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ORIGINAL ARTICLE

Diagnostic challenges in fine needle aspiration cytology of salivary gland lesions

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Abstract

Background: Fine needle aspiration cytology (FNAC) has been widely accepted as a safe method for diagnosis of salivary gland lesions and its accuracy is increased with increasing the experience of the physician. This study was conducted to examine the sensitivity, specificity and accuracy of FNAC of salivary gland lesions by cyto-histological correlation and to identify the discrepancies that contribute to false diagnoses. *Method:* A retrospective study was carried out over a 7-year period from 2003 to 2009 to review the cases of patients with salivary gland lesions who underwent FNAC with histopathological confirmation. *Results:* A total of 101 cases had cytological correlation of whom 76 (75.3%) were neoplastic (58.4% benign, 16.8% malignant) and 25 (24.7%) were non-neoplastic. Pleomorphic adenoma (PA) was the most frequent benign neoplasm while adenoid cystic carcinoma (ACC) was the most frequent malignant neoplasm. FNAC had a sensitivity of 80% and a specificity of 98.8% for overall benign and malignant diagnoses and positive predictive and negative predictive values of 92.3% and 96.4% respectively. The most common false negative cases were pleomorphic adenoma. *Conclusions:* This study demonstrated that FNAC of the salivary gland is a useful technique for diagnosis of salivary gland lesions. Combined with clinical and radiological findings, it can provide a preliminary assessment on which management decision can be based.

Keywords: fine needle aspiration, salivary gland lesions, cyto-histo correlation, challenges.

INTRODUCTION

Salivary gland lesions comprise 2-6.5% of all head and neck neoplasms in adults.[1] The common presentation is an enlarged mass which is usually accessible for fine needle aspiration cytology (FNAC).[1] The use of aspiration cytology was first reported by Kun in 1847. The procedure was reintroduced in 1930 by Martin & Ellis but the use of FNAC in the head and neck area, especially salivary glands, was promoted in 1950 and 1960 by Eneroth *et al*.[2] FNAC has been applied for the diagnosis of salivary gland lesions for more than three decades and was shown to be beneficial not only in the diagnosis and typing of salivary gland tumours but also in differentiating neoplastic lesions from non-neoplastic lesions.[3] At present, the accuracy of FNAC is improved by utilization of tumour marker studies, special stains and modern imaging techniques.[4]

Salivary gland tumours are not common; moreover, the associated histopathology of these tumours is extremely varied and complex due to the presence of epithelial and non-epithelial neoplasms, lymphomas, metastatic tumours and non-neoplastic lesions in the salivary glands. Although the typical cytological morphology of most salivary gland lesions is predictable, several confounding cytological factors make some FNA smears difficult to interpret. It is not surprising that some salivary gland malignancies cannot be identified by cytological morphology alone. Furthermore, some salivary gland malignancies can only be distinguished from their benign counterparts by the presence of capsular invasion, which is not assessable by FNAC.[5]

Although in some hospitals, FNAC is performed in the workup of all cases of salivary gland nodules, other authors limit the usage of FNAC only to a selected group of patients with suspected malignancy, metastatic carcinoma or lymphoma.[6]

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This retrospective analysis was conducted to determine the diagnostic yield of FNAC for salivary gland lesions, as well as establishing the relative causes of incorrect cytological interpretations.

MATERIALS AND METHODS

This retrospective study consisted of 101 FNA specimens of salivary glands which were verified by histopathological diagnosis over a seven-year period from January 2003 to December 2009 obtained from the archives of the Cytology Unit of Universiti Kebangsaan Malaysia Medical Centre (UKMMC). Cases reported as unsatisfactory were excluded from this study. The clinical information and the cytological and histopathological reports of patients were retrieved from the Integrated Laboratory Management System (ILMS).

Prior to performing the FNAC, written informed consent had been obtained from each patient. FNAC had been performed with a 22-gauge needle attached to a 20-ml disposable plastic syringe that was mounted on a handle (Cameco holder). Then, the obtained sample had been mounted onto glass slides and smeared. Multiple smears had been prepared and stained by both May-Grunwald-Giemsa (MGG) and Papanicolaou (Pap) stains. Cytological diagnoses based on the FNA smears were categorized into three categories namely benign, malignant and suspicious. The gold standard for diagnosis was based on the histopathological findings from the subsequent biopsy. The biopsy based diagnosis was categorized into either benign or malignant.

Both cytology and histology slides were reviewed by two pathologists who were blinded for the original diagnoses, and an attempt was made at consensus diagnoses in case of divergent opinions.

The diagnostic value of FNAC in comparison with histopathology was calculated for benign and malignant neoplasms using the following formulae:

Accuracy = (True Positive + True Negative) × 100/(True Positive + True Negative + False Positive + False Negative).

Sensitivity = (True Positive × 100) / (True Positive + False Negative).

Specificity = (True Negative × 100) / (True Negative + False Positive).

Positive predictive value = (True Positive × 100) /(True Positive + False Positive).

Negative predictive value = (True Negative × 100) /(True Negative + False Negative).

The results were then compared with the findings of other previous studies.

Ethics

This study was approved by the Universiti Kebangsaan Malaysia Ethical Committee.

RESULTS

A total of 101 cases of salivary gland lesions were included in the present study. 48 (48%) patients were males and 52 (52%) were females with an overall female predominance. The age of the patients ranged from 14 to 76 years with an average of 48 years. Salivary gland lesions were most observed in the fourth decade in women and seventh decade in men (Fig.1). Most of the patients (57, 56.4%) were Malay followed by Chinese (38, 37.6%) and Indian (4, 4%).

The parotid gland was the most commonly involved salivary gland (77 cases, 76.2%) followed by the submandibular gland (23, 22.8%). Only one benign cystic lesion was found in the submental gland. There were more neoplastic lesions (78 cases, 77.2%) compared to non-neoplastic lesions (23 cases, 22.8%) on FNAC (Table 1).

Non-neoplastic lesions

Among the non-neoplastic lesions, inflammatory lesions were predominant, most common being sialadenitis, found in seven out of twenty three cases , cystic lesions in six cases , followed by normal salivary gland in five cases , abscess in three cases , and granulomatous inflammation and sialadenosis in one case each (Table 2).

Neoplastic lesions

Of the 78 neoplastic lesions, 61 (78.3%) were reported as benign and 13 (16.7%) as malignant on FNAC. In one case (1.2%) a diagnosis of neoplastic lesion was offered on FNAC with no specific typing, and three (3.8%) cases were reported as suspicious of malignancy.

Benign neoplasms

Among the 61 benign neoplasms, pleomorphic adenoma (PA) was the most common lesion (43 out of 61 cases; 70.5%) followed by Warthin's tumour (18 cases; 29.5%). Thirty-four (79.1%) of the 43 pleomorphic adenomas occurred in the parotid gland and nine (20.9%) in the submandibular gland. All 18 cases of Warthin's tumour occurred in the parotid gland (Table 2).

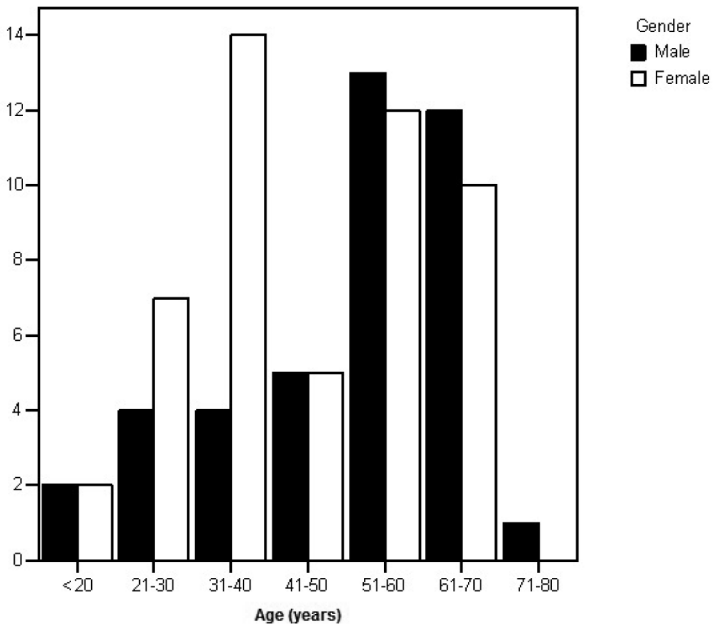

FIG.1: Age (years) and sex distribution of salivary gland lesions (n=101)

Malignant neoplasms

Among the malignant neoplasms, adenoid cystic carcinoma was the most common (5 out of 16 cases; 31.3%), followed by poorly or undifferentiated carcinoma (4 cases; 25%), acinic cell carcinoma (3 cases; 18.7%), and metastatic squamous cell carcinoma (1 case; 6.3%). There were three cases (18.7%) which were reported as suspicious for malignancy with no specific typing included. In one case, a differential diagnosis of PA and acinic cell carcinoma (well differentiated) was given but with features in favour of PA.

Three out of five cases of adenoid cystic carcinoma occurred in the parotid gland and two in the submandibular gland. Overall, malignancy was more common in the parotid gland (11 cases, 68.75%) compared with the submandibular gland (5 cases, 31.25%) (Table 2).

Histopathological correlation

Histopathological correlation was available for all 101 cases. 75.3% (59+17) cases were reported as neoplastic lesions and 25(24.7%) cases were reported as non-neoplastic lesions (Table 3).

Non-neoplastic lesions

Out of the 23 cases reported as non-neoplastic on cytology, five turned out to be benign neoplasms on histology.

Of 7 cases diagnosed as sialadenitis in FNAC, 4 were confirmed with biopsy while 3 cases turned out to be reactive lymph node, Warthin's

TABLE 1: The distribution of neoplastic and non-neoplastic salivary gland lesions on FNAC (n=101)

Type of salivary gland	Non-neoplastic	Neoplastic lesions			Total(%)
		Benign	Malignant	Suspicious*	
Parotid	14	52	9	2	77(76.2%)
Submandibular gland	8	9	4	2	23(22.8%)
Submental	1	0	0	0	1(1.0%)
Total (%)	23(22.8%)	61(60.4%)	13(12.8%)	4(4.0%)	101(100%)

*Suspicious of malignancy or neoplastic process without specific typing

TABLE 2: The distribution of salivary gland lesions based on FNAC (n=100*)

FNAC diagnosis	Parotid	Submandibular gland	Submental gland	Total
Neoplastic lesions				
Benign tumours				
Pleomorphic adenoma	34	9	-	43
Warthin's tumour	18	0	-	18
Malignant tumours				
Adenoid cystic carcinoma	3	2	-	5
Acinic cell carcinoma	3	0	-	3
Poorly or undifferentiated ca	3	1	-	4
Squamous cell carcinoma	0	1	-	1
Suspicious of malignancy	2	1	-	3
Non-neoplastic lesions				
Sialadenitis	3	4	-	7
Cystic lesion	3	2	1	6
Abscess	3	0	-	3
Normal salivary gland tissue	3	2	-	5
Sialadenosis	1	0	-	1
Granulomatous inflammation	1	0	-	1

*There was one neoplastic submandibular gland lesion with no specific typing which was not included in this table.

tumour and abscess (1 case each). Amongst the 5 cases that were found to be normal in FNAC, biopsy revealed 3 different diagnoses including basal cell adenoma, sialdenitis and fibroma attached to salivary gland (1 case each). Biopsy revealed one case that was diagnosed as abscess and another case with diagnosis of sialdenosis in FNAC turned out to be Warthin's tumour on histology. One case of cyst in FNAC was found to be sialadenosis on histology.

Neoplastic lesions

Of the three cases reported as suspicious for malignancy on cytology, two cases turned out to be carcinoma ex-pleomorphic adenoma on histology. One case that was reported as suggestive of PA with a differential diagnosis of well differentiated acinic cell carcinoma was confirmed as PA by histology. The neoplastic lesion with no specific typing reported on cytology was diagnosed as benign lymphoepithelial lesion on HPE.

Benign neoplasms

Out of 43 PAs reported on FNA, 37 (86%) were confirmed as PA on histology. There were six discrepancies in diagnoses. Three cases turned out to be malignant: one carcinoma ex-pleomorphic adenoma, one mucoepidermoid carcinoma and one diffused large B cell lymphoma respectively; two cases were normal salivary gland tissue and one case was a lipoma on histology.

Of 18 cases diagnosed as Warthin's tumour on FNAC, 14 (77%) correlated with histopathological diagnoses. On the other hand 4 cases of Warthin's tumour in FNAC were found to be lymphoepithelial lesion, xanthogranuloma and sialadenitis on histology while one case of acinic cell carcinoma in FNAC was diagnosed as Warthin's tumour on histology.

TABLE 3: The distribution of disease in the various salivary glands based on histology (n=101)

Salivary gland	Non-neoplasia	Benign neoplasm	Malignant neoplasm	Total(%)
Parotid	15	50	12	77(76.23%)
Submandibular gland	9	9	5	23(22.77%)
Submental gland	1	0	0	1(0.99%)
Total (%)	25(24.75%)	59(58.41%)	17(16.84%)	101 (100%)

TABLE 4: FNAC-histopathological correlation of salivary gland lesions (n=98*)

Diagnosis	Number of cases FNAC(n=98)	Same cytopathological diagnosis	Different diagnosis but same category	False positive	False negative
Non-neoplastic	23	14	9	-	-
Benign neoplasm					
Pleomorphic adenoma	43	37	3	-	3
Warthin's tumour	18	14	4	-	-
Malignant neoplasm					
Adenoid cystic ca	5	5	-	-	-
Acinic cell ca	3	2	-	1	-
Undifferentiated ca	4	4	-	-	-
Squamous cell ca	1	1	-	-	-

*There were three cases of suspicious for malignancy which were not included in this table.

After review the case of xanthogranuloma on HPE, was confirmed as infarcted Warthin's tumour with xanthogranulomatous reaction most likely secondary to the FNA.

Malignant neoplasms

Of 13 cases of malignant neoplasms reported by FNAC, all five cases of adenoid cystic carcinoma showed 100% correlation with histopathology (Table 4). Two of 3 cases (66.6%) of acinic cell carcinoma were confirmed as acinic cell carcinoma on histology, while one case (33.4%) turned out to be Warthin's tumour. Out of four cases of undifferentiated or poorly differentiated carcinoma on FNAC, 3 cases correlated with histological diagnoses, and one case was diagnosed as carcinosarcoma on histology. There was one case of metastatic squamous cell carcinoma in FNAC which was also confirmed by histology.

Diagnostic value

The FNAC and biopsy cross tabulation is shown in Table 5. Using histology as the gold standard, and after excluding four cases reported as suspicious of malignancy or neoplastic process on cytology, the overall diagnostic value of FNAC, (whether malignant or benign) were calculated as follows: sensitivity 80.0%, specificity 98.78%, positive predictive value 92.30%, negative predictive value 96.42% and diagnostic accuracy 95.87%.

DISCUSSION

In this study, the sensitivity and specificity of FNAC was 80% and 98% respectively (Table 5). The sensitivity and specificity of FNAC were previously reported to range between 57 to 100% and 79 to 100%, respectively, which correlates well with the results of the present study.

In this study, malignancies existed in 17 (16.8%) cases, benign neoplasms in 59 (58.4%), and other non-neoplastic lesions in the remaining 25 cases (24.8%). The rate of malignant lesions was consistent with the expected rate

TABLE 5: Cross-tabulation of FNAC and biopsy results for salivary glands (n=97)

		Biopsy result		Total
		Benign	Malignant	
FNAC result	Benign	81(TN)	3 (FN)	84
	Malignant	1 (FP)	12 (TP)	13
Total		82	15	97

TN, True negative; TP, True positive; FN, False negative; FP, False positive
Four cases which were reported as suspicious of malignancy or neoplastic process on cytology were excluded from cross-tabulation

of malignant disease, which ranged from 15% to 32% in an unselected population.[7] Adenoid cystic carcinoma was the most common salivary gland malignancy in the present study with 100% accuracy of FNAC diagnosis in all five cases.

Parotid gland was the most frequently involved salivary gland followed by submandibular and minor salivary gland. This finding was consistent with the results of other previous studies.[3] PA was the most commonly encountered lesion in our study with higher incidence of occurrence in the parotid gland, which is well documented by Nanda *et al* and Cohen *et al*.[3,7] In this study, out of the 43 cases diagnosed as PA on FNAC, 37 cases were confirmed by HPE. The results also revealed a sensitivity of 100% and a PPV of 86% in diagnosis of PA; these results were also compatible with the rates found in other studies which ranged between 77-100%.[4, 8] The most frequent interpretational difficulty in FNAC of salivary gland lesions involve variations in the expected cytology of PA,[9] and even though FNAC is fairly accurate in diagnosing PA, occasionally problems may be encountered when differentiating PA from adenoid cystic carcinoma, monomorphic adenoma and mucoepidermoid carcinoma. This problem was also observed in our study in which false-negative findings occurred in one case of carcinoma ex-pleomorphic adenoma, one case of mucoepidermoid carcinoma and in one case of lymphoma. In all of these cases, an incorrect interpretation of PA was made on cytology.

The diagnosis of PA is usually fairly straight forward when there is a good mixture of both components. Diagnostic problem can arise when there is a marked overgrowth of one of components.[10] For instance, predominancy of stromal material can be mistaken for mucus, such as in benign cyst or low grade mucoepidermoid carcinoma, and predominancy of myoepithelial cells can be mistaken for myoepithelioma or spindle cell soft tissue tumour.[10] Other sources of misdiagnosis include predominancy of epithelial cells, which may be mistaken for ACC or other epithelial neoplasms depending on cell type, and presence of a mixture of glandular, squamous and mucinous cells, which can be mistaken for mucoepidermoid carcinoma.[10] Diagnostic problems may also occur in the presence of hyaline globules or bizarre cells.[11]

Mucoepidermoid carcinoma, the most common malignant tumour of major salivary glands, often poses a diagnostic challenge in cytology. The challenge is not only in relation to cytodiagnosis but also in cytological typing. This is because most of the aspirated material in these cases is made up of partly degenerated epithelial cells. It was previously observed that false-negative diagnoses often occur due to fluid diluting the tumour cells, inflammatory cells, and debris obscuring the tumour cells or sometimes because of bland-looking intermediate cells misinterpreted as benign cells.[3] This occurred in one of our cases that was erroneously diagnosed as PA on FNAC but proved to be a mucoepidermoid carcinoma on HPE.

Carcinoma ex-pleomorphic adenoma is an uncommon event reported to occur in 3-4% of PA. Clinically, a sudden increase in size of a tumour, that was present for years, signals the possibility of a malignant change. The main problem is to obtain a representative sample from this kind of tumour. In addition, if the malignant component is low grade, it can be misinterpreted as benign.[12] Klijanienko, El-Naggar and Vielh found carcinoma ex pleomorphic adenoma to have the highest false negative rate (35.3%) amongst all malignant salivary gland tumours.[13] In a study by Verma and Kapila[11] all cases of carcinoma ex pleomorphic adenoma on histology were interpreted as benign on cytology and they concluded that it is difficult to identify carcinoma ex pleomorphic adenoma on cytology.[11] There was one carcinoma ex pleomorphic adenoma in our study, diagnosed on cytology as a PA. The cause of misdiagnosis was that the malignant component was low grade and no obvious malignant features were seen on FNAC. The important diagnostic clue was the presence of a four years history of recurrent PA with sudden increase in size, which was overlooked in our case.

In an attempt to analyse which, if any, features might indicate a greater likelihood of malignant transformation of PA, Auclair and Ellis studied the atypical histological features (hypercellularity, capsule violation, hyalinization, necrosis, cellular anaplasia and mitotic rate) of PA. It was observed that tumours that showed prominent zones of hyalinization or at least moderate mitotic activity were more likely to develop carcinoma than those that did not. Clinical findings at the time of initial diagnosis indicating a greater likelihood of malignant transformation were lesions that occurred in the submandibular gland, older patients, and large size of the tumour. A sudden increase in the growth rate of a tumour that has been present for many years gives clinical support to the diagnosis.[12]

One case of malignant lymphoma which was reported as suggestive of PA was found to be a diffuse large B cell lymphoma (DLBL) in subsequent biopsy. Review of cytology smears indicate that the material aspirated was inadequate and not representative of the lesion. The stromal fragment present in the smear was wrongly interpreted as stromal material of PA. Cytological interpretation should not be made based solely on stromal component alone. Multiple sampling and adequacy of material are important requirements and would reduce the likelihood of error.

Hughes *et al* (2005) studied 6249 cases of salivary gland tumours and found the highest false-negative rates in cases of lymphoma (57%), acinic cell carcinoma (49%), low-grade mucoepidermoid carcinoma (43%), and adenoid cystic carcinoma (33%). Similar findings were observed in this study with one low grade mucoepidermid carcinoma and one case of malignant lymphoma.[14]

Cytology is less accurate in diagnosing specific lesions, especially those with a prominent lymphoid component including Warthin's tumour (WT). Numerous pitfalls in FNAC diagnosis of WT were identified. Normal intra and periparotid lymph nodes, as well as a variety of neoplastic and inflammatory lesions, can yield an abundance of lymphocytes in FNAC. Other than WT, acinic cell carcinoma, which often has a lymphocyte-rich stroma, malignant lymphoma, chronic sialadentits, lymphoepithelial cyst, and benign lymphoepithelial lesions may also result in misdiagnosis.[15]

In this study, out of 18 cases diagnosed as WT on FNA, four cases turned out to be non-neoplastic lesions on histology (Table 4) and three cases which were reported as non-neoplastic on FNA were found to be WT on histopathological examination, giving a sensitivity and PPV of 77.7% and 77.7% respectively for diagnosis of WT. This was consistent with previous studies, in which the sensitivity ranged from 65-89%.[15] The only one false-positive result of this study occurred in a case of Warthin's tumour, which was cytologically misdiagnosed as an acinic cell carcinoma. Oncocytic cells in WT can mimic acinic cell carcinoma cells due to abundant granular cytoplasm and round nuclei. Furthermore in some cases, numerous naked nuclei of acinic cell carcinoma can be difficult to be distinguished from lymphocytes in the smear background of WT.[16] The smears in our case was haemorrhagic but cellular, showing cells arranged in loose sheets and clusters displaying relatively abundant granular cytoplasm, moderately high N/C ratio with prominent nucleoli. The background showed lymphocyte-like bare nuclei admixed with cell debris and tingible body macrophages. A cytology report suggestive of acinic cell carcinoma (well differentiated) was made.

Clinically a vast majority of malignant salivary gland tumours behave in a manner similar to benign tumours. Therefore the primary challenge of FNA is differentiating benign lesions from malignant lesions, followed by subtyping the malignancy.[4] Assessment of FNAC of suspected salivary gland lesions should follow a step by step approach. The first aim is to decide whether the lesion is of salivary gland origin. The next step is to identify the cells and their morphology to classify them into non-neoplastic, and neoplastic categories.[3] Some diagnostic problems do occur in differentiating PA from malignant lesions and cause diagnostic pitfalls.

Pitfalls in diagnosis may also be due to sampling problems including false negative diagnosis in cystic tumours (PA, WT, low grade MEC and ACC), small size of lesion, regenerative epithelial hyperplasia and squamous metaplasia in sialadenitis or WT. Moreover, other sources of diagnostic errors were shown to be due to epithelial atypia and high celluarity in PA and overlapping cytological features such as hyaline stromal globules which are initially regarded as diagnostic features of ACC can occur in other tumours.[12] This needs a diagnostic approach based on specific criteria for diagnosis to avoid misinterpretation of FNAC.

An adequate and representative specimen is essential for proper cytological evaluation to reduce errors in diagnosis. Relevant clinical data and radiological findings, along with cooperation between the clinician and cytopathologist are essential in order to use FNAC to its best advantage. One of the limitations of this study was utilizing the reports from various pathologists with different experiences. It was previously shown that the experience of the pathologist is related with diagnostic accuracy.[17] It is recommended for further researchers to assess diagnoses made by a limited number of pathologists and with similar level of experience in order to improve the diagnostic accuracy of salivary gland lesions.

In summary, the results of this study demonstrate that FNAC is a safe and reliable diagnostic tool, in terms of sensitivity and

specificity, for the assessment of salivary gland pathology. One limitation of this study was the presence of several pathologists with different levels of experience for the cytological interpretation. It was previously shown that the level of experience of the pathologist is an important factor in improving the diagnosis accuracy of FNAC. Therefore, it is recommended for further research to minimise the number of pathologists to reduce the effect of experience on the accuracy of FNAC diagnosis.

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