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Exiguous and Scarce-SMARCB1 Deficient Medullary Renal Cell Carcinoma

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Editorial

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Abbreviations: SNF: Sucrose Non Fermentable; INI: Integrase Interactor; DNA: Deoxyribonucleic Acid; NHEJ: Non Homologous End Joining; HIF: Hypoxia Inducible Factor; VHL: Von Hippel Lindau; CAN: Copy Number Alterations; EMA: Epithelial Membrane Antigen; RCC: Renal cell carcinoma.

Editorial

Switch / sucrose non fermentable (SWI/SNF) related, matrix associated, actin dependent regulator of chromatin subfamily B member 1 (SMARCB1) deficient medullary renal cell carcinoma is an exceptionally discerned, aggressive carcinoma associated with deficiency of SMARCB1 or integrase interactor 1(INI1). Neoplasm is associated with sickle cell trait or various sickle cell haemoglobinopathies wherein appearance of sickle shaped erythrocytes or drepanocytes may be pathognomonic. Tumefaction preponderantly arises within young subjects with sickle cell trait. SMARCB1 deficient medullary renal cell carcinoma demonstrates diverse histological configurations. Prognostic outcomes are inferior. Previously denominated as unclassified renal cell carcinoma with medullary phenotype and additionally designated as SMARCB1 deficient renal medullary carcinoma or renal medullary carcinoma, tumefaction is characteristically confined to renal medulla.

The infrequently encountered neoplasm configures < 0.5% of renal carcinomas. Although exclusively enunciated in subjects with sickle cell trait or associated with haemoglobin AS, neoplasm may exceptionally arise in individuals with haemoglobin S, β thalassemia, haemoglobin SC and homozygous SS disease or sickle cell anaemia.

Besides, neoplasms morphologically identical to renal medullary carcinoma may occur in individuals devoid of sickle cell trait, sickle cell disease or diverse haemoglobinopathies.

Majority (~90%) neoplasms incriminate the right kidney. Mean age of neoplastic emergence is 26 years although tumefaction may arise within 5 years to 69 years. A male predilection is encountered with male to female proportion of 2:1 [1,2].

SMARCB1 deficient medullary renal cell carcinoma frequently implicates right kidney and no site of disease occurrence within the renal medulla is exempt. Renal cortex may or may not be involved [1,2].

Tumefaction arises within renal medulla and disseminates from distal segment of collecting ducts. Tumour is posited to emerge from renal papillae or calyceal epithelium wherein oncogenesis may be triggered due to chronic medullary hypoxia and hypertonic environment engendered from sickled erythrocytes with ensuing microvascular occlusion. Surrounding ionic environment stimulates breakages within double stranded deoxyribonucleic acid (DNA) [1,2].

Ensuing chronic hypoxia induces repression of RAD51 and BRCA1 pathways which appear associated with enhanced fidelity homologous recombination initiating a switch to non-homologous end joining (NHEJ) repair pathways. Aforesaid mechanics may engender chromosomal deletions and translocations. Genetic translocations and deletions commonly contribute to inactivation or loss of expression of SMARCB1 gene which contributes as a chromatin re-modeller and tumour suppressor gene [2,3].

Incrimination of predominantly right kidney occurs due to divergence within vascular anatomy. Right renal artery

is particularly elongated, with consequently decimated vascular outflow and relative hypoxia.

SMARCB1 deficient medullary renal cell carcinoma exhibits inactivation of SMARCB1 or INI1 gene situated upon chromosome 22q11.2. Also, chromosomal translocations or deletions configure as significant driver mutations.

Decimation of SMARCB1 protein expression may ensue due to concurrent hemizygous loss and translocation or may be associated with homozygous loss of genetic material [2,3].

Loss of INI1 is accompanied by downregulation of p16INK4a and upregulation of cyclin D1 thereby stimulating unregulated progression within the cell cycle. Anomalies within hypoxia inducible factor (HIF) and *Von Hippel Lindau* (VHL) proteins may ensue.

Additionally, amplification of DNA topoisomerase II and gains within chromosome 8q upon sites of c-MYC may be encountered. Reoccurring focal copy number alterations (CNA) within genetic regions concordant with cellular proliferation in association with distinct CNA pattern with consequent Notch pathway activation may be enunciated.

Cytogenetic analysis delineates genomic rearrangements within chromosome 8 with consequent loss of 8p and gain of 8q [2,3].

Chromosomal gains of chromosomes 7, 8, 10 and 11 may occur along with loss of chromosomes 9 and 13. Additional genetic material of obscure genesis may amalgamate upon chromosome 10p with deletion of 7q. Nevertheless, di-centric chromosome composed of 13q and 21q may be expounded. Exceptional tumours with ABL genetic amplification or translocation are documented.

SMARCB1 deficient medullary renal cell carcinoma is contemplated to represent as a component of diverse conditions induced by sickle cell nephropathy in addition to disorders such as unilateral haematuria, papillary necrosis, renal infarct, nephrotic syndrome, pyelonephritis or inability of urinary concentration [2,3].

SMARCB1 deficient medullary renal cell carcinoma demonstrates cogent clinical symptoms as haematuria, abdominal pain, dorsolateral thoracolumbar pain, dysuria or loss of weight. Also, pyrexia, nausea, vomiting and palpable abdominal mass may manifest [2,3].

Clinically aggressive neoplasms configure with advanced stage disease upon initial representation wherein distant metastases into sites as pulmonary parenchyma, hepatic parenchyma, regional lymph nodes, adrenal gland, peritoneum, retroperitoneum or inferior vena cava may concur. Majority (~90%) of individuals represent with distant metastasis upon initial tumour discernment [2,3].

Cytological examination exhibits loosely cohesive cellular groups or sheets of tumour cells intermingled with disseminated singular cells. Tumour cells are high grade, pleomorphic and incorporated with pale, finely vacuolated cytoplasm and displaced nuclei. Tumour cell nuclei demonstrate a smooth perimeter, coarse or vesicular nuclear chromatin, prominent nucleoli, grooves within nuclear membrane and irregular nuclear membranes [2,3].

Grossly, neoplasm manifests as an inadequately circumscribed, lobulated, firm, rubbery, grey/white tumour confined to renal medulla. Characteristically, tumefaction extends into calyces and renal pelvis. Tumour magnitude varies from 4 centimetres to 12 centimetres with mean tumour diameter at 5.9 centimetres. Besides, satellite tumour nodules may appear within renal cortex or extend into perinephric adipose tissue or adipose tissue confined to renal sinus. Focal haemorrhage and tumour necrosis are commonly observed [3,4].

Upon microscopy, neoplasm depicts a variable morphological configuration. Distinctive tumour patterns as reticular, yolk sac tumour-like, sieve-like, cribriform, micro-cystic or adenoid cystic-like may emerge. Commonly, cords, nests, tubules, glandular articulations, tubulo-papillary structures and solid areas or sheet-like patterns of tumour cells may be enunciated, reminiscent of lesions of collecting duct carcinoma or fumarate hydratase (FH) deficient renal cell carcinoma. Tumefaction manifests with an infiltrative perimeter.

Neoplastic cells appear as pleomorphic and are permeated with eosinophilic cytoplasm, enlarged hyperchromatic nuclei with nuclear grooves, vesicular nuclear chromatin and prominent nucleoli. Tumour cells may display rhabdoid morphology. Encompassing stroma appears desmoplastic [3,4].

Focal haemorrhage may occur. Ischemic, geographic, central or comedo subtype of necrosis may ensue. Mitotic figures are abundant (Table 1).

Intra-tumoral neutrophils are significant and may configure an abscess. Besides, infiltrating lymphocytes appear amalgamated upon tumour periphery. Concurrence of abundant sickle shaped erythrocytes or drepanocytes is pathognomonic [3,4].

Ultrastructural examination exhibits cells adhered with tight junctions. Cells demonstrate enlarged intracytoplasmic

lumina which are pervaded with elongated slender microvilli. Besides, condensed fibrillary electron dense filamentous luminal deposits may be observed (Figures 1 & 2) [3,4].

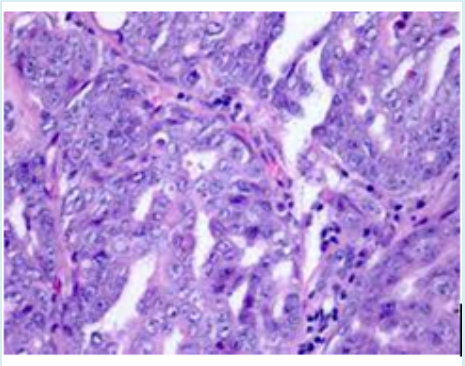

Figure 1: SMARCB1 deficient medullary renal cell carcinoma delineating sheets and papillae of pleomorphic cells imbued with eosinophilic cytoplasm, enlarged hyperchromatic nuclei with vesicular chromatin and prominent nucleoli [5].

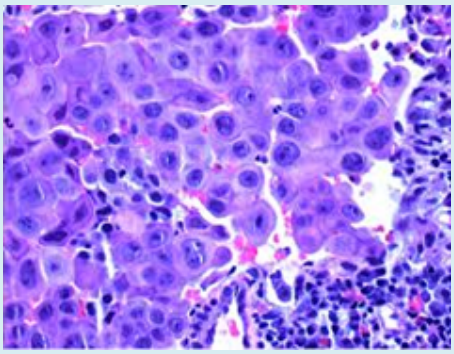

Figure 2: SMARCB1 deficient medullary renal cell carcinoma enunciating sheets and solid areas of pleomorphic cells incorporated with eosinophilic cytoplasm, enlarged hyperchromatic nuclei with vesicular chromatin and prominent nucleoli. Surrounding stroma is infiltrated by lymphocytes [6].

Molecular Variants	Mutated Genes	Genetic Location	Chaperone Genes
TFE3 rearranged RCC	Transcription factor binding to IGHM enhancer 3 (TFE3)	Xp11.23	ASPL,PRCC, SFPQ,CLTC, PARP14, RBM10, NONO,MED15
TFEB altered RCC	Transcription factor EB (TFEB)	6p21	MALAT1, CLTC, KHDRBS2, CADM2
ELOC mutated RCC	Elongin C	8q21.11	None
Fumarate hydratase deficient RCC	Fumarate hydratase (FH) gene	1q43	None
Succinate dehydrogenase deficient RCC	Succinate dehydrogenase (SDH)	SDHA: 5p15 SDHB: 1p35-p36. 1 SDHC: 1q21 SDHD:11q23	None
ALK rearranged RCC	Anaplastic lymphoma kinase (ALK)	2p23	VCL, TPM3, EML4, STRN, HOOK1
SMARCB1 deficient RCC	Subfamily B member 1(SMARCB1)	22q11.2	None

Table: Molecular characterization of renal cell carcinoma [4].

Tumour cells appear immune reactive to CAM5.2, AE1/AE3, CK7, CK20, vimentin, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), p53 and PAX8. Nearly 50% neoplasms appear immune reactive to OCT3/4. Besides, immune reactivity to Ulex, vascular endothelial growth factor (VEGF) or hypoxia inducible factor (HIF) may be discerned [7,8].

Tumour cells appear immune non-reactive to colloidal iron, desmin, Periodic acid Schiff's (PAS) stain or CK34βE12. Besides, loss of expression of SMARCB1 or integrase interactor 1(INI1), SNF 5 or BAF47 is observed [7,8].

SMARCB1 deficient medullary renal cell carcinoma requires segregation from neoplasms such as vinculin (VCL) anaplastic lymphoma kinase (ALK) fusion renal cell carcinoma, rhabdoid tumour of the kidney, high grade urothelial carcinoma, collecting duct carcinoma, metastatic germ cell neoplasm, fumarate hydratase(FH) deficient renal cell carcinoma and SMARCB1 deficient renal cell carcinoma with medullary-like features or renal cell carcinoma, unclassified with medullary phenotype. Besides, diverse carcinomas with SMARCB1 deficiency require exclusion [7,8].

Upon radiography, an infiltrative tumour confined to renal parenchyma is exemplified. Commonly, right kidney is incriminated. Besides, renal parenchyma demonstrates focal necrosis or caliectasis. Regional lymph node enlargement may ensue. SMARCB1 deficient medullary renal cell carcinoma emerges as a high grade, infiltrative adenocarcinoma. Evaluation of concurrent clinical, biochemical and haematological evidence of sickle cell haemoglobinopathy is recommended [7,8].

SMARCB1 deficient medullary renal cell carcinoma is appropriately alleviated with surgical manoeuvers as radical nephrectomy. Chemotherapeutic agents with platinum based regimens may be adopted. Also, alternative therapies or immunomodulatory drugs may be beneficially employed. Deficiency of SMARCB1 may be targeted for discerning therapeutic features as proteasome inhibition [7,8].

Neoplasm is associated with inferior prognostic outcomes and demonstrates median overall survival of 6 months to 13 months. Distant metastasis upon initial disease representation is associated with enhanced tumour associated mortality [7,8].

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5. Image 1 Courtesy: Pathology outlines.

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