Salivary Gland Neoplasms

MUSC Pathology Multi-Specialty Course
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Salivary Gland Neoplasms Outline

• Basic concepts of salivary glands histoanatomy
• Basic concepts in salivary gland pathology
• Challenges in the biopsy diagnosis of salivary gland neoplasms
• Select salivary gland neoplasms

Salivary Glands = Tubuloacinar Exocrine Gland

- Ductal (Excretory & Striated) derived:
  - Mucoepidermoid CA
  - Salivary Duct CA
  - Warthin tumor
  - Oncocytoma
  - Others
- Epithelial & Myoepithelial or Acinar derived:
  - Pleomorphic adenoma
  - Monomorphic (Basal cell) adenoma
  - Adenoid cystic CA (EMA), PLGA
  - Acinic cell adenocarcinoma
  - Others
**Major Salivary Gland Neoplasms**

- **Encapsulation and circumscription:**
  - All major gland neoplasms are encapsulated:
    - Benign → Noninvasive
    - Malignant → Invasive; exceptions include:
      - Mucoepidermoid carcinoma
      - Acinic cell adenocarcinoma
      - Adenoid cystic carcinoma
      - Mammary analogue secretory carcinoma
      - Epithelial-myoepithelial carcinoma
      - Noninvasive carcinoma ex pleomorphic adenoma
Pleomorphic Adenoma
Epithelial-Myoepithelial Carcinoma

Salivary Duct Carcinoma
PLGA

Myoepithelial CA Ex PA
CAMSG

Mucoepidermoid Carcinoma
Acinic cell adenocarcinoma
Salivary Duct Carcinoma

Adenoid Cystic Carcinoma

Acinic cell adenocarcinoma

DOG1

Salivary duct carcinoma
• Recurrent t(12;15) (p13;q25) translocation - ETV6-NTRK3 gene fusion
  MASC

Chromosomal Translocation in Salivary Gland Neoplasms

<table>
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Malignant Diagnostic Categories

- Malignant due to invasion
- Malignant due to cytomorphology
- Malignant by definition
**Features of Benign & Malignant Minor Salivary Gland Neoplasms**

- **Encapsulation and circumscription:**
  - All minor gland neoplasms are unencapsulated
  - Specific tumor-type defined by cytomorphology +/- growth pattern
  - Presence or absence of invasion: neurotropism, LVI, salivary gland parenchyma, soft tissue, bone

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**Shared Features between Benign and Low-Grade Malignant Salivary Gland Neoplasms**

- **Growth patterns:**
  - All salivary gland neoplasms are polymorphic
- **Cytomorphology:**
  - Isomorphic cell type(s) lacking significant nuclear pleomorphism, increased mitotic activity
- **Dual cell composition:**
  - Many neoplasms composed of epithelial & myoepithelial cells:
    - Light microscopy
    - IHC: cytokeratins, myoepithelial-related markers (p63, p40, calponin, S100 protein, others)

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**Intraoral Minor Salivary Gland BX “Low-Grade” Neoplasms**

- In limited sampling especially those without surrounding tissue to evaluated for invasion, differentiation often cannot be achieved as these neoplasms share overlapping:
  - Growth patterns
  - Cytomorphology
  - Cell composition
  - Immunohistochemical reactivity
• 35 year old female presented with a palate mass at the junction of the hard and soft palate with associated tingling sensation but no pain. The mass measuring approximately 2.5cm in greatest dimension appeared as a bulge with intact overlying epithelium. The mass was biopsied.
**Differential Diagnosis**

- Pleomorphic adenoma
- Monomorphic adenoma (Basal cell adenoma)
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Cribriform adenocarcinoma of minor salivary glands

**IHC in DDX of “Low-Grade” Salivary Gland Neoplasms**

- Pairing p63 and p40 reported to assist in differentiating pleomorphic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC):
  - PA: p63+; p40+
  - Cellular PA: p63+; p40+ or p63-; p40-
  - PLGA: p63+; p40-
  - AdCC: p63+; p40+
- Proliferation indices (Ki67 or MIB1)
  - PA: <5%
  - PLGA: <5%
  - AdCC: increased up to 20%

**Intraoral “Low-Grade” Minor Salivary Gland Tumor with Overlapping Morphology**

- Pleomorphic adenoma
- Basal cell adenoma
- Polymorphous low-grade adenocarcinoma
- Adenoid cystic carcinoma
- Invasion
- S-100 protein
Salivary Gland Neoplasms
FNAB &/or Biopsy
• Excellent and efficient first line diagnostic modality in guiding management of salivary gland lesions/neoplasms
• Differentiate nonneoplastic from neoplastic salivary gland lesions
• Diagnose benign neoplasms (pleomorphic adenoma, Warthin tumor, others)
• Differentiate low- and high-grade carcinomas

Low- & Intermediate-Grade Salivary Gland Carcinomas
Treatment
• Wide local excision:
  – Tumor free-margins
  – Same treatment for benign salivary gland neoplasms
• Neck Dissection:
  – Not indicated unless there is clinical evidence of neck disease
• Postoperative Radiation
  - Not indicated
  - Exception for adenoid cystic carcinoma
High-Grade Salivary Gland Carcinomas

**Treatment**

- **Radical extirpation:**
  - **Wide block surgical excision:**
    - May include facial nerve
    - Tumor free margins
  - **Neck Dissection:**
    - Indicated even in cN0 neck
- **Postoperative Radiation**
  - Indicated

“Low-Grade” Salivary Gland Neoplasms

**FNAB &/or Biopsy**

- Limitations of tissue may preclude a definitive diagnosis
- Presence of invasion diagnostic for carcinoma but may not allow for a specific diagnosis
- Absence of invasion does not exclude a diagnosis of carcinoma as evidence of invasion may be present in aspects of the neoplasm not sampled
- Use of “low-grade” likely engenders diagnosis of malignancy

Diagnostic Terminology

- Minor salivary gland neoplasm, not further specified
- **Recommendation:**
  - Additional sampling
  - Conservative but complete excision to include tumor free margins
  - Following complete excision a definitive diagnosis can be rendered
Select Salivary Gland Neoplasms
Outline

• Pleomorphic Adenoma (PA):
  – Atypical PA
  – Carcinoma ex Pleomorphic Adenoma
• Mucoepidermoid Carcinoma
• Adenoid Cystic Carcinoma
• Polymorphous Low-grade Adenocarcinoma & Cribriform Adenocarcinoma of Minor Salivary Glands

Pleomorphic Adenoma (PA) Definition

• Benign epithelial-derived tumor with epithelial and myoepithelial differentiation, and variable amount mesenchyme (stroma):
  – tubular/ductular structures enveloped by myoepithelial cells with associated copious chondromyxoid stroma

Pleomorphic Adenoma (PA) Clinical Features

• Most common salivary gland neoplasm
• F > M; wide age range including children
• Sites: major glands and minor glands
• Symptoms:
  – slow growing painless mass
  – airway obstruction, dysphagia, epistaxis
**Pleomorphic Adenoma (PA)**

**Immunohistochemistry**

- **Epithelial cells:**
  - Cytokeratins; EMA; CEA
  - Pleomorphic adenoma gene 1 (PLAG1)
  - Can be CD117 positive
- **Myoepithelial cells:**
  - Cytokeratins
  - p63, p40, S100 protein, SOX10, PLAG1
  - vimentin, calponin, GFAP, SMA, MSA, SMMS
Pleomorphic Adenoma Gene 1 (PLAG)

Pleomorphic Adenoma (PA)
Treatment and Prognosis

- Surgical resection
- Recurrence-free rates:
  - 5 year = 97%
  - 10 year = 94%
- Recurrences:
  - histology similar to primary
  - may be chondromyxoid rich/predominant
  - may be multinodular including nodules in soft tissues of the neck
Cellular Pleomorphic Adenoma

Cellular Pleomorphic Adenoma

Cellular Pleomorphic Adenoma, Chondromyxoid Stroma
Myoepithelial Cells

Plasmacytoid
Spindle

Myoepithelial Cells

p63
p40

Pairing p63 and p40

- IHC pairing p63 and p40 reported to assist in differentiating pleomorphic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC)
  - PA: p63 +; p40+
  - Cellular PA: p63+; p40+ or p63- ; p40-
  - PLGA: p63+; p40-
  - AdCC: p63 +; p40+
Chondromyxoid-Predominant PA

PA with Schwannoma-like changes

PA with squamous & mucous cell metaplasia
PA with cribriform growth

Cribriform growth

Adenoid Cystic Carcinoma  Pleomorphic Adenoma with cribriform growth

PA with “monster” nuclei
PA with Mitoses

Multinodular PA

Multinodular PA in Soft Tissues
Pleomorphic Adenoma (PA)
Atypical Features

- PAs that include atypical features but fall short for a diagnosis of carcinoma ex pleomorphic adenoma:
  - diffuse nuclear atypia
  - increased mitotic figures
  - irregular growth along periphery
  - foci of acellular hyalinization

PA with “Mushroom-like” Capsular Protrusion

PA extending into fat
PA with acellular hyalinization
submit entire tumor

Atypical Pleomorphic Adenoma
Treatment and Prognosis
• Similar to Pleomorphic Adenoma

PA with Intravascular Tumor Deposits
PA

Features Worrisome for Malignancy

• Clinical:
  – Submandibular gland
  – Older patient
  – Long-standing tumor
  – Larger tumor
  – Submandibular gland

PA - Features worrisome for but not diagnostic of malignancy

• Pathology:
  – Hypercellularity with diffuse anaplasia
  – Increased mitotic activity, atypical mitoses
  – Prominent zones of hyalinization; necrosis

Histologic Features Diagnostic for Malignancy in Pleomorphic Adenoma

• Definitive:
  – Invasive growth (VI, PNI, invasion of adjacent gland and/or soft tissues)
  – Metastatic disease
• Diagnosis = Carcinoma ex pleomorphic adenoma (CEPA)
Invasion into Nonneoplastic Salivary Gland

CEPA Histology
- Carcinoma arising in/from a PA:
  - Histologic Grade
    - High-grade (majority)
    - Low-grade
  - Invasiveness:
    - Invasive:
      - minimal (<4-6mm extension beyond border of PA)
      - not minimal (>4-6mm extension beyond border of PA)
    - Non-invasive (intracapsular)
CEPA
Histology

- Carcinoma arising in/from a PA:
  - residual PA readily identifiable to absent
- Malignant component:
  - High-grade:
    - Salivary duct carcinoma; undifferentiated, poorly-differentiated adenocarcinoma, squamous cell carcinoma

Salivary Duct Carcinoma
Salivary Duct Carcinoma

Apocrine Cell Features

Salivary Duct Carcinoma
Immunohistochemistry

- Cytokeratins, EMA, CEA positive
- Androgen receptor positive
- GATA3 positive
- BRST-2 positive
- Her-2/neu positive (membranous)
- ER and PR positive (minority)
- S100 protein, p63, calponin, SMA, vimentin negative
- Rare neuroendocrine differentiation
- PSA and PAP may be positive
- High proliferative index (25-80%) by Ki-1
CEPA
Histology

- Malignant component:
  - Low-grade:
    - MEC, PLGA, acinic cell adenocarcinoma, adenoid cystic carcinoma, myoepithelial carcinoma, others

Intracapsular or Noninvasive CEPA

- Salivary gland pleomorphic adenoma with foci of cytomorphologic malignant cells but without evidence of invasion
- Early stage in the development malignant transformation of pleomorphic adenoma
- Must submit entire tumor to exclude invasion
- In absence of invasion prognosis considered very good
CEPA Prognostic Factors

- Origin in major glands
- Recurrent or metastatic disease
- Invasiveness:
  - Invasion beyond 4-6mm - less prognostically favorable
  - Invasion <4-6mm - prognostically favorable
- Surgical Margins
- Histologic grade

Multistep Process in CEPA Development

WHO Blue Book 2017: 176

Intercalated Duct Lesion
Mucoepidermoid Carcinoma (MEC) Definition

- Malignant epithelial salivary gland tumor composed of epidermoid, mucous and intermediate cells

Mucoepidermoid Carcinoma Clinical Features

- Most common malignant salivary gland neoplasm
- F > M; 3rd - 5th decades
  - Most common pediatric malignant SG tumor
- Major gland - Parotid; Minor gland - palate
- Up to 2/3 of patients may be asymptomatic
Mucoepidermoid Carcinoma (MEC) Histologic Grading

- Low-grade
- Intermediate grade
- High-grade

MEC, low-grade
MEC, low-grade
Epidermoid Cells & Mucocytes

MEC, low-grade
Intermediate Cells

MEC, intermediate-grade
**Mucoepidermoid Carcinoma**

**Microscopic Grading**

- Proportion of cystic component relative to solid component
- Proportion of cell type
- Cellular maturation
- Mitoses
- Pattern of invasion
- Necrosis

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**Mucoepidermoid Carcinoma**

*Microscopic Grading*

- Intracystic component <20% 2
- Neural invasion 2
- Necrosis present 3
- 4 or more mitoses 3
- Anaplasia 4


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**Mucoepidermoid Carcinoma**

*Microscopic Grading*

- Low-grade 0-4
- Intermediate grade 5-6
- High grade 7 or more

**Mucoepidermoid Carcinoma**

*Microscopic Grading*

- Intracystic component less than 25% 2
- Tumor front invades in small nests and islands 2
- Pronounced nuclear atypia 2
- LVI 3
- Bony invasion 3
- 4 or more mitoses 3
- Perineural invasion 3
- Necrosis 3

* Brandwein et al. AJSP 2001;25:835-45

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**Mucoepidermoid Carcinoma**

*Microscopic Grading*

- Low-grade 0
- Intermediate grade 2-3
- High grade 4 or more

* Brandwein et al. AJSP 2001;25:835-45

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**MEC - Histologic Variants**

- Cystic
- Oncocytic
- Clear cell
- Sclerosing
  - with and without eosinophilia
MEC, Oncocytic Variant

Salivary Gland Tumors with Oncocytic Cells
- Oncocytoma; oncocytois
- Pleomorphic and monomorphic adenomas
- Acinic cell adenocarcinoma
- Mammary analogue secretory carcinoma
- Mucoepidermoid carcinoma
- Oncocytic carcinoma
- Salivary duct carcinoma

MEC, Clear Cell Variant
Salivary Gland Tumors with Clear Cells

- Clear cell carcinomas including hyalinizing type
- Pleomorphic and monomorphic adenomas
- Oncocytoma
- Acinic cell carcinoma
- Mammary analogue secretory carcinoma
- Mucoepidermoid carcinoma
- Epithelial-myoepithelial carcinoma
- Myoepithelial carcinoma
- Metastatic renal cell carcinoma

Epithelial-Myoepithelial Carcinoma (EMC)

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Epithelial-Myoepithelial Carcinoma (EMC)
Epithelial-Myoepithelial Carcinoma (EMC)

Mucoepidermoid Carcinoma Prognosis & Microscopic Grading

- Biologic behavior correlates to microscopic grade
- Exception is for submandibular gland MEC

Mucoepidermoid Carcinoma Prognosis & Microscopic Grade

- Low-grade = 305 patients:
  - 3% died of disease
- Intermediate-grade = 31 patients:
  - 10% died of disease
- High-grade = 41 patients:
  - 46% died of disease
Mucoepidermoid Carcinoma
Treatment and Prognosis

• Low or intermediate grade MEC:
  – wide local excision
  – 90% 5-year survival

Mucoepidermoid Carcinoma
Treatment and Prognosis

• High-grade MEC:
  – Wide block surgical excision to include nerves plus neck dissection
  – 40% 5-year survival

Warthin Tumor
Mucoepidermoid Carcinoma
MAML2 Translocation

• Identified in large proportion of MEC of the salivary gland:
  – low-grade
  – intermediate grade
• Highly specific for MEC

Adenoid Cystic Carcinoma
Definition
• Malignant epithelial salivary gland neoplasm of myoepithelial (abluminal) and epithelial (luminal) cells characterized by its histologic appearance, tendency to invade nerves and protracted but nonetheless relentless clinical course

Adenoid Cystic Carcinoma
Clinical Features
• App. 10-12% of all malignant salivary gland tumors
• No gender predilection except for submandibular tumors which predilect to women
• Wide age range and most commonly occurs in the 5th-7th decades of life; uncommon < 3rd decade
• Major salivary glands - parotid and submandibular glands:
  – up to 5% of all parotid gland neoplasms;
  – approx. 15% of submandibular gland neoplasms and represents the most frequently encountered malignant neoplasm of the submandibular gland

Adenoid Cystic Carcinoma
Clinical Features Cont’d
• Accounts from 30% to nearly half of epithelial tumors of minor salivary gland tumors; may involve the minor salivary glands throughout the upper respiratory tract:
  – Most frequently involves the palate;
  – Other sites of involvement include tongue, sinonasal tract, ceruminal glands of the external auditory canal and the lacrimal gland:
• Accounts for 50% of all lacrimal gland neoplasms
Adenoid Cystic Carcinoma

- Ductules/tubules
- Abluminal cells

Adenoid Cystic Carcinoma → PNI

Adenoid Cystic Carcinoma

Histologic Grading

• Grade 1:
  - mostly tubular, some cribriform
  - absence of solid
  - absence of nuclear pleomorphism or mitotic activity

• Grade 2:
  - pure cribriform pattern or mixed tubular/cribriform
  - solid patterns may be present but not >30%
  - slightly greater nuclear pleomorphism and mitotic activity than Grade 1
Adenoid Cystic Carcinoma
Grade 1

Adenoid Cystic Carcinoma
Grade 2

Reduplicated basement membrane
Adenoid Cystic Carcinoma
Histologic Grading

• Grade 3:
  – > 50% solid;
  – more significant nuclear pleomorphism and increased mitotic activity than Grade II;
  – necrosis often present

Adenoid Cystic Carcinoma
Grade 3

Adenoid Cystic Carcinoma
Immunohistochemistry

• Myoepithelial or basal (abluminal) cells:
  – cytokeratins, p63, p40, S100 protein, calponin, smooth muscle actin, smooth muscle myosin heavy chain and vimentin positive
  • cytokeratin tends to be less intensely reactive as compared to ductal cells
  – glial fibrillary acidic protein may be focally positive
Adenoid Cystic Carcinoma Immunohistochemistry

• Ductal (luminal) cells:
  – Cytokeratins (pancytokeratin, CK7, CK14, CK17, CK19), S100 protein, epithelial membrane antigen (EMA), CEA and c-kit (CD117) positive:
    • cytokeratin tends to be more intensely reactive as compared to myoepithelial or basal cells
Adenoid Cystic Carcinoma
Molecular Genetics

- Specific chromosomal translocation t(6;9)(q22-23;p23-24) involving the v-myb avian myeloblastosis viral oncogene homolog (MYB) and nuclear factor I/B (NFIB) genes results in MYB-NFIB gene fusion identified in AdCC:
  - identified irrespective of site of occurrence
  - gene fusion found in 30-50% of cases with increase to 86% when performed on frozen specimen

Adenoid Cystic Carcinoma
Treatment and Prognosis

- Wide excision
- Radiotherapy useful in controlling microscopic disease after initial surgery, in treating locally recurrent disease or as palliation management in unresectable tumors
- Chemotherapy is utilized as palliation in patients with advance disease

Adenoid Cystic Carcinoma
Treatment and Prognosis Cont’d

- Recurrence rates range from 16-85%
- Regional lymph node metastases uncommon ranging from 5-25%
- Distant metastasis ranges from 25-55%
- Survival rates:
  - 5-year overall survival: 60-90%
  - 10-year overall survival: 29-80%
  - 15-year overall survival: 29-55%
Adenoid Cystic Carcinoma
Treatment and Prognosis Cont’d

- VIIa paralysis: may be associated with worse prognosis and quicker demise
- Histologic grade:
  - Grades 1-2: 15 year survival rates:
    - Grade I: 39%
    - Grade II: 26%

Adenoid Cystic Carcinoma
Treatment and Prognosis Cont’d

- Grade 3:
  - Higher incidence of metastasis:
    - May metastasize even in clinically lower stage tumors (e.g., T1, T2)
  - Earlier fatal outcomes:
    - 14% 5-year survival
    - 5% 15 year survival

Adenoid Cystic Carcinoma
Treatment and Prognosis Cont’d

- Clinical stage:
  - Advanced stage associated with poorer outcome
    - Stage I: 75% 10-year survival;
    - Stage II: 43% 10-year survival;
    - Stages III-IV: 15% 10-year survival.
- Positive surgical margins and/or failure of local disease control following initial surgery:
  - Recurrent tumor is generally a sign of incurability
Adenoid Cystic Carcinoma
Differential Diagnosis

• Pleomorphic adenoma
• Basal Cell Adenoma
• Basal Cell Adenocarcinoma
• Polymorphous low-grade adenocarcinoma
• Cribriform adenocarcinoma of minor salivary glands

Basal Cell Adenoma

Basal Cell Adenoma, Tubular
Basal Cell Adenoma, Membranous

Basal Cell Adenocarcinoma
Basal Cell Adenocarcinoma

Definition
• Malignant epithelial salivary gland neoplasm characterized by a variety of histologic growth patterns and the tendency for at least some of the neoplastic cells to recapitulate the appearance of normal serous acinous cells characterized by the presence of cytoplasmic (zymogen type) secretory granules

Acinic Cell Adenocarcinoma

Definition
• Malignant epithelial salivary gland neoplasm characterized by a variety of histologic growth patterns and the tendency for at least some of the neoplastic cells to recapitulate the appearance of normal serous acinous cells characterized by the presence of cytoplasmic (zymogen type) secretory granules

Clinical Features
• Represents approximately 18% of all malignant salivary gland neoplasms and 6.5% of all salivary gland neoplasms
• F > M; wide age range from children to older adults with a peak incidence in the 7th decade of life
• Parotid gland (>80%); less common sites include submandibular, sublingual, intraoral
• Slow growing, solitary (nonfixed) mass:
  – months to years
  – pain and/or facial nerve involvement uncommon
Acinic Cell Adenocarcinoma
Tumor-Associated Lymphoid Proliferation (TALP)

- Seen in wide variety of salivary gland lesions:
  - Nonneoplastic: Neoplasms (benign and malignant)
  - Nonneoplastic: Sialadenitis; cysts
- Neoplasms:
  - Benign: Warthin tumor; sebaceous lymphadenoma
  - Malignant: Acinic cell adenocarcinoma; Mucoepidermoid Carcinoma; Mammary Analogue Secretory Carcinoma; Others

Acinic Cell Adenocarcinoma & TALP

Acinic Cell Adenocarcinoma & TALP
Acinic Cell Adenocarcinoma
Treatment and Prognosis
• Surgical excision treatment of choice
• Radiation therapy generally not used
• Indolent neoplasm cured by surgery:
  – approx. 35% recurrence rate;
  – approx. 16% metastatic rate;
  – approx. 16% disease-associated death rate
• 5-year disease specific survival of 91%
• Rarely may transformation (dedifferentiation) to histologically higher-grade neoplasm

Mammary Analogue Secretory Carcinoma*
(MASC)
Definition
• Distinctive salivary gland neoplasm with features resembling acinic cell adenocarcinoma and low-grade cystadenocarcinoma, and displaying strong similarities to secretory carcinoma of the breast
* Skalova et al. AJSP 2010;34:599-608
* WHO 2017: Secretory Carcinoma
**MASC**

**Clinical Features**
- M > F; age range 21-75 (mean, 46 years)
- Most common in parotid gland but may occur in other major glands as well as in minor salivary glands
- Most common presentation is as a painless mass
- No known cause(s)

**MASC**

**Histopathology**
- Overlapping features with acinic cell carcinoma including:
  - growth patterns
  - cell types except for presence of cells with intracytoplasmic basophilic granules

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![Image of histopathology](image-url)
MASC

Immunohistochemistry

- Mammaglobin and S100 protein: diffuse and strong reactivity in conjunction with appropriate light microscopic features considered diagnostic even without molecular evaluation
- GATA binding protein 3 (GATA3): consistent strong and diffuse staining (i.e., >50% of cells) limited to MASC and salivary duct carcinoma
MASC Molecular Genetics
• t(12;15) (p13;q25) ETV6-NTRK3 translocation

MASC
• Most/all “zymogen poor” acinic cell carcinomas are MASCs
• Prior to diagnosing acinic cell carcinoma of a non-parotid gland site, exclusion of other diagnostic considerations especially MASC is mandatory as many acinic cell carcinomas of non-parotid gland sites have been reclassified as MASCs

MASC Treatment and Prognosis
• Complete surgical resection
• Efficacy of radiotherapy uncertain
• Overall indolent clinical course reported:
  – mean disease-free survival of 92 months
  – majority of cases reported without evidence of disease from 27 months - 10 years
  – minority of cases with recurrent and/or metastatic disease
• High-grade transformation rare (3 cases):
  – poor prognosis
Neck Dissection in Salivary Gland Carcinomas

- Low-Grade Carcinomas:
  - Not indicated unless there is clinical evidence of neck disease
- Intermediate-Grade Carcinomas:
  - Not indicated unless there is clinical evidence of neck disease
- High-Grade Carcinomas:
  - Indicated irrespective of absence of neck disease (N0)

Low-Grade Salivary Gland Carcinomas That May Present with Neck Disease

- Any may be associated with nodal metastasis at presentation but more common in association with
  - Cribriform Adenocarcinoma of Minor Salivary Glands (CAMSG)
  - (Hyalinizing) Clear Cell Carcinoma
- May present with nodal disease usually with clinically apparent lesion (e.g., oral cavity)
- When diagnosing these cancers in particular recommend clinical evaluation for possible presence of neck disease

Cribriform Adenocarcinoma of Minor Salivary Glands (CAMSG)

Definition

- Submucosal invasive adenocarcinoma with cribriform, tubular/glandular and papillary growth, nuclear features reminiscent of thyroid papillary carcinoma and tendency to be associated in a high percentage of cases with nodal metastasis.
- Synonyms: Cribriform adenocarcinoma of the tongue and minor salivary glands (CATMSG)
- WHO 2017: classified under “Polymorphous Adenocarcinoma” (Polymorphous Low-Grade Adenocarcinoma [PLGA])
CAMS

Clinical

- F>M; adults over a wide age range from 21-85 years with a mean of 56.8 years
- Most common site of occurrence is tongue:
  - base of tongue a frequent location
  - other intraoral sites of occurrence include soft palate, buccal mucosa, tonsil, lip
  - may occur outside the oral cavity including major salivary glands
- Presentation may include:
  - intraoral mass
  - not infrequently may present with enlarged lateral neck mass
- Etiology: no known associated causes
CAMSG

Nuclear features similar to PTC

“Glomeruloid” body

CAMSG

Nodal Metastasis

CAMSG

Genetic Profile

• Alterations in PRKD gene family
• Recurrent gene rearrangements in PRKD1, PRKD2, PRKD3
• Activating mutation of PRKD1 (p.Glu710ASP, Exon 15)
• PRKD1 and PRKD3 rearrangements found in clinically aggressive tumors
### CAMSG
**Treatment and Prognosis**
- Complete surgical resection to include tumor-free margins is indicated
- Regional (cervical) lymph node metastasis:
  - High frequency (65%) at presentation
  - Should necessitate neck dissection as part of initial treatment protocol
- Highly favorable prognosis:
  - Majority of patients alive without disease or alive with recurrent disease over extended periods
  - Prognosis does not appear to be altered by presence of nodal metastasis

### Polymorphous Low-Grade Adenocarcinoma (PLGA)
**Definition**
- Malignant epithelial neoplasm of (minor) salivary gland origin characterized by its diverse (polymorphous) architecture, bland cytopathology, infiltrative growth and indolent behavior
- WHO 2017: Polymorphous Adenocarcinoma
- Formerly referred to as:
  - Terminal duct adenocarcinoma
  - Lobular carcinoma

### PLGA
**Clinical Features**
- Increasingly recognized
- F > M; occurs over a wide age range
- Sites:
  - Intraoral minor salivary glands (palate > other sites)
  - Major glands: malignant component in carcinoma ex mixed tumor
  - De novo neoplasm
- Symptoms: painless mass, bleeding, otalgia, paresthesia, pain
- No known etiologic factors
Multiple Growth Patterns

Peripheral “Swirling” Pattern

“Slate Gray” Stroma
Single Cell Filing

Isomorphic Nuclei

Perineural Invasion
Tyrosine-like Crystals

Squamous Metaplasia

PLGA Immunohistochemistry

- Cytokeratins, EMA, S-100 protein, vimentin positive
- variable CEA and MSA
- p63 and p40:
  - variable p63 reactivity but usually at least focally present
  - p40 negative
- Usually negative for other markers of myoepithelial cells (calponin, SMA, SMMS1)
- GFAP typically negative
PLGA
Differential Diagnosis

• Adenoid cystic carcinoma
• Pleomorphic adenoma
• Monomorphic adenomas
• Cribriform adenocarcinoma of minor salivary glands (CAMSG)

Pairing p63 and p40

• IHC pairing p63 and p40 reported to assist in differentiating pleomorphic adenoma (PA) from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (AdCC)
  – PA: p63 +; p40+
  – Cellular PA: p63+; p40+ or p63- ; p40-
  – PLGA/CAMSG: p63+; p40-
  – AdCC: p63 +; p40+
PLGA Treatment and Prognosis

• Complete surgical resection treatment of choice:
  – radiation reserved for those tumors with inadequate surgical margins or for recurrent tumors;
  – neck dissection is not indicated unless there is evidence of cervical adenopathy

PLGA Treatment and Prognosis

• Indolent neoplasm:
  – local recurrence (9-17%)
  – regional metastasis (9-15%):
    • may occur in absence of local recurrence
    • may occur years following diagnosis
  – Death due to PLGA rarely occurs
  – Rarely:
    • Malignant component of CEPA;
    • Transformation to histologically higher grade

PLGA Treatment and Prognosis

• Overall prognosis is excellent:
  – indolent behavior: 95% 10-year survival
  – local recurrence rate between 9% and 17%:
    • due to its slow growth rate, local recurrence typically occurs several years following initial treatment
  • Regional metastatic rate from 9% to 15%
  – may occur years following initial treatment
  • Distant metastases seldom reported
  • Death attributed to tumor unusual and occurs after prolonged periods
Salivary Gland Neoplasms
Summary

• Salivary gland lesions are diverse with overlapping clinical and pathologic features
• Diagnosis and DDX:
  • Cytomorphologic criteria supplemented by IHC & molecular pathology
  • FNAB &/or Biopsy:
    – Excellent initial diagnostic modality
    – Provides guidance to the surgeon
    – Limitations in sampling especially relative to differentiating benign neoplasms from some low-grade carcinomas

Salivary Gland Neoplasms
Conclusions

• Salivary gland lesions are diverse with overlapping clinical and pathologic features
• Diagnosis and DDX usually by made by light microscopic findings:
  – Histomorphologic criteria supplemented by IHC
  – Criteria for malignancy
  – Emerging role of molecular biology in diagnosis and differential diagnosis

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Questions?
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