Case Report

Rare histologic presentation of pleomorphic adenoma: A diagnostic dilemma

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Abstract

Pleomorphic adenoma is the most common benign salivary gland tumor deriving its name from varied morphological patterns in histopathology. The presence of chondromyxoid stroma in histopathology is characteristic of pleomorphic adenoma. Cellular variants without characteristic chondromyxoid stroma are rare and often pose a diagnostic challenge. We report a case of pleomorphic adenoma involving minor salivary glands of the palate presenting with a predominantly cellular histopathology. Immunohistochemical workup was pivotal in the diagnosis of this challenging case.

Keywords: Minor salivary glands, moderately cellular, palate, pleomorphic adenoma, salivary gland tumor

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INTRODUCTION

Salivary gland tumors are complex entities characterized by morphologic diversity and genetic heterogeneity.[1] Salivary gland tumors are rare constituting <0.5% of all cancers and only ~6% of head-and-neck cancers.[2] Eighty percent of all salivary gland tumors occur in the parotid of which 80% are benign. Minor salivary gland involvement (9%–23%) is less common than major salivary glands. However, tumors of minor salivary glands are more likely to be malignant.[2]

Pleomorphic adenoma is the most common benign salivary gland tumor.[3] It is common in the parotid gland followed by minor salivary glands of the palate and submandibular gland and is characterized by diverse morphological patterns (hence called mixed tumor).[4] It is a biphasic tumor defined by varying proportions of dual luminal ductal and abluminal myoepithelial cells.[2]

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Pleomorphic adenomas represent 45% of all minor salivary gland tumors.[5] Pleomorphic adenomas of minor salivary glands present with distinct clinical and histopathologic patterns. Classic cases of pleomorphic adenoma present as an even admixture of cellular and stromal elements. In rare instances, pleomorphic adenoma presents with a predominance of cellular stroma and a scanty stroma. This case report is one such example which was diagnostically challenging.

CASE REPORT

A 34-year-old female patient reported with the chief complaint of swelling in the right upper back region of the roof of the mouth for the past 1 month. History revealed that the patient had dull pain for the past 2 weeks and had noticed the swelling accidentally a month back. The pain

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aggravated on mastication and was relieved on medication. The patient developed the habit of pressing the swelling with her finger ever since she noticed it. During one such episode, she noticed mild bleeding from the swelling. She also added that the swelling neither increased in size nor she noticed any pus discharge. Medical, surgical, dental, family and personal history were noncontributory. There were no abnormalities detected on general physical examination and all her vitals were in the normal range. Extraoral examination did not reveal facial asymmetry or palpable lymph nodes.

Intraoral examination revealed a solitary, diffuse, ovoid and sessile mass on the right posterior part of the hard palate measuring 2 cm × 3 cm approximately [Figure 1]. It extended from 15 to 18 anteroposteriorly and mesiodistally from palatal gingival margins (in relation to 15–18) to 1 cm from mid palatine raphae. The surface of the lesion was smooth with the color of the adjacent normal mucosa. A focus of ulceration was seen on the surface measuring 0.2 cm in diameter. Involved teeth were not mobile. On palpation, inspectory findings of site, size, shape and surface were confirmed. The growth was nontender, nonfluctuant, firm in consistency and immobile. Clinical differential diagnosis included tumors of minor salivary gland origin such as pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma and polymorphous adenocarcinoma.

Routine hematological and radiological investigations were done. Baseline hematological parameters were within the normal limits. Orthopantamograph revealed no hard tissue involvement or any pathology related to it [Figure 2]. Computed tomographic (CT) sections revealed a soft-tissue density measuring 2.3 cm × 1.5 cm × 1.7 cm on the right roof of the oral cavity, in the right lateral aspect of the hard palate with no definite extension to retromolar regions, nasal cavity or pterygopalatine fossa. CT report concluded it as a neoplastic pathology and suggested histopathologic correlation [Figure 3]. A provisional diagnosis of minor salivary gland pathology of the right palate was established.

After obtaining informed consent from the patient, total excision of the lesion was done under local anesthesia [Figure 4]. The biopsy specimen was received in 10% buffered formalin. Microscopic examination of hematoxylin and eosin-stained section revealed a peripheral, incomplete capsule surrounding sheets, strands and cords of polyhedral squamous epithelial cells exhibiting duct-like structures containing eosinophilic material in the lumen [Figure 5a]. Angular- and stellate-shaped cells were also found interspersed with homogenous, eosinophilic, hyalinized areas [Figure 5b]. "Cribriform-like" pattern containing multiple cyst-like spaces was evident in few areas [Figure 5c]. Few plasmacytoid cells with eosinophilic cytoplasm and eccentrically placed nuclei representing myoepithelial cells were present [Figure 5d]. The lesion was predominantly cellular without the presence of chondromyxoid stroma. Characteristic epithelial component, hyalinized areas with the presence of plasmacytoid myoepithelial cells were suggestive of pleomorphic adenoma. However, adenoid cystic carcinoma and polymorphous adenocarcinoma were considered in histopathological differential diagnosis due to the presence of cribriform-like areas.

The predominantly cellular nature of the lesion with the presence of cribriform-like areas warranted immunohistochemical investigations for confirmatory diagnosis. Immunohistochemically, the tumor cells were positive for vimentin, smooth muscle actin [SMA, Figure 6a] and glial fibrillary acidic protein [GFAP, Figure 6b] affirming the diagnosis of pleomorphic

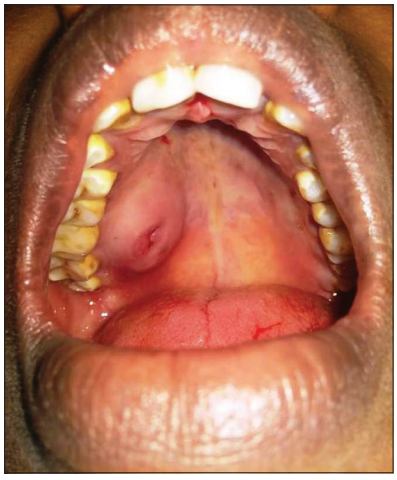

Figure 1: Intraoral photograph showing a solitary, diffuse and ovoid swelling in the right posterior hard palate

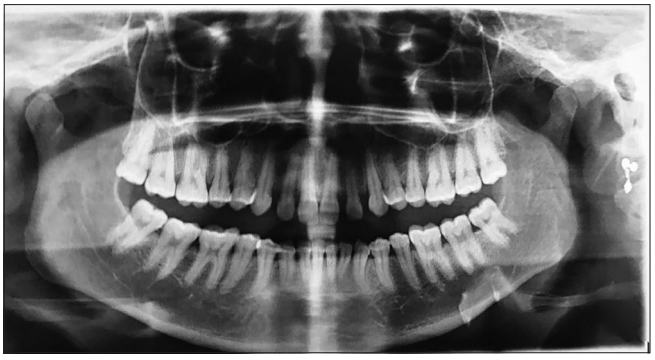

Figure 2: Orthopantamograph did not reveal any hard tissue involvement

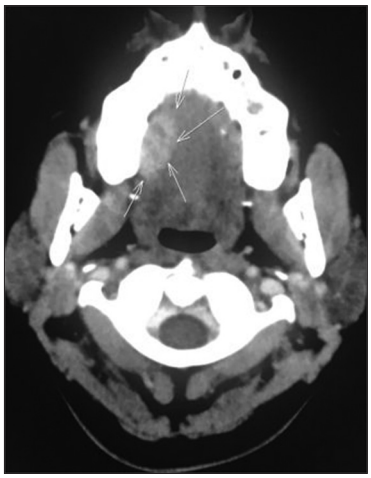

Figure 3: Axial computed tomography revealing a soft-tissue density in the right lateral aspect of the hard palate

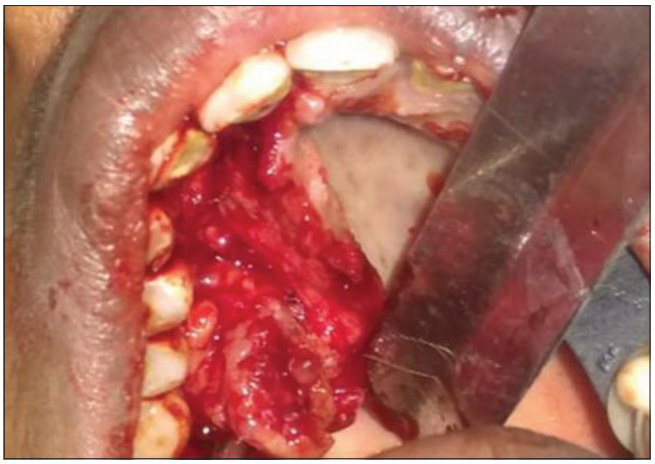

Figure 4: Excisional biopsy of the lesion under local anesthesia

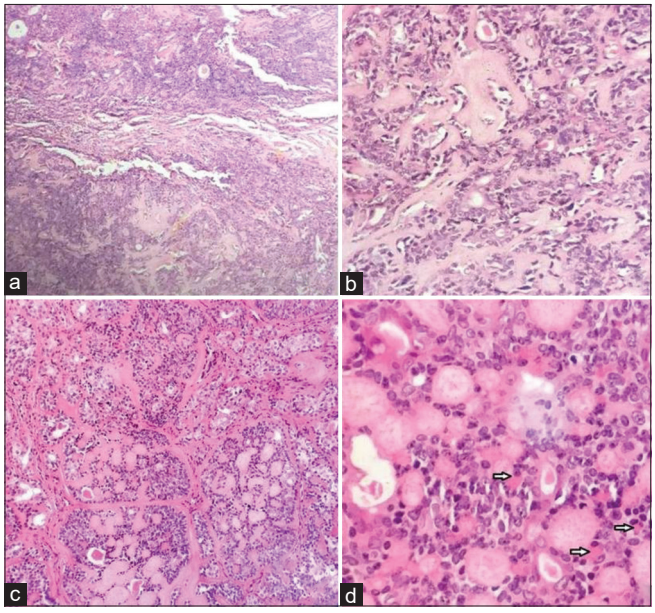

Figure 5: Histopathological images of hematoxylin and eosin stained sections. (a) Histopathological image showing moderately cellular lesion with sheets and strands of polyhedral squamous epithelial cells exhibiting duct-like structures containing eosinophilic coagulum interspersed with hyalinized areas (H&E stain, ×40). (b) Histopathological image showing duct-like structures, hyalinized areas with spindle-shaped, angular and stellate myoepithelial cells (H&E stain, ×100). (c) Histopathological image showing "cribriform-like" pattern containing multiple cyst-like spaces (H&E stain, × 200). (d) Histopathological image showing plasmacytoid myoepithelial cells (→) with eosinophilic cytoplasm and eccentrically placed nuclei (H&E stain, ×400)

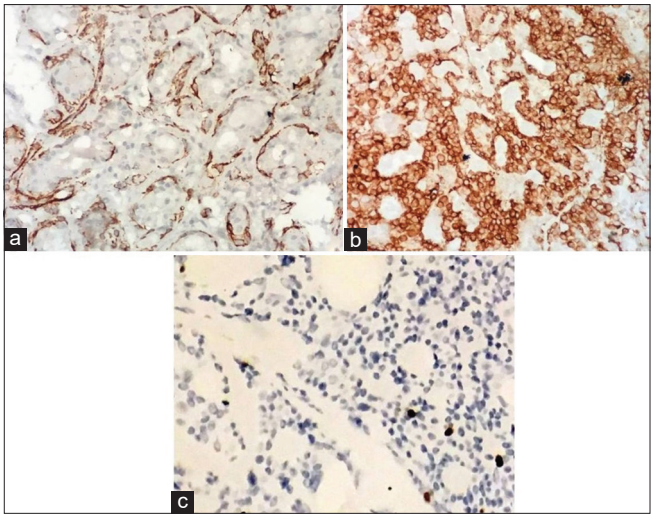

Figure 6: Immunohistochemical evaluation of tissue sections. (a) A population of spindle-shaped, angular and stellate myoepithelial cells exhibiting intense, cytoplasmic expression of smooth muscle actin (×400). (b) Tumor cells exhibited diffuse positivity for Glial Fibrillary Acidic Protein (×400). (c) Ki-67 labeling index was 4% (×400)

adenoma. Ki-67 labeling index [Figure 6c] was low (4%) supporting the benign nature of the lesion.

DISCUSSION

Pleomorphic adenoma is the most common benign salivary gland tumor with diverse cytomorphological and architectural manifestations.[6] It contributes to 53%–77% of parotid tumors, 44%–68% of submandibular tumors and 33%–43% of minor salivary gland tumors.[7]

Pleomorphic adenoma arises from the mixture of ductal and myoepithelial elements. The term "Pleomorphic adenoma" refers to the variable morphology in the basic tumor pattern, rarely are the individual cells pleomorphic. The term "Mixed tumor" also describes the variable morphology with a prominent appearing "stromal" component. However, the tumor is not truly "mixed" as it is not derived from more than one germ layer.

Pleomorphic adenoma is common in young and middle-aged adults in the third to sixth decades of life. It is the most common primary salivary gland tumor in children. It is more common in females with a female-to-male ratio

of 2:1.[6] The reported case was also a female in her third decade.

The parotid gland is the most common site followed by the palate (50% of intraoral tumors) and submandibular gland.[6] The tumor is usually solitary; however, metachronous and synchronous tumors are also reported.

Clinically, the tumor presents as a painless, slow-growing mass. It is firm and mobile. Palatal tumors are not movable because of the tightly bound nature of the palatal mucosa. Tumors involving the deep lobe of the parotid gland present as retrotonsillar mass or parapharyngeal space tumor.[7] Clinical differential diagnosis includes pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma and polymorphous adenocarcinoma.

Histopathologically, pleomorphic adenoma is composed of mixtures of epithelial and myoepithelial/stromal components in various patterns. Epithelial cells are usually arranged in cords, sheets, nests and islands forming duct-like structures containing eosinophilic coagulum. Myoepithelial cells may be spindled, oval, epitheliod, clear or plasmacytoid (hyaline cells).[6] Foci of mucous cells, sebaceous differentiation, oncocytic phenotype and squamous differentiation can be seen.[2] Stromal components are the result of myoepithelial differentiation. Myxoid, chondroid, osseous and lipomatous stroma are common in pleomorphic adenoma. Tyrosine-rich crystalloids and collagen-containing crystalloids can be seen in pleomorphic adenoma. These are glossy, eosinophilic and petal-shaped structures which are refractile and show radial arrangement surrounding a central core. The crystals stain deep purple with Masson trichrome stain, black with Verhoeff's stain and pink with Millon's reaction.

Encapsulation and presence of chondromyxoid stroma are characteristic of classic pleomorphic adenoma. Pleomorphic adenomas of palatal minor salivary glands usually present with incomplete capsule. The present case was moderately cellular [Foote and Frazell classification, Table 1][8] and lacked the typical chondromyxoid stroma. However, demonstration of plasmacytoid myoepithelial cells histopathologically was a definite clue toward pleomorphic adenoma. Further immunohistochemical workup helped us to rule out the close mimics and confirm the diagnosis of pleomorphic adenoma.

Table 1: Histopathological classification of pleomorphic adenoma by Foote and Frazell (1954)

Principally myxoid
Myxoid and cellular components present in equal proportion
Predominantly cellular
Extremely cellular

Immunohistochemistry remains an important adjunct in the diagnosis of minor salivary gland neoplasms. Tubuloglandular structures are positive for cytokeratins (CKs) 3, 10, 11, 13 and 16. Myoepithelial cells are positive for CK 13, CK 16 (focally), vimentin, pancytokeratin, SMA, muscle Specific Actin (HHF 35), calponin, CD 10 and p63. GFAP is expressed by almost 80% of pleomorphic adenomas and is usually negative in polymorphous adenocarcinomas.[9] Hence, demonstration of biphasic pattern immunohistochemically using markers for tubuloglandular structures and myoepithelial cells followed by confirmation with GFAP positivity aids in the definite diagnosis of pleomorphic adenoma.

The cribriform pattern is seen in numerous salivary gland tumors such as pleomorphic adenoma, basal cell adenoma, sialoblastoma, polymorphous adenocarcinoma, adenoid cystic carcinoma, epithelial myoepithelial carcinoma, low-grade cribriform cystadenocarcinoma, basal cell adenocarcinoma and salivary duct carcinoma. Immunohistochemistry-based differential diagnosis of salivary gland tumors with a cribriform structure primarily focus on myoepithelial marker SMA or calponin. In the present case, SMA positivity ruled out polymorphous adenocarcinoma, low-grade cribriform cystadenocarcinoma and salivary duct carcinoma. Low Ki-67 index excluded malignant tumors such as adenoid cystic carcinoma, epithelial myoepithelial carcinoma, basal cell adenocarcinoma and sialoblastoma. Further positive expression of GFAP directly ruled out polymorphous adenocarcinoma, basal cell adenoma, epithelial myoepithelial carcinoma and confirmed the final diagnosis of pleomorphic adenoma.[10]

Molecular signatures not only aid in the understanding of pathogenesis but also contribute as diagnostic tools and in prognostic determination.[11] Karyotypic abnormalities are present in around 70% of pleomorphic adenomas. Rearrangements on 8q12 results in the anomaly of pleomorphic adenoma gene 1 (PLAG 1), a cell-cycle associated zinc finger gene protein, nuclear oncoprotein and DNA binding transcription factor. Most common fusion products seen in pleomorphic adenoma are: CTNNB1-PLAG1[t(3,8) (p21;q12) and LIFR-PLAG1 [t(5,8)(p13, q12)]. Rearrangements of High Mobility Group protein gene (HMGA2) in $12q^{13\text{-}15}$ (8%) encodes a transcription factor. The fusion products are HMGA2-NFIB [t (9;12)] and HMGA2-FHIT [t (3;12)].[6]

Pleomorphic adenoma is treated by complete surgical excision. Enucleation is generally avoided due to the incomplete nature of capsule. Tumors of the superficial lobe of the parotid are removed by superficial parotidectomy. Involvement of deep lobe mandates total parotidectomy with preservation of facial nerve. Palatal tumors are treated by excision along with the periosteum and overlying mucosa.[12] Prognosis is good and cure rate is 90%. Recurrence rates are low. Female gender, young age at initial treatment and enucleation instead of parotidectomy are possible risk factors for recurrence. Malignant transformation rate is 6.2%. Malignant transformation is more likely in cases with multiple recurrences, the involvement of deep parotid lobe, male gender and older age.[7]

CONCLUSION

Salivary gland malignancies are complex and are often a diagnostic challenge. Advent of more specific immunohistochemical markers has simplified the diagnostic process. Molecular genetics has also unraveled significant molecular signatures in specific entities, thereby facilitating accurate diagnosis. Detailed knowledge of distinct presentations of common tumors is key to accurate diagnosis and avoid misdiagnosis to a greater extent. Early and accurate diagnosis with prompt therapy aid in a better prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Rito M, Fonesca I. Salivary gland neoplasms: Does morphologic diversity reflect tumor heterogeneity. Pathobiology 2018;85:85-95.
2. Seethala RR. Salivary gland tumors: Current concepts and controversies. Surg Pathol Clin 2017;10:155-76.
3. Ogle OE. Salivary gland diseases. Dent Clin North Am 2020;64:87-104.
4. Pérez-de-Oliveira ME, Leonel AC, de Castro JF, Carvalho EJ, Vargas PA, Perez DE. Histopathological findings of intraoral pleomorphic adenomas: A retrospective study of a case series. Int J Surg Pathol 2019;27:729-35.
5. Pramod Krishna B. Pleomorphic adenoma of minor salivary gland in a 14-year-old Child. J Maxillofac Oral Surg 2013;12:228-31.
6. El-Naggar AK, Chan JK, Grandis JR, Takata T, Slootweg PJ, editors. WHO Classification of Head and Neck Tumors. 4th ed. France: IARC: Lyon; 2017. p. 185-7.
7. Neville BW, Damm DD, Allen CM, Bouquet JE. Oral and Maxillofacial Pathology. 3rd ed. St.Louis: Saunders; 2009. p. 477-80.
8. Shafer WG, Hine MK, Levy BM. Sivapathasundaram B, editors. Shafer's Textbook of Oral Pathology. 8th Edition, India: Saunders; 2016. p. 266-70.
9. Curran AE, Allen CM, Beck FM, Damm DD, Murrah VA. Distinctive pattern of glial fibrillary acidic protein immunoreactivity useful in distinguishing fragmented pleomorphic adenoma, canalicular adenoma and polymorphous low grade adenocarcinoma of minor salivary glands. Head Neck Pathol 2007;1:27-32.
10. Nagao T, Sato E, Inoue R, Oshiro H, H Takahashi R, Nagai T, *et al*. Immunohistochemical analysis of salivary gland tumors: Application for surgical pathology practice. Acta Histochem Cytochem 2012;45:269-82.
11. Fonesca FP, Filho S, Altemani A, Speight PM, Vargas PA. Molecular signatures of salivary gland tumors: Potential use as diagnostic and prognostic marker. J Oral Pathol Med 2016;45:101-10.
12. Moon SY. Surgical management of the palatal pleomorphic adenoma. J Craniofac Surg 2019;30:e580-2.