Mini Review

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Limpid and Pellucid- Clear Cell Renal Sarcoma

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Initially scripted by Beckwith and Palmer, Morgan and Kidd and Marsden et al in 1978, clear cell renal sarcoma is an infrequently encountered neoplasm which expounds variable morphology and appears devoid of specific diagnostic markers. Genetic alterations within BCOR gene are implicated within tumorigenesis of clear cell renal carcinoma. Previously designated as 'bone metastasizing renal tumour of childhood', clear cell renal sarcoma is a frequently misinterpreted paediatric renal neoplasm. Tumour cells appear immune reactive to vimentin or Cyclin D1. Tumefaction is associated with significant predilection for bone metastasis. Clear cell renal sarcoma is constituted of miniature, uniform, plump, spherical cells delineating a 'clear' countenance which are pervaded with regular, fine nuclear chromatin. Tumour cell aggregates are segregated by a network of delicate, vascular septa. Chemotherapeutic agent doxorubicin emerges as a beneficial agent within the therapeutic armamentarium for alleviation of clear cell renal sarcoma. The exceptionally discerned clear cell renal sarcoma configures up to 5% of paediatric renal neoplasms. Mean age of disease discernment is 36 months although tumefaction may be observed within 2 months to 14 years. Nearly 50% neoplasms are enunciated within 3 years. Adolescents or adult population is exceptionally incriminated.

A male predilection is expounded with male to female proportion of ~2:1 [1,2]. Clear cell renal sarcoma is associated with bone metastases in up to 40% subjects, in contrast to <2% of individuals demonstrating Wilm's tumour. Nearly 5% of incriminated subjects exhibit distant metastasis upon initial disease representation, especially within sites such as bone, pulmonary parenchyma, brain or hepatic parenchyma. Contingent to disease stage, 5year survival of stage I tumour is ~97% and of stage IV neoplasm is ~50% [1,2]. Akin to high grade endometrial stromal sarcoma, clear cell renal sarcoma exhibits chromosomal translocation t (10;17) with consequent YWHAE - NUTM2B/E or FAM22B genetic fusion [2,3]. Besides, tumorigenesis occurs due to genetic aberration within BCOR gene. Internal tandem duplications within BCOR gene or BCL6 corepressor may be encountered in comprehensive (100%) instances of clear cell renal sarcoma. Generally, YWHAE – NUTM2 genomic fusion is absent. Downregulated vascular endothelial growth factor A (VEGF A) and precise genetic interactions may engender clear cell renal sarcoma with deregulation of pathways such as kinase regulation and metabolism of protein tyrosine kinase. Clear cell renal sarcoma demonstrates differential expression of ~2681 genes with genetic overexpression or downregulation, especially of VEGF A [2,3]. Cytological examination exemplifies tumour cells permeated with moderate quantities of pale blue cytoplasm. Cellular cords are enmeshed within minimal stromal fragments.

Spindle shaped cell variant exhibits septal cells enmeshed within a myxoid stroma [2,3]. Anaplastic variant exhibits tumour cells incorporated with bizarre, pleomorphic nuclei and coarse nuclear chromatin. Atypical mitotic figures are significant and discernible [3,4]. Grossly, an enlarged, unilateral, uni-centric tumefaction appears situated upon renal medulla or centric renal zone. Tumour exhibits an irregular, well defined interface abutting adjacent renal parenchyma. Mean tumour magnitude of 11 centimetres is enunciated. Cut surface appear firm, homogenous, gelatinous, tan or grey (Figure 1) [5,6]. Occasional intra-parenchymal cysts may be encountered [3,4]. Upon microscopy, classic clear cell renal sarcoma enunciates foci of cords or nests of miniature, plump cells segregated by a network of delicate,

vascular septa designated as 'chicken wire' capillaries. Spindle shaped tumour cells amalgamated adjacent to vascular septae are designated as 'septal cells' [3,4]. Additionally, tumour configurations as myxoid, sclerosing, cellular, epithelioid, trabecular, spindle cell, storiform, acinar, palisading verocay body subtype and anaplastic variants may be expounded. Tumefaction delineating anaplasia may be associated with hyperchromatic nuclei and giant nuclei (Table 1). Atypical mitotic figures may be discerned [3,4]. Low power magnification depicts a 'sharp' perimeter of tumour cell aggregates whereas high power magnification exemplifies subtle infiltration of neoplastic cells into uninvolved, peripheral renal parenchyma.

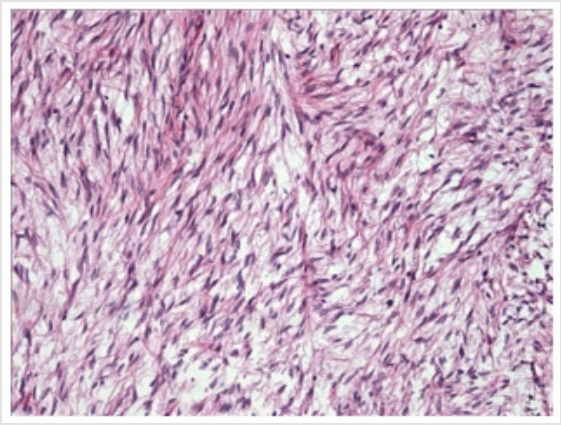

Figure 1: Clear cell renal sarcoma demonstrating aggregates of miniature, plump cells imbued with washed out nuclei, smooth nuclear chromatin and inconspicuous nucleoli and surrounded by delicate, vascular network. Spindle shaped septal cells abut traversing fibrous tissue septa [5].

Table 1: Histological characterization of molecular variants of renal cell carcinoma [4].

Molecular variants	Histological characteristics	IHC/FISH	Biological behaviour
TFE3 rearranged RCC	Papillary architecture, eosinophils, psammoma bodies	PAX8+, TFE3+, CD10+, achromatase+, CK7-, CAIX-, GATA3-	Metastasis may develop in up to 30 years
TFEB altered RCC	Biphasic, clear small & large cells, small cells around BM-like structures, hyalinization, papillary architecture	Histone K+, Melan A+, TFEB+ in patches	Aggressive biological behaviour
ELOC mutated RCC	Clear cell clusters traversed by fibro-muscular bands, branching, glandular, vesicular, tubular structures	CK7+, ELOC+, CAIX+, CD10+, nuclear ELOC	Aggressive biological behaviour
Fumarate hydratase deficient RCC	Papillary, solid, tubulo-cystic or sieve type, abundant eosinophilic granulocytes, perinuclear halo	PAX8+, SDHB abnormal, FH-, CK7-, TFE3-	Advanced stage with distant metastasis on diagnosis
Succinate dehydrogenase deficient RCC	Cuboidal cell nests or tubules, vesicles or flocculent cytoplasmic inclusions	PAX8+, EMA+, SDHB-, CK7-, CD117-HistoneK-, TFE3-, HMB45-,	Low grade, minimal metastasis, superior prognosis
ALK rearranged RCC	Eosinophilic, granulocytic stroma, cytoplasmic lumen, intracellular & extracellular mucins	PAX7+, CK10+, AMACR+, CD3+, CK+, ALK+. CAIX-, TFE45-, Histone K-, Melan A-HMB45-	Aggressive clinical course
SMARCB1 deficient medullary RCC	Infiltrative pattern, sieve or reticular appearance	SMARCB1-	Aggressive tumour, advanced stage, distant metastasis, overall survival~8 months

Akin to papillary thyroid carcinoma, tumour cell nuclei appear as 'washed out' and are pervaded with smooth nuclear chromatin and inconspicuous nucleoli. Mitotic figures are exceptional. An estimated 20% neoplasms demonstrate clear cells pervaded with intracytoplasmic vacuoles. Alternatively, an extracellular mucopolysaccharide matrix may bestow a 'clear cell' appearance (Figure 2). Vascular invasion is commonly encountered [3,4]. RCC: Renal cell carcinoma, IHC: Immunohistochemistry, FISH: Fluorescent in situ hybridization, HMB45:Human melanoma black 45, AMACR: Alpha methyacyl CoA racemase, CAIX: Carbonic anhydrase IX, ALK: Anaplastic lymphoma kinase, EMA: Epithelial membrane antigen, SDHB: Succinate dehydrogenase subunit B, FH: Fumarate hydratase,

ELOC: Elongin C, BM: Basement membrane. Tumour cells appear immune reactive to vimentin, cyclin D1, CD34 and p53. Tumour cells appear immune nonreactive to Wilm's tumour 1(WT1) antigen, CD56, epithelial membrane antigen (EMA), S100 protein, CD99, desmin, carcinoembryonic antigen (CEA), synaptophysin, cytokeratin AE1/AE3 and CAM5.2. Ki67 proliferative index varies up to 32% [7,8]. Clear cell renal sarcoma requires segregation from renal neoplasms such as clear cell carcinoma, malignant rhabdoid tumour, mesoblastic nephroma or Wilm's tumour [7,8]. Clear cell renal sarcoma may be appropriately treated with total nephrectomy. Postoperative, adjuvant chemotherapy may be beneficially employed. Radiation therapy of dorsolateral thoracolumbar zone appears advantageous. Combination chemotherapy with doxorubicin, vincristine and actinomycin is associated with significant amelioration, wherein doxorubicin is a crucial component which impacts clear cell renal sarcoma with curative intent [7,8].

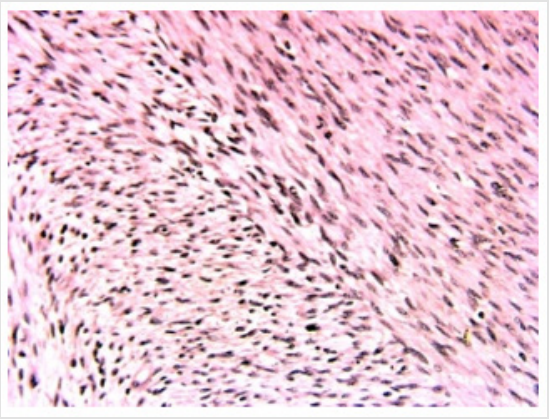

Figure 2: Clear cell renal sarcoma delineating clusters of miniature, plump cells incorporated with washed out nuclei, smooth nuclear chromatin and inconspicuous nucleoli surrounded by delicate, vascular network. Spindle shaped septal cells abut traversing fibrous tissue septa [6].

Factors contributing to prognostic outcomes emerge as

- Therapy with doxorubicin
- Precise tumour stage
- Age at initial tumour discernment
- Occurrence of tumour necrosis.

Inferior prognostic outcomes are observed with stage IV disease and incrimination of paediatric subjects [7,8].

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