Original Research Article

CYTOLOGICAL STUDY OF SALIVARY GLAND LESIONS IN ACCORDANCE WITH THE MILAN SYSTEM OF REPORTING SALIVARY GLAND CYTOPATHOLOGY

Abstract

Aim: Fine needle aspiration cytology is an essential diagnostic tool for preoperative diagnosis of salivary gland lesions. Due to overlapping cytological features and heterogeneity of the lesions, a universal classification system was proposed, known as the "Milan System of Reporting Salivary Gland Cytopathology (MSRSGC). This system helps clinicians to plan further diagnosis and management according to the risk of malignancy (ROM) in different categories. So, the aim was to stratify the lesions according to the system and calculate the risk of malignancy.

Study Design: Retrospective and prospective study.

Place and duration of study: Department of Pathology, Dr.D.Y.Patil Medical College, Hospital and Research Centre, Pune, between August 2016 and July 2021.

Methodology: A five year study was conducted on 100 cases. FNAC was performed and histopathological correlation was done wherever possible. The cytological diagnosis was reclassified as follows: Category 1: Non diagnostic (ND),Category 2: Non neoplastic (NN),Category 3: Atypia of undetermined significance (AUS),Category 4a: Neoplasm: Benign (NB),Category 4b: Neoplasm: Salivary gland neoplasm of uncertain malignant potential (SUMP),Category 5: Suspicious of malignancy (SM) and Category 6: Malignant (M).

Result: Total 100 cases were studied. Histopathological follow up was available in 38 cases. Case distribution in various categories were ND(0%), NN(36%), AUS(3%), NB(54%), SUMP(1%), SM(3%) and M(3%). Overall ROM reported were 0%, 11.11%, 100%, 0%, 100%, 100% and 100% respectively for each category. The diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value of the study was 94.74%, 75%, 100%, 100% and 100% respectively.

Conclusion: The Milan system is an universal 6-tier reporting system of lesions of salivary gland that helps with risk assessment and guides the clinicians for appropriate treatment.

INTRODUCTION:

Fine needle aspiration cytology (FNAC) is a procedure that is used all over the world for diagnosis of various salivary gland lesions. It is a minimally invasive procedure which is safe, economical and quite accurate in diagnosing numerous non neoplastic and neoplastic lesions.[1-4] Precise diagnosis of non neoplastic lesions can help prevent unnecessary surgeries. It also aids in planning further treatment strategy in case of neoplastic lesions.[5,6] FNAC is highly sensitive and specific in differentiating non-neoplastic from neoplastic lesions and benign from malignant. Various studies have shown sensitivity of FNAC ranging from 84 to 100% and specificity ranging from 90 to 100%.[5-10]

Inspite of such high specificity and sensitivity, diagnosing these lesions can be challenging owing to the diversity and heterogenicity of salivary gland tumors and overlapping morphological features.[11-14] Hence, many studies felt the need of a reporting pattern inorder to develop a risk stratification to classify salivary gland neoplasms and provide risk of malignancy (ROM) so as to plan the management or any ancillary test if required.[15,16]

Inorder to have a standard terminology for reporting salivary gland cytopathology, The American Society of Cytopathology and International Academy of Cytology proposed a six tiered international classification system called the "Milan System for Reporting Salivary Gland Cytopathology" (MSRSGC). (Table 1) This system guides the clinicians to plan the management according to ROM in different categories. It also avoids the confusion often faced by clinicians while interpretation of FNAC reports.[15,16]

Our study was conducted to reclassify the salivary gland lesions from the cytological diagnosis and to assess the ROM in different categories.

MATERIALS AND METHOD:

The study was conducted in Department of Pathology over a period of 5 years, from May 2016 to April 2021. FNAC was performed in 100 patients with salivary gland lesions, which were classified according to MSRSGC categories. Histopathological examinations of these cases were done wherever possible and a comparative study was carried out.

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and regional).

FNAC was done using 10ml syringe with 22 gauge needle from 2-3 different sites to ensure adequate material had been aspirated from different parts of the lesion. Few smears were air dried and stained with Leishman stain and remaining were fixed in 95% alcohol and stained with haematoxylin and eosin (H&E) stain.

The cytological features were evaluated, and cases were reclassified according to MSRSGC as follows:

Category 1: Non-diagnostic (ND)

Category 2: Non-neoplastic (NN)

Category 3: Atypia of undetermined significance (AUS)

Category 4a: Neoplasm: Benign (NB)

Category 4b: Neoplasm: Salivary gland neoplasm of uncertain malignant potential (SUMP)

Category 5: Suspicious of malignancy (SM)

Category 6: Malignant (M).

Out of the 100 cases, 38 specimens were available for histopathology. The specimens were fixed in 10% formalin and processed. The slides were stained with haematoxylin and eosin stain. The results were analysed statistically to calculate ROM for each category as well as to evaluate sensitivity, specificity and positive and negative predictive values in order to assess the diagnostic accuracy of FNAC.

RESULTS:

Distribution of cases in relation to age, sex and location of lesion is depicted in Table 2. The study showed mild male predilection with male to female ratio of 1.2:1. Maximum number of cases were seen in the age group of 21 to 40 years (40%), followed by 35% in age group of 41 to 60 years.

70% cases were seen to involve the parotid gland, 26% in submandibular gland and 04% cases in minor salivary glands.

Categorisation of cases according to MSRSGC is shown in table 3.

NB constituted the largest category (54%), followed by NN category (36%). AUS, SM and M categories were 3% each, SUMP was 1% and there were no ND cases in this study.

Out of 100, 38 cases were available for histopathological follow up. The histopathological comparison and ROM for each category has been shown in Table 3. There were no Non diagnostic cases, so ROM for category 1(ND) was 0%.

In category 2 (NN), out of 36 cases, 09 were available for histopathological examination. 6 cases were diagnosed correctly as non neoplastic lesions. 2 benign neoplasms (pleomorphic adenoma and basal cell adenoma) were diagnosed as non neoplastic lesions. A case of Mucoepidermoid carcinoma was diagnosed as benign cystic lesion. Therefore, ROM reported for this category was 11.11%.

Category 3 (AUS) comprised of 3 cases, only 1 case was available for histological follow up. It was diagnosed as Adenoid cystic carcinoma. So, ROM of this category was 100%.

Histological follow up of 21 cases out of 54 were available in category 4a (NB). All the benign neoplasms were confirmed as benign lesions on biopsy, there making the ROM of this category 0%.

Category 4b was the case where the malignant potential could not be ascertained. Only 1 such case was present in this category which was diagnosed as Adenoid cystic carcinoma. ROM reported for this category was 100%.

Category 5 (SM) had 3 cases. All these cases were available for follow up. The cases were diagnosed on histopathology as Adenoid cystic carcinoma, low grade mucoepidermoid carcinoma(MEC) and Metastasis of Squamous cell carcinoma in Parotid gland. ROM for this category was 100%.

3 cases of category 6(M) were confirmed on histopathology. The cases were Myoepithelial carcinoma, Carcinoma ex Pleomorphic adenoma and Adenoid cystic carcinoma. ROM for this category, like previous 2 categories was 100%.

Overall ROM of the 38 cases are 23.68%.

DISCUSSION:

FNAC , being a safe, economical and uncomplicated procedure is widely used for diagnosis of salivary gland lesions into non-neoplastic and neoplastic lesions. Neoplastic lesions can be further categorised as benign or malignant. Hence, this procedure is vital for providing a pre-operative diagnosis. However, inorder to have a universal pattern of reporting these lesions according to their malignant potential and plan of management, The Milan System of Reporting Salivary Gland Cytopathology was proposed. It classified FNAC diagnosis into six categories: ND, NN, AUS, NB, SUMP, SM and malignant with ROM of 25%, 10%, 20%, 5%, 35%, 60% and 90% for each category respectively.[15,17]

Our study also categorized salivary gland cytodiagnosis into six categories according to MSRSGC, and overall ROM was calculated.

Category 1(ND) includes the cases where material aspirated from the salivary gland lesions are insufficient for providing any information for diagnosis. Fortunately, in our study there were no non-diagnostic cases. So the ROM for this category was 0%. However in a study by Kala et al, 2 cases that were diagnosed as ND on cytology, were confirmed as chronic sialadenitis after histopathology. Loss of acini and marked fibrosis could be the possible reasons for the misdiagnosis. Another case of Adenoid cystic carcinoma was diagnosed as ND, as aspiration from the cystic areas yielded acellular smears.[15]

9 out of 36 cases were available for histological follow up in category 2(NN). 6 cases were confirmed to be non neoplastic. 2 cases were reclassified as benign neoplasms. A case of pleomorphic adenoma was diagnosed as non neoplastic as it showed cystic change, so aspiration from the cystic area showed cellular debris and histiocytes. A case which was mis-interpreted as benign cystic lesion was reclassified as low grade MEC after histological follow-up. The presence of cystic change, histiocytes, and foreign body granulomatous reaction against extravasated mucin led to false diagnosis.

The AUS category includes the cases, where a neoplastic lesion cannot be completely ruled out, and we had 3 cases in this category. Histological follow-up was available for only 1 case, which was reclassified as Adenoid Cystic Carcinoma (AdCC). The presence of occasional basaloid cell with atypia might be the reason of categorization into AUS on cytology.

Category 4a (Neoplastic: Benign) had 54 cases, out of which histological follow up was available in 21 cases. Pleomorphic adenoma (PA) (Figure 1)were the majority cases, followed by Basal cell adenoma and warthin's tumor (Figure2). In our study, all the benign cases were correctly diagnosed on cytology. No mismatch of diagnosis was seen after histopathological examination. Thus, making FNAC, a highly specific and sensitive tool to distinguish between benign and malignant lesions. However, few other studies did not show similar results. In another study, 3 cases of MEC were diagnosed as PA on cytology. Smears showed paucicellularity and bland epithelial cells which could be intermediate cells.[15] Studies done by Kotwal et al[18] and Noor et al[19] observed similar finding in their cases. Two cases of carcinoma ex PA were underdiagnosed as PA due to failure to recognize the malignant component; this could be due to sampling error in the FNAC. One case turned out to adenoid cystic carcinoma on histopathological examination. Adenoid cystic carcinoma is considered most common false-positive diagnosis for PA.

Category 4b (SUMP) includes those cases where cytological features are suggestive of a neoplastic lesion, but these features cannot distinguish efficiently between a benign and malignant neoplasm. We had 1 case diagnosed as SUMP, which was reclassified as AdCC on histological follow up. On FNAC, the smears showed tumor with magenta coloured matrix but cells were not arranged around hyaline globules, which is a typical feature of AdCC.

Suspicious for malignancy(SM) category is reserved for cases, where overall cytomorphological features suggest malignancy, but does not show all the criteria for a specific diagnosis of malignancy.[17] AUS, SUMP, and SM represent the intermediate categories in Milan system.[20] In our study, 3 cases were reported as suspicious for malignancy (Figure 3 and 4). After histopathology, these cases were confirmed as AdCC,

metastasis of squamous cell carcinoma in the parotid and low grade Mucoepidermoid carcinoma.

Category 6 (Malignant) includes cases where cytological features are diagnostic of malignancy. 3 cases diagnosed as malignancies on cytology in the current study were confirmed on histopathology as Myoepithelial carcinoma, AdCC and Carcinoma ex pleomorphic adenoma.

The overall risk of malignancy for nondiagnostic, nonneoplastic, atypia of undetermined significance, benign, SUMP, suspicious for malignancy and malignancy in our series were 0%, 11.11%, 100%, 0%, 100%, 100%, and 100%, respectively. The reported frequency in other studies varied from 0–25%, 10–18%, 2–7%, 18–50%, 50–75%, and 91–100% for each of non diagnostic, non neoplastic, benign, SUMP, suspicious for malignancy, and malignancy respectively.[10,15,16]

TABLES:

Table 1: The Milan System for Reporting Salivary Gland Cytopathology:

Diagnostic category	**Risk of Malignancy (%)**	**Management**
I.Non diagnostic	25	Clinical and radiologic correlation/ repeat FNAC
II.Non neoplastic	10	Clinical follow up and radiological correlation
III.Atypia of undetermined significance(AUS)	20	Repeat FNAC or surgery
IV.Neoplasm Neoplasm: Benign Neoplasm: Salivary gland neoplasm of uncertain malignant potential(SUMP)	 <5 35	 Surgery or clinical follow up Surgery
V. Suspicious for Malignancy(SM)	60	Surgery
VI.Malignant	90	Surgery

Table 2: Distribution of cases according to age, sex and site of involvement.

Parameter	No. of cases
Sex	
Male	55
Female	45
Age(years)	
<20	16
21-30	20
31-40	20
41-50	18
51-60	17
>60	09
Gland involved	
Parotid	73
Submandibular	23
Minor salivary gland	04

Table 3: Categorisation of cytodiagnosis according to Milan system along with histopathological correlation and risk assessment.

Category	**Cat1**	**Cat2**	**Cat3**	**Cat4a**	**Cat4b**	**Cat5**	**Cat6**	**Total**
No of cases	0	36	3	54	1	3	3	100
No of cases with histopathological follow up	0	9	1	21	1	3	3	38
Benign: Non-neoplastic	0	6	0	0	0	0	0	6
Benign: Neoplastic	0	2	0	21	0	0	0	23
Malignant	0	1	1	0	1	3	3	09
Risk of malignancy	0	01/09 11.11%	01/01 100%	0/21 0%	01/01 100%	03/03 100%	03/03 100%	09/38 23.68%

FIGURES:

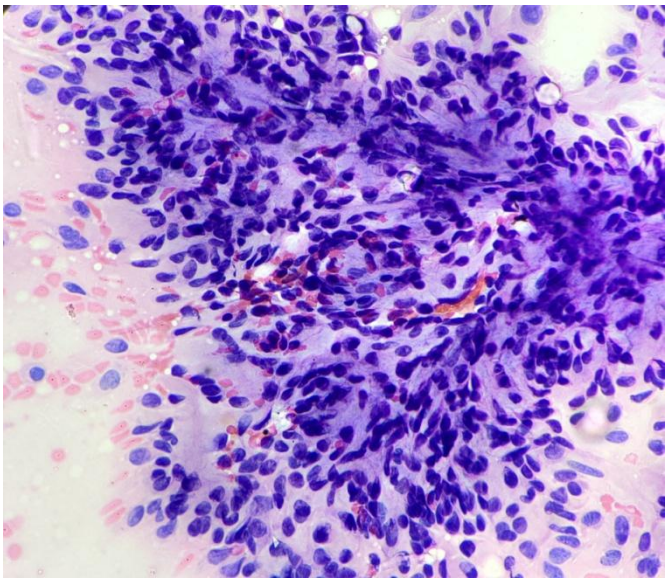

Figure 1: Pleomorphic Adenoma- round to oval epithelial cells and spindle shaped myoepithelial cells in chondromyxoid stroma (H&E,400X)

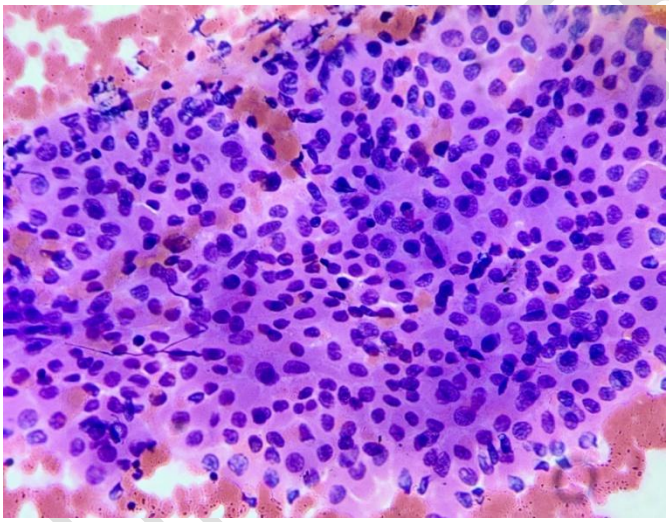

Figure 2: Warthin's Tumour- showing sheets of oncocytic cells with regular round nuclei. (H&E, 400X)

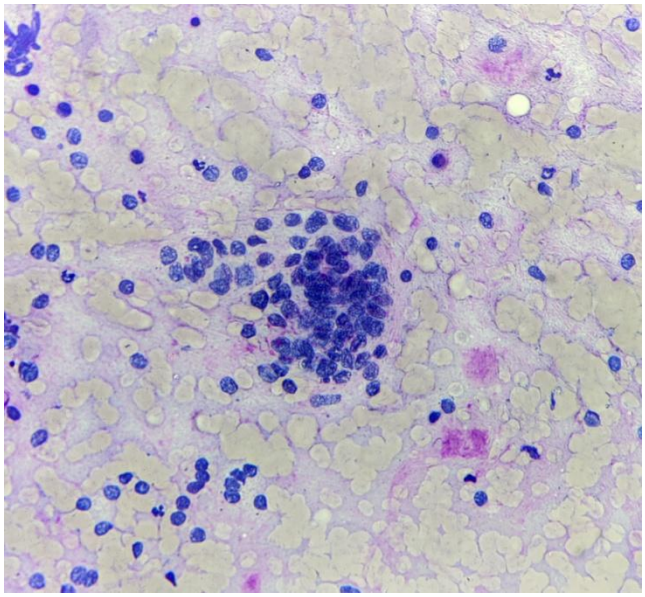

Figure 3: Adenoid Cystic Carcinoma- showing cluster of cells with round monomorphic nuclei, granular chromatin and inconspicuous nucleoli. (H&E,400X)

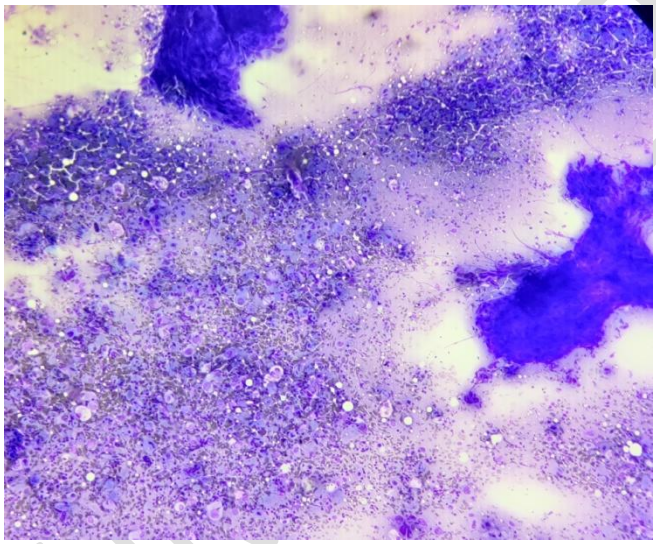

Figure 4: Mucoepidermoid Carcinoma- smears showing atypical epithelial cells (squamoid) arranged in clusters and sheets against a dirty background of mucus and debris (Leishman,100X)

CONCLUSION:

Owing to the heterogenous nature of salivary gland lesions, The Milan system provides a uniform 6 tier reporting approach which helps clinicians to plan the management in accordance with the risk stratification. False diagnosis can be avoided by repeat aspiration from multiple sites in cases of cystic lesions. An integrated approach of correlation with adequate clinical details, examination, and radiological findings helps in providing accurate preoperative diagnosis.

CONSENT

All authors declare that written informed consent was taken from all the patients for publication of this article and accompanying images. They were explained about the study and that no personal details would be disclosed. A copy of the written consent is available for review by the Editorial office/Chief Editor/ Editorial Board members of this journal.

ETHICAL APPROVAL

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and regional).Research Protocol No: IESC/PGS/2019/184.
All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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