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CASE REPORT

Salivary Duct Carcinoma of Parotid Gland: a Rare Tumor

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Introduction

Tumors of the salivary gland account for 3–4% of all head and neck malignancies [1]. About 70–90% of these tumors are located in parotid gland of which majority are benign and only 15% are malignant [1]. Mucoepidermoid carcinoma is the most common salivary gland malignancy followed by carcinoma ex-pleomorphic adenoma and acinic cell carcinoma. Other malignant tumors include adenoid cystic carcinoma, adenocarcinoma, squamous cell carcinoma, and poorly differentiated carcinoma [2]. Lymphoma of salivary glands is rare and commonly involves parotid gland. Parotid gland can harbor metastases to intraparotid nodes from tumors involving upper face particularly temple area and external auditory canal.

Salivary duct carcinoma (SDC) is an uncommon malignancy of salivary gland that arises from ductal epithelial cells with a reported incidence of 1–3% [3, 4]. It most commonly occurs in parotid gland [4–7]. It is known for a very aggressive behavior with early involvement of lymph nodes and a tendency for distant metastases.

Experience with SDC is limited and only a few cases have been reported in India. In this article, the authors describe a rare case of salivary duct carcinoma of the parotid gland and its management.

Case Report

A 45-year-old man presented with a history of painless swelling in the left parotid region for 2 years which had progressed rapidly in the last 2 months resulting in ulceration of overlying skin (Fig. 1). He was otherwise asymptomatic. On examination, there was a 3.5 × 3 cm firm swelling in the left parotid region which was relatively fixed and infiltrating overlying skin. Clinically, there was no evidence of facial nerve paralysis or involvement of deep lobe of the parotid gland. There was no cervical lymphadenopathy. The patient was evaluated in a different hospital 4 months back where needle aspiration was done from the swelling and was reported as pleomorphic

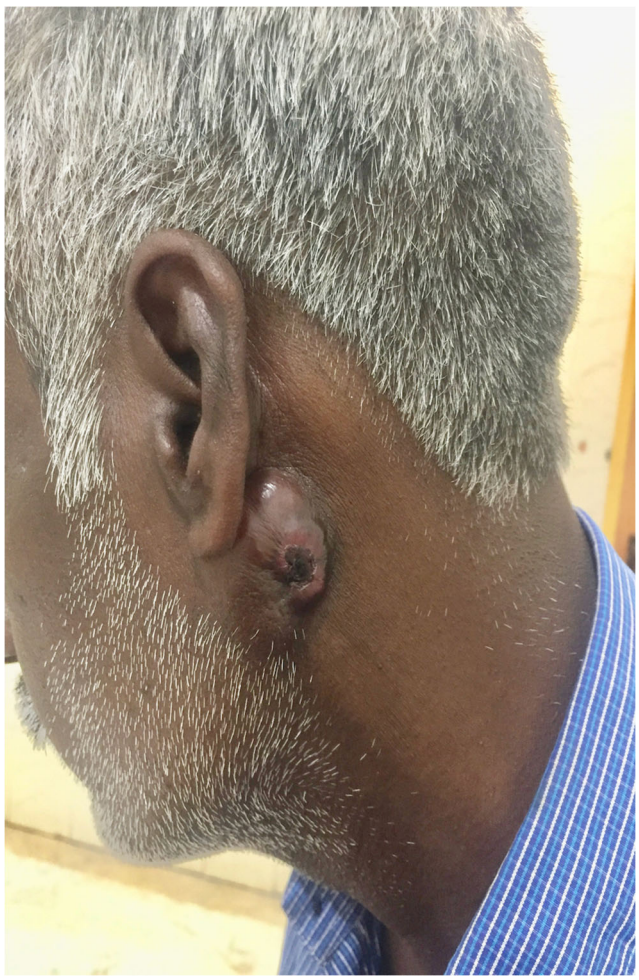

Fig. 1 Swelling in the left parotid region with skin infiltration

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adenoma. Magnetic resonance imaging was performed that showed an ill-defined irregular T1 and T2 hypointense lesion measuring 3 × 2.4 × 1.8 cm in superficial lobe abutting facial nerve (Fig. 2a, b). Deep lobe was uninvolved without any cervical lymphadenopathy. Chest x-ray did not show any metastases. A wedge biopsy of the ulcer was done and was reported as high-grade mucoepidermoid carcinoma. The tumor was clinically staged as cT4aN0M0 (Stage IVA).

The patient underwent total conservative parotidectomy with preservation of facial nerve (Fig. 3). Intraoperatively, there were no significant levels 2 and 3 lymph nodes. Corroborating this with clinical findings, it was decided not to address cervical lymph nodes. The defect was closed primarily after mobilization of surrounding skin. Postoperative period was uneventful.

Histopathological examination revealed a unifocal 4.3 × 4 × 2.2 cm tumor with gray-white cut surface infiltrating surrounding soft tissues and skin. All the margins including deep resection margin were free of tumor. Microscopically, tumor cells were arranged in cribriform and tubular pattern in either nests or cords. Tumor cells showed round to oval nucleus with a prominent nucleolus. Tumor cells had moderate to abundant eosinophilic cytoplasm with occasional atypical mitoses (Fig. 4a, b). Areas of necrosis, calcification, and cystic degeneration were present with focal areas of perineural and lymphovascular invasion. Three lymph nodes were identified out of which two showed tumor deposits without any extranodal extension. Pathologic staging was pT4aN1M0 (Stage IVA). Immunohistochemical analysis showed that tumor cells were positive for androgen receptor (AR) and negative for HER2 receptor (Fig. 5).

The patient then went on to receive adjuvant radiation therapy (60 Gy in 30 fractions, 2 Gy per fraction). Radiation field included tumor bed and ipsilateral levels I, II, III, and IV

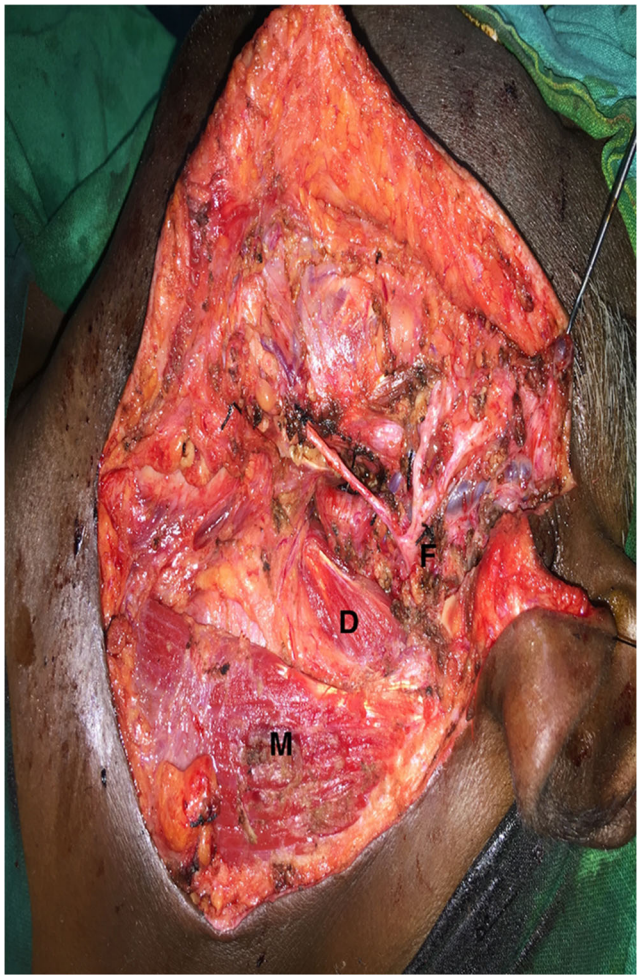

Fig. 3 Parotid bed after total conservative parotidectomy showing preserved facial nerve (F) and its branches, sternocleidomastoid muscle (M), and posterior belly of digastric (D)

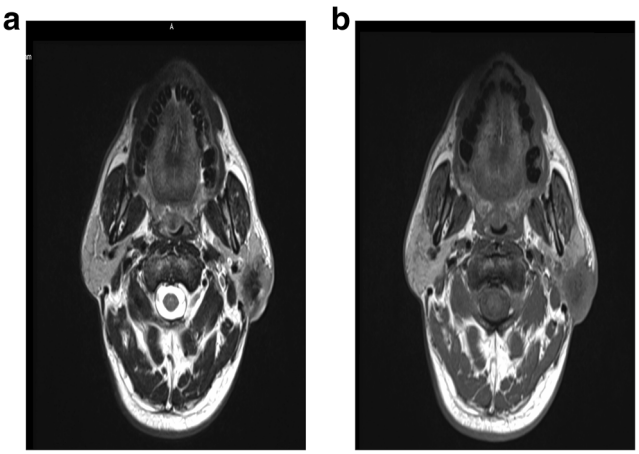

Fig. 2 **a** T2-weighted magnetic resonance imaging showing a hypointense lesion in superficial lobe of the parotid gland. **b** T1-weighted magnetic resonance imaging showing a hypointense lesion in superficial lobe of the parotid gland

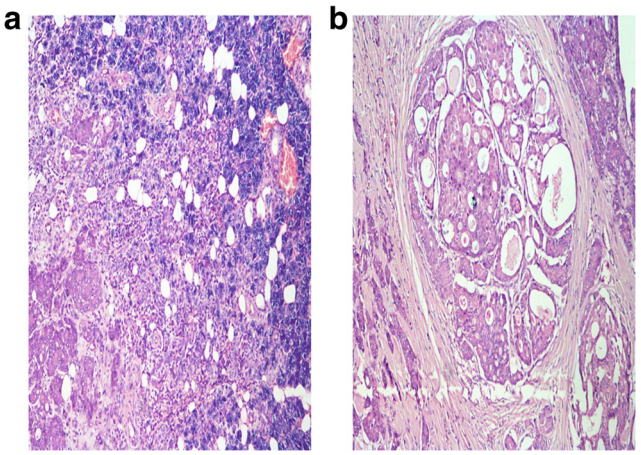

Fig. 4 **a** Tumor cells infiltrating salivary gland acini (hematoxylin and eosin; magnification, × 100). **b** Tumor cells arranged in cribriform pattern (hematoxylin and eosin; magnification, × 100)

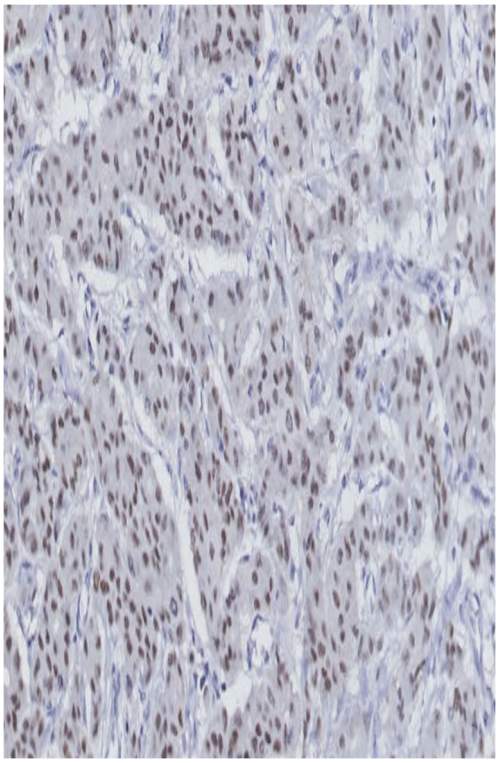

Fig. 5 Tumor cells expressing androgen receptor (magnification, × 100)

nodes. There is no evidence of recurrence after 1 year of follow-up.

Discussion

Salivary duct carcinoma was first described by Kleinsasser et al. as a special group of tumors which arose in ducts and had morphological features resembling ductal carcinoma of the breast [8]. The exact etiology is not known. Most of them arise de novo. Around 20–30% of tumors may arise from pre-existing pleomorphic adenoma [5, 6].

Salivary duct carcinoma most commonly affects elderly men in their 60s and 70s and in most series male to female ratio is 4–5:1 [3–7]. However, our patient was 45 years old which is very uncommon. Around 80–90% of these tumors occur in the parotid gland. Next common sites are submandibular gland (10–12%) and minor salivary glands (1–2%) [4–6]. Those that arise de novo are characterized by rapid onset and progression while some of them that develop from pre-existing pleomorphic adenoma have indolent course and progress rapidly after transformation. Pain is present in 20–30% of the cases and incidence of facial nerve paralysis is between 30 and 60% [5, 7]. These tumors usually present at an advanced stage with 60–70% having an extra-glandular extension at diagnosis [4, 5]. These have a propensity for early cervical lymph node involvement and 40–60% of patients have clinically positive lymph nodes [4, 5, 7]. Guzzo et al. observed that nodal involvement is related to the T stage. In their series, 58% of the patients had nodal involvement at the presentation of which 37.5% had T1, 71.4% had T2, 66.7% had T3, and 100% had T4 lesion [7]. In the present case, SDC of the left parotid gland probably arose from a pre-existing pleomorphic adenoma as evidenced by an indolent natural history of 2 years, FNAC diagnosis of pleomorphic adenoma, and rapid progression over 2 months before presentation. Clinically and radiologically, there was no evidence of lymph node involvement despite locally advanced tumor with skin infiltration.

Imaging helps in differentiating benign from malignant lesions and assesses the extent of involvement, facial nerve involvement, and lymph node metastases. MRI is superior to CT in soft tissue definition and detecting perineural spread [9]. Malignancies appear as ill-defined masses with central necrosis and infiltration to adjacent structures. They have low signal intensity on T1 and T2 weighted images [10]. The ability of MRI to differentiate SDC from other malignancies of the salivary gland is uncertain. Motoori et al. observed that SDC had type C enhancement on dynamic MRI and was hypointense on STIR and T2-weighted images [11]. This may be a clue to differentiate SDC from common salivary gland malignancies such as mucoepidermoid and adenoid cystic carcinomas.

Fine needle aspiration (FNA) is commonly performed for cytological diagnosis. However, it has a high false negative rate in detecting malignancies [12]. It is difficult to distinguish SDC from other salivary gland malignancies in view of the rarity of the tumor, limited experience of pathologists, and morphological diversity of salivary gland neoplasms.

Grossly, these tumors are firm, ill-defined masses with infiltration to surrounding soft tissues. Histologically, they resemble breast adenocarcinoma and have papillary, solid, or cribriform growth pattern [5]. These are characterized by an extensive desmoplastic reaction. Cells are large and polygonal with moderate to abundant eosinophilic cytoplasm. The nucleus is large with a prominent nucleolus and coarse chromatin. These are usually high grade with marked nuclear pleomorphism [7]. These tumors often demonstrate comedonecrosis which may undergo calcification similar to ductal carcinoma of the breast. Most of the literature lays emphasis on the presence of comedonecrosis in making the diagnosis. Although the pathological features of our case were similar to other cases, there was the absence of comedonecrosis. The authors believe that the presence of comedonecrosis is not essential for making a diagnosis of SDC. These have high proliferative activity and the Ki67 index is > 25% in the vast majority of cases [4, 6, 13]. Perineural invasion and lymphovascular invasion are seen in 70–90% of cases [14].

Most of these can be diagnosed using routine hematoxylin and eosin staining without the need for immunohistochemistry. However, in difficult cases, IHC can be used to differentiate

from other tumors and to confirm the diagnosis. These are always positive for androgen receptor (AR) and negative for estrogen (ER) and progesterone receptors (PR) [5, 6]. Nasser et al. evaluated sex hormone receptor status in 78 patients with salivary gland tumors. They found that SDC is always AR-positive and ER/PR negative. Apart from AR, only HER2 receptor status is significant for prognosis and treatment [15]. HER-2 overexpression is seen in 25–75% of cases [4, 16, 17]. These also stain positive for epithelial membrane antigen and cytokeratins. Gross cystic disease fluid protein, marker usually associated with lobular breast cancer, is positive in two-thirds of cases [18]. Some may be positive for prostate-specific antigen and S100 [19]. These are usually negative for basal myoepithelial markers such as CK 5/6 and 14 [20]. In our patient, tumor cells were positive for androgen receptor and negative for HER-2 receptor.

Differential diagnosis includes metastases from breast cancer or prostate cancer, oncocytic adenocarcinoma, adenocarcinoma not otherwise specified, and high-grade mucoepidermoid carcinoma [14]. Chances of metastases from breast cancer and prostate cancer to parotid are very rare with a reported incidence of 2% and 0.5% respectively [21]. A careful history and physical examination along with serologic and immunohistochemical studies will help in differentiating SDC from metastases. IHC analysis for androgen receptor is useful in differentiating these tumors from other malignancies as SDC are almost always positive for this receptor while it is negative in oncocytic adenocarcinoma, adenocarcinoma not otherwise specified, and mucoepidermoid carcinoma.

Given the aggressive nature of these tumors, most require multimodality management comprising surgery and radiotherapy. Total conservative or radical parotidectomy along with lymph node dissection is the mainstay of therapy [4–8]. Total parotidectomy is required even in T1 lesions. In the present case, total conservative parotidectomy was done as the facial nerve was not involved by the tumor. The facial nerve is sacrificed only if there is facial nerve paralysis on clinical examination or frank infiltration of nerve by the tumor [4].

Ipsilateral cervical lymph node dissection is required for regional control. Most of the authors have proposed lymph node dissection even in N0 neck arguing high incidence of nodal involvement and better regional control [4, 5]. In our case, prophylactic neck dissection was not performed as there was no evidence of lymph node involvement either clinically or radiologically. However, pathological examination revealed two out of three lymph nodes with tumor deposits and extra-capsular extension. However, the role of lymph node dissection in N0 neck is uncertain. There is no proof at present if this would result in improved regional control or overall survival. In a study reported by Guzzo et al., neck dissection was performed only in clinically involved nodes. Of 14 patients who did not undergo prophylactic neck dissection, only 19% developed nodal recurrence [7].

Given the aggressive nature of the tumor, adjuvant radiotherapy is required in all patients. RT has not been shown to improve overall survival but achieves better locoregional control [5]. Lewis et al. observed that local recurrence was 21% in those who received combined modality whereas it was 50% in those who underwent surgery alone [5]. Our patient received adjuvant radiation to the primary tumor site and the ipsilateral neck. No systemic chemotherapy or Trastuzumab was given.

Chemotherapy is primarily used in metastatic setting [7]. Since these tumors have a strong expression of androgen and HER-2 receptors role of anti-androgen and anti-HER2 targeted therapy has been evaluated. However, the beneficial effect is not proven at present. Limaye et al. studied the role of Trastuzumab in HER2+ SDC in the adjuvant and metastatic setting. They reported better survival in those who received Trastuzumab-based therapy in the adjuvant or palliative setting with a median survival of 32 months and 40 months respectively [17].

In unresectable cases, if patients are unfit for surgery or the patient refuses surgery, then radiotherapy alone or in combination with chemotherapy may have a role. Efficacy of these approaches is uncertain due to limited availability of data.

Patients with SDC have a poor prognosis and most of them do not survive more than 5 years [4, 5, 7]. Most patients develop local or regional recurrences within 2 to 3 years and majority die due to systemic dissemination [3–5, 7]. Factors that affect prognosis are the size of the lesion, nodal status, and HER2+ receptor status. Lesions that are < 2 cm appear to have a better prognosis. In a study by Guzzo et al., a 2-year survival was 62.5% and 25% in tumors < 2 cm and > 2 cm respectively [7]. Similar observations have been made by Delgado et al. [6]. Intraductal SDC is a variant with bland histological features that was first described by Delgado et al. [22]. These have an indolent course with fewer chances of nodal involvement and a favorable prognosis. Prophylactic neck dissection, as well as adjuvant RT, can be omitted in these tumors. Tumors with nodal involvement or HER2 overexpression appear to have a poor prognosis [4, 7]. Those that arose in pleomorphic adenoma may have a better prognosis [3, 6].

Conclusion

Salivary duct cancer is a very aggressive tumor that is difficult to differentiate from other salivary gland malignancies clinically, radiologically, and cytologically. Definitive diagnosis can be made only after histopathological examination and immunohistochemistry as these tumors are always positive for androgen receptor. Presence of comedonecrosis is not an absolute essential in making a histological diagnosis. These

tumors should be managed aggressively with surgery and adjuvant radiotherapy.

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