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Mire and Pelage-Mucoepidermoid Carcinoma Salivary Gland

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Abstract

Mucoepidermoid carcinoma of salivary gland is a frequently encountered, malignant neoplasm arising from salivary gland epithelium constituted of mucous cells, intermediate cells and epidermoid cells. Tumefaction is associated with specific chromosomal translocation t(11;19)(q14-21;p12-13) and CRTC1(MECT1)-MAML2 genetic fusion. Median age of disease emergence is 49 years and a mild female preponderance is observed. Neoplasm predominantly incriminates major salivary glands as the parotid gland. Tumefaction depicts a solid, cystic or dual configuration and is composed of neoplastic epidermoid cells demonstrating solid nests, sheets or cellular cords along with varying proportion of epidermoid cells, intermediate cells or mucocytes. Tumour cells appear immune reactive to pan-cytokeratin, CK5/6, p63, p40, epithelial membrane antigen(EMA), CK7 or CK14. Membrane bound mucins appear immune reactive to MUC1, MUC2, MUC4, MUC5AC and MUC5B. Mucoepidermoid carcinoma requires segregation from neoplasms such as pleomorphic adenoma with squamous cell and mucinous cell metaplasia, necrotizing sialometaplasia, Warthin tumour with squamous metaplasia, acinic cell carcinoma, mammary analogue secretory carcinoma (MASC), primary or secondary squamous cell carcinoma or salivary duct carcinoma. Preoperative assessment with ultrasonography or fine needle aspiration cytology may be beneficially employed. Tumefaction may be subjected to comprehensive surgical eradication with excision of broad perimeter of uninvolved, circumscribing soft tissue.

Keywords: Mucous; Epidermoid; Intermediate; Malignant; Stroma

Abbreviations: MASC: Mammary Analogue Secretory Carcinoma; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; FNAC: Fine Needle Aspiration Cytology; AFIP: Armed Forces Institute of Pathology; CT: Computerized Tomography.

Introduction

Mucoepidermoid carcinoma of salivary gland emerges as a commonly discerned, malignant neoplasm engendered from glandular epithelium. Characteristically, the epithelial neoplasm is constituted of mucous cells, intermediate cells and epidermoid cells. Additionally, tumour cells may display features of columnar cells, clear cells or oncocytoid change. Mucoepidermoid carcinoma is associated with specific chromosomal translocation t(11;19)(q14-21;p12-13) along with CRTC1(MECT1)-MAML2 genetic fusion.

Generally, the malignant salivary gland neoplasm is encountered within adults and paediatric subjects. Prognostic outcomes are contingent to tumour stage, site of tumour occurrence and status of surgical perimeter of

excised tissue.

Frequent and malignant, mucoepidermoid carcinoma of salivary gland represents up to 15% of salivary gland neoplasms. Median age of disease emergence is 49 years whereas adults between 15 years to 86 years can be incriminated. Paediatric instances manifest a median age of disease occurrence at 13 years wherein children between 11 years to 15 years may demonstrate the neoplasm. A mild female preponderance is encountered [1,2].

Majority (80%) of mucoepidermoid carcinomas exemplify chromosomal translocation t(11;19)(q14-21;p12-13) along with CRTC1(MECT1)-MAML2 genetic fusion. Aforesaid genetic alterations may be discerned with fluorescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) [1,2].

Mucoepidermoid carcinoma predominantly incriminates major salivary glands wherein parotid gland is frequently involved followed infrequency by submandibular gland or sublingual gland. Besides, minor salivary glands confined to palate, buccal mucosa or retromolar trigone may be implicated. Exceptionally, tumefaction may occur within sites such as sinonasal tract, nasopharynx, pulmonary parenchyma or intraosseous mandible. Mucoepidermoid carcinoma may possibly ensue following exposure to ionizing radiation [1,2].

An estimated one third (~33%) of subjects are asymptomatic. However, disease associated symptoms are variable and contingent to site of tumour emergence and magnitude. Commonly, neoplasm represents as a painless tumefaction engendering discomfort and localized pressure with variable adherence to circumscribing soft tissue. Neoplasm may appear as a rubbery or soft tumefaction [2,3]. Cytological examination of fine needle aspiration cytology (FNAC) smears frequently segregates neoplasms into low grade or high grade categories.

Low grade or intermediate grade mucoepidermoid carcinoma appears acellular or demonstrates hypo-cellular smears with prominent foci of extracellular mucin. Aggregates of epidermoid cells, intermediate cells and mucocytes appear disseminated within a cystic background. Epidermoid cells configure bland, cohesive, flattened, mono-layered sheets wherein cells demonstrate squamoid countenance or are permeated with dense cytoplasm with a well defined cellular perimeter.

Mucous cells configuring low grade neoplasms preponderantly appear to float within extracellular mucin pools. Foci of keratinization are generally absent. Abundant infiltrate of lymphocytes may emerge in ~ 20% neoplasms.

High grade mucoepidermoid carcinoma exhibits extensively cellular aspirates. Tumour cells depict high grade nuclear features constituted of pleomorphic nuclei incorporated with prominent nucleoli. Intermediate cells and mucous cells are infrequently encountered. Mitotic activity is enhanced. Focal tumour necrosis is commingled with the cellular content [2,3].

Upon gross examination, tumour appears well circumscribed with incomplete or absent encapsulation. Low grade mucoepidermoid carcinoma is frequently cystic. In contrast, high grade variant is commonly solid and necrotic with tan or pink hues.

Upon frozen section, high grade mucoepidermoid carcinoma may be misinterpreted as squamous cell carcinoma [3,4].

Upon microscopy, tumefaction depicts solid or cystic configuration or an admixture of dual patterns. Besides, papillary projections or glandular articulations may be discerned. Low grade mucoepidermoid carcinoma may appear partially encapsulated.

Neoplastic epidermoid cells configure solid cell nests, sheets or cellular cords. Tumour is composed of varying proportion of epidermoid cells, intermediate cells and mucocytes. Overt keratinization is exceptionally discerned [3,4].

Mucous cells appear encompassed within epidermoid cell nests or appear to layer cystic spaces. Intermediate cells may articulate distinct cell nests or pervade epidermoid cell clusters. Tumour cell aggregates are intermingled with foci of stromal sclerosis. Luminal or extracellular pools of mucin may be discerned. High grade lesions display fewer mucocytes or cystic spaces. Mitotic figures, tumour necrosis or focal cellular and nuclear pleomorphism are frequently enunciated. Besides, perineural, lymphatic or vascular invasion may ensue. Mucoepidermoid carcinoma may delineate distinct histologic variants as clear cell, oncocytic, sclerosing, Warthin-like, ciliated, spindle shaped cell or mucoacinar. Foci of clear cell change may appear due to cellular accumulation of glycogen [3,4].

Upon ultrastructural examination, adjoining epidermoid cells appear adherent with desmosomes. Mucous cells delineate mucous globules intermingled with stellate dissemination of mucoid substance [3,4] (Figures 1 & 2).

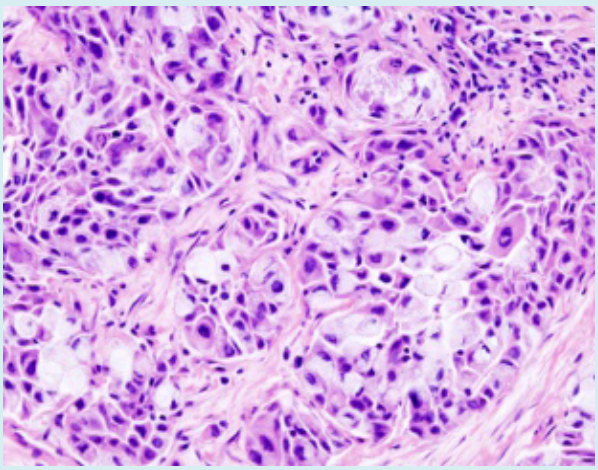

Figure 1: Mucoepidermoid carcinoma delineating an admixture of mucous cells, intermediate cells and epidermoid cells with minor component of clear cells, Tumour cells are imbued with pleomorphic nuclei. Fibrous tissue appears to encompass tumour cell aggregates [5].

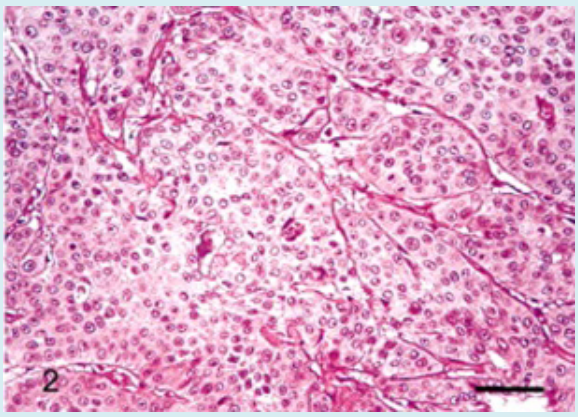

Figure 2: Mucoepidermoid carcinoma demonstrating an admixture of mucous cells, intermediate cells and epidermoid cells with intermingled mucoid substance. Pleomorphic nuclei and a component of clear cells is observed. Tumour parenchyma is traversed by vascularized fibrous tissue septa [6].

Mucoepidermoid Carcinoma can be Appropriately Graded with Specific Histological Grading Systems

- Armed Forces Institute of Pathology (AFIP) grading is comprised of criterion such as

a) intra-cystic component < 20% (2 points)
b) neural invasion (2 points)
c) tumour necrosis (3 points)
d) mitotic figures ≥4(3 points)
e) anaplasia (4 points).

- Thus assessed, neoplasm is graded as

a) low grade tumour (0-4 points)
b) intermediate grade tumour (5- 6 points)
c) high grade tumour (≥7 points)

- Brandwein et al grading is comprised of criterion such as

a) intra-cystic component < 25% (2 points)
b) infiltration of tumour front as miniature nests or cellular islands (2 points)
c) pronounced nuclear atypia (2 points)
d) lymphatic and vascular invasion (3 points)
e) bony invasion (3 points)
f) mitotic figures ≥4 (3 points)
g) perineural invasion (3 points)
h) tumour necrosis (3 points).

- Thus categorized, tumour is graded as

a) low grade (0 points)
b) intermediate grade (2- 3 points)
c) high grade (≥4 points)

- Modified Healy grading is constituted of

a) low grade tumour depicting

b) macro-cysts and micro-cysts
c) infrequently observed intermediate cells
d) exceptional mitotic figures
e) absent or minimal pleomorphic nuclei
f) well circumscribed tumefaction with broad perimeter
g) extravasation of mucin
h) fibrotic stroma

- Intermediate grade tumour delineating

a) micro-cysts and solid tumour component
b) abundant intermediate cells
c) few mitotic figures
d) mildly pleomorphic nuclei
e) lack of tumour circumscription
f) fibrotic stroma segregating tumour cell nests

- High grade tumour exhibiting
  a) predominantly solid tumour areas along with or devoid of micro-cysts
  b) perineural invasion
  c) lymphatic and vascular invasion
  d) infiltration of surrounding soft tissue
  e) several mitotic figures
  f) pleomorphic nuclei with prominent nucleoli
  g) predominant intermediate cells

Desmoplastic Stoma Memorial Sloan Kettering Cancer Centre (MSKCC) Grading

- Low grade tumour delineating

a) predominantly cystic pattern of growth (> 80%)
b) mitotic figures/10 high power fields (hpf)
c) well circumscribed tumour
d) absence of tumour necrosis

- Intermediate grade tumour enunciating

a) predominantly solid pattern of growth
b) 2-3 mitotic figures/10 high power fields (hpf)
c) well circumscribed or infiltrative neoplasm
d) absence of tumour necrosis

- High grade tumour exemplifying

a) solid tumour pattern although no pattern of neoplastic configuration is exempt
b) ≥ 4 mitotic figures/10 high power fields (hpf)
c) infiltrative neoplasm
d) presence of tumour necrosis [3,4].

Mucoepidermoid carcinoma appears immune reactive to pan-cytokeratin, CK5/6, p63, p40, epithelial membrane antigen(EMA), CK7 or CK14. Membrane bound mucins appear immune reactive to MUC1, MUC2, MUC4, MUC5AC and MUC5B.

Mucocytes are imbued with mucin which can be highlighted with mucicarmine and Periodic acid Schiff's(PAS-D) stain with diastase resistance. Occasional immune reactivity to SOX10, mammaglobin or GATA 3 may be encountered [7,8].

Mucoepidermoid carcinoma appears immune non reactive to S100 protein, glial fibrillary acidic protein(GFAP), calponin, muscle specific actin(MSA), androgen receptor(AR), HER2, DOG1 or CK20.

Low grade to intermediate grade mucoepidermoid carcinoma requires segregation from neoplasms such as pleomorphic adenoma with squamous cell and mucinous cell metaplasia, necrotizing sialometaplasia, Warthin tumour with squamous metaplasia, acinic cell carcinoma or mammary analogue secretory carcinoma (MASC). High grade mucoepidermoid carcinoma necessitates demarcation from tumours such as primary or secondary squamous cell carcinoma or salivary duct carcinoma [7,8].

Mucoepidermoid carcinoma of salivary glands may be subjected to definitive preoperative assessment with ~ultrasonography which is optimal for detecting miniature tumours confined to major salivary glands ~enlarged, reoccurring neoplasms may be subjected to computerized tomography (CT) in order to detect bone invasion [7,8].

Magnetic resonance imaging (MRI) can be beneficially adopted for discerning tumour metastasis confined to soft tissue. Advanced grade neoplasms delineating localized or regional metastasis may be subjected to 18-fluorodeoxyglucose positron emission computerized tomography (18-FDG PET/CT) for appropriate tumour discernment and ascertainment of metastasis. Preoperative assessment of tumefaction with fine needle aspiration cytology (FNAC) may be advantageously employed [7,8].

Radiographic features are pertinent to factors such as tumour magnitude, site of tumour emergence and grade of the neoplasm. Ultrasonography depicts a characteristic, partially or completely cystic, well circumscribed, hypoechoic lesion, in contrast to encompassing normal, hyperechoic parotid gland. Computerized tomography (CT) depicts diagnostic features pertinent to tumour grade. Low grade tumours are well circumscribed and demonstrate a cystic component. Occasionally, enhancing solid component or focal calcification may be encountered. High grade tumours appear solid with inadequately defined, neoplastic perimeter and infiltration into surrounding soft tissue. Upon magnetic resonance imaging (MRI), low grade tumours demonstrate an appearance identical to pleomorphic adenoma. High grade tumours appear as solid lesions. T2 weighted magnetic resonance imaging delineates decimated signal intensity and

an inadequately defined neoplastic perimeter [7,8].

Mucoepidermoid carcinoma of salivary gland may be optimally treated with comprehensive surgical extermination of the neoplasm. Conservative therapeutic strategies are recommended for managing stage I and stage II neoplasms. High grade mucoepidermoid carcinoma or neoplasms with tumour cells confined within surgical perimeter may be subjected to comprehensive surgical eradication of the neoplasm with excision of broad perimeter of uninvolved, circumscribing soft tissue. Dissection of regional, cervical lymph nodes is contingent to status of regional lymph nodes and histologic grade of the neoplasm.

Adjuvant radiotherapy and chemotherapy can be adopted as a therapeutic strategy for treating high grade tumours [7,8]. Mucoepidermoid carcinoma occurring in adults is associated with superior prognostic outcomes. Low grade neoplasms depict 5 year proportionate survival at ~98.8% whereas intermediate grade tumours delineate 5 year proportionate survival at ~97.4%. High grade tumours exhibit 5 year proportionate survival at ~67%. Incriminated paediatric subjects preponderantly exemplify low grade or intermediate grade tumours with 5 year proportionate survival of ~98% [5,6]. Factors contributing to inferior prognostic outcomes are designated as ~tumour confined to submandibular gland with frequently encountered regional lymph node metastases ~discernible tumour cells within surgical perimeter of resected neoplasm ~extra-parenchymal extension of the tumour ~occurrence of regional lymph node or distant metastases ~enhanced immune reactivity to MUC1[5,6].

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5. Image 1 Courtesy: Wikimedia commons.

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