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Fuchsia Flush-Chromophobe Renal Cell Carcinoma

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Editorial

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Abbreviations: SDH: Succinate Dehydrogenase; AMACR: Alpha Methyacyl Coa Racemase; CAIX: Carbonic Anhydrase IX; VIM: Vimentin; HALE: Colloidal Iron Stain; CK: Cytokeratin; TFE3: Transcription Factor Binding To IGHM Enhancer 3.

Editorial

Chromophobe renal cell carcinoma emerges as a solid tumefaction arsing from intercalated cells of distal convoluted tubules. Initially scripted in by Thoenes, et al in 1985, neoplasm is additionally designated as chromophobe renal cell carcinoma, classic variant [1].

Tumefaction is composed of solid sheets of pale staining, granular tumour cells incorporated with finely reticulated cytoplasm, irregular, wrinkled, hyperchromatic nuclei, perinuclear halos and a prominent cellular perimeter.

Chromophobe renal cell carcinoma comprises of 7% of adult renal epithelial neoplasms. Tumefaction predominantly exhibits a sporadic emergence and is incidentally discovered. A specific gender predilection is absent. Mean age of disease emergence is 58 years. Neoplasm represents as a solitary tumefaction commonly confined to renal cortex.

Tumours configuring a component of Birt-Hogg-Dubé syndrome appear as multiple lesions with a mean of 5.3 neoplasms. Mean age of initial discernment of renal tumours is 51 years [2,3].

The syndrome demonstrates autosomal dominant mode of disease transmission and exhibits miniature, dome shaped, papular fibrofolliculomas confined to face, neck and upper trunk in addition to renal tumours, pulmonary cysts and spontaneous pneumothorax.

Tumefaction exhibits genetic mutations within folliculin gene (FLCN) located upon chromosome 17p11.2 with consequent occurrence of premature truncation and loss of function of folliculin protein. Neoplastic cells depict multiple, complete losses within chromosomes 1, 2, 6, 10, 13, 17, 21 or Y [2,3].

Deoxyribonucleic acid (DNA) rearrangement breakpoints may be detected within TERT promoter region. Up to 30% of neoplasms display chromosomal mutations within TP53 and PTEN in addition to mutations within NRAS, mTOR, TSC1 or TSC2. Mitochondrial (mt) mutations occurring within DNA are concordant with MT-ND5. Elevated expression of genes encoding enzymes constituting Krebs cycle may be exemplified [2,3].

Additionally, sarcomatoid tumours delineate varied genetic anomalies. Diverse configurations of MiRNA expression appear to concur with disease progression, reoccurrence free tumour survival and overall survival [2,3].

Majority of neoplasms are confined to incriminated organ, configure disease stage T1 or stage T2 with absent regional lymph node (N0) and distant metastasis (M0). Prognostic outcomes are superior. Tumour reoccurrence or distant metastasis may appear in ~10% instances. Tumefaction delineates 5 year proportionate cancer specific survival at ~93% [3,4].

Cytological examination delineates clusters of singular cells and non-cohesive, mono-layered clusters and groups of miniature cells. Cellular magnitude varies from miniature cells to enlarged cells. Enlarged tumour cells are permeated

with clear, flocculent cytoplasm, miniature, eccentric nuclei and occasional nuclear pseudo-inclusions. Bi-nucleate tumour cells are frequently encountered [3,4].

Grossly, a well circumscribed, non-encapsulated tumour with tan to light brown hue is observed. Average tumour magnitude appears at 8 centimetres. Foci of tumour necrosis, haemorrhage and miniature cysts may be discerned. Occasionally, tumefaction enunciates a centric scar. Multifocal neoplasms are expounded in ~10% instances [3,4].

Upon microscopy, a characteristic, confluent configuration of solid sheets, nests, alveoli or trabeculae of tumour cells is enunciated. Neoplastic cells are pale staining with sharply defined cellular perimeter. Discernible dual population of tumour cells is described as:

- Type I cells which appear as enlarged, polygonal cells incorporated with abundant cytoplasm and well defined cellular perimeter, denominated as "plant-like' cell outline. A reticular tumour configuration is encountered.
- Type II cells emerge as miniature cells pervaded with finely granular, eosinophilic cytoplasm and irregular, wrinkled, angulated nuclei with coarse nuclear chromatin, described as 'raisinoid' nuclei.

Bi-nucleate cells and multi-nucleated cells are commonly exemplified. Tumour cells delineate perinuclear 'halos', a feature designated as 'koilocytic atypia'. Few mitotic figures may be encountered [3,4]. Encompassing stroma is minimal and constituted of incomplete fibro-vascular septa encircling solid sheets of neoplastic cells. However, 'chicken wire' vascular configurations are absent.

Eosinophilic variant of chromophobe renal cell carcinoma is comprehensively comprised of miniature eosinophilic cells. Miniature cells are pervaded with dense, homogeneous cytoplasm, marginal nuclei and clear cytoplasmic spaces, reminiscent of perinuclear halos. Bi-nucleate cells are common. Focal tumour necrosis and basement membrane or stromal substance is absent [3,4].

Upon ultrastructural examination, tumour cells exhibit cytoplasmic micro-vesicles, a feature which is pathognomonic and consistent. Aforesaid micro-vesicles emerge as membrane bound vesicles varying from 150 nanometres to 350 nanometres magnitude. The membrane bound micro-vesicles may be challenging to highlight upon sections stained with haematoxylin and eosin (H&E) stain. Chromophobe micro-vesicles are commonly amalgamated within perinuclear zone and appear concordant to perinuclear halos discernible upon light microscopy. Tumour cells are permeated with pale, reticular cytoplasm (Figures 1 & 2).

Although obscure, micro-vesicles are posited to originate from mitochondrial outpouchings or appear on account of defective mitochondrio-genesis. Eosinophilic cells appear to simulate neoplastic cells wherein mitochondria are numerically elevated. Frequently, mitochondria display tubulo-cystic cristae. Abridged, stubby microvilli are exceptionally encountered [3,4].

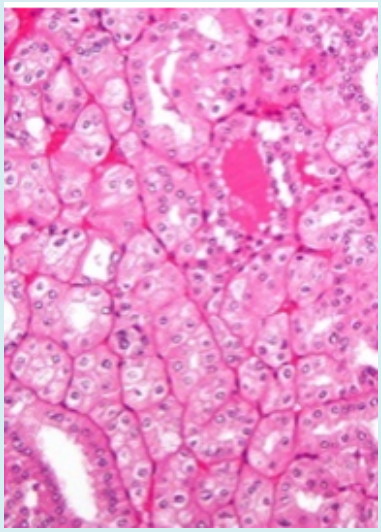

Figure 1: Chromophobe renal cell carcinoma demonstrating papillae and alveoli lined by enlarged cells imbued with eosinophilic cytoplasm and irregular wrinkled nuclei with perinuclear halos. Surrounding stroma is minimal [5].

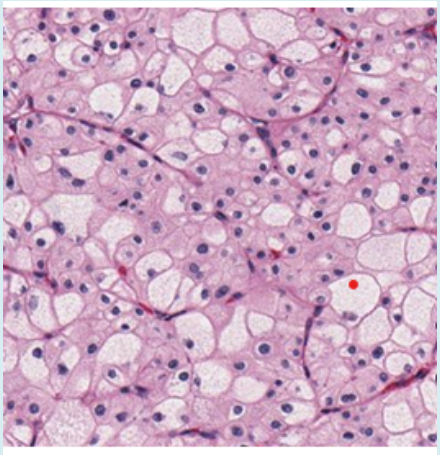

Figure 2: Chromophobe renal cell carcinoma delineating cords and papillae lined by tumour cells permeated with eosinophilic cytoplasm and wrinkled, irregular nuclei with perinuclear halos. Intervening stroma is minimal (Table 1) [6].

	Hale	KIT	CK7	S100A1	VIM	CAIX	AMACR	SDH	TFE3
Chromo-phobe RCC	+++	+++	+++	-	-	-	-	+++	-
Clear cell RCC	-	-	-	-	+++	+++	-	+++	-
Oncocytoma	-	+++	rare	+++	-	-	-	+++	-
Papillary RCC	-	-	+++	-	+++	-	+++	+++	-
Translocation RCC	-	-	-	-	-	-	++	+++	+++
SDH deficient RCC	-	-	-	-	-	-	-	-	-

Table 1: Immuno-reactive profile of renal cell carcinomas [3,4].

Neoplastic cells appear immune reactive to Hale's colloidal iron, CK7, CD117/c-KIT, E-cadherin, claudin 7, epithelial membrane antigen (EMA), MUC1, CK8, CK18, RCC, C10, parvalbumin, cytochrome c oxidase, DOG1, progesterone receptor (PR), PDL1 and 22C3. Tumour cells appear immune non-reactive to vimentin, carbonic anhydrase IX (CAIX), alpha methyacyl CoA racemase (AMACR), N-cadherin and cyclin D-1. Ki67 labelling index is minimal [7,8].

Chromophobe renal cell carcinoma requires segregation from neoplasms such as clear cell renal cell carcinoma. Besides, oncocytoma or eosinophilic papillary renal cell carcinoma requires demarcation from eosinophilic variant of chromophobe renal cell carcinoma. Notwithstanding, bilateral multifocal chromophobe renal cell carcinoma, oncocytoma or hybrid oncocytic chromophobe tumour (HOCT) may delineate foci of oncocytosis [7,8].

Upon imaging, an enlarged, well circumscribed, hypo-vascular tumefaction is observed. Upon administration of contrast medium, a homogeneous, minimally enhanced neoplasm is envisaged.Tumour may exhibit a central scar [7,8]. Fluorescent in situ hybridization (FISH) and single nucleotide pleomorphism (SNP) array may be beneficial for neoplastic ascertainment, in contrast to karyotyping.

Chromophobe renal cell carcinoma can be appropriately alleviated with surgical extermination. Additionally, cryo-ablation and systemic, targeted chemotherapy may be suitably adopted for neoplasms associated with distant metastasis. Antiangiogenic agents, tyrosine kinase inhibitors or mTOR inhibitors may be appropriately employed [7,8].

Factors contributing to inferior prognostic outcomes configure as

- Sarcomatoid configuration in ~5% of tumour parenchyma
- Microscopic foci of tumour necrosis
- Lesions with vascular invasion
- Tumour magnitude > 7 centimetres
- Enhanced clinical T stage
- Neoplastic stage contingent to pathological TNM staging
- Incrimination of male subjects.

Generally, grading of chromophobe renal cell carcinoma is non-concurrent to prognostic outcomes and appears superfluous [7,8].

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5. Image 1 Courtesy: Wikipedia.

6. Image 2 Courtesy: Research gate.

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