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Pleomorphic Adenoma: Features of Cellular Composition and Morphological Structure

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Abstract: Pleomorphic adenoma is the most common benign tumor of the salivary glands, characterized by high histological and morphological heterogeneity. This article examines the macroscopic and microscopic features of this neoplasm, its cellular composition, growth patterns, as well as histochemical and immunohistochemical characteristics. Special attention is given to the localization of the tumor in the parotid, submandibular, and minor salivary glands, which determine its clinical course and treatment strategy. Understanding the morphological features of pleomorphic adenoma plays a key role in its timely diagnosis and the selection of the optimal surgical approach.

Keywords: pleomorphic adenoma, salivary glands, histological heterogeneity, cellular composition, macroscopic features, histochemical markers.

Introduction. Pleomorphic adenoma represents the most common salivary gland neoplasm. Despite its epithelial origin, this tumour often contains a mesenchymal component. In 5-10% of cases, pleomorphic adenoma undergoes malignant transformation, making it the fourth most common malignant salivary gland tumour. The average rate of malignisation is 6.2% of all cases of this pathology, and carcinoma arising on the background of pleomorphic adenoma is about 12% of the total number of malignant salivary gland tumours [9,17].

Improvements in surgical techniques have significantly reduced the risk of recurrence. According to the World Health Organization (WHO) classification, pleomorphic adenoma is defined as a tumour containing cells of epithelial, myoepithelial and mucoid, myxoid or chondroid types.

Most commonly, pleomorphic adenoma develops in the parotid salivary gland, predominantly in its caudal and inferior regions. In about 20% of cases, the tumour is found in the submandibular gland and small salivary glands of the upper respiratory tract. Among intraoral localisations, the palate is most frequently affected, and less frequently the lip and cheek mucosa [15,16].

Objective. To analyze morphological, histological and cellular characteristics of pleomorphic adenoma of salivary glands, as well as peculiarities of its localization in order to emphasize the significance of this tumour in clinical and diagnostic practice.

Results. Pleomorphic adenomas are slow-growing tumours that can remain asymptomatic for a long time. As a rule, they manifest as a painless, gradually enlarging mass in the parotid region.

Depending on the localisation, the tumour may be located deep in the parotid gland tissue or at the border of the soft and hard palate [5,8].

The localisation of PA affects the clinical course, diagnostic approaches and treatment tactics. The main sites of occurrence are parotid, submandibular and minor salivary glands, each of which has its own anatomical and morphological features.

The most common pleomorphic adenoma affects the parotid salivary gland, accounting for up to 80% of all benign neoplasms of this localisation. The tumour usually develops in the superficial lobe of the gland, which facilitates its clinical detection. It appears as a dense, painless formation, mobile relative to the surrounding tissues. In rare cases, the tumour may be located in the deep lobe, which makes its palpation difficult and may lead to compression of facial nerve branches, causing paresis of mimic muscles [4].

Submandibular salivary gland PA is much less common and accounts for about 8-10% of all cases. In this localisation, the tumour is characterised by a denser attachment to the surrounding tissues, which complicates surgical removal. Unlike parotid localisation, a neoplasm in the submandibular gland can cause compression of the hyoid nerve, which leads to disorders of tongue function and salivation [6].

In small salivary glands (palate, lips, cheeks, retromolar region), pleomorphic adenoma is more often found on the hard palate. Such tumours are usually small in size, but can reach significant volumes, causing deformation of the mucosa and difficulty in speech or chewing. Due to the absence of a capsule and proximity to the underlying tissues, tumours in this location have a higher tendency to recur after removal [2].

Depending on the predominant structural elements, there are three main variants: solid, cystic, and mixed.

Solid type is characterised by dense accumulations of epithelial and myoepithelial cells with a minimal amount of stromal component. This variant shows a pronounced cellular compactness, which can make it difficult to histologically differentiate the tumour from other salivary gland neoplasms.

The cystic type includes cavities of various sizes lined with tumour epithelium. In some cases, secretory masses may be found in the lumen of cysts, which indicates functional activity of epithelial cells. This variant of growth is often accompanied by the formation of cystic structures containing serous or mucinous contents.

The most common is the mixed type, which combines glandular structures, myoepithelial complexes and a pronounced stromal component. The latter may be represented by chondroid, myxoid or fibrous tissue, which determines the heterogeneity of the tumour and its pleomorphic character [3,5,11].

Recurrent forms of pleomorphic adenomas are often characterised by dense attachment to the underlying tissues, which may complicate their removal. The size of the tumour varies depending on the salivary gland affected, and in some cases so-called giant pleomorphic adenomas may form. In most cases, these neoplasms are solitary, but synchronous or metachronous combination with other tumours is possible [1,12].

Histologically, pleomorphic adenomas are characterised by the presence of an encapsulated tumour, the structure of which may show haemorrhages and foci of necrosis. A comprehensive examination including both macroscopic and microscopic analyses is necessary for accurate diagnosis [20]. Different types of cells, including myoepithelial and mesenchymal cells, are found in pleomorphic adenoma and are actively proliferating. Sometimes acinar cells can also be found in the tumour, although this is rare. The tumour is surrounded by a connective tissue capsule, but its thickness may vary and in some areas the capsule may be absent. The myoepithelial cells in the tumour are variably shaped, and epithelial cells may form small ducts.

The internal structure of the tumour (stroma) varies, most often consisting of mucus (mucoid), cartilage (chondroid) or dense connective tissue (fibrous). Different types of stroma may be combined in the same tumour, and the number of epithelial cells may differ both in different tumours and within the same tumour [17].

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In about one third of pleomorphic adenoma cases, the amount of cellular component and stroma is in equilibrium. The most common variant of mesenchymal stroma is the mucoid (or myxoid) type. In some cases, nodules of myxoid stroma can be observed, which usually have indistinct borders [7].

A characteristic feature of pleomorphic adenoma is the presence of a transition zone between myoepithelial cells and mesenchymal tissue, which indicates possible metaplasia of myoepithelial cells. Immunohistochemical study shows that markers p63, CK5/6, CK8/18, vimentin and S-100 stain positively for both epithelial and mesenchymal cells in the tumour.

The p63 and p73 genes are involved in cell stemness maintenance and differentiation. Pleomorphic adenomas are characterised by the expression of a shortened isoform that lacks transactivation activity. In addition, nestin may serve as a useful marker to identify abluminal cells in salivary gland tumours.

Recent studies have expanded the understanding of the role of the PLAG1 gene in the development of pleomorphic adenoma (PA), one of the most common salivary gland tumours. PLAG1 has been found to be a key factor in transcriptional regulation and is rearranged and overexpressed in pleomorphic adenomas, especially in cases with 8q12 abnormalities, most commonly caused by the t(3;8)(p21;q12) translocation [9,21,23].

Immunohistochemical examination shows positive PLAG1 staining in tumour cells, regardless of the presence of genetic rearrangements. Histologically, pleomorphic adenoma may include various components such as ductal and myoepithelial cells as well as cartilaginous tissue. Immunohistochemical analysis using PLAG1 is an important diagnostic tool, especially in cases where PA mimics other salivary gland tumours. The intensity of PLAG1 staining plays a crucial role in confirming the diagnosis [21].

Pleomorphic adenoma shows a wide range of morphological patterns including epithelial, plasmacytoid and myoepithelial cells. Tumours containing large numbers of plasmacytoid-type myoepithelial cells are more common in pleomorphic adenomas of the minor salivary glands.

Plasmacytoid tumours usually stain positive for the proteins vimentin, cytokeratin, S-100 and GFAP, but do not contain the markers SMA and MSA. If the tumour is dominated by elongated (spindle-shaped) myoepithelial cells, such tumours are usually positive for SMA and MSA as well as other markers [14].

Pleomorphic adenoma may contain areas of thickened connective tissue (hyalinisation), cysts and even signs of tumour ingrowth into vessels (vascular invasion). Sometimes squamous (squamous cell) metaplasia occurs in the tumour, in which islets of epithelial tissue resembling skin are formed.

A rarer change is oncocytic metaplasia, in which the cells acquire a specific appearance characteristic of oncocytoma. Because of this, a pleomorphic adenoma with marked oncocytic metaplasia can be confused with acinosis-cell carcinoma, which is a malignant tumour. To clarify the diagnosis, additional markers such as CD10 and CK20 are used [19].

Lipometaplasia in pleomorphic adenoma is relatively rare, but it cannot be considered exceptional. In cases where adipose tissue constitutes a significant portion of the stromal component, such a variant is classified as a lipomatous pleomorphic adenoma characterised by a prominent lipomatous component. In addition, among fat-forming salivary gland tumours, lipoadenoma, myoepithelioma and pleomorphic adenoma are the most common. Importantly, necrosis in these tumours may occur due to infarction or aspiration. Another feature of pleomorphic adenoma is the ability to form bone tissue, which may appear either in the cartilaginous stroma or as a result of non-costal metaplasia. In addition, sebaceous gland metaplasia may develop in the tumour, as well as the deposition of crystalline material, which may serve as additional diagnostic features. In rare cases, pleomorphic adenoma may contain pigmented melanocytes or show schwannoma-like changes, which makes diagnosis difficult. Moreover, pigmented neoplasms such as mucoepidermoid carcinoma and adenoid cystic carcinoma are also found among salivary gland tumours, highlighting the difficulty in morphological differentiation of these processes [11].

PAs may demonstrate atypical histological features including hyalinisation, hypercellularity, cellular anaplasia, necrosis and capsular disruption. The diagnosis of atypical pleomorphic adenoma requires the presence of at least one, and preferably two or more, of these features. These tumours have an increased risk of malignant transformation, which is seen in 5-10% of cases, especially in recurrences.

Metastasising pleomorphic adenoma is a low-grade malignancy capable of local and distant metastasis. Metastases are most commonly detected in bone (45%), lymph nodes, skin, lung (36%) and abdomen (10%). Although previous surgical interventions (e.g. incomplete operations or enucleations) may contribute to recurrence, the occurrence of metastases is not always related to surgery and may be due to genetic mutations.

Malignant transformation develops gradually, including intracapsular carcinoma, former pleomorphic adenoma, and minimally invasive lesions. Currently, there are no histological parameters to accurately predict the risk of metastasis. Nevertheless, the disease is associated with high morbidity and mortality, with 5-year disease-free survival rates of 50-58% [10,13,18].

Diagnosis of PA of which most cases are diagnosed based on standard histological examination following parotidectomy or biopsy. However, in some cases there may be difficulties in differentiating PA from other salivary gland neoplasms such as adenocarcinoma, myoepithelioma, and adenoid cystic carcinoma (ADCC).

The morphological hallmark of PA is the presence of a fibrous capsule, but its absence in small tumours does not exclude this diagnosis. In addition, pleomorphic adenoma does not show features characteristic of malignant tumours, such as marked cellular atypia or invasion into surrounding tissues. The presence of modified myoepithelial cells, cartilaginous stroma, and positive immunohistochemical reaction for glial fibrillary acidic protein (GFAP) may serve as additional diagnostic criteria [22].

Conclusions. Pleomorphic salivary gland adenoma is the most common benign tumour characterised by high morphological and histological heterogeneity. Its macroscopic and microscopic features, diversity of cellular composition and growth variants require a complex approach to diagnosis and treatment.

The histological structure of pleomorphic adenoma determines its pleomorphism, which is expressed in the combination of epithelial, myoepithelial and stromal components represented by chondroid, myxoid or fibrous tissue. The variants of tumour growth, including solid, cystic and mixed types, determine its morphological diversity and potential difficulties in differential diagnosis.

Despite its benign nature, pleomorphic adenoma has the ability to recur, especially in case of insufficiently radical removal, and, in rare cases, may undergo malignant degeneration. Therefore, timely detection, morphological verification and adequate surgical treatment are key aspects in the management of patients with this pathology.

Thus, further studies aimed at investigating the molecular mechanisms of pleomorphic adenoma development, its immunohistochemical characteristics and factors contributing to malignisation remain relevant to improve diagnostic and therapeutic approaches.

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