelial carcinomas) followed by rarer histologies (McKenna 1984). Currently, locally advanced and metastatic diseases have few standard chemotherapeutic-based treatment options.

Mucoepidermoid carcinomas represent roughly 10% of all salivary gland tumors, benign or malignant, and when recurrent or metastatic have a poor prognosis. The grade of the tumor is also considered a prognostic factor in mucoepidermoid carcinomas, with high-grade tumors associated with worse survival and nodal metastases (Chen et al. 2014). The standard care of treatment is generally surgery with the option of adjuvant radiation therapy or definitive radiation therapy for inoperable tumors (Geiger et al. 2021). When patients develop recurrent or metastatic disease there are few chemotherapy options based on case series (Popalzai et al. 2011; Chintakuntlawar et al. 2016; Diwakar et al. 2019) and more recently targeted therapies for patients who possess specific molecular findings. The most frequent genomic alterations that drive mucoepidermoid carcinomas include mastermind-like 2 (MAML2) fusions, TP53 mutations, and POU6F2 mutations, although no targeted therapy currently exists (Kang et al. 2017). Here we present two cases of high-grade mucoepidermoid carcinomas with prolonged responses to pembrolizumab.

RESULTS

Clinical Presentation (Case 1)

An 81-yr-old women presented to her primary care physician with a left neck mass and a computed topography (CT) scan demonstrated a well-delineated hypodense lesion in the left parotid superficial lobe measuring 2.3 × 1.4 × 1.7 cm. An ultrasound (US)-guided core of the left parotid mass revealed a salivary gland neoplasm suggestive of mucoepidermoid carcinoma. Further staging imaging, including a magnetic resonance imaging (MRI) of the brain and a positron emission tomography/CT (PET/CT), was suggestive of possible temporal bone involvement, and locoregional adenopathy, but no clear evidence of distant metastatic disease. The case was reviewed in a multidisciplinary tumor board, and it was decided to proceed with a left total parotidectomy with left auriculectomy, mandibulectomy, lateral temporal bone resection, and left modified radical neck dissection. According to the American Joint Committee on Cancer (AJCC) cancer staging system, seventh edition, the patient was found to have stage IVB pT4bN0M0 6.4 × 4.4 cm large high-grade mucoepidermoid carcinoma with extension into the temporal bone and external ear canal and involved surgical deep margins. High-risk features included positive margins and perineural invasion. There was no evidence of lymphovascular invasion or extracapsular spread. Adjuvant concurrent chemoradiation therapy with weekly carboplatin was recommended because of the positive margins and large size of the tumor. Unfortunately, restaging imaging 1 mo after treatment completion demonstrated brain and spinal metastases, which were treated with stereotactic radiosurgery (SRS) and palliative radiation therapy, respectively. She subsequently had a local tumor recurrence at the left earlobe, measuring 1 cm. Next-generation sequencing (NGS) testing on her previous surgical specimen reported a CRTC1-MAML2 fusion, detected in roughly 60% of mucoepidermoid carcinomas, two TP53 missense mutations in codons 267 (R267W) and 282 (R282W), and no programmed death-ligand 1 (PD-L1) 22C3 expression (tumor proportion score of 0%). Because of the lack of targetable mutations and borderline performance status, she opted for pembrolizumab off-label (200 milligrams [mg] every 3 wk). The patient had a complete clinical and radiographic response after four cycles in the left earlobe mass, which was the only target lesion (Fig. 1). She continued to demonstrate a response to treatment but unfortunately exhibited interval progression in the
brain (progression-free survival [PFS] = 6.2 mo), for which she underwent palliative SRS. Because of the lack of progression outside of the brain, she continued on pembrolizumab for 25 cycles (18 mo) until she developed severe intracranial disease progression. The patient was reluctant to try whole-brain radiation therapy because of poor performance status and was referred to hospice (overall survival [OS] = 28.7 mo).

Clinical Presentation (Case 2)

A 57-yr-old man with no significant past medical history presented to an otolaryngologist with clear rhinorrhea and a palpable left-sided neck mass. A CT scan of the paranasal sinuses was ordered and demonstrated frontal, ethmoid, and sphenoid sinusitis with nasal polyposis, some ovoid configuration changes in the ethmoid cells and in the right maxillary sinus suggesting retention cysts, nasal septal deviation, and increasing osteoarthritis of the left temporomandibular joint. A needle core biopsy of the right parotid gland revealed a moderate to poorly differentiated carcinoma morphologically and immunohistochemically consistent with high-grade mucoepidermoid carcinoma with perineural invasion. Subsequently, a CT of the neck and chest was performed and demonstrated two nodules in the left and right lower lobes, and enlarged mediastinal and supraclavicular lymph nodes. Further staging imaging (PET/CT and MRI of the neck) demonstrated an ill-defined hypermetabolic lesion measuring 1.8 × 1.2 × 2.5 cm within the right parotid gland, and hypermetabolic right cervical, left mediastinal, and left supraclavicular lymphadenopathy compatible with metastasis. A fine-needle aspiration (FNA) of a left mediastinal lymph node (station 11) confirmed presence of metastatic poorly differentiated carcinoma consistent with the primary lesion. Therefore, stage was assessed as cT1N2M1 stage IVC per AJCC, seventh edition. He was started on pembrolizumab off-label (200 mg every 3 wk) as he refused chemotherapy, and restaging imaging after four cycles showed decreased fluorodeoxyglucose (FDG) avidity.

Figure 1. (Left) Positron emission tomography (PET) scan image and picture of left earlobe mass (∼1 cm in size) prior to pembrolizumab treatment. (Right) PET scan image and picture of resolved left earlobe mass after treatment with pembrolizumab, illustrating treatment response.
of all sites of disease; however, the response was assessed as stable disease. He continued on pembrolizumab and restaging imaging after seven cycles demonstrated complete response in all sites of disease with complete resolution of the right parotid gland (Fig. 2), cervical, and supravacularular disease. After 11 cycles of pembrolizumab (12 mo), the patient developed grade 2 pneumonitis secondary to the immunotherapy and treatment was held. After completing a course of steroids, the patient was rechallenged with pembrolizumab. Unfortunately, the patient experienced subsequent recurrence of immune-related pneumonitis, and pembrolizumab was permanently discontinued after 13 mo (12 cycles). NGS testing on his previous right parotid tumor biopsy reported an HRAS (Q61R) mutation with an allele frequency of 43% and TP53 frameshift mutation (L321Nfs*24*). The tumor showed a PD-L1 22C3 tumor proportion score of 20%. Because of disease progression 6 mo after discontinuing pembrolizumab (PFS = 20.6 mo), the patient was switched to carboplatin and paclitaxel, on which he maintained a stable response for 6 cycles (6 mo) followed by two cycles of maintenance nab-paclitaxel (2 mo). Unfortunately, the patient progressed in the liver, prevascular lymph nodes, and the brain after two cycles of maintenance nab-paclitaxel. He received gemcitabine with progression of disease and ultimately tipifarnib, a farnesyltransferase inhibitor which has shown antitumor efficacy in HRAS-mutated cancers, on an investigational new drug protocol without any significant benefit and was referred to hospice (OS = 42.6 mo).

**Genomic Analyses**

A Clinical Laboratory Improvement Amendments (CLIA)-certified institutional next-generation sequencing panel of 93 genes identified a CRTC1-MAML2 fusion, TP53 (c.844C > T; p.R282W) missense alteration, and another TP53 (c.799C > T; p.R267W) missense alteration in Case 1 (Table 1; Supplemental Tables 1 and 3). In Case 2, another CLIA-certified institutional next-generation sequencing panel of more than 87 genes identified a HRAS (p.Q61R, c.182A > G) missense alteration and a TP53 (p.L321Nfs*24*, c.963del) frameshift alteration (Table 1; Supplemental Tables 2 and 3).

**DISCUSSION**

Within the past decade, PD-L1 has grown steadily into a prominent therapeutic target across many solid tumor cancer types including lung cancer and head and neck squamous cell carcinoma (Burtness et al. 2018; Mok et al. 2019). The Food and Drug Administration (FDA)
approved pembrolizumab as a treatment option for any metastatic or unresectable solid tumors with a high tumor mutation burden (TMB) regardless of cancer type (Administration 2017). However, little information is known of PD-L1 expression and immune checkpoint inhibitor efficacy in malignant SGCs. This FDA approval of a treatment solely based on a biomarker instead of by cancer type is the first of its kind and lends to the idea of the value of studying PD-L1 expression within various cancers.

A 2016 study examined PD-L1 expression in 219 salivary gland surgical specimen and found that roughly 22.8% of the samples exhibited >1% PD-L1 expression by immunohistochemistry (Mukaigawa et al. 2016). However, those tissues that were marked as positive for PD-L1 expression were consistently correlated with poor prognosis and survival rates ($P < 0.001$). These results indicated a valuable potential target for metastatic/advanced SGCs. This FDA approval of a treatment solely based on a biomarker instead of by cancer type is the first of its kind and lends to the idea of the value of studying PD-L1 expression within various cancers.

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### Table 1. Variant table

| Gene          | Chromosome | HGV5 DNA reference          | HGV5 protein reference | Variant type | Predicted effect | dbSNP/dbVAR ID |
|---------------|------------|-----------------------------|------------------------|--------------|------------------|----------------|
| **Case 1**    |            |                             |                        |              |                  |                |
| TP53          | 17p13.1    | NC_000017.10:g.757794T > A  | NM_000546.6:c.844C > T | Missense     | NM_000546.6 > T  | rs28934574     |
|               |            | NC_000017.11:g.757794G > A  | NM_000546.6:c.844C > T | Missense     | NM_000546.6 > T  | rs55832599     |
| TP53          | 17p13.1    | LRG_321t3:c.799C > T        | NM_000546.6:c.799C > T | Missense     | NM_000546.6 > T  |                |
| CRT1-MAML2    | 19p13.11:  | LRG_321t3:g.18730C > T      | NM_000546.6:c.18730C > T | Fusion       |                  |                |
| **Case 2**    |            |                             |                        |              |                  |                |
| HRAS          | 11p15.5    | NC_000011.10:g.533874T > C  | NM_005343.4:c.182A > G | Missense     | NM_005343.4 > G  | rs121913233    |
|               |            | NC_000011.9:g.533874T > C  | NM_005343.4:c.182A > G | Missense     | NM_005343.4 > G  |                |
|               |            | NG_007666.1:g.6677A > G     | NM_005343.4:c.182A > G | Missense     | NM_005343.4 > G  |                |
|               |            | NG_001130442.2:c.182A > G  | NM_005343.4:c.182A > G | Missense     | NM_005343.4 > G  |                |
| TP53          | 17p13.1    | LRG_321t3:c.799C > T        | NM_000546.6:c.799C > T | Missense     | NM_000546.6 > T  |                |

Pharaon et al. 2022 Cold Spring Harb Mol Case Stud 8: a006189 5 of 9
significant response to immunotherapeutic combination of nivolumab plus ipilimumab in patients with recurrent/metastatic SGCs (Burman et al. 2021). Of the 32 patients enrolled, five were confirmed as responders (complete response and partial response, 16%) with at least a 66% tumor regression in target lesions. Correlative analyses of biopsy and blood samples are currently ongoing. The use of dual checkpoint blockade demonstrated promising best observed response; however, further analysis is necessary. Further, combination regimens with immune checkpoint inhibitors and with other agents are also being investigated in SGCs (NCT04209660, NCT03942653, and NCT03360890) (Table 2).

The two cases described in this report underwent NGS testing as well as PD-L1 22C3 immunohistochemistry. TPS was used to describe their PD-L1 expression because both patients underwent NGS and PD-L1 testing before combined positive scores (CPS) became the standard for PD-L1 expression in head and neck cancers. Although the two patients exhibited PD-L1 TPS score of <50%, they both had a prolonged clinical response to pembrolizumab. This is consistent with other studies and clinical trials demonstrating immune checkpoint inhibitor efficacy in patients with little to no PD-L1 expression (Hellmann et al. 2019). Recently, a retrospective analysis was published examining PD-L1 expression in

| Trial | Phase | Trial identifier | Histology | Drug(s) | Status | Primary objective(s) |
|-------|-------|-----------------|-----------|---------|--------|---------------------|
| Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/KEYNOTE-158) | II | NCT02628067 | Advanced solid tumors | Pembrolizumab | Active, recruiting | ORR assessed by RECIST 1.1 criteria of MK-3475 as monotherapy |
| Lenvatinib and pembrolizumab in people with advanced adenoid cystic carcinoma and other salivary gland cancers | II | NCT04209660 | Advanced adenoid cystic carcinoma, other salivary gland cancers | Pembrolizumab and lenvatinib | Active, recruiting | ORR assessed by RECIST 1.1 criteria of MK-3475 and lenvatinib as combination therapy |
| Androgen deprivation therapy (ADT) and pembrolizumab for advanced-stage androgen receptor (AR)-positive salivary gland carcinoma | II | NCT03942653 | Advanced AR-positive salivary gland cancer | Pembrolizumab and androgen deprivation therapy | Active, recruiting | ORR assessed by RECIST 1.1 criteria of MK-3475 and goserelin as combination therapy |
| Pembrolizumab with chemotherapy for poorly chemo-responsive thyroid and salivary gland tumors (iPRIME) | II | NCT03360890 | Salivary gland cancer, thyroid cancer | Pembrolizumab and docetaxel | Active, recruiting | ORR assessed by RECIST 1.1 criteria of MK-3475 and docetaxel as combination therapy |
| Study of nivolumab plus ipilimumab in patients with salivary gland cancer | II | NCT03172624 | Salivary gland cancer | Nivolumab and ipilimumab | Active, recruiting | ORR assessed by RECIST 1.1 criteria of nivolumab and ipilimumab as combination therapy |
| Nivolumab and ipilimumab and stereotactic body radiation therapy in treating patients with salivary gland cancers | I/II | NCT03749460 | Salivary gland cancer | Nivolumab, ipilimumab, and SBRT | Active, recruiting | Characterize the safety and tolerability of nivolumab, ipilimumab, and SBRT |

(ORR) Objective response rate, (SBRT) stereotactic body radiation therapy.
167 patients diagnosed with SGCs treated at a single institution from 1994 to 2017 (Vital et al. 2019). Only 28 patients (16.8%) were found to be PD-L1 positive in the tumor tissue. Interestingly, SGC tumors that were PD-L1-positive demonstrated a significantly higher tumor grade than PD-L1-negative tumors ($P = 0.035$). With the predominance of immunotherapy in the treatment of solid tumor malignancies, more analyses are needed to investigate the prognostic role of PD-L1 expression in SGCs.

The reported patients were both found to have specific significant mutations that have been previously reported on in SGCs. MAML2 fusions occur in roughly 60% of all mucoepidermoid carcinomas and are classically characterized as low-grade, indolent tumors. MAML2 fusions can have various fusion partners, most notably including CRCT1, CRCT3, and MECT1. In a whole-exome sequencing analysis of 18 mucoepidermoid carcinomas, Kang et al. (2017) reported a prevalence of MECT1–MAML2 translocations and TP53 mutations in majority of the tumors, suggesting their role as drivers of this cancer. The first case showcased a patient with the MAML2–CRCT1 fusion in a high-grade mucoepidermoid carcinoma—a rare incidence as MAML2 fusions are frequently found in low-grade cancers (Bishop et al. 2018). MAML2–CRCT1 fusion is reported to be associated with good prognosis, although further investigation is warranted (Okabe et al. 2006). Interestingly, Yang et al. (2019) observed that head and neck tumors with gene fusions but no predictive biomarkers of immunotherapy (i.e., low mutation burden, low immune cell infiltration) were associated with increased T-cell response because of neoantigens derived from gene fusion, suggesting potential immunogenicity associated with fusion-positive cancers.

The second patient exhibited an HRAS missense mutation, which has been reported in many different cancer types (Prior et al. 2012). HRAS mutations are found in 11% of all salivary gland tumors, including mucoepidermoid cancers (Kato et al. 2015). In fact, a study reported that HRAS-mutated head and neck squamous cell carcinoma (HNSCC) were associated with increased immune activity compared to HRAS-wild-type HNSCC (Lyu et al. 2019), suggesting the role of HRAS as a potential predictive biomarker for immunotherapy. However, this has not been recapitulated in salivary gland carcinomas. Although there are no approved therapies targeting HRAS, studies have reported encouraging results utilizing targeted therapy in HRAS-mutant cancers. Tipifarnib, a potent and highly selective inhibitor of farnesyl transferase, has been granted fast track designation by the FDA for HRAS-mutant HNSCC after preliminary results from a phase II trial showed rapid and durable responses to treatment in patients with high HRAS variant allele frequency ($\geq 20\%$) (Ho et al. 2021). The patient from Case 2 was treated with tipifarnib (because of his HRAS missense mutation) for $\sim 2$ wk, but because of worsening performance status and severe adverse events such as thrombocytopenia, he was advised to discontinue the treatment.

Treatment for advanced SGC is very limited because of poor or limited response to chemotherapy treatment and lack of targeted therapies. The major challenge in treating salivary gland cancers with immunotherapy is that they are a heterogenous group of cancers that vary in response to immune checkpoint inhibitors. As well, there is a lack of trials that focus on mucoepidermoid carcinomas alone. However, the above described experience with mucoepidermoid carcinomas suggests the need to further investigate immune checkpoint inhibitors alone or in combination with chemotherapy in these patients, independently of PD-L1 expression.

**METHODS**

The tumor tissue of Cases 1 and 2 were analyzed using two institutional CLIA-certified next-generation sequencing panels of 93 genes (Case 1) and more than 87 genes (Case 2) (Supplemental Tables 1 and 2).
ADDITIONAL INFORMATION

Data Deposition and Access
The pathogenic variant was deposited in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) under accession number SCV002104179.

Ethics Statement
The City of Hope Institutional Review Board approved this study and informed consent was obtained under IRB# 07047.

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Author Contributions
All authors participated in the methodology and in reviewing and editing the final manuscript. R.R.P., T.G., and E.G.M. participated in the conceptualization, data curation, and original draft preparation.

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