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Burnished and Luminous-Hyalinising Clear Cell Carcinoma

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Editorial

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Abbreviations: NOS: Not Otherwise Specified; EMA: Epithelial Membrane Antigen; SMA: Smooth Muscle Actin; MSA: Muscle Specific Actin; GFAP: Glial Fibrillary Acidic Protein; RNA ISH: RNA in Situ Hybridization; HPV: Human Papilloma Virus; MRI: Magnetic Resonance Imaging; FISH: Fluorescent in Situ Hybridization.

Editorial

Hyalinising clear cell carcinoma is a unique, exceptionally encountered, malignant neoplasm of salivary glands commonly incriminating minor salivary glands, especially intraoral glands. Typically, tumefaction exhibits genomic fusion EWSR1: ATF1. Besides, various fusion oncogenes or concurrent, variant genetic fusions are encountered.

Hyalinising clear cell carcinoma of salivary gland is comprised of bland, monomorphic tumour cells incorporated with clear to eosinophilic cytoplasm. Tumour cells configure nests, trabeculae or cellular cords embedded within a hyalinised stoma. Occasional glandular articulations or presence of intracellular mucin indicates the neoplasm to be a variant adenosquamous carcinoma.

Additionally designated as clear cell carcinoma, clear cell adenocarcinoma or clear cell carcinoma not otherwise specified (NOS), neoplasm exhibits dual stromal component designated as dense, hypo-cellular, hyalinised tissue which appears juxtaposed to desmoplastic stroma with foci of myxoid alterations. Ultrastructural examination and cogent immunohistochemistry with HMWK and p63 is indicative of a squamous lesion or neoplasm with focal squamous differentiation. The low grade, salivary gland neoplasm exhibits few instances of regional lymph node or distant metastases.

Hyalinising clear cell carcinoma of salivary gland typically incriminates subjects > 60 years although tumefaction exhibits a wide range of disease emergence. A mild female preponderance is encountered.

Hyalinising clear cell carcinoma predominantly (> 80%) emerges within intraoral minor salivary glands. Frequently, tumour is confined to base of tongue or soft palate. Few lesions are enunciated within major salivary glands, nasopharynx or larynx [1,2].

Majority (>80%) of neoplasms depict EWSR1::ATF1 genetic fusion. Besides, variant genetic fusion as EWSR1::CREM may be exemplified. Tumefaction appears devoid of MAML2 genetic fusion. Nevertheless, genetic rearrangements within PBX1, ZNF444 and POU5F1 are absent, thereby indicating non concurrent salivary gland equivalent of soft tissue myoepithelial tumour [1,2]. Hyalinising clear cell carcinoma of salivary gland is accompanied by history of brief duration of disease representation and emerges as a tumefaction confined to submucosal zone. Superficial mucosa may undergo ulceration. Neoplasm may be encountered incidentally, upon dental examination. Majority of lesions endorse a short history prior to medical detection [3,4].

Cytological examination exemplifies cohesive clusters of monomorphic epithelial cells incorporated with abundant, clear cytoplasm, uniform spherical to ovoid nuclei, granular nuclear chromatin, miniature nucleoli, nuclear grooves and intra-nuclear cytoplasmic inclusions. Bare nuclei stripped of cytoplasm are discerned. Myoepithelial cells are generally absent. Cellular aggregates display a prominent, intermingled tigroid substance [3,4].

Grossly, a grey/white, firm, well circumscribed tumefaction varying from 1.0 centimetre to 4.5 centimetre magnitude is encountered.

Hyalinising clear cell carcinoma is composed of anastomosing nests, trabeculae or cords of monomorphic tumour cells incorporated with clear or eosinophilic cytoplasm. Characteristically, circumscribing stroma configures as dense, hypo-cellular, hyalinised tissue abutting desmoplastic stroma which appears myxoid. Tumour cell aggregates appear contiguous with superimposed epithelium and may display a pagetoid pattern of tumour cell dissemination. Tumour cell aggregates delineate squamoid countenance although overt keratinization is absent. An estimated 50% neoplasms depict foci of mucinous differentiation or perineural invasion. Bone invasion is enunciated.

Focal pseudo-epitheliomatous hyperplasia may ensue. Mitotic activity is minimal. Tumour necrosis is uncommon [3,4]. Upon ultrastructural examination, tumour cells appear pervaded with abundant glycogen, desmosomes, peripheral tonofilaments and prominent interdigitating microvilli. Foci of reduplicating basal lamina may be encountered [3,4].

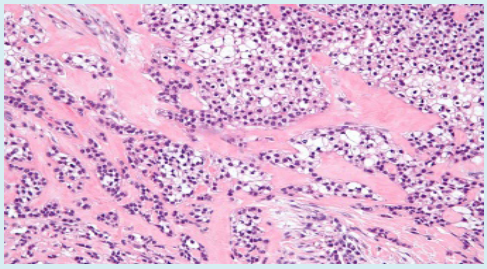

Figure 1: Hyalinising clear cell carcinoma demonstrating cords, nests and trabeculae of tumour cells imbued with clear cytoplasm surrounded by hypo-cellular, dense, hyalinised stroma juxtaposed with myxoid and desmoplastic stroma [7].

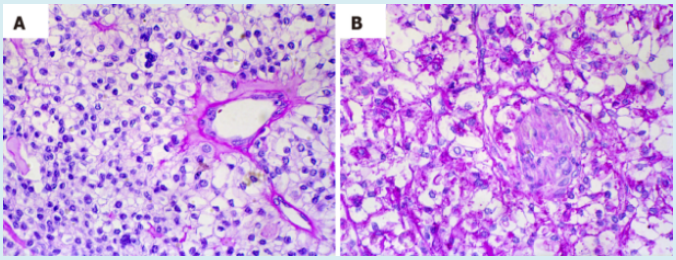

Figure 2: Hyalinising clear cell carcinoma enunciating cords, nests or trabeculae of tumour cells incorporated with clear cytoplasm. Circumscribing stroma is dense, hyalinised, hypo-cellular with adjoining desmoplastic and myxoid stroma [8].

Tumour subtype	Chromosome	Gene/Mechanism
Pleomorphic adenoma	8q12,12q13-15	PLAG1 or HMGA2 fusion/amplification
Basalcell 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

Table1: Genetic alterations in salivary gland tumours [4].

Hyalinising clear cell carcinoma appears immune reactive to pancytokeratin, p63, p40, CK7, CK19, epithelial membrane antigen (EMA) and CAM5.2. Around 70% neoplasms depict variable immune reactivity to p16.

Hyalinising clear cell carcinoma appears immune non-reactive to S100 protein, smooth muscle actin (SMA), muscle specific actin (MSA), calponin or glial fibrillary acidic protein (GFAP). RNA in situ hybridization (RNA ISH) exhibits high risk variants of human papilloma virus (HPV) [5,6].

Hyalinising clear cell carcinoma of salivary gland requires segregation from neoplasms such as mucoepidermoid carcinoma, squamous cell carcinoma, clear cell odontogenic carcinoma, epithelial-myoepithelial carcinoma, metastatic clear cell renal cell carcinoma or clear cell myoepithelial carcinoma [5,6].

Appropriate discernment of hyalinising clear cell carcinoma may be challenging upon singular histological examination on account of variable spectrum visualized upon morphology and immunohistochemistry.

Segregation from concurrent neoplastic entities incriminating salivary glands may be challenging. Thus, fluorescent in situ hybridization (FISH) for ascertaining ESWR genetic rearrangement appears optimal, recommended and mandatory [5,6].

Upon radiography, tumefaction depicts nonspecific features. Upon T1 weighted magnetic resonance imaging (MRI), tumefaction appears well demarcated and isointense. T2 weighted magnetic resonance imaging of the neoplasm delineates hyper-intense signal intensity [5,6].

Appropriate therapeutic strategy for managing hyalinising clear cell carcinoma emerges as primary surgical extermination of the neoplasm, especially lesions confined to sites amenable to surgical intervention. Tumefaction confined to base of tongue may be subjected to primary radiation along with or devoid of dissection of cervical lymph nodes. Singular radiotherapy or combination of radiotherapy

with chemotherapy may be beneficially adopted for treating reoccurring tumours.

A specific grading system for categorizing hyalinising clear cell carcinoma of salivary gland is absent. Few instances of the low grade neoplasm demonstrate regional lymph node or distant metastases. Localized or regional tumour reoccurrence emerges in up to 17% lesions [5,6]. Neoplastic reappearance is contingent to contributory factors as occurrence of tumour necrosis, tumour cells confined to surgical tissue perimeter, status of regional lymph nodes or exceptionally encountered neoplastic transformation into high grade lesions [5,6].

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7. Image 1 Courtesy: Wikipedia.

8. Image 2 Courtesy: Baishideng publishing group.