ABSTRACT

The salivary gland give rise to at least 24 histologically distinct tumors which account for about 2% of all primary salivary epithelial malignancies. Salivary duct carcinoma (SDC) is a rare malignant epithelial tumor predominantly occurring in major salivary glands, particularly parotid gland. Intraoral SDC involving minor salivary gland is uncommon accounting for 5% of all SDC. Histologically, it shows a striking resemblance to breast carcinoma of the ductal type, presenting intraductal and invasive component. It most commonly occur in males in fifth and sixth decade of life exhibiting an aggressive clinical behaviour with a tendency for early cervical lymphadenopathies and distant metastasis to the lungs and bones with a highly unfavourable prognosis. The infrequency and histological differentiation makes the diagnostic process difficult and also pose a problem of understanding this malignancy. So analysis of each confirmed case is of great importance. This manuscript describes a rare case of intraoral SDC diagnosed by microscopic examination and immunohistochemical markers.

Key words: Immunohistochemistry, salivary glands, salivary duct carcinoma

CASE REPORT

A 56 year old male reported with the complaint of ulceration in the right upper posterior region of jaw since 3 months. Clinical examination revealed an ulcerative lesion of size 3 cm x 3 cm on the palate extending from #15 region to #17 region, extending towards the mid palatine raphe (Figure 1).

History revealed that the ulcerative lesion was progressively increasing in size. The lesion was slightly raised with distinct margins, and no associated pain or numbness. No significant radiological findings were seen. Haematological investigations revealed an increased total leucocyte count (13000/mm$^3$) and a raised erythrocyte sedimentation rate (44 mm/hr). Incisional biopsy under local anaesthesia was performed and the specimen was sent for microscopic examination. Histopathology of the biopsy specimen revealed isomorphic basaloid to polygonal tumor cells in streaks, ducts and cribriform pattern with central comedonecrosis (Figure 2).

The tumor cells exhibited deeply basophilic nuclei with scanty cytoplasm and few mitotic figures. The adjacent stroma was collagenised with bundles of spindle shaped cells having a uniformly bland nuclei arranged in a storiform to parallel fashion, mixed with short interlacing fascicles. For a confirmatory diagnosis an immunoprofile of the tissue was done. The tumor cells were immunoreactive for cytokeratin (CK) 5&6/ epithelial membrane antigen (EMA) and immunonegative for S100 protein/p63/ muscle specific actin (MSA) and c-kit (CD117) (Figure 3). Stain for mucicarmine was also negative. The Ki67 proliferative index in the tumoral cells was 4%. Based on this a final diagnosis of salivary duct carcinoma was specified. To rule out the possibility of metastasis or other primary tumors, a chest X ray, prostate ultrasound, bone scintigraphy and laboratory test (PSA) was advised which revealed no significant findings. The tumor was staged as T2N0M0 and tumor was excised followed by radiotherapy. The surgical specimen
Figure 1: An ulcerative lesion of size 3 cm x 3 cm on the palate extending from #15 region to #17 region, extending towards the mid palatine raphe.

Figure 2: Microscopic examination revealed isomorphic basaloid to polygonal tumor cells in streaks, ducts and cribriform pattern with central comedonecrosis (H&E, X10). Inset shows the same in high power (H&E, X 40).

Figure 3: Immunohistochemistry showing tumor cells immunoreactive for cytokeratin (CK) 5&6/epithelial membrane antigen (EMA) and immunonegative for S100 protein/p63/muscle specific actin (MSA) and c-kit (CD117) and negative for histochemical stain mucicarmine.

was sent for histopathological analysis which confirmed it to be salivary duct carcinoma which showed tumor free surgical margins. After 2 years follow up, the patient was alive with no recurrence or metastasis.

DISCUSSION

Salivary duct carcinoma (SDC) is a rare malignant tumor that arises from the ductal epithelial cells of the salivary glands.\(^1\) SDC was first described by Kleinsasser et al in 1968 as Speichelgangcarcinome.\(^2\) It has also been termed as cribriform salivary carcinoma of excretory ducts and infiltrating salivary carcinoma.\(^3\) In 2005, SDC was defined as an independent entity by WHO, labelling it as “an aggressive adenocarcinoma, which resembled high grade breast ductal carcinoma”.\(^4\) SDC has an aggressive clinical behaviour and poor clinical outcome that is characterized by rapid growth of the disease, multiple nodal metastases, early distant metastasis, and a high rate of recurrence.\(^5\) Seventy-five percent of salivary duct carcinomas occur in the parotid gland. The peak incidence is in the seventh decade of life, and its occurrence in patients under age of 50 years is uncommon.\(^5\) SDC involving minor salivary glands is rare. Literature reveals that only around 37 cases of SDC originating in the intraoral minor salivary gland have been reported till date. They most frequently occurred on the palate followed by buccal mucosa/vestibule, tongue, maxilla, mandible, and upper lip, floor of mouth, hypopharynx and sinonasal tract.\(^6\) Typically there is history of recent onset and
TABLE 4: The microscopic features and immunoprofile of Salivary duct carcinoma and similar lesions and its differentiating criteria

<table>
<thead>
<tr>
<th>IMMUNOHISTOCHEMISTRY MARKERS</th>
<th>SALIVARY DUCT CARCINOMA</th>
<th>METASTATIC CARCINOMA OF BREAST</th>
<th>ADENOCARCINOMA NOT OTHERWISE SPECIFIED</th>
<th>SINO NASAL UNDIFFERENTIATED CARCINOMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestrogen receptors</td>
<td>occasionally positive</td>
<td>positive</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>Epithelial Membrane Antigen</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>variable positive</td>
</tr>
<tr>
<td>CK 5&amp;6</td>
<td>positive</td>
<td>negative</td>
<td>variable expression</td>
<td>Negative</td>
</tr>
<tr>
<td>p63</td>
<td>negative</td>
<td>-</td>
<td>positive</td>
<td>variable positive</td>
</tr>
<tr>
<td>S100</td>
<td>negative</td>
<td>-</td>
<td>positive</td>
<td>Negative</td>
</tr>
<tr>
<td>CD117</td>
<td>negative</td>
<td>-</td>
<td>positive</td>
<td>-</td>
</tr>
<tr>
<td>Smooth muscle actin (SMA)</td>
<td>negative</td>
<td>-</td>
<td>negative</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoembryonic antigen</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Comedonecrosis, eosinophilic cytoplasm of atypical cells, cellular pleomorphism and infiltrating cribriform pattern.</td>
<td>Similar to salivary duct cyst</td>
<td>Tumor cells arranged in solid sheets, cords, nests, glands, cystic spaces, and microglandular cribriform pattern diffusely infiltrating the fibrous stroma.</td>
<td>Consists of nests, trabeculae, sheets of medium sized polygonal cells often with an organoid pattern.</td>
</tr>
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</table>

rapid growth of a mass that may be painful and fluctuant in size. The present case was seen intraorally on the palate but was painless in nature and increasing in size.

Histogenesis of SDC is believed to be the excretory ducts or as a result of malignant transformation of ductal cells in pleomorphic adenoma.

SDC was previously divided into two categories, low grade and high grade variants. The low grade was recognized as rare, cystic proliferative carcinoma that resembled spectrum of breast lesions. Whereas high grade SDC tumors consist of solid invasive cancer nests with polygonal cancer cells surrounding a comedo necrosis as seen in the present case.

The most characteristic feature of SDC is that it displays a similar histological appearance to ductal breast carcinoma. But in this case possibility of metastatic breast carcinoma can be excluded because current patient was a male and laboratory investigations were negative for it. In female patients, studying estrogen, progestosterone receptors and immunohistochemical analysis of HER-2 protein may be beneficial.

SDC can be classified into three subtypes, according to intraductal or infiltrative predominance: 1) predominantly intraductal, where 90% of the tumors are intraductal; 2) predominantly infiltrative, where less than 20% of the tumor is intraductal; or 3) infiltrative, when the tumor is entirely infiltrative.

The WHO defines SDC as "an epithelial tumor of high malignancy with formation of relatively large aggregates resembling distended salivary ducts. The neoplastic epithelium shows a combination of cribriform, looping (roman bridging) and solid growth patterns, often with central necrosis both in primary lesion and lymph node metastasis. This extremely rare carcinoma resembles comedocarcinoma of the breast."

Microscopically, large and polygonal atypical cells having abundant and finely granular cytoplasm and prominent nucleoli, arranged in an irregular branching, cribriform or papillary growth patterns as well as single cell formation in the background of frequent necrosis can be observed. Similar findings were seen in this case.

Immunohistochemical analysis of the present case showed
positivity for epithelial markers including CK5& 6 and EMA. Expression of these markers suggest the predominance of ductal cells. Basal and myoepithelial markers i.e. muscle specific actin, p63, S100 and c-kit (CD117) were negative. Absence of reactivity to myoepithelial markers suggest that it is an invasive variant. The high grade variants are S100 negative. The negativity for p63 and S100 suggest it to be a high grade invasive variant. Based on the clinical presentation, histopathology and IHC interpretation, tumors such as metastatic carcinoma of breast, adenocarcinoma not otherwise specified and sinonasal undifferentiated carcinoma can be ruled out to confirm diagnosis of SDC. The microscopic features and immunoprofile of these similar lesions and its differentiating criteria have been tabulated in Table 4.

SDC is a rare aggressive type of salivary gland carcinoma with early distant metastasis and poor prognosis, so it requires radical surgical treatment. Adjuvant radiotherapy or chemotherapy may be indicated and is based particularly on post-operative pathologic findings such as grade of malignancy, bone or perineural invasion. Local recurrence occur in 35-66% patients and distant metastasis in 50-70 % and the most common sites are lungs, bone, brain, skin, liver and thyroid gland. Approximately 50% of the patients die of the disease within 4-5 years. Prognostic data concerning SDC of minor salivary gland origin remains limited, because the incidence of SDC of minor salivary gland origin is extremely low compared to that of SDC of major salivary gland origin. A relatively favorable prognosis in patients with SDC of minor salivary gland origin compared to SDC of parotid gland origin was suggested based on the finding that the former was associated with less frequent regional lymph node metastases in a review of the literature. However, this less aggressive behavioral tendency of SDC of minor salivary gland origin is most likely due to the relatively smaller tumor size, because SDCs of minor salivary gland origin are detected earlier than SDCs of major salivary gland origin.

CONCLUSION

Salivary gland pathologies are rare and poses a variety of diagnostic challenges owing to their diverse histological features in individual lesion and overlapping histological features similar to those observed in different tumor entities. SDC has infrequent occurrence and patient usually present in the late stage of disease with advanced metastasis leading to difficulties in diagnosing and treating it. Limited number of cases of SDC in the literature make it very challenging to recognize. Molecular diagnostic aids such as immunohistochemistry should be considered in assisting its final diagnosis.

REFERENCES