Salivary duct carcinoma - Role of accurate diagnosis for an accurate therapy

T.P.Keerthana¹, Leena Dennis Joseph¹, C N Sai Shalini¹, S Saravanan²

¹Department of Pathology, Sri Ramachandra institute of higher education and research, Chennai, Tamil Nadu
²Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu

ABSTRACT:
Salivary duct carcinoma is an aggressive subtype of primary salivary gland carcinoma with advanced stage at presentation, high rates of metastasis and recurrence. It is most commonly seen in parotid gland of older men with microscopic resemblance to high-grade breast ductal carcinoma. Salivary duct carcinoma mainly affects men over 50 years of age and accounts for 5% to 10% of all salivary gland malignancies. Characteristic histomorphology and immunohistochemical expression of Androgen Receptor (AR) aids the diagnosis of salivary duct carcinoma. Fine-needle aspiration typically reveals cytologic features of high-grade carcinoma. Heterologous alterations have been recognized in oncogenes and tumor suppressor genes such as TP53, HRAS, PIK3CA, PTEN, and BRAF as well as AR and HER2. Targeted therapy against these genes may help in broadening treatment options for salivary duct carcinoma. Salivary Duct Carcinoma is one of the most aggressive salivary malignancies with 33% local recurrence and 45% metastasis. We report a case of a 75 years old female patient, who presented with a swelling obliterating the retromandibular groove. FNAC & histopathology confirmed the diagnosis of salivary duct carcinoma.

KEY WORDS: androgen receptor; fine needle aspiration; human epidermal growth factor receptor 2; salivary duct carcinoma; salivary gland tumor; targeted therapy

Address for correspondence:
T.P.Keerthana,
Department of Pathology, Sri Ramachandra institute of higher education and research, Chennai, Tamil Nadu
Email: keerthana.om@gmail.com

How to cite this article:
Received: 02-04-2022; Accepted: 09-06-2022; Web Published: 22.06.2022
salivary gland carcinoma in the latest World Health Organisation classification, showing high rates of local recurrence and distant metastasis\textsuperscript{2,3}. It is most commonly seen in parotid gland of older men with microscopic resemblance to high-grade breast ductal carcinoma\textsuperscript{1}. Salivary duct carcinoma mainly affects men over 50 years of age and accounts for 5% to 10% of all salivary gland malignancies\textsuperscript{2,3}. Most of the salivary duct carcinoma arises from major salivary gland especially parotid gland\textsuperscript{2,4,5}.

**CASE DETAILS:**

A 75 year old female presented with chief complaints of swelling in the right parotid region for 1 month at the site of previous surgery (superficial parotidectomy 15 years back). Swelling was insidious in onset and with sudden increase in size. It was not associated with any pain or discharge. No history of fever, dysphagia, facial asymmetry and any other associated symptoms were noted. On local examination there was a 5 x 3 cms ovoid, hard swelling present in front of, beneath and extending behind the right ear lobe lifting it and obliterating retromandibular groove (Figure 1).

**FIGURE 1 Hard swelling below the ear lobe**

It extended superiorly 3 cm from zygomatic arch, inferiorly to angle of mandible, anteriorly 4 cms from angle of mouth and posteriorly just touching the mastoid. The swelling moved freely over the masseter muscle. Skin over the swelling was not pinchable. Previous parotidectomy scar was present over the swelling.
Fine Needle Aspiration Cytology (FNAC) of the right parotid swelling was done which showed highly cellular smears showing large and small clusters of atypical cells with abundant eosinophilic cytoplasm, round hyperchromatic nuclei, some of them showing prominent nucleoli. Occasional cells showed pleomorphism and mitosis was also noted (Figure 2). FNAC was signed out as Suspicious for malignancy, Milan system V. Possibility of carcinoma arising from pleomorphic adenoma cannot be ruled out. Following that total conservative parotidectomy was done which was a partially skin covered soft tissue mass measuring 6x6x2.5 cms, weighing 64 grams. External surface was grey yellow to grey brown. Cut surface showed a partially circumscribed grey white, firm lesion measuring 3.8x3x2 cm. Adjacent areas of normal salivary gland tissue were seen (Figure 3).

**FIGURE 2** Highly cellular smear showing large and small clusters of atypical cells with abundant eosinophilic cytoplasm, round hyperchromatic nuclei, some of them showing prominent nucleoli. Occasional cells show pleomorphism and mitosis. (H&EX400)

**FIGURE 3** Gross image showing a partially circumscribed grey white firm lesion.
Histologically, the tumor showed atypical cell proliferation with tumor cells arranged in a glandular/tubular architecture, comedonecrosis and a focal cribriform growth pattern. The tumor cells had abundant eosinophilic cytoplasm, large pleomorphic nuclei with conspicuous nucleoli(Figure 4, 5) The surgical margins were free of tumor. The tumor conferred to pT2Nx. By immunohistochemistry, the tumor cells were positive for HER2(Figure 6) and Androgen Receptor(Figure 7) Post-operative period was uneventful. The patient did not receive radiotherapy or chemotherapy.

**FIGURE 4:** Photomicrograph showing high grade nuclear morphology with pleomorphism (H&E X400).

![FIGURE 4](image)

**FIGURE 5:** Ductal lesions comprise pleomorphic, epithelioid tumor cells with cribriform growth pattern, roman bridge formation and intraductal comedonecrosis.

![FIGURE 5](image)
Salivary duct carcinoma (SDC) is an aggressive epithelial malignancy that resembles high grade mammary ductal carcinoma. It is characterized by tumor cell proliferation with comedonecrosis and cribriform growth pattern. The tumor cells are large, have abundant eosinophilic cytoplasm, large pleomorphic nuclei and conspicuous nucleoli. There are several histologic variants of SDC which includes mucin-rich, sarcomatoid, invasive micropapillary, oncocytic and rhabdoid. 20 to 59% of SDC cases arise from pre existing pleomorphic adenoma. SDC is the most common subtype of carcinoma ex pleomorphic adenoma. Encapsulated and minimally invasive SDC ex pleomorphic adenoma are shown to exhibit a better prognosis than widely invasive SDC ex pleomorphic adenoma. Most cases of SDC present at an advanced stage as there is no screening system for its early detection. Lesions having a high number of tumor buds (tumor cell clusters composed of up to 4 cells) and poorly differentiated clusters (tumor cell clusters composed of more than 5 cells without gland
formation) show a poorer prognosis than others. A risk stratification model was proposed by Nakaguro et al based on 4 histological features—prominent nuclear pleomorphism, mitoses, vascular invasion and poorly differentiated clusters. (Table 1)

<table>
<thead>
<tr>
<th>TABLE 1 Histologic Risk Stratification Model for Salivary Duct Carcinoma</th>
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<tbody>
<tr>
<td>Adverse prognostic factors</td>
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<tr>
<td>Prominent nuclear pleomorphism</td>
</tr>
<tr>
<td>More than or equal to 30 mitoses/10 high-power fields</td>
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<tr>
<td>Vascular invasion (H&amp;E stain)</td>
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<tr>
<td>More than or equal to 5 poorly differentiated clusters.</td>
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Total number of positive factors

<table>
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<tr>
<th>Number of Positive Factors</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>4</td>
<td>High risk</td>
</tr>
</tbody>
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**CYTOLOGY:**

Aspirates of SDC are composed of large tumor cells with abundant eosinophilic cytoplasm, large round to oval atypical nuclei with prominent nucleoli. Tumor cells are singled out and also form cohesive three dimensional clusters that occasionally exhibit a papillary cytoarchitecture. The necrotic background in FNAC correlates with comedonecrosis on histopathology. The differential diagnoses for SDC in fine needle aspiration samples include high-grade mucoepidermoid carcinoma, high-grade transformation of various primary salivary gland carcinomas, adenocarcinoma, not otherwise specified and metastatic cancers from other anatomic sites. Characteristic immunohistochemical findings on formalin fixed paraffin embedded (FFPE) cell block in the context of the corresponding high grade cytomorphologic features are sufficient to render a diagnosis of SDC on FNAC specimen.

**IMMUNOHISTOCHEMISTRY:**

A strong and diffuse Androgen Receptor (AR) expression is a characteristic feature in the diagnosis of SDC paired with a positive staining for GATA3/GCDFP-15. A p63 expression is useful for differentiating mucoepidermoid carcinoma from SDC, which shows a negative expression for SDC. Focal and weak expression of AR is also noted in pleomorphic adenoma, adenoid cystic carcinoma and acinic cell carcinoma. The sensitivities and specificities of AR expression for diagnosing SDC were 73 to 100% and 76 to 100% respectively. The SDC must be diagnosed based primarily on

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**International Journal of Head and Neck Pathology – Volume 5 – Issue 1 ©MM Publishers**
morphologic features with the support of AR immunohistochemistry.

16 to 83% of cases of SDC show human epidermal growth factor receptor by IHC or HER2 amplification by FISH or next generation sequencing. Evaluation of AR and HER2 status is recommended to help guide therapeutic strategies. Patients with AR and its coregulatory protein forkhead box protein A1(FOXA1) expression has been associated with improved prognosis. P53 extreme negative/positive staining which suggests TP53 point mutation and CK5/6 staining is associated with worse prognosis.

**MOLECULAR BIOLOGY:**

Mutations commonly described in SDC include TP53, PIK3CA, HRAS & PTEN. TP53 mutations including missense and truncating mutations, and PI3/AKT pathway activation evaluated by the p-Akt expression are associated with poor prognosis. SDC are microsatellite stable.

**TREATMENT:**

The main therapeutic approach for SDC is adequate and appropriate surgical resection. Elective neck dissection is recommended for patients with neck metastases and T3-4 (T3-Tumor larger than 4 cm and/or tumor having extraparenchymal extension, T4-Moderately advanced or very advanced disease) patients without neck metastasis. Regardless of T stage and margin status, post operative radiation therapy is an effective and appropriate therapeutic option. Overall response rate of taxane (paclitaxel or docetaxel) plus platinum (carboplatin) chemotherapy ranging from 39 to 50% for SDC. AR and HER2 targeted therapy

Treatment targeting AR and HER2 have been introduced. Drugs used for androgen deprivation therapy include AR blockers (bicalutamide) and leutinizing hormone releasing hormone analogues (leuprolide). The response rate for advanced or patients with recurrence was shown to be 17 to 65% and median overall survival was 17 to 44 months. Increased response rate and time to disease progression was noted with combination therapy of an anti-HER2 antibody (trastuzumab, ado-trastuzumab emtansine or pertuzumab) with conventional taxane based
The response rate changed from 65 to 100% and the median progression free survival was 3 to 18 months.

**CONCLUSION:**

The cytologic and histopathologic diagnosis of primary salivary gland tumors is challenging because of their histomorphologic diversity, histologic subtypes and low incidence. The dual role of immunohistochemistry and molecular biology has helped in the utilization of targeted therapy and hence overall disease prognosis.

**Declaration of patient consent**

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

**Financial support and sponsorship**

Nil

**Conflicts of interest**

There are no conflicts of interest

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