PLEOMORPHIC ADENOMA-A DIVERSIFIED BIZZARE TUMOR

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ABSTRACT- Pleomorphic adenoma is a lesion which accounts for the vast majority of all salivary tumors Pleomorphic adenomas are benign salivary gland tumors, which predominantly affect the superficial lobe of the parotid gland. The “pleomorphic” nature of the tumor can be explained on the basis of its epithelial and connective tissue origin. Their complexity is attributed to heterogeneity of the cells of origin of these lesions. The problem is compounded by the ability of these cells to differentiate and modify into various morphological subtypes resulting in a myriad of histomorphological patterns. The tumor has a female predilection between 30-50 years of age. Slowly progressing asymptomatic swelling is the usual presentation of the tumor. Surgical excision of the tumor mass forms the mainstay of treatment, with utmost care taken to preserve the facial nerve. The present article is aimed at reviewing and summarizing the concepts regarding the pathogenesis of pleomorphic adenoma along with its histogenesis and treatment.

INTRODUCTION

Pleomorphic adenoma (PA), also known as benign mixed tumor, is the most common salivary tumor, constituting up to two-thirds of all salivary gland neoplasms.¹ It exhibits wide cytomorphologic and architectural diversity. The tumor has the following 3 components:

- An epithelial cell component
- A myoepithelial cell component
- A stromal (mesenchymal) component

Mostly, PA is located in the parotid glands (85%), minor salivary glands (10%), and the submandibular glands (5%).³ In the majority of cases, tumors originate in the superficial lobe. Minor salivary gland tumors are frequently encountered on the palate, followed by the lip, cheek, tongue and floor of the mouth.⁴ PA usually manifest as a slow progressing asymptomatic, parotid gland swelling without facial nerve involvement.⁵ Complete excision is the criterion standard for treatment and essential for preventing recurrence and malignant transformation.⁵ It is most common in the third to sixth decades; the average age at presentation is between 43 and 46 years.⁷ Pleomorphic adenoma is seen more often in females than in males (2:1 ratio). The etiology of pleomorphic adenoma is unknown, the incidence of this tumor has been found to increase 15-20 years after exposure to radiation.⁸ The complexity of structure and the rarity in occurrence are a diagnostic dilemma for even experienced pathologists. The diagnostic criteria are overlapping, the classification systems are numerous, and the histopathological criteria may vary within the same tumor and in different areas of the same tumor.⁹

DISCUSSION

World Health Organization (1972) defined PA as a well-defined tumor characterized by its pleomorphic or mixed appearance. There is intermixing of the clearly recognizable epithelial component with mucoid, myxoid and chondroid component.¹⁰ The name “Pleomorphic Adenoma” was suggested by Willis due to its unique Histopathology characteristics.¹³ Pleomorphic adenoma is a morphologically complex entity as the epithelial and myoepithelial tumor cells can
differentiate into fibrous, hyalinized, mucoid, myxoid, chondroid, osseous, or lipomatous tissue. Classically, PA is an encapsulated tumor; with nonmalignant lateral extensions into the capsule commonly encountered.11 Macroscopically, PA is a well-circumscribed, round to oval Mass having white to tan cut surface, often shiny to translucent. The encapsulation is quietly variable and the multifocality is frequent in the recurrent tumors.12 Symptoms and signs depend on the location.2 Patients are often asymptomatic and the lesion is an incidental finding during unrelated medical or dental visit, as seen in our patient. As the tumor grows, later findings include ulceration, pain, paresthesia, dysphagia, speech impairment, referred otalgia or even, rarely, facial paralysis secondary to extrinsic compression of the seventh cranial nerve.6 On gross examination, a pleomorphic adenoma is a single firm, mobile, well-circumscribed mass. Its color may vary from whitish-tan to gray to bluish, and its size may range from a few millimeters to quite large or even giant.13-14 Physical examination alone does not suffice in distinguishing benign tumors of minor salivary gland from malignant types. Therefore a biopsy is indicated, which should be performed to ensure the lesion is benign.6 Degenerative and cystic changes may be seen on sectioning. It is not unusual to observe evidence of focal or massive infarction. Recurrent tumors characteristically tend to present as multiple nodules of variable size.2

Microscopically, in the parotid gland, the tumor is usually surrounded by a fibrous capsule of variable thickness that may be focally deficient, especially in more mucoid tumors. In minor salivary glands, no capsule is usually seen.15,16,17 The histopathology presents varied morphological patterns, showing epithelial and myoepithelial cells. Epithelial cells typically form duct-like structures associated with non-ductal cells presenting varying shapes and forms. The epithelial component consists of epithelial and myoepithelial cells with divergent growth patterns, including trabecular, tubular, solid, cystic, and papillary architecture. Pure epithelial cells are mainly cuboidal. Cells that exhibit myoepithelial features may have plasmacytoid, epithelioid, spindle, oncocytic or clear cell morphology.2 Figure 1 & 2 Myxoid, cartilaginous, hyaline, or osseous differentiation is appreciated in the stromal component. The stroma is presented as a mixture of gland-like epithelium and mesenchyma-like tissue in varying proportions.18 They can be divided into three groups: myxoid (80 % stroma), cellular (80 % cellular) and mixed (classic). The myxoid variant has more tendency to be recurrent. The differential diagnosis of PA consists of myoepithelioma, is a benign epithelial salivary gland tumor, having plasmacytoid or spindled myoepithelial cells. Additionally basal cell adenoma may also be involved in the differential diagnosis.18 When the cellular elements predominate, the result is an epithelial cell–rich or myoepithelial cell–rich (i.e.,cellular) pleomorphic adenoma, when the mesenchymal/stromal component predominates, the result is a stroma-rich pleomorphic adenoma). A pleomorphic
adenoma with an equal proportion of the 2 components is often referred to as a classic or mixed-type tumor.²

**HISTOGENESIS & PATHOGENESIS OF PLEOMORPHIC ADENOMA**

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The existence of reserve cells in normal salivary gland was originally postulated from observations of embryonic development of palatal minor salivary glands. These evolve as down growth of bilayered ducts, and it was assumed that the inner or luminal layer was derived from the outer or basal layer. The semi-pleuripotent reserve cell theory was further refined and developed by Batasakis et al. In an attempt to explain the histogenesis of salivary gland tumors, a bicellular theory of origin was proposed.¹⁹,²⁰ Two cells, the excretory duct reserve cell and the intercalated duct reserve cell, were presented as the hypothetical cells of origin for salivary gland neoplasms. It was argued that the excretory duct reserve cell gives rise to squamous cell carcinomas (SCC) and mucoepidermoid carcinomas, and that the intercalated duct reserve cell gives rise to all others. It was also shown that myoepithelial cells were responsible in part for the wide histologic variation of these neoplasms. As a highly and therefore, terminally, differentiated cell, the acinar secretary cell was said to play a minimal role in the parenchymal renewal and thus, was incapable of a significant role in tumor induction.⁹

**FIGURE 1.** Tubule/duct formations in pleomorphic adenoma. Well-defined inner epithelial lining, consisting of cuboidal cells with eosinophilic cytoplasm, which can focally be clear, is surrounded by collar of 1 or more layers of myoepithelial cells with mostly clear cytoplasm. Stromal in between contains dispersed spindled epithelioid cells

**Figure 2.** Myxoid stroma in pleomorphic adenoma. Dispersed spindle myoepithelial cells in stroma, some of which have stellate morphology.

Although, the "bicellular theory of origin" is the most widely-accepted, but there has
been little or no direct evidence to support this hypothesis. Most studies on the malignant salivary gland histogenesis claim that mucoepidermoid carcinoma, primary SCC and salivary duct carcinoma arise from the excretory duct, whereas polymorphous low grade adenocarcinoma, basal cell adenocarcinoma (BCA), adenoid cystic carcinoma (AdCC) and acinic cell carcinoma (ACC) are of intercalated duct origin.\(^{21,22}\) Adenocarcinoma, not otherwise specified (NOS) (AdC NOS) is assumed to arise from either of these reserve cells and carcinoma ex pleomorphic adenoma is of uncertain histogenesis.\(^9\)

**Multicellular histogenetic concept**  
It was proposed that differentiated cells at all the levels of the gland, including acinar and basal cells are capable of cell division. When autoradiography of neonatal rat salivary gland after tritiated thymidine administration was done, electron microscopy of these tissues revealed that duct basal cells, luminal cells at all levels of duct system and even acinar cells were capable of DNA synthesis and mitosis. However, there is considerable evidence for a multicellular theory of tumor histogenesis. That is, any of "multiplicity of cell types in normal salivary gland have the potential to give rise to any of various types of tumors occurring in this organ."  
In terms of tumor induction, it should be appreciated that "differentiated cells are capable of metaplastic alterations" e.g., epidermoid metaplasia has been demonstrated in acinar and myoepithelial cells of the salivary gland of the rat and in secretary cells of hamster tracheal mucosa. Current histogenetic classification of salivary gland tumors is based on the hypothesis that hat repair and replacement of terminally differentiated components of salivary gland such as duct epithelium and acinar cells are totally dependent on reserve or stem cells.\(^9\)

In most instances, the diagnosis of pleomorphic adenoma is made through Immunohistochemistry (IHC) in differentiating pleomorphic adenoma from other tumors. The following IHC stains have proved helpful:

- Keratin - Positive in luminal epithelial and abluminal basal/myoepithelial cells
- Cam 5.2 and EMA - Positive in luminal epithelial cells
- P-63 - Positive in abluminal basal and myoepithelial cells
- Calponin, maspin, S-100 - Positive in myoepithelial cells
- BMP - Positive in myoepithelial cells in myxoid and chondroid areas
- BMP-6 - Positive in the cells in cartilage and in inner ductal cells\(^3\)

PA is usually encapsulated and the treatment of choice is surgical excision with adequate surrounding tissue margins. Tumors of the minor salivary glands have lower risk for recurrence. The main cause of its recurrence is reported inappropriate surgery procedure of total tumor excision.\(^{23}\) Recurrence usually occurs in a multinodular fashion. In some cases, it involves microscopic elements, which render operative control extremely difficult and increase the risk of multiple further recurrences, as well as the risk of future malignant transformation. Recurrences have
been related to tumors with high mesenchymal content, particularly chondroid and myxoid stroma. In some series, recurrences seem to be more common in younger patients than in older ones. A wide resection with negative margins is usually recommended as an optimal choice in the treatment of PA. Because, almost half of all tumors arising from minor salivary glands are proclaimed as malignant. Therefore, some authors offer the application of a fine-needle aspiration or an incisional biopsy before the definitive surgery. Pleomorphic adenoma relapse is estimated to occur in 5% to 30% of cases and is almost always a result of incomplete surgical resection that especially manifests in the form of multiple foci and may be found to be aggressive.

Pleomorphic adenoma also carries a high rate of implantability; therefore, caution must be exercised not to rupture the capsule or leave residual tumor cells behind including the extensions into the surrounding tissues. The prognosis of PA after complete excision is excellent. According to a meta-analysis of parotid tumors, PA recurrence rate was estimated to be 3.4% after 5 years and 6.8% after 10 years.

CONCLUSION

Salivary gland tumors offer a myraid of diversity thus maintaining the ambiguity of these neoplasms. Still the enigma of diagnosing the salivary gland tumors continues challenging Oral Pathologists in routine practice. It is important for the pathologist to assess the cytoarchitectural features and cytoarchitectural profile of these neoplasms and correlate them with histiognetic concepts for better understanding which in turn will help in diagnosis and management of these lesions. Pleomorphic adenomas are frequently asymptomatic benign lesions, patients may not be aware of their existence, or the tumor is discovered incidentally in many cases. The treatment of choice after an appropriate workup is a complete excision.

REFERENCES


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