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Motley and Multifarious-Polymorphous Adenocarcinoma

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Polymorphous adenocarcinoma emerges as a malignant salivary gland neoplasm characteristically demonstrating cytological uniformity and predominant architectural diversity. Tumefaction preponderantly arises within minor salivary glands, especially glands confined to hard palate or soft palate.

Polymorphous adenocarcinoma exhibits a predilection (~60%) for minor salivary glands, especially the palate. Major salivary glands are implicated in < 5% instances.

Characteristically, molecular alterations within PRKD gene, especially PRKD1 E710D hotspot mutations may be encountered.

Polymorphous adenocarcinoma is additionally designated as terminal duct carcinoma, lobular carcinoma, low grade papillary adenocarcinoma, cribriform adenocarcinoma of minor salivary gland or polymorphous low grade adenocarcinoma.

Polymorphous adenocarcinoma is composed of singular cell type in entirety wherein tumour cells exhibit pale nuclei and open nuclear chromatin. Neoplasm enunciates significant architectural diversity and is composed of multiple architectural articulations.

Tumefaction exemplifies an indolent clinical course.

Polymorphous adenocarcinoma depicts a female predilection with female to male proportion of ~2:1. Mean age of tumour discernment is between 50 years to 60 years although neoplasm may appear within a comprehensive range of 16 years to 90 years [1,2].

Polymorphous adenocarcinoma predominantly (~89%) delineates hotspot genetic mutation PRKD1 E710D. Nearly 11% neoplasms demonstrate genomic fusions of PRKD1, PRKD2 or PRKD3 genes along with fusion partners ARID1A or DDX3X [1,2].

Cribriform adenocarcinoma of salivary gland preponderantly (~94%) exhibits PRKD1, PRKD2 or PRKD3 genetic fusion. Up to 20% neoplasms enunciate PRKD1 E710D genetic mutation [1,2].

Polymorphous adenocarcinoma of salivary gland commonly incriminates palate or oral cavity. Majority (~87%) of neoplasms arise within the palate. Besides, tumefaction may be exemplified within diverse primary sites as minor salivary glands of upper aero-digestive tract confined to oral cavity or situated upon floor of mouth, retromolar trigone, lip, lateral tongue, sinonasal tract, oropharynx as base of tongue or tonsil or nasopharynx. Additionally, major salivary glands as the parotid gland exemplifies the neoplasm in < 5% subjects.

Polymorphous adenocarcinoma frequently represents with a palpable tumefaction [2,3].

Fine needle aspiration cytology is challenging to perform upon the predominantly intra-oral neoplasm. Typically, neoplasm is constituted of uniform tumour cells permeated with ground glass nuclei, nuclear grooves or inconspicuous nucleoli.

Grossly, a classic, firm, lobulated, submucosal nodule or tumefaction with an infiltrative perimeter is encountered. Cut surface is grey/white to beige [2,3].

Upon microscopy, polymorphous adenocarcinoma depicts specific diagnostic criterion denominated as

- Cytological uniformity wherein neoplasm is comprehensively constituted of singular subtype of cells. Characteristically, tumour cells are incorporated with monomorphic, pale nuclei demonstrating prominent clearing of nuclear chromatin, reminiscent of nuclei of papillary thyroid carcinoma.
- Architectural diversity wherein neoplasm configures significantly variable architectural articulations as singular file of cells or trabecular, tubular, reticular, papillary, solid and cribriform cellular arrangement.

Targetoid articulations, nests and streaming of tumour cells surrounding peripheral nerves and vascular articulations is commonly observed.

Perineurial invasion is frequent and delineated in ~75% instances. Uncommon histological features emerge as micro-calcification, oncocytic change, presence of mucocytes and metamorphosis into high grade neoplasm denominated as significant nuclear atypia, prominent mitotic activity or tumour necrosis [3,4].

Contemporary World Health Organization (WHO) classification of salivary gland neoplasms designates cribriform adenocarcinoma of salivary gland as a variant of polymorphous adenocarcinoma. Tumefaction depicts a significant propensity for incriminating base of tongue or posterior tongue. Besides, major or minor salivary glands adjoining base of tongue may be incriminated [3,4].

Typically, tumefaction exhibits lobulated architecture wherein tumour parenchyma is traversed by distinct fibrous tissue septa. Besides, uniform solid, cribriform or micro-cystic architecture may be observed.

Tumour cells exemplify specific cytological features as optically clear, pale nuclei. Tumour cell aggregates demonstrate peripheral palisading of neoplastic nuclei. Additionally, peripheral clefts and glomeruloid structures are commonly encountered [3,4].

Neoplasm depicts significant, possible occurrence of regional lymph node metastasis. Immunohistochemistry is concordant to immune staining enunciated by polymorphous adenocarcinoma [3,4].

Polymorphous adenocarcinoma of salivary gland appears intensely and diffusely immune reactive to S100 protein, CK7 and SOX10. Variable immune reactivity to p63 (up to 100%) is encountered.

Polymorphous adenocarcinoma is immune non reactive to p40, epithelial membrane antigen (EMA), smooth muscle actin (SMA), muscle specific actin (MSA), glial fibrillary acidic protein (GFAP) or GATA3 [4,5].

Polymorphous adenocarcinoma of salivary gland requires segregation from neoplasms such as adenoid cystic carcinoma, secretory carcinoma or myoepithelial carcinoma [4,5].

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 [2].*

Characteristically, polymorphous adenocarcinoma can be appropriately discerned upon histological assessment of surgical tissue specimens or resection specimens [4,5].

Polymorphous adenocarcinoma is devoid of specific, diagnostic radiological features. Computerized tomography (CT) and magnetic resonance imaging (MRI) can be employed as a preoperative diagnostic modality in order to establish extent of disease and occurrence of bone invasion [4,5].

Polymorphous adenocarcinoma can be primarily treated with surgical extermination of the neoplasm with tumour free surgical perimeter, manoeuvers which appear curative [4,5].

Dissection of regional cervical lymph nodes is optimal for treating cribriform adenocarcinoma or tumefaction with regional lymph node metastasis. Postoperative radiation therapy emerges as an individual preference and may be adopted to alleviate tumours with neoplastic cells confined to surgical perimeter or lesions with perineurial invasion.

Generally, chemotherapy as a therapeutic strategy is employed for treating tumours associated with distant metastasis or non operable lesions [4,5].

Polymorphous adenocarcinoma is associated with superior prognostic outcomes. Tumefaction demonstrates 10 year disease specific survival of up to 99% and 10 year recurrence free survival of up to 88%.

An estimated 10% of papillary component or ~30% of cribriform architecture is an independent prognostic factor contributing to inferior outcomes [4,5].

Cribriform adenocarcinoma of salivary gland, contemplated as a variant of polymorphous adenocarcinoma as per the current World Health Organization (WHO) classification of salivary gland tumours, is associated with enhanced possible emergence (up to100%) of regional lymph node metastasis.

Tumours delineating PRKD1, PRKD2 or PRKD3 genetic fusion are endowed with ~50% possible emergence of regional lymph node metastasis [4,5].

Factors contributing to adverse prognostic outcomes are enunciated as enlarged tumour magnitude, advanced tumour stage, occurrence of tumour necrosis, lymphatic or vascular invasion, bone invasion or perineural invasion of enlarged peripheral nerves [4,5].

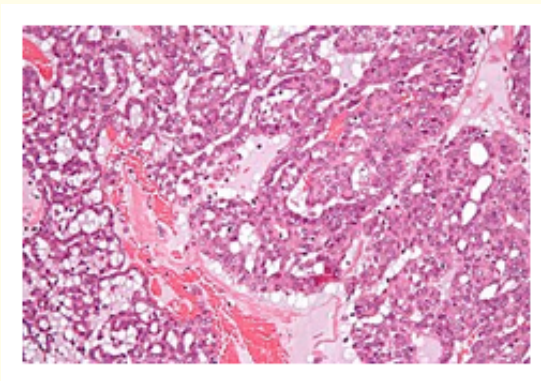

Figure 1: *Polymorphous adenocarcinoma depicting solid, micro-cystic and cribriform architecture. Single subtype of tumour cells are imbued with pale nuclei with peripheral palisading. Fibrous tissue septa traverse the neoplasm [6].*

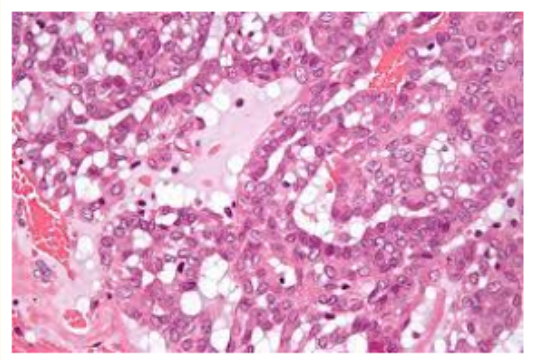

Figure 2: *Polymorphous adenocarcinoma demonstrating solid, micro-cystic and cribriform architecture. Tumour cells are permeated with clear nuclei with nuclear grooves and indistinct nucleoli. Fibrous tissue septa traverse the neoplasm [7].*

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6. Image 1 Courtesy: Libre pathology.
7. Image 2 Courtesy: Wikimedia commons.

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