

## Diagnostic discrepancies in fine needle aspiration diagnosis of parotid gland lesions in a resource limited hilly region

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### Abstract

The characteristic cytological features of parotid gland lesions have been well described in literatures, but there also exist cytological diagnostic pitfalls that make it difficult to form an accurate diagnosis in some cases.

**Aim:** To evaluate the sensitivity, specificity, along with positive predictive value, negative predictive value by Cyto- histological correlation in various lesions with an emphasis on discordant cases.

**Materials and Methods:** A retro-prospective study of 250 non- guided/palpable FNAC of suspected parotid gland enlargements were performed from 2006 to 2018 at tertiary care hospital. The cytological smears were stained with May grunwald giemsa, papanicolaou, hematoxylin eosin stains. Surgically resected specimens were received for histopathology in 103 relevant cases only. The cytologic and Histologic slides were studied, compared and correlated where ever possible and statistical analysis done.

**Result:** Out of 250 patients male to female ratio was 1.4: 1. The different categories of salivary gland lesions included: non neoplastic, benign and malignant constituted 109,108 and 33 cases respectively. Pleomorphic adenoma and mucoepidermoid carcinoma was the commonest benign and malignant neoplasm reported in this study respectively. False negative and false positive results were mainly due to cystic and papillary lesions. The sensitivity, specificity, along with positive predictive value, negative predictive value and diagnostic accuracy of present study was 68.42%, 98.80%, 92.85%, 93.25% and 93.20% respectively.

**Conclusion:** Though palpable FNAC of the parotid gland tumors is simple, rapid and cost-effective in a developing country but rate of characterization of specific type of parotid gland tumor is lower due to overlapping cytomorphology.

**Keywords:** Parotid swelling, Histopathology, Cytology, Morphological discordance.

### Introduction

Salivary glands an exocrine glands located in head and neck region are of major and minor types and the tumors originating from these glands comprise 6% of all head and neck neoplasms.<sup>1</sup> The superficial location, easy accessibility and high diagnostic accuracy make FNAC a popular method for evaluation in major salivary glands swelling. It has established its superior role over various types of biopsies like incision biopsy, frozen biopsy etc.<sup>2</sup> Most of the salivary gland lesions are benign in nature, carcinoma being uncommon. Salivary gland neoplasms possess diverse histological patterns which makes distinction between benign and malignant tumors difficult merely on the basis of FNAC, thus at times leading to unsatisfactory reporting.<sup>3</sup>

Although FNAC has lower rate of complication to the patient but as far as parotid gland lesions are concerned it is not free of diagnostic discrepancies especially in cases of benign tumor like- Pleomorphic adenoma, cystic lesions. Problem can be on both levels i.e., sampling error as well as error in interpretation due to overlapping features. There are several benign malignant look a-like tumors such as basal cell adenoma and adenoid cystic carcinoma that can be confused on FNAC.<sup>4</sup> Sometimes inflammatory lesions

of parotid may mimic epithelial malignant tumors as desquamated epithelial cells are commonly seen in these cases and may produce diagnostic confusion.<sup>5</sup> Malignant tumors can also be easily confused with benign tumors hence FNAC report should always be analyzed correlating clinical and radiological findings with other investigations.

The current study was done to evaluate non guided parotid gland swellings with fine needle aspiration cytology and comparison of its histological profile wherever available with an emphasis on discordant cases in a resource limited area.

### Materials and Methods

**Place of Study:** Department of Pathology, Government Medical College, Haldwani and associated Sushila tiwari hospital.

**Study Design:** Retrospective study (2006-2018)

**Study Population:** All patients of parotid gland tumors from Kumaon region and surrounding areas referred to Department of Pathology, Government Medical College Haldwani and Dr. Sushila Tiwari Government Hospital, Haldwani for FNAC and Histopathology examination after taking due informed consent.

**Statistical Analysis:** Statistical analysis will be done in terms of proportions or percentage. Statistical data will

be shown by diagrammatic representation wherever necessary.

#### **Inclusion Criteria**

1. All cases of palpable parotid gland swellings will be included.

#### **Exclusion Criteria**

1. Patient who will not give consent.
2. Neck swellings other than parotid gland swellings will be excluded.
3. Non cooperative patients.

#### **Equipment required for fine needle cytology of salivary gland lesions:**

1. 20 ml disposable plastic syringe
2. 23 Gauge disposable sterile needle
3. Cameco syringe holder
4. Spirit to clean the skin
5. Glass microscopic slides for smear preparation
6. 95% ethanol as fixative for smears
7. Sterile cotton swab and gauge pads
8. Sterile containers with tight cap to collect fluid obtained from cystic lesions
9. Coplin jar.

#### **Methodology**

**Consent:** An informed consent was taken from the subjects after enrolment.

**Technique of FNAC:** This study was carried out at tertiary care teaching hospital. Study was carried out on total 250 patients over a period of 12 years during 2006-2018 where after taking an informed valid written consent, the patient were clinically examined in detail. All medical reports were studied. The patient were explained the procedure in full detail. Under aseptic precautions FNAC was done from different sites of salivary gland swelling using a 20 ml syringe and 22-23 gauge needle fitted to aspiration handle directing the tip of needle towards the lesion and maintaining constant negative pressure by pulling back the plunger of the syringe. The material were taken with minimum passes (to minimize hemorrhage) without needle withdrawal. In the preparation of the cellular specimen from an FNA, the most important principle is that the diagnostic material should be within the barrel of the needle, not in the barrel of the syringe, to ensure that this relationship remains undisturbed, the needle should be disconnected from the syringe, the syringe refilled with air, and the two should be then reconnected. So the same was followed and the aspirate were then smeared on clean glass slides by gently laying one slide over the slide holding the material, permitting the weight of the spreader to spread the material, pulling the slides apart horizontally. FNA dried smears were stained with May Grunwald's Giemsa (MGG) stain and wet smears were stained with papanicolaou stain, haematoxylin and eosin (H&E) respectively and few special stains like PAS, PAS-AD, mucicarmine. All lesions were studied

under three categories which included benign, malignant and non- neoplastic. The cytological and Histopathological stained slides were studied, analyzed and correlated wherever it was available.

**Staining:** Steps of staining procedures used:

#### **H & E staining**

1. Preparation of Harris Hematoxylin
- Ingredients Hematoxylin powder: 2.5 g  
Absolute ethyl alcohol: 25 ml  
Potassium alum: 50 g  
Distilled water: 500 ml  
Mercuric oxide (or sodium iodide): 0.5 g  
Glacial acetic acid: 20 ml

#### **Procedure**

1. Dissolve hematoxylin in absolute alcohol.
  2. Add potassium alum (already dissolved in warm distilled water).
  3. Boil the mixture.
  4. Add mercuric oxide (or sodium iodide).
  5. Cool the solution by dipping in cool water.
  6. Add glacial acetic acid
  7. Preparation of EA -50
- 0.3mol Eosin Y: 20 ml  
0.04mol light green: 10 ml  
Phosphotungstic acid: 2.0 g  
Ethanol: 750 ml  
Methanol: 250 ml

#### **H & E Staining procedure**

1. Prepare the smear.
2. Wet fix in 95% ethyl alcohol for minimum 30 minutes.
3. Keep the smears in distilled water for two minutes.
4. Keep in Harris hematoxylin dye for 3-8 minutes.
5. Keep in distilled water for bluing for 5 minutes.
6. Dip the smears 2-3 times in 0.1% HCL water.
7. Rinse the smear with distilled water (2-3 dips).
8. Keep the smears in 1% aqueous Eosin for 1-2 minutes.
9. Wash the smears with distilled water.
10. Air dry the smear.
11. Mount with DPX.

#### **Papanicolaou staining**

1. Prepare the smear.
2. Wet fix the smear in 95% ethyl alcohol and keep for 30 minutes.
3. Rehydrate the smear in the sequence of 95%- 70%- 50% ethyl alcohol for 2 minutes each.
4. Keep the smear in distilled water for 2 minutes.
5. Keep the smear in Harris Hematoxylin for 3-10 minutes.
6. Keep the smear in distilled water for 5 minutes for bluing.
7. Dip the smear in 0.2% HCL water 2-4 times.
8. Keep the smear in 0.1% NH<sub>3</sub> water for maintenance of pH.
9. Dehydrate with sequence of 50%-70%-95% ethyl alcohol for 2 minutes each.

10. Keep the smear in OG-6 for 2 minutes.
11. Keep in 95% alcohol for 3 minutes.
12. Keep in EA-50 for 2 minutes.
13. Wash the smear with 95% ethyl alcohol for several changes.
14. Air dry the smear.
15. Mount with DPX.

### May-Grünwald-Giemsa staining

Stock solution preparation

#### 1. Acetate buffer

**A:**

Sodium di-hydrogen orthophosphat: 3.12 g

Distilled water: 100 ml

**B:**

Di-Sodium hydrogen orthophosphate: 2.83 g

Distilled water: 100 ml

#### Working acetate buffer

Solution A: 25.5 ml

Solution B: 24.5 ml

Distilled water: 50 ml

pH: 6.8

#### Giemsa stain

1. Dissolve 4 g Giemsa powder in 250 ml glycerol at 60<sup>o</sup> C with regular shaking.
2. Add 250 ml methyl alcohol.
3. Cap the bottle with air tight cap.
4. Shake the mixture and allow to stand for 7 days.
5. Filter before using.

#### Working Giemsa solution (Giemsa: Buffer= 1:9)

Stock solution: 4 ml

Acetate buffer: 96 ml

pH: 6.8

#### May-Grünwald stain

1. May-Grunwald powder: 0.5 g

2. Methyl alcohol: 100 ml

#### Working May-Grunwald solution

One part of May-Grunwald stock solution + one part of acetate buffer.

#### Steps of staining

1. Prepare the smears.
2. Air dry the smears.
3. Fix the air-dried smear specimen in methanol for 10 -20 minutes.
4. Pour May-Grünwald dye (Phosphate buffer+ May-Grünwald dye in 1:1) over the smear and keep for 10 minutes.
5. Wash the smear with running water and rinse with distilled water.
6. Pour working Giemsa stain (Giemsa + buffer in 9:1) over the smear and keep for 10 minutes.
7. Wash the smear with running water and rinse with distilled water.
8. Air dry the smear.
9. Mount with DPX.

### Result

Out of 250 patients included in the study male to

female ratio was 1.5:1. (Table 1) Age group varies from 7-81 years and majority cases were in 41-50 years of age. The most common presenting complaint was painless, progressive swelling. Benign lesions constituted 109 while non-neoplastic lesions and malignant lesions constituted 108 and 33 respectively. (Table 2) The most common benign lesion reported in present study is pleomorphic adenoma that was correlated with various other previously reported studies.<sup>6-8</sup>

In present study among all the parotid gland lesions FNAC, the rate of benign lesion in this study is 43.6%, in concordance with other studies ranging from 43% to 89%.<sup>6-8</sup> Rate of occurrence of malignant lesion in this study is 13.2%, in relation with other studies that reported the occurrence of malignant lesion between 14% - 35%.<sup>9</sup>

Out of 250 cases, histopathology was available in 103 cases and out of which 84 cases were correlated in both cytology and histology with discordant in 19 cases (Table 3, 4). One case was given as inconclusive on cytology but it turned out to be vascular malformation with papillary endothelial hyperplasia on histopathology. Two cases of suppurative pathology were misdiagnosed as pleomorphic adenoma. Six cases of chronic sialadenitis were misdiagnosed as pleomorphic adenoma. One case of Warthin's tumor was diagnosed as low grade mucoepidermoid carcinoma. Four cases of adenoid cystic carcinoma (ACC) were diagnosed as cellular pleomorphic adenoma. A case of epithelial myoepithelial carcinoma was diagnosed as pleomorphic adenoma. Similarly one case of mixed malignant tumor / carcinoma of parotid gland with foci of osteoclastoma / malignant giant cell tumor was diagnosed as mucoepidermoid carcinoma. A diagnosis of low grade carcinoma - (D/D myoepithelial cell carcinoma /acini cell carcinoma/Papillary adenocarcinoma/low grade Mucoepidermoid carcinoma) was given but on histology it was diagnosed as a Case of Polymorphous low grade adenocarcinoma (PLGA). One case of high grade mucoepidermoid carcinoma was diagnosed as poorly differentiated carcinoma. One Case in which possibility of lymphoepithelioma-like carcinoma can't be ruled out was diagnosed as lymphoepithelial cyst on FNAC.

In the present study ideal correlation of cytology with histopathology is not possible because of smaller sample size (only 103 biopsy cases out of total 250 cases) as biopsy is avoided in non-neoplastic cases and most of the cases which were diagnosed malignant in cytology were referred to the higher centres for further evaluation and treatment. 147 cases does not have histological profile as FNAC were requested by clinicians in non-neoplastic lesions also. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of present study was 68.42%, 98.80%, 92.85%, 93.25% and 93.20% respectively. (Table 1)

**Table 1: Demographic details:**

<b>Total</b>	250
<b>M:F</b>	1.5:1
<b>Concordant</b>	84
<b>Disconcordant</b>	19
<b>Sensitivity</b>	68.42%
<b>Specificity</b>	98.80%
<b>Positive predictive value</b>	92.85%
<b>Negative predictive value</b>	93.25%

**Table 2: FNAC diagnosis and categorization:**

<b>Category</b>	<b>Subtypes</b>	<b>Total</b>
Non neoplastic	Sialadenosis(33) Parotidinitis(1) Suppurative pathology(15) Sialadenitis(49) Mucocele(6) Lymphoepithelial cyst(2) Lymphoepithelial disease(1) Inconclusive(2)	109
Benign	Pleomorphic adenoma (91) Warthins (15) Benign tumor-(Pleomorphic adenoma/warthins)(1) Parotid tumor(1)	108
Malignant	Low grade tumors(differentials- MEC, acinic cell carcinoma, papillary adenocarcinoma, myoepithelial cell carcinoma) (1) Differentials- (basal cell CA, polymorphous low grade adenoca, solid variant of adenoid cystic carcinoma) (1) MEC (20) Acinic cell carcinoma (4) Adenoid cystic carcinoma (3) Poorly differentiated adeno carcinoma? CA ex Pleomorphic adenoma (2) Differentials-Low grade MEC, Acini cell carcinoma. Papillary adenocarcinoma, Myoepithelial cell carcinoma (1) Poorly differentiated carcinoma (1)	33

**Table 3: Cytohistological concordant correlation:**

<b>S. No.</b>	<b>FNAC</b>	<b>Histology</b>	<b>Total Cases (84)</b>
1	Chronic Sialadenitis	Chronic Sialadenitis	29
2	Warthin's tumor	Warthin's tumor	4
3	Pleomorphic adenoma	Pleomorphic adenoma	41
7	Poorly differentiated adenocarcinoma? CA ex Pleomorphic adenoma	High grade(poorly differentiated NOS-CA)CA EX Pleomorphic adenoma	2
8	Acinic cell carcinoma	Acinic cell carcinoma	2
9	MEC	MEC	6

**Table 4: Cytohistological Discordant cases:**

<b>Discordant(19)</b>	
<b>FNAC</b>	<b>Histology</b>
Non diagnostic (1)	Vascular malformation with papillary endothelial hyperplasia
Pleomorphic adenoma (2)	Suppurative pathology
Pleomorphic adenoma (6)	Chronic Sialadenitis

MEC (1)	Warthin's tumor
Pleomorphic adenoma (4)	Adenoid cystic carcinoma
Pleomorphic adenoma (1)	Epithelial myoepithelial CA
MEC (1)	Mixed malignant tumor-CA of salivary gland with foci of osteoclastoma/malignant giant cell tumor
Low grade CA-(D/D myoepithelial cell CA/Acinar cell CA/Papillary adenocarcinoma/low grade MEC) (1)	Polymorphous low grade adenocarcinoma
Poorly differentiated CA (1)	High grade MEC
Lymphoepithelial cyst (1)	Possibility of lymphoepithelioma- like carcinoma can't be rule out

## Discussion

The current study was done to evaluate parotid gland swellings with fine needle aspiration cytology and comparison of its histological profile wherever available with an emphasis on discordant cases. The specificity and diagnostic accuracy value of present study correlated with various other previously reported studies.<sup>10-14</sup>

FNAC specimens from parotid glands are difficult to diagnose for a number of reasons, including problems in sampling as well as difficulty in histological classification. A major roadblock in the histologic classification of salivary gland neoplasms is that the majority of these arise from the same cell lines (epithelial and myoepithelial).<sup>15</sup>

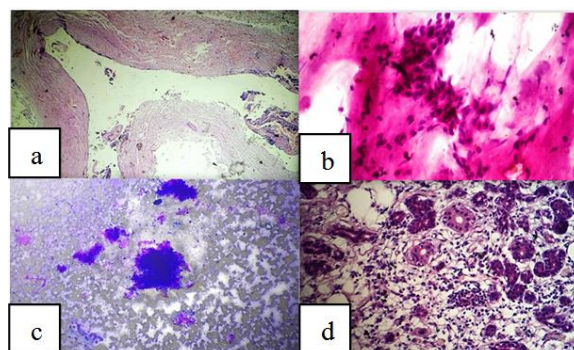
One of the common non-neoplastic lesions was chronic sialadenitis followed by chronic sialadenitis.<sup>16</sup> In the present study benign lesion were relatively more common than malignant lesion as correlated with various other studies.<sup>17-19</sup> The overall gross discrepancy between cytology and histopathology diagnosis was found in 11 cases. (Table 4)

One case was given as inconclusive on cytology but it turned out to be vascular malformation with papillary endothelial hyperplasia on histopathology (Fig. 1 a). This may be due to blood and its components in the smears. The reasons why a representative sample is not always obtained may be related to the positioning of the needle outside the target area and the presence of haemorrhagic, necrotic or cystic areas in the tumour so adequate and representative FNAC is a must to reach a diagnosis.

Two cases of suppurative pathology (Fig. 1 b ) was misdiagnosed as pleomorphic adenoma as smears of which showed cohesive sheets of ductal epithelial cells displaying unremarkable morphology along with fibroblastic and occasional myxoid stromal fragments against a haemorrhagic background containing scattered cystic macrophages and few groups of acinar cells. This may be due to inadequate sampling leading to inadequate inflammatory component in smears and

Romanowsky stain which led to diagnosis of pleomorphic adenoma.

Six cases of chronic sialadenitis (Fig. 1 c,d) was misdiagnosed as pleomorphic adenoma as smears of which show cohesive sheets of ductal epithelial cells displaying unremarkable morphology along with fibroblastic and occasional myxoid stromal fragments against a haemorrhagic background containing scattered cystic macrophages and few groups of acinar cells. Presence of myxoid stromal fragments and lack of adequate, representative sample led to misdiagnosis in this case. FNA of chronic sialadenitis may yield fibrotic stroma that may show metachromasia on rapid Romanowsky stain and, when seen together with ductal cells (which dominate such smears because of acinar cell atrophy) showing metaplastic squamous differentiation, a diagnosis of pleomorphic adenoma may be considered.<sup>20</sup> The adenomatoid hyperplasia of the mucous salivary gland, poorly cellular samples with only mucin and a few glandular and squamous elements may often be incorrectly identified as a benign condition such as mucocele or chronic sialadenitis. At other times there may be mucin present and a moderate amount of squamous and/or glandular epithelium.



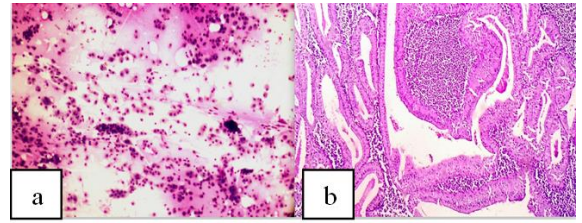
**Fig. 1(a): Vascular malformation: Papillary endothelial hyperplasia (a) & (b) (H&E X 100); (b): Inflammatory pathology (suppurative): Ductal epithelial cells embedded in fibromyxoid stromal like tissue fragments (misdiagnosed as PA) on a background containing occasional scattered cystic macrophages and acinar cells. (H&E X 400); (c):**

fibrotic stroma that showed metachromasia on rapid

**Chronic sialadenitis: Ductal epithelial cells embedded in fibromyxoid stromal tissue like fragments (misdiagnosed as PA) on a background containing occasional scattered cystic macrophages and acinar cells along with few inflammatory cell infiltrate. (MGG X 100); (d): Chronic sialadenitis: Atrophy of acini along with fibrotic stroma and chronic inflammatory infiltrate (H&E X 400)**

Mucoepidermoid carcinoma (MEC) is the most common malignant lesion reported in this study that is correlated with Nguansangiam et al.<sup>9</sup> Mucoepidermoid carcinomas are amongst the most difficult to diagnose on FNA material because the cellular components (squamous epithelium, glandular epithelium and mucin) vary greatly in their amount and their degree of differentiation. The well-differentiated variety is most difficult to delineate as a neoplasm and the poorly-differentiated tumor is difficult to tell what type of neoplasm it is. Three cytologic features have been cited as being more predictive of mucoepidermoid carcinoma: intermediate cells, clusters of overlapping nuclei, and squamous cells. The squamous elements that are present rarely show obvious keratinization. The exact definition of intermediate cells is confusing in the literature. These cells have been described as being small basal-like cells all the way up through immature squamous metaplastic cells.<sup>21</sup>

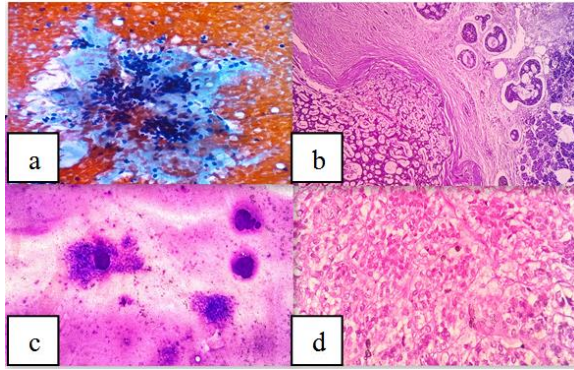
Diagnosis of low grade mucoepidermoid carcinoma is still difficult because it may be misdiagnosed as chronic sialadenitis, Warthin's tumor and pleomorphic adenoma.<sup>22</sup> As observed in the present study where one case of Warthin's tumor (Fig. 2 a, b) was diagnosed as low grade mucoepidermoid carcinoma on cytology, due to numerous groups, clusters as well as singly dispersed mucinophages- like cells along with a few small groups of intermediate-like cells on a mucoproteinaceous background containing sparse lymphocytes. In this case aspirate was mainly from cystic spaces which result in error in diagnosis due to presence of scattered and small groups of oncocytic cells with cytoplasmic vacuolation which leads to the misdiagnosis of mucinophages. So multidirectional multiple sampling is important to overcome problems of misdiagnosis due to selective sampling. Smears from Warthin's tumor usually show monolayered sheets of oncocytic cells with many lymphocytes in the murky background of amorphous granular debris, and rarely squamous metaplastic cells.<sup>23-25</sup>



**Fig. 2(a): Warthin's tumor: Singly dispersed mucinophages and small groups of intermediate cells simulating low grade MEC. (H&E X 100); (b): Warthin's tumor: Large cystic spaces lined by apocrine epithelial cells with eosinophilic homogenous material containing inflammatory cells and? mucinophages. Subepithelial collection of lymphoid cells (H&E X 400)**

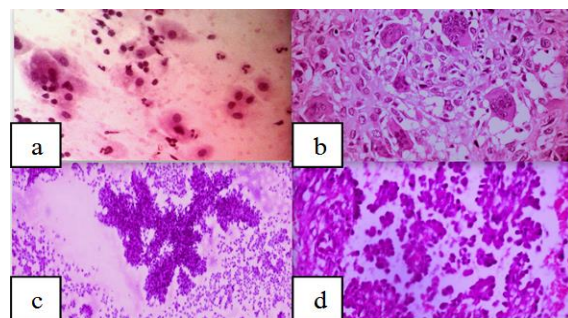
Four cases of adenoid cystic carcinoma (ACC) was diagnosed as Cellular pleomorphic adenoma. This may be because of absence of spherical / cylindrical shaped myxoid stromal component, cellular smears with cluster and sheets of uniform epithelial cells both embedded in and lying adjacent to the stroma which led to the misdiagnosis of Cellular pleomorphic adenoma (PA) (Fig 3 a). Biopsy revealed picture of ACC displaying multiple sheets of cells arranged in cribriform pattern and swiss cheese appearance containing globular myxoid ground substance with capsular and vascular invasion. (Fig 3 b) Whereas in ACC have stroma with straight sharp edges and are surrounded by the basaloid epithelial cells. Small amount of fibrillary stromal material is also seen in ACC similar to that seen in PA.<sup>26-28</sup> Bini Faizal and N Stow also described that in benign tumors, the cells interdigitate intricately with the fibrillary connective tissue associated with them. This is in contrast to the sharp interface between tumor cells and extracellular matrix material that forms the spheres and cylinders of ACC.<sup>29, 30</sup> Plasmacytoid myoepithelial cells are the most helpful cytomorphologic feature for distinguishing PA from ACC.<sup>29,31</sup> Lowhagen et al. advocate that if the cribriform structures appear together with any features of PA, a diagnosis of PA should be given.<sup>29,32-34</sup> The cytologic identification of ACC rests on adequate sampling and careful inspection of all material to rule out the possibility of benign PA.

A cases of epithelial myoepithelial carcinoma (Fig 3 c,d) was diagnosed as pleomorphic adenoma. Smears were comprised of acellular metachromatic material surrounding small cell cluster against a myxoid background and singly scattered large with vacuolated cytoplasm. The clue that in case of pleomorphic adenoma myoepithelial cell are closely intermingled with fibrillary myxoid background substance and presence of two cell population and 3-D arrangement of basement acellular material surrounds cellular aggregates in case of myoepithelial carcinoma was not taken into account leads to misdiagnosis.



**Fig. 3(a): Adenoid cystic carcinoma: basaloid cells embedded in and surrounded by myxoid material diagnosed as cellular pleomorphic adenoma. (PAP X 400); (b): Adenoid cystic carcinoma: Multiple sheets of cells arranged in cribriform pattern and swiss cheese appearance containing globular myxoid ground substance with capsular and vascular invasion. (HE X 100); (c): EMC: Blobs of chondromyxoid stromal fragments on a myxoid background simulating Pleomorphic Adenoma. (MGG X 100); (d): EMC: Cells arranged in tubular, cribriform and focal papillary pattern. Tubules lined by central cuboidal to low columnar epithelial cell and outer clear myoepithelial cells (H & E X400)**

Similarly case of mixed malignant tumor/carcinoma (Fig 4 a, b) of salivary gland with foci of osteoclastoma/malignant giant cell tumor was diagnosed as mucoepidermoid carcinoma as smears show atypical epithelial cells in dyscohesive sheets, groups as well as scattered forming stream of cells within mucinous material on a mucohaemorrhagic background along with fair number of cells have finely vacuolated cytoplasm (? mucin secreting cells). Since giant cells were present in focal small area where needle didn't hit during FNA hence lack of representative sample was reason for misdiagnosis that again highlights the importance of repeat/multidirectional FNA.



**Fig. 4(a): Mixed malignant tumor: Small groups of mucous cells, smaller intermediate cells mimic MEC. (PAP X 100); (b): Mixed malignant tumor: Foci of osteoclastoma or malignant giant cell tumor. (H&E X 400); (c): Polymorphous low grade adenocarcinoma: Anisomorphic plasmacytoid**

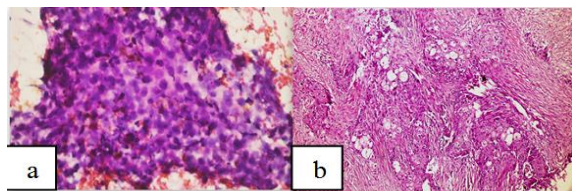
**shaped cells in groups, papillaroid clusters and few cells with nuclear grooves, few with cytoplasmic vacuoles on mucinous background mimicking Low grade CA. (PAP X100); (d): Polymorphous low grade adenocarcinoma: Glandular differentiation (H&E X400)**

In another case, the FNAC smears revealed highly cellular smears composed of anisomorphic plasmacytoid shaped cells disposed of in groups, papillaroid clusters and few cells with nuclear grooves, few with cytoplasmic vacuoles on a background containing mucinous material and few small hyaline globules. Few papillary tissue fragments also show fibrovascular core, and a diagnosis of low grade carcinoma/myoepithelial cell carcinoma /Acini cell carcinoma/papillary adenocarcinoma was given but on histology it was diagnosed as a case of polymorphous low grade adenocarcinoma (PLGA) (Fig 4 c,d). In this case misdiagnosis was perhaps made on the basis that mixed patterns of irregular sheets and pseudopapillary or papillary fragments of tumor cells and metachromatic stroma characterize the cytology of polymorphous low-grade adenocarcinoma.

PLGA, a common salivary gland neoplasm of oral cavity, palate, and upper lips, occurs mostly in older females. Cytological smears can have a prominent papillary architecture, but the papillae are composed of both epithelial and connective tissue components. Its differentiation from PCA is based on the presence of eosinophilic magenta-colored stromal red cores that branches with the associated epithelial papillary structures.<sup>24</sup> Stromal fragments may also be seen in the form of hyaline globules.<sup>35</sup> Hyaline globules were absent in both the epithelial sheets and cores of the papillae in Papillary cystadenoma.

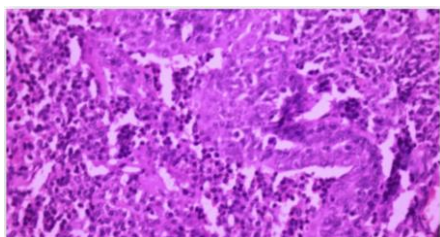
Salivary duct carcinoma occurs predominantly in the parotid. Smears show tubules, glands with occasional presence of the papillary architecture. The individual cells display features of overt malignancy including nuclear enlargement, high nuclear: cytoplasmic ratio, and prominent nucleoli as compared to the bland nuclear morphology in PCA. The background contains some necrosis, apoptotic bodies, and macrophages.<sup>23</sup>

One case of high grade mucoepidermoid carcinoma (Fig 5 a, b) was diagnosed as poorly differentiated carcinoma as smears were highly cellular and show loosely cohesive sheets, papillaroid clusters and groups of malignant cells with high N: C ratio, moderate to marked nuclear pleomorphism, irregular nuclei, 1-3 prominent nucleoli, with minimum to absent cytoplasm on haemorrhagic background containing similar atypical malignant cells. It is described that high grade mucoepidermoid CA can mimic other high grade CA.<sup>36</sup>



**Fig. 5(a): High grade MEC: Loosely cohesive sheets of malignant cells on haemorrhagic background simulating poorly differentiated CA. (MGG X 400); (b): High grade MEC: Sheets of malignant tumor cells with goblet cells and mitosis. (H&E X100)**

One Case in which possibility of lymphoepithelioma-like carcinoma can't be rule out (Fig 6) was diagnosed as Lymphoepithelial cyst on FNAC as smears show polymorphous population of lymphoid cells as well as scattered lymphohistiocytic aggregates on proteinaceous background with occasional groups of ductal epithelial cells. This occurred due to sampling error, where needle might have hit only cystic area. Therefore, it is advisable to suggest excisions for cystic lesions.<sup>37</sup>



**Fig 6: Possibility of lymphoepithelioma-like carcinoma can't be rule out: Focal dysplastic epithelial-myoepithelial Island surrounded by lymphoid cells mimicking lymphoepithelial lesion on FNA (H&E X400)**

Cystic lesions of salivary glands can either be non-neoplastic or malignant.<sup>38</sup> Examples of non neoplastic cysts are lymphoepithelial cysts, retention cysts and mucoceles. Warthin's tumor is commonest cystic neoplasm, but pleomorphic adenoma, mucoepidermoid tumour and acinic cell carcinoma can also be cystic. Malignancy should be suspected and followed by the surgical excision only in the case of numerous atypical cells associate with the absence of chondromyxoid stroma. Presence of the numerous keratin debris or mucoid material may be mistaken for keratin containing cyst, squamous cell carcinoma, or mucoepidermoid carcinoma and biopsy is essential to confirm our diagnosis.

Cystic lesions are well-known sources of false-negative diagnoses. Ways to avoid this unfortunate occurrence include re biopsying any residual cyst mass after draining. It has also been the experience of most observers that if cysts recur, it is wise to remove them. False-positive diagnoses are also a problem with cystic lesions. One of the most common

settings for this diagnostic pitfall is in a cyst with extensive squamous metaplasia. If it becomes irritated for any reason, such as by infection or radiation, considerable pleomorphism may occur and one would be tempted to entertain a diagnosis of squamous cell carcinoma.<sup>21</sup>

## Conclusion

Despite diagnostic pitfalls non-guided palpable FNAC still continues to be widely used diagnostic technique in developing countries due to its quick results and lack of complications, on the basis of which appropriate therapeutic management can be planned earlier. Multidirectional aspiration, repeat aspirations from different parts of gland and liberal sampling can improve results. Knowledge of pitfalls may prove to be helpful to avoid discordant diagnosis and reduce false interpretation and thus can prove to be a blessing in a resource limited area.

## Recommendation

Latest Milan system (2017)<sup>39</sup> given below should be adopted for improving the overall effectiveness of salivary gland FNAC to establish better communication between clinicians and pathologists which will ultimately leads to improved patients care. Six diagnostic has been devised namely: Non- diagnostic; Non-neoplastic; Atypia of undetermined significance (AUS); Neoplastic (Benign, Uncertain Malignant potential); Suspicious for malignancy and Malignant. They have mentioned management for each of these categories.

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