Surgical Pathology of minor salivary glands

«Diagnostic difficulties and pitfalls on diagnostic approach of minor salivary glands lumps»

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Minor Salivary glands

• Location: Submucosal connective tissue of Oral cavity and oropharynx

• Around 400-1000 of small size (1-2mm)

• They are predominantly mucous salivary glands except the serous glands/Von Ebner associated with the circumvallate papillae at the interface of the anterior two-thirds and posterior third of the tongue

• High concentration in the posterior hard palate and anterior aspect of soft palate
The minor salivary glands tumors consist a pathological group of high diversity, ranging from purely benign to low-intermediate-or high grade malignancies.

Overlapping features, between neoplastic and non-neoplastic lesions as well as between benign and malignant tumors
Indistinguishable clinically at initial stages
Cytology and heterogeneity of M.S.G. tumors

- 50% - 70% of the minor salivary glands (M.S.G) tumors are malignant
- However, more than 30% of the malignant tumors appear to have indolent and bland cytology
- Inside a tumor there are distinct foci of cellular heterogeneity. Different type or grade of differentiation neoplastic populations with different growth patterns along with non-neoplastic cells to include inflammatory cells, fibroblasts or reserve cells
- Therefore, a F.N.A.C has low sensitivity and specificity in distinguishing benign from malignant lesion
The role of neoplastic myoepithelial cells

• Play a prominent role with respect to the heterogeneity of the M.S.G. tumors

• Harbor the potential of de-differentiation, re-differentiation as well as trans-differentiation due to the genes instability, matrix factors and tumor factors produced by the epithelium.

• Show diverse morphology to include: **Angulate/basaloid cells, Epithelioid cells, Clear cells, Spindle cells, Plasmacytoid cells.**

• Stimulate the overproduction of matrix and basal membrane components.
Biphasic tumors

- The **Biphasic** minor salivary glands tumors show dual neoplastic cell type. One neoplastic population that derives from the *luminal cells* (secretory/epithelial) and a second cell population that has its origin from the *abluminal cells* (myoepithelial/basal cell)

- A SG tumor that shows two different types of cellular populations but only the one shows malignant changes is called bimorphic and not biphasic tumor.

- It is anticipated that the biphasic tumors show higher incidence of recurrence and unpredictable behavior and need regular follow-up.
Typical examples

MONOPHASIC TUMORS

• Myoepithelioma
• Canalicular adenoma
• Acinic cell carcinoma
• Salivary duct carcinoma

BIPHASIC TUMORS

• Pleomorphic adenoma
• Adenocystic carcinoma
• Epithelial- myoepithelial carcinoma
• Basal cell adenoma/adenocarcinoma
• Carcinosarcoma (ex-PA)
There are tumors of the minor salivary glands that derive directly from the pluripotent cells of the ductal system of the gland. The above cells could be differentiated to squamous, mucous or cylindrical as well as sebaceous cells.

- **Mucoepidermoid carcinoma** (mucous, intermediate, epidermoid)
- **Sebaceous adenoma or carcinoma**
- **Lymhadenoma**

- The squamous carcinoma of the final duct should be differentiated from de novo carcinoma and metastatic tumors.

• **REAL HYBRIDS EXIST BUT THEY ARE VERY SELDOM**
Classification of Salivary glands tumors

• Despite the overlapping between the matrix consistency, stain colour and cytology **three major groups** could be identified.

• **Basaloid tumors:** (blue tumors with H&E, increased ratio nuclei/cytoplasm- resemblance to pluripotent basal cells).

• **Clear cell tumors:** (Clear cells with H&E due to concentrated glygogen)

• **Oncocytic tumors** (epithelial cells with increased eosinophilic granular cytoplasm, H&E)
Venn’s diagram - 3 Overlapping cycles
Overlapping pathological and I.H.C features in minor salivary glands tumors
• **INTRA ORAL PLEOMORPHIC ADENOMA**

• 50% of minor salivary glands benign tumors.

• Characterized by pleomorphism of cellular growth patterns in loose connective tissue *matrix* that can show myxoid or mucous metaplasia and spindle cells “melt away” into it.

• *Cartilaginous metaplasia uncommon in intra-oral P.A.*

• The presence of plasmacytoid or hyaloid cells is almost pathognomonic for intra oral P.A.

• Microscopic intra and trans-capsular projections as well as satellite tumors are common features.

• **Non discrete capsule especially in soft palate** (demarcated but non-encapsulated)
PLEOMORPHIC ADENOMA

- **I.H.C indices** (GFAP) glial fibrillar acidic peptide, SMA, CK 14 and 5,6/7, characteristic of P.A.

- Molecular cytogenetics can be helpful in difficult d.d. cases

- **Translocations of chromosome 8**: t(3;8)(p21;q12) or t(5;8)(p11;q12) and overexpression of **PLAG1 gene in P.A.**

- Increased overlapping with other minor salivary glands tumors as well as with other tumors to include: Myxoma, chondrosarcoma, plasmacytoma etc.
Pleomorphic adenoma/pleomorphic adenocarcinoma (hard and soft palate border)
Differential diagnosis between Pleomorphic adenoma and low grade pleomorphic adenocarcinoma

- Peripheral and perineural infiltration

- «Single cell file, Indian file pattern» in the periphery due to the lack of synaptic proteins (Lobular breast Ca)

- “Washed out”, pale stain/ mucous or hyaloid matrix

- Negative for specific indices (GFAP and CD117), p63+/p40-, + S-100)

- Non biphasic tumor in comparison to P.A. and AdCa

- PRKD1 gene
Cribriform Adenocarcinoma

- Rare tumor/ Base of the tongue
- Cellular growth patterns surrounded by septum
- Nuclei open, clear, vesicular similar to papillary carcinoma of thyroid gland
- Surface covered by squamous epithelium
- Early lymphoid infiltration and neck metastases
- PRKD 1-3
Adenocystic carcinoma

• “Indolent and bland” Clinical appearance

• High infiltrative tumor (Ki 67 > 10%) causing early perineural infiltration with poor prognosis (10 y survival rate < 10%)

• Cribiform features – «Swiss cheese appearance» intervals of matrix clefts

• Angulated, hyperchromatic nuclei, scant cytoplasm.

• Biphasic tumor

• + p63/p40+, SMA+, CD117/c-kit, calponin

• MYB +
Differential diagnosis

• D.D. of P.A., polymorphous adenocarcinoma and adenoid cystic carcinoma may be particularly problematic due to overlapping cribriform features.

• Proliferation markers and I.H.C methods as well as the advent of molecular pathology now helps in the diagnosis of adenoid cystic carcinoma.

• Adenoid cystic carcinoma, though uncommon, could be the component of a true hybrid tumor.
Limitations of biopsy in M.S.G.tumors

- FNAC is an absolute indication in cases of inflammatory intraoral swellings for culture and antibiogram purposes.

- Is contraindicated for intraoral salivary gland tumors due to its limitations especially in differentiating benignancy from malignancy.

- Its value is limited in case of revealed frankly malignant cytology features. However, a confirmation incisional biopsy is mandatory.
• **Incisional biopsy** has relevant limitations with F.N.A.C due to overlapping histopathological features, in M.S.G tumors

• The limitation of incisional biopsy is more profound in monomorphic (bilayer) tumors eg basal cell adenoma/adenocarcinoma. In such case peripheral infiltration is the only histopathology criterion.

• Small biopsies or superficial punch biopsy should be avoided especially in palatal tumors

• **Incisional biopsy should be avoided in benign tumors due to the possibility of “seeding” especially on indication of pleomorphic adenoma**
Differential diagnosis between benign and low grade malignant tumor

Identification of:

1. Perineural infiltration
2. Angio-lymphoid infiltration
3. Infiltration of peripheral tissue (periosteum, bone, muscle)
4. Malignancy of classic morphology (acinic cell carcinoma, MEC, M.A.S.C. (without benign counterpart))
5. I.H.C expression of Calponin, telomerase ↑
6. Molecular cytogenetics specific characteristics (πχ CRTC1-MAML2, ETV6- NTRK3).
Dilemmas and “pitfalls”

in minor salivary gland tumor histopathology
1. The recognition of cribriform features in incisional biopsy is problematic and needs differentiation between P.A./pleomorphic adenocarcinoma/cribriform adenocarcinoma and especially with Adenoid cystic carcinoma (AdCC).

- Detailed examination of the whole specimen or more biopsies might be needed to identify all main characteristics of pleomorphic adenoma and safely exclude AdCC.

- I.H.C (GFAP/CD 117) and molecular cytogenetics (PLAG1 or MYB gene) can be of some help.
2. Intravascular deposits in the capsule are not uncommon in P.A. and should not be considered as a malignant sign if other criteria are not present.

3. The palatal P.A. might show squamous or mucous metaplasia as well as lymphoid infiltration. Since present there is a need for mucoepidermoid carcinoma differentiation.

- The lack of translocations t(11;19)(11;15), the lack of peripheral invasion along with myxoid stroma are in favor of P.A.
5. P.A. of high cellularity (myoepithelioma) along with oncocytic metaplasia, pleomorphic and hyperchromatic nuclei could give the impression of malignancy.

6. Superficial pseudo-epitheliomatous hyperplasia could be shown in intraoral P.A. as well as skin adnexa like squamous differentiation D.D. with epitheliomas.

7. Generally in “atypical” cases should have in mind the possibility of carcinoma ex pleomorphic adenoma.
Differentiate «pseudocapsular invasion» from true malignant invasion

**Lobular P.A.**

**INfiltrative CARCINOMA**
Tumor location and D.D.

• The majority of M.S.G. tumors are located in the palate except the **canalicular adenoma** and the (less common intraorally) **basal cell adenoma**. Both show preference of the upper lip.

• On the contrary **mucoceles** appear almost exclusively in the lower lip.

• The retromolar region is one of the most common locations of the mucoepidermoid carcinoma.
Canalicular adenoma

- Develops only in M.S.G.
- Monomorphic-Monophasic tumor
  Single layer of basal/cylindrical cells in vascular stroma
- Encapsulated and in upper lip (80%)
- Multifocal tumor

*Differentiation from basal cell adenoma that is (bilayer-palisading) biphasic tumor more common in parotid gland*
Mucoepidermoid carcinoma (MEC)

• Relatively common malignant tumor along with PAC and AdCC
• Usually cystic tumor with cystic areas surrounded by tubular growth patterns of epidermoid cells (low grade)

Clear and mucous cells is a common feature

_D.D._ meta renal Ca

Odontogenic clear cell tumor

_In MEC the presence of intermediate cells is pathognomonic_
Low grade mucoepidermoid carcinoma - Cystic tumor
Brandwein et al. grading system

Classification according to the cellular ratio and growth patterns

(Mucous cells - intermediate cells - Epidermoid cells)

Low grade M.E.C (mucous cells prominent) 10y survival rate=100%

Intermediate grade (intermediate cells prominent) 10y survival rate=70%

High grade (epidermoid cells dominant) 10y survival rate=40%

Show no characteristic I.H.C

Characterized by specific gene translocations t(11;19)(q21;p13) and genes fusions - CRTC1, MAML2
Mammary analogue Secretory carcinoma- (described in 2010)

Rare tumor with bland cytology and slow growth. However, may show unpredictable behavior. Overlapping features with Acinic cell carcinoma (ACC), P.A. and MEC

**D.D.**
- Lack of baseophilic cytoplasmic granules and expression of DOG-1 differentiation from A.C.C
- + S-100
- + mammoglobin in cystic areas
- Pathognomonic genes translocations
- \( t(12;15) \) ETV6-NTRK3
“Sieve-like” pattern of acinic cell carcinoma (zymogen granules) **BLUE TUMOR**/ “bubbling-like” pattern of Secretory carcinoma (colloid material) **PINK TUMOR**
Non-neoplastic lumps of M.S.Gs with Surgical significance
Sclerosing Polycystic Adenosis

• This is a rare disorder of the salivary glands that is thought to be inflammatory in origin, and resembles fibrocystic disease of the breast. Almost all cases have been reported in the parotid gland. Dense acellular fibrotic tissue with cystic dilatation of salivary ducts and acini remnants.

• D.D.
• Low grade MEC
• AdCC
• Cystadenocarcinoma
Necrotizing sialometaplasia

- Necrotizing sialometaplasia most commonly affects the palatal glands, presenting as a firm nodule that usually ulcerates, producing the appearance of malignancy.
- If left untreated, the lesions usually heal spontaneously in 4-6 weeks.
- Aetiology: Infarction of minor salivary glands (dentures, smoking, L.A.)
- Histopathology: Rounded islands of squamous cells in heavily inflamed fibropurulent tissue and necrosis
- D.D. Squamous cell carcinoma
  Mucoepidermoid carcinoma of high grade
Adenomatoid hyperplasia of M.S.G

• Unknown etiology - Idiopathic lump (1-3cm)
• Predisposing factor chronic trauma by dentures
• Predominantly in Palate
• In U.K. was first described by Scully in 1992 as «adenomatoid hyperplasia of minor salivary glands; Another sheep in Wolf’s clothing».
• Hyperplastic submucosal salivary glands, clusters of hypertrophic acini and overproduction of mucous and “spillage” in lesion stroma.
• Is Clinically indistinguishable from benign or malignant salivary glands tumors especially P.A. and pathologically from low grade mucoepidermoid carcinoma, in F.N.A.C

• Very rare almost forgotten diagnosis which is the main reason of not being included in preliminary differential diagnosis by the Clinicians

• Is not inflammatory and the treatment of choice is total excision

• There is a need for some caution, particularly in a small biopsy, because the diagnosis is to some extent one of exclusion, and occasional lesions are associated with an adjacent salivary gland tumour.

• Chromosomal aberrations have been identified t(2;14)(q21;q22) by Israel research Institution (2012). Is considered as benign tumor but for the time being is not known whether the chromosomal changes suggest malignant potential.
Granulomatous cheilitis

- Single manifestation of Melkerson-Rosenthal syndrome (palsy VII, facial swelling, oscheeoid tongue)
- 10-20 y old
- non-intestinal manifestation of Chrohn’s disease
- Needs differentiation from oncocytic tumors
- Treatment:
  - Local application of steroids or surgery
- 10%-25% risk of SCC development on the grounds of deep-purulent type
MUCOCELES

• **Extravasation cyst**: 90% of cystic lesions of minor salivary glands and mostly located in the lower lip. Children and young adults mostly affected

• **Retention cyst** (due to sialolithiasis- “stones”)
  • Intraorally in >40y adults with the exception of ranulæ that affect children

• When in upper lip or retromolar region needs differentiation from
  Canalicular carcinoma/ MEC, respectively

• **Treatment of choice is total excision**
New developments in I.C.H and molecular cytogenetics
New stains by using specific biological indices support the identification of tumors characteristics

The broader application of molecular pathology methods eg F.I.S.H (Fluorescence in situ hybridization probe)

Advance the diagnostic reliability of small biopsies or F.N.A.C.
The identification and knowledge of new chromosomal aberrations leads to the development of specific monoclonal antibodies for targeted mutations.

The potential and application of targeted therapy could lead to the improvement of malignant tumors prognosis.

However, the above specialized techniques can be provided for the time being, only by Institutions of high standards and experience.
Conclusion

«A wide range of neoplastic and non-neoplastic lesions arise in the intra-oral salivary glands and might be problematic even to the most experienced Specialist pathologist.

It's of great importance the careful examination of an adequate specimen or of the whole small tumor to establish reliable diagnosis.

However, the use of I.H.C or molecular pathology methods could improve the diagnostic accuracy in problematic cases.»

Thank you!