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Editorial

The Diminutive Seepage-Micro-secretory Adenocarcinoma

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Current World Health Organization (WHO) classification of salivary gland tumours comprises of neoplasms depicting characteristic genetic fusions which engender novel and contemporary neoplastic entities.

Micro-secretory adenocarcinoma of salivary gland (MSA) emerges as a distinct, contemporary, unique neoplasm with significant, consistent clinical and genetic features and an indolent clinical course. Initially scripted in 2019, the low grade tumefaction demonstrates characteristic histological features, immuno-phenotypic profile and repetitive genetic fusion MEF2C-SS18.

However, the recently described neoplasm is devoid of comprehensive, specific clinical or pathological spectrum wherein cogent biological behavior remains undocumented.

Immunohistochemistry for S100 protein, SOX10, p63, p40, smooth muscle actin (SMA), calponin and mammaglobin along with molecular assay comprised of targeted RNA sequencing, SS18 break apart fluorescent in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) for discerning MEF2C-SS18 genetic fusion may be beneficially adopted for appropriate tumor discernment.

Typical histological features, immunohistochemistry and genetic profile of micro-secretory adenocarcinoma of salivary gland may be adopted for appropriate categorization of the neoplasm. Generally, classic morphology and reactivity to relevant immune markers is adequate for neoplastic classification. Nevertheless, cogent molecular assay may be indicated to categorize the entity in instances devoid of classic morphology or immunostaining.

The low grade carcinoma with indolent clinical course exemplifies bland cytological and morphological characteristics with absence of significant cellular proliferation, subtle, categorical, focal neoplastic infiltration and destruction of encompassing soft tissues or perineural invasion, thereby categorizing the lesion as a carcinoma or malignant neoplasm [1,2].

The low grade tumefaction appears amenable to singular surgical eradication and is devoid of localized tumour reoccurrence or distant metastasis upon extended monitoring. Notwithstanding, minimal, gradual tumour progression within an extended duration, localized tumour reoccurrence or distant pulmonary metastases appears indicative of a malignant neoplasm [1,2].

Characteristically, micro-secretory adenocarcinoma of salivary gland is devoid of significant cytological atypia and demonstrates an obligate, specific MEF2C::SS18 genetic fusion [2,3].

Tumefaction is comprised of uniform micro-cystic tubules coated with mono-layered, cuboidal epithelium. Cystic articulations are imbued with intraluminal secretions which may be highlighted by Periodic acid Schiff's (PAS) stain [2,3].

Majority of neoplasms emerge as miniature, intraoral lesions confined to minor salivary glands. Essentially low grade, tumefaction predominantly incriminates oral cavity and is especially discerned within minor salivary glands confined to subsites such as palate or buccal mucosa. Parotid gland represents as a non oral site of tumour emergence.

Generally, tumefaction incriminates adult population. Micro-secretory adenocarcinoma of salivary gland may occur within 17 years to 83 years with mean age of disease discernment at 49.5 years. A mild female predominance is observed [2,3].

Grossly, micro-secretory adenocarcinoma appears as a well circumscribed, non encapsulated neoplasm implicating the salivary gland. Exceptionally, tumefaction of variable magnitude is confined to retromolar trigone [3,4].

Upon microscopy, micro-secretory adenocarcinoma of salivary gland consistently exhibits features as micro-cystic tubules or flattened intercalated duct-like cells imbued with monotonous, elliptical hyperchromatic nuclei. Abundant basophilic intraluminal secretions impact cystic structures. Circumscribing stroma appears fibromyxoid. Neoplastic cellular aggregates may egress encompassing tumor perimeter with subtle foci of infiltration [3,4].

Tumefaction is composed of epithelial cellular proliferation depicting subtle infiltration within adjoining skeletal muscle, adipose tissue or native seromucinous glands. Tumefaction configures micro-cysts.

Repetitive, distinct histological features appear as preponderantly micro-cystic tumour configuration demonstrating abundant, basophilic intraluminal secretions. Uniform, intercalated duct-like cells are permeated with attenuated, eosinophilic to clear cytoplasm and elliptical, monomorphic, hyperchromatic nuclei with indistinct nucleoli.

Tumour cell aggregates are circumscribed by variably cellular, fibromyxoid stroma and exemplify spherical margins depicting subtle foci of neoplastic infiltration [3,4].

Occasionally, fusion of micro-cysts may articulate dis-cohesive, cribriform structures. Cords of tumour cell cords may be encountered. Singular tumour cells are exceptional. Micro-cysts, cords and cribriform articulations are layered by singular coat of flattened epithelial cells pervaded with moderate, eosinophilic to clear cytoplasm and monomorphic, elliptical, hyperchromatic nuclei with indistinct nucleoli. Micro-cysts depict a variable calibre wherein the intra-luminal content delineates amphophilic to basophilic secretory substances which can be highlighted by mucicarmine. Circumscribing stroma is fibromyxoid and variably cellular [4,5].

Infrequently, morphological features as pseudo-epitheliomatous hyperplasia of superimposed squamous epithelium, accumulated tumour associated lymphoid proliferation (TALP) circumscribing the neoplasm, metaplastic bone, hyalinising fibrosis or psammomatoid calcification may be encountered.

Exceptionally, neoplasm may depict a solid growth pattern or spindle shaped cells, rosette-like cells or clear cells admixed with foci of classic micro-secretory adenocarcinoma [4,5].

Occasionally, perineural invasion may ensue. Lymphatic or vascular tumour infiltration is absent. Mitotic activity is minimal. Tumour necrosis is absent [4,5].

Benign Epithelial Tumours	Malignant Epithelial Tumours
Pleomorphic adenoma	Mucoepidermoid carcinoma
Basal cell adenoma	Adenoid cystic carcinoma
Warthin tumour	Acinic cell carcinoma
Oncocytoma	Secretory carcinoma
Salivary gland myoepithelioma	Micro-secretory adenocarcinoma
Canalicular adenoma	Polymorphous adenocarcinoma
Cystadenoma of salivary gland	Hyalinising clear cell carcinoma
Ductal papilloma	Basal cell adenocarcinoma
Sialadenoma papilliferum	Intra-ductal carcinoma
Lymphadenoma	Salivary duct carcinoma
Sebaceous adenoma	Myoepithelial carcinoma
Intercalated duct adenoma and hyperplasia	Epithelial-myoepithelial carcinoma
Striated duct adenoma	Mucinous adenocarcinoma
Sclerosing polycystic adenoma	Sclerosing micro-cystic adenocarcinoma
Keratocystoma	Carcinoma ex pleomorphic adenoma
Sialolipoma (mesenchymal tumour of salivary gland)	Carcinosarcoma of salivary glands
	Sebaceous adenocarcinoma
	Lympho-epithelial carcinoma
	Squamous cell carcinoma
	Sialoblastoma
	Salivary carcinoma (NOS) and emerging entities

Table: *WHO classification of salivary gland tumors (5th edition) [2].*

Micro-secretory adenocarcinoma of salivary glands appears consistently, diffusely and intensely immune reactive to CK14, CK18, S100 protein, p63 and SOX10. Myoepithelial markers as smooth muscle myosin heavy chain are frequently immune reactive in tumefaction which recapitulates intercalated ducts. Smooth muscle actin (SMA) is variably immune reactive and exhibits a focal, luminal distribution.

Neoplastic cells appear immune non reactive to p40, calponin and mammaglobin [4,5].

Proliferative activity is minimal, as demonstrated with minimal mitotic count. Besides, Ki67 proliferative index is beneath < 5%.

Duct forming micro-secretory adenocarcinoma of salivary gland necessitates segregation from neoplasms such as salivary gland adenocarcinoma not otherwise specified (NOS), intercalated-duct subtype of polymorphous adenocarcinoma, secretory carcinoma, mucinous adenocarcinoma with signet ring cell subtype or secretory myoepithelial carcinoma of salivary gland [4,5].

Features such as absence of cellular atypia or enhanced cellular proliferation within micro-secretory adenocarcinoma of minor salivary glands may concur with benign salivary gland neoplasms as pleomorphic adenoma wherein cogent demarcation between the tumours may be challenging. Notwithstanding, cell-poor zones intermixed with abundant fibro-myxoid stroma encountered within micro-secretory adenocarcinoma of salivary gland appear intensely reminiscent of pleomorphic adenoma. Nevertheless, characteristic monomorphic

tubules or micro-cysts exemplified within micro-secretory adenocarcinoma are coated with singular epithelial cell layer, in contrast to neoplastic tubules configuring pleomorphic adenoma which are coated with dual epithelial cell and myoepithelial cell layer.

Typically, micro-secretory adenocarcinoma of salivary glands depicts MEF2C-SS18 genetic fusion. Fluorescent *in situ* hybridization (FISH) exemplifies SS18 break apart [4,5].

Characteristically discerned MEF2C-SS18 genetic fusion may be demonstrated with diverse molecular methodologies as RNA sequencing, SS18 fluorescent in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR).

RNA sequencing exhibits identical breakpoints upon exon 7 of MEF2C gene and exon 4 of SS18 gene [4,5].

Micro-secretory adenocarcinoma may be suitably treated with singular surgical eradication of the neoplasm.

Generally, tumor reoccurrence or distant metastasis is absent. However, instances documenting delayed, localized tumour reoccurrence or distant metastases categorize micro-secretory adenocarcinoma as a low grade, malignant entity [4,5].

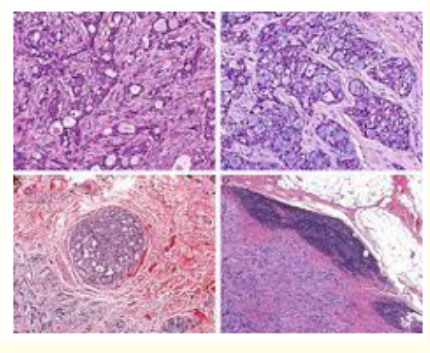

Figure 1: *Micro-secretory adenocarcinoma demonstrating micro-cysts and tubules lined by mono-layered, flattened epithelial cells imbued with eosinophilic cytoplasm, elliptical hyperchromatic nuclei and indistinct nucleoli. Encompassing stroma is fibromyxoid [6].*

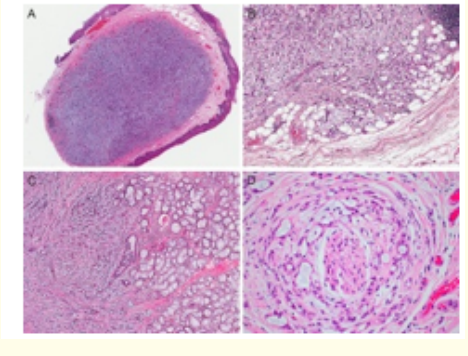

Figure 2: *Micro-secretory adenocarcinoma delineating micro-cysts and tubules coated by mono-layered epithelium pervaded with eosinophilic cytoplasm, ovoid hyperchromatic nuclei and indistinct nucleoli. Neoplastic aggregates are enmeshed within a fibromyxoid stroma [7].*

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6. Image 1 Courtesy: Ingenta connect.

7. Image 2 Courtesy: Research gate.

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