



VARIABLE METAPLASTIC ENTITIES IN PLEOMORPHIC ADENOMA - A REVIEW OF A RARE CASE REPORT WITH A NOTE ON ITS SIGNIFICANCE

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SUMMARY

Pleomorphic adenoma is the most common benign salivary gland neoplasm principally affecting the parotid gland of the salivary gland and the palate of the minor salivary gland. The term pleomorphic is assigned due to its varied histopathological presentation. We hereby describe a rare case of pleomorphic adenoma in a male patient in his 7th decade of life complaining of swelling in the hard palate for the past 3 years. This case report emphasizes the unique representation of squamous and lipomatous differentiation which was erroneously diagnosed as OSCC or mucoepidermoid carcinoma. We have also included a literature search of such cases that exhibited lipomatous and squamous differentiation in PA listed from the last 10 years.

Key words: pleomorphic adenoma, minor salivary gland, lipomatous differentiation, squamous differentiation.

INTRODUCTION

The benign salivary gland tumor termed pleomorphic adenoma (PA) is a benign mixed tumor previously referred to as enclavoma, branchioma, endothelioma, and enchondroma. Willis is credited for suggesting the term pleomorphic adenoma. (1, 2) It is reported in 80% of benign salivary gland tumors. It comprises 54%-65% of the total salivary gland neoplasia, thus indicating that benign tumors (PA) most frequently arise in the major and minor salivary gland. 80% of PA is reported in the parotid gland, while 10% present in the submandibular gland and sublingual glands respectively. The occurrence of PA in the minor salivary gland in descending order is 50%-60% in the hard palate, 15%-20% in the upper lip, and 8%-10% in the buccal mucosa. (3, 4) Most commonly, PA is noticed in the average range of 40-60 years of age with a high predilection for females. (5) The clinical presentation reveals a slow growing swelling which is not associated with pain. It is not fixed to the deeper tissues and it rarely affects the facial nerve. (6) It has a spectrum of histopathological features comprised of epithelial & myoepithelial cells in ductal and non-ductal patterns in the mesenchymal stroma comprised of chondroid, myxoid and osseous areas. Histomorphologically, authors have also reported cases of this benign salivary gland tumor that exhibits either squamous metaplasia or lipomatous and mucinous differentiation in their connective tissue stroma. (3, 7, 8)

We hereby present a case report of PA occurring in the minor salivary gland present in the palate in an adult patient with unusual histologic representation of squamous, mucinous and lipomatous differentiation in the same case.

CASE REPORT

A 70-year-old male patient visited the Oral and Maxillofacial Pathology Department in the Kalinga Institute of Dental Sciences, Bhubaneswar, Odisha with a principal complaint of a bulge in the hard palate for 3 years. (Fig-

ure 1a) The patient reported a painless swelling in the hard palate region which was small in size initially and enlarged gradually to the present size. The patient was apparently healthy with no past medical concerns. The past dental history revealed an edentulous maxilla with an extraction of 37, 46, 47, 48 prior to the appearance of the swelling. During an extra-oral examination, there were no signs of facial asymmetry and lymphadenopathy. Intra-oral examination revealed a lobulated swelling measuring 7×5 cm in the hard palate that extends in the antero-posterior direction encompassing the incisive papilla and maxillary tuberosity and partly involving the soft palate, medially from the midline to the alveolar crest on either side of the maxilla. The covering mucosa seemed stretched and smooth. On palpation the swelling was firm in consistency, non-tender with well-defined margins. The occipitomental radiograph revealed mixed radiopacity and radiolucency of the maxillary sinus and expansion of the palatal shelves of the maxilla. (Figure 1b) Based on the clinical and radiograph findings, a multilocular cystic swelling was inferred as the provisional diagnosis. Incisional biopsy was done and three bits of tan-colored irregularly shaped tissue specimen were sent for histopathological evaluation.

The histopathological examination revealed an amalgamation of polygonal epithelial and spindle-shaped myoepithelial components along with mucoid, myxoid, chondroid and hyalinised stroma encapsulated within the fibrous capsule. (Figure 2a-2c) Cystic spaces were seen in the connective tissue stroma of varying sizes which contained nests of epithelial cells manifesting squamous differentiation and formation of keratin pearl. (Figure 3d) The tumor also exhibited fat cells interspersed between epithelial and myoepithelial components and surrounded by ducts, minor salivary gland acini, endothelial lined blood vessels and chronic inflammatory cell infiltrate suggestive of lipomatous differentiation. (Figure 2e) Epithelial cells were arranged in sheets, interlacing strands and duct-like structures

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containing mucoid material, which was confirmed by the PAS stain. (Figure 2f) The final diagnosis was concluded as Pleomorphic adenoma with squamous, mucinous and lipomatous differentiation. The excision of the whole encapsulated mass was done surgically. The pathological determination was consistent with the report of the incisional biopsy. The surgery was uneventful. The patient was later reviewed for a couple of years. No history of recurrence was seen.

DISCUSSION

Neoplasm development in the salivary gland is very infrequent. It constitutes only 3% of all head and neck tumors. Salivary gland neoplasms commonly develop in the major salivary gland. Only 22% of cases are reported in minor salivary glands according to past literature. Benign PA usually arises in major and minor salivary glands and accounts for two third of salivary gland neoplasms. (9, 10).

The etiopathogenesis of pleomorphic adenoma is unknown but reports of its incidence are reported on exposure to long-term radiation and use of tobacco. Recent studies have also stated that the origin of neoplasm might also be associated with the simian virus (SV 40). Cytogenetic studies have hypothesized that increased expression of PLAG1 (zinc finger proto oncogene) results in the initiation of the mixed tumor. The increased expression of PLAG1 is attributed to chromosomal rearrangement of 8q12 which regulates β -catenin expression located on the CTBNNB1 gene promoter and leukemia inhibitory factor receptor (LIFR) gene located on chromosome 5. Other genetic alterations like insertions and amplifications can also induce PLAG1 expression that can be ascertained by molecular techniques like the reverse transcription polymerase chain reaction. Mutation in 12q13-15 such as rearrangements or amplifications of the HMG2 gene is also implicated in the induction of benign PA and malignant counterparts such as carcinoma ex pleomorphic adenoma (11).

According to the site, the palate (42.63%) is the most prevalent site of development and its frequency in descending order occurs in the lip, buccal mucosa, retro molar area, tongue and the floor of the mouth (12, 13, 14). Under histopathologic examination the neoplastic cells of the mixed tumor have the potential to undergo differentiation into fibrous, myxoid, chondroid and osseous tissue. (6) Our case report on pleomorphic adenoma comprises extensive histologic variations such as squamous metaplasia and lipomatous differentiation. Pleomorphic adenomas of the palate are mostly seen in the elderly i.e. 4th to 6th decade of life, which is in consistence with our case as stated by Arumugam et al (14). Pleomorphic adenomas are reported to have a female predilection, which is in contrast to our case. Similar reports were reported by Sonal et al and Gaurav et al. (8, 15).



Figure 1a. Intraoral clinical presentation of a lobulated swelling in the hard palate measuring 7 cm x 5 cm and overlying mucosa appearing pale, stretched and smooth.

Figure 1b. Occipitomental radiograph revealed mixed radiopacity and radiolucency of the maxillary sinus and expansion of the palatal shelves of the maxilla.

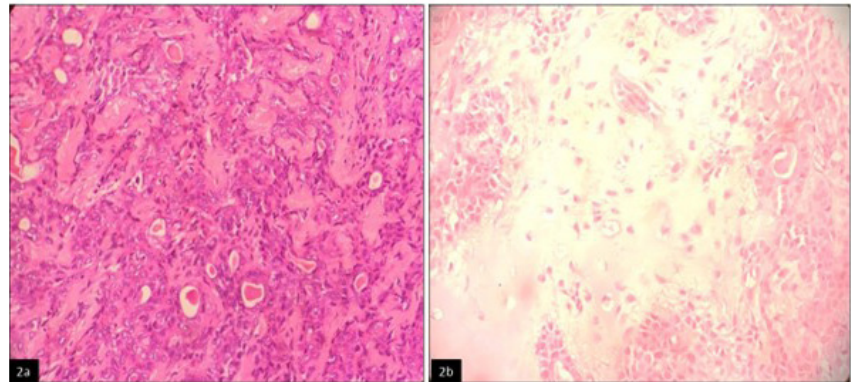


Figure 2. Histopathological pictures

2(a) Photomicrograph showing epithelial and myoepithelial cells with mucoïd areas in pleomorphic adenoma (x10, hematoxylin and eosin stain), **2(b)** Malignant cells admixed with chondroid and osseous areas in pleomorphic adenoma (x10, hematoxylin and eosin stain).

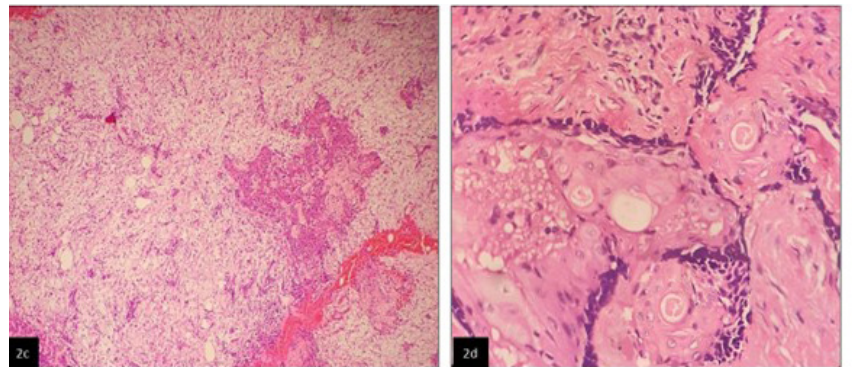


Figure 2(c) Photomicrograph showing sheets of neoplastic cells in a background of myxoid stroma of pleomorphic adenoma (x10, hematoxylin and eosin stain), **2(d)** tumor cells with squamous metaplasia (x40 hematoxylin and eosin stain).

Clinically, several authors have reported that pleomorphic adenoma arising in the palate appear as a slow-growing, painless, non-ulcerated swelling which is fixed to the mucosa of the hard palate in correspondence with our case (9, 10, 14).

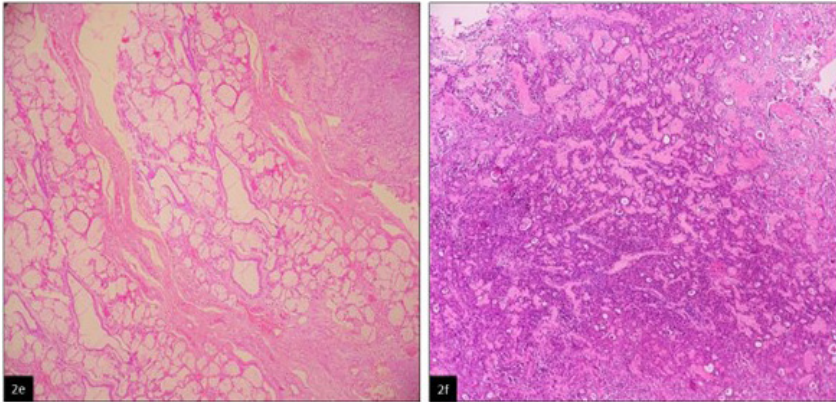


Figure 2(e) Photomicrograph showing tumor cells with lipomatous differentiation (x10, hematoxylin and eosin stain), **2(f)** sheets and islands of tumor cells with mucoid deposit in pleomorphic adenoma (x10, PAS stain).

and consequently the central cells undergo metaplasia. PA with extensive areas of squamous metaplasia can be misdiagnosed as oral squamous cell carcinoma or mucoepidermoid carcinoma or carcinoma ex pleomorphic adenoma (17). However, it can be differentiated from the abovementioned malignancies by the presence of myoepithelial cells which were variable and ranging from angular, spindle-shaped ones to rounded or oval-shaped ones with an eccentrically placed nucleus. The myoepithelial cells are believed to produce mucoid material responsible for the myxomatous stroma and various stromal alterations including differentiation into cartilaginous, osseous and chondroid areas produced by the myoepithelial cells (16). Few cases of this benign neoplasm also exhibit lipomatous differentiation as demonstrated in our case. Siefert et al is credited for the use of the term lipomatous pleomorphic adenoma. The exact mechanism of this fat cell metaplasia is not completely explainable. The most probable mechanism is that the myoepithelial cells being transformed into lipomatous metaplasia or entrapment of fat cells within the tumor during its expansion might be associated in the histogenesis of lipomatous variant of pleomorphic adenoma (18). (Table 2)

The treatment modality of PA emerging from the minor salivary gland involves a complete wide excision of the encapsulated mass including normal tissue as the margin. Enucleation is contraindicated as it can result in the rupture of the capsule and seeding of neoplastic cells resulting in recurrences. Recurrent PA is prone to malignant alteration such as carcinoma ex pleomorphic adenoma, carcinosarcoma and metastasizing pleomorphic adenoma. Malignancy incidence varies from 1.6% for less than 5 years to 9.4% with a longer duration of more than 15 years as reported by Khalesi S Et al. Chromosomal aberrations in 12q genes, HMGIC, HMGA2, and MDM2 are indicated in the malignant change of PA into carcinoma ex pleomorphic adenoma (19).

CONCLUSION

PA is considered one of the common benign salivary gland tumors seen with diverged histopathological representation. These overlapping histological features can result in misdiagnoses of the tumor owing to amendment in the therapeutic approach. Hence, an early diagnosis of the tumor, along with total wide excision, is a prerequisite in the prevention of local recurrence and malignant transformation.

Declaration of Interests

Authors declare no conflicts of interest.

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No	Age in years	Gender	Site	References
1	84 years	Female	Left Jugulodigastric region	Donohoe, E (22)
2	35 years	Female	Palate	Kaveri, H (23)
3	57 years	Female	Right neck region	Ito, H (24)
4	39 years	Female	Palate	Singh, A (25)
5	50 years	Female	Palate	Sharma, S(26)
6	70 years	Male	Right parotid	Jitendra, NG (27)
7	26 years	Male	Palate	Rajana, ST (28)
8	37 years	Male	Palate	Jaishahankar HP (29)
9	62 years	Male	Palate	Pattanayak, R (30)
10	60 years	Female	Soft palate	Pattanayak, R (30)

Table 1. Ten-year literature search of case reports of pleomorphic adenoma with squamous metaplasia.

No	Age	Gender	Location	Histopathological features	Reference
1	58	Male	Hard palate	Lipomatous metaplasia	Klibi- Farah F (20)
2	32	Female	Hard palate	Lipomatous metaplasia	Musayev, J (21)
3	24	Male	Hard palate	PA with significant adipose tissue component	Donohoe, E (22)

Table 2. Lipomatous differentiation of pleomorphic adenoma arising in the hard palate reported in ten years.

Histopathologically, in accordance with the nomenclature, pleomorphic adenoma shows pleomorphism or a wide diversity of histologic presentation. The tumor consists of epithelial and myoepithelial components. The stroma is myxomatous and neoplastic cells are arranged in various patterns. The tumor exhibits an unequal ratio of epithelial to myoepithelial components. The epithelial element appears as polygonal in shape, arranged in ductal patterns or sheets in the background of myxomatous stroma. These epithelial cells undergo squamous metaplasia with islands showing keratin pearl formation and mucinous differentiation also as depicted in our case (16) (Table 1). Infarction and ischemia in the intratumoral region are responsible for the transformation into squamous metaplasia. The genetic switch of cytokeratin filaments results in gradual dedifferentiation and hyperplasia of acinar and ductal cells,

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