

# KERATINIZING PLEOMORPHIC ADENOMA- A QUICK REVIEW ON THE RARE VARIANT

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**Abstract:** *The presence of numerous keratin pearls on microscopic study is a feature commonly seen in well-differentiated squamous cell carcinoma. Pleomorphic adenoma (PA) can show the presence of squamous metaplasia with keratin pearls as a rare finding. This article present a short review on this rare variant of pleomorphic adenoma which exuberant squamous metaplasia and keratin cysts formations in salivary gland keratinizing pleomorphic adenoma .*

**Keywords:** *Pleomorphic adenoma variants, salivary gland benign tumors, keratinizing pleomorphic adenoma.*

## 1 INTRODUCTION:

Pleomorphic adenoma is the most common benign salivary gland tumor. It accounts for a majority of all salivary gland neoplasms.<sup>1,2</sup> Willis coined the term Pleomorphic Adenoma. The etiology of pleomorphic adenoma is unknown, but the incidence of this tumor has been increasing in the last 15-20 years in relation to the exposure of radiation. In most studies, it represents 45-75% of all salivary gland tumors; the annual incidence is approximately two to three and a half cases per 100,000 population. Pleomorphic adenoma occurs in individuals of all ages; however, it is most common in the third to sixth decades. Pleomorphic adenoma incidence is slightly more in females than in males (2:1 ratio). Pleomorphic adenomas account for 70-80% of benign salivary gland tumors and the incidence in intraoral minor salivary glands is 40%–50%<sup>2,3</sup>. Pleomorphic adenoma is especially common in the parotid gland and it predominantly affects superficial lobe of the parotid gland<sup>4</sup>. Distribution among the various salivary glands is as follows:

- Parotid gland: 84%
- Submandibular gland: 8%
- Minor salivary glands: 6.5%

The neoplasm is usually slow-growing, painless, and firm mass on palpation<sup>5</sup>, which may be present for many years. Symptoms and signs mainly depend on size, location, and potential to undergo malignant transformation. In the parotid gland, signs of facial nerve weakness occur when the tumor is large or if it undergoes malignant change. Pleomorphic adenoma in the deep lobe of the parotid gland may present as an oral retro tonsillar or para-pharyngeal mass which is visible or usually palpable. Rapid enlargement of a tumor nodule should raise a concern of malignant change. Minor salivary gland tumors may present with a variety of symptoms, including dysphagia, hoarseness, dyspnea, difficulty in chewing, and epistaxis dependent on the site of the tumor. Possible complications to treatment include the risk of recurrence and malignant transformation

The morphological patterns has wide variations including presence of squamous cells, mucous cells, oncocytes, sebaceous cells, bone, adipose tissue, and crystalline materials.<sup>1-3</sup> There are several unusual histological findings in pleomorphic adenoma that may mimic malignancy, like extensive squamous metaplasia mimicking squamous cell carcinoma (SCC). This can be a source of potential diagnostic pitfall. Focal squamous metaplasia is found in about 20% of pleomorphic adenoma.<sup>6</sup> This squamous metaplasia is attributed to ischemia, repair following infarction, and necrosis of the salivary gland. Rarely extensive squamous metaplasia with cystic changes is reported.<sup>1,2</sup> And this variant of extensive squamous metaplasia with keratin-filled cysts is rarely reported in Pleomorphic Adenoma.

#### **KERATINISING PLEOMORPHIC ADENOMA:**

There is extensive squamous metaplasia by which many glandular cells are transformed into squamous cells, resulting in multiple squamous epithelium-lined cysts containing keratotic lamellae in the deep as well as in the superficial regions

PA is characterized by great histologic diversity. Histopathologically, PA of salivary gland is usually unencapsulated. The epithelial components are seen forming ducts, small cysts, cellular nests, sheets of cells, anastomosing cords, and foci of keratinizing squamous or spindle cells. Myoepithelial cells appear as angular or spindled, while some cells are round with eccentric nuclei and hyalinized eosinophilic cytoplasm<sup>7</sup>. Its histological patterns may vary considerably among different parts of the same tumor. Among the varied patterns, keratinizing pleomorphic adenoma shows extensive squamous metaplasia with keratin pearl formation.<sup>8,9</sup>

The presence of numerous keratin pearls is frequent presentation of well-differentiated squamous cell carcinoma<sup>11</sup> and a common feature of a number of reactive or neoplastic conditions of the salivary glands, such as chronic sialadenitis, radiation change of salivary glands and necrotizing sialometaplasia, mucoepidermoid carcinoma (MEC), PA, basal cell adenoma and Warthin's tumor and trichoadenoma.

Focal squamous metaplasia in PA can be related to ischemia, repair following infarction, and necrosis of the salivary gland and may be found in about 25% of the PA. Pathogenesis of squamous metaplasia and keratin pearl formation in PA has been proposed as the dedifferentiation of the acinar cells and subsequent hyperplasia of acinar, duct luminal, and myoepithelial cells. However, PA with extensive squamous metaplasia is rarely reported and can

signify a potential pitfall in the histopathological diagnosis. PA with extensive keratin-filled cysts lined by squamous epithelium is referred to in the literature as “cystic PA with extensive adnexa-like differentiation,”<sup>7</sup>

#### DIFFERENTIAL DIAGNOSIS FOR KERATINIZING PLEOMORPHIC ADENOMA:

Because of the presence of extensive squamous metaplasia and keratin, a variety of differential diagnoses can be considered. They are:

- conventional SCC,
- adenoid, or adenosquamous cell carcinoma,
- mucoepidermoid carcinoma,
- benign condition such as necrotizing sialometaplasia.<sup>10</sup>

Conventional SCC is an important differential diagnosis in cases showing extensive squamous metaplasia like the present case. SCC may invade or entrap normal-appearing salivary glands.<sup>10</sup> But in keratinizing pleomorphic adenoma, there is absence of dysplasia in squamous islands and presence of typical area of pleomorphic adenoma with focal chondromyxoid area. Adenoid SCC and adenosquamous cell carcinoma were not considered due to the absence of any true glands/ducts with atypia and absence of intracytoplasmic mucins. There was absence of cellular and nuclear atypia, necrosis, capsular invasion, an aggressive growth pattern, and nerve or surrounding tissue infiltration.

Pleomorphic adenomas, particularly of minor salivary glands of palate, may contain large areas of squamous and mucinous metaplasia, thereby arising the suspicion of mucoepidermoid carcinoma.<sup>11</sup> It is usually distinguished from mucoepidermoid carcinoma by at least focal presence of characteristic ductal and myoepithelial proliferation and myxochondroid stroma. In mucoepidermoid carcinoma, prominent keratinization and keratin pearl formation are rare<sup>12,13</sup> and MEC should have infiltrative borders with the cystic spaces of MEC lined by mucous cells. Keratinization, if present in MEC, is found exclusively in the high-grade group, which is characterized by predominantly solid growth, significant nuclear pleomorphism and paucity of mucinous cells. In fact, among salivary gland tumors, keratinization is much more commonly seen in benign tumors. However, even if the features diagnostic of PA are identified, the differential diagnosis may still include a MEC arising in a preexisting PA. However, MEC ex PA is exceedingly rare and is usually a high grade malignancy.<sup>14,15</sup>

#### IMMUNOHISTOCHEMISTRY:

Different immunohistochemical studies reported that the squamous epithelium lining the keratin cyst formations shows homogeneous positivity for high-molecular-weight (HMW) cytokeratin (CK), while some cells express low-molecular-weight (LMW) CK (CK7 and CK19) and p63. Luminal cells may also show positive immunostaining for epithelial membrane antigen, S-100 and carcinoembryonic antigen. The pattern of CK expression suggests that the cells expressing Hmw CK have undergone squamous metaplasia, but those expressing Lmw CK and p63 have not yet undergone squamous metaplasia. These morphologically similar squamoid cells are metaplastic squamous cells and ductal epithelial cells showing squamoid features depending on the immunohistochemical and morphologic profiles, respectively. Positive immunostaining for myoepithelial cell markers such as Hmw CKs, p63, S-100, vimentin, and occasionally for smooth muscle actin, muscle-specific actin and glial fibrillary acidic protein (GFAP) was reported in abluminal cells. Immunopositivity, either focal for CK7, CK19, vimentin, GFAP and S-100 or frequent for Hmw CKs was also reported for cells in solid sheets, nests and cords presented<sup>12</sup>

**TREATMENT:**

Wide local excision is the treatment of choice in these lesions. Although PA has a low proliferative rate, interestingly, the epithelial lining of the large keratin-filled cyst shows a higher proliferative index than the other areas. It may signify that the squamous metaplasia resulting in the large keratin-filled cyst in PA may be clinically significant, probably related to an important growth potential.<sup>12</sup>

**2 CONCLUSION:**

PA presenting with numerous keratin pearls with squamous metaplasia and keratin-containing cyst along with the presence of habits in the patient can pose diagnostic dilemma. The use of special stains in histopathology can significantly solve this challenge instead of the expensive immunohistochemistry procedures. Hence, it is important to be aware of the presence of keratin pearls in PA and the need to distinguish it from malignant lesions to avoid unnecessary aggressive therapy

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