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Reposition and Reshuffle-Alk Rearranged Renal Cell Carcinoma

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Editorial

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Editorial

ALK rearranged renal cell carcinoma emerges as an infrequently discerned renal neoplasm associated with genetic rearrangements of anaplastic lymphoma kinase (ALK) gene situated upon chromosome 2p23. Paediatric neoplasms may simulate renal medullary carcinoma wherein tumefaction is confined to renal medulla.

Tumour cells manifest diffuse expression of ALK protein wherein ALK genetic rearrangement may be appropriately discerned by fluorescent in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR) or ribonucleic acid (RNA) sequencing.

ALK rearranged renal cell carcinoma represents as a heterogeneous neoplasm. Eosinophilic, mucin producing tumour cells appear as polygonal, rhabdoid, signet ring or spindle shaped cells pervaded with intracytoplasmic vacuoles.The contemporary ALK rearranged renal cell is additionally designated as ALK rearrangement associated renal cell carcinoma, ALK translocation renal cell carcinoma or ALK renal cell carcinoma.

Neoplasm represents with diffuse, infiltrative pattern of tumour evolution.Tumefaction confined to adults exhibits heterogeneous, solid architecture in combination with diverse configurations as mucinous, cribriform, signet ring cell or solid, rhabdoid pattern. Additionally, high grade eosinophilic cells permeated with intracytoplasmic lumina may be discerned [1,2].

Neoplasm is composed of noncohesive aggregates of enlarged polygonal or spindle shaped cells incorporated with intracytoplasmic vacuoles and vesicular nuclei. Tumour cell clusters are encompassed within a lymphoid and plasma-cellular inflammatory infiltrate.

The exceptionally discerned neoplasm exhibits a bimodal distribution and incriminates paediatric population with sickle cell trait within 6 years to 19 years and adults devoid of sickle cell trait within 33 years to 61 years. African paediatric subjects are frequently implicated. Tumefaction configures ~ 3.5% of paediatric renal carcinomas and ~0.5% of adult renal carcinomas [1,2].

ALK rearranged renal cell carcinoma exhibits VCL-ALK genetic fusion and TPM3-ALK genetic fusion. Infrequently, genomic fusions such as STRN-ALK, EML4-ALK, HOOK1-ALK and clonal inversion of chromosomal region 2p23 may be observed. ALK1 copy numbers appear elevated. Besides, ALK copy number gain arises in ~10% of clear cell renal cell carcinomas and is associated with inferior cancer specific survival [1,2].

ALK rearranged renal cell carcinoma manifests as a solitary tumefaction commonly confined to renal medulla, renal pelvis or mid- zone of renal parenchyma [2,3].

Anaplastic lymphoma kinase (ALK) configures as a component of insulin receptor tyrosine kinase superfamily and is minimally expressed within the central nervous system.ALK genetic rearrangement articulates as an oncogenic driver mutation occurring within preliminary stage of carcinogenesis.

A subset of paediatric subjects with sickle cell trait may exemplify ALK rearranged renal cell carcinoma [2,3].

Majority of neoplasms manifest with cogent clinical symptoms as haematuria, abdominal pain, dorsolateral thoracolumbar pain or periumbilical pain. Tumefaction is incidentally discovered in ~one third (33%) of incriminated subjects. Upon initial representation, tumour is predominantly confined to stage T1a or stage T1b [2,3].

Grossly, paediatric neoplasms are confined to renal medulla wherein an irregular, solid tumefaction with infiltrative perimeter may be encountered [3,4].

Incriminated adult individuals enunciate a well demarcated, solid neoplasm confined to mid-zone of renal parenchyma. Tumour appears tan, brown, whitish or grey/white and is devoid of a pseudo-capsule. Tumour magnitude varies from 3 centimetres to 7 centimetres. Cut surface exhibits cystic change or focal haemorrhage [3,4].

Upon microscopy, paediatric neoplasms appear infiltrative and exhibit diffuse, sheet-like dissemination of neoplastic cells. Tumour cells appear spherical, elliptical or polygonal and are permeated with abundant, mildly granular, eosinophilic cytoplasm with intracytoplasmic mucin and frequently discerned intracytoplasmic lumens. Tumour cell nuclei are moderately polymorphic, preponderantly vesicular and incorporated with miniature nucleoli. Nuclear grooves and intra-nuclear vacuoles are occasional. Tumour cell aggregates are enmeshed within abundant extracellular mucin. Neoplastic cell aggregates are circumscribed by lymphoid and plasma-cellular inflammatory infiltrate. Foci of intravascular sickling may ensue [3,4].

Neoplasms confined to adults display heterogeneous tumour architecture comprised of solid, mucinous, cribriform, reticular, tubular or papillary articulations. Sheets of non-cohesive tumour cells are intermingled with disseminated singular cells. Neoplastic cells appear to infiltrate renal parenchyma. Additionally, eosinophilic polygonal cells, rhabdoid cells or signet ring cells with intracytoplasmic vacuolization are enunciated [3,4] (Figures 1 & 2).

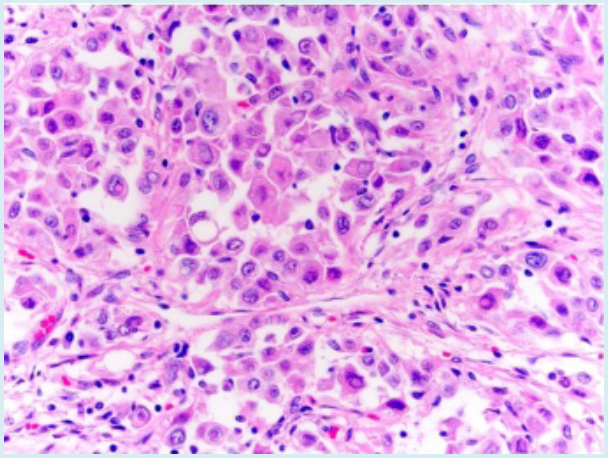

Figure 1: ALK rearranged renal cell carcinoma demonstrating sheets of cells imbued with eosinophilic cytoplasm, intracytoplasmic vacuoles, polymorphic nuclei and miniature nucleoli. Tumour cells infiltrate renal parenchyma [5].

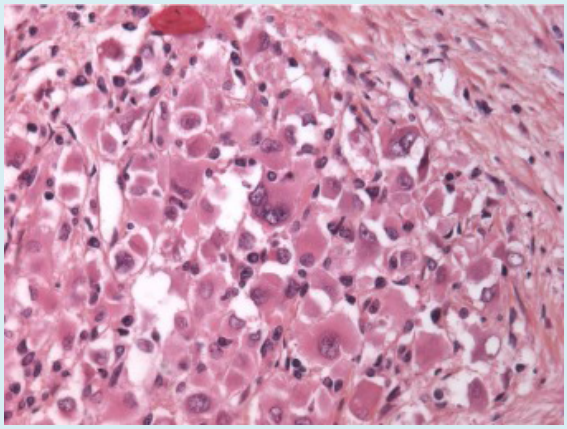

Figure 2: ALK rearranged renal cell carcinoma exhibiting clusters of cells pervaded with eosinophilic cytoplasm, intracytoplasmic mucin, vesicular nuclei and inconspicuous nucleoli. Tumour cells infiltrate the renal parenchyma [6].

Tumour parenchyma may demonstrate psammoma bodies and scattered foamy macrophages. Ultrastructural examination, exhibits tumour cells pervaded with bundles of tonofilaments. Besides, intercellular junctions, desmosomes, intracytoplasmic lumina layered by microvilli and lipofuscin-like lysosomal structures may be encountered [3,4] (Table 1).

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

Table 1: Histological characterization of molecular variants of renal cell carcinoma [3].
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 anaplastic lymphoma kinase (ALK), PAX8, integrase interactor 1(INI1), AE1/AE3, CAM5.2, CK7, epithelial membrane antigen (EMA), low molecular weight cytokeratin (LMWCK), p53, vimentin , CD10 or α-methyacyl CoA racemase (AMACR). Majority of neoplasms appear immune reactive to TFE3.

Tumour cells are immune non-reactive to renal cell carcinoma (RCC) antibodies, CD117/c- KIT, S100 protein, human melanoma black 45(HMB45) antigen, Melan A, cathepsin K and Wilm's tumour (WT1). Ki67 proliferative index is minimal < 5% [7,8].

ALK rearranged renal cell carcinoma requires segregation from neoplasms such as renal medullary carcinoma, collecting duct carcinoma, MiT family translocation renal cell carcinoma, papillary renal cell carcinoma, mucinous tubular and spindle cell carcinoma, unclassified renal cell carcinoma or distant metastasis arising from ALK rearranged pulmonary adenocarcinoma.

Upon ultrasonography, tumefaction articulates a hypoechoic mass confined to renal medulla [7,8]. Computerized tomography (CT) exhibits an iso-dense tumefaction. Contrast enhanced computerized tomography (CT) delineates minimally enhancing or heterogeneous neoplasm. ALK rearranged renal cell carcinoma may be appropriately eradicated with surgical extermination [7,8]. Preliminary stages of the primary tumour may be suitably managed with radical nephrectomy or nephron-ureterectomy.

ALK rearranged renal cell carcinoma is optimally responsive to chemotherapeutic agents as ALK inhibitor alectinib. Besides, akin to ALK rearranged pulmonary carcinoma, neoplasm may be treated with kinase inhibitors as crizotinib [7,8].

Paediatric subjects demonstrating VCL-ALK rearranged renal cell carcinoma appear devoid of tumour reoccurrence or distant metastasis. Adults delineating non VCL-ALK rearranged renal cell carcinoma are associated with inferior prognostic outcomes in ~33% instances.

However, precise determination of factors contributing to disease emergence may be challenging as the infrequently encountered neoplasm is subjected to limited monitoring [7,8].

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5. Image 1 Courtesy, Pathology outlines.

6. Image 2 Courtesy, Science direct.

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