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Salivary and Nonadnexal Oncogenesis: Mucoepidermoid Carcinoma

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Abstract

Mucoepidermoid carcinoma was initially scripted in 1924. It is a definitive malignancy comprising of variable permutations of squamous cells, mucus-secreting cells and intermediate cells. A proportionate 35% of the major and minor salivary gland tumours are configured by the neoplasm and two-thirds of the lesions usually manifest in the parotid. Mucoepidermoid carcinoma may anomalously be situated in the breast, eustachian tube, pulmonary bronchi, thyroid, palate and occasionally in the sub-glottis. Females are frequently affected, contrary to the males, at an estimated ratio of 3:2. The tumours generally arise in the fifth decade of life, the emergence may extend from 15 years to 86 years. Although mucoepidermoid carcinoma is a common salivary gland malignancy in children. The neoplasm may also appear as a non-adnexal, non-melanocytic tumour and may exceptionally ensue in the skin. The non-adnexal neoplasm usually mimic the salivary gland counterparts.

Keywords: Mucoepidermoid carcinoma; Salivary gland; Malignancy; Non-adnexal tumor; Non-melanocytic tumor

Analysis and Attributes

Mucoepidermoid carcinoma commonly commences from the subepithelial mucus glands that may configure the upper respiratory and digestive tracts [1-3]. The supra-glottis sub-site of the larynx displays an abundance of sub-epithelial mucous glands, thus the supra-glottic tumour may be a well classified lesion [4,5]. Mucoepidermoid carcinomas conventionally exhibit a histological designation of low, intermediate and high grade neoplasm. The high grade tumours may be inadequately delineated and are primarily constituted of squamous epithelial cells and intermediate cells. Low grade tumours may be appropriately defined and comprise of mucus secreting and squamous epithelial cells [5,6]. The intermediate variety may commonly be designed amidst the two associated variants. The evaluation of the histological grade is an invaluable methodology, frequently employed to predict the prognosis and therapeutic outcomes of the neoplasm in the major and minor salivary glands.

Clinical Aspects

The tumour depicts a painless, fixed, indolent, persistent lump that may precipitously enlarge, prior to detection [1,2]. Tenderness, otorrhoea, dysphagia and trismus are frequent, accompanying features. Intra-oral tumours are bluish red, fluctuant, lesions which may simulate mucocoeles or vascular lesions and may infiltrate the bony substratum [1,2].

Naked Eye Inspection

The tumour is well-circumscribed and incompletely encapsulated. The high grade tumours are infiltrative and fixed with a extraneous scarfing [1,3]. Predominantly, the tumour is below 4 centimetres in magnitude and is accompanied by variable cysts containing brownish fluid. Low grade tumours may be mucinous, gray/white and well delineated [1,3]. The tumours belonging to the category of sweat gland origin are typically of ≤ 0.6 cm in dimension, may be ulcerated, non-encapsulated, flesh coloured and painless nodules [6,7]. The specific non adnexal tumours may be well-demarcated, multi-lobulated, nodulo-cystic and may exemplify a dermal expansion.

Microscopic Elucidation

Mucoepidermoid carcinoma classically configures sheets, islands, duct like structures and cysts which may be laminated by intermediate, mucous, clear or epidermoid cells [1,3]. Papillary projections may ingress into the lumen of the cysts or glandular structures. Divergent proportions of intermediate, mucous and epidermoid cells (Figure 1) may be encountered in the neoplasm:

- Intermediate cells frequently emerge as small, basal cells with scanty basophilic cytoplasm and may be transformable to enormous, ovoid cells with abundant pale to eosinophilic cytoplasm. Extensive adaptations into the epidermoid or mucous cells may be probable.
- Mucous cells (mucocytes) may be demonstrated singularly or may abound in clusters and usually exhibit a pale, foamy cytoplasm, a distinct cell outline and miniature, compressed nuclei situated at the tumour cell perimeter. Mucocytes may prominently adhere to the incorporated cysts or duct linings. Special stains such as mucicarmine may be employed to determine the mucocytes in lesions in which they may be inadequate.
- Epidermoid cells (Figure 2) with abundant, basophilic cytoplasm are usually numerous, though they may be inadequate and singularly dispersed. Keratin pearls or dyskeratosis are features which may be generally absent. Oncocytic metaplasia may be infrequent [1-3]. Histological and adjunctive features are mentioned in Table 1 [1].

Table 1: Histological and adjunctive features.

Cellular Morphology	Mucous	Squamous	Intermediate	Clear
Cellular Pattern	Cords, Ducts	Sheets, Cysts	Clusters	Islands
Grade	Intra-cystic component >20% 2 points	Neural invasion 2 points	Necrosis, Mitosis(4 or more/ hpf) 3 points each	Anaplasia 4 points
	Low Grade 0-4	Intermediate Grade 5-7	High Grade > 7	
Low Grade	Mucinous cells	Intermediate cells	Bland Nuclei	Glandular spaces
High Grade	Atypical squamous cells	Intermediate cells	<20% intra-cystic component	No in situ Squamous Carcinoma
Immunohistoch-chemical stains	Low grade CK7, CK14	Anti-mitochondrial antibodiesp63	PTAH (oncocytic variant)	CK20
Sweat Gland origin (Non-adnexal)	Dermal Lobules, Cribriform Pattern	Intermediate, Mucinous, Clear, Epidermoid	Mucin, p63 EMA, pCEA Keratin, CK20,GCD FP-15 negative	CRTC1 rearranged MAML2, t(11:19) negative
Electron Microscopy	Luminal epithelial cells	Myoepithelial Cells		
Molecular /Cyto-genetic aspects	t(11:19) CRCT1-MAML2 fusion	q(14:21) CRCT3-MAML2 fusion	p(12:13)	MAML2 (Oncocytic variant)

Tumour Grading

High grade tumours (Figure 3) generally depict cytological atypia, numerous mitosis, zones of necrosis with predominant neural invasion and hyalinization of the stroma [1,3]. Mucoepidermoid carcinoma (Figure 4) exhibits a variable clinical picture Tumour grading methodologies based on a microscopic numerical score may be employed for assessing diagnostic aspects and prognostic outcomes [8,9]. The grading is contingent to quantification of cellular fractions, the extent of cellular atypia, the frequency of mitosis, the presence of necrosis and the characteristics of tumour invasion [10]. Random foci of sebaceous glands, goblet cells and an inflammatory reaction to the mucinous / keratinous exudate may be demonstrated. Low grade tumours (Figures 5 and 6) demonstrate an absence of prominent nuclear atypia, abundant mitosis or extensive necrosis [1,3].

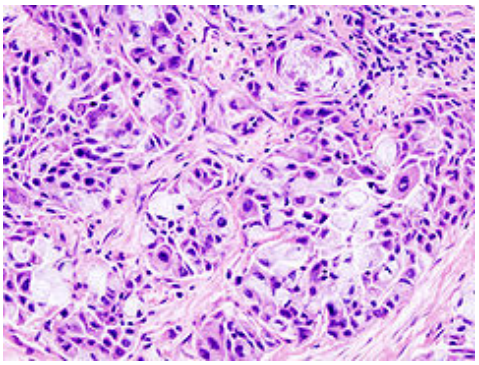

Figure 1: Squamous cells, clear cells, intermediate cells and mucinous cells in varying proportions.

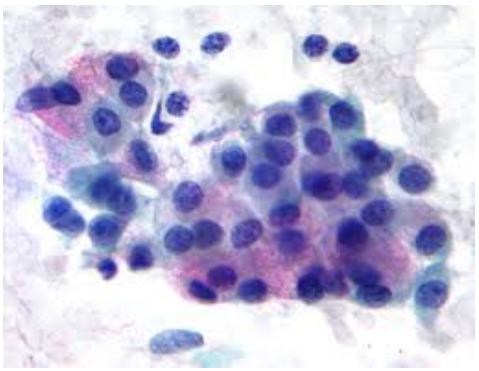

Figure 2: Mucoepidermoid carcinoma with predominant epidermoid cells and mucin-aspiration cytology.

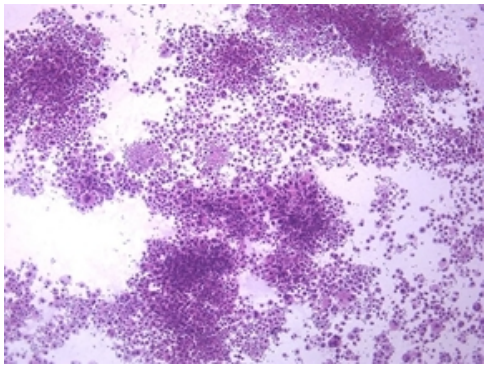

Figure 3: High grade mucoepidermoid carcinoma with squamous and intermediate cells aspiration cytology.

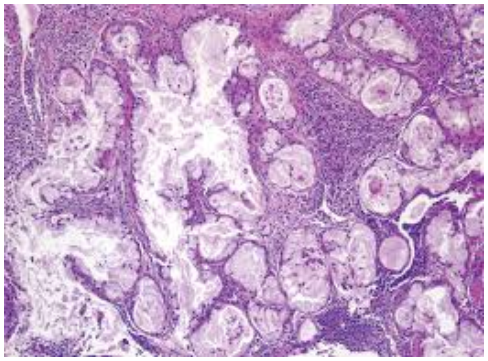

Figure 4: Mucoepidermoid Carcinoma with pools of mucin and clusters of sqaumous cell.

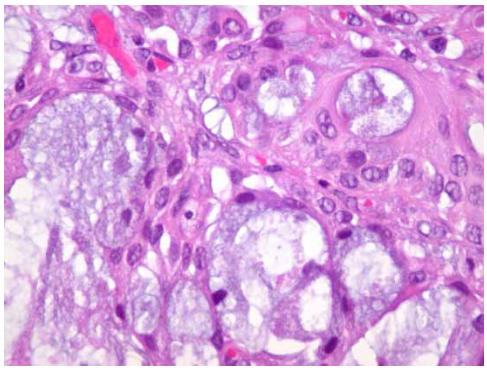

Figure 5: Low grade mucoepidermoid carcinoma with preponderant mucin, intermediate and clear cells with few squamous cells.

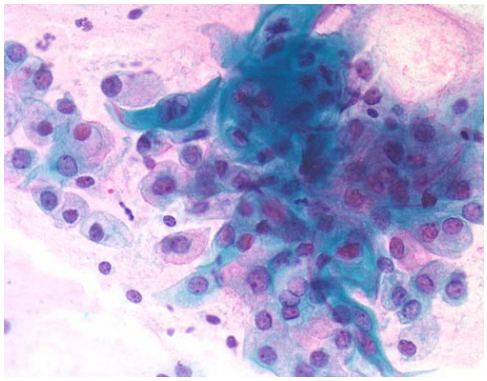

Figure 6: Low grade mucoepidermoid carcinoma with mucin, squamous and intermediate cells-aspiration cytology.

Variants of Muco-epidermoid Carcinoma

- The non adnexal tumours are usually low to intermediate grade lesions. The oncocytic variant is an infrequent occurrence (<10%). The tumour is comprised of a majority (>60%) of oncocytic cells, is preponderant in females and arises frequently in the submandibular or parotid gland [2,3]. Microscopy displays a low grade, cystic pattern of the tumour, constituted of medium sized oncocytic cells. Conditions that require a distinction from the oncocytic variant of the muco-epidermoid carcinoma are the acinic cell carcinoma, oncocytoma, oncocytic carcinoma, pleomorphic adenoma and concomitant tumour metastasis situated in the lung, breast, kidney [1,3].
- The high grade tumours may be classified as adenosquamous carcinomas. They display features of glandular or squamous differentiation. In addition, a component of low grade, uniform, epidermoid, intermediate, mucinous or clear cells may be exhibited with a cystic configuration. Glandular spaces with mucin, mildly atypical nuclei, scattered mitosis, peritumoral fibrosis and a perineural invasion may also be demonstrated [1,3].

Ultrastructural Inspection

The electron microscopic examination demonstrates a combination of luminal epithelial cells and a myoepithlial element with elongated cytoplasmic processes [1].

Immunohistochemical Evaluation

The tumour cells generally elucidate simple mucin type carbohydrate antigens, T, Tn and syalosyl Tn. Categories of mucus specific to mucoepidermoid carcinoma are MUC1, MUC 2 and MUC4, MUC5AC and MUC5B (MUC3 is predominantly delineated in adenoid cystic carcinoma) [1]. MUC 1 is ubiquitous in high grade tumours and MUC 3 is universally found in low grade tumours. The immune -markers of myoepithelial cells such as calponin, p-63, CD10, cyto-keratin 5/6, cyto-keratin 14, S-100 and α smooth muscle actin may be non-reactive [11,12].

Divergent Interpretation

Mucoepidermoid carcinoma essentially requires a distinction from necrotizing sialometaplasia, chronic sialdenitis, cystadenoma, cystadenocarcinoma, squamous cell carcinoma, epithelial myoepithelial carcinoma, clear cell carcinoma (not otherwise specified), adenosquamous carcinoma, poorly differentiated adenocarcinoma and metastatic tumours [1,3]. The differentiation of the non adnexal, sweat gland tumours may be from the high grade adenosquamous carcinoma involving the epidermis with a well differentiated adenocarcinomatous component, a metastatic high grade salivary gland tumour and a mucinous metaplasia [4].

Therapeutic Options

High grade tumours situated in the larynx and tumours of the major or minor salivary glands may be aggressively treated with a primary surgical intervention. Diverse sub-sites of the neoplasm and various histological grades may necessitate variable avenues of therapy. Partial laryngectomy may be prescribed for a supra-glottic low grade carcinoma and total laryngectomy may be applicable for sub-glottic tumours [11,12]. Additional treatment regimens may be required to maintain the function of the larynx and to achieve a tumour exempt surgical perimeter [3,4]. The employment of radiotherapy as a primary therapeutic modality may enunciate favourable as well as unfavourable treatment outcomes. It may be utilized as an adjunctive therapy in order to treat concomitant cervical lymph node enlargement [3,4]. The therapeutic decisions may vary according to the grade of the tumour, localization of the tumour and the clinical profile of the patient. For sub-glottic or low grade muco-epidermoid tumours, oncologic safety and therapeutic recommendations may be achieved by ensuring a surgical resection concordant with a tumour free perimeter while conserving the laryngeal function [4].

Conclusion

The results of the therapy is contingent to the clinical stage and site of the tumour, the histological grade and adequacy of the surgical resection. Comprehensive 5 year survival varies from 0 to 43% for high grade tumours, 62 to 92% for intermediate grade and 92to 100% for low grade tumours [1,3]. Indications of a poor prognosis may be the male sex, involvement of the submandibular gland, extra-glandular extension, vascular invasion, elderly patients, presence of necrosis, a high mitotic rate, enhanced cell proliferation as measured by MIB -1 antibody, DNA ploidy, the activation of the ERK-1/ERK-2 pathway and a high histological grade [1,3]. Mucoepidermoid carcinoma located in the sub-glottis or larynx is an exceptional neoplasm. The lack of early detection of laryngeal tumours may be attributable to the difficulty in identification of the neoplasm beyond the salivary gland. Inadequate sampling of the tumour and discrepancies of interpretation during the course of specimen evaluation and atypical locations of the lesions may also be implicated [4]. High grade mucoepidermoid carcinoma may be denominated as adenosqaumous carcinoma, especially in the larynx or be fallaciously described as squamous cell carcinomas [1,3].

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