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CASE REPORT

Salivary Gland Tumors: A Diagnostic Dilemma!

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Abstract Salivary gland tumors generate considerable interest because of their heterogeneous and variable histology, grade of malignancy, and clinical behavior. Fine needle aspiration cytology (FNAC) is considered the first diagnostic modality for salivary neoplasms due to its ready availability and ease of performance. However it cannot always be relied upon in isolation, and should be used in conjunction with other investigations like incisional biopsy. We present two cases, which highlight the drawbacks of relying on FNAC alone, which resulted in misdiagnosis of adenoid cystic carcinoma as pleomorphic adenoma.

Keywords Fine needle aspiration cytology · Salivary gland neoplasm · Pleomorphic adenoma · Adenoid cystic carcinoma

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Introduction

Arriving at a definite histopathological diagnosis still remains a challenge despite many recent advances in diagnosis and treatment of salivary gland tumours. These tumors generate considerable interest because of their heterogeneous and variable histology, grade of malignancy, and clinical behavior [1].

Fine-needle aspiration (FNA) cytology has been a widely used diagnostic technique and is considered to be the first tissue-based procedure applied to establish a diagnosis before any surgical intervention of a lesion. It is relatively inexpensive, quick to do, well accepted by patients, associated with low morbidity, and has a relatively high diagnostic accuracy [2]. However, its role in the diagnosis of salivary gland neoplasms is controversial due to the histological diversity of salivary gland lesions attributed to the presence of multiple tissues types and growth patterns, overlapping cytological features of malignant and benign tumors, quantitatively limited tissue sample collected and inexperience of cytopathologists in fine needle aspiration cytology (FNAC) reporting [1, 3].

The mainstay of FNAC in salivary gland disease is distinguishing benign from malignant. The sensitivity and specificity reported is high for benign lesions, whereas it decreases in cases of malignant tumors. This is not surprising in light of the great variety of morphological patterns found in malignant salivary gland tumors. It is possible to confuse malignant tumours such as mucoepidermoid and adenoid cystic carcinoma (ACC) with benign tumours such as pleomorphic adenoma and vice versa. Hence, it cannot always be relied upon in isolation, and should be used in conjunction with other investigations [4].

Fine needle aspiration cytology for salivary gland disease has not gained universal acceptance because of

reported complications of haemorrhage, turnout seeding within the needle tract, infection and lack of confidence in diagnostic accuracy [2]. Errors may occur in sampling tumours such as carcinoma arising in a pleomorphic adenoma where FNAC can miss the malignant component [4].

We present two case reports, which highlight the drawbacks of relying on FNAC alone, which resulted in misdiagnosis of ACC as pleomorphic adenoma.

Case Reports

Case Report 1

A 32 year old male complained of a swelling on the right side of neck since 5 years. The swelling was soft, painless and peanut sized initially and gradually grew to the present size. The swelling was not associated with any discharge or increase in size on eating.

On examination, there was a solitary swelling in the right side of the neck measuring 2 × 2 cm. The swelling extended 0.5 cm below the lower border of the mandible to the level of thyroid cartilage inferiorly and 2 cm behind the midline up to the angle of the mandible posteriorly. On palpation, the swelling was non-tender, firm in consistency, with no local rise in temperature. Intraoral examination revealed no significant findings. The submandibular gland duct orifice was patent.

Fine-needle aspiration cytosmear showed few clusters of epithelial cells, along with fibromyxoid fragments and a background of red blood cells. Ultrasonography (USG) revealed a well-defined hypo echoic lesion measuring 26 × 23 mm with surrounding normal submandibular gland and two enlarged submandibular lymph nodes measuring 11 × 14 mm.

Correlating the FNAC and USG findings, a provisional diagnosis of pleomorphic adenoma of the submandibular gland was made. The lesion was excised under GA. Excisional biopsy was reported as ACC of the submandibular gland. The patient was subjected to radiotherapy. After 2 years of follow up, there has been no sign of recurrence till date.

Case Report 2

A 35 year old male patient reported with the chief complaint of swelling in the left cheek since 3 years. The swelling gradually increased to the present size and was not associated with any pain or discharge.

On examination, there was a well-defined, solitary swelling in the left cheek region, measuring 2 × 2 cm. On palpation, the swelling was non-tender, firm in consistency, mobile with no local rise in temperature. Skin over the swelling was normal. Intraoral examination revealed obliteration of the left upper buccal vestibule.

Fine-needle aspiration showed few clusters of epithelial cells, along with fibromyxoid fragments and a background of red blood cells. USG revealed a well-defined hypo echoic lesion measuring 24 × 21 mm.

The lesion was provisionally diagnosed as pleomorphic adenoma after correlating FNAC and USG findings. Wide excision of the lesion was performed through an intraoral approach under GA. The final biopsy however reported the specimen to be ACC. The patient did not report for follow up.

One month post operatively patient again reported to our hospital with a recurrent swelling in the same area extending up to the temporal region. Re-exploration was done using Weber-Fergusson incision. The excised specimen reported the recurrent tumor as ACC. He was referred to a higher center for radiotherapy and further management but unfortunately he did not report.

Discussion

History and clinical examination remain important elements in the work-up of salivary gland pathologies. The typical signs and symptoms of malignancy, such as rapid growth, facial palsy, pain, and enlarged lymph nodes are present in only 10–35 % of salivary gland carcinomas [5]. Majority of cancers have unremarkable features and are indistinguishable from benign salivary gland neoplasms on clinical criteria alone, as was observed in both of our cases.

Imaging studies such as ultrasound (USG), magnetic resonance (MRI) and computed tomography (CT) can help to further characterize a salivary gland lesion. USG is a fast and non-invasive procedure and the imaging modality of choice in salivary gland pathologies. It is conclusive in majority of these lesions because of its multiplanar and real-time scanning and its high resolution, but it is incapable of reliably characterizing large lesions and masses involving the deep lobe of the parotid gland, which is obscured by the mandible [1]. USG in both cases, revealed well-defined, hypoechoic lesions and thus, in correlation with FNAC findings, a provisional diagnosis of pleomorphic adenoma was made.

For further evaluation of the exact extent and nature of the tumours, cross sectional imaging such as CT or MRI must be performed [6].

Computed tomography is the method of choice when inflammatory disease is suspected and coronal and sagittal reconstructions can be helpful in the evaluation of perineural spread [6]. MRI is the method of choice for palpable masses with a strong suspicion of neoplastic lesions [7].

Recently, new MR technologies such as Dynamic Contrast-Enhanced MRI (DCE-MRI), Diffusion-Weighted

MRI (DW-MRI) and Proton MR Spectroscopy (MRS) have shown promising results in the differentiation between benign and malignant salivary gland tumours [8].

Malignant salivary gland tumours can be differentiated from pleomorphic adenomas but not from Whartin tumours using DCE-MRI at a time of peak enhancement of 120 S [6].

The differentiation of benign and malignant masses is often difficult, however new MR techniques such as DCE-MRI, DW-MRI and MRS have already shown promising results and further research with larger scale studies on these particular methods have to be performed [6]. These investigations however are not readily available in all centers.

Clinical examination and conventional imaging techniques alone usually cannot reliably distinguish between benign and malignant diseases nor subclassify the pathologic process.

Fine needle aspiration cytology is widely used as a first-line technique for the diagnosis of salivary gland pathologies [1]. Kun first described aspiration cytology in 1847. The procedure was reintroduced in 1930 by Martin and Ellis [9]. FNAC of salivary glands was developed by Eneroth et al. [10] between the 1950s and the 1960s.

Since the salivary glands are located superficially, they are easily accessible to FNA and any palpable mass in the salivary glands may be aspirated. FNA is a cost-effective procedure that allows avoidance of unnecessary investigations and operations. Some centers have been able to reduce the number of patients with salivary gland masses undergoing surgery by 30 % by using FNA biopsy as a primary diagnostic tool. The procedure can be safely performed as an office procedure and is well tolerated by the patients [11].

Although 75 % of all tumors in the parotid gland and 20 % of all tumors of the minor salivary gland are benign, FNAC is helpful in distinguishing between benign and malignant pathology and salivary and other nonsalivary pathology. However many studies have highlighted its limitations including a high rate of false-negative results and poor accuracy for distinguishing between the various types of malignant salivary gland tumours [1].

The accuracy of diagnosis of malignancy exceeds 90 % in most series, although the type of malignancy can be difficult to determine [2]. However tumours such as PA are heterogeneous and it can be difficult to distinguish salivary adenomas from malignant lesions such as low-grade polymorphous adenocarcinoma, and ACCs due to the considerable overlap between the morphological patterns of salivary gland tumours found on cytology [4].

Adenoid cystic carcinoma is considered to be the second most common malignant salivary tumor, presenting clinically as long-lasting swellings, which can be painful and ulcerated, involving more frequently intraoral minor salivary glands and the submandibular gland [13]. However, in both of our cases, the lesions presented as slow growing, painless masses with no surface changes or nerve involvement thus giving the impression of a benign pathology.

Owing to its homogeneous cellularity, about one-third of all ACC are cytologically interpreted as benign neoplasms, especially PA, and several authors have called attention to the importance of evaluating the stromal component of ACC, a hallmark of its cytologic differential diagnosis [13]. It is also necessary to include PA as cytologic differential diagnosis of ACC especially when there is hypercellularity, scanty matrix, when ductal lumen formation mimics cylinders or frank cylinderomatous foci are present. But this tumor frequently shows plasmacytoid, ovoid, and spindle-shaped cells with dense and abundant cytoplasm, and the metachromatic substance is more fibrillar and irregular [12, 14, 15].

It is also quite possible that on fine needle aspiration biopsy, pleomorphic adenomas may be mistaken for other types of tumors such as mucoepidermoid carcinoma or ACC. The difficulties in distinguishing cytologically between some types of pleomorphic adenoma and well-differentiated ACC have been pointed out by Layfield and co-workers [12]. Tanaka et al. [16] in their study on aspiration cytology of tumors of major salivary glands found that ACC and low-grade malignancies such as mucoepidermiod carcinoma and acinic cell carcinoma were the lesions most frequently misdiagnosed. Both our cases were reported as PA on FNAC and reported as ACC after histopathological examination (HPE) of the excised specimen.

However, some cytologic features have been suggested to aid differentiation of PA and ACC: The embedding of the neoplastic cells within the extracellular matrix is characteristic of PA, in contrast to the smooth interface between tumor cells and intercellular matrix that forms the spheres and cylinders in ACC, although these features are not always easily identifiable [1, 12, 16].

The major salivary glands are associated with the lowest FNAC accuracy rates for differentiating benign from malignant disease and have questioned the use of FNAC in salivary gland lesions. Reported sensitivity rates often lie between 60 and 80 % but vary widely with the lowest rates of 38 % and 55 % reported by Balakrishnan et al. and Atula et al. FNAC is notoriously unreliable in recognizing the specific nature of malignant salivary gland tumours and providing a precise classification and grade [1]. A “negative” needle biopsy result must be analyzed critically based on the clinical picture [12]. The probability of tumour seeding also appears to depend on the number of passes made, which is particularly relevant to FNAC because needle aspiration often has to be repeated several times before a satisfactory smear is obtained [1].

According to literature since 1994, sensitivity, specificity, and diagnostic accuracies of FNAC in the salivary glandular lesions has been reported as 70–100, 91–100, and 84–98.3 %, respectively. Singh Nanda et al. reported that sensitivity, specificity, and positive and negative predictive values were 84.61, 91.66, 91.60, and 85.00 %, respectively, in benign salivary gland lesions, but 84.61, 86.48, 68.75, and 94.11 %, respectively, in malignant salivary gland lesions. There were no differences in sensitivity, but specificity and the positive predictive values were higher in the benign salivary gland lesions while the negative predictive value was higher in malignant lesions. Brennan et al. reported differences in the sensitivity and specificity between initial FNAC and repeated FNAC as 70 and 93 and 84 and 95 %, respectively [10].

However, it is important to emphasize that although ACC has well defined cytologic diagnostic criteria, the literature reports FNAC false-negative results of up to 33 % and specificity of near 50 % for this tumor [13].

Some authorities advocate the use of image-guided FNAC, which may be more accurate than FNAC. However, the problems associated with tumour heterogeneity still remain, as does the risk of a false negative result in tumours with malignant transformation such as carcinoma ex-pleomorphic adenoma. This could be attributed to the pathologist's skill, technique, interest and experience, which are important variables that influence FNAC results and likely account for the variance of sensitivity and specificity. Morton found, when comparing the results of clinicians and pathologists carrying out FNAC, that pathologists obtained 7 % unsatisfactory aspirates compared with 37 % by the clinicians. Others have suggested that the cytopathologist rather than the clinician should perform the aspiration [1, 2].

Frozen section (FS) has been discussed as an alternative approach to guide treatment intraoperatively but has also been associated with a high rate of diagnostic errors and low sensitivity. In recent years, percutaneous image-guided core needle biopsy (CNB) has gained widespread popularity for tissue sampling particularly of deep-seated masses throughout the body, however its limitation being a high probability of tumor seeding [1].

Although Hematoxylin-Eosin staining is still the gold standard used for the diagnosis, immunohistochemistry (IHC) can enhance the accuracy and be a helpful tool to assess parameters such as the cell nature and differentiation status, cell proliferation and tumor protein expression. For these reasons, IHC should be considered a method that can be used to assist the final diagnosis, and its results themselves do not directly indicate a definitive diagnosis [17].

Conclusion

The cytology of salivary gland lesions presents substantial difficulties to the cytopathologist as the complexity and variety of morphologic patterns contrast with the small size of the FNAC specimen. The unparalleled diversity of salivary gland lesions, which can be difficult to characterize even on paraffin section, make their diagnosis one of the most challenging areas in cytopathology [1].

In both of our cases we performed FNAC, which was suggestive of Pleomorphic adenoma relying on which, the treatment plan was framed. But due to the limitations of this diagnostic technique we missed the actual diagnosis, which increased the morbidity by many folds.

The highlight of this paper is that, while FNA is the mainstay of diagnosis of salivary gland tumors, it cannot always be relied upon in isolation, and should be used in conjunction with other investigations like incisional biopsy, IHC and newer MR technologies.

To increase the diagnostic accuracy in benign salivary glandular lesions, triple assessment consisting of cytologic features, clinical information, and radiologic findings is essential. Recognition of aspiration sites and the correlation with radiologic findings are important, and a detailed cytologic examination based on both typical and non-typical cytologic features will be needed [10].

We also propose that a specialized head and neck FNAC cytology request form should be used in every case to improve the quality of the clinical information available to the reporting cytologist, and that the results should be audited prospectively [4].

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