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ORIGINAL ARTICLE

Salivary duct carcinoma: Correlation of morphologic features by fine needle aspiration cytology and histopathology

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ABSTRACT

Background: Salivary duct carcinoma (SDC) is a highly aggressive primary salivary gland neoplasm that resembles intraductal and infiltrating breast carcinoma. **Objectives:** To review cytomorphologic features of histology proven SDC and evaluate potential pitfalls in cytologic diagnosis. **Materials and Methods:** Fine needle aspiration cytology (FNAC) of five histologically proven SDCs were reviewed. **Results:** One patient was an elderly male (61 years), while the other four patients were younger, in their fourth decade (average age: 38 years). The initial cytologic diagnoses in two of the cases were poorly differentiated carcinoma with differential diagnosis of SDC and high grade mucoepidermoid carcinoma, while in the third case, a possibility of malignant mixed tumor was suggested. In fourth and fifth cases, the diagnosis was suggestive of pleomorphic adenoma with cystic change. The spectrum of cytologic changes included flat sheets and cohesive papillary and three-dimensional clusters. There was moderate to severe nuclear pleomorphism and atypia. Cribriform pattern and necrosis were occasionally identified. Prominent bright granular metachromatic stroma was seen in two of the cases interpreted as pleomorphic adenoma with cystic change and in the tumor reported as suggestive of malignant mixed tumor. The fifth case showed numerous cyst macrophages and apocrine cells with mild nuclear atypia. **Conclusion:** FNAC of SDC is difficult to interpret because of overlapping cytomorphologic features. Bland cytomorphologic features in some cases and several clinical pitfalls are demonstrated in our series.

KEY WORDS: Fine needle aspiration cytology, mucoepidermoid carcinoma, pleomorphic adenoma, salivary duct carcinoma

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INTRODUCTION

Salivary duct carcinoma (SDC) is an unusual but very aggressive type of salivary gland carcinoma with a poor prognosis.[1-6] Early diagnosis and treatment are important as this tumor is known to metastasize early.[2,4,6]

SDC is similar histologically to intraductal and infiltrating carcinoma of the breast. Comedonecrosis is a common feature. Aggressive biologic behavior with a high incidence of lymph node metastasis, local recurrence and significant mortality justify categorization of SDC as a high grade malignancy in the current classification of salivary gland neoplasms.[7]

We analyzed the cytomorphologic features in fine needle aspiration cytology (FNAC) and studied the difficulties related to specific diagnosis and differential diagnosis in five patients with histologically proven SDC.

MATERIALS AND METHODS

Five histologically confirmed cases of parotid gland SDCs were identified from histopathology files of our institute. FNAC slides and clinical details of the five patients were retrieved from cytopathology files. FNAC was performed using 23- or 25-gauge needles mounted on 10 ml syringe. All the smears were air dried for May Grunwald Giemsa (MGG) stain and alcohol fixed for Papanicalaou (PAP) stain. All subsequent surgical specimens were fixed in 10% buffered formalin, embedded in paraffin and sectioned at 5 μm and stained with hematoxylin and eosin and alcian PAS stains. FNAC slides were quantified for the following morphologic findings: cellularity, fine cytoplasmic vacuolation,

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abundant eosinophilic cytoplasm, apocrine cells, indistinct cell borders, nuclear pleomorphism, nuclear membrane irregularity, chromatin clumping, nuclear eccentricity, metachromatic stroma, necrosis, cyst macrophages, mitotic activity, papillary pattern, cribriform configuration and three-dimensional clusters. Among these, cellularity, nuclear pleomorphism, metachromatic stroma and mitotic activity were semiquantitatively assessed using the scores given below.

Semiquantitative Scoring System

a. Cellularity: Hypocellular smears +, moderate cellularity ++, high cellularity +++
b. Nuclear pleomorphism: Absent –, minimal +, marked pleomorphism ++
c. Metachromatic stroma: Absent –, <2 low power field (LPF) +, 2–5 LPF ++, >5 LPF +++
d. Mitotic activity/high power field (HPF): Absent –, occasional +, numerous ++

The remaining parameters were quantitated for their presence or absence.

RESULTS

The clinical findings, initial cytologic and final histopathologic diagnosis are summarized in Table 1. Cytologic findings in the five cases with semiquantitative assessment of morphologic findings are presented in Table 2.

Two tumors (Cases 2 and 3) were interpreted cytologically as poorly differentiated carcinoma with a possibility of SDC. One of the tumors had a differential diagnosis of high grade mucoepidermoid carcinoma. Cells were arranged in sheets and cohesive clusters with abundant eosinophilic cytoplasm, indistinct cytoplasmic boundaries, round to oval pleomorphic nuclei with coarsely clumped chromatin, inconspicuous nucleoli, and nuclear membrane irregularity [Figure 1a]. High mitotic activity, necrosis and dyscohesive tumor cells were also seen. Three-dimensional papillary clusters and cribriform pattern were also seen at foci. The differential diagnosis of mucoepidermoid carcinoma was suggested in view of the younger age of the patient (36 years) coupled with the presence of scattered clusters of tumor cells with vacuolated cytoplasm and rare intracytoplasmic mucin like droplets. Both the cases had bright metachromatic stroma [Figure 1b] prominently seen in MGG stain.

One tumor (Case 1) was signed out as suggestive of malignant mixed tumor. The patient was a 40-year-old male who had undergone superficial parotidectomy 1 year back at an outside hospital. The histopathology report of the earlier surgical specimen revealed pleomorphic adenoma. The original slides and blocks were not available for review. There was a recurrence of multiple nodules at the surgical site. FNAC showed cellular smears with sheets and three-dimensional clusters of polygonal cells [Figure 1c]. Nuclei were round to oval with coarsely clumped chromatin, irregular nuclear membrane and inconspicuous nucleoli. The cytoplasm showed fine vacuolation in MGG stain [Figure 2a]. The cells were intimately admixed with prominent granular metachromatic stroma.

Fourth patient (Case 4) was a 35-year-old female with swelling below the right ear and it was slowly increasing in size. The swelling was nontender with restricted mobility. There was no facial palsy. FNAC smears showed moderate cellularity with clusters of round to oval eccentric nuclei [Figure 2b] admixed with numerous cyst macrophages [Figure 2c]. MGG stained smears showed prominent metachromatic stroma. Nuclear pleomorphism was minimal [Figure 2d].

The fifth patient (Case 5) was a 42-year-old female with recurrent swelling in the parotid region. The patient had mild pain since few days. There was a history of previous excision 4 years back

Table 1: Correlation of cytology and histopathology diagnosis

Case No.	*Age/sex*	*Clinical findings*	*Initial cytologic diagnosis*	*Final histopathology diagnosis*
1	40/M	Operated a year back; recurrence with multiple nodules; previous HPE report showed pleomorphic adenoma	Positive for malignancy; suggestive of malignant mixed tumor	High grade SDC
2	36/M	Not available	Poorly differentiated carcinoma; differentials include SDC and high grade mucoepidermoid carcinoma	High grade SDC
3	61/M	Right parotid swelling 6 × 7 × 4 cm; firm to hard with mild tenderness, gradually increasing in size and associated with pain; facial nerve palsy present	Poorly differentiated carcinoma favoring SDC	High grade SDC
4	35/F	Swelling below right ear increasing in size 4 × 3 cm, nontender with restricted mobility Ultrasound revealed irregular hypoechoic mass with fluid collection	Pleomorphic adenoma with cystic change	High grade SDC
5	42/F	Swelling in left parotid region excised 4 years back, previous HPE report showed pleomorphic adenoma, slides were not available for review Swelling recurred at the same site with pain and measured 6.5 × 4 × 3 cm	Benign salivary gland tumor	Low grade SDC

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Table 2: Semiquantitative assessment of cytologic features

Cytologic features	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Cellularity	++	++	++	+	+
Fine cytoplasmic vacuolation	Present	present	Present	Absent	Absent
Abundant eosinophilic cytoplasm	Absent	Present	Present	Absent	Absent
Apocrine cells	Absent	Absent	Absent	Present	Present
Indistinct cell borders	Absent	Present	Present	Absent	Absent
Nuclear pleomorphism	++	++	++	+	-
Nuclear membrane irregularity	Present	Present	Present	Absent	Absent
Chromatin clumping	Coarse	Coarse	Coarse	Absent	Absent
Nuclear eccentricity	Absent	Absent	Absent	Present	Absent
Metachromatic stroma	++	–	–	+++	++
Necrosis	Absent	Present	Present	Absent	Present
Cyst macrophages	Absent	Absent	Absent	Present	Present
Mitotic activity/HPF	–	++	++	–	–
Papillary pattern	Absent	Absent	Present	Absent	Absent
Cribriform configuration	Absent	Absent	Present	Absent	Absent
Three-dimensional clusters	Absent	Absent	Present	Absent	Absent

Semiquantitative scoring, Cellularity: Hypocellular smears +, moderate cellularity ++, high cellularity +++, Nuclear pleomorphism: Absent –, minimal +, marked pleomorphism ++, Metachromatic stroma: absent –, <2 low power field (LPF) +, 2–5 LPF ++, >5 LPF +++, Mitotic activity/HPF: Absent –, occasional +, numerous ++

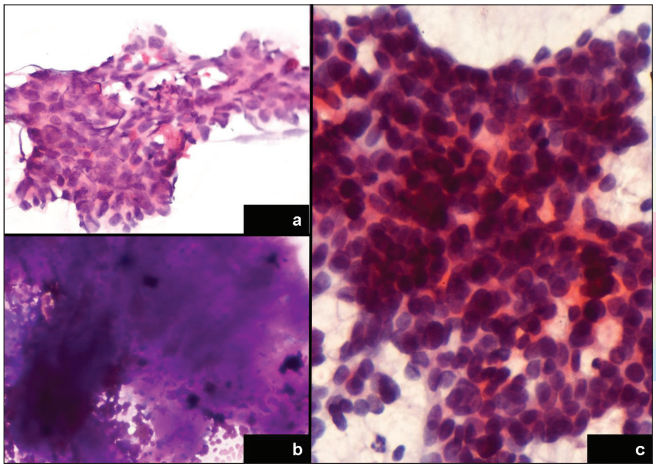

Figure 1: (a) Sheets of cells with marked nuclear atypia and irregular nuclear contours (PAP, ×200); (b) prominent metachromatic stroma in background (MGG, ×200); (c) cribriform pattern (MGG stain, ×200)

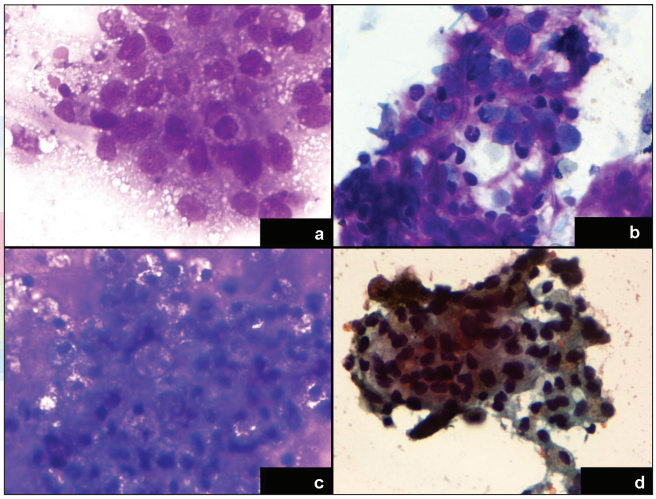

Figure 2: (a) vacuolated cytoplasm (MGG, ×400); (b) cells in pseudopapillary clusters, bland nuclear morphology and myxoid matrix (MGG, ×400); (c) numerous cyst macrophages in a background of mucin (MGG, ×200); (d) apocrine cells arranged in cribriform pattern with mild nuclear pleomorphism (PAP, ×200)

at an outside hospital. The histopathology slides of the previous excision biopsy were not available for review. FNAC done on the recurrent swelling showed moderately cellular smears with sheets of cyst macrophages and occasional clusters of cells with round to oval nuclei and minimal nuclear pleomorphism. Many cells also showed apocrine change [Figure 2d]. The background showed bright metachromatic stroma in MGG stain.

Histologically, the first four tumors had features of high grade SDC with prominent comedonecrosis and high mitotic activity. Two of the tumors revealed lymphatic and perineural invasion.

Fifth case was low grade SDC and it was cystic on gross examination and showed intraductal proliferation exhibiting cystic ducts with micropapillary, tufted and plaque like intraluminal proliferation. Some of the ducts were distended by solid or pseudocribriform proliferation with varied cystic dilatation and exhibited mild nuclear atypia. There were no goblet cells and mucin stains were negative.

DISCUSSION

SDC is an uncommon but distinctive type of salivary gland tumor that mimics the histologic patterns of intraductal and infiltrating ductal carcinoma of the breast. It is one of the most aggressive types of salivary gland carcinoma with a marked tendency toward distant metastases and local recurrence. Kleinsasser *et al.*[8] first described SDC in 1968. Patients commonly present with rapidly growing mass, often with facial nerve involvement, localized pain and cervical adenopathy.[4,9] Approximately, 76% of the

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patients reported with this condition have been men. The age range at presentation is 22–91 years with a peak incidence in the sixth and seventh decades.[10] Young age at diagnosis, primary tumor >3.0 cm and origin in submandibular gland, all worsen the prognosis.[1,8] Even with aggressive therapy, prognosis is poor with a mortality rate of 60–70%.[3,11-14]

On gross examination, the tumors are usually poorly circumscribed and often multinodular, sometimes with scattered cysts and focal areas of necrosis. They often induce fibrotic reaction.[15]

Mucicarmine and alcian blue PAS stains occasionally demonstrate luminal or interstitial reactivity, but the tumor cells generally are negative although Hui *et al.*[16] reported occasional intracellular mucin. Perineural infiltration and lymphatic infiltration are frequently present.

Twenty five cases describing the cytomorphology of SDC by FNAC have appeared in the literature.[17-22] The cytomorphologic features described in this reports include broad flat sheets of cells, tightly cohesive three-dimensional clusters, papillary and cribriform configurations, large polygonal or low columnar cells with abundant, granular cytoplasm and eccentric, hyperchromatic nuclei. Conversely, polygonal cells with round to oval hypochromatic nuclei having prominent nucleoli have also been described. Nuclear atypia has ranged from mild to moderate to "malignant". A necrotic background has been observed in some, but not all cases. A report by Elsheikh *et al.* discusses the differential diagnostic considerations in SDC by FNAC. These authors included high grade mucoepidermoid carcinoma, acinic cell carcinoma, oncocytic neoplasms, papillary cystadenocarcinoma and polymorphous low grade adenocarcinoma in the differential diagnosis.

Although oncocytic neoplasms are the only benign entities in this differential diagnosis, Elsheikh *et al.* mention only briefly the characteristic features distinguishing SDC from oncocytic neoplasms. They stated that SDC usually shows a higher nuclear/cytoplasmic ratio, less granular cytoplasm and many three-dimensional clusters. They emphasized that cribriform pattern and comedonecrosis are absent from oncocytic lesions.[19]

A series by Fyrat *et al.* included one case that was misdiagnosed as an oncocytic neoplasm and another case in which atypical Warthin tumor was included in the differential diagnosis. However, it can be difficult to distinguish apocrine cells from oncocytes in cytologic smears and oncocytes are much more commonly observed in salivary gland aspirates. Both apocrine cells and oncocytes exhibit granular cytoplasm and round nuclei with prominent nucleoli, but oncocytes generally show more finely granular cytoplasm than apocrine cells. The later may exhibit apical cytoplasmic protrusions or snouts which are not seen in oncocytes, but such apical protrusions may be more evident in histologic or cell block material than in smears.[20]

The authors concluded in retrospect that the presence of cribriform areas and a background of necrosis should have prompted a consideration of SDC in the first case. Oncocytic appearing areas in SDC are generally apocrine rather than being truly oncocytic.[22]

The most useful feature for distinction SDC from an oncocytic neoplasm by FNAC is the presence of cribriform groups. Absence of cribriform and papillary groups, however, leads to inconclusive diagnosis and, as noted in previous reports, this feature is also more apparent on cell block material than in histologic smears.[17,18,21,23]

High grade mucoepidermoid carcinoma was described by Elsheikh *et al.*[19] as the most difficult neoplasm to be distinguished cytologically from SDC. In the absence of papillary groups or cribriform areas, one may not be able to distinguish such an aspirate from high grade mucoepidermoid carcinoma or squamous carcinoma.[19]

None of the three subsequent reports describing the cytomorphologic findings on SDC confirmed the presence of intranuclear inclusions or emphasized the importance of nuclear eccentricity.[17-19]

Some of the previous reports of SDC claim that cytologic findings are sufficiently characteristic to suggest a specific diagnosis.

In general, FNAC of parotid masses have a high accuracy with over 99% specificity and 85% sensitivity.[24,25] Immunohistochemistry (IHC) with AR, GCDFP-15 and p63, as well as morphometric analysis of these tumors can be very useful adjuncts in cytologic diagnosis of SDCs. Mucin rich variant of SDC with large pools of extracellular mucin has been described and this variant carries poor prognosis. IHC with carcinoembryonic antigen (CEA), cytokeratins, S-100 protein, estrogen receptor (ER), progesterone receptor (PR) and HER 2/neu have low sensitivity and specificity, while mucin antigen profile MUC2, MUC5B, and MUC6 have shown positivity in mucin rich variant. IHC studies have revealed a consistent expression of androgen receptor (AR) and GCDFP-15. Negative expression of p63 is another sensitive test in the diagnosis of SDC.[26,27]

Gal *et al.*[28] described intranuclear inclusions and nuclear eccentricity as a characteristic cytologic finding in SDC. He also described naked nuclei with anisokaryosis, chromatin clumps and clear vacuolar zones in his case report.

None of our five cases demonstrated the presence of intranuclear inclusions though nuclear eccentricity was observed in one of the five cases.

Klijanienko[29] described intranuclear vacuoles and binucleate cells. He also described abundant cytoplasm with basophilic cytoplasm on MGG stain with numerous cytoplasmic vacuoles in addition to oncocytic cells with abundant eosinophilic cytoplasm. Some of the tumors showed dense mucoid background

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with microvacuolated cells and extensive necrosis, resulting in misdiagnosis with mucoepidermoid carcinoma and squamous cell carcinoma, respectively.[29]

Morphometric analysis of area of nucleus revealed statistically significant differences with nuclear area in SDC being larger than high and intermediate grade mucoepidermoid carcinomas while being smaller than that of squamous cell carcinoma ex-pleomorphic adenoma.[30] SDC is more common in men with a peak incidence in sixth and seventh decades.[31]

In our series, we observed that four of the five cases were patients presenting at a younger age group and two were females. The relative morphologic and clinical heterogeneity of SDC may preclude specific cytologic diagnosis. Although adequate sampling may ensure diagnosis of a high grade carcinoma with a possibility of SDC, the distinction of SDC with mild nuclear atypia or low grade histology may be difficult or impossible on the basis of cytomorphology alone.[32] However, ancillary studies such as quantitative morphometry, IHC with a panel of antibodies, AR, GCDFP-15 and p63, are helpful in the definitive diagnosis of SDC by FNAC.

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