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Commentary

The Jutting Eaves-Papillary Renal Cell Carcinoma

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Papillary renal cell carcinoma emerges as a well circumscribed, malignant neoplasm incriminating the renal cortex. Tumefaction is predominantly comprised of characteristic papillary structures or tubulo-papillary articulations.

Papillary or tubulo-papillary configurations are layered by miniature, basophilic cells or enlarged, eosinophilic cells. Foamy macrophages or psammoma bodies may or may not be discerned. Neoplastic cells appear immune reactive to alpha methylacyl CoA racemase (AMACR). Neoplasm mandates segregation from diverse renal cell carcinomas delineating a papillary architecture.

Notwithstanding, preceding terminology of tubulopapillary renal cell carcinoma, renal papillary adenocarcinoma or chromophil renal cell carcinoma is not recommended.

Papillary renal cell carcinoma is commonly encountered in adults and configures ~20% of renal cell carcinomas. A male predilection is observed with male to female proportion of ~2:1. Tumefaction preponderantly incriminates the renal cortex [1,2].

Low grade neoplasms delineate alterations within MET gene. High grade tumefaction enunciates genomic aberrations within CDKN2A, MYC pathway and NRF2-ARE pathway. Besides, aberrations within Hippo signalling pathway, SWI/SNF complex and chromatin modifier pathways may be encountered.

Molecular biomarkers pertaining to papillary renal cell carcinoma remain obscure. Low grade neoplasms depict genomic gains confined to chromosome 7 and 17 along with loss of Y chromosome. Genomic mutations within MET gene may occur [1,2].

Aggressive neoplasms display genetic mutation or promoter methylation within CDKN2A. Appropriate categorization of high grade papillary renal cell carcinoma requires exclusion of fumarate hydratase (FH) genetic mutation along with TFE3 genomic rearrangements [1,2].

Of obscure aetiology, papillary renal cell carcinoma is commonly associated with end stage renal disease. Neoplasm is posited to arise from progenitor-like cellular population amalgamated within proximal renal tubules of end stage renal disease [1,2].

Papillary renal cell carcinoma emerges as an asymptomatic neoplasm and is incidentally discovered upon adoption of diverse imaging techniques. Hereditary lesions delineating germline mutations of MET gene or neoplasms concurrent with chronic renal disease may appear as multifocal or bilateral [1,2].

Cytological examination exhibits distinct papillary fragments incorporated with fibro-vascular cores. Low grade neoplasm is composed of cohesive clusters of miniature cells pervaded with bland nuclei. Foci of intracellular hemosiderin pigment deposition and foamy macrophages may be observed [2,3].

Grossly, majority of neoplasms appear well circumscribed and encompassed within a pseudo-capsule. Tumour demonstrates a yellow/tan or red/brown hue. Cut surface is variegated, granular or friable and delineates variable areas of necrosis and cystic degeneration [2,3].

Upon microscopy, tumour demonstrates a predominantly papillary or tubulo-papillary architecture.

Papillae and tubules are layered by dual tumour cell population constituted of miniature cuboidal cells permeated with basophilic nuclei and inconspicuous nucleoli or enlarged cells pervaded with eosinophilic or clear cytoplasm and prominent nucleoli. Tumour cells may exhibit a linear or pseudostratified configuration [2,3].

An estimated 50% lesions configure heterogeneous neoplasms demonstrating an admixture of aforesaid patterns.

Tumour parenchyma is commonly infiltrated by foamy macrophages. Psammoma bodies and deposits of hemosiderin pigment may be encountered [2,3].

Generally, neoplasm may delineate biphasic configuration comprised of alveolar and squamoid articulations. Tumefaction is constituted of dual cell population as nests of enlarged, eosinophilic, squamoid cells encompassed by miniature amphophilic cells demonstrating an alveolar configuration [2,3].

Nearly ~15% tumours depict aggressive biological behaviour. Additional configurations may emerge as:

- Warthin-like papillary renal cell carcinoma comprised of papillae demonstrating layering epithelial cells imbued with eosinophilic cytoplasm, encompassed within a dense infiltrate of chronic inflammatory cells as lymphocytes, reminiscent of Warthin's tumour of the salivary gland. The high grade neoplasm enunciates aggressive biological behaviour [3,4].
- Solid or pseudo-solid papillary renal cell carcinoma delineates an architecture comprised of solid tumour cell sheets engendered due to compression of adjacent tubular and papillary structures which are layered by miniature cells incorporated with uniform, low grade nuclei. Neoplasm exhibits indolent clinical behaviour [3,4].
- Papillary renal neoplasm with reversed polarity is comprised of papillae layered by tumour cells pervaded with abundant, eosinophilic cytoplasm and apical nuclei with linear configuration. Tumefaction frequently demonstrates KRAS genetic mutations and expounds as tumour grade I or grade II as per World Health Organization (WHO) or International Society of Urologic Pathologists (ISUP) classification. Tumour cells are immune reactive to GATA3 and immune non reactive to alpha methylacyl CoA racemase (AMACR) or vimentin. Additionally designated as oncocytic low grade papillary renal cell carcinoma or papillary renal cell carcinoma subtype IV, tumour expresses stage T1a. In contrast to classic papillary renal cell carcinoma, tumour magnitude is decimated. Neoplasm depicts an indolent biological behaviour and disease progression remains undocumented. Segregation from the high grade, eosinophilic papillary renal cell carcinoma is mandated.

Inferior prognostic outcomes are concurrent with neoplasms exhibiting distinct morphological configurations as solid, micro-papillary, hobnail cells or micro-cystic architecture [3,4].

Grade I: Tumour cell nucleoli inconspicuous or basophilic, miniature at 400x
Grade II: Tumour cell nucleoli conspicuous at 400x and inconspicuous at 100x
Grade III: Tumour cell nucleoli conspicuous at 100x and appear eosinophilic
Grade IV: Tumour cells exhibit significant nuclear pleomorphism/ tumour giant cells/foci of rhabdoid or sarcomatoid cellular dedifferentiation.

Table 1: *International society of urological pathology grading of renal cell carcinoma [3,4].*

	AMACR	CK7	Vimentin	CAIX	CD117	TFE3	FH	SDH
Papillary RCC	+	Variable	+	-	-	-	+	+
Clear cell RCC	-/+	-	+	+	-	-	+	+
Chromophobe RCC	-	+	-	-	+	-	+	+
Oncocytoma	-	-	-	-	+	-	+	+
TFE3 rearranged RCC	+	-	-	-	-	+	+	+
FH deficient RCC	Variable	-	Variable	-	-	-	-	+
SDH deficient RCC	-	-	-	-	-	-	+	-

Table 2: *Immunohistochemistry of renal cell carcinoma [3,4].*

RCC: Renal Cell Carcinoma; FH: Fumarate Hydratase; SDH: Succinate Dehydrogenase.

Papillary renal cell carcinoma is immune reactive to alpha methylacyl CoA racemase (AMACR), CK7, PAX8, AE1/AE3, epithelial membrane antigen (EMA), CAM5.2, vimentin or GATA3.

Tumour cells appear immune non reactive to carbonic anhydrase IX (CAIX), CD117, Wilm's tumour 1 (WT1) antigen and CD57.

Low grade papillary renal cell carcinoma requires segregation from neoplasms such as clear cell papillary renal cell tumour, metanephric adenoma, mucinous tubular and spindle cell carcinoma, fumarate hydratase (FH) deficient renal cell carcinoma or MiT family translocation renal cell carcinoma [5,6].

High grade papillary renal cell carcinoma necessitates demarcation from acquired cystic disease associated renal cell carcinoma, succinate dehydrogenase (SDH) deficient renal cell carcinoma, anaplastic lymphoma kinase (ALK) rearranged renal cell carcinoma, renal medullary carcinoma or collecting duct carcinoma [5,6].

Papillary renal cell carcinoma can be appropriately diagnosed with morphological evaluation followed by cogent immunohistochemistry. Segregation of high grade papillary renal cell carcinoma from diverse high grade renal neoplasms is mandated [5,6].

Tumefaction is devoid of specific radiological features. Upon imaging, a homogenous, solid, hypo-vascular tumour is encountered, in contrast to non papillary renal cell carcinoma. Foci of cystic alterations and calcification may be discerned.

Surgical extermination is a recommended mode of therapy for alleviating papillary renal cell carcinoma. Besides, surgical ablation may be adopted for eradicating localized disease [5,6].

Advanced neoplasms or tumours associated with distant metastasis may be treated with selective MET kinase inhibitors, VEGF inhibitors, tyrosine kinase inhibitors with multiple targets and PD-1/PDL1 inhibitors.

In contrast to diverse clear cell renal cell carcinomas, papillary renal cell carcinoma is accompanied by superior prognostic outcomes [5,6].

Inferior prognostic outcomes appear within:

- High grade lesions or neoplasm with enhanced tumour stage as per World Health Organization (WHO) or International Society of Urologic Pathologists (ISUP) classification.
- Tumours delineating ATP binding cassette subfamily C member 2 (ABCC2) brush border [5,6].

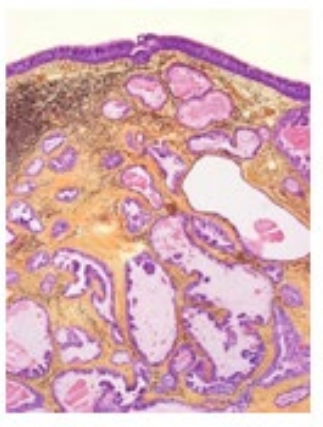

Figure 1: *Bronchiolar adenoma demonstrating adenoid structured lined by basal layer and luminal layer surrounded by a fibrotic stroma infiltrated by chronic inflammatory cells. Papillary articulations are absent [8].*

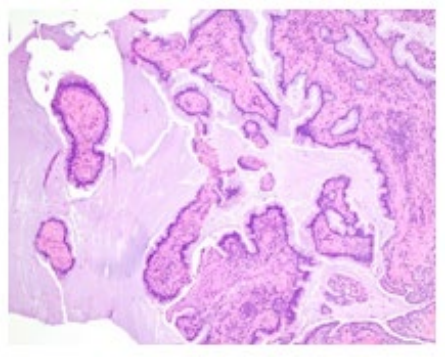

Figure 2: *Bronchiolar adenoma delineating adenoid articulations lined by basal layer and luminal layer surrounded by a fibrotic stroma infiltrated by chronic inflammatory cells. Papillary configurations are absent [9].*

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7. Image 1 Courtesy: Wikipedia.com.

8. Image 2 Courtesy: Libre Pathology.

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