

TITLE: Histopathology of the Major Salivary Glands

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INTRODUCTION

Neoplasms of the major salivary glands constitute only a minor portion of head and neck neoplasms. Less than 2% are malignant, and account for only 6% of head and neck cancers, 0.3% of all cancers. Most neoplasms occur in the parotid (75%) with few occurring in the sublingual glands (0.8%). The remainder is equally distributed between the submandibular gland and minor salivary glands.

Proportion of malignant and benign varies with the gland of origin. 75% of parotid neoplasms are benign and 25% malignant, whereas 18% of sublingual gland neoplasms are benign and 82% malignant. The submandibular gland neoplasms are about equal with 57% benign and 43% malignant. The incidence of salivary gland neoplasms rises at age 15 and peaks at 65-75, with the incidence of malignancy increasing after the 4th and 5th decades. Malignant neoplasms occur most often in men.

SALIVARY GLAND MICROANATOMY

Saliva is transported from the central structure of the salivary unit, the acini, in a complex ductal system to the oral cavity. The system is a bilayer with an internal luminal layer and an external reserve layer. The internal layer forms the acini and the ductal epithelium, while the external layer forms the myoepithelium and the reserve cells.

The Bicellular theory postulates that neoplasms arise from one of two ductal types, the intercalated ducts and the excretory ducts. In this theory, the intercalated ducts give rise to pleomorphic adenomas, Warthin's tumors, oncocytomas, acinic cell carcinomas and adenoid cystic neoplasms. The excretory ducts give rise to squamous cell carcinomas and mucoepidermoid carcinomas.

The Multicellular theory states that striated ducts give rise to oncocytic tumors, acinar cells to acinic cell carcinomas, excretory ducts to squamous cell and mucoepidermoid

carcinomas, and the intercalated duct and myoepithelial cells to pleomorphic adenomas.

CLASSIFICATION OF SALIVARY NEOPLASMS

There currently exist two classification systems for salivary gland neoplasms, the World Health Organization and the Armed Forces Institute of Pathology. The WHO classification includes the following categories: adenomas, carcinomas, nonepithelial tumors, malignant lymphomas, secondary tumors, unclassified tumors and tumor-like lesions. The AFIP scheme includes categories of benign epithelial neoplasms, malignant epithelial neoplasms, mesenchymal neoplasms, malignant lymphomas, metastatic tumors, and non-neoplastic tumor-like conditions.

BENIGN NEOPLASMS

Pleomorphic Adenoma: The histology of pleomorphic adenomas contains a mixture of epithelial, myoepithelial and stromal components. The epithelial cells can be found in nests, sheets or in trabeculae. The stroma contains myxoid, chondroid, fibroid and osteoid elements. Pleomorphic adenomas have no true capsule, but contain tumor pseudopods. Necrosis and mitosis are rarely seen. The glandular areas stain with CEA, S100, actin, and epithelial membrane antigen. The mesenchymal areas stain with S100 and actin only.

Warthin's Tumor: These neoplasms have papillary projections into cystic spaces, surrounded by lymphoid stroma. The epithelium is a double cell layer containing luminal cells and basal cells. The stroma consists of mature lymphoid follicles with germinal centers.

Basal Cell Adenoma: Basal cell adenomas consist of solid nests of cells with scant cytoplasm and hyperchromatic nuclei. They have a tendency for peripheral palisading. There are various types of basal cell adenomas. The solid type is the most common, with solid nests of tumor cells. They have hyperchromatic, round nuclei with indistinct cytoplasm. There is peripheral palisading with scant stroma. The trabecular form contains cells that are elongated in a trabecular pattern with a vascular stroma. The tubular form contains multiple duct-like structures with a columnar cell lining and a vascular stroma. Finally, the membranous form contains thick eosinophilic hyaline membranes surrounding nests of tumor cells. They have a "jigsaw puzzle" appearance.

Oncocytoma: Oncocytomas contain cords of uniform cells and a thin fibrous stroma. The cells are large and polyhedral shaped, with a distinct cell membrane. They have a granular, eosinophilic cytoplasm with a central, round, vesicular nucleus. Oncocytomas stain positive for cytokeratin, epithelial membrane antigen, and phosphotungstic acid:hematoxylin and negative for S100, glial fibrillary protein and smooth muscle actin.

Canalicular Adenoma: These neoplasms are well circumscribed tubular structures lined by columnar or cuboidal cells. They contain a vascular stroma.

Myoepithelioma: Myoepitheliomas contain spindle shaped cells with uniform, central nuclei. Their cytoplasm is granular with either an eosinophilic or fibrillar cytoplasm. Some contain plasmacytoid cells that are polygonal with eccentric oval nuclei.

MALIGNANT NEOPLASMS

Mucoepidermoid carcinoma: These malignant neoplasms contain mucous producing cells as well as epidermoid cells. There are three grades of mucoepidermoid carcinoma. The low grade tumors have more mucous producing cells than epidermoid cells. They contain prominent cysts and have mature cellular elements. Intermediate grade tumors have an equal amount of mucous producing and epidermoid cells. They contain fewer and smaller cysts and have increasing pleomorphism and mitotic figures. The high grade mucoepidermoid carcinomas have more epidermoid cells than mucous producing cells with a solid tumor cell proliferation. These are often mistaken for squamous cell carcinomas.

Adenoid cystic carcinomas: These tumors can be found to have three patterns, the most common is the cribriform pattern. These have the classic “Swiss cheese” appearance. The tubular pattern contains layered cells forming duct-like structures with a basophilic mucinous substance. The solid pattern has solid nests of cells without cystic or tubular spaces.

Polymorphous low grade adenocarcinoma: These tumors contain isomorphic cells with indistinct borders and uniform nuclei. They have a classic peripheral “Indian-file” pattern. Polymorphous low grade adenocarcinomas stain markedly positive for S100, epithelial membrane antigen, and cytokeratins. They stain less predictably with CEA and Muscle specific actin.

Acinic cell carcinomas: Acinic cell carcinomas contain both solid and microcystic patterns. Polyhedral cells are found in small sheets with numerous cysts. They contain small dark eccentric nuclei with a basophilic granular cytoplasm. These tumors stain positive for cytokeratins and CEA and have mixed results with other immunostains.

Adenocarcinoma: These are heterogeneous tumors with the presence of glandular structures and absence of an epidermoid component. Diagnosis requires exclusion of other specific salivary gland carcinomas.

Malignant mixed tumors: Malignant mixed tumors are a group of tumors that have components of different tumor types. These forms include **Carcinoma ex-pleomorphic adenoma** in which the carcinoma develops in the epithelial component of preexisting pleomorphic adenoma. The carcinomatous component is similar to an adenocarcinoma and the cells have an undifferentiated appearance. Also, **Carcinosarcoma** which is a true malignant mixed tumor. It has a biphasic appearance and contains both carcinomatous and sarcomatous components. The sarcomatous component is dominant and resembles a chondrosarcoma while the carcinomatous component is similar to a moderately to poorly differentiated ductal carcinoma. **Metastatic mixed tumor** is metastatic deposits of otherwise typical pleomorphic adenoma.

Epithelial-Myoepithelial carcinomas: These tumors contain a dual epithelial component. Cells contain irregular, eccentric nuclei with vacuolated cytoplasm. The immunohistochemical profiles reveal a dual cell origin: the epithelium stains positive with cytokeratins and the myoepithelium stains with S100 and actin.

Salivary duct carcinoma: These malignant neoplasms have large polygonal cells with

well defined borders. The cells have pleomorphic nuclei with prominent nucleoli and granular eosinophilic cytoplasm. IHC patterns are similar to breast cancer except they stain negative for estrogen and S100 and cytokeratins, but positive for CEA and epithelial membrane protein.

Squamous cell carcinoma: These tumors are infiltrating nests of tumor cells. The well differentiated form displays keratinization, whereas poorly differentiated tumor has a lack of keratinization.

Undifferentiated carcinoma: These are high grade tumors with high mitotic activity, scant cytoplasm and hyperchromatic nuclei. IHC reveals positive staining for cytokeratins and epithelial membrane antigen and equivocal staining for neuroendocrine markers.

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