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Editorial

The Ravaged Conduit--Intercalated Duct Lesions-Salivary Gland

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Intercalated duct lesions represent as a morphological spectrum ranging from intercalated duct hyperplasia to intercalated duct adenoma. The essentially benign, miniature lesions simulate cytological and immunological profile of normal intercalated ducts.

Miniature intercalated duct lesions are frequently discovered incidentally whereas intercalated duct adenomas appear enlarged and may represent with distinct clinical symptoms.

Intercalated duct lesions preponderantly arise within the parotid gland followed in frequency by submandibular gland. Few lesions may be confined to the oral cavity. Tumefaction is commonly confined to the parotid gland, in contrast to submandibular gland, in a proportion of 3:1.

The lesions emerge within 19 years to 80 years with mean age of disease emergence at 53.8 years. A female predominance is encountered with female to male proportion of ~1.7:1 [1,2].

Intercalated duct hyperplasia emerges as an incidental (~70%) discovery upon morphological assessment of a salivary gland neoplasm. A male preponderance is encountered with male to female proportion of ~3:1. The lesion is commonly discerned within the sixth decade [1,2].

Intercalated duct lesions are concurrent with and configure as a precursor of diverse salivary gland neoplasms as epithelial-myoepithelial carcinoma, basal cell adenoma, basal cell adenocarcinoma, pleomorphic adenoma, Warthin's tumour, acinic cell carcinoma, mucoepidermoid carcinoma or hybrid tumours with a component of intercalated duct lesion morphologically adjunct to a distinctive neoplasm as a basal cell adenoma or epithelial-myoepithelial carcinoma. Intercalated duct lesions may concur with chronic parotitis [2,3].

Intercalated duct hyperplasia is postulated to be a precursor lesion of salivary gland neoplasms as epithelial-myoepithelial carcinoma [2,3].

Molecular assay delineates distinctive pathogenic mutations, especially genomic mutations within CTNNB1 gene as encountered within hyperplastic and hybrid lesions. Intercalated duct adenoma may delineate hotspot genomic mutations within HRAS genes, akin to epithelial-myoepithelial carcinoma, thereby indicating a true neoplastic nature of intercalated duct lesions and molecular concordance with basal cell adenoma and epithelial-myoepithelial carcinoma [3,4].

Macroscopically, lesions predominantly emerge as miniature, diffuse, unifocal or multifocal lesions. Typically, lesion magnitude varies from one millimetre to 8 millimetres [3,4].

Grossly, intercalated duct adenoma represents as a discrete, well defined, partially or completely encapsulated tumefaction, in contrast to intercalated duct hyperplasia [3,4].

Upon microscopy, lesion is comprised of proliferating ducts commingled with acinar cell aggregates. Constituent ducts are coated with singular epithelial cell layer. Occasionally, acinic cells may be expounded. Besides, luminal and abluminal layer of epithelial cells may be encountered [4,5].

Typically, acinar cells demonstrate atrophic alterations as loss of zymogen granules or decimated cell volume wherein the lesion morphologically simulates intercalated ducts [4,5].

Intercalated duct hyperplasia and adenoma delineate proliferation of miniature ducts coated with epithelial cells impregnated with eosinophilic to amphophilic cytoplasm and miniature, bland nuclei. Circumscribing layer of myoepithelial cells appears inconspicuous [4,5].

Histologically, intercalated duct lesions appear reminiscent of normal intercalated ducts wherein lesions vary from hyperplasia to encapsulated adenoma or hybrid tumours [5,6].

Intercalated duct hyperplasia configures a non encapsulated lesion composed of proliferating intercalated ducts surrounded by minimal stroma. The cellular component is admixed with acinic and mucous cells constituting normal salivary gland parenchyma.

Intercalated duct adenoma configures as a benign lesion composed of proliferating ducts layered by dual epithelial cell layer [5,6].

Intercalated duct adenoma emerges as spherical, discrete, well defined, partially to completely encapsulated tumour nodule with a circumscribing fibrous capsule of variable density. Tumefaction appears disparate from normal salivary gland parenchyma [5,6].

Hybrid neoplasms depict a mixed configuration composed of partially encapsulated adenoma-like lesion commingled with irregular, hyperplasia-like, singular or multiple foci confined to tumour periphery. Hybrid zones comprised of hyperplastic intercalated duct foci demonstrating transition into discrete adenomatous areas may be discerned. Pre-eminently, amalgamated or hybrid intercalated duct lesion is constituted of proliferation of miniature ducts layered by epithelial cells impregnated by eosinophilic to amphophilic cytoplasm and miniature, bland nuclei [5,6].

Tumour subtype	Chromosome	Gene/Mechanism
Pleomorphic adenoma	8q12,12q13-15	PLAG1 or HMGA2 fusion/amplification
Basal cell adenoma	3p22.1,16q12.1,16p13.3, 5q22.2	CTNNB1, CYLD, AXIN1, APC mutation
Myoepithelioma-oncocytic	8q12	PLAG1 fusion
Sialadenoma papilliferum	7q34	BRAFV600E mutation
Sclerosing polycystic adenoma	3q26.32	PIK3CA mutation high
Mucoepidermoid carcinoma	t(11;19)(q21;p13), t(11;15) (q21;q26),9p21.3	CRTC1-MAML2 CRTC3-MAML2 CDKN2A deletion
Adenoid cystic carcinoma	6q22.23, 8q13,9q34.3	MYB or MYBL1 fusion/activation/ amplification, NOTCH mutation
Acinic cell carcinoma	9q31, 19q31.1	NR4A3 fusion/activation, MSANTD3 fusion/amplification

Secretory carcinoma	t(12;15)(p13;q25), t(12;10)(p13;q11), t(12;7)(p13;q31), t(12;4)(p13;q31), t(10;10)(p13;q11)	ETV6-NTRK3 or ETV6-RET or ETV6-MET or ETV6-MAML3 or VIM-RET fusion
Micro-secretory adenocarcinoma	t(5q14.3)(18q11.2)	MEF2C-SS18 fusion
Polymorphous adenocarcinoma		
Classic subtype	14q12	PRKD1 mutation
Cribriform subtype	14q12, 19q13.2, 2p22.2	PRKD1, PRKD2 or PRKD3 fusion
Hyalinising clear cell carcinoma	t(12;22), q(21;12)	EWSR1-ATF1 or EWSR1-CREM fusion
Basal cell adenocarcinoma	16q12.1	CYLD mutation
Intra-ductal carcinoma		
Intercalated duct subtype	10q11.21	RET fusion
Apocrine subtype	3q26.32, 11p15.5	PIK3CA, HRAS mutation
Salivary duct carcinoma	17q21.1, 8p11.23, 17p13.1, 3q26.32, 11p15.5, Xq12, 10q23.31, 9p21.3	HER2, FGFR1 amplification, TP53, PIK3CA, HRAS mutation, AR copy gain, PTEN, CDKN2A loss
Myoepithelial carcinoma	8q12, t(12;22)(q21;q12)	PLAG1 fusion, EWSR1 rearrangement
Epithelial-myoepithelial carcinoma	11p15.5	HRAS mutation
Mucinous adenocarcinoma	14q32.33, 17p13.1	AKT1 E17K or TP53 mutation
Sclerosing microcystic adenocarcinoma	1p36.33	CDK11B mutation
Carcinoma ex pleomorphic adenoma	8q12,12q13-15, 17p13.1	PLAG1 or HMGA2 fusion/ amplification, TP53 mutation
Sebaceous adenocarcinoma	2p21	MSH2 loss

Table: *Genetic alterations in salivary gland tumours [5].*

Immunohistochemically, intercalated duct lesion simulates the staining pattern of normal intercalated ducts. Ductal cells of intercalated duct lesion appear diffusely immune reactive to cytokeratin CK7 and S100 protein with focal immune reactivity to lysozyme A and oestrogen receptors. Circumscribing myoepithelial cell layer encompasses the ducts. However, non-lesional ducts appear immune non reactive to S100 protein. A subset of lesions delineate nuclear localization of β catenin [6,7].

Intercalated duct adenoma requires segregation from neoplasms as basal cell adenoma, basal cell adenocarcinoma or epithelial-myoepithelial cell carcinoma [6,7].

Upon ultrasonography, a hypo-echogenic tumefaction of variable magnitude appears confined to the parotid gland or various sites of tumour emergence. Besides, submandibular or abutting lymph nodes may be enlarged [7,8].

T1 weighted contrast-enhanced magnetic resonance imaging (MRI) exemplifies accumulation of contrast within the neoplastic core and absence of definitive contrast accumulation within the capsule.

T2 weighted contrast-enhanced magnetic resonance imaging (MRI) of the implicated gland expounds a well encapsulated tumour with enhanced signal intensity [7,8].

Surgical intervention remains a preferred mode of therapy. Intercalated duct lesions may be suitably subjected to surgical extermination of the neoplasm [7,8].

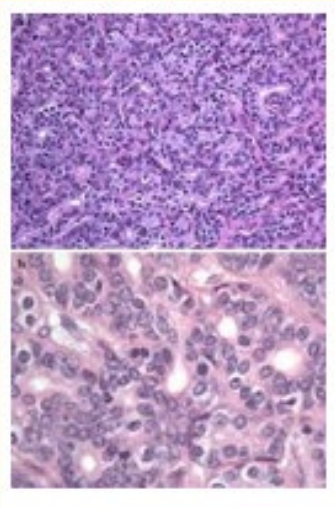

Figure 1: *Intercalated duct lesion demonstrating proliferating ducts layered by epithelium imbued with eosinophilic cytoplasm and bland, miniature nuclei. Circumscribing layer of myoepithelial cells is encountered [9].*

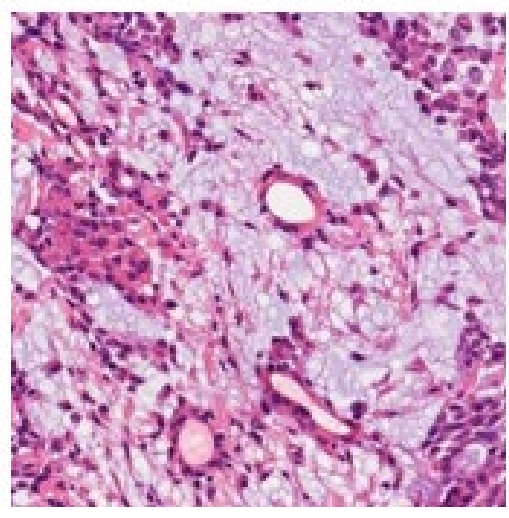

Figure 2: *Intercalated duct lesion delineating proliferating ducts lined by epithelium impregnated with eosinophilic cytoplasm and bland, miniature nuclei. Surrounding myoepithelial cell layer is observed. The ductal component is encompassed with mildly inflamed fibrotic tissue [10].*

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9. Image 1 Courtesy: Europe PMC.

10. Image 2 Courtesy: Research gate.

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