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Diagnostic Importance of Fine Needle Aspiration Cytologyin Diagnosing Pleomorphic Adenoma at Unusual Locations with Literature Review

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Abstract

Salivary glands are unique secretory glands due to its histological diversity and heterogeneity. More than 90% pleomorphic adenoma (PA) are found in majorsalivary gland i.e. parotid. This tumor is known to occur at various other anatomical locations apart from the major salivary glands. 8% of PAs involve the minor salivary glands of which 60-65% in the palate and 5.5% at minor salivary glands of cheek. Less frequent sites such as lacrimal gland, external auditory canal, breast and parapharyngeal space, reported sparsely in English literature. PA at breast and external auditory canal (EAC), can be challenging and may lead to a misdiagnosis, as invasive carcinoma. Involvement of parapharyngeal space are also rare and constitute less than 0.5% of head and neck neoplasm. We are presenting here a series of 10 cases of PA at unusual sites with an aim to highlight the role of FNAC, which has sufficiently high accuracy rate and can be a useful guide in making decisions for further management.

Keywords: Pleomorphic Adenoma; Unusual Sites; Aspiration Cytology; Diagnostic Accuracy.

Introduction

Pleomorphic adenoma (PA) is the most common benign tumour of salivary gland origin and accounts for about 60% of all salivary neoplasms [1]. The morphological diversity results from amalgamation of epithelial and stromal components.

The parotid gland is the most common site of PA and most often presents in the lower pole of the superficial lobe. About 10% of the tumors arises in the deeper portions of the gland which may presents as a parapharyngeal mass that constitutes just 0.5% of total head neck tumours [1]. PA are known to occur in other minor salivary gland sites, approximately in 8% of the cases including the lip, buccal mucosa and tongue, where 800–1,000 minor salivary glands located throughout the oral cavity [2]. Cytological diagnosis of this lesion can be very challenging, especially when limited sampleis available from unusual locations, such as breast, parapharyngeal space, lacrimal gland, external auditory canal.

Although quite unique in its morphology with associated clinical findings, cytological findings shares some similarities with differential diagnoses of phyllodes tumor, fibroadenoma, and metaplastic carcinoma in breast [3,4], in PA of breast. PA at external auditory canal is also very rare and thought to arise from ceruminous glands [5].

Awareness of this entity even at unusual locations should permit a definitive diagnosis by aspiration cytologywith the aid of imaging studies and is equally applicable to deep-seated lesions.

Materials and Methods

Clinical and pathological data was retrieved for the patients who were suspected as pleomorphic adenoma at unusual sites on cytology, which were confirmed on histopathology (Table 1). The aspirations were done by a 23 G needle attached to a 10-ml disposable

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syringe. The smears made were air-dried and stained with May–GrünwaldGiemsa (MGG), smears were also fixed in 95% ethanol and stained with Papanicolaou stain.

A cytological analysis was done and morphological features noted in individual case is tabulated in Table 2.

In case no 1 & 2, both patients were young and presented with proptosis and painless swelling of right eye since one year and eight months respectively (Figure 1a & 1b). The clinical differentials given were of malignancy and fungal infection. CT scan finding of case 2 revealed a well-defined, extra caval, enhancing, homogenous, soft tissue lesion with

Table 1: Clinical presentation, location and radiological findings with suspected clinical differential diagnoses

Case No.	Age/ Sex	Presenting symptoms and location of lesion	Radiological findings	Clinical differential diagnosis
1	35/M	Proptosis, **right eye**, painless mass – since one year	CT scan showed enhancing isodense soft tissue lesion in lateral aspect of extraconal space of right orbital cavity with erosion of lateral wall. Right eye ball displaced inferiorly with normal optic nerve.	1. Fungal infection 2. Neoplastic condition
2	25/M	Proptosis, **right eye,** painless mass - since 8 months	CT scan showed well defined, extra caval, enhancing, homogenous, soft tissue lesion with inferomedial displacement of ocular bulb with mild exophthalmos.	3. Fungal infection 4. Neoplastic condition
3	10/M	Proptosis, **right eye,** painless mass – since 6 months	CT scan showed ovoid heterogeneously enhancing mass lesion with few foci of calcification in right lacrimal fossa causing medial and downward displacement of right eye ball.	5. Fungal infection
4	13/F	Gritty sensation with presence of small nodule in **upper eyelid, left eye,** painless swelling - since ten months	CT scan showed small mildly enhancing ovoid soft tissue density lesion seen envolving inner aspect of eyelid on left side.	6. Pterygium 7. Meibomian gland carcinoma
5	42/F	Small painless firm nodule over **left cheek** – since ten year	USG revealed 2.5 x 2cm well defined soft tissue lesion in superficial aspect of left buccal region.	8. Fibroma 9. Mucoepidermoid carcinoma
6	30/F	Solitary mobile painless **right breast** mass in upper outer quadrant since last 6 months	USG showed lobulated, hypoechoic, soft tissue lesion at 2'o clock position.	10. Fibroadenoma 11. Ductal adenoma
7	26/M	Red colored painless nodular mass in **oral cavity** present in the soft palate, since 6 months	CT showed a well-defined, enhancing, hypodense soft tissue lesion of size 2 x 1.5 x 1.2 cm originating from left side of soft palate.	12. Pyogenic granuloma 13. Odontogenic cyst
8	15/M	Painless nodular mass towards the **base of tongue**, presented with difficulty in swallowing and change in voice, since 8 months	CT showed a large 7.5 x 5.5 x 4.5 cm heterogeneously enhancing tumor in the right parapharyngeal space.	14. Neoplastic condition **15.** Heterotopic tissue mass
9	32/M	Small painful firm nodule towards the **right external ear canal** – since 4 months	USG revealed hypoechoic soft tissue density lesion envolving the cartilaginous part of external ear.	16. Fibroma 17. Obstruction and blockage of ceruminous gland 18. Nerve sheath tumor
10	24/F	Small painless reddish bulge over the **upper lip** noticed since 6 months	USG showed small hypoechoic lesion with minimal internal vascularity at right upper lip.	19. Inflammatory pathology 20. Benign neoplastic condition

Table 2: Cytological findings with Cytological differential diagnosis in individual cases

Case No.	Cytological findings	Cytological diagnosis
1.	Scant cellularity with presence of occasional cluster of myxoid stromal fragment mimick fibrillary material. Occasional singly scattered plasmacytoid cells also seen.	Benign nerve sheath tumor / Benign mixed tumor
2.	Moderate cellularity with presence of occasional fragment of ductal epithelial cells tend to form gland and acini also. Stromal fragment not seen.	Meibomian gland tumor/ Benign mixed tumor
3.	Scant to moderate cellularity revealed mixed stromal epithelial fragments dispersed singly and in sheets with fibrillary chondromyxoid stroma.	Benign mixed tumor
4.	Scant cellularity with presence of occasional cluster of epithelial cells in acinar pattern and few singly scattered plasmacytoid cell.	Meibomian gland tumor / Benign mixed tumor
5.	Scant cellularity with presence of predominantly singly scattered plasmacytoid cells and chondromyxoid fragment.	Benign mixed tumor / plasmacytoma
6.	Moderate cellularity with presence of ductal epithelial cells forming gland and acini along with stromal fragments and plasmacytoid cells.	Benign proliferative breast disease
7.	Cellular smear with presence of predominantly plasmacytoid cells and cluster of ductal epithelial cells.	Plasmacytoma / Mixed tumor
8.	Moderately cellular smear with presence of ductal epithelial cells mainly in cluster with few singly scattered plasmacytoid cells.	Plasmacytoma / Mixed tumor
9.	Scant cellularity with presence of few spindle cell cluster and chondromyxoid fibrillary material.	Spindle cell lesion / mesenchymal tumor
10.	Scant cellularity with presence of only myxofibrillar material and mixed inflammatory cells mainly lymphocytes.	Inflammatory pathology / lymphoepithelial lesion

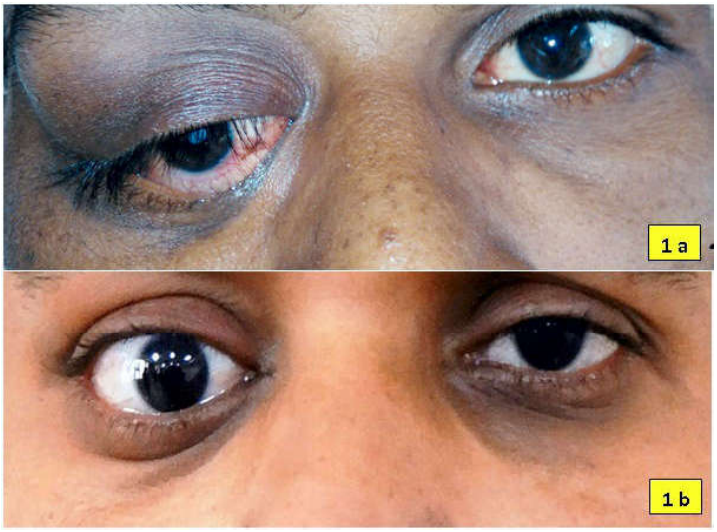

Fig. 1a & 1b: Clinical photograph showing proptosis of right eye in a 25 years and 35 years old patient

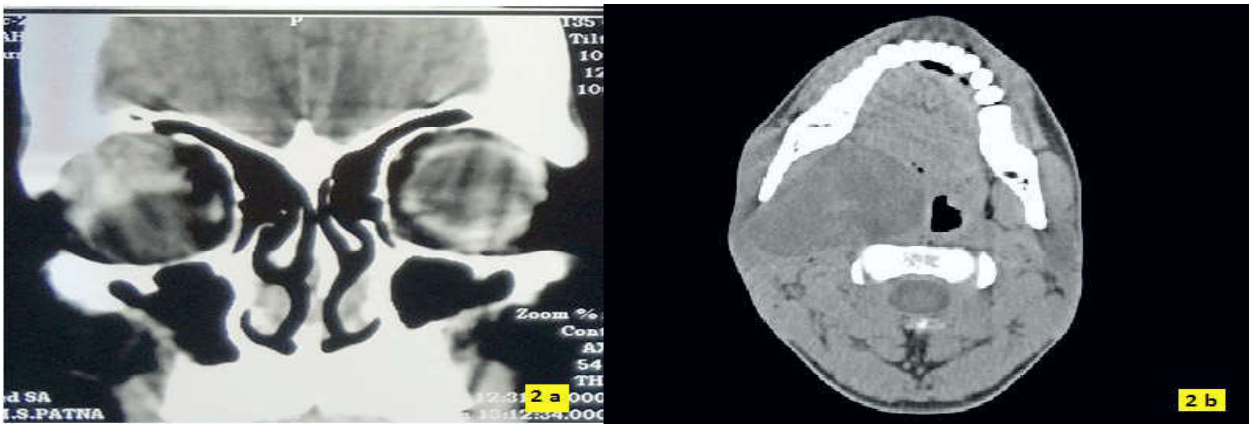

Fig. 2a: Computed tomography scan showed well defined, extra caval, enhancing, homogenous, soft tissue lesion with inferomedial displacement of ocular bulb with mild exophthalmos. **Fig. 2b:** Computed tomography scan showed a large 7.5 x 5.5 x 4.5 cm heterogeneously enhancing tumor in the right parapharyngeal space

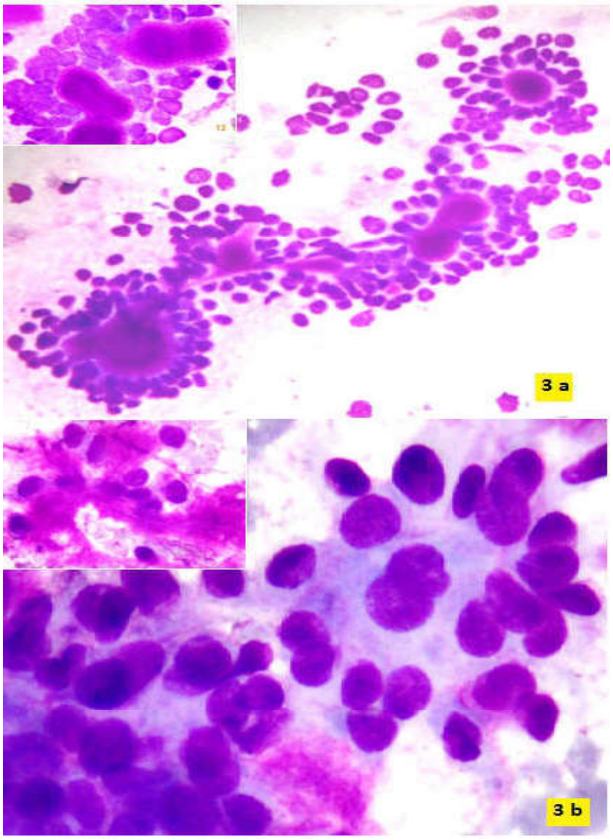

Fig. 3a: Photomicrograph showing hyaline stromal globules surrounded by epithelial cells resembling adenoid cystic carcinoma like areas (MGG stain 10 x 10). Inset showing hyaline globules. **3b:** Photomicrograph showing bland epithelial cells arranged in cohesive clusters, individually or in tubular arrangements in extracellular myxoid stroma (MGG stain 10 x40). Inset shows- myoepithelial cells embedded in chondromyxoid stroma

inferomedial displacement of ocular bulb with mild exophthalmos (Figure 2a). Cytomorpholological features of both cases were suggestive of benign mixed tumour.

FNA of case no. 3 & 4 had been done under sedation with ultrasound guidance. On follow up, none of the above mentioned cases showed recurrence.

Case no. 5, aspiration from the cheek swelling yielded mucoid fluid. Cytology raises the suspicion of low grade mucoepidermoid carcinoma and adenoid cystic carcinoma but characteristic chondromyxoid stroma was also present. Cytological diagnosis of pleomorphic adenoma with adenoid cystic like areas was made. (Figure 3a & 3b)

Case no. 6, 7, 9 &10, aspiration from the breast lump, soft palate, right external ear and upper lip swelling respectively, none of these cases were suspected clinically as pleomorphic adenoma, even in cytology, mixed tumor was kept in second differential diagnosis.

Case no. 8 where patient presented with a painless nodular mass towards the base of tongue with difficulty in swallowing and change in voice since 6 months. CT showed a large 7.5 x 5.5 x 4.5 cm heterogeneously enhancing tumor in the right parapharyngeal space (Figure 2b). Ultrasound guided FNA cytology was done yielded whitish mucoid material. Cytology raises the suspicion of pleomorphic adenoma which was excised and confirmed on histopathology.

Discussion

The term pleomorphic adenoma was first suggested by Wills [6]. PA is defined by WHO in 1972 as "a circumscribed tumour characterized by its pleomorphic or mixed appearance clearly recognizable epithelial tissue being intermingled with tissue of mucoid, myxoid or chondroid appearance" [6]. It often presents in 3rd to 6th decade of life with slight female predilection [7]. The synonym "mixed tumour" is a misnomer, though it comprises of a mixture of epithelial and mesenchymal cells [7]. It usually presents as slow growing or painless mass. The diagnosis of pleomorphic adenoma is made on the basis of history, clinical examination, cytomorphology and histopathology [8]. Computed tomography scan and magnetic resonance imaging studies can provide information regarding location, size, and extension of tumor.

Most common benign epithelial tumor of lacrimal gland is pleomorphic adenoma [9]. Tumors of the lacrimal gland are unusual location for fine needle aspiration cytology [10]. FNAC of orbital lesion is now increasingly popular, especially with advent of imaging technique.Diagnosis is based on clinical characteristics and radiologic findings, and can usually be made prior to surgical intervention. Lacrimal gland neoplasms constitutes 7-9% of all orbital tumors [9]. Amongst all, the pleomorphic adenoma of lacrimal gland comprises 3-5% of all orbital tumors, 25% of all lacrimal gland lesions and 50% of epithelial lacrimal gland tumors [11]. Clinically it presents as a painless, progressive, slow growing mass with exophthalmos. The age incidence of this entity is usually found in adults and rare in extremes of age. Histologically, the lacrimal glands are similar to the histology of salivary glands in the lobular structure. It is composed of acini with an inner layer of cuboidal to columnar zymogen-bearing cells and an outer layer of myoepithelial cells [9,11].

In our case series, four cases of pleomorphic adenoma of lacrimal gland was diagnosed on cytology

and later on confirmed on histology. Clinical differential diagnoses in these four cases were fungal infection, pterygium and neoplastic etiology. The cytological diagnosis of PA was rendered and it was a great relief for clinicians. Tumour was surgically excised and after excision all cases regain their visual acuity. In a study of unusual locations of PAs done by Nouri H et al, only one case of lacrimal gland PA was diagnosed out of seven cases [12]. In a study done by Rodrigo R et al on primary epithelial neoplasms of lacrimal gland, the diagnosis of five cases of lacrimal gland PA was made out of twelve cases [9].

Most common site of occurrence of pleomorphic adenoma in minor salivary glands are the palate (42.8 – 68.8%), followed by lips (10.1%) and cheeks (5.5%) [6]. PA cheek usually presents as painless, well circumscribed, firm, slow growing submucosal mass [13]. Patients usually present in their 4^{th} to 6^{th} decades of life with slight female predilection. In our case, it was presented as 2.5 x 2 cm firm nodule over left cheek since one year. Unguided aspiration was done. Cytological diagnosis of pleomorphic adenoma with adenoid cystic like areas was made which was confirmed on histology. Differential diagnoses reported as lipoma, fibroma, neurofibroma, buccal abscess, dermoid cyst, rhabdomyoma, sebaceous cyst, mucoepidermoid carcinoma and polymorphous low grade adenocarcinoma in a cheek mass, pleomorphic adenoma should be considered in the differential diagnosis of cheek mass [14].

Pleomorphic adenoma in the breast is a very rare entity. Less than 100 cases reported till date [3,4].Both breast glands and salivary glands are tubuloacinar exocrine glands, hence pleomorphic adenoma may develop from those glands. Even male breast can also develop from pleomorphic adenoma. It often occurs in women in 3^{rd} to 6^{th} decade. Female: male ratio is 10:1. It is asymptomatic usually and clinically presents as well circumscribed, firm, palpable retro areolar lump [3]. First case of pleomorphic adenoma in breast was reported by Lecene in the year 1906 [4]. Most common differential diagnoses of pleomorphic adenoma of breast is ductal adenoma, fibroadenoma, intraductal papilloma with chondro–osseous differentiation, metaplastic carcinoma, mucinous/ colloid carcinoma and phyllodes tumour [3,4].

Among minor salivary gland, palate is the most common intraoral site of pleomorphic adenoma [15]. It presents clinically as a painless, slow growing, apparently fixed mass on the postero–lateral aspect of soft palate [16]. Often it presents in 4^{th} to 6^{th} decades of life with female: male ratio is 2:1. The likelihood of malignancy in salivary gland neoplasm is inversely proportional to the size of the gland. The differential diagnoses reported of palatal swelling are palatal abscess, pyogenic granuloma, odontogenic and non-odontogenic cysts, salivary gland tumors and soft tissue tumors (fibroma, neurofibroma). The diagnosis was confirmed on the basis of case history, clinical examination, cytomorphology and histomorphology.

Pleomorphic adenoma of parapharyngeal space may arise either as a primary (de novo) neoplasm or as a extension from the deep lobe of parotid gland. Primarily it may arise from the aberrant or displaced epithelial rests of salivary gland tissue within a lymph node which is very rare [1,17].

Pleomorphic adenoma at parapharyngeal space constitutes 80–90% of all benign neoplasms of parapharyngeal space [18]. Literature review have shown very few cases of primary pleomorphic adenoma of parapharyngeal space. It may presents with dysphagia, odynophagia, dysarthria, hoarseness of voice or can be silent clinically. In our case patient presents with dysphagia and hoarseness of voice. Clinical differentials given were neoplastic condition and heterotopic tissue mass. FNA was done under the guidance of ultrasonography preoperatively for definite management. The diagnosis of mixed tumour was given on cytology which was confirmed by histopathology.

Pleomorphic adenoma of external auditory canal arise from cerumen secreting modified apocrine glands [5]. It is an unusual anatomic site and slightly more common in males than females. Previously it was called ceruminoma. Approximately 5% of all external ear tumours are benign adenomas [19]. It usually presents as well defined, slow growing, painless mass. First case of pleomorphic adenoma arising in the ear canal was reported by Mark and Rothberg in 1951 [20]. Benign tumours of ceruminous glands are ceruminous adenoma, ceruminous pleomorphic adenoma and syringocystadenoma papilliferum [21]. In our case a small painful, firm nodule was present towards the right external auditory canal. FNA was performed and diagnosis of pleomorphic adenoma was suspected, which was confirmed on histopathology.

Pleomorphic adenoma of lip is a rare entity. It mainly affect females in their 4^{th} - 6^{th} decades of life. Definitive etiology is not known. There is a predilection for benign tumours to occur on the upper lip, whereas malignant lesions predominate on the lower lip [22]. Our case, a 24 years old female presented as small (1.5 x 1cm), painless reddish bulge over the right upper lip since one month with the complaint of loss of sensation over the bulge. Aspiration was done and cytology was conclusive of pleomorphic adenoma.

Wide complete surgical excision is the treatment of choice in all unusual locations of pleomorphic adenoma. Higher recurrence rate is observed in tumours having incomplete excision, rupture or spillage of tumour during removal, excess of chondromyxoid stroma, protuberances beyond main tumour (satellitosis) and young age.The likelihood of malignancy is increased with tumour recurrence. Factors associated with an increased risk of malignant transformation are; older age, long – standing tumour, submandibular location, and large size, areas of hyalinization and presence of moderate mitotic activity [23].

Conclusion

Morphological diversity of pleomorphic adenoma makes the diagnosis of this tumour a challenging task for pathologist, radiologist as well as for clinicians. Hence, one should be aware of its various anatomic sites of occurrence especially at unusual locations where likelihood of misdiagnosis is more. Proper pre-operative clinical, radiological and cytological evaluation should be done with the understanding of anatomical occupancy, pathology of the disease and must be carefully evaluated in order to exclude other differentials. An optimum but generous approach is mandatory to avoid any form of risk.

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