"An Analytical Approach to the Diagnosis of Salivary Gland and Selected Head & Neck Tumors"

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Queen Elizabeth Hospital
Hong Kong

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Dr. John K. C. Chan is Consultant Pathologist at Queen Elizabeth Hospital in Hong Kong. His training includes fellowships at Stanford University Medical Center and Yale School of Medicine. He has served as an Honorary Clinical Lecturer at the University of Hong Kong for many years, and has been on the editorial boards of numerous pathology medical journals. He was the founding Editor-in-Chief of "Advances in Anatomic Pathology". He is a participant in numerous academic societies, and has been the recipient of many scholarships and awards. His 300+ publications on varied fields of pathology, and his authorship or co-authorship of six books, especially highlight his expertise in all fields of anatomic pathology. This is the third time that Dr. Chan has addressed the CTTR.
# TABLE OF CONTENTS - TOPIC LIST

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis List</td>
<td>4</td>
</tr>
<tr>
<td>The normal salivary glands</td>
<td>5</td>
</tr>
<tr>
<td>Salivary gland neoplasms: Overview</td>
<td>7</td>
</tr>
<tr>
<td>Pleomorphic adenoma: The commonest type of salivary gland tumor and a great mimicker</td>
<td>10</td>
</tr>
<tr>
<td>Salivary gland epithelial tumors: Approach to diagnosis</td>
<td>14</td>
</tr>
<tr>
<td>Common errors in diagnosis of salivary gland tumors</td>
<td>22</td>
</tr>
<tr>
<td>Salivary gland tumors that commonly pose problems in diagnosis</td>
<td>24</td>
</tr>
<tr>
<td>Case 1: Acinic cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Case 2: Mucopidermoid carcinoma, low-grade</td>
<td></td>
</tr>
<tr>
<td>Case 3: Myoepithelial carcinoma (low grade), arising in pleomorphic adenoma</td>
<td></td>
</tr>
<tr>
<td>Case 4: Polymorphous low grade adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Case 5: Adenoid cystic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Salivary gland tumors with cribriform pattern</td>
<td>46</td>
</tr>
<tr>
<td>Case 6: Salivary duct carcinoma</td>
<td></td>
</tr>
<tr>
<td>Oncocytic lesions</td>
<td>52</td>
</tr>
<tr>
<td>Case 7: Oncocytic adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Case 8: Mucopidermoid carcinoma, oncocyic variant (with clear cells)</td>
<td></td>
</tr>
<tr>
<td>Case 9: Nodular oncocyic hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Clear cell tumors</td>
<td>59</td>
</tr>
<tr>
<td>Case 10: Clear cell oncocytoma</td>
<td></td>
</tr>
<tr>
<td>Case 11: Epithelial-myoepithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Basaloid cell tumors</td>
<td>66</td>
</tr>
<tr>
<td>Case 12: Basal cell adenoma with myoepithelium-derived stroma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell lesions</td>
<td>73</td>
</tr>
<tr>
<td>Case 13: Necrotizing sialometaplasia</td>
<td></td>
</tr>
<tr>
<td>Cystic lesions of salivary gland</td>
<td>75</td>
</tr>
<tr>
<td>Case 14: Acinic cell carcinoma, papillary-cystic variant</td>
<td></td>
</tr>
<tr>
<td>Progression of salivary gland tumors</td>
<td>80</td>
</tr>
<tr>
<td>Case 15: Carcinoma ex pleomorphic adenoma (intracapsular)</td>
<td></td>
</tr>
<tr>
<td>Case 16: Dedifferentiated acinic cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Case 17: Dedifferentiated adenoid cystic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Lymphoid lesions of salivary gland</td>
<td>88</td>
</tr>
<tr>
<td>Case 18: Chronic sclerosing sialadenitis (Kuttner tumor)</td>
<td></td>
</tr>
<tr>
<td>Case 19: Extranodal marginal zone B-cell lymphoma of MALT</td>
<td></td>
</tr>
<tr>
<td>Small cell tumors of head and neck</td>
<td>94</td>
</tr>
<tr>
<td>Case 20: Small cell carcinoma, Merkel cell type (Merkel cell carcinoma) of salivary gland</td>
<td></td>
</tr>
<tr>
<td>Case 21: Offactory neuroblastoma with glandular component</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelial tumors of head and neck</td>
<td>100</td>
</tr>
<tr>
<td>Case 22: Lymphoepithelial carcinoma of salivary gland, EBV+</td>
<td></td>
</tr>
<tr>
<td>Case 23: Lymphadenoma</td>
<td></td>
</tr>
<tr>
<td>Spindle cell tumors of salivary gland and head &amp; neck</td>
<td>109</td>
</tr>
<tr>
<td>Case 24: Glomangiopericytoma (Hemangiopericytoma-like tumor)</td>
<td></td>
</tr>
<tr>
<td>Image captions</td>
<td>117</td>
</tr>
<tr>
<td>Image pages (color plates)</td>
<td>131</td>
</tr>
<tr>
<td>Contact the CTTR</td>
<td></td>
</tr>
<tr>
<td>Case number</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Acinic cell carcinoma</td>
</tr>
<tr>
<td>2</td>
<td>Mucoepidermoid carcinoma, low-grade</td>
</tr>
<tr>
<td>3</td>
<td>Myoepithelial carcinoma (low grade), arising in pleomorphic adenoma</td>
</tr>
<tr>
<td>4</td>
<td>Polymorphous low grade adenocarcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>6</td>
<td>Salivary duct carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>Oncocytic adenocarcinoma</td>
</tr>
<tr>
<td>8</td>
<td>Mucoepidermoid carcinoma, oncocytic variant (with clear cells)</td>
</tr>
<tr>
<td>9</td>
<td>Nodular oncocytic hyperplasia</td>
</tr>
<tr>
<td>10</td>
<td>Clear cell oncocytoma</td>
</tr>
<tr>
<td>11</td>
<td>Epithelial-myoepithelial carcinoma</td>
</tr>
<tr>
<td>12</td>
<td>Basal cell adenoma with myoepithelium-derived stroma</td>
</tr>
<tr>
<td>13</td>
<td>Necrotizing sialometaplasia</td>
</tr>
<tr>
<td>14</td>
<td>Acinic cell carcinoma, papillary-cystic variant</td>
</tr>
<tr>
<td>15</td>
<td>Carcinoma ex pleomorphic adenoma (intracapsular)</td>
</tr>
<tr>
<td>16</td>
<td>Dedifferentiated acinic cell carcinoma</td>
</tr>
<tr>
<td>17</td>
<td>Dedifferentiated adenoid cystic carcinoma</td>
</tr>
<tr>
<td>18</td>
<td>Chronic sclerosing sialadenitis (Kuttner tumor)</td>
</tr>
<tr>
<td>19</td>
<td>Extranodal marginal zone B-cell lymphoma of MALT</td>
</tr>
<tr>
<td>20</td>
<td>Small cell carcinoma, Merkel cell type (Merkel cell carcinoma) of salivary gland</td>
</tr>
<tr>
<td>21</td>
<td>Olfactory neuroblastoma with glandular component</td>
</tr>
<tr>
<td>22</td>
<td>Lymphoepithelial carcinoma of salivary gland, EBV+</td>
</tr>
<tr>
<td>23</td>
<td>Lymphadenoma</td>
</tr>
<tr>
<td>24</td>
<td>Glomangiopericytoma (Hemangiopericytoma-like tumor)</td>
</tr>
</tbody>
</table>
THE NORMAL SALIVARY GLANDS

APPLIED ANATOMY

- Three pairs of major salivary glands: parotid, submandibular and sublingual.
- Parotid gland: superficial and deep lobes are separated by the facial nerve. Most salivary gland tumors arise from the superficial lobe and present as facial swellings. Tumors that occur in the deep lobe often expand through the parapharyngeal space, manifesting as pharyngeal swelling. About 20 lymph nodes and randomly distributed lymphoid aggregates are normally present in the parotid gland, with the latter component representing the mucosa-associated lymphoid tissue (MALT). Conventional types of nodal lymphoma occurring in intraparotid lymph nodes may present as salivary gland tumor. Conversely, salivary gland tissues can be found in intra-parotid, para-parotid and cervical lymph nodes, and are believed to give rise to Warthin tumor and other salivary gland tumors in lymph nodes mimicking metastatic disease.
- Submandibular and sublingual glands: unlike parotid gland, there is no lymph node or large nerve coursing through the parenchyma.
- ~ 500-1000 lobules of minor glands dispersed in the submucosa of the oral cavity (lateral margins of the tongue, lips, buccal mucosa, palate and glossopharyngeal area). Among them, the palate is the predilection site for salivary gland neoplasms.
- Seromucinous glands of the nasal cavity, larynx, and bronchi, although not producing saliva by definition, are histologically similar to the minor salivary glands and share a similar repertoire of neoplasms.

HISTOLOGY

Tissue organization

- Salivary lobules consist of variable proportions of serous and mucous cells. The parotid gland is exclusively serous, the submandibular gland mixed seromucinous, and the sublingual gland predominantly mucous; the minor glands are seromucinous or predominantly mucous depending on location.
- Salivary glands are tubuloacinar exocrine glands. The acini are the secretory units situated at the terminus. The secretion reaches the oral cavity via the conducting unit, consisting of intercalated, striated, interlobular, excretory and salivary ducts.
- Preservation of the lobular architecture is an important feature favoring a diagnosis of non-neoplastic process over a tumor.
- The entire glandular structure is a two-tiered organization which comprises luminal (acinar and ductal cells) and abluminal cells (myoepithelial and basal cells). The secretory acini and the intercalated ducts are wrapped by myoepithelial cells. The striated ducts and the subsequent conducting units are lined by simple or pseudostratified columnar epithelium which gradually transforms into stratified squamous epithelium in the salivary duct, and they are supported by basal cells.

Cellular morphology and immunophenotypic profile

Luminal cells

- Serous cells are pyramidal, with basal nuclei and abundant basophilic cytoplasm rich in zymogen granules that are PAS positive (diastase-resistant) and mucicarmine negative
- Mucous cells are cuboidal to columnar, and have pale, finely vacuolated cytoplasm containing sialomucins. They are PAS (diastase-resistant) and mucicarmine positive
- Luminal cells of the intercalated ducts are cuboidal, with eosinophilic to amphiphilic cytoplasm and centrally located nuclei.
- Striated ducts are lined by columnar cells with granular cytoplasm (mitochondria-rich) and subnuclear vertical striations due to the prominent basal folds in the plasma membrane.
- Luminal cells are readily highlighted by immunostaining for cytokeratin, carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA). CD117/c-kit is negative in the normal salivary gland cells, but is interestingly often positive in the luminal (glandular) cells of various types of salivary gland tumors.

**Abluminal cells**
- Myoepithelial cells are modified epithelial cells situated between the luminal cells and the basement membrane. They are stellate-shaped with cytoplasmic processes embracing the acini, or spindle-shaped surrounding the intercalated ducts. They show dual epithelial and smooth muscle phenotype.
- Myoepithelial cells produce extracellular matrix such as basement membrane materials and myxoid substances, which may account for the diverse morphology of various salivary gland tumors.
- Myoepithelial cells are best highlighted by immunostaining for p63, high molecular weight cytokeratin (including CK14), calponin, actin, and variably glial fibrillary acidic protein (GFAP).
- The abluminal cells in the striated ducts, excretory ducts and salivary ducts are basal cells, which differ ultrastructurally from myoepithelial cells in the absence of myofilaments. They maintain the capacity of multidirectional differentiation. They are immunoreactive for p63 and high molecular weight cytokeratin, but not the myoid markers.

**Amylase +**

<table>
<thead>
<tr>
<th>Pan-cytokeratin +</th>
<th>High M.W. cytokeratin +</th>
<th>EMA +</th>
<th>CEA +</th>
<th>Vimentin +</th>
<th>p63 +</th>
<th>myoid markers -</th>
</tr>
</thead>
</table>

**Metaplastic change and other cell types**
- Oncocytic cells, characterized by abundant eosinophilic granular cytoplasm due to accumulation of mitochondria, are uncommon below the age of 50, but increase thereafter until being almost universal above the age of 70. They show variable replacement of the normal cells of ducto-acinar units.
- Adipose tissue is normally a conspicuous component of the parotid gland, which increases in proportion with age.
- Groups of sebaceous glands may occur in the parotid gland, and represent the normal counterpart of the salivary sebaceous neoplasms.
<table>
<thead>
<tr>
<th>BENIGN EPITHELIAL TUMORS</th>
<th>MALIGNANT EPITHELIAL TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pleomorphic/monomorphic adenoma family</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>Carcinoma ex pleomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td>Metastasizing pleomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>Basal cell adenoma</td>
<td>Basal cell adenocarcinoma</td>
</tr>
<tr>
<td>Myoepithelioma</td>
<td>Myoepithelial carcinoma</td>
</tr>
<tr>
<td><strong>Oncocytic tumors</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Warthin tumor</td>
<td>Carcinoma arising in Warthin tumor</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Oncocytic carcinoma</td>
</tr>
<tr>
<td><strong>Sebaceous tumors</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>Sebaceous carcinoma</td>
</tr>
<tr>
<td>Sebaceous lymphadenoma</td>
<td>Sebaceous lymphadenocarcinoma</td>
</tr>
<tr>
<td><strong>Adenoma with additional stromal component</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Lymphadenoma</td>
<td>Malignant transformation of ductal papilloma</td>
</tr>
<tr>
<td>Lipoadenoma (Sialolipoma)</td>
<td></td>
</tr>
<tr>
<td>Adenofibroma</td>
<td></td>
</tr>
<tr>
<td><strong>Ductal papillomas</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Inverted ductal papilloma</td>
<td></td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td></td>
</tr>
<tr>
<td>Sialadenoma papilliferum</td>
<td></td>
</tr>
<tr>
<td><strong>Other benign tumors</strong></td>
<td><strong>Malignant counterpart</strong></td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>Cystadenocarcinoma</td>
</tr>
<tr>
<td>Canalicular adenoma</td>
<td></td>
</tr>
<tr>
<td>Keratocystoma</td>
<td></td>
</tr>
<tr>
<td>Salivary gland anlage tumor</td>
<td></td>
</tr>
<tr>
<td>Sclerosing polycystic adenosis</td>
<td></td>
</tr>
<tr>
<td><strong>Other salivary gland-type carcinomas</strong></td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td></td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Polymorphous low grade adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Epithelial-myoepeithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma (NOS and hyalinizing variant)</td>
<td></td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td></td>
</tr>
<tr>
<td>Intraductal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sialoblastoma</td>
<td></td>
</tr>
<tr>
<td><strong>Undifferentiated carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma (Merkel and pulmonary-types)</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td><strong>&quot;Non-specific&quot; carcinomas</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma NOS</td>
<td></td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Signet ring cell adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
</tbody>
</table>
GENERAL FEATURES

- Sex predilection: Females are more commonly affected than males, except for Warthin tumor and high grade carcinomas.
- Epithelial tumors constitute 80-90% of all salivary gland tumors, with the majority being benign (75%), and pleomorphic adenoma is the commonest (about 65% of all tumors).
- The parotid gland is the commonest site for occurrence of salivary gland tumors.
- Some tumor types show predilection to occur either in the major or minor salivary glands, and thus knowledge on the site of tumor can aid in diagnosis.

<table>
<thead>
<tr>
<th>Tumors occurring exclusively or predominantly in major glands</th>
<th>Tumors occurring exclusively or predominantly in minor glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warthin tumor</td>
<td>Canalicular adenoma (lip, buccal mucosa)</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>Polymorphous low-grade adenocarcinoma (palate)</td>
</tr>
<tr>
<td>Basal cell adenoma/adenocarcinoma</td>
<td>Cystadenoma/cystadenocarcinoma (lip, buccal mucosa)</td>
</tr>
<tr>
<td>Oncocytoma/oncocytic adenocarcinoma</td>
<td>Inverted papilloma (lip, buccal mucosa)</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Intraductal papilloma (lip, buccal mucosa)</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>Sialadenoma papilliferum (palate)</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

- Salivary gland tumors are generally rare in children. In patients under the age of 18, half of the epithelial tumors are malignant, with low grade mucoepidermoid carcinoma being the commonest.
- In infants, mesenchymal tumors (hemangioma and lymphangioma) are the commonest, and some unusual tumors such as sialoblastoma and salivary gland anlage tumor occur almost exclusively in this age group.

SALIVARY GLAND CARCINOMAS

- The sites of occurrence with respect to the number of cases in descending order are: parotid gland, submandibular gland, palate, cheek, and tongue.
- However, tumors have the highest chance of being malignant if they arise from the retromolar area (89.7%), floor of mouth (88.2%), tongue (85.7%), and sublingual gland (70.2%), while only approximately 20% of all parotid tumors are malignant.
- Among the salivary gland carcinomas, the commonest histologic types in descending order are: mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma NOS and acinic cell carcinoma, with polymorphous low grade adenocarcinoma replacing adenocarcinoma NOS in the minor salivary glands.
- Age of presentation is similar to or slightly older compared with benign tumors.
- In practice, most malignant salivary gland tumors are not clinically distinguishable from the benign ones, except when they show rapid increase in size, pain, fixation to adjacent structures, ulceration, or cervical lymph node enlargement.
Behavior of salivary gland carcinomas

- Some salivary gland carcinomas are biologically low grade:
  - acinic cell carcinoma
  - polymorphous low grade adenocarcinoma
  - basal cell adenocarcinoma
  - epithelial-myoepithelial carcinoma
  - clear cell carcinoma
  - cystadenocarcinoma
- Some are biologically high grade:
  - salivary duct carcinoma
  - most cases of carcinoma ex pleomorphic adenoma
  - undifferentiated carcinoma
    - oncocytic carcinoma
- Some span a range of behavior according to grade:
  - mucoepidermoid carcinoma
  - adenoid cystic carcinoma

- The prognosis of an individual tumor type is further influenced by clinical stage and margin status.
- Some studies have shown high proliferative fraction (Ki67 index), DNA aneuploidy, and expression of p53 protein to be associated with a worse prognosis.
- Since some salivary gland tumors are notorious for pursuing a protracted clinical course and late recurrence or metastasis, long-term follow-up is usually required to ascertain that cure is truly achieved.
- The survival curves of the three major types of salivary gland carcinoma are most instructive (see below: mucoepidermoid carcinoma, acinic cell carcinoma and adenoid cystic carcinoma respectively). The plateau in the curve after an initial drop indicates that a significant proportion of patients with mucoepidermoid carcinoma can be cured of their tumors. Acinic cell carcinoma is indolent, but unfavorable events may not become manifest until after 10 years. Although the short-term survival for adenoid cystic carcinoma is good, the long-term outcome is bleak, that is, a high proportion of patients eventually succumb to the tumor.
PLEOMORPHIC ADENOMA:
THE COMMONEST TYPE OF SALIVARY GLAND TUMOR AND A GREAT MIMICKER

Pleomorphic adenoma is singled out for discussion here because this is the commonest salivary gland tumor, and it is also an important differential diagnosis for the various types of salivary gland tumors.

**Salient diagnostic criteria of pleomorphic adenoma**
- Circumscribed
- Dual luminal and abluminal cell differentiation
- At least focal "melting" of abluminal cells into stroma
- Plasmacytoid hyaline cells, if present
- Chondromyxoid stroma, if present

**DEFINITION**
- A benign neoplasm consisting of cells with epithelial (luminal) and myoepithelial (abluminal) differentiation, accompanied by variable amounts of characteristic stroma.
- The diverse morphology results from amalgamation of cellular and stromal components.
- The coexistence of apparently epithelial and mesenchymal elements gives rise to the synonym "mixed tumor".
- Pleomorphic adenoma is now widely accepted as a pure epithelial tumor with divergent differentiation instead of collision of epithelial and mesenchymal tumors.
- The monoclonal origin of both the epithelial and mesenchymal elements has also been supported by molecular analysis.

**CLINICAL BEHAVIOR**
- Pleomorphic adenoma can occur in major glands or minor glands.
- When it occurs in the minor glands, ulceration of the overlying mucosa or apparent fixation to the surrounding tissue can be seen rarely.
- Pleomorphic adenoma can also occur in various mucosal sites such as nasal cavity, bronchus, skin (also known as chondroid syringoma), breast, and soft tissues.
- The treatment of choice is complete surgical excision.
- The recurrence rates at 5 and 10 years following complete excision are 3.4% and 6.3% respectively.
- Enucleation alone, rupture or spillage of tumor during removal, presence of protuberances beyond the main tumor, abundance of chondromyxoid stroma, and young age are associated with a higher recurrence rate.
- In most instances, the recurrent tumor maintains the original histology; however, with each recurrence, there is an increased possibility of malignant transformation.

**PATHOLOGY**

**Growth pattern**
- Thinely encapsulated.
- A few small, smooth-contoured buds (protuberances) may protrude through the fibrous capsule.
- Occasionally, tumor islands may appear outside the capsule at a short distance from the main tumor mass, but serial sectioning usually demonstrates that such satellites are, in fact, outgrowths continuous with the main tumor mass and should not be regarded as invasion.
- Rarely, pleomorphic adenoma can grow entirely within a dilated duct.
- Pleomorphic adenoma is characterized by highly variable growth patterns in different areas of the same tumor.

### Basic cellular organization
- The prototypic histologic appearance consists of tubular structures enveloped by myoepithelial mantles submerging in a chondromyxoid stroma.
- The interface between the tumor islands and the stroma is usually poorly demarcated.
- The myoepithelial mantle radiates centrifugally, forming sheets, clusters, lattices and isolated cells, where they appear to “melt” into the sea of stroma they produce.
- While the “melting” phenomenon is characteristic, it can be focal, and some areas of the tumor can be composed of tubules or trabeculae well delineated from the stroma.
- There may even be foci resembling mucoepidermoid carcinoma or adenoid cystic carcinoma, but carcinoma ex pleomorphic adenoma should not be diagnosed unless a discrete expansile lesion is formed.

### Luminal cell component
- The luminal cell component takes the form of anastomosing tubules, cysts, ribbons, and solid sheets.
- The cells may be columnar, cuboidal or flat.
- The duct lumen may be empty or contain eosinophilic colloid-like material, which is PAS-positive diastase-resistant and variably mucicarmine positive.
- Rarely, metaplastic change to squamous, sebaceous, oncocytic or clear cells can occur.
- Very occasionally, the epithelium may form goblet or mucous cells, which in association with squamous epithelium, can lead to an erroneous interpretation of mucoepidermoid carcinoma.

### Myoepithelial component
- Myoepithelial or modified myoepithelial cells appear as cuboidal, spindly, stellate, plasmacytoid hyaline, non-descript epitheloid, and hydropic clear cells.
- The spindle or cuboidal cells surround the ducts in a single layer, thick mantle or radiating corona.
- Can form non-descript sheets, trabeculae and even cribriform structures.
- Plasmacytoid hyaline cells represent the most distinctive form of modified myoepithelial cells; they are oval-shaped, with homogeneous eosinophilic hyaline cytoplasm. The nucleus is round and eccentrically.
located, with a tendency for peripheral margination of the dense chromatin. Plasmacytoid hyaline cells are so named because of their resemblance to plasma cells, but they are larger, show less coarse clumping of the chromatin, and lack perinuclear Golgi zone. They are usually arranged in aggregates or sheets, often with focal areas of non-cohesive growth. Since their occurrence is restricted to pleomorphic adenoma and myoepithelioma, their identification is of great diagnostic value, especially in small biopsies. There can be transitional forms which show overlapping features with other types of myoepithelial cells.

- Stellate or spindly myoepithelial cells occur singly, or form anastomosing strands, suspended in an abundant myxoid matrix.
- Uncommonly, myoepithelial cells may merge into squamous nests or cystic squamous-lined structures filled with keratin, suggesting an ability to differentiate towards the squamous lineage.
- In occasional cases, myoepithelial cells dominate the tumor.
- Rarely, skeletal muscle differentiation and scattered melanocytes can occur, the latter also imparting a pigmented macroscopic appearance to the tumor.

**Stroma**

- Extracellular stroma is one of the defining components of pleomorphic adenoma, although it can be scanty to abundant. It is composed mostly of acidic mucosubstances produced by the modified myoepithelial cells, and is positive for Alcian blue, but variably positive for PAS. The stroma takes the form of a mixture of chondroid (hyaline cartilage), myxoid, chondromyxoid, hyaline, and very rarely, osseous and adipose tissues.
- Of interest, adipose cell differentiation is uncommon except in cutaneous sites. Isolated or groups of stellate, oval or polygonal cells are suspended in the matrix.
- The presence of chondromyxoid stroma in a salivary gland tumor is practically pathognomonic of pleomorphic adenoma.
- In tumors in which chondromyxoid matrix predominates, the ductal structures is most likely found in the peripheral zone immediately beneath the capsule.
- Tumors with very scanty or no extracellular stroma are often called “cellular pleomorphic adenomas”; they can be recognized by the focal "melting" of the myoepithelial mantles.
- It has been suggested that recurrence is more frequent for stroma-rich tumor, which has a higher chance of spillage of mucoid stroma during operation. Highly cellular tumors, on the other hand, may be more prone to malignant change.
- Homogenous, fibrillary or radiating hyaline material can be interspersed among the epithelial or myoepithelial cells.
- Crystalloids composed of collagenous substance, tyrosine, and oxalate can develop between the cellular or stromal components.
- Tyrosine crystals often appear as “daisy-heads” in the myxoid stroma.
- Elastic fibers are present in variable amounts in most pleomorphic adenomas, and they are particularly abundant in long-standing lesions. They show up as globular masses or irregular bands with fluffy outlines by elastic stain. These thick elastic fibers are diagnostically helpful because they are uncommon in other salivary gland tumors.
Fine needle aspiration-associated changes

- Fine needle aspiration commonly results in hemorrhagic tracts and micronecrosis, accompanied by variable reparative changes.
- Complete or incomplete infarction can also occur.
- There can be florid reactive proliferation of the myoepithelium, which can protrude into the fibrous capsule or show nodular bulging beneath the endothelium of veins.
- Atypical squamous metaplasia is also common.

IMMUNOHISTOCHEMISTRY

- The main application of immunohistochemistry is to demonstrate the co-existence of glandular and myoepithelial components when the diagnosis is uncertain.
- The glandular component, which may be inconspicuous, can be highlighted by EMA, CEA or c-kit.
- The myoepithelial and modified myoepithelial cells are positive for cytokeratin, but not EMA and CEA. Although CK14 and various myoid markers (such as actin and myosin) mark the normal myoepithelium nicely, the pattern of staining in neoplasms is anarchic: the staining of neoplastic myoepithelium can be patchy or totally negative, while that in the luminal cells can even be stronger! The myoepithelial component is commonly positive for S100 protein and GFAP, although S100 immunoreactivity can also be variably observed in the luminal cells. Currently the most reliable markers for the neoplastic myoepithelial components are p63 and calponin.
- Ki-67 proliferative index is low (mean 1.6%).

MAJOR DIFFERENTIAL DIAGNOSES

- Monomorphic adenoma, e.g., basal cell adenoma, myoepithelioma
- Adenoid cystic carcinoma
- Polymorphous low grade adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Mucoepidermoid carcinoma

Various mesenchymal tumors, e.g., nerve sheath tumor, smooth muscle tumor
SALIVARY GLAND EPITHELIAL TUMORS: APPROACH TO DIAGNOSIS

RENDERING A DIAGNOSIS

- Salivary gland tumors not uncommonly pose problems in diagnosis due to their rarity, broad morphologic spectrum, complex cytoarchitecture, and morphologic overlap among the different tumor types.
- Picture matching approach does not work because of marked morphologic overlap among the different tumor entities.
- Therefore it is important to understand the basic cytoarchitectural features of each tumor type, in particular whether the tumor shows dual luminal-abluminal cell differentiation, so that a diagnosis can be made logically through analysis of the cellular components, cell arrangement and extracellular components.

Major pathologic features to assess in diagnosis of salivary gland tumors

- Presence of absence of invasion (definite invasion signifying a malignant neoplasm)
- One or two cell type (diagnostic possibilities limited to a few entities if there is dual luminal-abluminal cell differentiation)
- Growth pattern (e.g. microcystic pattern being a strong indicator for diagnosis of acinic cell carcinoma)
- Cytologic composition
- Amount and type of stroma

ANALYTIC APPROACH TO DIAGNOSIS

The diagnostic problem

- Warthin tumor often has a stereotyped appearance, and rarely causes problem in diagnosis.
- Most pleomorphic adenomas do not pose problems in diagnosis either, because of the presence of the characteristic chondromyxoid stroma.
- However, the histologic spectrum of each tumor entity can be very broad, and there is considerable morphologic overlap among the various entities. For example, although a cribriform pattern is highly characteristic of adenoid cystic carcinoma, this can be seen focally in pleomorphic adenoma, basal cell adenoma, polymorphous low grade adenocarcinoma, salivary duct carcinoma and epithelial-myoepithelial carcinoma – tumors with very different prognoses.
- Adenoid cystic carcinoma may have a minor component with clear cells, focally mimicking epithelial-myoepithelial carcinoma.
- Therefore, in formulating a diagnosis, one should not rely on isolated microscopic fields of the tumor, but should take the overall features into consideration, the most important of which are:
  - tumor borders
  - cellular composition
  - architectural arrangement
  - cytologic features
  - stromal components
- If the patterns appear non-diagnostic, thorough sampling of the tumor will often prove rewarding because some diagnostic foci can often be identified.
Morphologic assessment

**Invasive or not?**

- The tumor interface with adjacent tissues, either at the macroscopic or microscopic level, is the single most important parameter to assess.
- Benign tumors are circumscribed, while malignant tumors have infiltrative borders, with the following exceptions: some acinic cell carcinomas and carcinomas ex pleomorphic adenoma may have circumscribed borders, while Warthin tumor complicated by infarction or inflammation can result in a lot of adhesions to the surrounding, mimicking malignant neoplasm clinically or grossly. The presence of smooth-contoured protuberances beyond the capsule is still within the acceptable morphologic spectrum of pleomorphic adenoma.
- The pattern of infiltration also differs among different types of carcinomas – this tends to be of pushing type in epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, myoepithelial carcinoma (except high grade ones), and acinic cell carcinoma; whereas the other carcinomas usually exhibit irregular tongue-like infiltrative growth.
- The importance of identification of invasion cannot be overemphasized. A presumptive diagnosis of adenoid cystic carcinoma must be wrong if tissue infiltration is not identified; similarly, this diagnosis should be viewed with some skepticism if extensive sampling of the tumor fails to reveal perineural invasion.
- Since adenoid cystic carcinoma may overlap morphologically with basal cell adenoma and sometimes pleomorphic adenoma, identification of invasion is one of the most important parameters for making the distinction.
- For some tumors, the presence of frank invasive features alone automatically moves the designation from the benign to the malignant category even if the tumor is morphologically bland-looking, for example, myoepithelial, basal cell and oncocytic neoplasms.
- The implication is that the tumor borders must be adequately sampled for examination.
- In some circumstances, a definitive diagnosis may not be possible without the opportunity to assess the tumor borders, such as in needle or incisional biopsies.

**Does the tumor show dual cellular population or only a single line of differentiation?**

- The following Table lists the various salivary gland tumors with dual luminal and abluminal cell differentiation. Identification of this feature greatly narrows down the differential diagnoses.
- For instance, adenoid cystic carcinoma can be difficult to distinguish from polymorphous low grade adenocarcinoma, but the former shows dual cell differentiation whereas the latter does not.
- Canalicular adenoma can be distinguished from basal cell adenoma by the lack of abluminal cell component.
- In some tumors, careful search and detailed morphologic analysis, sometimes aided by judicious application of immunohistochemistry, is required to identify dual-cell type differentiation.
- Adenocarcinoma NOS exceptionally can show dual-cell differentiation, but by definition should lack diagnostic features of adenoid cystic carcinoma and basal cell adenocarcinoma.
- Some polymorphous low grade adenocarcinomas can also show very focal dual-cell type differentiation.
- Although basal cells (abluminal cells) are inconspicuous in oncocytoma at the light microscopic level, they are often evident on immunostaining in the form of attenuated cells.
## SALIVARY GLAND TUMORS WITH DUAL LUMINAL-ABLUMINAL CELL DIFFERENTIATION

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Architectural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma*</td>
<td>Proliferated abluminal cells &quot;melt&quot; into stroma at least focally; chondroid matrix and plasmacytoid hyaline cells characteristic if present</td>
</tr>
<tr>
<td>Basal cell adenoma*</td>
<td>Basaloid cells predominate; tumor islands and trabeculae well demarcated from stroma; no chondroid matrix or plasmacytoid hyaline cells</td>
</tr>
<tr>
<td>Warthin tumor*</td>
<td>Oncocytic luminal and basal cells; papillary pattern; prominent lymphoid stroma</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma®</td>
<td>Basaloid abluminal cells predominate over luminal cells; cribriform structures common; most cystic spaces are pseudocysts lined by abluminal cells</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma®</td>
<td>Large and clear abluminal cells; cribriform structures very rare</td>
</tr>
<tr>
<td>Basal cell adenocarcinoma®</td>
<td>Basaloid cells predominate; luminal cells or glandular structures usually sparse; tumor lobules often show jigsaw puzzle pattern</td>
</tr>
</tbody>
</table>

* Circumscribed; ® Invasive

### Architectural arrangement

- Some tumors exhibit architectural features that may provide important clues to their diagnosis (See Table).
- When extravasated mucin is seen in a fibrous stroma with chronic inflammatory cell infiltration, the most likely diagnosis is low grade mucoepidermoid carcinoma.
- For any 'difficult-to-classify' carcinoma, the possibility of carcinoma ex pleomorphic adenoma has to be considered.
- Some tumors that are commonly partially or completely cystic include Warthin tumor, cystadenoma, cystadenocarcinoma, mucoepidermoid carcinoma and the papillary-cystic variant of acinic cell carcinoma.

<table>
<thead>
<tr>
<th>Architectural pattern</th>
<th>Diagnoses to consider</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcystic</td>
<td>• Acinic cell carcinoma&lt;br&gt;• Polymorphous low grade adenocarcinoma (focal)&lt;br&gt;• Myoepithelioma (some cases)</td>
<td>Acinic cell carcinoma should be the first consideration whenever microcystic pattern is prominent, especially when accompanied by a lymphoid infiltrate.</td>
</tr>
<tr>
<td>Cribiform</td>
<td>• Adenoid cystic carcinoma&lt;br&gt;• Salivary duct carcinoma&lt;br&gt;• Intraductal carcinoma&lt;br&gt;• Pleomorphic/basal cell adenoma (focal)&lt;br&gt;• Polymorphous low grade adenocarcinoma (focal)&lt;br&gt;• Cribiform adenocarcinoma of the tongue</td>
<td>Cribiform structures are highly characteristic, but not diagnostic, of adenoid cystic carcinoma. Most of the spaces in the cribriform plates in adenoid cystic carcinoma are in continuity with the stroma rather than true glandular spaces. The cribriform structures in salivary duct carcinoma and intraductal carcinoma are however true glandular spaces.</td>
</tr>
<tr>
<td>Tubular</td>
<td>• Adenoid cystic carcinoma</td>
<td>A tubular pattern is common in salivary gland tumors. Assessment of the tumor interface with the surrounding tissues, cellular composition and differentiation, and the cytomorphology of the tumor cells is helpful in arriving at the diagnosis.</td>
</tr>
<tr>
<td></td>
<td>• Polymorphous low grade adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Epithelial-myoepithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adenocarcinoma, NOS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pleomorphic/basal cell adenoma (focal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cystadenoma and cystadenocarcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Salivary duct carcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Oncocytoma and oncocytic carcinoma (rare cases)</td>
<td></td>
</tr>
<tr>
<td>Fascicular</td>
<td>• Myoepithelioma and myoepithelial carcinoma</td>
<td>The presence of spindly cells in fascicles, excluding mesenchymal tumors, is usually indicative of presence of myoepithelial differentiation, except polymorphous low grade adenocarcinoma.</td>
</tr>
<tr>
<td></td>
<td>• Basal cell adenoma with myoepithelium-derived stroma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pleomorphic adenoma (focal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Polymorphous low grade adenocarcinoma (focal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Epithelial-myoepithelial carcinoma (focal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Various mesenchymal tumors</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>• Warthin tumor</td>
<td>Analysis of the tumor cells covering the papillae is helpful in diagnosis. Dual cell differentiation is seen in Warthin tumor and epithelial-myoepithelial carcinoma, sialadenoma papilliferum, and intraductal papilloma</td>
</tr>
<tr>
<td></td>
<td>• Cystadenoma and cystadenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ductal papillomas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acinic cell carcinoma, papillary-cystic variant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adenocarcinoma, NOS (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Polymorphous low grade adenocarcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Epithelial-myoepithelial carcinoma (very focal)</td>
<td></td>
</tr>
<tr>
<td>Lattice</td>
<td>• Myoepithelioma and myoepithelial carcinoma</td>
<td>The lattice pattern is a prominent feature of some myoepithelial neoplasms, but is rare in other salivary gland tumors. Ectomesenchymal chondromyxoid tumor of the tongue (not a salivary gland tumor) also shows a prominent lattice growth pattern.</td>
</tr>
<tr>
<td></td>
<td>• Pleomorphic adenoma (focal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adenoid cystic carcinoma (focal, in areas of extensive hyalinization)</td>
<td></td>
</tr>
</tbody>
</table>

**Cytologic features**

- When certain cell types are found in a salivary gland tumor, they may provide important clues to classification (See Table below).
- The presence of vacuolated cells should raise the possibilities of acinic cell carcinoma and sebaceous neoplasms.
- For practical purposes, the majority of clear cell salivary gland tumors are malignant.
- Squamous nests with or without keratinization can be seen in a variety of tumors. Importantly, frank squamous features such as intercellular bridges and keratinization are almost never seen in low to intermediate grade mucoepidermoid carcinomas; the correct diagnosis is probably pleomorphic adenoma or Warthin tumor with squamous metaplasia.
- Neoplastic oncocytic cells, such as in Warthin tumor, oncocytoma and oncocytic carcinoma, tend to undergo squamous metaplasia in response to injury from ischemia or inflammation; such metaplastic squamous cells often exhibit variable degrees of atypia, inviting a misdiagnosis of squamous cell carcinoma or mucoepidermoid carcinoma.
- When the following tumors are encountered in the salivary gland, the possibility of metastasis should always be considered before accepting them as primary neoplasms: squamous cell carcinoma, clear cell carcinoma, small cell carcinoma, lymphoepithelial carcinoma and neuroendocrine carcinoma.

<table>
<thead>
<tr>
<th>Constituting a prominent component</th>
<th>Present focally</th>
<th>Non-neoplastic lesion potentially mistaken for neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oncocytic cells</strong></td>
<td>Warthin tumor</td>
<td>Oncocytic metaplasia</td>
</tr>
<tr>
<td></td>
<td>Oncocytoma</td>
<td>Oncocytosis</td>
</tr>
<tr>
<td></td>
<td>Oncocytic carcinoma</td>
<td>Nodular oncocytic hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Oncocytic cystadenoma</td>
<td></td>
</tr>
<tr>
<td><strong>Squamous cells</strong></td>
<td>Warthin tumor or oncocytic neoplasm with squamous metaplasia</td>
<td>Pleomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma (primary, metastasis, or invasion from adjacent sites)</td>
<td>Basal cell adenoma or adenocarcinoma (centers of cell islands)</td>
</tr>
<tr>
<td></td>
<td>Adenosquamous carcinoma</td>
<td>Sebaceous adenoma or adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>High grade mucoepidermoid carcinoma</td>
<td>Epithelial-myoeoepithelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>Keratoceystoma</td>
<td></td>
</tr>
<tr>
<td><strong>Basaloid cells</strong></td>
<td>Basal cell adenoma</td>
<td>Epithelial-myoeoepithelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>Basal cell adenocarcinoma</td>
<td>Polymorphous low grade adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Pleomorphic adenoma</td>
<td>Canalicul ar adenoma</td>
</tr>
<tr>
<td></td>
<td>Adenoid cystic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphadenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basaloid squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sialoblastoma</td>
<td></td>
</tr>
<tr>
<td><strong>Spindle cells</strong></td>
<td>Myoepithelioma</td>
<td>Lymphoepithelial sialadenitis</td>
</tr>
<tr>
<td></td>
<td>Myoepithelial carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salivary gland anlage tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pleomorphic adenoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucoepidermoid carcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Various benign and malignant mesenchymal tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Basal cell adenoma or adenocarcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epithelial-myoeoepithelial carcinoma (some cases)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphoepithelial carcinoma (some cases)</td>
<td></td>
</tr>
</tbody>
</table>
Stromal components

- Eosinophilic hyaline or basement membrane-like material generally indicates presence of myoepithelial or basal cell differentiation, with the exception of hyalinizing clear cell carcinoma (which show pure luminal cell differentiation).

- In fact, stromal hyaline material can be the first clue to the diagnosis of salivary gland-type tumor for neoplasms occurring outside the major salivary glands. The hyaline material is found around cell islands, in the pseudoglandular spaces, or interspersed as bands (such as in pleomorphic adenoma and myoepithelioma) or droplets among the tumor cells (such as membranous basal cell adenoma and basal cell adenocarcinoma).

- Elastic fibers are often present in abundance in long-standing pleomorphic adenoma, usually in the form of thick or fluffy branching fibers. They can provide a clue to the existence of this tumor in the scenario of carcinoma ex pleomorphic adenoma. They are also helpful to identify an infarcted tumor as pleomorphic adenoma.

- Stromal mucin, which appears lightly basophilic in hematoxylin-eosin-stained sections, is such a common finding in salivary gland tumors that it is not of much discriminatory value in tumor classification. Nonetheless, when present in abundance, the most likely candidate is pleomorphic adenoma.

- The presence of cartilage in a salivary gland tumor is practically synonymous with a diagnosis of pleomorphic adenoma. Occasionally, it can also be seen in carcinomasarcoma and carcinoma ex pleomorphic adenoma.

The presence of thick fluffy elastic fibers in a salivary gland tumor is a strong pointer towards a diagnosis of pleomorphic adenoma.
HISTOCHEMISTRY
- Histochemical studies have only a limited role in the diagnosis of salivary gland tumors.
- Although staining for mucosubstances and basement membrane materials in adenoid cystic carcinoma is often mentioned, such stains do not help in the establishment of this diagnosis.
- Any salivary gland tumor with luminal cell differentiation can have epithelial-type mucin (usually PAS-positive diastase-resistant) in the lumens. Many tumor types are associated with production of basement membrane-like material (PAS-positive diastase-resistant), especially those showing myoepithelial or basal cell differentiation.
- Variable amounts of acidic stromal mucin (Alcian blue-positive, but PAS-negative) may also be found in many types of salivary gland tumors, such as pleomorphic adenoma and adenoid cystic carcinoma.
- The limited applications of histochemistry include:
  o Aid in diagnosis of acinic cell carcinoma by PAS-diastase to demonstrate serous cell differentiation.
  o Aid in diagnosis of high-grade mucoepidermoid carcinoma by demonstrating intracytoplasmic mucin. Mucin stains are often not required for the diagnosis of low- to intermediate-grade mucoepidermoid carcinomas because mucin is often obvious in routine histologic sections.
  o PAS-diastase can aid in detection of focal luminal cell differentiation in a predominantly basal cell or myoepithelial cell neoplasm, such as the solid type of adenoid cystic carcinoma, or clear cell-rich epithelial-myoepithelial carcinoma.
  o Phosphotungstic acid hematoxylin stain may help in diagnosis of the clear cell variant of oncocytoma, by highlighting the mitochondria.

IMMUNOHISTOCHEMISTRY
- Currently, immunohistochemical staining has only a limited role in the diagnosis of salivary gland tumors. Its main applications are:
  o To delineate whether there is two-cell type differentiation in tumors with complex architecture, although results can be disappointing as a result of aberrant immunophenotypes.
  o To confirm the diagnosis of myoepithelioma/myoepithelial carcinoma by demonstrating the appropriate immunophenotype.
  o Ki67 proliferative index may be useful in distinguishing an adenoma from a carcinoma (Ki67 index usually <5% vs. >10%).

GENETIC STUDIES
- Genetic studies have identified several recurrent events in pleomorphic adenoma (rearrangement of chromosomes 8q12 and 12q13-15), mucoepidermoid carcinoma (translocation of chromosomes 11q21 and 19p13), adenoid cystic carcinoma (structural or molecular alterations at 6q, 8q and 12q), and salivary duct carcinoma (amplification of HER-2).
- Gene expression profiling studies using microarrays have also identified genes that can separate benign salivary gland tissue from neoplasms, and demonstrated differential profiles in pleomorphic adenoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, acinic cell carcinoma and salivary duct carcinoma.
- However, currently molecular studies have no established role in routine diagnosis.
INTERPRETATION OF NEEDLE OR INCISIONAL BIOPSIES OF SALIVARY GLAND TUMORS

- A diagnosis of salivary gland tumors from needle or incisional biopsy is sometimes easy, for example, pleomorphic adenoma is readily recognized when the typical chondromyxoid matrix is seen or the characteristic plasmacytoid hyaline cells are present.

- However, it is not always possible to render a definitive diagnosis; it may even not be possible to tell whether the tumor is benign or malignant. The difficulties stem from the morphologic overlap among the different tumor types, and difficulties in proper assessment of the tumor borders in biopsies.

- For example, a biopsy showing tubules with dual luminal and abluminal cell differentiation may represent a pleomorphic adenoma, basal cell adenoma, adenoid cystic carcinoma, epithelial-myoeipithelial carcinoma, or even adenocarcinoma, NOS. In the absence of more definitive diagnostic features, only a descriptive diagnosis of “salivary gland neoplasm” can be made, and complete excision or a larger size biopsy is required to arrive at a definitive diagnosis.

The most important parameters to assess in diagnosis of salivary gland tumors are:

- **tumor borders, tumor borders and tumor borders**…. (with invasion indicating a diagnosis of carcinoma)

- **one versus two-cell-type differentiation** (presence of two cell-type markedly narrows down the list of differential diagnoses)
## Overdiagnosis of Malignancy

<table>
<thead>
<tr>
<th>Benign tumor</th>
<th>Misdiagnosed as...</th>
<th>Overdiagnosis of malignancy</th>
<th>Clues or features favoring the correct diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warthin tumor or oncocytoma with squamous and/or mucinous metaplasia</td>
<td>Squamous cell carcinoma or mucoepidermoid carcinoma</td>
<td></td>
<td>• Extreme rarity of primary squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Lack of invasive growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Convoluted cystic architecture of Warthin tumor</td>
</tr>
<tr>
<td>Pleomorphic adenoma with squamous and mucinous metaplasia (often post-fine needle aspiration)</td>
<td>Mucoepidermoid carcinoma</td>
<td></td>
<td>• Low-grade mucoepidermoid carcinoma never frankly squamous in appearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Merging of atypical squamous cells with residual oncocytic cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Prominent reparative features</td>
</tr>
<tr>
<td>Pleomorphic adenoma or basal cell adenoma with cribriform architecture</td>
<td>Adenoid cystic carcinoma</td>
<td></td>
<td>• Lack of invasive growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• &quot;Melting&quot; of myoepithelial cells into the stroma at least focally</td>
</tr>
<tr>
<td>Clear cell variant of oncocytoma</td>
<td>Clear cell carcinoma or mucoepidermoid carcinoma</td>
<td></td>
<td>• Lack of invasive growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Presence of typical oncocyes at least focally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Positive staining for PTAH and anti-mitochondrial antibody</td>
</tr>
<tr>
<td>Non-sebaceous lymphadenoma</td>
<td>Lymphoepithelial carcinoma</td>
<td></td>
<td>• Lack of significant nuclear atypia (although mild nuclear atypia is acceptable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Glandular differentiation (morphologic or immunohistochemical) is present at least focally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• EBV negative</td>
</tr>
</tbody>
</table>
### UNDERDIAGNOSIS OF MALIGNANCY

<table>
<thead>
<tr>
<th>Underdiagnosis of malignancy</th>
<th>Clues or features favoring the correct diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant tumor</strong></td>
<td><strong>Misdiagnosed as ...</strong></td>
</tr>
<tr>
<td>Cystic mucoepidermoid carcinoma</td>
<td>Benign cyst or cystadenoma</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma with prominent mucin extravasation</td>
<td>Mucocle</td>
</tr>
<tr>
<td>Polymorphous low grade adenocarcinoma</td>
<td>Pleomorphic or basal cell adenoma</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma in mucosal sites</td>
<td>Pleomorphic or basal cell adenoma</td>
</tr>
<tr>
<td>Oncocytic variant of mucoepidermoid carcinoma</td>
<td>Oncocytoma</td>
</tr>
<tr>
<td>Cystic or papillary-cystic variant of acinic cell carcinoma</td>
<td>Benign cyst</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Pleomorphic or basal cell adenoma</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>Lymphadenoma</td>
</tr>
</tbody>
</table>

- **Cells lining the cyst are multilayered in at least some foci**
- **Intraluminal nodules of cells**
- **Multiplicity of cell types**
- **Epithelial islands in fibrous wall or beyond**
- **Presence of pools of extravasated mucin in the major salivary gland mandates careful search for a low-grade mucoepidermoid carcinoma, since extravasation mucocle is extremely rare**
- **Invasive borders**
- **Neural invasion common**
- **Lack of dual cell differentiation**
- **Chondromyxoid stroma absent**
- **Diverse growth patterns**
- **Pale nuclei**
- **Invasive growth, if identifiable in the biopsy**
- **Tubules strangulated by hyalinized stroma**
- **Focal cribriform structures**
- **Invasive growth**
- **Other cell types (e.g., epidermoid, intermediate and mucinous cells) present in some foci**
- **Inflamed fibrous stroma**
- **Hobnailed lining cells**
- **Vacuolated lining cells**
- **Focal cellular tufts projecting into lumen**
- **Acinar cell differentiation (PAS+ granular cytoplasm) in the lining cells**
- **Tumor islands in fibrous wall focally**
- **Invasive growth often present**
- **Definite nuclear atypia (albeit sometimes mild)**
- **Tumor cells exhibit squamoid/squamous rather than glandular features at the morphologic or immunohistochemical level**
- **EBV in tumor cells, if present**

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**Salivary Gland Tumors**

CTTR 119th Cancer Seminar
CASE 1

Clinical history
- A 21-year-old female noted the presence of a left parotid mass for 5 to 6 years. She sought medical attention because of recent increase in the size of the mass.
- The left parotid gland was excised.
- The specimen consisted of salivary gland tissue harboring a circumscribed, bosselated, oval, tan-colored solid tumor measuring 1.9 x 1.2 x 1.2 cm.

Salient histologic features
- Tumor shows bosselated contour, and there is focal invasion in broad fronts into the parotid parenchyma
- Nodules of solid tumor separated by thin fibrous septa
- The nodules comprise columns and small packets of polygonal cells with abundant basophilic cytoplasmic granules (sometimes with a foamy quality).
- There are interspersed smaller cuboidal cells with no granules, resembling intercalated duct cells.
- There are some interspersed small luminal spaces filled with secretion, focally with formation of a microcystic pattern.

Diagnostic considerations
This case shows the characteristic histologic features (with numerous heavily granulated cells consistent with acinar cells) of acinic cell carcinoma, and should not cause problems in diagnosis. However, variants of acinic cell carcinoma can pose significant diagnostic difficulties.

Immunophenotype and special stains (not required for diagnosis of this case)
- PAS-diastase: many positive granules in cytoplasm
- Pan-cytokeratin: highlights mostly the intercalated duct-like cells but not the acinar cells
- CAM5.2 (low molecular weight cytokeratin): highlights intercalated duct-like cells and some acinar cells
- EMA: highlights the lumens
- p63: no basal or myoepithelial cells within tumor
- SMA: no myoepithelial cells within tumor

Diagnosis
Parotid gland – Acinic cell carcinoma
Major pitfalls in diagnosis of acinic cell carcinoma
- Reluctance to render a diagnosis of malignancy in a young patient.
- Reluctance to render a diagnosis of malignancy in a tumor with circumscribed or pushing borders.
- Difficulties in diagnosing acinic cell carcinoma when the tumor cells do not show obvious acinar features (with numerous granules).
- Mistaking the papillary-cystic variant for benign cystic lesions or tumors.

ACINIC CELL CARCINOMA
Definition
A neoplasm demonstrating differentiation towards serous acinar cells (at least focally). There is no myoepithelial participation.

Salient diagnostic criteria of acinic cell carcinoma
- Tumor with identifiable acinic cell differentiation (which is often focal)
- In addition to acinic cells, intercalated duct-type cells and nonspecific glandular cells are common
- Microcystic pattern, if present, is highly characteristic
- Diagnosis can be aided by: PAS-diastase stain (intracytoplasmic granules) or amylase immunohistochemistry

Clinical features
- Most frequent sites of occurrence are the parotid gland (84%) and submandibular gland (4%), followed by the buccal mucosa, upper lip and palate.
- Sex: slight female predominance.
- Age: mean 44 years, but children can also be affected.
- Acinic cell carcinoma has also been reported in antronasal mucosa, larynx, mandible, breast, lung, and pancreas. However, because of the indolence of acinic cell carcinoma, the presence of salivary gland primary years ago must be meticulously excluded before it can be accepted as a primary in these sites.
Presentation: slow-growing mass with or without pain.

Clinical behavior
- This indolent tumor pursues a protracted clinical course.
- In the Mayo Clinic series including 65 patients with long follow-up of up to 45 years, 44% of patients had local recurrence, 19% had metastasis, and 25% died of disease.
- Local recurrence and metastasis are often delayed, sometimes to more than 30 years after the initial presentation.
- Overall survival probabilities are 90% at 5 years, 83% at 10 years, and 67% at 20 years.
- Acinic cell carcinomas arising from the minor glands appear to be associated with a better prognosis.
The treatment of choice is complete surgical excision, supplemented by post-operative radiotherapy if resection margin is involved.
Pathology

- Typically forms a solitary mass or multiple nodules, and invades in broad fronts.
- Compactly cellular with little sclerotic stroma except for the occasional traversing fibrous bands.
- Lymphoid aggregates, with or without lymphoid follicle formation, can be present.
- Commonly a mixture of growth patterns comprising a number of cell types that recapitulate the acinar-intercalated duct unit.
- In general, the nuclei are bland-looking, and mitotic figures are rare.
- Growth patterns:
  - organoid sheets traversed by ramifying delicate blood vessels
  - sheets punctuated by microcystic spaces
  - cords
  - intertwining solid or near-solid tubules
  - coalescent acini
  - cysts
  - thyroid follicle-like structures
- The microcystic pattern is the most characteristic, although it is not invariably present. Formation of these microcysts is thought to result from lack of ducts to conduct away secretions and breakdown products, causing accumulation of fluid between the cells. Occasionally the microcysts coalesce to form larger cystic cavities. The microcystic spaces differ from true glandular spaces in that the surrounding cells lack orientation around the spaces.
- Cell types:
  - Acinar cells possess basophilic granular cytoplasm (PAS-diastase positive) and basally located nuclei. In contrast to normal acinar cells, these cells are polygonal instead of triangular, there is a greater variability in size with nuclear hyperchromasia, and they frequently show a range of granularity even in the same microscopic field. Some cells can exhibit a reticulated or foamy quality in the cytoplasm. Not uncommonly, the nuclei are lined up in characteristic "regimented" rows.
  - Intercalated duct-type cells, which are cuboidal, with central nuclei and pink cytoplasm. They often form small, closely packed glandular structures.
  - Nonspecific glandular cells that are generally small, with eosinophilic to amphophilic cytoplasm, often forming sheets.
  - Vacuolated cells with a solitary or multiple clear vacuoles: highly suggestive of acinic cell carcinoma when present.
  - Hobnail cells: most common in papillary-cystic variant.
  - Clear cells (due to tissue processing artifact or alteration of organelles rather than glycogen accumulation)
- Prone to ischemia and infarction either spontaneously or after fine needle aspiration, resulting in secondary hemorrhage, lipogranulomatous reaction, and/or cystic degeneration. Hemosiderin deposition in the fibrous stroma and even inside the tumor cells is common.

Confirmation of diagnosis

- PAS-diastase granules in cytoplasm of tumor cells (although such granules can be sparse and focal)
- Immunostaining for amylase (but only 15% of cases are positive).
Prognostic factors

- The most important prognostic indicators are clinical stage and resection margin status.
- Histologic grading has not been found to be a reliable predictor of prognosis, although frequent mitoses or high proliferative index (MIB1 index >5%), focal necrosis, neural invasion, gross invasion, desmoplasia, atypia, and depletion of lymphocytes in stroma have been associated with more frequent recurrences and metastases.
- One study suggests that tumors accompanied by a dense lymphoid stroma with well-developed germinal centers and showing microcystic growth pattern throughout have a particularly favorable prognosis (no recurrence or metastasis on follow up of 19 months to 14 years).

Differential diagnosis

- Oncocytoma
- Adenoid cystic carcinoma
- Adenocarcinoma NOS or cystadenocarcinoma
- Normal salivary gland tissue, especially in biopsies
- Metastatic thyroid carcinoma
- Granular cell tumor

CASE 2

Clinical features

- A 64-year-old male had a history of operation for left parotid tumor 20 years ago, but the diagnosis was unknown.
- He recently presented with a mass over the left jaw region.
- The left parotid gland was excised. The cut surface of the specimen revealed a lesion with irregular borders, and a solid-cystic appearance.

Salient histologic features

- No identifiable normal salivary gland tissue. The tissues present include skeletal muscle, fibrofatty tissue and lymph nodes.
- There is a non-circumscribed lesion comprising multiple cystic glands. Sometimes there are large cystic spaces into which papillary fronds project.
- The cysts are lined by bland-looking mucinous epithelium, often supported by an underlying layer of nondescript cells (intermediate cells).
- Prominent pools of extravasated mucus (sometimes containing suspended histiocytes), and mucus is present also within the sinusoids of some lymph nodes.
- The sclerotic stroma shows aggregates of chronic inflammatory cells.

Diagnostic considerations

This case actually shows the fairly characteristic histologic features of low-grade mucoepidermoid carcinoma. However, since the mucinous cells are so bland-looking and there are extravasated pools of mucus, a benign diagnosis, such as cystadenoma or duct ectasia, may be considered. However, the non-circumscribed growth and presence of a significant population of intermediate cells are against a diagnosis of cystadenoma.
**Immunophenotype and special stains** (not required for diagnosis of this case)
- Mucicarmine stain highlights the cytoplasm of the mucinous cells, the secretion in the lumens, and the extravasated mucus
- Cytokeratin 5/6: Mucinous cells negative; intermediate cells positive
- CAM5.2 (low M.W. cytokeratin): both mucinous and intermediate cells positive
- p63: intermediate cells highlighted
- Smooth muscle actin: Negative

**Diagnosis**
Parotid gland – Low grade mucoepidermoid carcinoma

**Major pitfalls in diagnosis of mucoepidermoid carcinoma**
- Reluctance to render this diagnosis in children and young adults
- Reluctance to render a diagnosis of malignancy because the tumor cells are so bland-looking (low grade mucoepidermoid carcinoma)
- Predominantly cystic low-grade mucoepidermoid carcinoma misdiagnosed as benign cystic lesion
- Paucicellular tumor with abundant extravasated mucus misdiagnosed as mucocele
- Paucicellular sclerosing variant misdiagnosed as inflammatory lesion
- Clear cell variant misdiagnosed as clear cell carcinoma
- Oncocytic variant misdiagnosed as oncocytoma
- Benign salivary gland tumors (pleomorphic adenoma, Warthin tumor, oncocytoma) with squamous/mucoepidermoid metaplasia misdiagnosed as mucoepidermoid carcinoma

**MUCOEPIDERMOID CARCINOMA**

**Definition**
- An invasive malignant neoplasm that comprises mucous-secreting cells, epidermoid cells, and intermediate cells in variable combinations, forming cysts and solid islands.

**Salient diagnostic criteria of mucoepidermoid carcinoma**
- Invasive borders
- Sclerotic stroma (common)
- Chronic inflammatory infiltrate (common)
- Characteristic epithelial islands/cysts comprising mucinous, squamoid and intermediate cells
- If frankly squamous or keratinous, probably not a low or intermediate grade mucoepidermoid carcinoma

**Clinical features**
- The commonest malignant salivary gland neoplasm in adults and childhood.
- Typically presents as a slow-growing painless mass.
- About one-third of patients experience tenderness, pain, drainage from the ipsilateral ear, dysphagia, and trismus.
- Age: 1st to the 9th decades, peaking in the 4th decade.
• Sex: slight female predilection.
• Commonest sites: parotid gland (45%) and palate (21%)

Pathology
• Most cases exhibit irregular invasive borders, at least focally.
• Haphazardly dispersed mucin-filled cysts and tumor nests
• Cell types (variable proportions):
  o Mucous cells
  o Squamoid (epidermoid) cells
  o Intermediate cells (nondescript in appearance)
• Stroma is characteristically sclerotic and abundant, with chronic inflammatory cell infiltration and occasional extravasated mucin pools.
• Rarely, there can be a densely lymphoplasmacytic infiltrate admixed with tumor islands, scattered multinucleated giant cells in the stroma, or melanin pigmentation.

Low grade mucoepidermoid carcinoma
• Variable-sized, mucin-filled cystic structures constitute a high proportion of the tumor
• Abundant mucous cells
• However, irregular-shaped epithelial islands are almost always present
• The squamoid cells are never frankly squamous; keratinization is practically never seen
• Bland nuclei, and mitotic figures rare
• Mucin-containing cysts may rupture, allowing escape of mucus into the stroma, eliciting an inflammatory response and subsequently sclerosis. The lymphoid infiltrate can be exuberant and accompanied by lymphoid follicles, imparting an erroneous impression of metastatic deposit in lymph node.

High grade mucoepidermoid carcinoma
• More solid areas and few cystic spaces.
• The solid areas are formed by large polygonal squamoid cells with pale to eosinophilic cytoplasm and distinct cell borders, as well as nondescript intermediate cells.
• Squamous features are often better developed compared with low grade tumors — there can be intercellular bridges and even individual cell keratinization, but keratin pearls are rare.
• Cellular pleomorphism, nuclear hyperchromasia, and mitotic figures are more impressive
• Coagulative necrosis may be present.
• Mucous cells are usually sparse, and staining for mucin may be required to identify them.
• Rarely, a component of low-grade mucoepidermoid carcinoma is present, suggesting that the high-grade tumor arises through progressive loss of differentiation.

Intermediate grade mucoepidermoid carcinoma
• Lies histologically between the low- and high-grade tumors.
• Cystic spaces do not constitute a significant portion of the tumor.
• Some degree of nuclear pleomorphism is present.
• Epidermoid features are generally more obvious than in the low grade tumors.
Variants of mucoepidermoid carcinoma

- Clear cells are not uncommon – cytoplasmic clearing is due to accumulation of glycogen. The cells located in the peripheral portions of the clear cell islands are often much smaller, with eosinophilic cytoplasm, and a squamous quality. Occasionally clear cells constitute a major portion of the tumor, rendering distinction from other clear cell tumors problematic. The clear cell variant appears to be more common in the palate.
- Focal spindle cell growth
- Oncocytic change – the rare oncocytic variant (oncocyes accounting for >60% of cell population) can potentially be confused with Oncocytoma
- Sclerosing variant – prominent central keloid-like sclerosis and lymphoid infiltrate at the periphery. Because of the paucity of tumor islands, which are often confined to the peripheral zone, this variant may be mistaken for an inflammatory lesion.

Immunohistochemistry

- Cytokeratin positive
- Variable staining for EMA, CEA and S100
- p63 positive in intermediate, squamous and clear cells, but myoepithelial markers such as actin and calponin are negative.
- In contrast to squamous cell carcinoma, mucoepidermoid carcinoma often expresses cytokeratin 7.

Genetic features

- Translocation involving mucoepidermoid carcinoma translocated 1 (MECT1) and mastermind-like gene family (MAML2), located at chromosome 19 and 11 respectively, is the most frequent genetic alteration in mucoepidermoid carcinoma
- The gene fusion can be detected by in-situ hybridization or RT-PCR in up to 70% of cases. This is not detected in Warthin tumor, despite earlier claims otherwise.

Prognostic factors

- The behavior is strongly correlated with the clinical stage and histologic grade.
- Cure is possible, especially for low and intermediate grade tumors.
- Several two- or three-tiered grading systems are in use.
- Recently, a new grading system using 5 histopathologic features has been shown to be reproducible and of prognostic significance.
- Nonetheless, a recent Mayo Clinic study shows that grade and stage are less important if radical surgery is performed.
- Submandibular mucoepidermoid carcinomas have significant metastatic potential irrespective of histologic grade, for example, 13% of patients with low grade tumor died of tumor.
- High proliferative index (mitotic count >2/10 HPF or MIB1 index greater than 10%), expression of MUC1, vascular invasion, involved margins and aneuploidy are also associated with a poor prognosis.
Mucoepidermoid carcinoma: Standard 3-tier grading system

<table>
<thead>
<tr>
<th>Histologic parameters for grading</th>
<th>Low grade</th>
<th>Intermediate grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts</td>
<td>Many macrocysts and microcysts</td>
<td>Some cysts</td>
<td>Few cysts</td>
</tr>
<tr>
<td>Mucinous cells</td>
<td>Many</td>
<td>Some</td>
<td>Few</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>Few</td>
<td>Few or some</td>
<td>Many</td>
</tr>
<tr>
<td>Cytology</td>
<td>Bland</td>
<td>Some atypia</td>
<td>Significant cellular pleomorphism</td>
</tr>
<tr>
<td>Biologic potential</td>
<td>Locally infiltrative; slow-growing</td>
<td>Intermediate</td>
<td>Highly infiltrative; rapid-growing</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0-6%</td>
<td>20-39%</td>
<td>61-78%</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Very rare</td>
<td>Some cases (lymph node 22%)</td>
<td>Common (44-72%; commonly lymph node; distant metastasis in 33%)</td>
</tr>
<tr>
<td>5-year survival rate</td>
<td>92%</td>
<td>70-83%</td>
<td>22-42%</td>
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</tbody>
</table>

Mucoepidermoid carcinoma: AFIP grading system (only applicable to intraoral and parotid tumors)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Intracystic component &lt; 20%</td>
<td>+2</td>
</tr>
<tr>
<td>Neural invasion</td>
<td>+2</td>
</tr>
<tr>
<td>Necrosis</td>
<td>+3</td>
</tr>
<tr>
<td>Mitoses ≥ 4/10HPF</td>
<td>+3</td>
</tr>
<tr>
<td>Anaplasia (nuclear pleomorphism, increased N/C ratio, large nucleoli, anisochromia, hyperchromasia)</td>
<td>+4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total score</th>
<th>Interpretation</th>
<th>Frequency among all mucoepidermoid carcinomas</th>
<th>Recurrence rate</th>
<th>Regional lymph node metastasis</th>
<th>Died of tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>Low grade</td>
<td>84%</td>
<td>7.5%</td>
<td>2.5%</td>
<td>0%</td>
</tr>
<tr>
<td>5-6</td>
<td>Intermediate grade</td>
<td>9%</td>
<td>8.3%</td>
<td>0%</td>
<td>8.3%</td>
</tr>
<tr>
<td>7-14</td>
<td>High grade</td>
<td>7%</td>
<td>40%</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Differential diagnosis

1. Mucoceles – Mucoceles are extremely rare in the major salivary glands. In a major gland showing unexplained mucin pools associated with fibrosis and chronic inflammation, the most likely diagnosis is low grade mucoepidermoid carcinoma. Extensive sampling will usually reveal the diagnostic tumor islands.

2. Warthin tumor with squamous/mucinous metaplasia

3. Pleomorphic adenoma with squamous differentiation

4. Cystadenoma or cystadenocarcinoma

5. Poorly differentiated adenocarcinoma (versus high grade mucoepidermoid carcinoma)

6. Squamous cell carcinoma. Features favoring a diagnosis of mucoepidermoid carcinoma over squamous cell carcinoma include: identification of interspersed mucinous tumor cells, predominantly sclerotic rather than desmoplastic stroma, presence of a component of low grade mucoepidermoid carcinoma, immunoreactivity for cytokeratin 7, and immunoreactivity for MUC5AC.
CASE 3

Clinical features
- A 44-year-old female presented with a mass in the left side of her mouth, located under the tongue.
- The mass was excised. The specimen consisted of a red-tan mass measuring 3.4 x 3.2 x 2.0 cm.

Salient histologic features
- Tumor invades the minor salivary glands in broad fronts, with residual ducts between tumor nodules (this feature may not be evident in all slides)
- Sheets and anastomosing islands of plasmacytoid hyaline cells and nondescript ovoid cells; nuclear atypia minimal to mild, with low mitotic-activity
- Focally, there are interspersed myxoid stroma or small vacuoles. In areas, the plasmacytoid hyaline cells are suspended in myxoid stroma.
- A very minor component of pleomorphic adenoma identified focally (not seen in circulated slides)

Diagnostic considerations
This is obviously a myoepithelial neoplasm (with plasmacytoid hyaline cells being highly characteristic). Although nuclear atypia is mild and mitotic activity is low, the definite invasion puts it into the category of myoepithelial carcinoma (albeit “low grade”). On further search, a minor component of pleomorphic adenoma is identified.

Immunophenotype
- Cytokeratin: +
- 34βE12 (high M.W. cytokeratin): +
- S100 protein: +
- GFAP: + (focal)
- p63: 50% cells positive
- Calponin: + (very focal)
- Actin: –
- p53: –
- Ki67 index: 3%

Diagnosis
Tongue – Myoepithelial carcinoma (low grade), arising in pleomorphic adenoma

Main problems in diagnosis of myoepithelial tumors
- Determining whether it is benign or malignant, or borderline
- Recognizing the myoepithelial nature of the tumor (which may require immunohistochemical confirmation)
MYOEPITHELIOMA

Definition
- A benign tumor composed exclusively, or almost exclusively, of neoplastic cells exhibiting myoepithelial differentiation.
- While some investigators require total absence of ductal component for this designation, most accept the presence of a minor epithelial component (e.g., less than 5-10%).

Pleomorphic adenoma, basal cell adenoma and myoepithelioma can be envisaged to lie on a continuum: myoepithelioma may represent an extreme form of basal cell adenoma without a ductal component whereas basal cell adenoma is "pleomorphic adenoma minus the characteristic stroma", and pleomorphic adenoma lies in the middle of this continuum.

Clinical features
- Most frequently affects the parotid gland and palate.
- Presentation: painless mass
- Peak age and sex: 3rd to 5th decade with no sex predilection.
- Prognosis is excellent and recurrence is not expected with complete excision. Nonetheless, it can be difficult to predict the biologic behavior of a myoepithelial tumor on histologic grounds, in that metastasis may unexpectedly develop in an apparently benign-looking lesion.

Pathology
- Often thinly encapsulated or circumscribed
- Morphologic spectrum of neoplastic myoepithelial cells:
  - Spindly
  - plasmacytoid hyaline
  - epithelioid
  - clear
  - oncocytic
- Either a single cell type predominates in a tumor, or there can be a mixture of cell types.
• Myoepitheliomas of the minor glands tend to be composed of plasmacytoid cells, and those of the parotid, spindle or epithelioid cells.
• Stromal usually scanty, but variable amounts of myxoid or hyaline stroma can be present. Collagenous crystalloids are variably present. However, by definition, there should not be any chondroid matrix.
• Spindle cells are elongated, with central vesicular nuclei and eosinophilic cytoplasm. They form variable interlacing fascicles. Those examples accompanied by abundant collagen may mimic solitary fibrous tumor.
• Plasmacytoid hyaline cells in myoepithelioma are identical to those seen in pleomorphic adenoma; they are frequently accompanied by a loose myxoid stroma. They form non-descript islands and sheets, or are suspended in myxoid matrix in the form of isolated cells, cords or aggregates, and in the absence of true chondroid differentiation.
• Epithelioid cells are large polygonal cells with eosinophilic cytoplasm and centrally located bland nuclei. They commonly show a reticular, trabecular or solid growth pattern.
• Clear cells are rich in glycogen. They are usually present only focally, but can occasionally be so prominent as to pose difficulties in distinction from other clear cell tumors.
• The presence of rare enlarged hyperchromatic nuclei in a background of benign-appearing cells is acceptable.

Immunohistochemistry and ultrastructural studies
• Pan-cytokeratin as well as myoepithelial markers (calponin, S100, GFAP, actin, CK14, p63) are generally positive, but the frequency of positivity and percentage positive cells with the individual markers are highly variable.
• S100 has been reported to be the most useful marker, but it lacks specificity.
• Many cases also express EMA, but only rarely CEA. Ultrastructural studies are useful to confirm myoepithelial differentiation by identifying both epithelial (hemidesmosomes) and myoid features (myofilaments with focal densities, pinocytotic vesicles).

Differential diagnoses
• Pleomorphic adenoma or basal cell adenoma
• Myoepithelial carcinoma
• Various mesenchymal lesions e.g., nerve sheath tumor, nodular fasciitis, solitary fibrous tumor
• Plasmacytoma

MYOEPITHELIAL CARCINOMA (MALIGNANT MYOEPITHELIOMA)
Definition
• A myoepithelial tumor which demonstrates cytologic atypia and a potential for aggressive behavior.
• All grades between benign myoepithelioma and myoepithelial carcinoma can be seen, and distinction of the latter from the former depends on demonstration of infiltrative growth, cellular atypia, frequent mitoses and coagulative necrosis.
• A designation "myoepithelial neoplasm of uncertain malignant potential" may be appropriate for a tumor that exhibits some worrisome features but falls short of frank infiltrative growth.
Clinical features
- Peak age: 6th decade, about ten years older than the benign counterpart.
- Approximately one half of cases arise from a pre-existing pleomorphic adenoma or myoepithelioma, particularly in recurrences.
- Sites of involvement: parotid gland (commonest), but other major or minor glands can also be affected.
- An intermediate- to high-grade carcinoma.
- Approximately one third of patients die, another third have recurrences, mostly multiple, and the remaining third are disease-free.
- Commonest site of distant metastasis is the lung, followed by the liver and vertebra.
- The diverse clinical outcomes reported in different series probably reflect the different leniency in rendering a diagnosis of malignancy in a myoepithelial tumor.

Pathology
- Most tumors show pushing type of infiltration.
- Tumor islands exhibit a cellular periphery and frequently necrotic or myxoid central zone.
- Like myoepithelioma, it may show one or more of the following cell types: spindle, epithelioid, plasmacytoid hyaline and clear cells. Can show metaplastic squamous (often with keratinization) or sebaceous change.
- Nuclear atypia ranges from mild to marked.
- Growth patterns: solid, fascicular, trabecular, and lace-like; glandular structures are not found.
- Stroma: variable amounts of myxoid, collagenous or hyaline stroma.
- According to Nagao et al, myoepithelial carcinoma can be distinguished from benign myoepithelioma by a mitotic count greater than 7 per 10 high power fields or Ki-67 index greater than 10%.
- On the other hand, rare cases of myoepithelial carcinomas can be bland-looking and exhibit a low mitotic count; demonstration of invasive growth is essential to establish their malignant nature in such cases.
Immunohistochemistry

- To render a diagnosis of myoepithelial carcinoma, the myoepithelial differentiation has to be substantiated by immunohistochemistry or electron microscopy.
- Immunohistochemical profile is similar to the benign counterpart. Tumor cells express p63, calponin, S100 protein, CK14, EMA and, variably, cytokeratin (90%), actin (70-80%), GFAP (50%) but not CEA.

Differential diagnoses

- Myoepithelioma
- Various sarcomas (leiomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor)
- Interdigitating dendritic cell sarcoma (S100+, but myoid markers negative)
- Melanoma (S100+, HMB45+)
- Various clear cell tumors (for clear cell myoepithelial carcinoma)

CASE 4 (#27092)

Clinical features

- A 46-year-old male presented with a several months' history of a painless lump on the right posterolateral base of the tongue. The overlying mucosa was intact.
- Following a diagnostic biopsy, wide local excision was performed.

Salient histologic features

- Mucosa covered by stratified squamous epithelium
- There is an infiltrative tumor comprising individual tubules, coalesced tubules and complex glandular islands. In focal areas, the tubules show a streaming pattern
- Single cell type – cuboidal cells with oval, bland-looking pale nuclei

Diagnostic considerations

The features are highly characteristic of polymorphous low grade adenocarcinoma. Those not fully conversant of this entity may have difficulties distinguishing it from an adenoid cystic carcinoma or pleomorphic adenoma.

Immunophenotype

- p63: + (extensive)
- S100: + (extensive)
- Calponin: -
- Ki67 index: 4%

Diagnosis

Tongue – Polymorphous low grade adenocarcinoma
**CASE 4b (CT02-491)**

**Clinical features**
- A 78-year-old man presented with a lesion (1 cm) in the soft palate
- The shelled-out nodule was circumscribed, white and rubbery

**Salient histologic features**
- No surface epithelium seen in circulated slides
- Tumor shows focal circumscription, but there is definite invasion into surrounding tissues and minor salivary glands
- Cytoarchitecture very similar to Case 4, except that papillae are present focally, and there are areas with interspersed hyaline stroma

**Immunophenotype**
- p63: + (extensive)
- S100: + (extensive)
- Calponin: -
- Ki67 index: 2%

**Diagnosis**
Soft palate – Polymorphous low grade adenocarcinoma

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**Greatest difficulties in diagnosis of polymorphous low grade adenocarcinoma:**
- Reluctant to label the tumor as malignant because of the remarkable blandness of the cells – but the presence of invasion makes this an unequivocal carcinoma
- This carcinoma is also not uncommonly misdiagnosed as adenoid cystic carcinoma

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**POLYMORPHOUS LOW GRADE ADENOCARCINOMA (PLGA)**

**Definition**
- A malignant tumor characterized by infiltrative growth, morphologic diversity and cytologic uniformity
- Other designations include lobular carcinoma, terminal duct carcinoma, and low grade papillary adenocarcinoma.

**Major diagnostic criteria of polymorphous low grade adenocarcinoma**
- Infiltrative pattern
- Low grade cytology, with uniform, pale-staining nuclei
- Great variety of growth patterns (sclerosing adenosis-like pattern being most characteristic, if present)
- Single cell type (myoepithelium absent or only very focal) on light microscopy
Clinical features
- PLGA occurs almost exclusively in the minor salivary glands.
- When it occurs in the major glands, it is usually the malignant component in carcinoma ex pleomorphic adenoma.
- Commonest sites: palate (60-70%), buccal mucosa (16%), upper lip (12%), retromolar area, base of tongue
- Peak age: 5th and 6th decades
- Sex: female predominance
- Presentation: asymptomatic mass with or without ulceration.

Clinical behavior
- A low grade neoplasm, with more than 95% of patients being alive after a mean follow-up of 10 years
- Local recurrence and regional metastasis rates are 9-17% and 9-15% respectively, which may occur up to 14 years after initial treatment (mean, 7 years).
- Tumor with a predominant papillary configuration has been reported to carry a higher incidence of cervical lymph node metastasis.

Unifying features of the various adenocarcinomas of the salivary gland grouped by cytologic grade (excluding mucoepidermoid, acinic cell and adenoid cystic carcinomas)

<table>
<thead>
<tr>
<th>Entities included</th>
<th>Low grade adenocarcinoma</th>
<th>High grade adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Polymorphous low grade adenocarcinoma</td>
<td>Salivary duct carcinoma</td>
</tr>
<tr>
<td></td>
<td>Epithelial-myoepithelial carcinoma</td>
<td>Oncocytic carcinoma</td>
</tr>
<tr>
<td></td>
<td>Basal cell adenocarcinoma</td>
<td>High grade adenocarcinoma, NOS</td>
</tr>
<tr>
<td></td>
<td>Cystadenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low grade adenocarcinoma, NOS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unifying histologic features</th>
<th>Low grade adenocarcinoma</th>
<th>High grade adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrative growth</td>
<td>Slow-growing and indolent</td>
<td>Fast-growing</td>
</tr>
<tr>
<td>Minimal or mild nuclear atypia</td>
<td>May recur if incompletely excised</td>
<td>Early and frequent metastasis to lymph nodes and distant sites</td>
</tr>
<tr>
<td>Infrequent mitoses</td>
<td>Regional lymph node metastasis 5-15%</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Coagulative necrosis uncommon</td>
<td>Distant metastasis very rare</td>
<td></td>
</tr>
</tbody>
</table>

Pathology
- Despite the gross circumscription of the tumor, infiltrative growth is obvious histologically, with invasion of salivary gland lobules, adjacent adipose tissue or muscle. Perineural invasion is common (76%).
- Growth patterns are diverse: simple tubules, complex or fused tubules, trabeculae, single-cell files, targetoid swirls, solid nests, fascicles, and cribriform, papillary or papillary-cystic structures.
- Most commonly observed patterns are: tubular, trabecular and solid.
A relatively diagnostic feature is the targetoid pattern formed by concentrically arranged cords and narrow tubules of cells, reminiscent of sclerosing adenosis of the breast.

There is generally one single cell type (ductal cell) that forms all these structures.

The tumor cells have round pale nuclei with fine, evenly distributed chromatin and indistinct nucleoli. Cytoplasm is lightly eosinophilic.

Tumor cells may assume cuboidal, columnar, spindly or polygonal shapes.

Necrosis or mitosis is very rare.

Myoepithelial cells are absent or at most present very focally at the light microscopic level.

Hyalinized eosinophilic stroma that occasionally displays myxoid change.

Immunohistochemistry

- Immunoreactive for cytokeratin, EMA and S-100 protein (usually diffuse and strong)
- Staining for GFAP is generally negative, except for occasional positive cells in some cases.
- p63: positive in a proportion of tumor cells in a haphazard distribution, or positive extensively but without an abluminal localization pattern
- Markers for myoepithelial differentiation (smooth muscle actin, smooth muscle myosin heavy chains, calponin) are negative.
- Proliferative index is low (mean Ki67 index 1.56% to 7%).

Major differential diagnosis

- Pleomorphic adenoma
- Adenoid cystic carcinoma

PLGA versus pleomorphic adenoma

- Invasive
- Predominantly single cell type, instead of dual luminal and abluminal cell differentiation
- No chondroid matrix
- No plasmacytoid hyaline cells
- No "melting" of myoepithelial layer into surrounding stroma
- Lack of GFAP staining in a mesenchymal-like cell population adjacent to epithelial nests

PLGA versus adenoid cystic carcinoma

- Tumor cells have much paler nuclei, and they possess more cytoplasm
- Abluminal cells absent or at most focal
- Cribriform structures uncommon
- Lack of abundant hyaline material intricately associated with the epithelial units
- EMA staining often diffuse rather than confined to the glandular lumens
- S-100 protein staining often extensive and intense
- p63 immunostaining haphazardly or extensively distributed, contrasting with the peripherally located cells of the tumor islands in "regimented" pattern of adenoid cystic carcinoma
CASE 5

• A 58-year-old female presented with recurrent left nasal bleeding.
• A reddish mass was found at the sphenoethmoidal recess. Biopsy revealed a salivary gland-type tumor, but failed to yield a definitive classification of the neoplasm.
• The tumor was curetted through a left rhinotomy.

Salient histologic features
• Surface respiratory epithelium intact
• Main tumor comprises large nodules formed by complexly anastomosed long narrow tubules of two cell type, intimately admixed with abundant hyaline material and basophilic mucousubstance
• Some cribriform structures are also formed
• Within the large tumor nodules, some tumor cells appear spindly
• Cells that line the narrow lumens have pink cytoplasm; the outer basaloid cells have smaller and darker nuclei
• The tubules that are found between the surface epithelium and the tumor nodules underneath are possibly invasive

Diagnostic considerations
Invasive growth is not totally convincing, but the growth pattern (in particular formation of cribriform structures) and cytologic composition suggest a diagnosis of adenoid cystic carcinoma.

Immunophenotype
• Cytokeratin CAM5.2: Ductal cells highlighted, but some basaloid cells are also stained
• p63: basaloid cells nicely highlighted
• Smooth muscle actin, calponin: basaloid cells positive
• Ki67 index: 2%

Diagnosis
Paranasal sinus – Adenoid cystic carcinoma

Comments
This case posed considerable difficulties in diagnosis in the biopsy specimen, because the borders of the tumor could not be assessed. In specific, a firm distinction between adenoid cystic carcinoma and pleomorphic/basal cell adenoma could not be made. The difficulty was compounded by the low proliferative fraction.

Diagnosis of adenoid cystic carcinoma in mucosal sites from biopsies can be particularly problematic, because of difficulties in concluding where or not there is invasive growth.

ADENOID CYSTIC CARCINOMA

Definition
• An invasive neoplasm composed predominantly of basaloid cells with myoepithelial/basal cell differentiation, accompanied by interspersed ductal structures.
• Characterized by cribriform, tubular and/or solid patterns of growth and a myxohyaline stroma.
Major diagnostic criteria of adenoid cystic carcinoma

- Invasive borders
- Cribriform structures almost always present, at least focally
- Two-cell type (although basaloid cells can predominate, rendering it difficult to identify ductal epithelium)
- Variable amounts of hyaline material and basophilic mucinous material intricately associated with the tumor islands

Clinical features

- Age: 4th to 6th decades
- Sex: slight female predominance
- Common sites of involvement: parotid gland, submandibular gland and palate.
- This tumor has also been reported in lacrimal glands, auditory canal, upper respiratory tract, lung, digestive tract, skin, breast, prostate, and lower female genital tract.
- Presentation: slow-growing swelling. Large tumors often cause fixation to skin or deeper tissues. There may also be tenderness, pain and facial nerve palsy due to the marked propensity of the tumor for neural invasion. Palatal tumors often ulcerate. Bone invasion may occur without radiographic changes as the tumor infiltrates through the marrow spaces.
- The tumor has often invaded well beyond the clinically apparent borders.

Clinical behavior

- Generally indolent, but the long-term prognosis is poor. The 5-year survival is about 80-75%, but the 10-year survival drops dismally to 30-54%.
- Majority of affected patients (80-95%) eventually die of the disease after a protracted clinical course characterized by multiple local recurrences and metastases.
- Distant metastasis (most commonly lung, bone and soft tissue) is more common than regional lymph node metastasis, and often occurs 5 to 10 years after initial treatment.

Pathology

- Infiltrative growth is usually obvious, and perineural invasion is very common.
- The three characteristic growth patterns (cribriform, tubular and solid) are present in variable combinations.
- The stroma is fibrous with variable amounts of myxohyaline material rather than desmoplastic, and cartilage is not formed.
- Sometimes extensive hyalinization results in "strangulation" of the tumor islands, to the extent that few tumor cells remain or a lace-like pattern is produced.

Cribriform pattern

- The most characteristic feature of adenoid cystic carcinoma.
- Almost always found, albeit very focally sometimes
- Variable-sized, smooth-contoured, discrete to coalescent islands comprising small, uniform basaloid cells punctuated by round rigid spaces, giving rise to a "Swiss cheese" appearance
Most spaces are not glandular lumens, but represent stromal invaginations (pseudocysts); continuity with the stroma can sometimes be demonstrated. These spaces are filled with eosinophilic hyaline material (PAS positive, diastase resistant) and/or lightly basophilic myxoid ground substance (Alcian blue positive).

Within these cribriform islands, there are occasional true narrow glands lined by low cuboidal cells with eosinophilic cytoplasm. A thin eosinophilic cuticle may be present along the luminal border, and the lumen may contain PAS-positive diastase-resistant eosinophilic secretion.

Occasionally, the glandular structures are abortive, manifesting as a small collection of vacuolated cells with eosinophilic cytoplasm.

Exceptionally, the luminal cells may exhibit oncocytic changes.

The neoplastic basaloid cells constitute the major cell population. They possess round or angulated nuclei, and scanty cytoplasm with indistinct cell borders. Some cells may have pale to clear cytoplasm. Nuclear pleomorphism is usually mild, and mitotic figures are usually few or absent.

**Tubular pattern**
- Elongated tubules are lined by a single layer of ductal epithelial cells surrounded by a single or multiple layers of basaloid cells.
- This is the architectural pattern in which glandular lumens are most easily and consistently found.
- They are often embedded in abundant hyaline stroma, to the extent that may appear strangulated.

**Solid pattern**
- Smooth-contoured or focally jagged sheets and islands of closely packed basaloid cells, with few or no interspersed pseudocysts.
- The basaloid cells, in comparison to those seen in the cribriform and tubular patterns, usually exhibit more significant nuclear pleomorphism and mitotic activity. Coagulative tumor necrosis is not uncommon.
- Few true glandular lumens.
- The solid growth pattern is rarely present in a pure form, and if so, may be extremely difficult to diagnose.

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**Diagram**: Diagram showing the architecture of salivary gland tumors, including ductal epithelium and secretion.
Immunohistochemistry

- The basaloid cells express cytokeratin, vimentin, S-100 protein (usually patchy staining), actin (variably), calponin and p63
- Interspersed ductal epithelial cells express cytokeratin (strongly), CEA, EMA and c-kit (CD117)
- The stromal hyaline material can be highlighted by staining for type IV collagen and laminin

Genetic features

- The most frequent cytogenetic aberrations involve chromosomes 6p, 9p and 17p12-13
- t(6;9)(q21-24;p13-23) reported in several tumors has been considered a primary event in at least a subset of adenoid cystic carcinomas.
- Microsatellite marker analysis shows frequent losses at 6q23-qter, 12q, 13q21-q22, and 19q.
- A study of 25 tumors has found a high frequency of loss of heterozygosity at 6q23-25 and this alteration is correlated with unfavorable clinical outcome.

Prognostic factors

- Prognosis is significantly influenced by the histologic grade, which is determined by the proportion of the various growth patterns.
- Tumors showing tubular and cribriform patterns represent lower grade growths. The solid pattern is associated with large tumor size, earlier and more frequent recurrence, higher incidence of metastasis, and earlier fatal outcome.
- On analysis of the long-term survival rates of 79 cases of adenoid cystic carcinoma, Szanto et al found that carcinomas with significant solid areas (>30% of tumor area) have cumulative 5-year and 15-year survival rates of only 14% and 5% respectively, compared with 92% and 39% for tumors without a significant solid component.

<table>
<thead>
<tr>
<th>Criteria for grading</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular and cribriform patterns, with no solid areas; cytologically bland; few or no mitoses</td>
<td>Pure cribriform pattern, or mixed pattern but with &lt;30% solid area; cytologically more atypical than grade I</td>
<td>&gt;30% solid area; usually with necrosis; more cellular atypia and mitoses</td>
<td></td>
</tr>
<tr>
<td>Behavior of tumor</td>
<td>Usually small-sized tumor that may even have a capsule; amenable to complete excision; protracted clinical course</td>
<td>Intermediate behavior</td>
<td>Larger tumor that is difficult to excise completely; frequent early recurrence; often resulting in death within 4 years</td>
</tr>
<tr>
<td>15-year survival rate</td>
<td>39%</td>
<td>26%</td>
<td>5%</td>
</tr>
</tbody>
</table>

- Advanced clinical stage, location in minor gland, large tumor size (>2-4 cm), bone invasion, involved excision margins, non-diploid DNA content, high S-phase fraction, and high Ki67 index have been reported to be poor prognostic factors.
Differential diagnosis
- Basal cell adenoma/adenocarcinoma and pleomorphic adenoma
- Epithelial-myoepithelial carcinoma
- Polymorphous low grade adenocarcinoma
- Basal cell adenocarcinoma
- Basaloid squamous cell carcinoma

Adenoid cystic carcinoma versus basal cell adenoma or pleomorphic adenoma
- Invasion of the surrounding parenchyma or nerves
- Usual prominence of cribriform structures
- Lacks the "melting" myoepithelial pattern and chondroid matrix of pleomorphic adenoma; the occasional hyaline or myxoid change within the larger tumor islands of adenoid cystic carcinoma should not be mistaken for a "melting" phenomenon

Adenoid cystic carcinoma versus epithelial-myoepithelial carcinoma
- Clear cells absent or only very focal
- Well developed cribriform structures are common (such structures are rare in epithelial-myoepithelial carcinoma
- Branching glandular lumens are rare
- Basophilic mucosubstance commonly present in microcystic spaces

Adenoid cystic carcinoma versus polymorphous low grade adenocarcinoma
- Tumor cells have less cytoplasm and more hyperchromatic nuclei
- Prominent abluminal cell component (abluminal cells absent or at most focal in PLGA)
- Cribriform structures much more common
- Abundant hyaline material often intricately associated with the epithelial units
- EMA staining is confined to the glandular lumens rather than diffuse
- S-100 protein staining is often patchy and less intense
- p63 immunostaining highlights the peripherally located cells of the tumor islands in "regimented" pattern, in contrast to the haphazardly or extensively distributed positive cells in PLGA
<table>
<thead>
<tr>
<th>Site of occurrence</th>
<th>Adenoid cystic carcinoma, solid variant</th>
<th>Basal cell adenocarcinoma</th>
<th>Basaloid squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major or minor glands</td>
<td>Major or minor glands</td>
<td>Mucoosal sites, such as larynx, hypopharynx, base of tongue</td>
</tr>
<tr>
<td>Architectural patterns</td>
<td>Although islands and diffuse sheets predominate, some cribriform structures are almost always present; comedo necrosis may be present in some large solid islands</td>
<td>Discrete jigsaw puzzle-like islands; rarely may show trabecular or tubular pattern; cribriform structures absent or very focal; comedo necrosis rare</td>
<td>Lobules and trabeculae with festooning and frequent comedo necrosis</td>
</tr>
<tr>
<td>Intercellular hyaline droplets</td>
<td>Very rare</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Basophilic mucosubstance in stroma or empty spaces</td>
<td>Common</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Cellular palisading at periphery of tumor islands</td>
<td>Usually not evident</td>
<td>Often a prominent feature</td>
<td>Usually not evident</td>
</tr>
<tr>
<td>Predominant cell type</td>
<td>Mostly basoid cells with dark nuclei and a monotonous appearance; luminal cells very sparse</td>
<td>Basaloid cells include small dark cells and bigger paler cells; luminal cells very sparse</td>
<td>Basaloid cells with pale and atypical nuclei and frequent mitoses; true glandular cells rare</td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>Rare</td>
<td>Sometimes present in the centers of cell islands</td>
<td>Commonly present (often in the form of frank squamous cell carcinoma or carcinoma-in-situ)</td>
</tr>
</tbody>
</table>
SALIVARY GLAND TUMORS WITH CRIBRIFORM PATTERN (Case 6)

Salivary gland tumor types with a cribriform growth pattern
- Adenoid cystic carcinoma (commonest)
- Salivary duct carcinoma (commonest)
- Intraductal carcinoma
- Pleomorphic/basal cell adenoma (focal)
- Polymorphous low grade adenocarcinoma (focal)
- Cribriform adenocarcinoma of the tongue (which is probably merely a subtype of polymorphous low grade adenocarcinoma)

APPROACH TO DIAGNOSIS OF SALIVARY GLAND TUMOR WITH A PROMINENT CRIBRIFORM GROWTH PATTERN
- A salivary gland tumor exhibiting a significant cribriform pattern is most likely an adenoid cystic carcinoma or salivary duct carcinoma.
- Adenoid cystic carcinoma can be recognized by the dual cell differentiation (with predominance of basaloid cells) and the abundant intermixed hyaline and mucinous materials.
- Salivary duct carcinoma can be recognized by the single type of proliferated cells and significant nuclear pleomorphism. Intraductal carcinoma is distinguished from salivary duct carcinoma by the pure intraductal growth as confirmed by immunohistochemistry (intact myoepithelium around all epithelial units).
- Rarely, a cribriform pattern may be observed in pleomorphic adenoma or basal cell adenoma, mimicking adenoid cystic carcinoma, but the correct diagnosis can be made because the tumor is not invasive.

CASE 6 (#29106)
Clinical features
- A 61-year-old male presented with a right neck mass noticed for about one month. The mass was quite firm, immobile and tender.
- The right submandibular gland was excised, revealing numerous white-tan confluent nodules forming a central mass measuring 2.2 cm in greatest dimension.

Salient histologic features
- The tumor invades the submandibular gland parenchyma
- Large, smooth-contoured islands of tumor are disposed in a sclerotic to desmoplastic stroma
- The tumor islands show a cribiform to solid-comedo growth pattern
- Constituent cells show pleomorphic vesicular nuclei, prominent nucleoli and mitotic activity. The cytoplasm has an apocrine quality
- Some islands are apparently surrounded by a layer of smaller and darker cells
Diagnostic considerations

This is obviously a high-grade carcinoma. The features are compatible with salivary duct carcinoma. However, since many tumor islands are apparently surrounded by a layer of smaller cells with dark nuclei, the possibility of intraductal carcinoma or a component of intraductal carcinoma needs to be raised.

Immunophenotype

- p63 and actin demonstrate no myoepithelium around any of the tumor islands!
- BRST-2: +
- Androgen receptor: + (moderate)
- c-erbB2: + (weak)
- p53: -

Diagnosis

Submandibular gland – Salivary duct carcinoma

Comment

Although the possibility of intraductal carcinoma is raised based on morphologic features, immunostaining shows complete absence of residual myoepithelial cells, indicating that all tumor islands in this tumor are invasive! This illustrates the difficulties in distinguishing between in-situ and invasive growth on morphologic grounds.

CASE 6b (#30332)

Clinical features

- M/51, presenting with a mass in the right neck
- Radical parotidectomy and modified radical neck dissection performed after extensive work-up
- Parotid gland measured 7 x 5 x 2.5 cm. The tumor involved the superior portion, measuring 3 x 2 x 2 cm. It was tan and firm, with irregular borders.

Salient histologic features

- This is a frankly invasive high-grade carcinoma (cytologically similar to case 6)
- In contrast to Case 6, cribriform structures are not as prominent
- Instead, the tumor forms mostly irregular islands that infiltrate an inflamed desmoplastic stroma
- Some tumor islands show central necrosis
- Focal micropapillary pattern

Immunophenotype

- In contrast to case 6, p63 does demonstrate a minor intraductal component in this tumor
- Androgen receptor: + (moderate to strong)
- c-erbB2: + (strong)
- p53: + (strong)

Diagnosis

Parotid gland – Salivary duct carcinoma, with focal micropapillary pattern
SALIVARY DUCT CARCINOMA

Definition
- An aggressive malignant tumor morphologically reminiscent of invasive ductal carcinoma of the breast.
- Can occur de novo or as the malignant component in carcinoma ex pleomorphic adenoma.

Salient diagnostic criteria of salivary duct carcinoma
- Invasive growth
- High nuclear grade
- Cytoplasm often shows an apocrine or semi-apocrine quality
- Rounded tumor islands with cribriform and solid-comedo architecture, resembling mammmary intraductal carcinoma (but in fact mostly representing invasive rather than in-situ tumor islands)
- Variable component of invasive carcinoma resembling conventional invasive ductal carcinoma of breast

Clinical features
- Age: mostly elderly (peak incidence 6th and 7th decades)
- Sex: male to female ratio of 3-6:1
- Sites of disease: parotid gland (80%), submandibular gland, minor glands of the oral cavity (rare).
- Presentation: rapidly enlarging parotid mass associated with facial nerve palsy (42%), pain (23%) and cervical lymphadenopathy (35%).

Clinical behavior
- One of the most aggressive salivary gland carcinomas. The tumor mortality can be as high as 77% at a mean follow-up of 3 years.
- Local recurrence occurs in 35-66% of patients, lymph node metastasis in 66%, and distant metastasis in 50-70%.
- Most frequent sites of distant metastases are the lung, bone and brain.

Pathology
- The infiltrative tumor resembles mammmary intraductal carcinoma and invasive ductal carcinoma
- The intraductal-like component shows cribriform, papillary-cystic or solid patterns, often with prominent comedo necrosis. However, most of them are not genuine intraductal proliferations since a myoepithelial layer is lacking and similar structures can be seen in metastatic deposits.
- The obviously infiltrative component consists of cords, nests, small glands and single cells.
- The neoplastic cells in both components have an apocrine appearance with abundant eosinophilic cytoplasm, large pleomorphic vesicular nuclei and prominent nucleoli. Cytoplasmic mucin is occasionally present.
- Mitotic figures are easy to find.
- The stroma is densely fibrous or desmoplastic.
- Vascular invasion, perineural invasion, intravascular tumor emboli and invasion of adjacent structures are common.
Sarcomatoid variant (dedifferentiated salivary duct carcinoma)
• Comprises anaplastic spindle cells, bizarre multinucleated giant cells, rhabdoid cells, and rarely, osteosarcomatous cells
• These cells frequently demonstrate focal immunohistochemical and ultrastructural evidence of epithelial differentiation.

Mucin-rich variant
• Mucinous/colloid carcinoma in which clusters of carcinoma cells with or without cytoplasmic mucin float in mucin pools.

Invasive micropapillary variant
• Morule-like tumor cell clusters without fibrovascular cores, surrounded by clear space, morphologically similar to micropapillary variant of breast or urothelial carcinoma.

Prognostic factors
• Previous studies suggest that tumor size smaller than 3 cm is associated with a more favorable prognosis, but this is not confirmed by the Mayo Clinic series.
• Histologic parameters are of prognostic significance, although the micropapillary variant may be more aggressive.

Immunohistochemistry
• Diffuse strong staining for cytokeratin, EMA, and CEA.
• Almost all cases express androgen receptor, which is a characteristic, although not specific, feature of salivary duct carcinoma. Estrogen and progesterone receptors are usually negative.
• Most cases overexpress c-erbB2.
• Usually focally positive for gross cystic disease fluid protein-15 (GCDFP-15 or BRST-2)
• Typically negative for S100 protein and myoepithelial markers.
• Some cases can express prostatic acid phosphatase, prostatic specific antigen or cytokeratin 20.
• Ki67 index is high (mean 21.3%).
• Staining for myoepithelial markers shows that a genuine in-situ (intraductal) component characterized by a surrounding rim of attenuated myoepithelium is usually minor.

Genetic features
• Frequent loss of heterozygosity in chromosome 9p21, 6q, 16q, 17p, 17q regions.
• Mutations and overexpression of TP53 gene and protein are frequent.
• HER-2/neu gene amplification occurs in 36% and protein overexpression in 100%.
• Inactivation of CDKN2A/p16 gene is associated with tumor progression.

Major differential diagnosis
• Metastatic breast or prostate carcinoma – A clinical history of breast carcinoma, positive estrogen/progesterone receptor, and negative androgen receptor strongly favor a diagnosis of metastatic mammary carcinoma. Immunostaining for the GCDFP-15 (BRST-2) is not useful in the differential diagnosis because most salivary duct carcinomas are also positive.
• High grade mucoepidermoid carcinoma – Mixture of cell types such as epidermoid cells and goblet cells is not seen in salivary duct carcinoma.
• Oncocytic carcinoma
• Cystadenocarcinoma
• Intraductal carcinoma – Important to distinguish from salivary duct carcinoma because of its excellent prognosis. But definition, there is no stromal invasion (as confirmed by presence of intact myoepithelial layer around all tumor islands)

INTRADUCTAL CARCINOMA (SO-CALLED LOW GRADE SALIVARY DUCT CARCINOMA OR LOW GRADE CRIBRIFORM CYSTADENOCARCINOMA)
The concept of intraductal carcinoma of salivary gland and problems in terminology
• Intraductal carcinoma, first described by Chen in 1983, is not a recognized entity in the 2005 WHO classification.
• Characterized by pure intraductal proliferation of tumor cells, and probably represents the in-situ counterpart of salivary duct carcinoma.
• The concept of intraductal carcinoma has not gained wide acceptance because some salivary duct carcinomas with an apparently pure intraductal-like growth still pursue an aggressive course, and an intraductal-like component can sometimes be found in the metastases. These observations can be attributable to the indiscriminate use of the term "intraductal" which, by definition, should require the presence of an intact myoepithelial layer as in mammary intraductal carcinoma.
• Strictly defined as such, intraductal carcinoma represents a tumor of low malignant potential, with behavior similar to the mammary counterpart.
• This entity has often been reported in the literature under the designation "low grade salivary duct carcinoma". However, the term "intraductal carcinoma" is more appropriate because it emphasizes the fundamental feature and avoids potential confusion with the vastly more aggressive salivary duct carcinoma.
• The term "low-grade cribriform cystadenocarcinoma" adopted in the new WHO classification is even more confusing, and its use is discouraged.

Clinical features
• Most frequently affects the parotid gland of the elderly (mean age 62 years)
• Slight female predilection
• Minor salivary gland (e.g., tongue, palate, oral cavity) can also be affected.
• Outcome excellent after complete excision, with no metastasis or mortality at follow-up of 2 to 12 years, irrespective of nuclear grade. Recurrence can occur as a result of incomplete resection.

Pathology
• Multiple smooth-contoured ducts with epithelial cell proliferation forming cribriform, fenestrated, solid-comedo, micropapillary or Roman-bridge patterns, similar to the architectural patterns observed in atypical ductal hyperplasia or intraductal carcinoma of the breast.
• Constituent cells generally show low to intermediate grade, but sometimes high grade, cytologic atypia. Some cells can appear apocrine.
• The attenuated layer of myoepithelial cells around the cell islands may or may not be evident on light microscopy.
• The stroma is sclerotic.
• In occasional cases, there is a microscopic invasive component morphologically identical to salivary duct carcinoma, either at presentation or in recurrence. The clinical significance of microinvasion remains uncertain, but the prognosis appears favorable.

### Prerequisites for diagnosis of intraductal carcinoma

- A diagnosis of intraductal carcinoma can be confidently made only when invasive component has been ruled out after complete sampling
- Mandates immunostaining to demonstrate an intact myoepithelial layer around each tumor island, because it is notoriously difficult to differentiate between in-situ and invasive ductal carcinoma
ONCOCYTIC LESIONS (Cases 7-9)

Salivary gland lesions composed predominantly of oncocytes
- Oncocytoma
- Oncocytic carcinoma
- Oncocytosis / nodular oncocytic hyperplasia
- Warthin tumor
- Oncocytic cystadenoma
- Oncocytic variant of mucoepidermoid carcinoma

APPROACH TO DIAGNOSIS OF SALIVARY GLAND LESION PREDOMINATED BY ONCOCYTES
- Assess the cytology of the cells to confirm that they are indeed oncocytes, not other cell types with abundant granules (such as acinic cell carcinoma or granular cell tumor). The granules should be brightly eosinophilic and of uniform size.
- The diagnosis of Warthin tumor and oncocytic cystadenoma should be straightforward because of the characteristic architectural features.
- Before shortlisting to the possibilities of oncocytoma, oncocytic carcinoma, oncocytosis and nodular oncocytic hyperplasia, it is important to consider the possibility of oncocytic variant of mucoepidermoid carcinoma, which can show a striking resemblance to oncocytoma or oncocytic carcinoma. Scrutinize the tumor for evidence of cytoplasmic mucin in tumor cells, and the formation of microcysts or glands containing mucin in the lumens – there is often at least a minor component showing the typical histologic features of mucoepidermoid carcinoma.

WARTHIN TUMOR
Definition
- Tumor composed of bilayered oncocytic and basaloid epithelium forming cystic structures, papillae and glands which are accompanied by a dense lymphoid stroma.

Clinical features
- The second most common salivary gland tumor.
- Almost restricted occurrence in the parotid glands and the periparotid lymph nodes.
- Age: 6th to 7th decades
- Sex: male predominance (5-26:1)
- Presentation: doughy to cystic mass in the inferior pole of the parotid gland.
- Can manifest a variety of symptoms, such as pain, facial weakness, ipsilateral ear symptoms (earache, tinnitus and deafness).
- Sudden painful increase in size associated with acute pain (known as papillary cystadenoma lymphomatosum syndrome) has been postulated to be caused by leakage of fluid into the surrounding and retrograde infection from the oral cavity via the Stensen duct.
- Rarely, facial nerve palsy may be seen in tumors complicated by inflammation and fibrosis, which may be mistaken clinically or intraoperatively for carcinomas.
• Multicentric in 12-20%, and bilateral in 5-14%.
• Superficial parotidectomy or enucleation of tumor is curative. The rare recurrences (<2%) are believed to represent second primary or an expression of multifocal lesion.
• In old patients or those with poor surgical risk, observations without surgery may be an option.

Pathology
• Comprises irregular cystic structures with the lining epithelium thrown into papillary folds.
• The epithelium can also show downward extension to form loosely arranged or closely packed tubular glands.
• The epithelium consists of two layers — a luminal layer of oncocytic columnar cells supported by a discontinuous layer of oncocytic basal cells. The nuclei of the luminal cells appear uniform and display palisading towards the free surface. Their brightly eosinophilic granular cytoplasm is due to accumulation of mitochondria. The basal cells possess round to oval nuclei and small but conspicuous nucleoli.
• The lumens of the cysts contain thick proteinaceous secretions, cellular debris, cholesterol crystals and sometimes laminated bodies that resemble corpora amylacea.
• A distinct layer of basement membrane separates cystic lining from the lymphoid stroma, which consists of small lymphocytes and some plasma cells, histiocytes and mast cells. Germinal centers and sinusoids can be seen in some cases.
• Sometimes there may be a granulomatous reaction with Langhans-type giant cells.
• The origin of the lymphoid cells is still controversial: residual normal nodal lymphoid tissue versus reactive lymphoid proliferation against the neoplasm.
• Tumors developing in extraparotid (such as cervical) lymph node can potentially be misinterpreted as metastatic Warthin tumor.

Metaplastic Warthin tumor
• The epithelial component can undergo metaplastic change to squamous, mucous cells or even ciliated cells, especially in response to inflammation or infarction.
• Sometimes the tumor undergoes infarction, either spontaneous or following fine needle aspiration, and the tumor cells can be obscured by the necrosis, granulation tissue, inflammatory reaction and fibrosis. Worse still, cellular atypia and pseudoinfiltrative appearance of the metaplastic squamous epithelium in the residual tumor often invite an erroneous diagnosis of squamous cell or mucoepidermoid carcinoma.
• Lack of true infiltrative growth into the surrounding parenchyma and merging of the atypical squamous islands with oncocytic epithelium should point to the correct diagnosis.

Differential diagnosis
• Oncocytoma – It differs from oncocytoma in: (1) presence of a prominent lymphoid component, papillae and glands rather than trabeculae and packets, and (2) conspicuous basal cells (which are inconspicuous in the latter tumor).
• Squamous cell or mucoepidermoid carcinoma – The squamous metaplastic Warthin tumor, particularly if infarcted, can be mistaken for squamous or mucoepidermoid carcinoma. Squamous metaplasia of Warthin tumor usually lacks keratinization, which is seen in most squamous cell carcinomas. In contrast to low grade mucoepidermoid carcinoma, there is no definite infiltrative growth and the tumor cells appear more frankly squamous.
CASE 7
Clinical features
- A 70-year-old male presented with a parotid mass of unknown duration.
- The parotid gland was excised.

Salient histologic features
- The tumor comprises variable-sized glands lined by oncocytic cells with mild nuclear atypia and distinct nucleoli
- The stroma is sclerotic
- At the interface with the parotid gland, there is definite invasion into the salivary gland parenchyma

Immunophenotype (not required for diagnosis of this case)
- p63 surprisingly demonstrates basal/myoepithelial cells around the oncocytic glands
- p53:

Considerations
This oncocytic neoplasm shows very bland cytologic features. Thus the diagnosis of malignancy here (instead of oncocytoma) is based solely on the finding of convincing invasive growth.

Diagnosis
Parotid gland – Oncocytic adenocarcinoma

ONOCYTOMA
Definition
- Oncocytoma is a discrete, encapsulated tumor consisting exclusively of oncocyes and lacking features of other defined tumor types.
- Occasionally, oncocytoma and Warthin tumor may even coexist.

Clinical features
- Most commonly occurs in the parotid gland of older adults (mean age 58-77 years) without gender predilection
- Surgical excision is the treatment of choice and recurrence is uncommon (0-10%).

Pathology
- Circumscribed tumor
- Growth pattern: trabeculae, packets, diffuse sheets and rarely glands, separated by thin fibrous septa or scanty loose vascularized stroma.
- The oncocyes (mitochondria-rich cells) are polygonal or cuboidal, with abundant eosinophilic granular cytoplasm, central round nuclei and often distinct nucleoli.
- Focally, sebaceous, goblet cell or squamous differentiation and psammoma bodies may be present.
Although many studies dispute the presence of myoepithelial or basal cells in oncocytoma, such cells (with an attenuated appearance) can indeed be often demonstrated by immunostaining for p63 or CK14.

Tyrosine-rich crystals can be found in the tumor and adjacent striated ducts of some oncocytomas. Oncocytoma is prone to infarction either spontaneously or following fine needle aspiration. The necrotic cells manifest as ghost shadows or eosinophilic granular material. The residual viable tumor or adjacent salivary epithelium commonly undergoes squamous metaplasia with atypical ( reparative) nuclei, mimicking squamous cell carcinoma.

Differential diagnosis
- Various salivary gland tumors with prominent oncocytic change, most notably Warthin tumor, pleomorphic adenoma, basal cell adenoma, and oncocytic variant of mucoepidermoid carcinoma.
- Acinic cell carcinoma—Similar by virtue of the similar cell arrangement (cellular groups or cords) and cytoplasmic granularity, especially at intraoperative frozen section. However, the nuclei of acinic cell carcinomas are peripherally located, in contrast to the central round nuclei in oncocytoma.
- Clear cell oncocytoma may also be mistaken for other clear cell salivary gland tumors.

ONCOCYTIC CARCINOMA (MALIGNANT ONCOCYTOMA)
Definition
- A pure oncocytic tumor that demonstrates malignant histologic features.

Clinical features
- Most cases occur in the parotid gland of patients aged over 60 years.
- Some cases may arise from a preexisting oncocytoma.
- A high grade neoplasm associated with frequent recurrence (56%) and metastasis (80%), most commonly to the lung, kidney, liver, thyroid, mediastinum and bone.
- The average reported survival for patients with metastasis is 3.8 years. Tumors less than 2 cm in diameter are associated with a better prognosis that larger tumors.

Pathology
- An unencapsulated, single or multinodular, tumor that shows infiltration of the salivary gland parenchyma and surrounding connective tissue.
- The oncocytic cells show variation in size and shape and nuclear pleomorphism, although nuclear atypia may be minimal in some cases.
- Growth pattern: trabeculae, sheets, nests or ducts
- Frequent atypical mitoses
- Perineural and vascular invasion can be seen
- Coagulative tumor necrosis appears to be specific for oncocytic carcinoma versus oncocytoma, and may confer an ominous prognosis; it must not be confused with tumor infarction, which can also be seen in oncocytoma.
Metastasizing oncocytoma and oncocytic neoplasm of uncertain malignant potential

- The malignant nature of most oncocytic carcinomas is easily recognized by the nuclear pleomorphism and infiltrative borders.
- Some investigators, however, suggest that there may not be a sharp histologic distinction between oncocytoma and oncocytic carcinoma, and an otherwise bland-looking tumor may rarely develop metastasis unexpectedly. These tumors may represent metastasizing oncocytoma, akin to metastasizing pleomorphic adenoma, and both portend a poor clinical outcome.
- For tumors showing borderline atypical features, such as cellular atypia alone, occasional mitotic figures, or limited local invasion, use of the designation "oncocytic neoplasm of uncertain malignant potential" may be appropriate to indicate uncertainties about their behavior.

CASE 8
Clinical features

- A 25-year-old female presented with a left parotid mass.
- The parotid gland was excised, revealing a discrete tumor nodule measuring 1.5 cm in maximum dimension.

Salient histologic features

- Tumor shows partial circumscription, and focal pushing-type of invasion into the salivary gland parenchyma (this feature may not be seen in all slides)
- Crowded large solid islands and trabeculae of oncocytic cells, with some admixed islands of clear cells
- Occasional punctuated by small rounded spaces containing mucin

Diagnostic considerations

Oncocytoma is usually composed of a pure population of cells (although some cells may show cytoplasmic clearing). In this case, the presence of cytoplasmic mucin and mucin-containing cystic spaces, and the presence of occasional non-oncocytic tumor islands makes a diagnosis of oncocytoma most unlikely. Instead, the latter features suggest a diagnosis of mucoepidermoid carcinoma.
**Immunophenotype and special stains** (not required for diagnosis of this case)
- p63: most oncocytic cells are negative. Some non-oncocytic cells located in the outer layers of the cell islands are positive
- Mucicarmine: occasional tumor cells contain cytoplasmic mucin
- PAS: Glycogen demonstrated in clear cells

**Diagnosis**
Parotid gland – Mucoepidermoid carcinoma, oncocytic variant (also with clear cells)

**Oncocytic variant of mucoepidermoid carcinoma** is always an important consideration for salivary gland tumors rich in oncocyes. This has to be considered in particular for young patients, since oncocytoma and oncocytic carcinoma occur predominantly in older subjects.

**CASE 9**

**Clinical features**
- A 69-year old male presented with a left parotid mass.
- Left superficial parotidectomy was performed.
- The cut surfaces of the parotid gland revealed multiple tan-brown nodules that apparently extended into the fat.

**Salient histologic features**
- Multiple, variable-sized, rounded, expansile nodules comprising trabeculae and packets of oncocyes
- Some interspersed aggregates of lymphocytes, with lymphoid follicle formation
- In some areas, the nodules have less well defined contours, with the oncocytic cells merging gradually into normal ductal/acinar cells

**Diagnostic considerations**
Because of the multiplicity of nodules and lack of fibrous capsule, this oncocytic lesion is more in keeping with nodular oncocytic hyperplasia than oncocytoma. In view of the lack of destructive invasion, bland appearance of the oncocyes, and merging into benign salivary units, a diagnosis of oncocytic adenocarcinoma is not considered.

**Immunophenotype** (not required for diagnosis of this case)
- p63 and 34<sup>ß</sup>E12 demonstrate basal cells at the base of trabeculae and around the packets of oncocyes

**Diagnosis**
Parotid gland – Nodular oncocytic hyperplasia
ONOCYTOSIS AND NODULAR ONOCYTIC HYPERPLASIA

Oncocytosis
- Oncocytosis is a diffuse oncocytic metaplastic process in the salivary gland, often associated with atrophy of the surrounding parenchyma.
- The lobular architecture is preserved, and there is no nodule formation.

Nodular oncocytic hyperplasia
- Also known as "multifocal nodular oncocytic hyperplasia"
- Nodular oncocytic hyperplasia consists of multiple nodules of closely packed oncocytes within the salivary gland
- The various oncocytic lesions (oncocytoma, oncocytosis and nodular oncocytic hyperplasia) could represent a spectrum of a single entity. Although distinguishing features have been described for these three conditions, given the similarly excellent prognosis and treatment modality, it may not be worthwhile to make great efforts to achieve definite distinction in controversial cases.
- Features favoring interpretation of nodular oncocytic hyperplasia over onc cytoma:
  - Multiple rather than single nodule
  - The nodules often show a lobular distribution
  - The nodules may be irregular in contour, and show gradual merging into the normal ducts and acini
  - Lack of capsule around the nodules (oncocytoma is often surrounded at least focally by a fibrous capsule)
  - Clear cell change is not uncommon
- Basal cells can be demonstrated among the oncocytes in both onc cytoma and nodular oncocytic hyperplasia, and thus they cannot be used for their distinction.
# Clear Cell Tumors (Cases 10-11)

## Differential Diagnoses of Salivary Gland Tumors with Prominent Clear Cells

<table>
<thead>
<tr>
<th>Nature of Clear Cells</th>
<th>Cause of Clearing</th>
<th>Growth Pattern</th>
<th>Cytologic Features of Clear Cells</th>
<th>Staining Properties of Clear Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell oncocyctoma</td>
<td>Oncocytes</td>
<td>Glycogen</td>
<td>Solitary; encapsulated or circumscribed; cells arranged in trabeculae or packets</td>
<td>Centrally located, round nuclei; peripheral rim of cytoplasm may retain pink granularity</td>
</tr>
<tr>
<td>Clear cell nodular oncocyctic hyperplasia</td>
<td>Oncocytes</td>
<td>Glycogen</td>
<td>Multiple nodules; cells arranged in trabeculae or packets</td>
<td>Centrally located, round nuclei; peripheral rim of cytoplasm may retain pink granularity</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>Ductal cells</td>
<td>Glycogen</td>
<td>Infiltrative; solid or trabecular growth; sclerotic or hyalized stroma</td>
<td>Polygonal cells with water-clear cytoplasm; nuclei central or eccentric</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma, clear cell variant</td>
<td>Intermediate cells; mucinous cells</td>
<td>Glycogen and mucin respectively</td>
<td>Infiltrative; inflamed fibrous stroma; clear cells form large islands and sheets traversed by delicate fibrovascular septa; focally islands of epidermoid, intermediate and mucinous cells; some cystic spaces</td>
<td>Intermediate clear cells are large cells with water-clear cytoplasm; mucinous cells have flocculent cytoplasm</td>
</tr>
<tr>
<td>Epithelial-myoeplithelial carcinoma</td>
<td>Myoepithelial cells</td>
<td>Glycogen</td>
<td>Infiltrative, often with pushing borders; ductal structures lined by inner cuboidal cells and outer clear myoepithelial cells</td>
<td>Polygonal cells with basally located or central nuclei; water-clear cytoplasm</td>
</tr>
<tr>
<td>Clear cell myoepithelioma or myoepithelial carcinoma</td>
<td>Myoepithelial cells</td>
<td>Glycogen</td>
<td>Lobules, nests, trabeculae and fascicles; may have collagenous spherules</td>
<td>Polygonal or spindly cells with water-clear cytoplasm; variable degrees of nuclear atypia, often admixed with a population of cells with eosinophilic cytoplasm</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>Acinic cells</td>
<td>Tissue processing artifact</td>
<td>Infiltration in broad fronts; microcystic pattern</td>
<td>Peripherally located nuclei; sparse basophilic granules in some cells</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>Neoplastic renal epithelial cells</td>
<td>Glycogen and lipid</td>
<td>Prominent sinusoids or delicate fibrovascular septa; hemorrhage and hemosiderin deposition; some glandular structures</td>
<td>Water-clear cytoplasm; variable nuclear atypia</td>
</tr>
<tr>
<td>Sebaceous adenoma or adenocarcinoma</td>
<td>Sebaceous cells</td>
<td>Lipid</td>
<td>Tumor lobules comprise of groups of mature sebaceous cells surrounded by basaloid cells</td>
<td>The sebaceous cells contain multiple small honeycombed vacuoles</td>
</tr>
</tbody>
</table>
Caution!
Clear cell tumors of the salivary gland should be considered malignant until proven otherwise.

APPROACH TO DIAGNOSIS OF CLEAR CELL TUMORS OF THE SALIVARY GLAND

- Epithelial-myoepithelial carcinomas are readily recognized by the bicellular population – ductal structures lined by cells with eosinophilic cytoplasm are interspersed among the clear cells, although ductal structures can be sparse in occasional cells.
- For tumors comprising a pure or almost pure population of water-clear cells, the main considerations are:
  - Clear cell carcinoma
  - Mucoepidermoid carcinoma, clear cell variant
  - Clear cell myoepithelioma or myoepithelial carcinoma
  - Metastatic renal cell carcinoma
- Metastatic renal cell carcinoma can often be distinguished from clear cell carcinoma of salivary gland by the following features:
  - Presence of glands at least focally
  - Intraglandular hemorrhage
  - Delicate fibrovascular septa or sinusoids separating the tumor islands or glands
- Clear cell mucoepidermoid carcinoma can be recognized by the following features:
  - Presence of a more typical component of mucoepidermoid carcinoma (such as islands of squamoid cells, and cysts lined by mucinous and intermediate cells) on further search
  - The cells located at the periphery of the clear cell islands or adjacent to the stroma/fibrovascular septa are often smaller in size or assume a non-clear cell appearance
- Distinction between clear cell myoepithelial carcinoma and clear cell carcinoma can be very difficult because of marked overlap in architecture and cytology. Immunostaining is required for a firm distinction (myoepithelial phenotype in myoepithelial carcinoma, and pure ductal phenotype in clear cell carcinoma).
- For clear cell tumors in which the clear cells retain focal granularity, consider clear cell oncocytic lesions and acinic cell carcinoma.

CASE 10
Clinical features
- A 65-year-old male presented with a left parotid mass.
- Left parotidectomy was performed, revealing a circumscribed light-brown tumor with bosselated contour, measuring 2.3 x 1.9 x 1.4 cm.

Salient histologic features
- Well circumscribed tumor nodule with bosselated contour
- Trabeculae of polygonal cells separated by delicate vasculature
- Polygonal cells have clear or finely granular cytoplasm. Occasional oncocytes present.
- No normal salivary gland tissue interspersed within the tumor nodule
Diagnostic considerations
Although there are clear cells, this case should not pose difficulties in recognition of its oncocytic nature because there are typical oncocyes and many clear cells maintain a fine granularity in the cytoplasm.

Immunophenotype and special stains (not required for diagnosis of this case)
- PAS: abundant glycogen in clear cells
- p63: basal cells demonstrated at the base of the trabeculae of tumor cells

Diagnosis
Parotid gland – Clear cell oncocytoma

CLEAR CELL ONCOCYTOMA
- Clear cells are present in 11% of oncocytomas as a dominant or partial component. The architecture is otherwise the same as conventional oncocytoma in terms of architecture.
- The cytoplasmic clearing is due to glycogen accumulation, but a sparse granularity is still evident.
- Transition of clear cells to typical oncocyes can often be identified.
- Clear cell oncocytoma appears to show a higher frequency of bilateral tumors and recurrence in comparison to conventional oncocytoma.
- Note that there is also a clear cell variant of nodular oncocytic hyperplasia.

CASE 11 (#30304)
Clinical history
- A 72-year-old female presented with a right submandibular mass.
- The submandibular gland was excised, and the cut surface revealed multiple whitish to brown nodules, with the largest one measuring 1 cm.

Salient histologic features
- Multinodular tumor, invading in broad fronts into the salivary parenchyma
- Within the nodules, there are closely packed narrow tubules comprising two cell types (inner layer of ductal cells with pink cytoplasm, and outer layer of clear cells, which are much larger and which have paler nuclei)
- Some hyaline to myxoid stroma is interspersed among the tubules
- Focally, there are cleft-like glandular spaces, resulting in a frond-like growth pattern
- There are occasional cribriform structures

Diagnostic considerations
This case shows the prototypic features of epithelial-myoepithelial carcinoma, with the basic units of this tumor type (narrow tubules lined by pink cells, surrounded by an outer layer of clear cells) being very obvious.
Immunophenotype and special stains (not required for diagnosis in this case)
- PAS: abundant glycogen in clear cells
- CAM5.2: ductal structures selectively highlighted
- 34BE12: surprisingly, the ductal structures rather than the clear cells are highlighted
- EMA: luminal and cytoplasmic staining of the ductal cells
- p63, S100, smooth muscle actin: clear cells highlighted

Diagnosis
Submandibular gland – Epithelial-myoepithelial carcinoma

CASE 11b (#30405)
Clinical features
- F/61, presenting with parotid mass
- Parotidectomy performed, revealing a 4 cm tan-colored tumor with homogeneous appearance

Salient histologic features
- Multiple infiltrative nodules separated by sclerotic stroma
- Islands of clear cells or pale cells traversed by hyaline material; the cells have vesicular nuclei and distinct nucleoli; some mitotic figures are seen
- Occasional interspersed narrow tubules lined by cells with eosinophilic cytoplasm are identified

Diagnostic considerations
Probably due to fixation artifact, many tumor cells do not appear as clear as in the more classical examples (such as Case 11), and thus this case is less easy to recognize as epithelial-myoepithelial carcinoma. However, immunostaining clearly delineates the presence of dual cell differentiation.

Immunophenotype and special stains
- PAS: Clear cells are glycogen-rich
- Clear cells are highlighted by p63 and smooth muscle-actin
- Ki67 index is up to 20%

Diagnosis
Parotid gland – Epithelial-myoepithelial carcinoma (there is progression to myoepithelial carcinoma in some foci: not included in the circulated slides)

Comments
This case is less well differentiated than Case 11. There is marked coalescence of the basic glandular units, to that extent that glandular lumens are difficult to identify. Nuclear atypia is also more significant.
EPITHELIAL-MYOEPITHELIAL CARCINOMA

Definition

- A malignant tumor composed of ductal structures lined by a single layer of ductal cells which are surrounded by a single or multiple layers of clear myoepithelial cells.
- The counterpart in the breast is adenomyoepithelioma.

Clinical features

- Age: peak incidence is in the sixth and seventh decades
- Sex: slight female predominance
- Approximately 60% of cases occur within the parotid gland, while submandibular gland and intraoral minor salivary gland are responsible for the rest. The tumor has also been reported to occur in lacrimal gland, lung, bronchus, trachea, nasal cavity, nasopharynx and liver.
- Most patients present with an asymptomatic mass, and a minority of patients have pain and facial weakness.
- A relatively low grade malignancy. Recurrence is reported in 30-40% of cases, which may occur as long as 28 years after initial surgery. Regional lymph node metastasis occurs in 10-20% of cases, but distant metastasis (lung, kidney, and brain) is uncommon (9%).
- Tumor-associated mortality is low (0-9%). Fonseca et al report that tumors with more than 20% of cells showing nuclear atypia are associated with a poorer prognosis.

Major diagnostic criteria of epithelial-myoepithelial carcinoma

- Infiltrative borders
- Discrete or merged tubules of two-cell types
- Clear cytoplasm in outer myoepithelial layer
- Tubules not uncommonly show branching lumens
- Cribriform pattern rare

Pathology

- Grossly, the tumor is typically multinodular and circumscribed.
- Histologically, the tumor invades the surrounding parenchyma in broad fronts, resulting in multiple tumor nodules separated by sclerotic stroma. Perineural and vascular invasion are sometimes seen.
- Within the tumor nodules, the stroma can be scanty, loose, myxoid, hyalinized or fibrous.
- The prototypic bicellular architecture consists of a tubular structure lined by ductal cells surrounded by one or several layers of clear cells, which are further enveloped on the outside by a well-defined basement membrane.
- The tubular luminal cells are cuboidal, with round, bland-looking nuclei and a moderate amount of pink cytoplasm, reminiscent of intercalated duct cells. Rarely, there can be squamous differentiation.
- The clear cells are polygonal, considerably larger in size, and have abundant water-clear cytoplasm. The cytoplasmic clearing is due to accumulation of glycogen. These cells exhibit myoepithelial immunophenotype and ultrastructural features.
- In some tumors, discrete tubules give way to coalesced tubules, complex glandular structures, papillary-cystic structures, trabeculae, and large sheets of clear cells delineated by thick basement membrane.
- In clear cell-predominant areas, the small ductal cells can be difficult to find, hence distinction from clear cell carcinoma can be problematic.
Rarely, fascicles of spindly clear (myoepithelial) cells can be formed.

In most cases, cytologic atypia is mild, and the mitotic count is low. However, rare cases may show transition to areas with a greater degree of nuclear atypia, more solid growth and frequent mitoses, suggesting that the tumor can evolve to a higher-grade epithelial-myoepithelial carcinoma. This phenomenon is apparently associated with a more aggressive behavior.

Rare cases of dedifferentiation to poorly differentiated carcinoma no longer recognizable as epithelial-myoepithelial carcinoma have also been reported.

Immunohistochemistry and special studies

- The ductal cells are strongly positive for pan-cytokeratin and variably positive for S100 protein, but are negative for myoepithelial markers.
- The clear cells are positive for pan-cytokeratin (often weakly), high molecular weight cytokeratin, p63, S100 protein, calponin and actin. The proliferation (Ki67) index is low: <1% for ductal cells, and <3% for myoepithelial clear cells. Ploid analysis shows that most tumors (>80%) are diploid.

Major differential diagnosis

- This tumor has to be distinguished from other clear cell tumors, especially for cases showing coalescent islands and sheets of clear cells. Careful scrutiny and extensive sampling may be required to detect the diagnostic bilocelllar architecture in some cases. The clear cells in epithelial-myoepithelial carcinoma exhibit myoepithelial differentiation, whereas those of clear cell carcinoma do not.
- Both epithelial-myoepithelial carcinoma and adenoid cystic carcinoma are infiltrative neoplasms with dual ductal-myoepithelial differentiation. The following features favor the former diagnosis:
  - The abluminal cells are much larger, with clear cytoplasm and pale nuclei (clear cells, if present in adenoid cystic carcinoma, are very focal)
  - Rarity of cribriform structures
  - Rarity of lightly basophilic mucosubstance in microcystic spaces
  - Irregular branching glandular lumens, if present
  - Lower proliferative (Ki67) index

CLEAR CELL CARCINOMA, NOT OTHERWISE SPECIFIED

Clinical features

- Also known as clear cell adenocarcinoma, is composed of polygonal epithelial cells with water-clear cytoplasm without evidence of myoepithelial differentiation.
- It is a diagnosis of exclusion, in that features characteristic of other neoplasms, most notably epithelial-myoepithelial carcinoma, clear cell oncocytea, mucoepidermoid carcinoma, acinic cell carcinoma, clear cell myoepithelial tumor, sebaceous carcinoma and metastatic renal cell carcinoma should be absent.
- Most frequently occurs in the fifth to seventh decades with no gender predilection
- Most reported cases arise from the minor salivary glands of the oral cavity as a painless slow-growing mass, and some may ulcerate or cause fixation to adjacent tissues.
- It is a low-grade, locally invasive tumor, with a tendency for locoregional recurrence. Cervical lymph node metastasis only rarely occurs, and mortality due to this tumor is exceptional. Wide excision is the treatment of choice; the role of adjuvant radiotherapy remains to be elucidated.
Major diagnostic criteria of clear cell carcinoma (NOS)

- Infiltrative tumor
- Islands and trabeculae of clear cells, with no bicellular pattern
- Clear cells show no immunohistochemical or ultrastructural evidence of myoepithelial differentiation

Pathology

- The tumor is poorly circumscribed and shows whitish-tan cut surfaces
- Composed of sheets, streaming columns, nests and cords of large, polygonal clear cells that show mild variation in size
- The cells possess discrete cell membrane and abundant clear cytoplasm due to accumulation of glycogen (PAS positive and diastase-sensitive, mucicarmine negative). The nuclei are centrally or eccentrically located, and have finely granular chromatin and inconspicuous nucleoli. Nuclear atypia ranges from mild to moderate.
- A subpopulation of tumor cells can have eosinophilic cytoplasm.
- Mitotic figures are rare.
- There is no duct formation. Variable amount of fibrous stromal can be present.

Immunohistochemistry and special studies

- Focally to diffusely immunoreactive for cytokeratin.
- In contrast to metastatic renal cell carcinoma, the tumor expresses high molecular weight cytokeratin and CEA.
- Myoepithelial markers should be negative
- Ultrastructural and immunohistochemical studies have demonstrated only ductal but not myoepithelial differentiation.

Variant: Hyalinizing clear cell carcinoma

- A subgroup of clear cell carcinoma
- Most cases originate from minor salivary glands, but major glands can also be affected.
- The oral cavity, particularly the base of tongue and palate, is the most common site
- Rare cases have been reported in the larynx, nasopharynx, hypopharynx, mandible and maxilla.
- The tumor usually presents as a slowly growing and painless submucosal mass.
- The clinical course is indolent. Nonetheless, multiple recurrences over many years can occur in some cases, and cervical lymph node and lung metastasis can rarely occur.
- Wide local excision with or without radiotherapy is the treatment of choice.
- Histologically, the infiltrative tumor comprises uniform clear cells and cells with eosinophilic cytoplasm, forming solid nests, trabeculae, cords and streaming columns of one to two cell width. The stroma is characterized by abundant, thick parallel strands of fibrous tissue associated with hyalinized and myxoid substance, admixed with cellular fibrous (desmoplastic) tissue. The hyalinized stroma resembles amyloid, but is PAS-positive and congo red-negative.
- Immunohistochemical staining reveals diffuse positivity of tumor cells for cytokeratin and EMA and focal positivity for CEA.
- Myoepithelial markers (S-100 protein, l-calponin and smooth-muscle actin) are consistently negative. Electron microscopy reveals tonofilaments, well-formed desmosomes and hemidesmosomes, confirming the pure epithelial differentiation of the tumor.
BASALOID CELL TUMORS (Case 12)

Salivary gland tumors predominated by basaloid cells
- Basal cell adenoma and variants (such as lymphadenoma)
- Pleomorphic adenoma (cases rich in basaloid cells)
- Canalicular adenoma
- Basal cell adenocarcinoma
- Adenoid cystic carcinoma
- Basaloid squamous cell carcinoma
- Sialoblastoma

APPROACH TO DIAGNOSIS OF BASALOID CELL TUMORS
- Basaloid cells refer to small to medium-sized cells with high nuclear-cytoplasmic ratio and relatively dark-staining nuclei, resembling normal basal cells.
- Canalicular adenoma has a distinct architectural pattern and site of involvement (oral cavity), such that it should not pose problems in diagnosis. Nonetheless, there can be cases showing overlap features between canalicular adenoma and basal cell adenoma.
- A circumscribed tumor comprising predominantly basaloid cells is most likely a basal cell adenoma or pleomorphic adenoma. The borderline between the two entities is not always sharp, but a distinction is not that important because both entities are benign. In general, basal cell adenoma shows more uniform growth pattern throughout, do not show "melting" of basaloid cells into stroma, and lack chondromyxoid stroma.
- For infiltrative basaloid cell tumor, the major considerations are basal cell adenocarcinoma, adenoid cystic carcinoma and basaloid squamous cell carcinoma. (See Table following "basal cell adenocarcinoma"). Basaloid squamous cell carcinoma does not occur in the major salivary glands.

CASE 12
Clinical features
- A 40-year-old female presented with a right upper cervical mass of unstated duration.
- Superficial parotidectomy was performed.
- In the specimen, there was a well circumscribed nodule measuring 2 x 1 x 1 cm, with a uniform, light tan, firm cut surface.

Salient histologic features
- Well circumscribed tumor (may not be evident in the circulated slides)
- Anastomosing islands and trabeculae of basaloid cells, with interspersed narrow glandular spaces lined by cuboidal cells
- These basaloid cells islands and trabeculae are sharply delineated from the stroma, which harbors fascicles of plump spindly cells
Diagnostic considerations
This is obviously a basal cell adenoma. But it shows the unusual morphologic feature that there is a cellular stroma that does not merge with the main tumor units like in pleomorphic adenoma. These stromal cells are believed to be derived from myoepithelium.

Immunophenotype (not required for diagnosis in this case)
- Spindle cells in stroma – CAM5.2 and 34βE12 negative; EMA negative; S100 strong positive; very rare cells smooth muscle actin positive; p63 negative
- Tumor trabeculae – CAM5.2 highlights the cells that surround the ductal spaces; 34βE12 and p63 highlights the basaloid cells around the ducts.

Diagnosis
Parotid gland – Basal cell adenoma with myoepithelium-derived stroma

BASAL CELL ADENOMA
Definition
- A benign tumor composed of basaloid cells sharply delineated from the stroma by basement membrane-like material.
- Usually exhibits a monotonous solid, trabecular, tubular or membranous growth pattern.
- Chondromyxoid stroma should, by definition, be absent.

Clinical features
- Presentation: solitary, slow-growing, otherwise asymptomatic mass.
- Age: peaks at 6th to 7th decade
- Sex: female predilection
- About 70% occur in the parotid glands, and 10-20% the upper lip.
- Membranous basal cell adenoma, also known as dermal analogue tumor, is a distinctive variant that may be associated with cutaneous adnexal tumors. It shows no gender predilection.
- Surgical excision is the treatment of choice. Recurrence is rare except for the membranous type, which is associated with a recurrence rate of 25% because of its multifocal nature.
- Basal cell adenoma may rarely undergo malignant transformation (carcinoma ex-adenomorph adenoma, 4%) to basal cell adenocarcinoma, adenoid cystic carcinoma, salivary duct carcinoma, or adenocarcinoma NOS. The transformation rate is much higher in the membranous subtype, up to 28%.

Pathology
- Well circumscribed, with or without a fibrous capsule.
- Small basaloid cells possess round, uniform, basophilic nuclei and scant cytoplasm. Nuclear pleomorphism and mitoses are not seen.
- Sometimes, two populations of basaloid cells, dark and light cells, can be discerned.
- Some ductal structures lined by cells with a greater amount of eosinophilic cytoplasm are commonly interspersed among the basaloid cells.
- The tumors are usually predominated by one type of architecture, but a mixture of patterns can sometimes be seen.
Solid type

- Growth pattern: broad bands, smooth-contoured jigsaw puzzle-like islands, and solid masses with peripheral palisading.
- The basaloid cells are sharply demarcated from the loose, often highly vascularized stroma by basement membrane. This feature is in contrast with the centrifugal or “melting” growth of pleomorphic adenoma.

Trabecular type

- Interconnected narrow or broad trabeculae of cells, producing a reticular pattern

Tubular type

- Discrete or anastomosing tubules lined by two distinct layers of cells, with inner cuboidal ductal cells surrounded by an outer layer of basaloid cells.
- The lumen frequently contains PAS-positive eosinophilic secretion.
- Rarely, cribriform structures are formed or constitute the predominant pattern, mimicking adenoid cystic carcinoma.

Basal cell adenoma with myoepithelium-derived stroma

- Characterized by spindle-cell rich stroma that separates the cords and islands of basaloid cells.
- These spindle cells are strongly positive for S-100 protein and show ultrastructural features of myoepithelium, although actin and p63 are often negative.
- This tumor is distinguished from pleomorphic adenoma by the sharp demarcation of the abluminal basaloid cells from the stroma.

Membranous type

- More likely multifocal and multinodular.
- Presence of abundant, thick, eosinophilic and PAS-positive hyaline basal lamina material around the smooth-contoured tumor islands. The hyaline material also insinuates between individual cells in the form of droplets.
- There can be some interspersed glandular lumens in the tumor islands.
- Focal squamous metaplasia can occur.
- Membranous basal cell adenoma is histologically identical to dermal cylindroma. Familial cases accompanied by multiple cylindromas, trichoepithelioma, eccrine spiradenoma and milia constitute an autosomal Brooke-Spiegler syndrome (familial cylindromatosis or Turban tumor syndrome). Germline mutations of the cylindromatosis gene (CYLD), a tumor suppressor gene located at chromosome 16q12-q13, has been implicated in these familial cases.

Immunohistochemistry

- Dual luminal-abluminal cell differentiation
- Epithelial markers (cytokeratin, CEA, EMA) can be demonstrated in the luminal cells
- Myoepithelial markers (p63, calponin, actin, GFAP, S100) can be variably demonstrated in the peripherally-located basaloid cells.
BASAL CELL ADENOCARCINOMA

Definition
- A low grade malignant neoplasm with cytologic resemblance to basal cell adenoma.
- Diagnosis of malignancy usually rests on demonstration of infiltration of surrounding salivary lobules, nerves or blood vessels.

Clinical features
- Median age is 60 years, with no gender predilection.
- Most tumors arise de novo in the parotid gland, and less commonly, submandibular gland, oral cavity and upper respiratory tract.
- The tumors may arise from pre-existing basal cell adenoma, particularly the membranous subtype, or other monomorphic adenomas, in approximately 23% of cases.

Clinical behavior
- Generally low grade carcinomas with local destruction and a tendency for recurrence; regional lymph node or distant metastasis occur infrequently.
- The outcome is favorable with adequate surgical treatment.
- However, tumors arising in minor salivary glands appear to have a higher recurrence rate (71%), metastatic rate (21%) and mortality (29%) compared with those arising in major glands (corresponding figures 37%, 11%, 3%).

Pathology
- Predominantly solid growth, characterized by jigsaw puzzle-like islands of basaloid cells with peripheral palisading, usually invading in broad fronts.
- Small areas with trabecular or membranous arrangement are frequently seen.
- Rarely, well-defined tubular structures with two-cell type lining can be identified focally.
- Like basal cell adenoma, two distinctive basaloid cell populations, small dark cells and large pale cells, are present.
- Focal squamous differentiation is seen in 25% of cases, and some tumor cells may assume a spindly appearance.
- Within the basaloid cell islands, there can be small numbers of interspersed glandular spaces lined by cuboidal cells.
- Cases showing nuclear atypia and readily identified mitotic figures are easy to recognize as being malignant. However, most cases have a relatively bland cytologic appearance, and only identification of infiltrative growth permits a diagnosis of malignancy.
- Perineural infiltration or intravascular invasion are present in 25-35% of cases.

Major differential diagnosis
- Basal cell adenoma
- Adenoid cystic carcinoma, solid variant
- Undifferentiated carcinoma
- Basaloid squamous cell carcinoma
- Myoepithelial carcinoma
### Myoepithelial, basal cell or oncocytic

**Contrasting features of malignant tumors predominated by basaloid cells: adenoid cystic carcinoma (solid type), basal cell adenocarcinoma and basaloid squamous cell carcinoma**

<table>
<thead>
<tr>
<th>Site of occurrence</th>
<th>Adenoid cystic carcinoma, solid variant</th>
<th>Basal cell adenocarcinoma</th>
<th>Basaloid squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Major or minor glands</td>
<td>Major or minor glands</td>
<td>Mucosal sites, such as larynx, hypopharynx, base of tongue</td>
</tr>
<tr>
<td>Architectural patterns</td>
<td>Although islands and diffuse sheets predominate, some cribriform structures are almost always present; comedo necrosis may be present in some large solid islands</td>
<td>Discrete jigsaw puzzle-like islands; rarely may show trabecular or tubular pattern; cribriform structures absent or very focal; comedo necrosis rare</td>
<td>Lobules and trabeculae with festooning and frequent comedo necrosis</td>
</tr>
<tr>
<td>Intercellular hyaline droplets</td>
<td>Very rare</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Basophilic mucousubstance in stroma or empty spaces</td>
<td>Common</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Cellular palisading at periphery of tumor islands</td>
<td>Usually not evident</td>
<td>Often a prominent feature</td>
<td>Usually not evident</td>
</tr>
<tr>
<td>Predominant cell type</td>
<td>Mostly basaloid cells with dark nuclei and a monotonous appearance; luminal cells very sparse</td>
<td>Basaloid cells include small dark cells and bigger paler cells; luminal cells very sparse</td>
<td>Basaloid cells with pale and atypical nuclei and frequent mitoses; true glandular cells rare</td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>Rare</td>
<td>Sometimes present in the centers of cell islands</td>
<td>Commonly present (often in the form of frank squamous cell carcinoma or carcinoma-in-situ)</td>
</tr>
</tbody>
</table>
CANALICULAR ADENOMA

Clinical features
- Occurs most commonly in the elderly, with a mean age of 65 years
- Female predilection.
- Site of disease: primarily an oral lesion (upper lip 74%, buccal mucosa 12%)
- Presentation: non-ulcerated, painless mass that grows slowly.
- Recurrence does not occur after complete excision.

Pathology
- Usually small (<3 cm)
- Well circumscribed, with or without a capsule.
- Multifocal lesions are not uncommon.
- Composed of bilayered strands of cells which abut and separate haphazardly, giving rise to single files, beads, canaliculi and pseudopapillae.
- The epithelial cells that form the strands are cuboidal to columnar, with a moderate amount of amphophilic cytoplasm and regular oval nuclei. Cellular pleomorphism and mitoses are not seen.
- The stroma is characteristically edematous with many capillaries and sinusoids; it can be so loose that tumor strands may appear to be “floating in the air”.
- Foci of basaloid cells may be present, rendering it difficult to distinguish from basal cell adenoma, particularly the trabecular variant, although the distinction is unimportant for management purposes.

Immunohistochemistry and electron microscopy
- Exclusive luminal cell differentiation without myoepithelial or basal cell participation
- Tumor cells are positive for cytokeratin, vimentin, S100 protein and infrequently EMA.

SIALOBLASTOMA

Definition
- Also known as embryoma, congenital carcinoma or congenital basal cell adenoma
- A tumor of newborn or infant which is composed of primitive-appearing cells with occasional ductal formation, recapitulating embryonic salivary tissue.

Clinical features
- Occurs in major salivary glands, most commonly in the parotid
- Age: At birth or within first or second years
- Presentation: asymptomatic mass. Occasional cases can be associated with skin ulceration, facial paralysis, obstruction to delivery, congenital nevi, and concomitant hepatoblastoma.

Clinical behavior
- Clinical behavior highly variable.
- Approximately 1/3 cases develop local recurrence, and 6% develop regional lymph node metastasis.
- Increase in anaplasia and proliferative activity have been reported in multiple recurrences.
- Complete surgical excision is the treatment of choice; adjuvant radiotherapy may be indicated for recurrence or incomplete excision.
Pathology
- Well-circumscribed or infiltrative
- Closely packed or loosely scattered islands of cells separated by fibromyxoid stroma.
- Most cells are primitive-looking, basaloid and possess large ovoid vesicular nuclei and a small amount of cytoplasm. They form cellular ductules and solid organoid nests with vague palisading of nuclei at the periphery of the tumor islands.
- Mild nuclear atypia and variable mitotic activity.
- Focally, ducts lined by larger polygonal to cuboidal cells with eosinophilic cytoplasm can be identified, and the ductal lumens often contain secretory product.
- Focally, cribriform structures reminiscent of adenoid cystic carcinoma can be present.
- Immunostaining for cytokeratin highlights the ductal structures. The basaloid cells show staining for S100 protein and actin in the peripherally located cells.
SQUAMOUS CELL LESIONS (Case 13)

### Salivary gland lesions with prominent squamous features
- Warthin tumor, oncocytic neoplasm or pleomorphic adenoma with squamous metaplasia
- Squamous cell carcinoma (primary, metastasis or invasion from adjacent sites)
- Adenosquamous carcinoma
- High grade mucoepidermoid carcinoma
- Keratocystoma
- Necrotizing sialometaplasia

### Diagnostic considerations for frankly squamous proliferations in salivary gland
- By probability, it is much more likely to be a benign lesion than malignant tumor
- The most likely diagnosis is squamous metaplasia of Warthin tumor, pleomorphic adenoma or oncocytoma (squamous differentiation is particularly common after FNA or infarct). These possibilities must be seriously considered before rendering a diagnosis of squamous cell carcinoma or intermediate/high grade mucoepidermoid carcinoma
- In the minor glands, necrotizing sialometaplasia is obviously another important differential diagnosis
- A diagnosis of low-grade mucoepidermoid carcinoma is almost certainly wrong if the tumor shows frank squamous features

### CASE 13
#### Clinical history
- F/78 presented with a soft palate mass
- Excision biopsy revealed an adenoid cystic carcinoma
- Two weeks after the excision, a wide margin excision of the soft palate was performed

#### Salient histologic features
- Covered by stratified squamous epithelium, with areas of ulceration
- Underlying tissue shows acute suppuration and granulation tissue formation.
- There are grouped nests of proliferated stratified squamous epithelium with mild to moderate nuclear atypia. Some cells are individually keratinized.
- In the vicinity of the squamous nests, there are some small empty spaces containing mucin or histiocytes

#### Main differential diagnoses
- Reactive squamous proliferation
- Squamous cell carcinoma or mucoepidermoid carcinoma

#### Diagnostic considerations
The preserved lobular architecture is against a diagnosis of squamous cell carcinoma. Overall features are compatible necrotizing sialometaplasia given the lobular architecture and presence of some "empty" spaces formed by drop-cut (necrosis) of preexisting acinar cells. There are also occasional mucinous cells among the squamous cells, supporting that the squamous epithelium arose through metaplasia.
Diagnosis
Palate - Necrotizing sialometaplasia
(In the current case, the tissue injury/ischemia from the prior surgery probably led to the development of necrotizing sialometaplasia)

NECROTIZING SIALOMETAPLASIA
• An important differential diagnosis of squamous lesions of salivary gland.
• A reactive, self-limiting condition.
• Affects almost exclusively the minor glands.
• Commonest presentation: ulcerated palatal lesion.
• Etiology: Most probably has an ischemic etiology, such as vasculitis, atheromatous emboli and prolonged intubation. Some cases have been associated with herpes infection, traumatic injury or prior surgery.
• Most important histologic feature distinguishing this lesion from carcinoma: preserved lobular configuration, i.e. lack of infiltrative growth
• Pathology:
  o Lobular architecture
  o Partial or complete necrosis of salivary lobules (“empty” acinar spaces)
  o Florid squamous metaplasia of the adjacent ducts and acini, with variable extension of squamous epithelium into necrotic lobules, similar to the phenomenon seen in the prostate around areas of infarct.
  o Squamous epithelium can show some degree of nuclear atypia
  o Inflammatory infiltrate often present
  o Overlying squamous epithelium commonly exhibits pseudoepitheliomatous hyperplasia.

SQUAMOUS CELL CARCINOMA
• Primary salivary gland squamous cell carcinoma is extremely rare
• Invasion from an adjacent squamous cell carcinoma or metastasis should always be excluded.
• This entity is seldom diagnosed with confidence in the minor salivary gland since it is not possible to rule out a mucosal squamous cell carcinoma.
• This tumor mainly affects elderly males. Most patients present with fast-growing, hard, fixed mass. Regional lymph node involvement and facial nerve palsy are common.
• 5-year survival is only around 30%.
• Pathology:
  o Infiltrative growth
  o Moderately to well-differentiated squamous cell carcinoma consisting of sheets and islands of squamous cells with readily identifiable keratin formation and intercellular bridges.
  o Lack of intracellular mucin (i.e. high grade mucopeidermoid carcinoma is the major differential diagnosis)
  o Desmoplastic stroma
CYSTIC LESIONS OF SALIVARY GLAND (Case 14)

Major cystic lesions of salivary gland
- Mucoepidermoid carcinoma, cystic
- Acinic cell carcinoma, papillary-cystic variant
- Cystadenoma and cystadenocarcinoma
- Keratocytoma
- Polycystic disease
- Sclerosing polycystic adenosis
- Lymphoepithelial cyst
- Retention cyst
- Malignant lymphoma accompanied by cystic change in ducts

APPROACH TO DIAGNOSIS OF CYSTIC LESIONS OF SALIVARY GLAND
- Cystic variant of mucoepidermoid carcinoma and papillary-cystic variant of acinic cell carcinoma are not uncommonly misdiagnosed as benign cyst (retention cyst) or cystadenoma. The mistake can be avoided by paying close attention to the cells that line the cysts as well as the presence of tumor islands in the fibrous walls. In fact, retention cysts are extremely rare in the major salivary glands.
- Other cystic entities have characteristic histologic features to permit their recognition.
- When malignant lymphoma (mostly low grade MALT lymphoma) involves the salivary gland, the entrapped ducts can undergo cystic change, resulting in the formation of a multicystic mass.

CASE 14
Clinical history
- M/28, presented with a right parotid mass
- After an inconclusive fine needle aspiration, the right parotid gland was excised
- Specimen revealed a cyst measuring 2 x 1.5 x 1.5 cm

Salient histologic features
- A cystic cavity lined by stratified cells
- The cells are cuboidal and occasional hobnailed, and have amphophilic cytoplasm. Many cells show vacuolation.
- Nuclei are round and relatively bland-looking.
- In areas, microcystic spaces are formed within the stratified lining cells

Diagnostic considerations
This lesion can potentially be mistaken for some form of benign cyst or cystadenoma. However, the amphophilic cytoplasm (suggesting presence of zymogen granules), focal microcystic pattern and vacuolated cells are highly characteristic of acinic cell carcinoma.
Special stains
• PAS – Small numbers of intracytoplasmic granules present in some cells that line the cyst

Diagnosis
Parotid gland – Acinic cell carcinoma, papillary-cystic variant (cystic variant)

PAPILLARY-CYSTIC VARIANT OF ACINIC CELL CARCINOMA
• This rare variant of acinic cell carcinoma is characterized by large cystic spaces lined by simple or stratified cuboidal epithelium with some papillary projections
• The papillae are covered by hobnailed cells, intercalated duct-like cells, vacuolated cells, non-specific glandular cells, and non-descript cells, which possess eosinophilic to amphophilic cytoplasm, central nuclei and indistinct cell borders
• Fibrovascular cores may or may not be found.

Vacuolated and hobnailed cells are particularly characteristic of the papillary-cystic variant of acinic cell carcinoma. Their identification may thus provide an important histologic clue to the correct diagnosis.

SCLEROSING POLYCYSTIC ADENOSIS
Clinical features
• A lesion of uncertain nature characterized by a striking morphologic resemblance to fibrocystic changes of the breast.
• Age: 9 to 80 years of age (mean, 33 years)
• Sex: F>M
• Most cases arise in the major salivary glands, but intracranial minor salivary glands can also be affected.
• The patients present with slow-growing mass.
• Recurrence occurs in almost one-third of cases but most likely due to multifocal disease. No metastasis or mortality has been reported so far.

Pathologic features
• Well-circumscribed and partially encapsulated
• Multiple ducts, cysts, glands, and acinar structures arranged in a lobular pattern.
• The sclerotic stroma shows focal lymphocytic infiltration.
• The glandular epithelial cells exhibit a spectrum of foamy, apocrine-like granular, and mucinous appearance. Some cells contain large, brightly eosinophilic granules.
• There can be variable degrees of epithelial hyperplasia forming solid aggregates and cribriform structures.
• There are also strangulated tubules reminiscent of sclerosing adenosis.
• Ductal epithelial atypia ranging from mild dysplasia to carcinoma-in-situ can be found in almost 40% of cases.
• Immunohistochemically, the luminal epithelial cells express CEA, BRST-2, estrogen receptor (20%) and progesterone receptor (80%), but not c-erbB2.
• A continuous layer of myoepithelial cells can be demonstrated around the ducts and acini.
POLYCYSTIC DISEASE OF PAROTID GLAND

- A developmental malformation believed to result from defects and dilatation of the intercalated ducts.
- Most patients present in childhood as recurrent parotid swelling.
- Histologically, the lobular architecture is preserved.
- The extent of involvement varies from lobe to lobe.
- The lesion comprises honeycombed, lattice-like cysts of variable sizes and shapes lined by flat cuboidal to low columnar or apocrine-like cells. Occasional striated ducts of acinar units appear to communicate with the cysts.
- The cyst lumens often contain flocculent secretion and sometimes laminated microliths.
- A mild chronic inflammatory infiltrate is commonly present in the fibrous septa.

CYSTADENOMA

Definition

- A rare, non-invasive epithelial tumor characterized by cystic proliferation of benign ductal epithelium.

Clinical features

- Sites of occurrence: equally in the major glands and minor glands (most notably the lip, buccal mucosa, palate and tonsil).
- Mean age is 55 years, with a female predilection.
- Presentation: asymptomatic slow-growing cyst with or without fluctuance.
- Complete excision is curative.

Pathology

- Well circumscribed with or without a fibrous capsule.
- A single or multiple variably-sized cysts separated by dense fibrous stroma.
- Cysts are lined by attenuated, cuboidal or columnar epithelial cells, which may be thrown into papillary folds. Focal or extensive mucous, oncocytic and rarely squamous metaplasia of the epithelial cells can occur.
- The nuclei are bland, and mitoses are extremely rare.
- The lumens of the cysts contain proteinaceous fluid.

Differential diagnosis

- Low grade mucoepidermoid carcinoma (infiltrative; presence of some solid islands; mixture of cell types)
- Cystadenocarcinoma (presence of definite invasion)
- Duct ectasia
- Polycystic disease
- Sclerosing polycystic adenosis
CYSTADENOCARCINOMA
Clinical features
- A rare low grade malignant tumor representing the malignant counterpart of cystadenoma.
- Majority of patients are above 50 years old (mean age 59).
- About 65% occur in the major salivary glands, and the rest affects the buccal mucosa, lips and palate.
- Presentation: slow growing asymptomatic mass. Palatal tumor may erode the bone.
- Local recurrence and regional lymph node metastasis rates are 7.5% and 10% respectively.

Pathology
- The malignant nature of the tumor is manifested by invasion of the surrounding tissue.
- Perineural invasion occurs in 9% of cases.
- The tumor comprises numerous variably-sized cysts with frequent intraluminal papillary processes. Foci of solid growth and extraluminal extension are evident in some cases.
- The cysts are lined by small cuboidal, large cuboidal or columnar cells, or a mixture of these cells. Cellular atypia is usually mild to moderate, but nucleoli are usually prominent.
- Tumors composed predominantly of pseudostratified tall columnar cells appear to have a higher rate of metastasis.
- The stroma ranges from being fibrotic, sclerotic, hyalinized to desmoplastic.

Differential diagnosis
- Cystadenoma – cystadenocarcinoma is distinguished from cystadenoma by the presence of invasion, foci of solid growth and, in some cases, cytologic atypia.
- Salivary duct carcinoma – cystadenocarcinoma is distinguished by the low nuclear grade and lack of comedo necrosis.

It is important to distinguish cystadenocarcinoma from papillary-cystic acinic cell carcinoma and mucoepidermoid carcinoma because it requires less radical operation and has a better prognosis.

KERATOCYSTOMA
Clinical features
- A rare benign tumor consisting of multiple cystic structures and solid nests formed by benign squamous epithelial proliferation.
- All cases affect the parotid glands of children or young adults (age 8-38 years) as a painless mass.
- No recurrence after complete excision.

Pathology
- Multiple, randomly-disposed cystic structures and solid nests of squamous cells.
- Cysts are lined by non-dysplastic stratified squamous epithelium with ortho- or parakeratosis but lacking a granular layer. The cystic lumens are filled with lamellated keratin. The basal layer is demarcated from the stroma by basement membrane.
- The stroma is fibrotic with moderate amounts of chronic inflammatory cells. Foreign-body reaction against keratin released from the ruptured cysts are also present.
- The squamous cells express pan-cytokeratin and CK14, but not S-100 protein or actin.
LYMPHOEPITHELIAL CYST

Definition
- Characterized by epithelium-lined cysts with a dense lymphoid stroma in the wall.
- It has been proposed to arise from cystic proliferation of salivary inclusions in intraparotid lymph node.
- Its incidence has greatly increased over the past two decades because of the association with human immunodeficiency virus (HIV) infection.

Lymphoepithelial cyst unassociated with HIV infection
- Typically occurs in adults (average age 45 years) with a male predominance
- Usually presents as parotid swelling, and is curable by surgical excision.
- Almost always solitary
- The cysts often have an undulating luminal surface, and are lined by stratified squamous epithelium, although the epithelial lining can be cuboidal, columnar or respiratory type.
- Beneath the epithelium, there is a thick band of lymphoid tissue whose base is often well demarcated from the surrounding salivary parenchyma.
- Lymphoid follicles are frequently present, and small lymphocytes may infiltrate the epithelium.

HIV-associated lymphoepithelial cyst
- Also known as cystic lymphoid hyperplasia
- Commonly presents as bilateral parotid swelling accompanied by cervical lymphadenopathy.
- The swellings are slow-growing and painless.
- Males are more frequently affected than females (7:1), with the peak age spanning from 2nd to 4th decades.
- The cyst may represent the first clinical manifestation of HIV infection concurrent with persistent generalized lymphadenopathy syndrome.
- Usually comprises multiple variable-sized cysts, lined by stratified squamous or glandular epithelium.
- The lymphoid tissue exhibits florid lymphoid hyperplasia similar to that found in lymph node of persistent generalized lymphadenopathy. There is explosive follicular hyperplasia, follicle lysis, increased monocytoïd B cells, increased vascularity and plasma cell infiltrate.
- Lymphoepithelial lesions may be found
- There can be scattered multinucleated giant cells
### PROGRESSION OF SALIVARY GLAND TUMORS (Case 15-17)

#### DIFFERENT MODES OF TUMOR PROGRESSION IN SALIVARY GLAND TUMORS

<table>
<thead>
<tr>
<th>Phenomenon</th>
<th>Relationship of components</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant transformation</td>
<td>Benign tumor → Malignant tumor</td>
<td>• Pleomorphic adenoma → Carcinoma ex pleomorphic adenoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Basal cell adenoma → Carcinoma (including basal cell adenocarcinoma)</td>
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<tr>
<td></td>
<td></td>
<td>• Myoepithelioma → Myoepithelial carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>• Warthin tumor → Carcinoma or lymphoma</td>
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<tr>
<td></td>
<td></td>
<td>• Oncocytoma → Oncocytic carcinoma</td>
</tr>
<tr>
<td>Stromal invasion</td>
<td>In-situ carcinoma → Invasive carcinoma</td>
<td>• Intraductal carcinoma → Salivary duct carcinoma</td>
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<tr>
<td></td>
<td></td>
<td>• In-situ carcinoma arising in pleomorphic adenoma → Invasive carcinoma (intracapsular, microinvasive and frankly invasive carcinoma)</td>
</tr>
<tr>
<td>Overgrowth</td>
<td>Carcinoma with dual cell differentiation → pleomorphic carcinoma with oneline differentiation</td>
<td>• Epithelial-myoepithelial carcinoma → myoepithelial carcinoma</td>
</tr>
<tr>
<td>High grade progression</td>
<td>Same tumor type, from low grade → high grade</td>
<td>• Adenoid cystic carcinoma (low grade → high grade)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mucoepidermoid carcinoma (low grade → high grade)</td>
</tr>
<tr>
<td>Dedifferentiation</td>
<td>Carcinoma → High-grade malignant neoplasm with loss of original line of differentiation</td>
<td>• Dedifferentiated acinic cell carcinoma</td>
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<tr>
<td></td>
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<td>• Dedifferentiated adenoid cystic carcinoma</td>
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<td>• Dedifferentiated mucoepidermoid carcinoma</td>
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<td>• Dedifferentiated epithelial-myoepithelial carcinoma</td>
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<td></td>
<td></td>
<td>• Dedifferentiated polymorphous low grade adenocarcinoma</td>
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<tr>
<td></td>
<td></td>
<td>• Dedifferentiated salivary duct carcinoma (sarcomatoid variant)</td>
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<td>• Dedifferentiated myoepithelial carcinoma</td>
</tr>
</tbody>
</table>
PROGRESSION IN SALIVARY GLAND TUMORS
- Tumor development or progression is a multi-step process, often involving sequential accumulation of genetic changes.
- Salivary gland tumors provide a great opportunity to elucidate the mechanisms of tumor progression because of:
  - Complexity of cytoarchitecture of salivary gland tumors
  - Existence of many different types of indolent tumors, providing the "soil" for accumulation of new mutations, and hence tumor progression (risk increasing with duration of harboring the tumor)

![Diagram showing progression from normal cell to benign tumor to malignant tumor to higher grade tumor](image)

CASE 15
Clinical features
- A 55-year-old man presented with a several year history of speech disturbance and a slowly growing mass in the nasopharynx, distorting his palate and filling his oropharyngeal airway.
- CT scan revealed an 8 x 6 cm tumor, which compressed the neurovascular bundle, the carotid space and the parapharyngeal space.
- The mass was excised, and it measured 5.9 x 5.5 x 4.5 cm. The cut surface revealed a circumscribed to encapsulated mass which was grey-white to tan, with focal mucoid and hemorrhagic areas

Salient histologic features
- Encapsulated tumor
- There is a component of classical pleomorphic adenoma: anastomosing tubules of two-cell type, "melting" into a myxoid stroma with stellate and spindly cells; thick elastic fibers are present
- There is another component of obviously malignant cells arranged in islands and cords – the cells have much larger and pleomorphic nuclei, and show mitotic activity. Foci of necrosis and hyalinization are present
- On more careful assessment, many islands of malignant cells are apparently still enwrapped by the residual myoepithelial component of the pleomorphic adenoma, suggesting that the malignant cells are transformed ductal cells.

Immunophenotype (not required for diagnosis of this case)
- Pleomorphic adenoma component: myoepithelial component highlighted by S100, calponin and p63; Ki67 index <2%
- Carcinoma component: p53+ (moderate positive); c-erbB2+ (focal and weak); Ki67 index 30%. Some but not all islands are still surrounded by residual p63+ myoepithelium, i.e. in-situ growth.

Diagnosis
Nasopharynx – Carcinoma ex pleomorphic adenoma (intracapsular)
CARCINOMA EX PLEOMORPHIC ADENOMA

Definition
- Malignant transformation of a pre-existing pleomorphic adenoma, usually in the setting of long-standing tumor or in tumor with multiple recurrences.
- Incidence: 1.9% to 23.3% (mean 6.2%) according to different series. The risk increases with the duration of the tumor, with an incidence of 1.6% for tumors present for less than 5 years, increasing to 9.5% for tumors present for more than 15 years.

Sequential evolution
- Carcinoma in-situ: in the earliest phase, carcinoma cells replace ductal luminal cells while retaining an intact non-atypical neoplastic myoepithelial layer.
- Intracapsular carcinoma: stromal invasion develops upon further progression of the carcinoma, but without violation of the fibrous capsule of the parent pleomorphic adenoma.
- Invasive carcinoma: extracapsular invasion subsequently follows
  - Microinvasive
  - Frankly invasive

Clinical features
- Malignant transformation is heralded by rapid growth after a long period of minimally perceptible increase in size.
- Signs of malignancy also include fixation to surrounding tissues, ulceration, facial nerve palsy and regional lymphadenopathy.
- Age: mean 61 years, about one decade older than pleomorphic adenoma.
- The majority of patients present with stage III/IV disease (65%). Most patients develop recurrence and metastases, and the overall 5-year survival is 30%.

Pathology
- The tumor is usually larger than its benign counterpart.
- Most cases are frankly infiltrative; areas of necrosis or hemorrhage are common.
- Malignant component is characterized by widespread significant cellular pleomorphism, high mitotic count, atypical mitotic figures, coagulative necrosis, and presence of an expansile or infiltrative nodule within the parent adenoma.
- In most cases, the malignant component dominates the tumor.
- Classification of malignant component: most frequently a high grade carcinoma (85% of cases) such as adenocarcinoma NOS or salivary duct carcinoma, but sometimes adenosquamous carcinoma, undifferentiated carcinoma or sarcomatoid carcinoma. Low grade carcinoma such as polymorphous low grade adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, epithelial-myoeipithelial carcinoma and myoepithelial carcinoma can also occur infrequently.
- Transitional zones with morphologic features intermediate between the malignant and benign components may be present.
- The residual pleomorphic adenoma may be difficult to find and often appears hypocellular or markedly hyalinized. The clues of its existence are:
  - Hyalinized or calcified nodule within or directly adjacent to the carcinoma
  - S-100 protein or actin-positive spindle cells in the nodule
  - Thick fluffy elastic fibers (best highlighted by elastic stain)
  - Clinical history of recurrent pleomorphic adenoma or long-standing mass.

CTTR 119th Cancer Seminar
Salivary Gland Tumors
Cell types that undergo malignant change in pleomorphic adenoma

- Pure epithelial (luminal cells) in 75%
- Mixed epithelial-myoepithelial in 19%
- Pure myoepithelial in 6%

Intracapsular carcinoma
Microinvasive carcinoma

Carcinoma in-situ or atypical pleomorphic adenoma

Prognosis

- Most important prognostic factor is the extent of extracapsular invasion.
- Carcinoma in-situ and intracapsular carcinoma have no metastatic potential, with the exception of a single reported case with cervical lymph node metastasis.
- In several large series, excellent prognosis has been found in tumors with extracapsular invasion less than 8 mm, 5 mm, or 1.5 mm beyond the capsule respectively. That is, the optimal cut-off point to define a category of invasive carcinoma ex pleomorphic adenoma with minimal metastatic potential is currently unsettled, but the different findings may reflect difficulties in making reproducible measurements.
- In addition, poor outcome has been found to be associated with (1) high histologic grade of malignant component (5 year survival 30% vs. 96% for low histologic grade), (2) high pathologic stage, (3) carcinomatous component >50%.
Genetic studies
- Alterations or rearrangements of chromosome 8q21 and 12q13-15 are frequent in carcinoma ex pleomorphic adenoma, similar to its benign counterpart.
- Amplification and overexpression of genes in chromosome 12q13-15, including CDK4, HMGIC and MDM2, may represent important genetic events in the malignant transformation.
- c-erbB2 overexpression or gene amplification occurs in from 21% to 82% of cases. It has been suggested that c-erbB2 staining may aid in distinguishing carcinoma ex pleomorphic adenoma from atypical pleomorphic adenoma.
- Alterations of p53 gene are found in 29-67% and p53 protein overexpression in 41% to 75% of cases, suggesting that the gene may play a role in transformation.
- The Ki67 proliferative index is increased (mean 35%) compared with the parent pleomorphic adenoma.

Carcinoma ex pleomorphic adenoma: clues to diagnosis
- Coagulative necrosis
- Extensive hyalinization
- Expansile foci within the parent adenoma
- Significant cellular atypia
- Readily found or bizarre mitotic figures
- Any unusual-looking or difficult-to-classify salivary gland tumor → search for a parent pleomorphic adenoma

Potential pitfall in diagnosis of carcinoma ex pleomorphic adenoma
The possibility of metastatic carcinoma (from other sites) occurring in a pleomorphic adenoma always needs to be considered, if a component of in-situ carcinoma is not identified.

ATYPICAL PLEOMORPHIC ADENOMA
- Acceptable “worrisome features” for pleomorphic adenoma:
  - Protuberances through fibrous capsule
  - Vascular tumor plug
  - Isolated enlarged or pleomorphic nuclei in a background of bland-looking cells
- Rare pleomorphic adenomas may exhibit atypical features such as diffuse mild nuclear atypia and presence of occasional mitotic figures but without coagulative tumor necrosis or formation of an expansile mass. Under such circumstance, the designation “atypical pleomorphic adenoma” may be appropriate.
- A conservative designation is justified (i.e. calling this atypical instead of “carcinoma ex pleomorphic adenoma”) because the prognosis is excellent even if there were already carcinomatous changes, as long as there is no invasion beyond the capsule.

What to do when there are uncertainties about the presence of carcinomatous change in pleomorphic adenoma?
Since carcinoma ex pleomorphic adenoma confined to the parent adenoma (intracapsular form) has no metastatic or recurrence potential if completely excised, it is preferable to err on the benign side if there are atypical/pleomorphic cells within a pleomorphic adenoma short of frank carcinomatous change – giving a diagnostic label of “atypical pleomorphic adenoma”.
DEDIFFERENTIATION OF SALIVARY GLAND CARCINOMAS

Definition

- "Dedifferentiation" refers to the transformation of a salivary gland carcinoma to a high grade carcinoma in which the original line of differentiation is no longer evident.
- A wide variety of salivary gland carcinomas have been reported to show dedifferentiation, although this is an uncommon event:
  - Acinic cell carcinoma
  - Adenoid cystic carcinoma
  - Polymorphous low grade adenocarcinoma
  - Mucoepidermoid carcinoma
  - Epithelial-myoepithelial carcinoma
  - Myoepithelial carcinoma
  - Salivary duct carcinoma
- Almost all of these (with the exception of salivary duct carcinoma) are indolent tumors. New genetic alterations may accumulate, eventuating in development of high-grade carcinoma.

Clinical features

- Dedifferentiation can occur either:
  - at initial presentation
  - at relapse
- Commonly there is recent onset of rapid tumor growth in a long-standing tumor, resulting in bulky disease
- Recurrence and metastasis are common
- Very poor prognosis (accelerated clinical course compared with original carcinoma type)

Common pathologic features

- More frankly invasive growth
- Coagulative necrosis
- Significant nuclear atypia and pleomorphism
- Increased mitotic activity
- Common histologic types:
  - Poorly differentiated adenocarcinoma
  - Undifferentiated carcinoma (which can be sarcomatoid)
- Aneuploidy

Genetic changes that mediate dedifferentiation

- No consistent genetic changes
- Single or multiple genes may be involved
  - P53 mutation (with strong p53 expression) [so far not demonstrated in dedifferentiated acinic cell carcinoma]
  - Increased cyclin D1 expression
  - c-erbB2 protein overexpression / gene amplification
  - Loss of expression of Rb
CASE 16
Clinical features
- A 42-year-old male underwent a right superficial parotidectomy because of presence of a parotid mass.
- The cut surface of the parotid gland revealed a 3.5 x 3.5 x 3 cm mass that was tan to pale yellow.

Salient histologic features
- Acinic cell carcinoma with a microcystic/solid growth pattern, invading in broad fronts. The cells have amphophilic cytoplasm and only mildly atypical oval nuclei. Occasional cells are heavily granulated.
- Another more frankly invasive carcinoma component with more atypical cells – larger nuclei with vesicular appearance and readily identified mitotic figures.

Diagnostic considerations
There is an obvious component of acinic cell carcinoma, growing in the form of smooth-contoured islands with interspersed microcystic spaces. There is another obviously high-grade carcinoma component growing in the form of more jagged islands and showing necrosis. Thus the diagnostic criteria for dedifferentiated acinic cell carcinoma are met. Of interest, some tumor foci show intermediate features between acinic cell carcinoma and high-grade carcinoma.

Immunophenotype
- Acinic cell carcinoma component: c-erbB2+ (weak); p53-; Ki67 index 10%; surprisingly some islands are surrounded by p63+ myoepithelial/basal cells, suggesting a partial in-situ growth phase
- High grade carcinoma component: c-erbB2+ (weak); p53-; Ki67 index 50%; no p63+ myoepithelium around the tumor islands

Diagnosis
Parotid gland – Dedifferentiated acinic cell carcinoma

DEDIFFERENTIATED ACINIC CELL CARCINOMA
- Dedifferentiation of acinic cell carcinoma to a high grade adenocarcinoma, poorly differentiated carcinoma or undifferentiated carcinoma can rarely occur at presentation or in the recurrent tumor.
- Usually the two components are juxtaposed to each other without transition.
- Dedifferentiated acinic cell carcinoma is associated with rapid tumor growth, significant pain, facial nerve palsy, bulky tumor and an extremely poor prognosis.

CTTR 119th Cancer Seminar Salivary Gland Tumors
CASE 17
Clinical features
- A 75-year-old female presented with a rapidly growing right submandibular mass.
- The right submandibular gland was excised, and right radical neck dissection was performed.
- The specimen revealed a firm, well-delineated tumor measuring 2.8 x 2.0 x 1.3 cm, and an adjacent nodule measuring 2.0 x 1.7 x 1.5 cm.

Salient histologic features
- An infiltrative tumor
- Large islands and sheets of large tumor cells with marked nuclear atypia, mitotic activity and central necrosis.
- There is also a component of adenoid cystic carcinoma with a predominantly tubular growth pattern; some cribriform structures are also present.

Diagnostic considerations
The component of high-grade carcinoma is obvious. If one is not careful, one may miss the intermingled, less conspicuous component of adenoid cystic carcinoma (with predominance of tubular growth pattern). With combination of the two components, the diagnosis should be dedifferentiated adenoid cystic carcinoma.

Immunophenotype (not required for diagnosis in this case)
- Adenoid cystic carcinoma: p63 highlights the abundant “regimented” myoepithelial/basal cells. c-erbB2 and p53 are negative. Ki67 index 4%.
- High grade carcinoma: p63 highlights residual (neoplastic) myoepithelial/basal cells around some islands, indicating that the transformed cells represent luminal cells. c-erbB2 strong positive, and p53 negative. Ki67 index 40%.

Diagnosis
Submandibular gland – Dedifferentiated adenoid cystic carcinoma

DEDIFFERENTIATED ADENOID CYSTIC CARCINOMA
- Dedifferentiation of adenoid cystic carcinoma is associated with bulky disease, frequent local recurrence and metastasis, and rapidly fatal outcome.
- It can occur ab initio or in recurrent tumors.
- The dedifferentiated component is usually represented by poorly differentiated adenocarcinoma, sarcomatoid carcinoma or undifferentiated carcinoma.
- p53 gene mutation, Her2/neu overexpression, cyclin D1 overexpression and loss of Rb expression have been variably demonstrated in the dedifferentiated component in contrast to the parent adenoid cystic carcinoma.
LYMPHOID LESIONS OF SALIVARY GLAND (Cases 18-19)

Lymphoid proliferations in salivary gland
- Lymphoepithelial sialadenitis
- Chronic sialadenitis, nonspecific
- Chronic sclerosing sialadenitis (Kuttner tumor)
- Cystic lymphoid hyperplasia (Lymphoepithelial cyst in HIV+ subjects)
- Malignant lymphoma
- Leukemic infiltration

APPROACH TO DIAGNOSIS OF LYMPHOID LESIONS IN SALIVARY GLAND (BENIGN OR MALIGNANT LYMPHOID INFILTRATE?)
- Heavy lymphoid infiltrates in the salivary gland can pose difficulties in interpretation, particularly in regards to their benign or malignant nature.
- In benign infiltrates, the normal lobular septa of the salivary gland are often preserved. In malignant infiltrates, the lobular septa are often obliterated or infiltrated by the lymphoid cells.
- In cystic lymphoid hyperplasia, the lymphoid proliferation corresponds to that seen in early HIV infection, i.e. explosive follicular hyperplasia, thin or absent mantles, and follicle lysis.
- In either reactive or malignant lymphoid proliferation, the epithelial units of the salivary gland are not uncommonly infiltrated by lymphoid cells, forming lymphoepithelial lesions, although they are very rare in Kuttner tumor.
- Absence of basement membrane droplets within the lymphoepithelial units renders a diagnosis of lymphoepithelial sialadenitis unlikely. On the other hand, presence of basement membrane droplets in the epithelial units can be seen in lymphoepithelial sialadenitis or MALT lymphoma supervening on lymphoepithelial sialadenitis.
- Note that the possibility of Kuttner tumor has to be considered only for submandibular lymphoid lesions.

Features favoring a diagnosis of MALT lymphoma over reactive lymphoid hyperplasia or sialadenitis

<table>
<thead>
<tr>
<th>Morphologic features</th>
<th>Immunohistochemical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of collars of clear cells (monocytoid B cell-like) around the epithelial islands is considered the earliest evidence of a supervening lymphoma</td>
<td>Demonstration of diffuse dense sheets of B cells, with few intermingled T cells</td>
</tr>
<tr>
<td>&quot;Cavitation&quot; of epithelial islands by large clusters of lymphoid cells</td>
<td>Aberrant immunophenotype of B cells e.g., co-expression of CD43</td>
</tr>
<tr>
<td>Infiltrative growth, with infiltration of the lobular fibrous septa or nerves</td>
<td>Demonstration of light chain restriction</td>
</tr>
<tr>
<td>Many atypical plasma cells, if present</td>
<td></td>
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</tbody>
</table>

CTTR 119th Cancer Seminar
Salivary Gland Tumors
CASE 18
Clinical features
- 70-year-old man
- Presented with left submandibular swelling.
- Examination revealed an enlarged, firm but mobile left submandibular gland.
- The left submandibular gland was excised. The cut surfaces revealed vaguely preserved lobular architecture, and the tissue was rubbery to firm and tan-colored.

Salient histologic features
- Lobular architecture of salivary gland preserved, and in fact lobules are accentuated as a result of sclerosis of the lobular septa
- The salivary lobules show atrophy of the acini; some small ducts remain, and are intermingled with numerous small lymphocytes and plasma cells
- Reactive lymphoid follicles also present
- Some small ducts contain inspissated secretion, or show concentric fibrosis
- Lymphoepithelial lesions are not seen

Diagnostic considerations
The histologic features of this case are prototypic for Kuttner tumor.

Immunophenotype (not required for diagnosis of this case)
- CD20: nodular aggregates of B cells
- CD3: some admixed T cells
- Immunoglobulin: no light chain restriction
- IgG4: many plasma cells positive

Diagnosis
Submandibular gland – Chronic sclerosing sialadenitis (Kuttner tumor)

CHRONIC SCLEROSING SIALADENITIS (KUTTNER TUMOR)
Clinical features
- A chronic inflammatory disease believed to result from inspissated secretion, stones or microliths, and perpetuated by ascending infection.
- The recent demonstration of abundant IgG4-positive plasma cells in the lesion raises a possible relationship with the IgG4-associated sclerosing lymphoplasmacytic pancreatitis/cholangitis syndrome.
- Affects almost exclusively the submandibular gland, and is called Kuttner tumor in its advanced stage as it presents clinically as a hard swelling indistinguishable from a tumor.
- The disease can be bilateral
- Mean age is 42-44 years, with slight male predominance.
Pathology

- The histologic features vary according to stage of evolution and severity of the inflammation.
- The lobular architecture is preserved and the degree of involvement varies from lobule to lobule.
- In the early stages, lymphoplasmacytic infiltrate commences around the salivary ducts, followed by periductal fibrosis. Focal squamous and mucous metaplasia and proliferation of the duct epithelium follow, but lymphoepithelial lesions are absent or rare. The ducts may contain inspissated secretion.
- The lymphocytic infiltrate and fibrosis intensify and gradually involves the whole lobule associated with atrophy of the acini. Reactive lymphoid follicles are frequently present.
- In the advanced stage, there is marked fibrosis and loss of parenchyma, resembling liver cirrhosis.
- On immunostaining, T cells predominate and they show an intimate relationship with ducts and acini. B cells are mostly restricted to the lymphoid follicles.
- Kuttner tumor is under-recognized and not uncommonly misdiagnosed as lymphoepithelial sialadenitis; it can be distinguished from the latter by the scarcity or lack of lymphoepithelial lesions and its usually more prominent sclerosis.
- On the other hand, sclerosing follicular lymphoma mimicking Kuttner tumor and, rarely, MALT lymphoma complicating Kuttner tumor have been reported.

Kuttner tumor is still an underrecognized entity. It is not uncommonly misdiagnosed as lymphoepithelial sialadenitis (myoepithelial sialadenitis).

CASE 19
Clinical features

- A 24-year-old male presented with swelling behind the right ear, which had been slowly enlarging over two years.
- Examination revealed a 4.6 cm swelling in the tail of the right parotid.
- During surgery, most of the right parotid gland was found to be replaced by the lesion.
- The specimen was ovoid and measured 6.0 x 4.5 x 2.5 cm, and the cut surface showed that most of the parotid gland was replaced by yellowish-white tissue with interspersed cystic areas.

Salient histologic features

- Dense infiltrate of small lymphoid cells, traversed by rare delicate fibrous septa
- Acini are lost
- There are many lymphoepithelial lesions surrounded by collars of clear cells (resembling monocytoid B cells); basement membrane-like droplets are present within these epithelial units
- Background cells include small lymphoid cells, plasma cells, lymphoplasmacytoid cells; reactive lymphoid follicles are interspersed
- In some slides, the ducts show cystic dilatation, and the lining glandular cells are extensively infiltrated by the lymphoid cells
Diagnostic considerations
The massive lymphoid infiltrate and presence of pale collars of lymphoid cells around the lymphoepithelial lesions support a diagnosis of MALT lymphoma.

Immunophenotype
- Dense sheets of CD20+ B cells (including many that infiltrate into the epithelial units)
- Not many admixed CD3+ T cells
- Immunoglobulin: some plasma cells are positive (polytypic), but most cells are negative
- CD5: negative
- CD21: meshworks of follicular dendritic cells highlighted in the reactive follicles

Diagnosis
Parotid gland – Extranodal marginal zone B-cell lymphoma of MALT

LYMPHOEPITHELIAL SIALADENITIS (LESA)
Definition
- Previously known as myoepithelial sialadenitis or benign lymphoepithelial lesion
- Characterized by lymphoid infiltration in the salivary gland parenchyma, atrophy of acini, and ductal proliferation with formation of lymphoepithelial lesion (formerly called epimyoepithelial islands).
- The term “myoepithelial sialadenitis” is misleading because there is no good evidence of myoepithelial participation in the characteristic lymphoepithelial lesions.

Clinical features
- LESA mainly affects the parotid (80-85%) and submandibular glands (10-15%)
- Presentation: recurrent, diffuse, firm swelling. Pain in 40%. Bilateral disease in 20%.
- A high proportion of affected patients (50-84%) manifest clinical and laboratory evidence of Sjogren syndrome.
- Female predominance (M:F = 1:3)
- Peak age: 4th to 7th decades.
- LESA is a risk factor for the development of salivary gland lymphoma, especially when associated with Sjogren syndrome or other related connective tissue diseases such as rheumatoid arthritis. The increased risk is estimated to be 44-fold, and 80% of the lymphomas are of extranodal marginal zone B-cell (MALT) type.
- The incidence of lymphoma in LESA has been reported from 20-28%.
- Because of the increased risk for lymphoma and difficulties in ruling out presence of lymphoma in small biopsies or fine needle aspirates, parotidectomy appears to be the treatment of choice.
- Long-term follow-up for the associated autoimmune conditions as well as for development of lymphoproliferative disease is still required after operation.

Pathology
- Discrete or ill-defined borders, but the lobular architecture of the salivary gland is preserved.
- The lymphoid infiltrate apparently begins in the periductal areas and gradually replaces the lobules. It comprises small lymphocytes and plasma cells with or without germinal center formation.
• Marked atrophy or loss of acinar tissue, but proliferation of the residual ductal epithelium and insinuation of lymphocytes into the epithelium result in the characteristic lymphoepithelial lesions (epimyoepithelial islands).
• Lymphoepithelial lesions comprise round to irregular solid islands of cells, which may be punctuated by small residual ductal lumens. The epithelial cells are plump spindly, polygonal to syncytial, and have uniform oval nuclei with fine chromatin, reminiscent of intraductal epithelial hyperplasia of the breast. Hyaline basement membrane-like material is often seen among the cells.
• Rarely, squamous metaplasia and keratinization can occur.
• On immunostaining, the epithelial cells in the lymphoepithelial lesions are immunoreactive for cytokeratin.
• The lymphoid cells in the lymphoepithelial lesions are mostly B cells. The lymphoid cells in between represent a mixture of B and T cells, with the former outnumbering the latter.

### PRIMARY LYMPHOMA OF SALIVARY GLAND

- Primary lymphomas of the salivary gland are rare, accounting for only 2.4 to 4.5% of salivary gland tumors, with most cases occurring in the parotid (50-93%) and submandibular glands.
- To qualify for primary salivary gland lymphoma, the main bulk of the disease should be located in the salivary gland.
- However, it is often difficult to distinguish between lymphoma arising in the salivary gland proper (primary salivary gland lymphoma) and those in the lymph nodes embedded in the salivary gland (conventional nodal lymphoma) on clinical or histologic grounds. The latter lymphoma types show no difference in morphology and prognosis from those arising in other lymph nodes. The commonest types are Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma, but any nodal lymphoma type can occur.
- MALT lymphoma is the commonest primary salivary gland lymphoma, followed by diffuse large B-cell lymphoma and follicular lymphoma.
- Rarely, peripheral T-cell lymphoma, anaplastic large cell lymphoma and NK/T cell lymphoma can occur as primary salivary gland lymphomas, and they often pursue an aggressive course.

**MALT lymphoma (extranodal marginal zone B cell lymphoma of MALT type)**

### Clinical features
- The best known predisposing factors for MALT lymphoma of the salivary gland is LESA or Sjogren syndrome and hepatitis C infection.
- Median age: 61 years (range 55-65 years)
- Sex: female predominance
- Presentation: a slow-growing mass in the salivary gland. Cervical lymph node involvement is found in almost 30%.
- A serum monoclonal component (IgG or IgM) is detected in 25%
- Overall prognosis is excellent with a 5-year survival of 85-90%.
- Local therapy, such as surgery or radiotherapy, appears to be adequate.
- Poor prognostic factors include transformation to diffuse large B cell lymphoma (incidence 12%) and advanced age.
Pathology
- Grossly, the tumor is non-circumscribed, firm, and tan-colored.
- Interspersed cysts formed by dilatation of the ducts are a common finding.
- The histologic features are similar to MALT lymphomas occurring elsewhere, often featuring a mixture of cell types (commonly including clear cells reminiscent of monocytoid B cell), reactive lymphoid follicles, and many lymphoepithelial lesions.
- The involvement of the salivary gland can be extensive and destructive, or can still be accompanied by preserved lobular architecture.
- Lymphoepithelial lesions are ducts markedly expanded and distorted by neoplastic lymphoid cells, which may produce "abscesses" in the proliferated epithelium.
- The lymphoid cells within and around the ducts are typically larger than the rest of the tumor cells, with oval to indented nuclei and abundant pale-staining to clear cytoplasm, resembling monocytoid B cells.
- Commonly, there are variable numbers of plasma cells, which usually occur in clusters; they may show mild atypia, and may contain Dutcher bodies.
- Isolated interspersed large lymphoid cells with round nuclei and distinct nucleoli are commonly present.
- In occasional cases, wreaths of epithelioid histiocytes surround the lymphoepithelial lesions.

Immunohistochemistry
- Dense sheets of B cells (CD20+)
- Light chain restriction can often be demonstrated.
- CD5, CD10 and cyclin D1 are negative.
- May show aberrant coexpression of CD43.

Genetic features
- Translocation t(14;18) with IGH/MALT fusion and trisomies 3 and 18 have been demonstrated in a proportion of cases, whereas t(11;18), the translocation most frequently found in MALT lymphoma of the stomach and lung, is very rare.

Diffuse large B-cell lymphoma arising in MALT lymphoma
- MALT lymphoma can transform to a diffuse large B-cell lymphoma, when the behavior becomes more aggressive.
- However, there is no universally accepted minimum criterion on how to define large cell transformation.
- A supervening large B-cell lymphoma can certainly be diagnosed when there are dense sheets or large clusters of large cells.
- The greatest problem is when there is an increase in large cells, which are still intimately intermingled with the small cells. In such circumstance, a designation such as "MALT lymphoma with increased large cells" is justified. There is recent evidence that presence of large cells in more than 5% already confers a slightly worse outcome compared with conventional MALT lymphoma.
SMALL CELL TUMORS OF HEAD AND NECK (Cases 20-21)

CASE 20
Clinical features
• A 72-year-old male presented with a mass in the right upper neck.
• Examination confirmed the mass to be located in the submandibular gland.
• The excised submandibular gland contained a circumscribed, firm, tan-colored nodule measuring 2.0 cm.

Salient histologic features
• A highly infiltrative neoplasm in the submandibular gland
• Diffuse sheets and irregular islands of small cells, traversed by delicate fibrovascular septa
• The small tumor cells have round nuclei, finely stippled chromatin, and scanty cytoplasm; numerous apoptotic bodies
• Stroma shows chronic inflammatory cell infiltration

Diagnostic considerations
This is a small cell malignancy traversed by delicate fibrovasculature, thus neuroendocrine tumor would be an important consideration.

Immunophenotype
• Cytokeratin +
• Cytokeratin 20 +
• Synaptophysin +
• Chromogranin +
• TTF-1 -
• CD117 -

Diagnosis
Submandibular gland – Small cell carcinoma, Merkel cell type (Merkel cell carcinoma)

SMALL CELL CARCINOMA OF SALIVARY GLAND
Definition
A malignant tumor characterized by small epithelial cells (<30μm) with scant cytoplasm, fine chromatin, and inconspicuous nucleoli.

Classification
(1) Neuroendocrine type
   a) Merkel cell subtype
   b) pulmonary subtype
(2) Ductal type (very rare)
Clinical features
- Most frequently occurs in the parotid gland.
- Age: 5th to 7th decades (mean 54-56 years)
- Sex: male predilection
- Presentation: fast-growing mass with or without concomitant cervical lymphadenopathy. Facial nerve palsy is noted in 60%. Pain is only occasionally present.

Clinical behavior
- An aggressive malignancy
- Local recurrence and distant metastasis have been reported in more than 50% of patients at 2-26 months after diagnosis.
- Overall survival 40-50%. This figure is comparable to that of Merkel cell carcinoma of the skin, and much superior to that of small cell carcinoma of the lung or other extrapulmonary sites.
- A better prognosis has been found to be associated with Merkel cell subtype, small tumor size (<3-4 cm) and expression of more neuroendocrine markers.

Pathology
- A widely infiltrative tumor growing in a diffuse or cord-like pattern, often traversed by delicate fibrovascular septa
- Tumor cells are slightly larger than lymphocytes, with finely stippled chromatin and inconspicuous nucleoli.
- The nuclei are susceptible to crushing artifact resulting in deformation and clumping of nuclei as well as diffusion of chromatin material.
- Necrosis is common
- Vascular and perineural invasion are common.
- In the Merkel cell subtype, the nuclei tend to be round, non-molded, resembling blown-up balloons, with pale and “washed-out” chromatin.
- In the pulmonary subtype, tumor cells are often short spindly with nuclear molding; there can be pseudorosette formation
- However, the morphologic features of these two subtypes overlap and the distinction may not be made with certainty on histologic examination alone.
- Isolated ductal differentiation and squamous differentiation with keratinization have been described in rare cases, and these tumors are termed ductal-type small cell carcinoma

Immunohistochemistry
- According to a recent large series, 73% of small cell carcinomas of the salivary gland express cytokeratin 20 (Merkel cell subtype); these cases demonstrate a longer overall survival than the CK20-negative group (pulmonary subtype).
- Both subtypes express neuroendocrine markers such as chromogranin, synaptophysin and CD56.
- The Merkel cell subtype expresses neurofilament, but not thyroid transcription factor-1.
- Some cases may also express CD117 or CD99.

Differential diagnosis
- Lymphoma – Lymphoma cells grow in a more permeative manner, usually with persistence of residual glandular structures even in areas of extensive involvement. This is in contrast to the extensive destruction and frequently total replacement of glandular structures in small cell carcinoma. Lymphoma cells often possess more irregularly folded nuclei and denser chromatin, and they do not form
anastomosing cords or nests. Definitive distinction between the two tumors can be achieved by immunostaining (such as leukocyte common antigen and cytokeratin).

- Solid-type adenoid cystic carcinoma – Cribriform structures can often be found after careful search. Some tumor cells are positive for S-100 protein, actin and calponin, and focal ductal structures show immunoreactivity for CEA and EMA. Small cell carcinoma is negative for these markers except EMA.
- Metastatic small cell carcinoma or cutaneous Merkel cell carcinoma – Clinical history, examination and clinical work-up are essential for this distinction.

Most small cell carcinomas of the salivary gland are Merkel cell carcinomas, characterized by immunoreactivity for cytokeratin 20. The prognosis is better than conventional extrapulmonary small cell carcinomas.

### Small cell malignancies in mucosal sites of head and neck

- Malignant lymphoma or leukemia
- Olfactory neuroblastoma
- Alveolar rhabdomyosarcoma
- Small cell neuroendocrine carcinoma
- Malignant melanoma (small cell variant)
- Primitive neuroectodermal tumor/Ewing sarcoma

### APPROACH TO DIAGNOSIS OF SMALL CELL MALIGNANCIES IN MUCOSAL SITES OF HEAD AND NECK

- Malignant tumors comprising small cells are difficult to classify based on morphologic assessment alone. Immunohistochemical evaluation is almost always required.
- Tumors showing highly permeative growth, irregular nuclear foldings and angiocentricity should be strongly suspected to represent lymphoma.
- Alveolar rhabdomyosarcoma is an under-diagnosed entity in mucosal sites. It is commonly misdiagnosed as small cell carcinoma, in particular since cytokeratin is not uncommonly positive. The tumor occurs mostly in young adults. The alveolar packeting and cellular dehiscence typical of alveolar rhabdomyosarcoma may not be evident. Look for occasional tumor cells that have a greater amount of eosinophilic cytoplasm (rhabdomyoblasts). Diagnosis can be readily confirmed by immunostaining for desmin and myogenin, if this possibility is taken into consideration.
- Malignant melanoma, being a great histologic mimicker, obviously needs to be considered as well.
- If there are prominent interspersed delicate blood vessels or fibrovascular septa, and/or focal fibrillary matrix, the main differential diagnoses would be:
  - Olfactory neuroblastoma
  - PNET/Ewing sarcoma
  - Small cell neuroendocrine carcinoma
- In most circumstances, olfactory neuroblastoma can be readily diagnosed from the highly characteristic histologic features:
  - Smooth-contoured islands of small tumor cells
  - Loose stroma with prominent "glomeruloid" blood vessels
  - Tumor cells have round nuclei and stippled chromatin
  - Occasionally, there is admixed fibrillary matrix or immature ganglion cell differentiation
Small cell neuroendocrine carcinoma often grows in the form of sheets, islands and trabeculae rather than nests. Nuclear molding is common.

**CASE 21**

**Clinical features**
- 72-year-old female
- Presented with left epistaxis
- Examination revealed a mass in the left nasal cavity. The lesion was removed in piecemeal.

**Salient histologic features**
- Variable-sized nests of small cells separated by a richly vascularized stroma (with almost glomeruloid blood vessels)
- Small cells have fairly uniform oval nuclei, stippled chromatin, and indistinct cell borders. Apoptotic bodies prominent.
- Fibrillary matrix present in some foci, accompanied by a lower cellularity and presence of some cells resembling immature ganglion cells
- Some islands merge into clear cells that sometimes form glandular structures. In areas, there are pure glandular structures with or without clear cells.

**Diagnostic considerations**
This tumor comprises discrete islands of small cells; the accompanying fibrillary matrix and richly vascularized stroma support a diagnosis of neural/neuroendocrine neoplasm. In specific, features are highly characteristic of olfactory neuroblastoma. The interesting feature is presence of many glandular structures – with some located within the cell islands and others occurring as pure glandular units. The question is: are these true glandular (epithelial) structures or are these some sort of neuroepithelial rosettes? Some glands contain mucin in the lumen and may suggest true epithelial differentiation. But then they do exhibit a rosette-like quality.

**Immunophenotype**
- Primitive small cells: cytokeratin 5% cells positive in dendritic pattern; synaptophysin 20% cells positive; S100+ sustentacular cells around some islands; Ki67 index high; E-cadherin positive (slightly weaker than other cells)
- Cells in vicinity of fibrillary matrix: cytokeratin -; synaptophysin + (strong); no S100+ sustentacular cells; Ki67 index low; E-cadherin negative
- Glandular units: cytokeratin + (strong); synaptophysin -; no S100+ sustentacular cells; Ki67 index low; E-cadherin + (strong)

**Diagnosis**
Nasal cavity – Olfactory neuroblastoma, with glandular component
(Immunohistochemical results suggest that the glandular units exhibit genuine epithelial differentiation rather than neuroepithelial rosette formation. Perhaps this indicates presence of divergent differentiation, which is not too surprising given the close interaction of the normal olfactory nerves with the olfactory glandular epithelium.)
Comments
Most cases of olfactory neuroblastoma do not show glandular differentiation like the current case. The prominent glandular differentiation can lead to a misdiagnosis of adenocarcinoma from a biopsy specimen.

OLFACTORY NEUROBLASTOMA
Definition
- A malignant neuroectodermal tumor believed to be derived from the olfactory membrane of the sinonasal tract.
- Also known as “esthesioneuroblastoma”

Clinical features
- Age: Two age peaks (one in 2nd – 3rd decade; another in 6th decade)
- Sex: No sex predilection
- Presentation: Nasal obstruction, epistaxis, symptoms of local invasion (facial swelling, proptosis, pain, rhinorrhoea)
- Rare cases may present with frontal lobe tumor
- Typical site of disease: Upper part of nasal cavity in the region of the cribriform plate

Clinical behavior
- Slow-growing tumor
- Locally invasive, with involvement of the paranasal sinuses, palate, orbit, base of skull. There is a tendency to invade through the cribriform plate into the cranial cavity.
- Metastasis occurs in about 20-30%, especially to lymph nodes, lungs and bones
- 5-year and 10-year survival rates 78% and 71% respectively.
- Complete surgical excision (craniofacial resection including removal of cribriform plate) followed by radiotherapy is the treatment of choice

Pathology
- Discrete, smooth-contoured tumor nests comprising small cells with uniform round nuclei, stippled chromatin and ill-defined cytoplasmic borders. Some cells may be larger, resembling immature ganglion cells. Some cases may show a greater degree of nuclear pleomorphism and mitotic activity.
- Fibrillary matrix may be present.
- Some cases may have Homer-Wright rosettes or true Flexner rosettes
- Richly vascularized “angiomatoid” stroma
- Calcification may occur
- Sometimes, there is hyperplasia of the overlying olfactory epithelium
- Rare findings:
  - Melanin pigmentation
  - Focal glandular differentiation
  - Focal squamous differentiation
  - Rhabdomyoblastic differentiation
Grading (Hyams)

- Grade 1 – Well differentiated, with lobular architecture and uniform nuclei, accompanied by prominent neurofibrillary matrix
- Grade 2 – Similar to Grade 1, but neurofibrillary matrix is less prominent
- Grade 3 – More nuclear atypia; neurofibrillary matrix often scanty; necrosis
- Grade 4 – Poorly differentiated (overlapping morphologically with small cell carcinoma), with significant nuclear anaplasia; no neurofibrillary matrix; necrosis

Immunophenotype

- Synaptophysin, chromogranin +
- Cytokeratin: more often negative, but focal positive or even sometimes extensive positive staining can occur
- CD99 negative
- S100+ sustentacular cells around tumor islands
LYMPHOEPITHELIAL TUMORS OF HEAD & NECK (Cases 22-23)

Lymphoepithelial tumors of head and neck
- Lymphoepithelial carcinoma
- Lymphadenoma
- Sebaceous lymphadenoma and lymphadenocarcinoma
- Ectopic thymoma
- Lymphoepithelial sialadenitis
- Lymphoepithelial cyst

APPROACH TO DIAGNOSIS OF LYMPHOEPITHELIAL TUMORS OF HEAD AND NECK
- Sebaceous lymphadenoma/lymphadenocarcinoma should be easy to diagnose because of the characteristic sebaceous cells
- The presence of jigsaw puzzle-like lobulation would strongly suggest a diagnosis of ectopic thymoma. The diagnosis can be readily confirmed by immunostaining: the dendritic-appearing epithelial cells are highlighted by cytokeratin stain, and immature lymphocytes by TdT stain.
- In lymphoepithelial carcinoma and lymphadenoma, the epithelial component is obviously the proliferative component; while in lymphoepithelial sialadenitis, the lymphoid component is more striking.

CASE 22
Clinical history
- F/47
- Presented with a lump over the angle of the left jaw, noticed for approximately one year
- Examination revealed a mass in the left submandibular gland
- The excised gland showed a partly circumscribed, whitish, firm mass measuring 1.5 cm in maximum dimension

Salient histologic features
- Infiltrative neoplasm traversed by sclerotic septa
- Heavy infiltration of small cells, with many interspersed reactive lymphoid follicles
- Scattered in the lymphoid stroma are irregular islands of tumor cells with indistinct cell borders, vesicular nuclei and prominent nucleoli
- Some lymphoid cells also infiltrate into the tumor islands

Diagnostic considerations
Prototypic case of lymphoepithelial carcinoma.

Immunophenotype and genotype (not required for diagnosis of this case)
- Cytokeratin +
- Lymphoid cells: more B cells than T cells (also more B than T cells within the islands of carcinoma)
- In-situ hybridization for EBER (EBV early RNA) +
**Diagnosis**  
Submandibular gland – Lymphoepithelial carcinoma, EBV+

**Comment**  
This patient is an Asian, and thus the association with EBV is expected.

**LYMPHOEPITHELIAL CARCINOMA OF SALIVARY GLAND**  
**Clinical features**
- Lymphoepithelial carcinoma, previously known as malignant lymphoepithelial lesion or lymphoepithelioma-like carcinoma, is a rare carcinoma with a much higher prevalence among Eskimos and Southern Chinese than Caucasians.
- The tumor is almost invariably associated with EBV in Eskimos, Chinese and Japanese. In contrast, EBV is often but not invariably absent in Caucasians.
- Age: Usually adults with a mean age of 44.5 years
- Sex: No definite or slight female predominance.
- Most frequently arises from the parotid and submandibular glands as an asymptomatic swelling with or without pain; minor salivary glands can also be affected.
- No association with Sjogren syndrome.
- Facial nerve palsy is uncommon, but fixation to underlying tissue or skin occurs in advanced cases.
- Regional lymph node metastasis is seen in approximately 40% of patients at presentation.
- Local recurrence and distant metastasis can occur during the course of disease.
- Lymphoepithelial carcinoma has the best prognosis among the undifferentiated carcinomas. Although previous studies have reported poor outcome (survival as low as 17%), more recent series with patients treated by combined surgery and radiotherapy report survival figures of 75-86%.

**Relationship with lymphoepithelial sialadenitis (benign lymphoepithelial lesion)**
- In the past, lymphoepithelial carcinoma was thought to originate through malignant transformation of lymphoepithelial sialadenitis.
- This contention is now rejected by most investigators.
- Previous reports of benign lymphoepithelial lesion adjacent to lymphoepithelial carcinoma probably represent reactive changes in the residual salivary parenchyma or misinterpretation of the less pleomorphic tumor islands with interspersed amyloid globules as lymphoepithelial lesions (epimyoepithelial islands).

**Pathology**
- Morphologically identical to lymphoepithelial carcinoma occurring elsewhere in the body, especially undifferentiated carcinoma of the nasopharynx.
- The infiltrative tumor grows in diffuse sheets, anastomosing islands, nests or cords, separated by a variable desmoplastic stroma.
- The tumor cells are typically large with lightly eosinophilic cytoplasm and indistinct cell borders. They possess vesicular nuclei and prominent nucleoli.
- In some cases, the nuclei are smaller and nucleoli are inconspicuous, making recognition of the malignant nature of the lesion difficult.
- Focal squamous differentiation can occur.
The tumor cells can sometimes be spindly.
Amyloid globules can occur among the tumor cells.
Tumor necrosis and mitotic figures are usually evident.
The tumor is characteristically densely infiltrated by lymphocytes and plasma cells, sometimes with lymphoid follicle formation. Histiocytes sometimes infiltrate the tumor islands, producing a starry-sky appearance. Non-caseating granulomas with or without multinucleated giant cells are found in some cases.
Perineural or lymphovascular invasion can be present.

Immunohistochemistry and special studies
- Cytokeratin +
- EMA +
- Generally exhibit squamous features on ultrastructural examination, such as desmosomes and tonofilaments.
- In-situ hybridization for EBV is positive in all cases of Eskimo, Southeastern Chinese and Japanese origin, and only rarely in other ethnic groups.

Differential diagnosis
- Metastatic nasopharyngeal carcinoma -- Lymphoepithelial carcinoma is histologically, immunohistochemically and ultrastructurally indistinguishable from nasopharyngeal undifferentiated carcinoma. Since nasopharyngeal carcinoma is by far commoner, clinical examination as well as endoscopic examination with biopsies should be undertaken to exclude this possibility before a diagnosis of lymphoepithelial carcinoma of salivary gland is made.
- Large cell undifferentiated carcinoma (which has a worse prognosis)
- Lymphoepithelial sialadenitis -- The neoplastic islands seen in lymphoepithelial carcinoma differ significantly from the lymphoepithelial lesion of lymphoepithelial sialadenitis; the latter lack epithelial atypia and often accompanied by basement membrane-like material. In-situ hybridization for EBV-encoded RNAs (EBER) is consistently negative in the epithelial islands in lymphoepithelial sialadenitis except for a few scattered lymphocytes, whereas EBV is commonly positive in the epithelial cells in lymphoepithelial carcinoma.

LYMPHOEPITHELIAL CARCINOMA OF MISCELLANEOUS MUCOSAL SITES IN HEAD AND NECK

Nasopharynx
- The nasopharynx is the prototype site for the occurrence of lymphoepithelial carcinoma (see below)

Nasal cavity and paranasal sinuses
- Sinosal lymphoepithelial carcinoma is rare, and most reported cases have originated from Southeast Asia, where nasopharyngeal carcinoma is also prevalent. More common in nasal cavity than paranasal sinuses.
- Age: adults in the 5th to 7th decades
- Sex: male predominance of approximately 3 to 1.
- Nearly all sinonasal lymphoepithelial carcinomas show a strong association with EBV
- Presentation: nasal obstruction, bloody nasal discharge or epistaxis. Intracranial extension may cause proptosis and cranial nerve palsy. There may be regional cervical lymph node and/or distant metastasis at presentation.
• Careful examination and biopsy of the nasopharynx is required to exclude local-regional spread from a primary nasopharyngeal carcinoma.

• Sinonasal lymphoepithelial carcinoma must be distinguished from the vastly more aggressive sinonasal undifferentiated carcinoma (SNUC). SNUC is characterized by tumor cells with discrete cell borders, pleomorphic and smaller nuclei, coarse chromatin, frequent mitoses and frequent necrosis. EBV status is also helpful since SNUC, except for rare cases from Asians, are EBV-negative.

• Responds favorably to local-regional radiotherapy even in the presence of cervical lymph node metastasis. Distant metastasis (most often to bone), however, is associated with a poor prognosis.

Oral cavity

• Lymphoepithelial carcinoma accounts for only 0.8% to 2% of all oral or oropharyngeal cancers.

• Sex: male predominance of approximately 1.5 to 1

• Age: 16 to 80 years, with a mean of 55 years

• Tumors occurring in Chinese are usually positive for EBV, while those occurring in Caucasians are usually negative. The racial difference in the association with EBV is similar to lymphoepithelial carcinoma occurring in the major salivary glands.

• More than 90% of cases occur in the tonsil and tongue base areas. The remaining cases are found in the palate and buccal mucosa. It is plausible that at least a proportion intra-oral LEC have originated from minor salivary glands.

• Presentation: intra-oral mass, which may be ulcerated. Some tumors can be bilateral. A proportion of patients present with neck mass due to regional lymph node involvement (cervical node involvement occurs in ~70% of cases at presentation).

• The tumor is radiosensitive, and a high percentage of cases can achieve local control even in the presence of regional lymph node metastasis. Local, regional and distant failures occur in 3%, 5%, and 19% of cases respectively. Distant metastasis is associated with poor prognosis.

Larynx, hypopharynx and trachea

• Very rare

• Sex: male predominance of 4 to 1

• Age: mean 60 years

• In contrast to nasopharyngeal carcinoma, almost all reported cases have occurred in Caucasians

• Etiology: History of heavy smoking and alcohol abuse is noted in some patients, raising the possibility that these represent risk factors similar to those of conventional squamous cell carcinoma of the hypopharynx, larynx and trachea. EBV is detected in less than one-fourth of cases.

• The tumors occur with approximately equal frequency in the larynx and hypopharynx. About two-thirds of the laryngeal tumors are found in the supraglottic region. Tracheal lymphoepithelial carcinoma is exceedingly rare.

• Presentation: hoarseness (most common), neck mass, sore throat, cough, otalgia, dysphagia or hemoptysis.

• A significant proportion (three-fourths) of patients develop regional lymph node metastasis at presentation or during early course of the disease. Distant metastasis (especially to liver, lung, mediastinum, and skin) eventually develops in about one-third of patients.

• Aggressive tumor, with a propensity for regional lymph node and distant metastasis. A mortality rate of 30% at median follow up of 21 months has been reported.
NASOPHARYNGEAL CARCINOMA (NPC)

Overview
- NPC shows marked geographic differences in its prevalence, being most prevalent among southern Chinese.
- There is near consistent association with Epstein-Barr virus (EBV), irrespective of ethnic origin of patient.
- NPC is also the prototype of a family of morphologically distinctive tumours – the lymphoepithelial carcinomas – that can arise in a variety of sites, such as other head and neck mucosal sites, salivary gland, lung and thymus.

Histologic subtyping of NPC
- The term “NPC” is reserved for a carcinoma arising in the nasopharyngeal mucosa that shows light microscopic or ultrastructural evidence of squamous differentiation.
- In the new WHO classification, three subtypes are recognized: keratinizing squamous cell carcinoma, nonkeratinizing carcinoma (differentiated or undifferentiated) and basaloid squamous cell carcinoma. Adenocarcinoma and salivary gland-type carcinoma are excluded.

(1) Keratinizing squamous cell carcinoma
- Arises de novo or as a radiation-induced carcinoma occurring many years after radiation therapy for nonkeratinizing NPC.
- Compared with nonkeratinizing carcinoma, advanced tumour growth is more common (76% versus 55%) while lymph node metastasis is less common (29% versus 70%).
- Pathology: irregular tumor islands, accompanied by an abundant desmoplastic stroma. There is obvious squamous differentiation, in the form of intercellular bridges and/or keratinization over most of the tumour.
- For de novo keratinizing squamous cell carcinomas, data on EBV association are conflicting. Recent studies suggest that EBV is almost always positive in areas endemic for NPC, often positive in intermediate incidence areas, but only infrequently positive in low incidence areas. The EBV copy number in the tumor cells tends to be low. On in-situ hybridization, the nuclear signals of EBV encoded early RNA (EBER1) are usually confined to the less differentiated cells.
- For radiation-induced cases, there is no association with EBV.

(2) Nonkeratinizing carcinoma
- This histological subtype shows practically 100% association with EBV, irrespective of ethnic origin
- Can be further subdivided as “differentiated” (more common) or “undifferentiated”; lymphoepithelial carcinoma is considered a morphologic variant of undifferentiated carcinoma.
- The density of lymphocytes and plasma cells is highly variable.
- The undifferentiated subtype is characterized by syncytial-appearing large tumour cells with indistinct cell borders, round to oval vesicular nuclei, and large central nucleoli. The cells often appear crowded or even overlapping. They can sometimes be spindly and grow in the form of fascicles.
- The differentiated subtype shows cellular stratification and pavementing, often with a plexiform growth, reminiscent of transitional cell carcinoma of the bladder. The relatively small tumour cells show fairly well-defined cell borders and sometimes vague intercellular bridges.
(3) Basaloid-squamous cell carcinoma.
- Morphologically identical to the same tumour more commonly occurring in other head and neck sites.
- From the limited data, the tumour shows lower clinical aggressiveness compared with morphologically identical tumors in other head and neck sites.
- Among 4 cases tested for EBV, all three Asian cases are positive, while one Caucasian case is negative.

Problems in diagnosis on nasopharyngeal biopsies

Crush artefacts causing problems in diagnosis
- Crush artefacts are common in nasopharyngeal biopsies, making it difficult to determine whether the distorted cells represent carcinoma cells or merely lymphoid cells.
- The correct diagnosis may be reached by finding better preserved areas, where tumor cell clusters are more convincing.
- Short of that, immunostaining for cytokeratin is of great help in reaching a diagnosis of NPC. (In non-neoplastic nasopharyngeal mucosa, cytokeratin immunostaining highlights the sharply delineated surface and crypt epithelium, with no positive cells in the stroma other than those in seromucinous glands. Mucosa involved by NPC typically shows irregular clusters of cytokeratin-positive cells infiltrating the stroma.)

NPC masked by lymphoid cells or granulomas
- In some examples of NPC, particularly the lymphoepithelial carcinoma variant, the tumor islands are infiltrated by large numbers of lymphocytes and plasma cells. The broken up carcinoma cells can be mistaken for large lymphoid cells.
- In contrast to lymphoma, the cell borders are poorly defined. Presence of intercellular, and less commonly intracellular, spherical amyloid globules, if present, points strongly toward a diagnosis of NPC (amyloid globules, which are derived from keratins of tumor cells, are present in about 10% of all NPCs).
- The epithelial nature of the cellular proliferation (cohesive growth) will usually become more obvious at medium magnification.
- The diagnosis of NPC can be further confirmed by immunostaining for cytokeratin.
- Some cases of NPC are accompanied by scattered or numerous epithelioid granulomas, which may mask the tumor islands. Since granulomatous inflammation is very uncommon in the nasopharynx, nasopharyngeal biopsy showing granuloma should be scrutinized for NPC.

Benign cellular components or changes mimicking nonkeratinizing carcinoma
- Germinal centre cells can be mistaken for carcinoma because of presence of cellular clusters lacking well-defined mantle zones, and presence of large cells with vesicular nuclei and distinct nucleoli. The identification of admixed centrocytes (smaller "atypical" cells with irregular-shaped or angulated nuclei) and tingible-body macrophages would suggest the lymphoid nature of the large cells, which can be further confirmed by immunostaining (leukocyte common antigen positive, cytokeratin negative).
- Tangentially sectioned crypts, because of their deep location within the mucosa, presence of enlarged vesicular nuclei and expansion by intraepithelial lymphocytes, may be mistaken for NPC. In contrast to the latter, there is no frank invasive growth, the nuclei are not as large and thus not so crowded, and
the nucleoli are not as prominent. On immunostaining for cytokeratin, the smooth contours of the crypts (some obviously in continuity with the surface epithelium) are evident.

- In reactive lymphoid hyperplasia, there is an increase of large lymphoid cells (immunoblasts), raising a suspicion of carcinoma. In contrast to the latter, the large cells are non-cohesive and have well-defined amphophilic to plasmacytoid cytoplasm. The diagnosis can be further confirmed by positive immunostaining of the large cells for lymphoid markers and lack of cytokeratin immunoreactivity.

- The lymphoid tissue-associated venules lined by plump endothelial cells with vesicular nuclei may be mistaken for clusters of carcinoma cells. The presence of distinct basement membrane around the groups of cells, lack of large nucleoli, and negative staining for cytokeratin would be against the diagnosis of carcinoma.

**Nonkeratinizing carcinoma or lymphoma?**

- Distinction between NPC (nonkeratinizing carcinoma) and large cell lymphoma can at times be very difficult, especially since NPC cells can appear non-cohesive as a result of presence of many infiltrating lymphocytes and plasma cells.

- On the other hand, the interface of a large cell lymphoma with the residual lymphoid tissues of the nasopharynx can be deceptively sharp, mimicking carcinoma.

- Features favoring a diagnosis of carcinoma include: presence of definite cohesive cell groups in some foci (best appreciated at medium magnification) and the generally poorly defined cell borders; the diagnosis can be readily confirmed by immunostaining for cytokeratin.

- Significant irregular nuclear foldings, amphophilic cytoplasm and permeative single-file infiltration in the stroma, if present, would favour a diagnosis of lymphoma.

- Less commonly, NPC shows dispersed growth of tumor cells and an eosinophil infiltrate, leading to a misdiagnosis of Hodgkin lymphoma. Again identification of cohesive growth in some foci and cytokeratin immunoreactivity will support a diagnosis of NPC.

**Diagnostic issues of NPC presenting initially as lymphadenopathy**

- NPC may present initially as cervical lymph node metastases.

- The diagnosis of carcinoma is usually easy when lymph node involvement is extensive; the nasopharyngeal primary can be suggested by the location of the lymph node (especially jugulo-digastric node) and the syncytial appearance of the tumor cells. The clinical scenario, morphology, and positive in-situ hybridization for EBER will provide a strong support for the nasopharyngeal origin.

- Lymph nodes showing focal or patchy involvement by NPC may be misdiagnosed as reactive lymphoid hyperplasia, non-Hodgkin lymphoma or classical Hodgkin lymphoma as a result of submergence of the tumour cells in the lymphocyte-rich background. Furthermore, in approximately one fifth of cases, there are epithelioid granulomas (sometimes necrotizing), which can mask the metastatic NPC. The most important clues to diagnosis are the syncytial quality of the cytoplasm and presence of vague cellular clusters at medium magnification. Diagnosis can be readily confirmed by cytokeratin immunostain.

**Assessment of post-treatment biopsies**

**Persistent tumor on biopsy**

- After radiation therapy, it may take many weeks (up to 10 weeks) for all tumor cells to disappear histologically.

- The "persistent" radiated carcinoma cells usually show injury in the form of enlarged and bizarre nuclei, accompanied by an increased amount of cytoplasm that is often finely vacuolated, i.e. N/C ratio preserved.
• Presence of residual tumor within 10 weeks of completion of radiotherapy does not necessarily mean persistent disease, i.e. this per se is not a sufficient indicator for intensification of treatment. The result can be reported as "Residual carcinoma cells present, but uncertain as to whether they are viable. Suggest to repeat biopsy every two weeks." Remission is defined by two subsequent negative biopsies.

**Radiation change in normal tissues**

- Radiation-induced changes in the normal nasopharyngeal mucosa can be mistaken for malignancy. The surface or crypt epithelium can exhibit enlarged, hyperchromatic or even bizarre nuclei, but such changes can be recognized as benign because they are limited to some but not all cells (random cytologic atypia) and the normal nuclear-cytoplasmic ratio is maintained.
- Radiation-induced epithelial atypia should not persist beyond one year, because the abnormal cells are normally shed and replaced by proliferated cells from the basal layer cells. If there are uncertainties as to whether the atypical cells represent carcinoma-in-situ or irradiated normal epithelial cells, positive in-situ hybridization for EBER would strongly favor the former interpretation.
- After radiotherapy, it is common to find bizarre stromal cells (radiation fibroblasts) with large smudged nuclei or large vesicular nuclei with prominent nucleoli; these atypical cells can persist forever. These cells can be distinguished from residual or recurrent carcinoma by their occurrence as single cells and by the amphophilia of the cytoplasm.
- The stroma frequently contains ectatic blood vessels showing variable degrees of radiation injury such as enlarged prominent endothelial cells and abundant fibrinoid deposits.

**Radiation-induced tumors**

- Radiation-induced tumours in the nasopharynx typically develop after a long latency period, and usually take the form of keratinising squamous cell carcinomas or sarcomas (especially osteosarcomas).

---

**CASE 23**

**Clinical history**

- Female, 49-year-old
- Presented with a four-month history of a painful left parotid mass.
- A left total parotidectomy was performed. The specimen revealed a well circumscribed, pink-tan, glistening nodule measuring 2.0 x 2.0 x 1.4 cm.

**Salient histologic features**

- Circumscribed tumor with bosselated contour
- Heavy infiltrate of small lymphoid cells, with lymphoid follicle formation
- Scattered solid and cystic epithelial islands comprising ovoid cells with oval pale nuclei
- Sometimes glandular cells are formed towards the luminal side of the cystic islands
- Sebaceous cells not seen

**Diagnostic considerations**

This case looks at lot like a sebaceous lymphadenoma minus the sebaceous cells.
Immunophenotype (not required for diagnosis of this case)
- Lymphoid component: more B than T cells
- EMA: highlights the luminal borders and tumor cells
- Cytokeratin 14: highlights mostly cells in peripheral portion of the islands
- S100: -

**Diagnosis**
Parotid gland -- Lymphadenoma

**LYMPHADENOMA**

**Clinical features**
- A rare tumor in which the adenoma is accompanied by a dense lymphoid infiltrate.
- There is resemblance to sebaceous lymphadenoma minus sebaceous component. Also known as “non-sebaceous lymphadenoma”
- It is likely that lymphadenoma is not a distinctive tumor type, but is merely a basal cell adenoma or cystadenoma accompanied by a heavy lymphoid infiltrate.
- All cases have occurred in the parotid glands of male patients ranging in age from 17-57 years.
- Complete surgical excision is curative.

**Pathology**
- Circumscribed tumor
- Comprises an adenomatous proliferation accompanied by a dense lymphoid background.
- The latter is generally considered to represent tumor-associated lymphoid proliferation, thus conventional salivary gland adenomas occurring within lymph nodes are excluded.
- The epithelial component can take the form of anastomosing trabeculae, islands, solid tubules, cystically-dilated glands filled with proteinaceous materials or papillary structures. The cyst or gland lining cells are cuboidal to columnar without significant cytologic atypia. The trabeculae are composed of basaloid cells.
- In some cases, the lymphocytes are so abundant that the epithelial component is obscured (mimicking a mixed small and large cell lymphoma), and PAS-diastase can be used to highlight the basement membrane-like material around the epithelial islands, unveiling the epithelial component.

**Differential diagnosis**
- Sebaceous lymphadenoma
- Lymphoepithelial sialadenitis -- Lymphadenoma can be distinguished from lymphoepithelial sialadenitis by the circumscribed borders and presence of a more proliferative epithelial component
- Lymphoepithelial carcinoma

<table>
<thead>
<tr>
<th>Borders</th>
<th>Lymphadenoma</th>
<th>Lymphoepithelial carcinoma</th>
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<tbody>
<tr>
<td>Nuclear pleomorphism</td>
<td>Absent or mild</td>
<td>Mild to significant</td>
</tr>
<tr>
<td>Line of differentiation</td>
<td>Glandular differentiation can be identified at least focally</td>
<td>Differentiation, if present, is of squamous type</td>
</tr>
<tr>
<td>EBV in epithelial component</td>
<td>Absent</td>
<td>Commonly positive in Orientals and Eskimos</td>
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SPINDLE CELL TUMORS OF SALIVARY GLAND AND HEAD & NECK (Case 24)

<table>
<thead>
<tr>
<th>Epithelial tumors</th>
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<tbody>
<tr>
<td>Myoepithelioma or myoepithelial carcinoma</td>
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<tr>
<td>Pleomorphic adenoma (some cases)</td>
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<tr>
<td>Mucoepidermoid carcinoma, spindle cell variant</td>
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<tr>
<td>Adenofibroma</td>
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<td>Salivary gland anlage tumor</td>
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<tr>
<td>Ectopic thymoma (type A thymoma)</td>
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<td>Sarcomatoid carcinoma / carcinosarcoma</td>
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<th>Mesenchymal tumors</th>
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<tr>
<td>Glomangiopericytoma</td>
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<tr>
<td>Solitary fibrous tumor</td>
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<tr>
<td>Inflammatory pseudotumor</td>
</tr>
<tr>
<td>Miscellaneous mesenchymal tumors, e.g. nasopharyngeal angiofibroma, fibromatosis, nerve sheath tumor, smooth muscle tumor</td>
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</tbody>
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CASE 24
Clinical features
- Female, 70-year-old
- Presented with left nasal obstruction.
- A mass was discovered in the nasal cavity, and was removed in piecemeal.

Salient histologic features
- Mucosa covered by intact respiratory epithelium
- In the stroma, there are nodules of spindly cells separated by a loose stroma
- Spindly cells have bland-looking elongated nuclei, and a moderate amount of eosinophilic cytoplasm
- They form intersecting long fascicles
- Many admixed mast cells
- On more careful assessment, some ectatic vascular spaces ("pericytomatous") are present, particularly in the superficial portion of the tumor. In the deeper portion of the tumor, there are many interspersed delicate capillary spaces.

Immunophenotype (not required for diagnosis of this case)
- Cytokeratin: -
- Smooth muscle actin: +
- CD34: focal weak +
- Ki67 index: < 1%
Diagnosis
Nasal cavity – Glomangiopericytoma (hemangiopericytoma-like tumor)

Comments
This case depicts the typical histologic features of glomangiopericytoma. Practically every case of this tumor entity looks like this. It usually does not give an impression of hemangiopericytoma as a result of the striking fascicular growth pattern, but it often imparts an impression of a smooth muscle tumor (especially since the interspersed vascular spaces may not be conspicuous).

SINONASAL GLOMANGIOPERICYTOMA
Nomenclature
• Originally known as hemangiopericytoma-like tumor or sinonasal hemangiopericytoma
• To avoid confusion with hemangiopericytoma (which by itself is also a controversial entity), the tumor is renamed “glomangiopericytoma” in the new WHO classification, acknowledging the overlap of the entity with glomus tumor. The cell of origin is probably a modified perivascular glomus-like myoid cell.

Clinical features
• Glomangiopericytoma is a distinctive tumor of the sinonasal tract that is clinically, morphologically and biologically different from soft tissue-type or dura-based hemangiopericytoma.
• Predilection sites: nasal cavity and paranasal sinuses
• Most patients present with nasal obstruction, epistaxis, or non-specific findings.

Clinical behavior
• Indolent tumor, with an overall 5-year survival of >90% achieved with complete surgical excision.
• Recurrence, which develops in up to 30% of cases, may occur after many years.
• Aggressive-behaving glomangiopericytomas are uncommon.

Pathology
• A subepithelial well-delineated but unencapsulated cellular tumour
• Comprises of closely packed cells, forming short fascicles.
• There are interspersed capillary-sized to large patulous vascular spaces that may have a “staghorn” or “antler-like” configuration.
• The uniform neoplastic cells are elongated, oval, or rarely cuboidal. They possess vesicular to hyperchromatic, round to oval to spindle-shaped nuclei, and lightly eosinophilic cytoplasm. Mild nuclear pleomorphism and occasional mitotic figures may be present, but necrosis is not found.

Immunohistochemistry
• Actin + (extensive or patchy)
• Desmin –
• CD34 –
• Cytokeratin –
SOLITARY FIBROUS TUMOR

Clinical features
- A benign fibroblastic or myofibroblastic neoplasm which was initially described in the pleura but is recognized now in almost all sites in the body.
- Has been reported in the major salivary glands and various head and neck sites (such as nasal cavity, nasopharynx, orbit).
- Presentation is usually in the form of a painless mass.
- Almost all patients have uneventful clinical course following local excision.

Pathology
- Typically well circumscribed
- Haphazard growth of short spindle or plump cells with scanty cytoplasm that are intimately admixed with collagen.
- There are typically hypocellular (collagen-rich) areas alternating with hypercellular (tumor cell-rich) areas.
- Pericytomatic vessels are frequently seen.
- An adipocytic variant with interspersed islands of adipose cells is also recognized.
- CD34 is strongly and diffusely positive.
- CD99 and bcl-2 are also commonly positive.
image captions:

CASE 1
Acinic cell carcinoma, classical. (A) The tumor invades the parotid parenchyma in pushing fronts. (B) The microcystic growth pattern and basophilic quality of the tumor cell cytoplasm are diagnostic of acinic cell carcinoma. (C) Most cells possess eccentrically-placed small nuclei and abundant basophilic granules in the cytoplasm. (D) In addition to the predominant population of acinic cells in this case, there are interspersed small groups of cuboidal cells resembling intercalated duct cells.

CASE 2
Mucoepidermoid carcinoma, low grade. (A) There is an infiltrative lesion comprising cysts disposed in an inflamed sclerotic stroma. There are also papillary fronds projecting into a cystic space (left field). (B)(C) Some cysts are lined by bland-looking mucinous epithelium with uniform basal nuclei. Note the sclerotic stroma infiltrated by plasma cells and lymphocytes. (D) On closer scrutiny, there is often a thin layer of smaller (intermediate) cells beneath the mucinous cells. (E) In areas, there are pools of extravasated mucin, in which some histiocytes float.

CASE 3
Malignant myoepithelioma, low grade, probably arising in pleomorphic adenoma. (A) The borders of the tumor are difficult to assess, but there appears to be invasion. (B) There are solid sheets of tumor, sometimes accompanied by a myxoid stroma. (C) Many tumor cells have the appearance of plasmacytoid hyaline cells. The nuclei show minimal to mild nuclear atypia, and mitotic figures are rare. (D) Some tumor cells have a nondescript appearance, forming solid sheets. (E) There is a minor component with cytoarchitectural features compatible with pleomorphic adenoma.

CASE 4
Polymorphous low grade adenocarcinoma. (A) The tumor has infiltrative borders. This field shows isolated or complex narrow glands. (B) Some narrow glands show a streaming pattern. (C) Complex solid tumor islands punctuated by glandular spaces. (D) The glands are lined by cells with bland-looking, pale-staining nuclei.

CASE 4b
Polymorphous low grade adenocarcinoma. (A) The tumor looks similar to Case 4, except that papillae are formed in focal areas. (B) Another difference from Case 4 is the presence of extracellular basement membrane-like material in some areas.

CASE 5
Adenoid cystic carcinoma in paranasal sinus. (A) The tumor involves the respiratory mucosa. It is difficult to assess whether there is invasive growth or not. (B) In many areas, there are anastomosing solid narrow tubules separated by abundant basement membrane-like material. (C) In other areas, complex cribriform structures are formed. (D) Discrete cribriform structures characteristic of adenoid cystic carcinoma are seen in the left field. Some tumor tubules are seen in the right field. (E) The tumor cells show a basaloid appearance. There are interspersed solid ductules lined by cells with more eosinophilic cytoplasm.
CASE 6
Salivary duct carcinoma. (A)(B) This is an invasive tumor with a cribriform and solid-comedo growth pattern. There is an accompanying sclerotic stroma. (C) The polygonal tumor cells show significant nuclear pleomorphism. The cytoplasm exhibits an apocrine quality.

CASE 6b
Salivary duct carcinoma. (A)(B)(C) In contrast to Case 6, the tumor infiltrates in the form of irregular islands. However, the apocrine quality of the cytoplasm and the high nuclear grade characteristic of salivary duct carcinoma are evident. (D) Focally, a micropapillary growth pattern is evident.

CASE 7
Oncocytic adenocarcinoma. (A) Since this oncocytic neoplasm shows definite invasion into the parotid parenchyma, it has to be considered malignant. (B)(C) The tumor comprises glandular structures lined by oncocytic cells with mildly atypical nuclei and low mitotic activity.

CASE 8
Mucoepidermoid carcinoma, oncocytic variant. (A) The tumor shows invasion into the parotid parenchyma. It comprises predominantly islands of oncocytic cells. (B)(C) Trabeculae of oncocytic cells are interspersed by occasional mucin-filled spaces. (D) There are also some interspersed islands of water-clear cells.

CASE 9
Nodular oncocytic hyperplasia. (A)(B) There are multiple nodules of oncocytic cells. These nodules apparently still maintain the contours of the preexisting lobules. There are some interspersed lymphoid aggregates. (C) The oncocytic cells are arranged in trabeculae and small packets. (D) Note areas where the oncocytic cells merge into the normal acinar and ductular cells.

CASE 10
Clear cell oncocytoma. (A) The tumor nodule has a bosselated contour. (B) It comprises trabeculae of polygonal cells separated by sinusoidal blood vessels. Many cells show clear cytoplasm. (C) Although occasional cells show water-clear cytoplasm, most clear cells retain a fine granularity in areas within the cytoplasm.

CASE 11
Epithelial-myoepithelial carcinoma. (A) The tumor invades the parotid parenchyma in pushing fronts. Even at this low magnification, tubules comprising two types of cells (including clear cells) are already evident. The tumor also forms papillary fronds projecting into cystic spaces. (B) In the right field, there are discrete tubules lined by an inner layer of “pink” ductal cells and an outer layer of clear myoepithelial cells. In the left field, the tubules appear to have coalesced to form more complex sheets. (C) In areas where the architecture is more complex, clear cells may predominant and the ductal structures may not be so conspicuous. (D) Higher magnification to show the bicellular composition typical of epithelial-myoepithelial carcinoma. The clear myoepithelial cells are usually much larger than the more darkly-stained ductal cells.

CASE 11b
Epithelial-myoepithelial carcinoma (less well differentiated compared with Case 11). (A) The tumor invades the salivary gland parenchyma, accompanied by a sclerotic stroma. (B) The tumor grows in the form of large solid nodules comprising mostly nondescript polygonal cells with pale, and occasionally clear,
cytoplasm. (C)(D) Focally, a minor ductal component with more deeply stained cytoplasm is evident. Note the presence of hyaline material among the tumor cells.

CASE 12
Basal cell adenoma with myoepithelium-derived stroma. (A) The tumor comprises anastomosing trabeculae and islands clearly delineated from the cellular stroma. (B) Within the cell islands and trabeculae, small ductal structures are interspersed in the background of basaloid cells. (C) Loose fascicles of delicate spindly cells are present in the stroma. These cells do not appear to merge into the epithelial islands or trabeculae. (D) The spindly cells are immunoreactive for S100 protein.

CASE 13
Necrotizing sialometaplasia. (A) Beneath the ulcerated surface, there is a remarkable squamous proliferation. Note however the preserved lobular architecture. (B) There are islands of squamous cells with mild to moderate nuclear atypia. In areas, there is intraepithelial infiltration of inflammatory cells. (C) There are nests of atypical squamous cells. Mitotic figures are seen. (D) In the vicinity of the squamous nests, there are small empty spaces filled with mucus, representing necrotic acinar units.

CASE 14
Acinic cell carcinoma, papillary-cystic variant. (A) In the parotid gland, there is an epithelium-lined cyst. (B) In areas, the cyst is lined by a single layer of uniform cuboidal cells. Note that some cells show fine vacuoles in the cytoplasm. (C) In other areas, there are stratified cells with formation of a microcystic pattern. Occasional cells have a hobnailed appearance. (D) Some cells contain PAS-positive diastase-resistant cytoplasmic granules.

CASE 15
Carcinoma ex pleomorphic adenoma (intracapsular). (A) The entire tumor shows complete encapsulation. (B) The left field shows classical pleomorphic adenoma, which merges into an in-situ carcinoma in the right field. The large atypical malignant cells have apparently replaced the inner ductal cells, and are still surrounded by neoplastic myoepithelial cells. (C) The malignant cells show prominent nucleoli. (D) In areas, the malignant cells infiltrate into the stroma, although still within the confines of the parent pleomorphic adenoma.

CASE 16
Dedifferentiated acinic cell carcinoma. (A) The left field shows acinic cell carcinoma invading in pushing borders, while the right field shows a high-grade carcinoma with a jagged pattern of infiltration. (B) Acinic cell carcinoma in the left field shows only mild nuclear atypia, while the high-grade carcinoma in the right field shows more pleomorphic nuclei and prominent mitotic activity. (C) Acinic cell carcinoma component with microcystic growth pattern. (D) High-grade carcinoma component with significant nuclear atypia and mitotic activity.

CASE 17
Dedifferentiated adenoid cystic carcinoma. (A) This infiltrative tumor shows two components: adenoid cystic carcinoma in the left and upper fields (comprising mostly tubules), and a high-grade carcinoma forming large islands. (B)(C) The high grade carcinoma (left field) shows necrosis. Adenoid cystic carcinoma with tubular growth pattern is evident in the right field. (D) Note the striking difference in cytology between the two components.
CASE 18
Kuttner tumor. (A) The submandibular gland shows accentuation of the lobular pattern as a result of fibrosis in the septa. There is moderate lymphoid infiltration, with lymphoid follicle formation, accompanied by loss of salivary secretory units. (B) A lymphoid follicle is shown. There is marked loss of acini. Some ductules are disposed in a cellular fibrous stroma infiltrated by chronic inflammatory cells. (C) There is periductal fibrosis, and the lumens often contain inspissated secretion. Note the presence of many plasma cells in the background. (D) A significant proportion of the plasma cells secrete IgG4.

CASE 19
Extranodal marginal zone B-cell lymphoma of MALT. (A) The salivary parenchyma is massively infiltrated by lymphoid cells. There are scattered reactive lymphoid follicles. Even at this low magnification, lymphoepithelial lesions surrounded by collars of pale cells are evident. (B) There are prominent lymphoepithelial lesions. (C) The cells that infiltrate the expanded epithelial units resemble monocytoïd B-cells. Note the presence of hyaline droplets within the lymphoepithelial lesion. (D) In the background, there are sheets of small lymphoid cells admixed with lymphoplasmacytoid cells and some plasma cells.

CASE 20
Small/Merkel cell carcinoma of salivary gland. (A) Sheets of small tumor cells are traversed by delicate fibrovascular septa. (B) The tumor cells have plump, round nuclei with fine chromatin. There are many scattered apoptotic bodies. (C) The tumor cells are immunoreactive for cytokeratin 20.

CASE 21
Olfactory neuroblastoma with glandular differentiation. (A) The tumor comprises islands and sheets of small cells traversed by elaborate fibrovascular septa. (B) In most areas, the tumor comprises small cells with stippled chromatin. There are many admixed apoptotic bodies. (C) In focal areas, there is formation of fibrillary matrix. The accompanying cells show a finer chromatin pattern and a slightly greater amount of amphophilic cytoplasm. (D) In many areas, the small tumor cells merge into glandular structures with pale to clear cytoplasm.

CASE 22
Lymphoepithelial carcinoma of salivary gland. (A) At low magnification, there is a dense lymphoid infiltrate, accompanied by some reactive follicles, raising the possibility of lymphoma. (B) In many areas, the carcinomatous islands (upper field and left lower field) do not appear conspicuous due to the presence of many infiltrating lymphoid cells. (C) However, in some areas, there are more obvious carcinomatous islands. (D) The carcinomatous cells can be recognized by the indistinct cell borders and large nucleoli. (E) The islands of carcinoma can be readily highlighted by immunostaining for cytokeratin.

CASE 23
Lymphadenoma. (A)(B) The tumor has a bosselated contour. It comprises solid and cystic epithelial islands disposed in a dense lymphoid stroma. (C)(D) The epithelial islands resemble transitional epithelium with glandular metaplasia.

CASE 24
Glomangiopericytoma of nasal cavity. (A) Beneath the respiratory epithelium, there are variable-sized nodules of tumor separated by a loose stroma. (B) The tumor comprises interlacing fascicles of uniform spindly cells. The interspersed capillaries may not appear striking. (C) The spindly cells have uniform nuclei and lightly eosinophilic cytoplasm. There are many scattered mast cells. (D) In some areas, especially the superficial portion, a pericytomatos vascular pattern is often evident.
California Tumor Tissue Registry

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Contributors of Tumor Tissue Material to the Registry Files
The California Tumor Tissue Registry is pleased with its association with Loma Linda University School of Medicine, which is providing Continuing Medical Education credit for this meeting.

Loma Linda University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.

This program has been planned and implemented in accordance with ACCME essentials and standards. The Loma Linda University School of Medicine Office of Continuing Medical Education relies on its CME faculty to provide program content that is evidence-based and free of commercial bias. Therefore, in accordance with ACCME standards, any faculty and/or provider industry relationships will be disclosed.

The California Tumor Tissue Registry has been providing excellence in cancer diagnosis and education since 1947.
This is the third time that Dr. John K. C. Chan, Consultant Pathologist at Queen Elizabeth Hospital in Hong Kong, has addressed the CTTR.

His 1996 seminar on “Endocrine Neoplasms” received one of the highest ratings ever, as did his “Simplified Approach to Lymphoma Diagnosis in December, 2001”. His training includes fellowships at Stanford University Medical Center and Yale School of Medicine. He has served as an Honorary Clinical Lecturer at the University of Hong Kong for many years, and has been on the editorial boards of numerous pathology medical journals. He is currently Editor-in-Chief of “Advances in Anatomic Pathology”. He is a participant in numerous academic societies, and has been the recipient of many scholarships and awards. His 300+ publications on varied fields of pathology, and his authorship or co-authorship of six books, especially highlight his expertise in all fields of anatomic pathology. As those in attendance at his previous seminars can attest, Dr. Chan is adept at simplifying complex subjects.

This is a seminar that practicing pathologists cannot afford to miss!

Educational Contents and Media:

2. Correlating clinical histories
3. Six hour lecture, incorporating projected images of each case and other illustrative materials.
4. Comprehensive printed color syllabus, including diagnosis, discussion, and appropriate references from pertinent medical literature.

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Seminar Objectives (by JCK Chan):

- Understand minimum cytoarchitectural features for the diagnosis of various salivary gland tumors
- Be able to use an analytic approach to diagnose salivary gland tumors, even for difficult or unusual-looking cases, instead of using a “picture-matching” approach (which does not work well due to marked overlapping of histologic features)
- Be familiar with problems in the diagnosis of salivary gland tumors as a result of changes induced by fine needle aspiration
- Be updated as to newly recognized salivary gland tumors and tumor variants
- Understand new concepts in salivary gland tumorigenesis, and criteria for the diagnosis of malignant change in a largely benign tumor or dedifferentiation into a malignant tumors
- Be familiar with selected newly-described extra-salivary head and neck tumors, or tumors with significant new insight into their pathobiology

Don Chase & Weldon Bullock, Executive Directors of the CTTR invite you to attend this extraordinary seminar. We hope to see you in San Diego!