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Original Research Article

Mucoepidermoid Carcinoma of Salivary Gland: An Elusive Cytology

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Abstract

Context: Mucoepidermoid carcinoma (MEC) is the most common malignancy of salivary glands accounting for 5–10% being more common in the parotid gland, followed by minor salivary glands, especially palate. It is one of the most problematic tumours due to elusive features. FNAC is a valuable tool to pre-operatively assess surgical management. However due to its morphological heterogeneity, overlapping architectural patterns and nuclear features a high false negative rate is seen. *Aims:* To elucidate the cytomorphological features of MEC. To explore the accuracy and pitfalls of FNAC in MEC by comparing it with final histopathological diagnosis. *Methods and Material:* This retrospective study was conducted on 15 cases of salivary gland lesions which were diagnosed as MEC on FNAC or later from biopsy/excision specimens by histopathology. The case details and slides were retrieved from the archives for a 10 year period (2006–2015). The cytological features were compared with the final histopathological diagnosis. *Results:* Out of 15 cases, 7 cases were concordant while 8 cases were found to be discordant with the final histopathological diagnosis. Underdiagnosis and overdiagnosis were noted and the overall diagnostic accuracy was 46.6%. *Conclusions:* This study of salivary gland tumours emphasizes the inherent problems in cytologic diagnosis of MEC as low & intermediate grade lesions are commonly underdiagnosed as benign.

Keywords: Fine Needle Aspiration Cytology (FNAC); salivary gland; Mucoepidermoid Carcinoma (MEC).

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Introduction

Mucoepidermoid carcinoma (MEC) is the most common malignant neoplasm of the salivary gland accounting for 5–10% of cases.[1] It is seen in all age groups and more common in the age groups of 35–65 years, peaking at 4th decade.[2] However, it is the second most common tumour in pediatric age group.[3] Most common site is the parotid gland (45%), followed by palate (21%). Female

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predilection is seen.[2]

Fine Needle Aspiration Cytology (FNAC) is a valuable tool to preoperatively assess and to plan surgical management. It is quick, simple and reliable and allows wide sampling of the lesion. Different studies reveal high sensitivity & specificity with very few pitfalls.[4] It facilitates accurate diagnosis in majority of tumors. However, it carries a high false negative rate in the diagnosis of specific types of tumour mostly MEC (mainly low grade) due to overlapping cytomorphology with benign lesions. Therefore, given the common prevalence and heterogeneity of MEC, proper sampling & knowledge of its morphologic complexity is critical to an accurate diagnosis.[5] MEC has been observed as one of the most problematic tumours for cytological diagnosis.[1] High grade neoplasms are easily recognized as malignant. On the other hand, low grade neoplasms are less often recognized as malignant & underdiagnosed resulting in treatment delays and inappropriate pre-operative management.[5] The problem is further accentuated in diagnosis of low grade tumours that present as cystic lesions because of failure to obtain diagnostic material.[1]

Materials and Methods

The study was conducted on 15 retrospective cases of salivary gland lesions which were diagnosed as MEC either on FNAC or by histopathological study of excision biopsy specimens. The case details and slides were retrieved from the archives for a 10 year study period (2006–2015). FNAC was performed using 23 gauge needle attached to a 5 ml syringe. Wet smears were fixed in 95% isopropyl alcohol. Slides were stained by papanicolaou (pap) and also Hematoxylin & Eosin. Air dried smears were also prepared & stained with Leishman stain. On subsequent follow up, these patients underwent surgery & the specimens were sent for histopathological studies. Based on the histopathological diagnosis the patients were grouped into low, intermediate and high grade based on the standard grading system for MEC. The cytological features were compared with final histopathological diagnosis. Concordant & discordant cases were noted.

Results

The study included 15 patients with salivary gland lesions in which cytological diagnosis was confirmed by subsequent histopathological study. In the study, 12/15 patients (80%), MEC arose in the parotid region, more on the right side (8/12 cases), rest from right submandibular gland, right soft palate & left maxillary sinus, each accounting for 6.7%. Average size was 5.5 × 4.5 cm. The age group affected was 15–70 years. Males were predominant in the study accounting for 9 (60%) cases and M:F ratio was 1.5:1 (Table 1).

Table 1: Summary of age, sex, site distribution with cytological and histopathological diagnosis

Cases	Age & Sex	Location	Cytological Diagnosis	Histopathological Diagnosis
1	65/M	Rt parotid	MEC	MDSCC*
2	60/M	Lt parotid	MEC (Low grade)	MEC (Low grade)
3	22/M	Rt parotid	MEC (Low grade)	MEC (Low grade)
4	70/F	Rt parotid	Suspicious of MEC	MEC (Low grade)
5	66/F	Rt submandibular	MEC (Intermediate grade)	MEC (Intermediate grade)
6	61/M	Lt maxillary sinus	MEC (Low grade)	Radicular cyst
7	69/F	Lt parotid	Infected cyst	MEC (Low grade)
8	25/M	Rt parotid	Cystic lesion	MEC (Intermediate grade)
9	20/F	Rt parotid	Cystic lesion	MEC (Sclerosing MEC with cystic low grade areas)
10	37/M	Lt parotid	Cystic lesion	MEC (Low grade)
11	24/F	Rt parotid	Suspicious of MEC	MEC (Intermediate grade)
12	24/M	Rt soft palate	Suspicious of MEC	Pleomorphic adenoma
13	15/F	Rt parotid	Cystic lesion	MEC (Low grade)
14	60/M	Lt parotid	Warthin tumour	MEC (Low grade)
15	42/M	Rt parotid	Suspicious of MEC	MEC (Low grade)

*MDSCC: Moderately differentiated squamous cell carcinoma

Out of total 15 patients, 7 (46.6%) diagnosed as MEC on cytology were confirmed by histopathological studies (concordant cases) which included 4 low grade (Fig. 1) and 2 intermediate grade MEC**.** One patient was diagnosed as MEC by FNAC but final histopathological diagnosis was Moderately differentiated squamous cell carcinoma. This case is included as concordant case as both are malignant lesions and do not vary in treatment modalities. The smears of low grade MEC were sparsely cellular with mucin producing cells showing vacuolated cytoplasm in singles. Background showed plenty of mucin. Smears of intermediate grade MEC showed mucin producing cells and few clusters of intermediate cells. Intermediate cells have round to oval nuclei with moderate amount of eosinophilic cytoplasm. Background showed mucin.

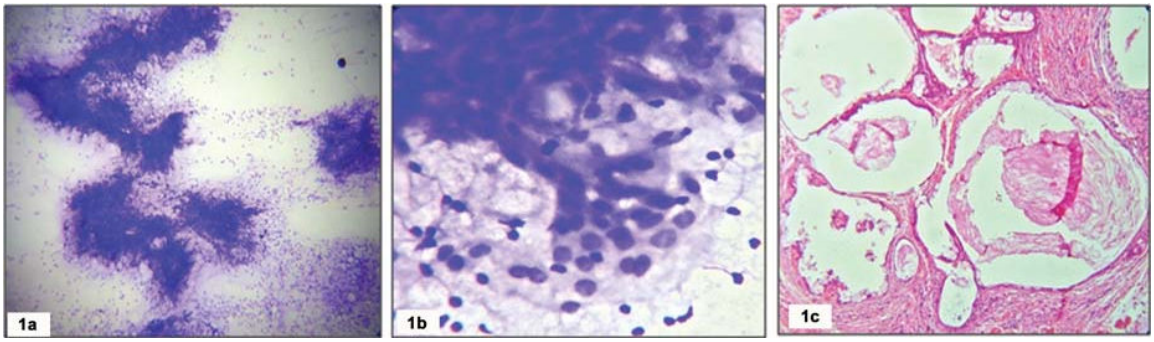

Fig. 1: Low grade MEC

(a) Highly cellular smear showing cells in clusters along with discohesive cells (Leishman 100X)

(b Mucin producing cells displaying oval nuclei with vacuolated cytoplasm (Leishman 400X)

(c) Paraffin section showing multiple cysts lined by mucin producing cells (H&E 100X).

Out of total 15 patients, 8 (53.3%) cases were discordant with the final histopathological diagnosis. 6 (40%) cases were underdiagnosed and 2 (13.3%) were overdiagnosed on FNAC. Among 6 (40%) underdiagnosed cases, 5 (33.3%) were reported as cystic lesion on FNAC and one (6.7%) was reported as Warthin tumour which again had features of cystic change**.** Most common cause of discordance in our study is underdiagnosis of low and intermediate MEC as cystic lesion on FNAC possibly due to hypocellularity of smears and presence of many cyst macrophages (Fig. 2).

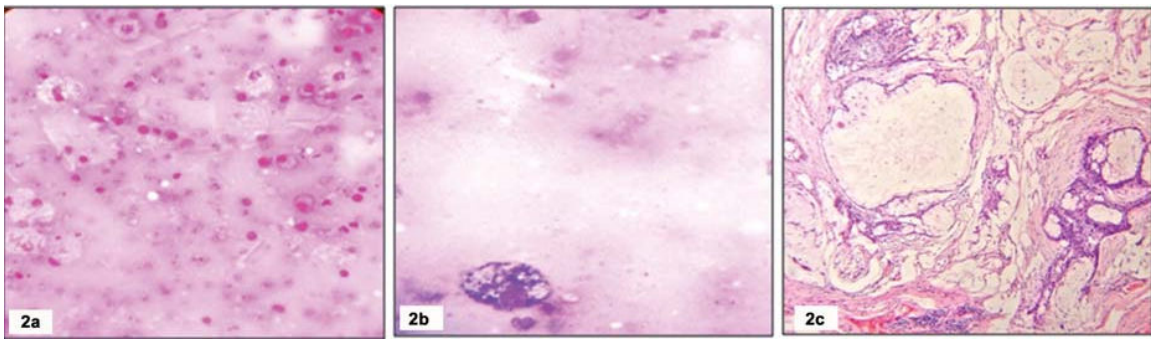

Fig. 2: Low grade MEC reported as cystic lesion on FNA

(a) Sparsely cellular smear with cyst macrophages and few inflammatory cells (H&E 100X)

(b) Muciphage with vacuolated cytoplasm and background showing mucin. No epithelial cells seen (H&E 400X)

(c) Paraffin section showing cystic spaces lined by mucin producing cells with few intermediate cells and lumen filled with mucin (H&E 100X).

One case was reported as Warthin tumour on FNAC due to presence of plenty of lymphocytes along with cyst macrophages. Histopathology of this case showed MEC with lymphocytic infiltrate in adjacent stroma (Fig. 3).

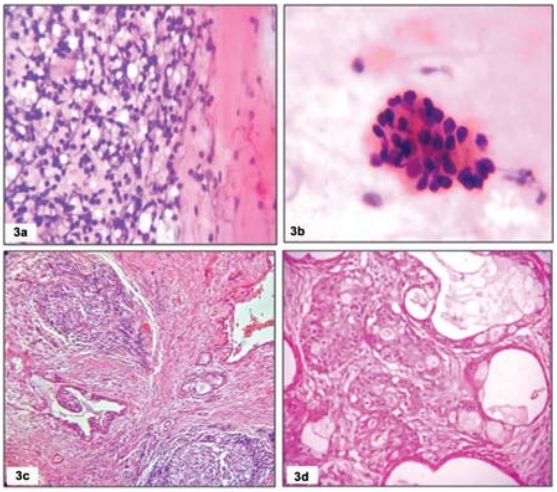

Fig. 3: Low grade MEC reported as Warthin tumour on FNA

(a) Smear showing abundant lymphocytes (H&E 400X)

(b) Smear showing a cell cluster with abundant eosinophilic cytoplasm (H&E 400X)

(c) Paraffin section showing dense lymphocytic infiltrate with few cystic spaces (H&E 100X)

(d) Paraffin section showing cystic spaces lined by mucin producing cells, intermediate cells and foci of squamous metaplasia (H&E 400X).

Among 2 (13.33%) cases overdiagnosed as MEC on cytology, final histopathological diagnosis was Radicular cyst and Pleomorphic adenoma. Case of radicular cyst on cytology showed only cyst macrophages with mucoid background. Cyst macrophages were misinterpreted as muciphages and hence diagnosis of possibility of MEC cannot be ruled out was suggested. Case of pleomorphic adenoma was misdiagnosed on cytology as MEC due to presence of vacuolated cytoplasm in myoepithelial cells. Some of myoepithelial cells showed moderate eosinophilic cytoplasm which were misinterpreted as intermediate cells of MEC. Myxoid background was confused with mucin (Fig. 4). In the present study, diagnostic accuracy was found to be 46.6%.

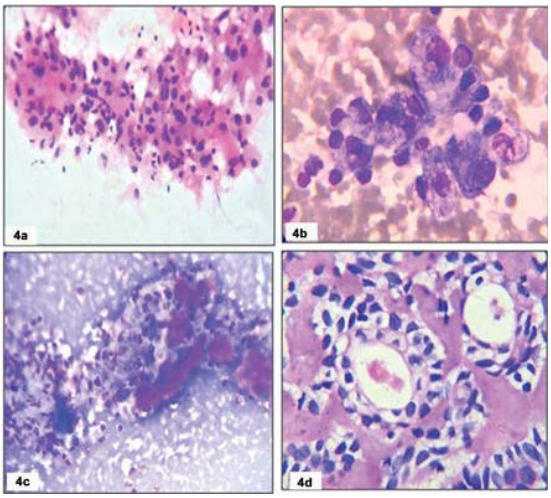

Fig. 4: Pleomorphic adenoma reported as suspicious of MEC on FNA

(a) Moderately cellular smear showing cells with round to oval nuclei and eosinophilic cytoplasm (H&E 100X)

(b) Smear showing cells with vacuolated cytoplasm (Leishman 400X)

(c) Background showing myxoid material and neutrophils (Leishman 100X)

(d) Paraffin section showing myoepithelial cells with vacuolated cytoplasm and myxoid stroma (H&E 400X).

Discussion

MEC is the most common malignancy of salivary glands in adults. Parotid gland is the most common site followed by minor salivary glands including palate, tongue and floor of mouth.[6] MEC is a tumor of duct origin and arises from pluripotent reserve cells of excretory ducts that are capable of differentiating into mucous, columnar and squamous cells.[2] They are well circumscribed unencapsulated tumours, and can infiltrate overlying skin and metastasize to regional lymph nodes & distant organs.[6]

FNAC of salivary gland though a very common investigation modality presents several interpretation challenges in the diagnosis of tumours like MEC due to morphological heterogeneity, overlapping architectural patterns & nuclear features.[4] The goal of the present study was to identify pitfalls of FNAC in cytological diagnosis of MEC.

Major difficulty in diagnosing MEC on FNA is related to sampling error, so it is necessary to identify various cellular & acellular components to reach a differential diagnosis based on various criterias like nuclear atypia, cell type (mucinous, squamous, oncocytic, myoepithelial), metaplastic change, presence or absence of lymphocytic infiltrate, presence of extracellular material (chondromyxoid matrix, mucin, necrotic debris). Metaplastic changes that occur in benign salivary gland neoplasms induced by repeated FNA makes it even more difficult to diagnose low grade MEC.[5] MEC is composed of a mixture of squamous, intermediate and mucus-producing cells in varying proportion.[6]

Mucoepidermoid carcinoma are graded by most using three tiers: low, intermediate and high grade. The three most commonly used grading systems are: the AFIP (Armed Forces Institute of Pathology) grading system, the Brandwein system and modified Healey system. AFIP and Brandwein system are point based, assigning point values to each adverse histologic parameters. More the point score, higher is the grade. The modified Healey system is a non- point based system. AFIP grading system assigns 2 points each for intra-cystic component less than 20% and neural invasion, 3 points each for necrosis and mitosis 4 or more per 10 HPF (High Power Field) and 4 points for anaplasia. So, after adding the individual points, if the total score is between 0 to 4 it is considered as low grade, 5 to 6 as intermediate grade and 7 to 14 as high grade MEC. On the other hand, Brandwein point based system assigns 2 points each for intracystic component less than 25%, pronounced clear atypia and tumour invasion in small nests or islands and 3 points each for lymphatic/ vascular invasion, bony invasion, perineural invasion, necrosis and greater than 4 mitosis per 10 HPF. If the total score is 0, it is considered as low grade, 2 to 3 as intermediate grade and 4+ as high grade MEC.

Low grade MEC shows greater than 50% of mucous elements, intermediate grade shows 10% to 50% while high grade MEC shows less than 10% of mucous elements.[2] The needle aspirates of MEC may be classified based on the same criteria used for histologic grading.[6]

Grading of MEC into low, intermediate and high grade is important in view of prognosis and treatment aspects. Low grade MEC is treated by surgical intervention whereas high grade MEC is managed by adjuvant radiotherapy and neck dissection. Treatment of intermediate grade MEC is controversial. Low-grade MEC are often difficult to recognize as malignant tumors.[6]

Low-grade MEC accounts for about 80% of all MECs and is well recognized for its potential false-negative diagnostic pitfall, owing to the bland cytologic features and hypocellular nature of many of these tumors.[8] Aspirate is usually thick mucoid fluid. Smears show large mucus-secreting cells in loose cellular groups exhibiting abundant foamy or vacuolated to clear cytoplasm and low N/C ratios. When in singles, they can be easily confused with foamy histiocytes. Intermediate cells are present in cohesive clusters with rounded small uniform nuclei and scant eosinophilic cytoplasm. Cells showing mature squamous cell differentiation (keratinization) are almost never seen in low-grade MEC.[6]

High-grade MEC yield cellular smears showing predominantly intermediate and squamous cells in singles or clusters. The cells have large hyperchromatic nuclei. Very few scattered mucus-producing cells are seen. Occasionally, malignant squamous "pearls" can occur. Mitoses and necrosis may be present.[6]

Aspirates of intermediate-grade MEC are more cellular than those of low-grade tumors showing intermediate cells interspersed with mucin-producing cells.[6]

Concordance rate and discordance rate in our study was 46.7% (7/15) and 53.3% (8/15) respectively. Similar study done by Joseph TP *et al.* over a period of 2 years showed that out of 6 histopathologically confirmed cases of MEC, 2 cases were correctly diagnosed on cytology, 2 as

neoplasm with cystic degeneration & remaining 2 as pleomorphic adenoma. So, their concordance rate was 33.3% & discordance rate was 66.6%.[1]

In our study, diagnostic accuracy was 46.6%. Joseph TP *et al.* found diagnostic accuracy of 33.3% in their study.[1] Main cause of discordance in our study was diagnosis of low and intermediate grade MEC as Benign cystic lesion which accounted for 5/8 discordant cases. The causes for this was sparse cellularity of smears, bland cytological features and failure to demonstrate mucin secreting/ intermediate cells.

According to Joseph TP *et al.*, 2/4 discordant cases were misdiagnosed as cystic lesion & thus concluded that low grade MEC is one of the most difficult neoplasms to diagnose on FNAC.[1] Rupani AB *et al.* reported a case of low grade MEC in a 13 year old female child with right parotid swelling which was misdiagnosed as intermediate grade MEC on FNAC. Hence, they concluded that low grade MEC is most difficult to diagnose by FNAC due to paucicellular smears with thick mucinous material in the background.[9] Edwards and Wasserman stated that cystic lesions constitute majority of false negative diagnosis in cytology of salivary gland lesions due to failure in obtaining diagnostic material.[10] According to Kumar Mahesh *et al.*, the cytological diagnosis of low grade MEC can be challenging due to spatial heterogeneity & various histologic components.[3]

In the present study, a case of moderately differentiated squamous cell carcinoma was misdiagnosed as MEC on FNAC. Similar observation was noted by Kumar Mahesh *et al.* who stated that high grade MEC may be difficult to recognize & hence misdiagnosed as poorly differentiated squamous cell carcinoma.[3]

The diagnosis of MEC by FNAC is most difficult for low grade tumours. It may be due to the fact that these tumours yield scanty cellular aspirate containing only a few clusters of cells with bland nuclear features. Clue to the diagnosis is provided by the cystic nature of the tumour and sparsely cellular mucoid smear. A careful search for few mucus-producing cells is essential in such cases. However, in their absence, one must consider the possibility of a mucocele/mucus retention cyst. The presence of a persistent mass after aspiration of a cystic tumor points towards the possibility of a low-grade MEC.[6] Other important differential diagnosis are lymphoepithelial cyst, branchial cyst and Warthin's tumour.[1] Adequate sampling of various components is very essential to arrive at a correct diagnosis.[3]

In a study by Joseph TP, 2 cases of low grade MEC were broadly diagnosed in cytology as neoplasm with cystic degeneration due to decreased cellularity of the smears despite repeated aspirations & failure to demonstrate separately all the 3 cell types.[1] Inflammatory cells and macrophages may mask neoplastic epithelial cells and thus result in an erroneous diagnosis of an inflammatory lesion. Intermediate cells with finely vacuolated cytoplasm may be mistaken for macrophages. This difficulty arises mostly in low-grade MEC with a large cystic component.[11]

Aspirates from high-grade MEC may be difficult to differentiate from other high-grade carcinomas like salivary duct carcinoma and adenocarcinoma, not otherwise specified. The background of mucin, chronic inflammatory cells along with few groups of intermediate and squamous cells may be mistaken for oncocytic cells of Warthin's tumour. However, the oncocytic cells of Warthin's tumour contain granular eosinophilic cytoplasm with uniform nucleus. Extensively keratinised malignant squamous cells are usually not seen in MEC. When present, it points towards diagnosis of squamous cell carcinoma, especially metastatic from an upper aerodigestive tract or lung tumour. Rarely, aspirates from chronic sialadenitis may mimic MEC. In sialadenitis, the ductal cells show straight edges with branching, scant cytoplasm and uniform nuclei. Squamous metaplasia may occur but epithelial heterogeneity is absent.[11]

MEC is probably the most difficult to diagnose accurately by FNAC. Many times, MEC is misdiagnosed as Pleomorphic adenoma as it is a recognized pitfall.[4] Kotwal *et al.* observed this in his case series in which 75% of lesions were misdiagnosed as pleomorphic adenoma.[12] This was because intermediate cell population of MEC closely resemble the basal or myoepithelial cells of Pleomorphic adenoma. Also, occasional squamous or mucinous differentiation is noted in Pleomorphic adenoma. The myxoid ground substance can sometimes be mistaken for mucin leading to misdiagnosis of pleomorphic adenoma as malignant.[9] Stranded stroma and crushed nuclei can also mimic myxoid stroma of pleomorphic adenoma.[4] However, myxochondroid stroma is usually not seen in MEC. Detection of intracellular mucin is the key feature to diagnose MEC. Romanowsky stain could help in the recognition of stroma. Special stains like mucicarmine and Periodic Acid Schiff (PAS) would undoubtedly help to detect intracellular mucin.[4] MEC can be misdiagnosed as oncocytoma when smears show

hypocellularity with benign looking cells showing abundant eosinophilic cytoplasm.[4]

A definitive diagnosis of MEC require the smears to show coexistence of cells showing squamous differentiation and mucin-secreting cells. Unequivocal evidence of both is not always found, particularly in cystic tumors. In such cases, only a tentative or differential diagnosis can be offered, suggesting further investigation.[13]

Conclusion

Though MEC is the most common malignant salivary gland tumour, it is most prone for misdiagnosis on FNAC due to morphological heterogeneity, overlapping nuclear and cytological features with other benign salivary gland lesions. Of these, low grade MEC is most difficult to identify on cytology especially when they present as cystic lesion. Squamous cell carcinoma can be misdiagnosed as high grade MEC and vice versa.

Conflicting Interest: Nil

References

1. Joseph TP, Joseph CP, Jayalakshmy PS, Poothiode U. Diagnostic challenges in cytology of mucoepidermoid carcinoma: Report of 6 cases with histopathological correlation. J Cytol. 2015;32:21–24.
2. Giriyan SS, Sushma K. Mucoepidermoid Carcinoma: high grade of Parotid gland. Int J Sci Res. 2015;4:440–43.
3. Kumar M, Ratnakar P, Srivastava S. Cytological Diagnosis of Mucoepidermoid Carcinoma of Parotid – A Diagnostic Dilemma. Int J Med Sci Pub Health. 2013;2:462–64.
4. Aan NU, Tanwani AK. Pitfalls in Salivary Gland Fine Needle Aspiration Cytology. Int J Pathol. 2009;7:61–65.
5. Wade TV, LiVolsi VA. Montone KT, Baloch ZW. A Cytohistologic Correlation of Mucoepidermoid Carcinoma: Emphasizing the Rare Oncocytic Variant. Pathol Res Int. 2011:1–6.
6. Elhosseiny A. Salivary glands. In: Koss LG, Melamed MR, editors. Koss Diagnostic Cytology & Its Histologic Bases. 5th ed. Lippincott Williams and Wilkins: Wolters Kluwer; 2006.p.1230–1261.
7. Seethala RR. An update on grading of salivary gland carcinomas. Head and neck pathol. 2009;3:69–77.
8. Mukunyadzi P. Review of Fine-Needle Aspiration Cytology of Salivary Gland Neoplasms, With Emphasis on Differential Diagnosis. Am J Clin Pathol. 2002;118:100–115.
9. Rupani AB, Kavishwar VS, Achinmane V, *et al.* Fine needle aspiration cytology of low grade mucoepidermoid carcinoma of the parotid gland: A diagnostic challenge. J Cytol. 2008;25:115–16.
10. Edwards PC, Wasserman P. Evaluation of cystic salivary gland lesions by fine needle aspiration: An analysis of 21 cases. Acta Cytol. 2005;49:489–94.
11. Kocjan G, Shah KA. Salivary Glands. In: Gray W, Kocjan G, editors. Diagnostic Cytopathology. 3rd ed. Churchill Livingstone: Elsevier; 2010.p. 231–252.
12. Kotwal M, Gaikwad S, Patil R, *et al.* FNAC of salivary gland- A useful tool in preoperative diagnosis or a cytopathologists riddle.J Cytol. 2007;24:85–8.
13. Orell SR, Kijanienko J. Head and neck; salivary glands. In: Orell SR, Sterrett GF, editors. Fine Needle Aspiration Cytology. 5th ed. Edinburgh: Churchill Livingstone- Elsevier; 2012.pp.38–76.