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Case Report

Androgen deprivation therapy in metastatic salivary duct carcinoma of submandibular gland – A case report

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ABSTRACT

Salivary duct carcinomas (SDCs) are aggressive rare neoplasms. Whose diagnosis and treatment are a clinical challenge to both the treating doctor as well as the pathologist. Primary surgery with or without neck dissection followed by adjuvant radiation treatment is preferred for those with localized SDCs. Even with localized disease, the 5-year survival is <30%. For metastatic disease, the treatment options are limited. Two important biomarkers identified in SDCs are androgen receptors (ARs) and human epidermal growth factor receptor 2 receptors. Androgen deprivation therapy has evolved from the treatment of prostatic malignancies and various androgen-targeted agents are already in use for prostatic cancers. This case study represents the successful treatment of a metastatic SDC of the submandibular gland with AR-targeted agents. This patient has undergone treatment with multiple lines of Androgen targeted agents which is still ongoing. The main Androgen targeted agents used in this particular patient are Abiraterone and Enzalutamde. The patient has already achieved a disease-free survival of 30 months. Further studies have to be conducted to target ARs and more agents need to be tried.

Keywords: Androgen deprivation therapy, Salivary duct carcinoma, Androgen targeted therapy, Abiraterone acetate, Enzalutamide

INTRODUCTION

Salivary duct carcinoma (SDC) was first described by Kleinsasser *et al.*[1] in 1968, as an uncommon salivary gland tumor with a histological resemblance to ductal carcinoma of the breast. They reported the incidence of SDC as 1–3% among all salivary gland tumors. It usually affected elderly males and was found less often in young adults.[2] This tumor was found to exhibit aggressive clinical behavior with a tendency for early cervical lymphadenopathy and distant metastases to the lungs and bones Thus, the prognosis of SDC was considered highly unfavorable. Aggressive clinical management, including radical surgery and postoperative radiation therapy in the early stage of the tumor, appeared to be the only treatment for long-term survival. The article by Moriki *et al.*[3] clearly mentioned that the diagnosis of SDC is difficult and immunostaining for androgen receptor (AR) on cytological smears is useful for the diagnosis of these patients. A review of the literature indicated that immunohistochemically SDC expressed AR in the majority of the patients.[4] The present case study reviews the clinical data of a patient with SDC in the right submandibular gland and discusses the role of androgen deprivation therapy (ADT) in such patients.

CASE REPORT

Patient consent was taken for journal submission as a case report. A 68-year-old lady presented to our outpatient clinic in January 2019 with a painless swelling of the right submandibular gland that had been apparent for a 2-month duration. It was painless initially but the patient experienced pain as it advanced to the present state. There was no history of fever or other constitutional symptoms. The patient also had no history of diabetes, hypertension, cardiac diseases, or tuberculosis. Physical examination revealed a firm lump of size 4*3 cm with restricted mobility in the right submandibular region which was not fixed to the overlying skin. There were multiple significant right level I, II, III, and level IV lymph nodes, and the largest one measured 2*1 cm. Further clinical examination did not reveal any abnormality in other head-and-neck sites including the oral cavity. Other systems including the central nervous system, cardiovascular system, respiratory, and gastrointestinal systems were normal.

Investigations

Imaging

Contrast-enhanced computed tomography (CT) head-and-neck on February 6, 2019, revealed a necrotic soft-tissue density lesion within the right submandibular gland and right cervical lymphadenopathy. Whole body positron emission tomography-CT (PET-CT) on February 21, 2019, revealed fluorodeoxyglucose (FDG) avid heterogeneously

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enhancing mass lesion involving the right submandibular gland and FDG avid extensive right level I, II, III, IV, and V lymphadenopathy. PET-CT also revealed FDG avid soft-tissue nodules involving the anterior segment of the left lung upper lobe and FDG non-avid multiple soft-tissue nodules scattered in the bilateral lung parenchyma. No other FDG avid primary/secondary malignancies were noted elsewhere.

Histopathology

Fine needle aspiration cytology from the right submandibular gland swelling (February 07, 2019) showed atypical cells in clusters, sheets, and in a vague acinar pattern. Atypical cells had a moderate amount of cytoplasm pleomorphic hyperchromic nucleus and were reported as poorly differentiated carcinoma. A true cut biopsy from the same site done on February 23, 2019, showed fibro collagenous and adipose tissue with an invasive neoplasm composed of cells arranged in sheets, solid nests, interlacing cords, and vague glandular patterns. Individual cells had moderate eosinophilic granular cytoplasm and moderately pleomorphic hyperchromatic nuclei. Focal areas of necrosis and perineural invasion were seen. Fragments of skin with dermis showed similar neoplasm. No salivary gland/Lymph node tissue was seen in the sections studied. Histopathology report came as poorly differentiated carcinoma with oncocytic features and immunohistochemistry was required for specific diagnosis. Immunohistochemistry revealed diffuse positivity of AR. The tumor cells were also positive for CK and GATA3. The tumor cells were negative for human epidermal growth factor receptor 2 (HER2)nu amplification, estrogen receptor (ER), and progesterone receptor(PR). The diagnosis was thus confirmed as AR-positive SDC of the right submandibular gland.

Treatment

In view of metastatic disease, the intent of treatment for this particular patient was palliative. The case was discussed in the multidisciplinary tumor board of the institution and the treatment plan was decided as palliative chemotherapy followed by consolidation palliative radiotherapy (RT) to the right neck if there was a good response to chemotherapy. The patient was also planned for ADT after her initial phase of chemotherapy and radiotherapy. Palliative chemo administered at our center was Paclitaxel 175 mg/m^2 + Carboplatin AUC5 IV q21 days and she completed six cycles on August 2019. Since she had a good response, consolidation radiation treatment 55 Gy in 20 fractions with external beam radiation therapy (6MV photons) was given to the right submandibular region and right level I–IV Neck nodes. She completed her radiation treatment on October 2019. As per the plan, she had been on ADT since then. The regimen given was Tab. Abiraterone 500 mg 1-0-1 along with Tab. Prednisolone 5 mg 1-0-1.

Her last follow-up with abiraterone was on February 2021 and by then she had got disease-free survival of 24 months with Abiraterone acetate. The patient reported in February 2021 with episodes of headache and altered sensorium. On evaluation with an MRI brain, she was found to have multiple enhancing lesions bilateral cerebellum suggestive of brain metastasis. After explaining her poor prognosis, she was managed with palliative whole brain radiation therapy 20 Gy over five fractions which were completed in February 2021. She was put on the second line Androgen targeted agent Tab. Enzalutamide this time.

Her last follow-up visit was on July 2021 and she had already achieved disease-free survival of 5 months with enzalutamide-based androgen-targeted treatment. This patient with metastatic SDC has already achieved a disease-free survival of 30 months with multiple androgen-targeted agents and her treatment is still ongoing.

DISCUSSION

SDCs are aggressive neoplasms generally affecting elderly males. Majority of the patients present rapidly enlarging firm masses with the propensity of cervical lymph node spread (40–80%).[5] In the present case study, the patient was an elderly female with right cervical lymphadenopathy.

Due to the rarity of this neoplasm, the diagnosis of SDC is a clinical challenge both to the clinician and to the pathologist. The close differentials were metastatic lymph node and salivary gland carcinoma arising from the submandibular gland. Although SDC morphologically resembles ductal breast carcinoma the lack of expression of ER/PR may be helpful in the diagnosis.[6] In SDC, 16–83% show HER2 expression. AR and HER2 expression is not specific for SDC; however, evaluation of AR or HER2 status is recommended to help guide therapeutic strategies. Trastuzumab-based HER2 targeted therapy can be tried in SDC s but this patient lacks its expression. Revised SDC classification based on biomarker immunoprofiling by Takase *et al.*[7] is useful for predicting the patient's survival or for selecting appropriate therapy. Based on biomarkers Takase *et al.* classified SDCs into four groups: 1. Apocrine A (AR+/HER2−/Ki-67-low), 2. Apocrine B (AR+/HER2−/Ki-67-high), 3. Apocrine HER2' (AR+/HER2+), and 4. Double negative (AR−/HER2−).

SDC is a rare and aggressive salivary gland malignancy for which treatment is surgical resection and neck dissection, with adjuvant radiation therapy reserved for the more advanced forms. However, the 5-year recurrence-free survival rate remains at ~30%.[8] Immunohistochemical studies are necessary for a definite diagnosis. ADT evolved from the treatment of prostatic cancers and is definitely an option for those patients with metastatic disease. The present case showed improved outcomes with Abiraterone and enzalutamide-based treatment.

Abiraterone acetate was identified to be a potent and selective irreversible inhibitor of CYP17. The CYP17 enzyme is a cytochrome P450 (CYP) enzyme. Located in the endoplasmic reticulum of the testis, ovaries, adrenals, and placenta, CYP17 drives the synthesis of glucocorticoids and sex hormones.[9] Abiraterone acetate is proven to be effective in suppressing testosterone and showed survival benefits in prostate cancers. Enzalutamide (formerly known as MDV3100) is a rationally designed and targeted AR inhibitor that competitively binds to the ligand-binding domain of the AR and inhibits AR translocation to the cell nucleus, recruitment of AR cofactors, and AR binding to deoxyribonucleic acid. Enzalutamide significantly prolongs the survival of men with metastatic castration-resistant prostate cancer after chemotherapy.[10]

Furthermore, additional studies focusing on the etiology, mechanism of SDC, and targeting of ARs are required.

CONCLUSION

Two important biomarkers identified in SDCs are ARs and HER2 receptors. This case study represents the successful treatment of a metastatic SDC of the right submandibular gland with multimodality treatment including AR-targeted agents. The patient already achieved a disease-free survival of 30 months and the treatment is still going on. Further studies are required to target ARs and more agents are to be tried in this clinical setting.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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