

CASE REPORT

Intraoral salivary duct carcinoma: A case report and a brief review

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ABSTRACT

Salivary duct carcinoma (SDC) is a rare, extremely aggressive malignancy arising in the ductal epithelium of the salivary glands. SDC occurs almost exclusively in the major salivary glands with parotid gland predominantly affected. Only isolated cases involving minor salivary glands have been reported in the literature. We report an unusual case of extensive SDC occupying the right cheek and the maxillary sinus, possibly arising from the minor glands of the buccal mucosa or from the mixed glands of the maxillary sinus in a 71-year-old man. The case was subjected to a panel of immunohistochemical markers like pan cytokeratin, low molecular weight cytokeratin (LMW CK), high molecular weight cytokeratin (HMW CK), CK 7, CK 20, CD 117, carcinoembryonic antigen (CEA), S-100, p63, Gross cystic disease fluid protein (GCDFP-15) and estrogen receptor (ER) to arrive at a definitive diagnosis.

Key words: Comedonecrosis, minor salivary glands, salivary duct carcinoma

INTRODUCTION

Salivary duct carcinoma (SDC) is a rare aggressive malignancy, with a propensity for invasive growth, resulting in early regional and distant metastases.^[1] The term “salivary duct carcinoma” was first used by Kleinsasser and Klein in 1968 who considered SDC analogous to ductal carcinoma of the breast.^[2] It has also been termed cribriform salivary carcinoma of excretory ducts, infiltrating salivary duct carcinoma and intraductal carcinoma.^[3] Previously grouped with adenocarcinoma not otherwise specified,^[4] it was classified as a distinct clinicopathologic entity by the World Health Organization (WHO) in 1991.^[5]

Since its initial introduction, the term SDC has been used in a more generic sense by many observers for any primary adenocarcinoma demonstrating focal ductal differentiation. This term should be reserved only for tumors that histologically resemble ductal carcinoma of the breast. It is defined in the new 2005 World Health Organization (WHO) classification as “an aggressive adenocarcinoma which resembles high grade

breast ductal carcinoma.”^[6] Eighty-eight percent of all cases of SDC occur in the parotid gland, approximately 8% arise in the submandibular gland and only 4% occur in the minor salivary glands.^[4] SDC is believed to arise from the excretory ducts or as a result of malignant transformation of ductal cells in pleomorphic adenoma.^[7] The peak incidence of SDCs is in the sixth and seventh decades of life and it is predominant in males.^[8]

CASE REPORT

A 71-year-old male presented to our hospital with a facial swelling in January 2009. The patient reported that the swelling initially presented as a firm lemon sized nodule of the right buccal mucosa approximately 10 years ago. He had noticed that the lesion had been increasing in size over the past 3 months, accompanied by occasional symptoms of pain.

On examination, there was multinodular swelling of the right side of the face with enophthalmos of the right eye. The contour of the right eyelids was altered. Assessment of vision showed complete loss of vision on the affected side. The lesion was measuring approximately 8 × 6 × 5 cms, with a smooth bosselated surface and an ill-defined edge [Figures 1 and 2]. The skin over the swelling was normal but stretched. Swelling was non tender, firm, without any ulceration or discharge.

Intraorally, the swelling was non-tender, firm, immobile and non-compressible involving the buccal mucosa, obliterating

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the right upper buccal vestibule [Figure 3]. The mucosa over the swelling was intact. The head and neck examination revealed paresthesia and motor nerve deficiency on the affected side. Submandibular and cervical lymph nodes were palpable.

Radiographs revealed a maxillary sinus involvement and extension into the floor of the orbit. The alveolus and hard palate were secure [Figure 4]. High resolution ultrasonography showed a hyperechoic solid vascular mass involving the right cheek. The mass has separated the masseter from the ramus with submasseteric spread. It had involved the skin and subcutaneous space. There was no evidence of regional lymph node enlargement. Salivary gland tumor or carcinoma of maxillary sinus was considered provisionally based on history, clinical presentation and radiographic findings. Extensive involvement of cheek and vestibule, sparing of the alveolus and palate further pointed that this lesion was probably arising from minor salivary glands of buccal mucosa. Chest X-ray revealed no abnormalities.

Fine needle aspiration cytology (FNAC) of the swelling showed a cellular aspirate comprising cohesive three – dimensional clusters of epithelial cells with nuclear atypia. The branching sheets of cells with a cribriform pattern were also noted. Cells were large and polygonal with round to oval, pleomorphic, eccentric or centrally placed nuclei and prominent nucleoli [Figure 5]. Microscopy of the an incisional biopsy from the buccal vestibule revealed an infiltrative, proliferative, submucosal neoplasm characterized by irregularly shaped ductal and tubular structures with cystic spaces of varying sizes. Tumor cells were cuboidal to polygonal with moderate to abundant eosinophilic cytoplasm with nuclear atypia [Figure 6]. Based on the above findings the case was provisionally diagnosed as malignant salivary gland tumor. The case was subjected to surgical excision. The histopathology revealed circumscribed nests of tumor cells in solid, cribriform and papillary configurations [Figures 7 and 8]. Central, comedo-type necrosis was noted in few nests [Figure 9]. The neoplastic epithelial cells were accompanied by a dense fibrous connective tissue stroma. Circumscribed tumor nests/



Figure 1: A multinodular swelling of the right side of the face with enophthalmos of the right eye

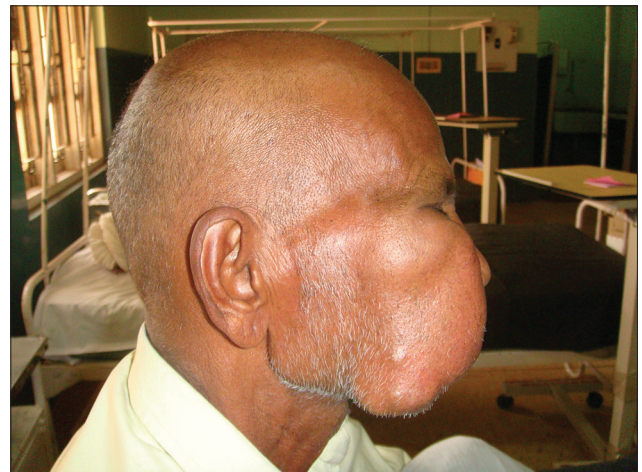


Figure 2: A multinodular swelling of the right side of the face extending from corner of eye to inferior border of mandible



Figure 3: Intraoral view shows the mass occupying the buccal vestibule and buccal mucosa



Figure 4: Radiograph shows a soft tissue mass covering the maxillary sinus, extending into infratemporal area and the floor of the orbit

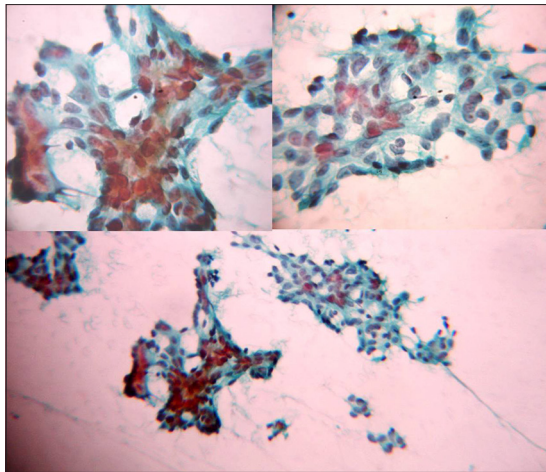


Figure 5: Cellular aspirate with groups of cells form branching sheets and cribriform clusters. Cells are polygonal with oval, enlarged, pleomorphic nuclei and prominent nucleoli. [Pap, x100; (Inset; Pap, x400)]

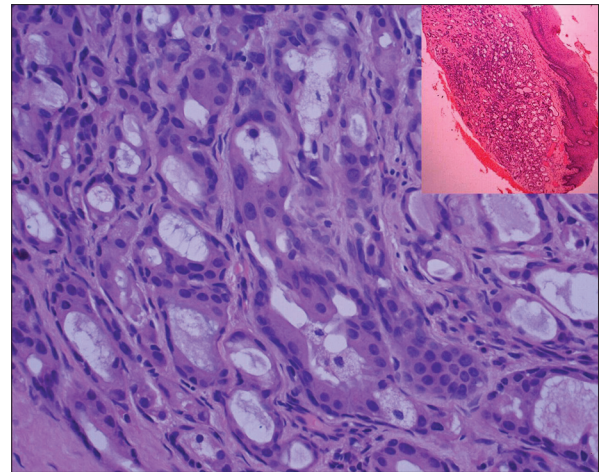


Figure 6: Incisional biopsy reveals submucosal infiltrative tumor mass with ductal and tubular structures. Tumor cells show cellular and nuclear atypia. [H&E, x400; (Inset; H&E, x40)]

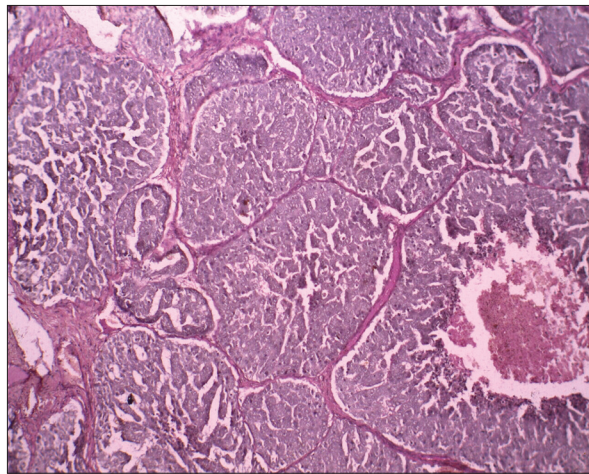


Figure 7: Solid island of tumor shows central comedo necrosis. Periodic Acid Schiff (PAS) stain sharply demarcated interstitial fibrous stroma from the epithelial components (PAS, x100)

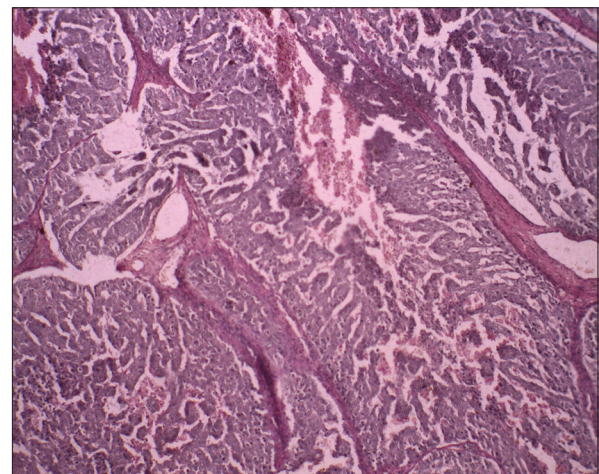


Figure 8: Nests of tumor cells show papillary and micropapillary configurations. The neoplastic epithelial cells are accompanied by a dense fibrous connective tissue stroma (PAS, x100)

intraductal growths varied in size. The larger tumor islands typically had large central cystic spaces. The tumor cells for rim of several cells thick around the cystic space [Figure 10]. In addition to the intraductal and circumscribed tumor nests, infiltrative tumor elements were usually evident at the periphery. Most of the tumor cells appeared cuboidal and polygonal with moderate amount of eosinophilic cytoplasm, pleomorphic vesicular nuclei and prominent nucleoli. Mitotic figures varying from moderate to high were noted [Figure 11]. A stretch of maxillary sinus lining and mixed glands of maxillary sinus were also seen lying close to the tumor components. The above features were suggestive of salivary duct carcinoma arising from minor salivary glands. To confirm the diagnosis tumor was subjected for panel of immune histochemical (IHC) markers. Tumor cells showed positivity for pan cytokeratin, CK7 [Figure 12], mild diffuse staining for low molecular weight cytokeratin (LMW CK) and negative for CK 20, high molecular weight cytokeratin (HMW CK),

carcinoembryonic antigen (CEA), c-kit (CD -117), S-100, p63, Gross cystic disease fluid protein (GCDFFP-15) and estrogen receptor (ER) [Figure 13]. Radiotherapy was advised following the surgical removal of the tumor.

Based on the clinical presentation, histopathology and IHC interpretation, tumors such as polymorphous low grade adenocarcinoma (PLGA), papillary cystadenocarcinoma (PCA), basaloid squamous cell carcinoma (BSCC), small cell carcinoma (SmCC), sinonasal undifferentiated carcinoma (SNUC) and metastatic tumors (lung carcinoma, melanoma with an epithelioid pattern) were excluded to the confirm the diagnosis of SDC.

DISCUSSION

Intraoral SDC is a rare malignant neoplasm, accounting for less than 2% of all malignant minor salivary gland tumors of

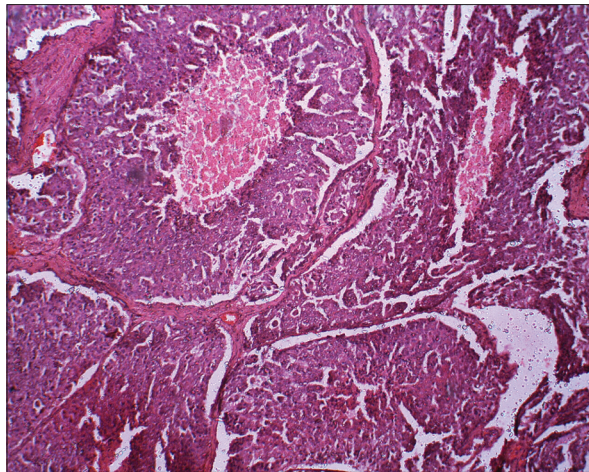


Figure 9: Central, comedo-type necrosis noted intraductal tumor nest. [H&E, ×100]

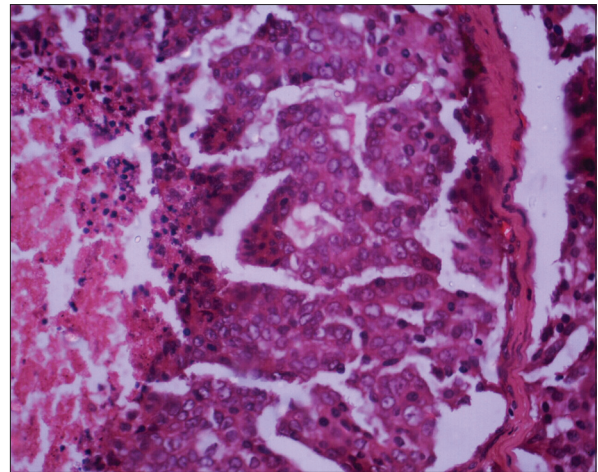


Figure 10: The tumor cells for rim of several cells thick around the cystic space. Islands of tumor cells with papillary intraductal projections. [H&E, ×400]

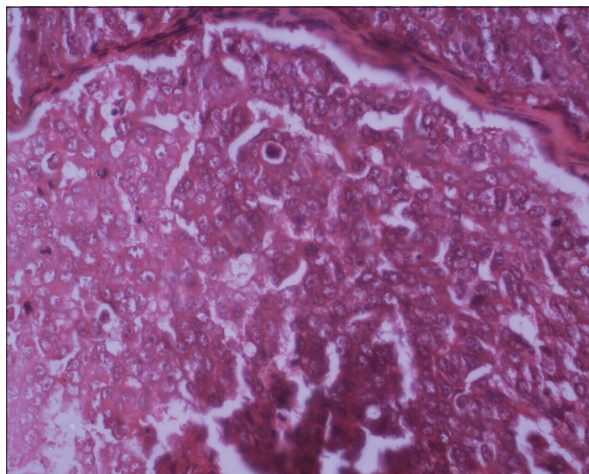


Figure 11: Tumor cells are cuboidal and polygonal with eosinophilic cytoplasm, pleomorphic vesicular nuclei and prominent nucleoli. Mitotic figures varied from moderate to high were noted. [H&E, ×400]

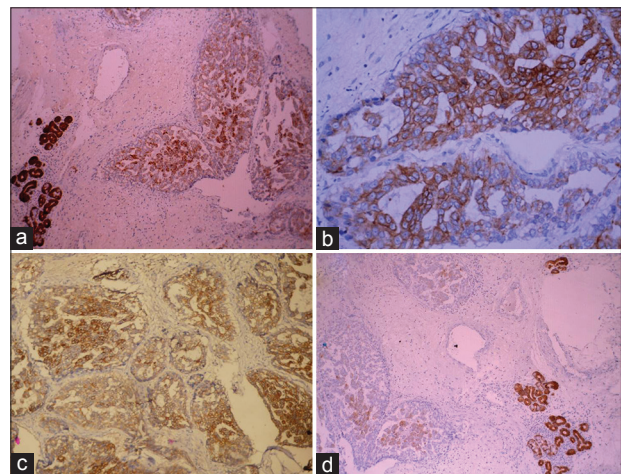


Figure 12: Tumor cells show immunopositivity for (a) CK7, ×100; (b) CK 7, ×400; (c) pan cytokeratin, ×100; (d) mild diffuse staining for LMW CK, ×100

the oral cavity as reported in a recent series.^[4] To the best of our knowledge, based on evidence in the literature, only 35 cases of SDC have occurred in the minor salivary glands, including the present case^[1,2,4,5,7-12] The male to female ratio reported in these studies is approximately 2:1. The patients ranged from 23-80 years of age, which suggest that, like parotid gland SDC, minor salivary gland SDC occurs primarily in elderly men.^[5] Typically, there is history of recent onset and rapid growth of a mass that may be painful and fluctuate in size. Occasionally, patients have longer clinical histories, with one report of an approximately 38- year history; facial paresis may be present.^[6] Even the present case is with a longer clinical history of 10 years. Although it is difficult to determine the predominant location of SDC in the minor salivary glands because of the limited number of cases, they occurred most frequently on the palate (20 cases) followed by buccal mucosa/ vestibule (4 cases), the tongue (2 cases), the maxilla (4 cases), the mandible (1) and the upper lip (1), floor of mouth (1), hypopharynx (1), sinonasal tract (1).^[1,2,4,5,7-12]

The WHO defines salivary duct carcinoma as “an epithelial tumor of high malignancy with formation of relatively large cell 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 the primary lesion and the lymph node metastases. This extremely rare carcinoma resembles comedocarcinoma of the breast.”^[1]

SDC is characterized by aggregates of large cuboidal cells with intraductal and invasive components, atypical mitotic figures, arrangement in combinations of cribriform, papillary and solid patterns and comedonecrosis. It is characterised microscopically by intraductal tumor island with papillary, cribriform or solid configurations of cells with central comedonecrosis. Neoplastic cells are pleomorphic, with round and clear nuclei and eosinophilic cytoplasm.^[4] Occasionally SDCs will have papillary areas with fibrovascular cores. They differ from true micropapillary variant, as they

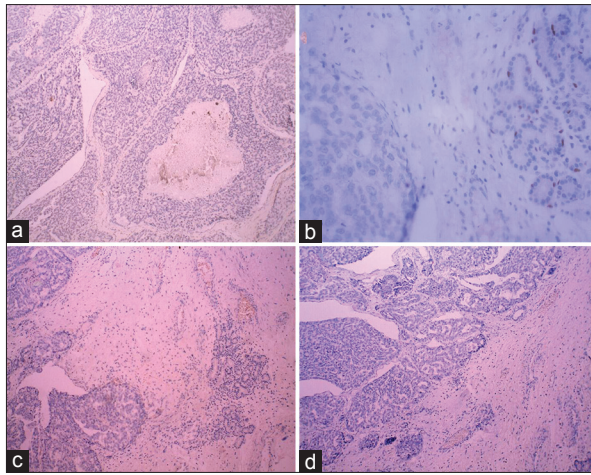


Figure 13: Tumor cells were negative for (a) CD 117, $\times 100$; (b) p63, $\times 400$; (c) CK 20, $\times 100$ and (d) GCDFF-15, $\times 100$

display morula-like clusters of cells without fibrovascular cores, each surrounded by a clear space.^[6] The present case showed solid and papillary/micropapillary patterns with focal comedonecrosis, all of which are consistent with the WHO description of SDC.

To make a definitive diagnosis of SDC, some investigators require circumscribed epithelial nest with central comedonecrosis. Histologically, SDCs can be confused with metastatic deposits from breast carcinoma, sweat duct carcinoma and prostate carcinoma.^[7]

IHC evaluation of the tumor cells indicated that SDC is composed of predominantly ductal cells with no myoepithelial cell involvement. The strong expression of cytokeratin in the tumor cells is supported by the majority of studies on SDCs.^[8] Immunohistochemical analyses have shown that SDC typically demonstrates epithelial markers, including cytokeratin, EMA and CEA.^[3,4]

SDC is reactive for LMW CK and HMW CK, including CK7 in every case, but CK 20 only occasionally shows weak focal staining. There is expression of other epithelial markers such as EMA and usually CEA and the apocrine marker, GCDFF-15. S-100 protein is negative. CD-117 and myoepithelial markers are negative.^[6] Unlike breast cancer, ER expression has been demonstrated only very occasionally, progesterone receptors positivity appears to be slightly more common, 20% of cases; in contrast, more than 90% of SDC express androgen receptors.^[6,13] Antigen profiles in SDC similar breast carcinoma have been reported, with positivity for GCDFF-15.^[1] Metastatic breast carcinoma can be excluded based on gender, clinical examination, mammography, positivity for ER and negativity for CEA differentiates SDC and ductal carcinoma of breast. It has been suggested that the presence or absence of ER might be a feature for distinguishing between SDC and metastatic breast carcinoma.^[3]

High grade invasive variant of SDC was the entity first recognised and reported because it is the most commonly encountered, representing greater than 90% of the cases.^[6] High grade SDC shows cribriform growth pattern, frequent comedonecrosis, predominantly cells are polygonal, well-defined cytoplasmic border, powdery eosinophilic cytoplasm, round to oval vesicular nuclei, prominent nucleoli. Cellular composition is monomorphous mainly made of ductal cells, peripherally scattered myoepithelial cells. Tumor cells are S-100 negative and variable HMW CK expression is noted in high grade variant.^[14] The present case showed histopathologic features like high grade SDC. IHC is necessary to evaluate for the presence or absence of a myoepithelial layer may be necessary to establish whether these are truly *in situ* or invasive.^[6] To accept a tumor as purely *in situ*, a thorough histologic sampling of the tumor to rule out invasion with IHC demonstration of basal or myoepithelial layer (CK14, calponin, p63, SMA) is necessary. Absence of reactivity to myoepithelial markers suggests that it as an invasive variant. The high grade variants are usually S-100 negative.^[6] Lack of S-100 and p63 expression in the present case is suggestive of a high grade invasive variant.

DIFFERENTIAL DIAGNOSIS

PLGA is a malignancy having uniform, bland cytologic features that is almost always of minor salivary gland origin, exhibiting many of the patterns described in SDC, including perineural invasion. However, pleomorphism, mitotic activity and comedonecrosis are characteristics of SDC that distinguishes it from PLGA.^[1,15]

SDC is an intraductal and infiltrating neoplasm with a variety of growth patterns, including cell nests, lobules with central comedo type necrosis akin to solid adenoid cystic carcinoma (AdCC).^[6,15] Tumor cell morphology and lack of p63, S-100 and CD -117 expression rules out AdCC.

PCA is rare malignant tumor characterised by predominantly cystic growth that often exhibits intraluminal papillary growth. The buccal mucosa, lips and palate are most frequently involved minor gland sites. The tumor consists of haphazardly arranged cysts that are partially filled with mucin, varying in size and shape and have limited intervening fibrous connective tissue. In about 75% of the cases the lumen of cysts exhibit varying degrees of papillary proliferation. The columnar cell-rich tumors often predominates in the intraluminal papillary areas and account for their “gastrointestinal” appearance, but the cells usually fail to stain for neutral mucin.^[16] PCA shares papillary and cystic growth patterns with SDC. However, unlike SDC, it lacks the cribriform pattern, apocrine-like cells and comedonecrosis.^[15]

BSCC is considered in the differential diagnosis of SDC in minor salivary glands or seromucinous gland sites. BSCC produce basement membrane-like material and

have cribriform and solid areas. BSCC reveals greater nuclear pleomorphism, squamous differentiation, prominent necrosis and frequent mitoses. But BSCC also shows focal keratinisation the presence of surface squamous dysplasia, *Ca in Situ* or invasive carcinoma. BSCC is mucosa –based and most common sites still remain in the base of tongue. The macroscopic descriptions of BSCC have been those of an exophytic mass as well as a flat lesion with central ulceration. IHC staining features BSCC shows 100% keratin staining with HMW CK (34bE12), 79% with an AE1/AE3, 83% for LMW CK 8/18 (CAM 5.2), 83% EMA, 53% CEA, 39% S- 100 noted by some authors.^[6]

SmCC (poorly differentiated neuroendocrine carcinoma) has been reported in several sites throughout head and neck including salivary glands. Tumor cells show multidirectional differentiation in salivary gland SmCC. SmCC is composed of sheets of hyperchromatic round to oval to spindle cells with minimal cytoplasm, inconspicuous nucleoli and focal necrosis. In majority of cases they are immunoreactive to CK 20 and EMA,^[6] to lesser extent to CK 7, thus differing from SDC.

SNUC is a highly aggressive, undifferentiated anaplastic carcinoma without obvious squamous or glandular differentiation with severe dysplasia of overlying epithelium in few instances. Involvement of nasal cavity, maxillary antrum, sinus, orbit and cranial cavity is frequent. SNUC consist of nests, trabeculae, sheets of medium size polygonal cells, often with an organoid appearance. Nuclei are round to oval, pleomorphic and hyperchromatic. Individual cell necrosis and central comedo-type necrosis of cell nests are common. IHC shows positivity for pan cytokeratin, CK 7, CK 8 and CK 19 and negative for keratin 4, CK5/6, CK 14. Variably positive for EMA, NSE, CD 99, P63 and negative CEA and S-100.^[6] This was considered because antral mucosa was evident along with mucous minor salivary glands suggesting that tumor must have arisen from mucous glands of antral mucosa.

Several primary salivary gland tumors have histologic features similar to those occurring in other regions of the body. It is imperative to rule out a metastasis from another source before considering a tumor as primary. Specific conflicts in differential diagnosis include metastatic breast carcinoma versus primary ductal carcinoma, metastatic squamous cell carcinoma (SCC) versus primary SCC, metastatic small cell carcinoma versus primary small cell carcinoma, metastatic undifferentiated carcinoma from nasopharynx versus primary lymphoepithelial or undifferentiated carcinoma and metastatic renal cell carcinoma versus primary clear cell carcinoma.^[17]

Metastatic tumors comprise about 5% of all malignant tumors of salivary glands. Almost 70% of cases occur in males. The majority of cases are SCC and melanoma is second in frequency. 80% of secondary (Metastatic) tumors are

metastases from head and neck neoplasms. 10% originate from distant tumors among which lung carcinoma (especially small cell carcinoma), kidney and breast carcinomas are the most common.^[18]

The most common cancers to metastasize to the oral cavity include those from the lungs (one third oral metastases), kidneys, breast (one fourth of oral examples in females), skin (melanoma) and prostate (rarely into soft tissues). The microscopic appearance of the metastatic deposit will resemble that of the primary tumor.^[19] Based on the thorough clinical examination and investigations metastatic tumors were excluded.

SDC can be distinguished from the above lesions by characteristic histopathologic features like comedonecrosis, eosinophilic cytoplasm of atypical cells, cellular pleomorphism and infiltrating cribriform pattern.^[12] The outcome of SDC is unfavorable. Most of the cases reported in literature have an aggressive nature. There is local spread as distant metastasis to brain, liver, adrenals, bone, skin and thyroid. Lymph node metastasis is seen in 60% cases, recurrence in 33% cases^[7] A review of the literature and reported cases suggests that SDC in the minor salivary glands does not frequently spread lymphatically. The rate of lymph node metastases in minor salivary gland SDC is approximately 22%, which is lower than the 83% reported in the literature for major salivary gland SDC.^[11] SDC originating in the minor salivary glands had a relatively favorable prognosis compared with parotid SDC.^[5]

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