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DIAGNOSTIC PROBLEMS IN CYTOLOGICAL DIAGNOSIS OF MUCOEPIDERMOID CARCINOMA: REPORT OF 6 CASES WITH HISTOPATHOLOGICAL CORRELATION

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ABSTRACT:

Background: Mucoepidermoid carcinoma (MEC) is a malignant salivary gland neoplasm with extreme morphologic heterogeneity and hence rendering a definitive fine needle aspiration cytology (FNAC) diagnosis of this neoplasm is really challenging. The present study was undertaken to elucidate the cytological features of MEC and explore the diagnostic accuracy and pitfalls by comparing with subsequent histopathology. **Material and Methods:** The present study was conducted over a period of 1.5 years wherein we obtained six histopathologically confirmed cases of MEC. These patients were initially subjected to FNAC. The cytologic features studied included presence of mucous cells, intermediate cells, and squamous cells. Presence of background mucinous material was also noted. The cytological features were compared with the subsequent histopathology. **Results**: Of the 6 cases of MEC, a definite cytological diagnosis was possible only in 3 cases. Of the remaining 3 cases, 1 cases was broadly diagnosed in cytology as Chronic sialadenitis, 1 cases was underdiagnosed as pleomorphic adenoma and 1 case was diagnosed as nonspecific malignant epithelial neoplasm. **Conclusion:** A satisfactory aspirate with all three types of cells; mucous, intermediate and squamous cells may not be obtained in all cases of MEC for providing a definite diagnosis. Hence, a good clinicoradiological correlation, a high index of suspicion and repeated aspirations especially in cystic lesions may be particularly helpful in difficult cases. In addition, while dealing with mucinous cystic lesions with low cellularity, the importance of early excision should be communicated to the clinician since the possibility of low-grade MEC cannot be excluded.

Key words: Cystic lesions; diagnostic challenges; fine needle aspiration; histopathology.

INTRODUCTION:

Fine needle aspiration cytology (FNAC) is an important diagnostic tool for the preoperative assessment of salivary gland lesions and it helps the clinician to plan further management. The procedure is safe and economical with acceptable diagnostic accuracy, especially in experienced hands. However, the employment of FNA for the diagnosis of salivary gland lesions remains controversial with the opponents stating that it

has a high false negative rate and may fail to diagnose specific tumor type.**(1,2)**

Mucoepidermoid carcinoma (MEC) is the most common malignant neoplasm of salivary gland origin, and it accounts for 5-10% of all salivary gland neoplasms with the majority of them involving the parotid gland.**(3)** It has been observedas one of the most problematic tumors for cytological diagnosis.**(4)** This diagnostic difficulty is more common in low-grade tumors that usually present as cystic lesions. Edwards and Wasserman,**(5)** and Mavec *et al*.**(7)** stated that most false negative diagnosis in cytology of salivary gland lesions were related to cystic lesions due to failure to obtain diagnostic material. A partially solid and cystic tumor may be misdiagnosed as being entirely cystic if the solid component is not sampled and it was advocated by them that in all FNACs tentatively diagnosed as a mucinous cystic lesion, the referring clinician should be informed that a low-grade MEC cannot be ruled out. Suspicious masses with negative results in FNAC should be re-aspirated.**(8)** The present study was undertaken to elucidate the cytomorphological features of MEC and explore the diagnostic accuracy and pitfalls by comparing with subsequent histopathology.

Materials and Methods

The study cohort included cases of salivary gland lesions that where referred to the cytology laboratory of our institute over a 1.5 years period. They were subjected to FNAC after recording the relevant clinical details. Among these, 6 cases were MEC.

Fine needle aspiration cytology was performed using a 23 gauge needle attached to a 5 mL syringe. Wet smears fixed in 95% isopropyl alcohol were taken up for staining by H&E method. Dry smears were also prepared and stained using May-Grunwald-Giemsa (MGG) stain. The cytologic features studied included presence of mucous cells, intermediate cells, and squamous cells. Presence of background mucinous material was also noted which appears as blue violet in MGG and pale pink in H&E stained smears.

On subsequent follow-up, these patients underwent surgery, and the specimens were sent to the histopathology laboratory. The specimens were fixed in 10% formalin. Paraffin blocks were made, and Hematoxylin and Eosin stained sections were prepared. The cases were grouped into low, intermediate and high grade based on the standard grading system for MEC. Special stain for mucin (mucicarmine, PAS-D or alcian blue at pH 2.5) was done in relevant cases. The cytological diagnosis was compared to the histopathological diagnosis. Cases that were underdiagnosed in cytology were re-evaluated to assess the diagnostic pitfalls.

RESULTS

In the present study, there were 6 histologically confirmed cases of MEC. The age range affected was 25-50 years. The parotid gland was the most common site involved. The appearance of MEC in FNA smears was found to be highly variable and posed difficulties in diagnosis. Of the 6 histologically proven cases, 3 were correctly diagnosed in FNA. Smears showed variable cellularity with mucin-secreting vacuolated cells, intermediate cells, and a few squamous cells. Mucinous material was seen in the background .

One cases of MEC were broadly diagnosed in cytology as Chronic sialadenitis due to aspiration of the mucinous material containing macrophages and inflammatory cells and the similarity of intermediate cells of mucoepidermoid carcinoma to regenerating, metaplastic epithelial cells in chronin sialadenitis. two histologically proven cases of MEC were underdiagnosed as pleomorphic adenoma and nonspecific malignant epithelial neoplasm in cytology. Review of the smears in these cases showed epithelial cells in clusters. Some cells showed squamoid features that were interpreted as metaplastic squamous cells that are commonly seen in pleomorphic adenoma. However, definite vacuolated cells were not seen even after an extensive search. Chondromyxoid

material, typical of pleomorphic adenoma was also not seen.

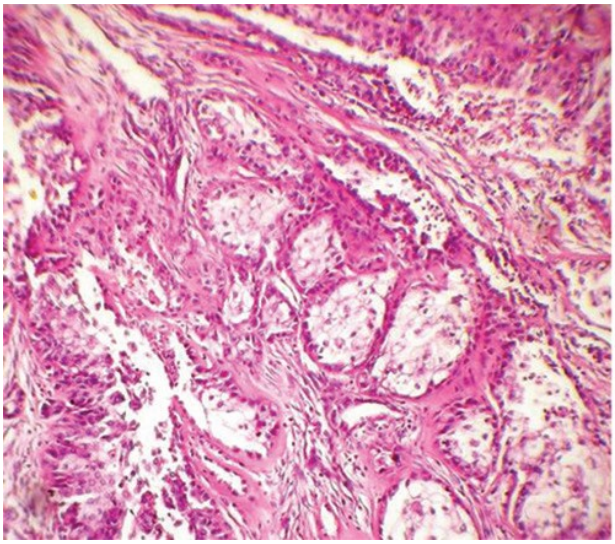
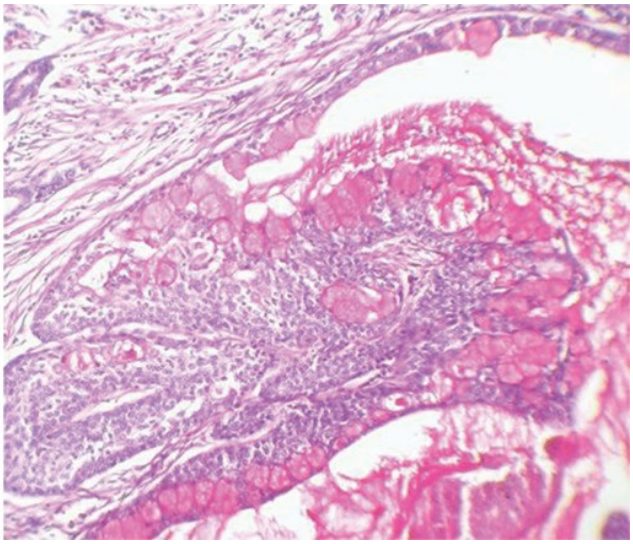


Figure-1



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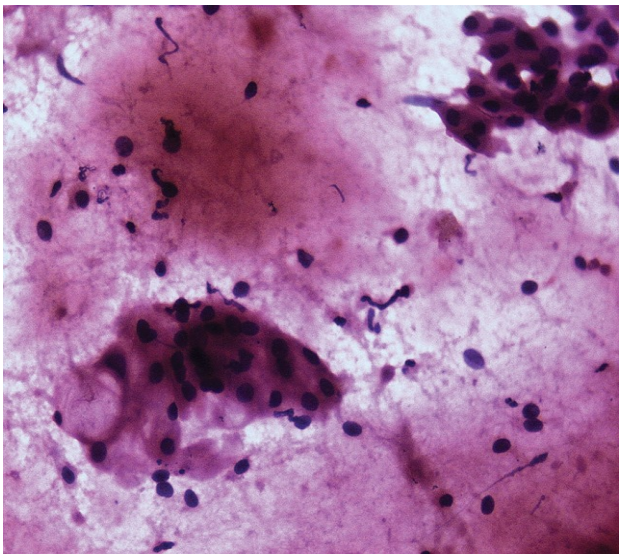

Figure -3

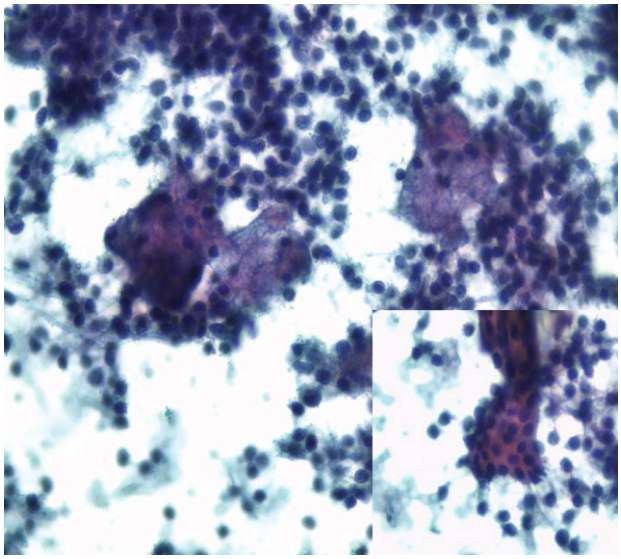

Figure-4

Figure 1: Microphotograph H/P showing neoplastic cells lining cystic spaces (H&E, 10x).
Figure 2:H/P Mucus cells showing intracytoplasmic mucin positivity(H/P Mucicarmine, 10x)
Figure 3: Microphotograph of fine needle aspiration cytology smear showing intermediate cells in clusters (Giemsa, 40x)
Figure 4: Microphotograph of fine needle aspiration cytology smear showing mucin-secreting vacuolated cells, intermediate cells and a few squamous cells in a background of mucin (H&E, 40x)

DISCUSSION

The most common malignant tumor in this study was MEC. Six cases were diagnosed on histopathology Of the 6 cases, 3 cases were correctly diagnosed in FNAC.

Smears showed intermediate cells, mucin-secreting vacuolated cells and a few squamous cells in a dirty background containing mucus. We reported diagnostic accuracy of 50% for MEC in our study.

In one cases of low-grade MEC , a diagnosis of chronic sialadenitis was made in cytology. This could be attributed to the decreased overall cellularity of the smears and presence of mucinous material containing macrophages along with inflammatory cells. According to Orell *et al*.,**(8)** a definitive diagnosis of MEC requires the coexistence in smears of cells showing squamous differentiation and of mucin-secreting cells. Unequivocal evidence of both is not always found,especially in cystic tumors, wherein only a tentative diagnosis can be offered. one cases of histologically proven MEC was underdiagnosed as pleomorphic adenoma and one case was diagnosed as nonspecific malignant epithelial neoplasm in cytology. This is a well-recognized pitfall. Kotwal *et al*.**(10)** observed the same in his case series in which 3/4 lesions were misdiagnosed as pleomorphic adenoma. Review of the cytology smears in both cases showed epithelial cells in clusters and a few cells with squamoid features. These cells were interpreted as metaplastic squamous cells. Moreover, mucin-secretingcells were not identified. Low-grade MEC is one of the most difficult neoplasms to diagnose in FNAC.**(5,11)** The presence of metaplastic squamous cells and sometimes goblet cells in pleomorphic adenoma adds to the diagnostic confusion.**(12)** However, it should be noted that if a squamous component is selectively sampled and if the metaplastic cells appear atypical, the possibility of low-grade MEC may be considered.**(8)**

Grading of MEC**(13)** is based on:

1. Proportion of cystic and solid components.
2. Proportion of different cell types mucin-secreting, intermediate and squamous cells.
3. Presence and degree of cytomorphologic atypia.

Low-grade tumors are usually cystic with predominantly mucin-secreting cells and intermediate cells in a dirty mucinous background. Cells show bland nuclear features. The most important differential diagnosis to be entertained in this context is mucus retention cyst, lymphoepithelial cyst, branchial cyst and Warthin's tumor.**(5)**

Intermediate grade tumors show a greater proportion ofintermediate cells and squamous cells with mild to moderate atypia.**(13)**

Smears of high-grade tumors show obviously malignant squamous epithelial cells and a few intermediate cells. Mucin-secreting cells may be difficult to find, and it may be impossible to distinguish a high-grade MEC from metastatic squamous cell carcinoma.**(8,14)**

With the advances in radiology, there are some features that favor the diagnosis of MEC. Magnetic resonance imaging (MRI) is superior in defining tumor characteristics and extension. Low signal intensity (SI) on T2-weighted images and postcontrast ill-defined margins of a parotid tumor are highly suggestive of malignancy. Low SI on T2-weighted images is the single best MRI finding in MEC.**(15)** Pleomorphic adenoma is typically hyperintense on T2-weighted sequences. Since MRI is expensive and requires more examination time, ultrasound remains to be the first line of investigation. Role of computed tomography in the diagnosis of salivary gland tumors is limited.**(15)** Recently ancilliary studies like reverse transcription polymerase chain reaction (RT-PCR) and fluorescent *in situ* hybridization (FISH) have found to be useful in the diagnosis of morphologically ambiguous cases of MEC. A distinct translocation t**(11;19)** (q21;p13) and the resultant MEC translocated 1-mastermind like gene family) (MECT1-MAML2) fusion transcript have been detected in 38-81% of MEC cases. In addition, studies indicate that fusion-positive tumors behave in a less aggressive fashion with a significantly lower risk of local recurrence, metastases, or tumor-related death compared to fusion-negative ones.

The MECT1-MAML2 fusion transcript has been found in MECs with variant translocations such as t(11;17) and t(11;13), as well as in tumors with apparently normal karyotypes and trisomies.The most frequently encountered trisomies were +7, +8, and +X. In the case of pleomorphic adenoma, pleomorphic adenoma gene-1 and high motility group 2 containing fusion genes serve as diagnostic markers that can be detected using RT-PCR or FISH.

CONCLUSIONS

Fine needle aspiration cytology has an important role in the preoperative evaluation and categorization of various salivary gland lesions. Proper sampling of lesions and adequate cellularity of the smears are the prerequisites for an accurate diagnosis. In cases where all the three components are seen, a definite cytologic diagnosis of MEC should be made. Regarding the cytologic evaluation of cystic lesions in particular, repeated aspirations and centrifugation of the smears are very useful measures to increase the cell yield. In addition, while dealing with mucinous cystic lesions with low cellularity, the importance of early excision should be communicated to the clinician since the possibility of lowgrade MEC cannot be excluded.

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