CASE REPORT

Minor salivary gland neoplasm with squamous metaplasia: Overlapping histopathological features and diagnostic challenges.

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Abstract

Context: Pleomorphic adenoma (PA) is the most common salivary gland tumor, primarily arising in the parotid gland but occasionally in minor salivary glands.

Introduction: This case highlights a rare PA variant with extensive squamous metaplasia, potentially linked to tobacco smoking.

Background: Atypical features along with squamous metaplasia can mimic malignancies like mucoepidermoid carcinoma and squamous cell carcinoma, risking misdiagnosis and inappropriate treatment.

Case presentation: A 43-year-old male presented with a slow-growing mass and a history of tobacco smoking. Histopathology revealed a well-demarcated tumor with extensive squamous metaplasia, keratin pearls, and typical PA features, including epithelial and myxoid stromal components. The resemblance to malignant tumors necessitated further diagnostic clarification.

Management and prognosis: The treatment approach involved wide surgical excision under general anesthesia. The patient was advised to maintain proper oral hygiene and tobacco cessation counseling was given. The overall prognosis was considered favorable.

Clinical implication: This case illustrates the diagnostic challenges of rare pleomorphic adenoma presentations, offering insights to improve clinical understanding and patient outcomes.

Conclusion: Awareness about pleomorphic adenoma variants is essential for clinicians and pathologists to avoid misdiagnosis. Comprehensive evaluation and cautious interpretation of histopathological findings are critical.

Key words: Pleomorphic Adenoma, Squamous Metaplasia, Tobacco, Parotid

Introduction

Salivary gland tumors are the most heterogeneous group of tumors with greatest diversity of morphological features. They are relatively uncommon. However, the majority of these neoplasms are benign and malignant salivary gland neoplasms represent 5% of all cancers of head and neck. The incidence of different salivary gland tumors among the Western population is 2.5 to 3 per 100,000 per year. But its incidence is still lesser in the Indian population.[1] The classification system of salivary gland tumors is very dynamic, with incorporation of various novel entities over a period of time.[2]

There are various etiological factors identified for the development of salivary gland tumor, with the exposure to ionizing radiation being the only factor that showed a strong positive association.[3] Interestingly, studies indicate that smoking significantly contributes to the development of salivary gland tumors, particularly Warthin tumor. Even though, no connection was observed with pleomorphic adenoma, the potential increased risk of malignant tumors warrants further studies and investigations.[4] Salivary gland tumors are most challenging to diagnose among head and neck pathologies because of its morphological diversity and rarity.[5] Pleomorphic adenoma (PA) is the most common benign salivary gland tumor with complex and unusual morphological features. Morphologic diversity in this neoplasm is attributed to tumor cell products and metaplastic changes.[1]

This article discusses a case of PA with distinctive features, emphasizing on the diagnostic challenges as well as the importance of excisional biopsy and immunohistochemistry in preventing overdiagnosis. This case is noteworthy as it presents a PA exhibiting extensive squamous metaplasia

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in association with long-term tobacco use, accompanied by clinically evident erythematous and hyperkeratotic mucosal changes, which is an uncommon presentation that underscores the potential influence of chronic tobacco-induced irritation on epithelial transformation within salivary gland tumors.

Case report

A 43-year-old male patient reported at the clinic with a swelling for five years, in the posterior part of the hard palate, extending to the soft palate and crossing the midline medially. It was initially small but gradually increased in size. There was no pus discharge, and it was non-tender. History of tobacco use and alcohol consumption for 15 years was reported.

On examination, a pedunculated, smooth surfaced mass measuring 5x5x4 cm was identified, that extended from 16, 17 and 18 regions toward the soft palate and crossing midline. The mass was firm to hard and non-tender on palpation. The clinical diagnosis and provisional diagnosis indicated a benign salivary gland tumor, however, the differential diagnoses included mucoepidermoid carcinoma and squamous cell carcinoma.

The radiographic findings obtained are as follows:

- The CBCT showed bone erosions over right palatal region, with respect to 16, 17, 18 regions and mid-palatal region.
- The CT scan revealed an ill-defined heterogeneously enhancing lesion, arising from the hard palate. Also, no extension towards adjacent anatomical structures was shown.

For further evidence, multiple incisional biopsies were performed from three different sites. The first sample was taken from the keratinized surface of the lesion which was cream-white in color and firm in consistency. The second one from the antero-lateral margins of the lesion, and the third one from the socket region of the tooth 18, which appeared greyish white. (Figure 1).

Microscopically, the lesion exhibited parakeratinized stratified squamous hyperplastic epithelium overlying a cellular connective tissue stroma with proliferating ductal and myoepithelial cells. Neoplastic cells within the connective tissue formed duct- like structures and cystic spaces containing eosinophilic coagulum. Additionally, the epithelial-connective tissue interface was indistinct in focal areas, accompanied by intense chronic inflammatory cell infiltration. The tumor cells demonstrated cellular and nuclear pleomorphism, with some areas showing squamous epithelial-like differentiation. (Fig. 1). Mucicarmine staining yielded negative results.

Based on microscopic findings, a diagnosis of minor salivary gland neoplasm with epithelial and myoepithelial components was made. However, the possibility of salivary gland malignancy remained uncertain and required further evaluation following excision and additional investigations chiefly due to extensive cellularity with minimal stroma and cellular atypia. The treatment approach involved wide surgical excision under general anesthesia. Histopathological evaluation of excisional specimen revealed epithelial and myoepithelial cells, arranged in tubular and glandular patterns, while myoepithelial cells exhibited spindle to plasmacytoid morphology. Cystic areas contained eosinophilic material, and the stroma varied from hyalinized to myxoid. Squamous metaplasia with keratinization was evident (Fig. 2). No tumor infiltration into adjacent tissues was observed, and surgical margins were clear. Subsequently, immunohistochemistry (IHC) was performed for further clarifications using three different markers like CK-7, Ki-67 and S-100 (Fig. 2).

- CK-7 showed positive expression in ductal epithelial cells of tumor.
- Ki-67 showed 10% positive staining.
- S-100 exhibited positive staining in myoepithelial cells and adipocytes.

On the basis of microscopic examination of excisional bi-

Table 1: Microscopic differential diagnosis.

Differential Diagnosis	Features of the present case that excluded the given differential diagnosis.
Mucoepidermoid Carcinoma	The squamous cells present are associated with keratin formation as evident in excisional biopsy. Absence of mucous cells. Mucicarmine negativity. Positive for myoepithelial markers on IHC evaluation. No Significant atypia and infiltration on excisional biopsy evaluation.
Carcinoma ex-pleomorphic adenoma	No Significant atypia and infiltration on excisional biopsy evaluation. No Sudden increase in tumor size reported though the lesion is massive.
Epithelial myoepithelial carcinoma	No multinodular, infiltrative growth pattern and no significant atypia after evaluation of excisional biopsy. Focal presence of chondromyxoid stroma and only 10% ki 67 positivity.
Squamous cell carcinoma	No marked cytological atypia, gradual clinical progression, and positive staining for salivary gland ductal markers and myoepithelial markers.

opsy specimen and immunohistochemistry, the final diagnosis was confirmed as pleomorphic adenoma with squamous metaplasia. Following surgical excision, an obturator was provided during the healing period. The patient was advised to maintain proper oral hygiene and tobacco cessation counseling was given. The overall prognosis was considered favorable over a 6 month follow up period.

Discussion

PA is the most common benign salivary gland tumor with a malignant transformation rate of 6%.[6] The term pleomorphic adenoma was first introduced by Willis.[7]

PA most commonly affects the parotid gland, accounting for 45% to 63% of cases, followed by submandibular gland (53% to 72%), and minor salivary glands (33% to 41%). The palate is the most frequent site of occurrence (60% to 65%), while involvement of sublingual glands is rare. It predominantly affects females of fourth to sixth decades of life, with the male-to-female ratio of approximating 4:6 and an average age of onset around 43 years. It is usually seen as a small, painless, quiescent nodule which slowly begins to increase in size, sometimes showing intermittent growth.[1,2] The reported case was a gradually growing mass, which attained a huge size over a period of 5 years. But on examination the surface of the lesion exhibited a small area of erythema and an adjacent area of hyperkeratosis.

Histogenesis and Pathology:

Known for its diverse histological appearances, they are derived from a mixture of ductal and myoepithelial elements. The terms PA and mixed tumor reflect attempts to describe its distinctive histopathological features; however, neither term is entirely precise. While the overall tumor pattern is highly variable, the individual cells rarely exhibit pleomorphism.8 In this case certain areas exhibited pleomorphism along with squamous differentiation. These findings along with patient's history of tobacco use and clinical changes in the surface of the lesion created a diagnostic dilemma. Squamous metaplasia, though seen occasionally in PA, imposed a challenge in accurate diagnosis in the present case. Other than squamous metaplasia, mucous, sebaceous and oncocytic metaplasia may be noted in pleomorphic adenoma, but the present case was devoid of such findings.[9]

PA with squamous metaplasia closely resembles squamous cell carcinoma and other malignancies, which highlights the critical need for a comprehensive clinical, radiological, and histopathological evaluation. Additionally, a thorough understanding of molecular genetics is essential for accurate differentiation.[10]

Though PA arises from ductal and myoepithelial cells, the latter is responsible for characteristic stromal changes and mor-

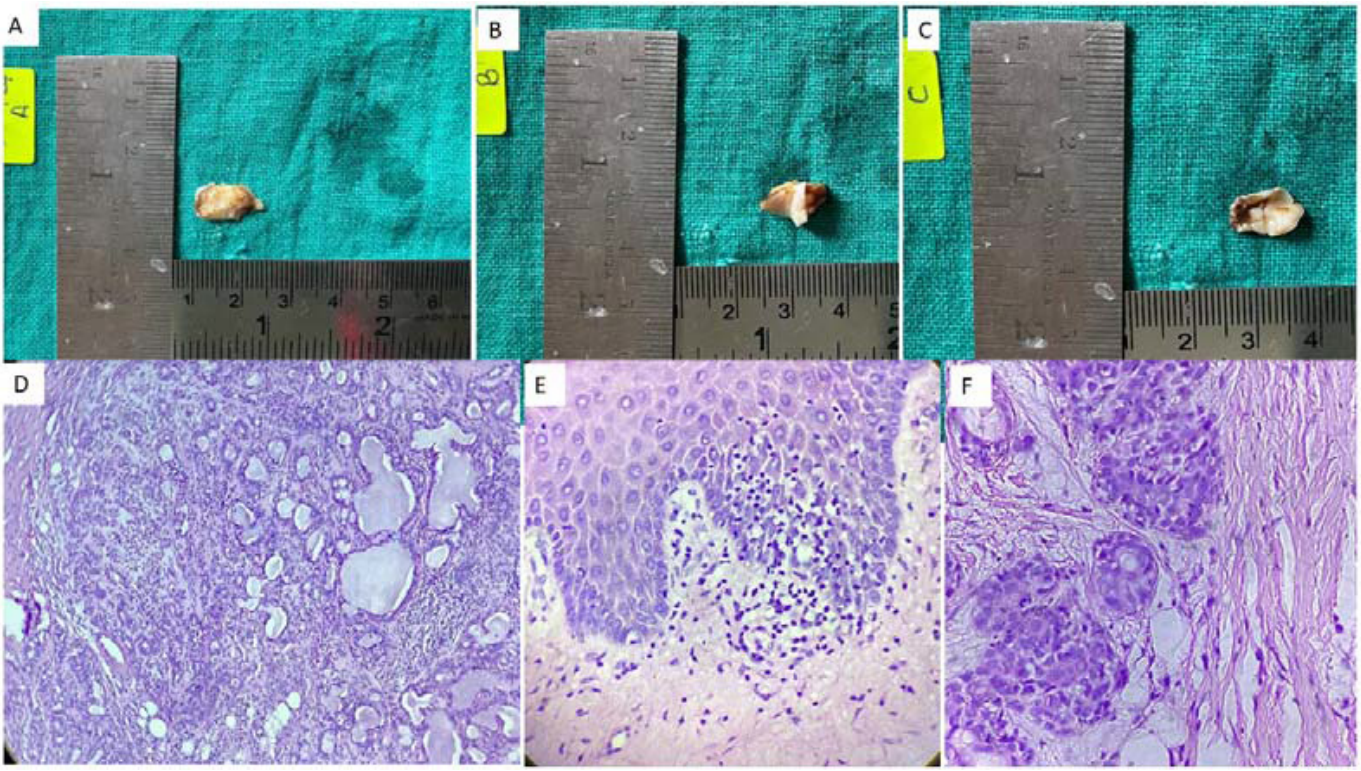

Fig. 1. Multiple incisional biopsies from 3 different sites of the lesion such as surface of the lesion **(A),** the antero-lateral margins of the lesion **(B)** and the posterolateral region of the lesion near 18 region **(C).** Hematoxylin and Eosin-stained sections of incisional biopsy specimen exhibiting neoplastic cells within the connective tissue forming duct- like structures and cystic spaces containing eosinophilic coagulum **(D).** Indistinct epithelial-connective tissue interface in focal areas, with chronic inflammatory cell infiltration **(E).** The tumor cells showing cellular and nuclear pleomorphism, with some areas exhibiting squamous epithelial-like differentiation **(F).**

phological diversity of this neoplasm. The proliferating myoepithelial cells are either spindle or plasmacytoid types. The stroma exhibits chondromyxoid areas, osseous areas and adipose tissues. However, the proportion of cellular and stromal components varies, ranging from highly cellular to predominantly myxoid.[1] The present case was more cellular in nature.

Pathological analysis of minor salivary gland PA reveals that these tumors are typically unencapsulated. Chondromyxoid changes are less prominent, while myoepithelial cell proliferation – particularly of the plasmacytoid type – is more pronounced.[1,11] Chondromyxoid changes were minimal especially in incisional biopsy specimen in this case. The literature also suggests that the metaplastic changes are more frequently observed in minor gland tumors.[12]

Squamous metaplasia:

The significant feature associated with this case is the squamous metaplasia. Squamous metaplasia is considered as an incidental microscopic finding in various benign and malignant tumors. It is seen in 25% of all PAs.[13] The exact origin remains unclear; however, these changes are thought to arise from various factors, including chronic irritation, trauma, infarction, ischemia and post-infarction repair. Ischemic changes can lead to changes in the genetic programming of cytokeratin filaments.[9] PA with extensive squamous metaplasia is commonly found in the minor salivary glands, with the hard palate being the most frequent site, as in the present case. Masticatory trauma may be a contributing factor to squamous metaplasia.[13] Chronic smoking may also be a possible contributing factor to ischemia.[14] In the present case squamous metaplasia would have resulted due to ischemia and smoking could be one among the predisposing factor. Presence of myoepithelial and ductal cells were confirmed by the positive staining with S100 and CK7 respectively. Ki-67 showed positive staining only in 10% of the lesional tissue. These IHC findings were used to confirm diagnosis of PA and to rule out the possibility of malignancy.

Molecular aspects:

At the molecular level, mutation of proto-oncogenes PLAG1 and HMGA2 can lead to their overexpression.15 The chromosome usually affected is 8q12.2 Recurrent tumors and carcinoma arising from PA over express Muc1 gene.[16] PLAG1 usually aids in the diagnosis of benign tumors, differentiating it from malignant histotypes.[10] Though molecular analysis wasn't performed in the present case immunohistochemical analysis was done to rule out malignancy.

Differential diagnosis:

PA with squamous metaplasia may overlap with many other salivary gland tumors in their histological appearance such

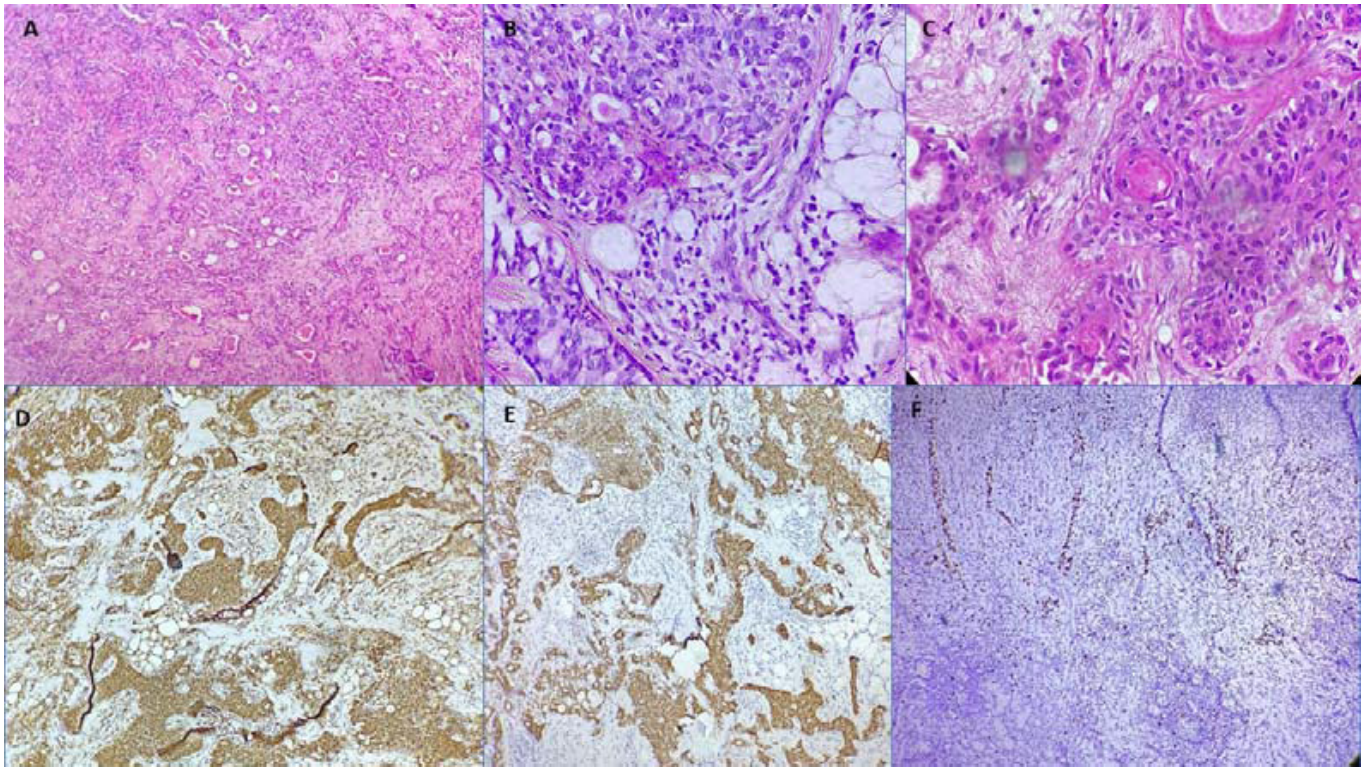

Fig. 2. Hematoxylin and eosin-stained excisional specimen showing epithelial and myoepithelial cells, arranged in tubular and glandular patterns, cystic areas containing eosinophilic material, and the stroma varying from hyalinized to myxoid **(A)**, proliferating myoepithelial cells in high power view **(B),** Squamous metaplasia with keratinization **(C).** Immunohistochemical staining with S-100 exhibiting positive staining in myoepithelial cells and adipocytes (D), CK-7 showing positive expression in ductal epithelial cells of tumor **(E)**, Ki-67 showing 10% positive staining **(F)**.

as mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma, epithelial-myoepithelial carcinoma and squamous cell carcinoma.[7,8,11] The present case was distinguished from all these entities considering various findings specifically after the evaluation of excisional biopsy specimen and immunohistochemistry. (Table 1)

Conclusion

Pleomorphic adenoma of the palatal minor salivary glands, though common, can exhibit marked morphological variations and metaplastic alterations that pose diagnostic challenges. In cases associated with long-term tobacco exposure, alterations such as erythematous and hyperkeratotic changes in the overlying mucosa may further complicate the clinical picture. Therefore, a comprehensive evaluation, integrating histopathological examination, immunohistochemical analysis, and advanced diagnostic techniques is essential to establish an accurate diagnosis and ensure appropriate management. Given these complexities, both clinicians and pathologists must carefully assess each case, maintaining a high level of diagnostic acumen to formulate an optimal treatment plan.

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