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# The Collocating Receptacle-Collecting Duct Carcinoma

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**Editorial**

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**Keywords:** Renal Cell Carcinoma; Single Nucleotide Polymorphism; Collecting Duct Carcinoma; Glandular Articulations; Cohesive Cell Nests

**Abbreviations:** TFE3: Transcription Factor Binding To IGHM Enhancer 3; ALK: Anaplastic Lymphoma Kinase; RCC: Renal Cell Carcinoma; FH: Fumarate Hydratase; SDH: Succinate Dehydrogenase; SNP: Single Nucleotide Polymorphism.

## Editorial

Collecting duct carcinoma configures as an exceptionally discerned renal cell carcinoma contributing to < 1% of renal neoplasms and depicts an aggressive clinical course. Tumefaction is confined to renal medulla and is posited to arise from principal cells of distal collecting ducts of Bellini. Collecting duct carcinoma is additionally designated as Bellini duct carcinoma or carcinoma of collecting ducts of Bellini. Therapeutic response to immunotherapy and chemotherapy is minimalistic. Prognostic outcomes are extremely adverse.

Tumefaction is comprised of irregular, infiltrating tubules layered with pleomorphic, high grade cells incorporated with intracytoplasmic mucin. Tumour cell aggregates are encompassed with significantly desmoplastic stroma infiltrated by inflammatory cells.

Definitive criterion of ascertainment of collecting duct carcinoma are designated as

➢ Major diagnostic criteria comprised of
- Incrimination of renal medulla
- Preponderant tubular architecture
- Significantly desmoplastic stroma
- Tumour comprised of high grade cuboidal cells or hobnail cells
- Infiltrative pattern of tumour evolution

➢ Minor diagnostic criteria constituted of
- Enlarged tumours confined to centric sites
- Tubulo-Papillary neoplastic architecture
- Encompassing stroma infiltrated by inflammatory cells, especially neutrophils
- Extensive tumour infiltration into renal parenchyma, extra-renal sites or vascular configurations
- Tumour cells immune reactive to mucin [1,2].

Definitive tumour categorization necessitates exclusion of various subtypes of renal cell carcinoma, urothelial carcinoma and foci of distant metastasis from diverse primary neoplasms.

A male predilection is observed with male to female proportion of 2:1. Mean age of disease emergence is 55 years whereas median age of disease occurrence varies from 43 years to 63 years. Nevertheless, collecting duct carcinoma incriminates subjects between 8 years to 83 years. Analgesic nephropathy may contribute to neoplastic emergence [1,2].

Collecting duct carcinoma is devoid of specific molecular alterations. Loss of chromosome 3p or trisomy 7 and trisomy 17 are absent. Neoplastic cells depict complex chromosomal aberrations, especially copy number loss or loss of heterozygosity within chromosomes 1p, 6, 8, 9, 14 and 22. Genetic amplification of HER2 / neu is observed. Genomic alterations within NF2, SETD2, SMARCB1 and CDKN2A genes may occur [2,3].

Whole exome sequencing and transcriptome sequencing or RNA sequencing exhibits reoccurring somatic single nucleotide variants (SNVs) within MLL gene. Besides, somatic mutations with SNVs may occur within ATM, CREBBP, PRDM1, CBFB, FBXW7, IKZF1, KDR, KRAS, NACA, NF2, NUP98, SS18, TP53 or ZNF521 genes.

Single nucleotide polymorphism (SNP) array demonstrates homozygous deletion within CDKN2A gene. SNV analysis enunciates nonsense mutation of CDKN2A gene along with obscure somatic status [2,3].

Dysregulation within solute carrier family genes along with overexpression of SLC7A11 or cystine transporter xCT, a cisplatin resistance associated gene may be exemplified.

Additionally, downregulation of solute carrier genes as SLC3A1, SLC9A3, SLC26A7 and SLC47A1 may be expressed. Besides, upregulation of keratin 17 and downregulation of MARC2 or cubulin may be discerned [2,3].

RNA sequencing analysis exhibits enhanced aerobic glycolysis and overexpression of immune genes. Molecular heterogeneity within distinct neoplastic subtypes may be expounded with cell signalling concurring with metabolic and immune alterations [2,3].

Whole genome sequencing may delineate repetitive somatic mutations within BM14, MTUS1, GAK, DST, ASPM, CDC27, RNF213 and XIRP2 genes. Alterations within TP53, RB1 and CDKN2A genes are documented. Copy number variations and chromosomal mutations appear unique and diverse from genetic alterations encountered within urothelial carcinoma and various renal cell carcinomas. Tumefaction with CDKN2A genetic alterations are associated with inferior overall survival (OS) [2,3].

Collecting duct carcinoma preponderantly arises from centric zone of renal medulla. Nevertheless, enlarged tumours may incriminate renal cortex and renal medulla.

An estimated two thirds (~66%) of implicated individuals depict cogent clinical symptoms as pain, gross haematuria, loss of weight, fatigue and tumour palpable within dorsolateral thoracolumbar zone [2,3].

Cytological examination exhibits glandular articulations, cohesive cell nests and singularly disseminated tumour cells. Neoplastic ells appear as eosinophilic, vacuolated and permeated with intracytoplasmic mucin, enlarged, irregular, hyperchromatic nuclei, vesicular nuclear chromatin and enlarged nucleoli. Foci of ductal or tubular differentiation may be observed. Layering epithelium may be benign, dysplastic or exhibits malignant metamorphosis.

Encompassing stroma is significantly desmoplastic and infiltrated by inflammatory cells as neutrophils. Foci of sarcomatoid modifications may be observed. Exfoliation of malignant collecting duct carcinoma cells while examining smears of urine cytology is documented [2,3].

Grossly, a firm, greyish or whitish tumour mass infiltrating surrounding renal parenchyma is observed. Neoplasm is confined to renal medulla although renal cortex and renal medulla may concurrently be implicated. Tumour magnitude varies from 2.5 centimetres to 12 centimetres with a mean tumour diameter of 5 centimetres.

Cut surface exhibits frequent foci of haemorrhage, necrosis and cystic alterations. Satellite tumour nodules and foci of renal vein invasion may be encountered. Tumour infiltration of peri-renal adipose tissue and adipose tissue confined to renal sinus may ensue [3,4].

Upon microscopy, tumefaction exhibits a complex architecture. Neoplasm is poorly circumscribed, multinodular and exemplifies infiltration of circumscribing parenchyma. A predominantly interstitial pattern of tumour evolution is observed. Glomeruli are preserved.

Cords, tubules, glandular articulations or tubulo-papillary structures are layered by neoplastic cells and appear to infiltrate surrounding desmoplastic stroma which is invaded by inflammatory cells. Additionally, solid sheets, sheet-like articulations, tumour cell nests, tubulo-cystic pattern, cord-like structures, papillary articulations, micro-papillary configurations or singular, disseminated cells may be enunciated [3,4].

Minor neoplastic components emerge as sieve-like, cribriform, intra-cystic, papillary and reticular or yolk sac tumour-like configurations. Intra-cystic tumour articulations are associated with delicate fibro-vascular cores and focal hyalinization. Irregular neoplastic channels are layered with pleomorphic cuboidal cells or hobnail cells incorporated with eosinophilic cytoplasm and intracytoplasmic or intraluminal mucin. Tumour cell nuclei appear enlarged, pleomorphic and pervaded with coarse nuclear chromatin and prominent nucleoli [3,4].

Mitotic activity is significant. Apoptotic cells and focal necrosis are commonly observed. Foci of micro-cystic alterations may occur on account of dilatation of tubular structures. Foci of sarcomatoid differentiation may ensue. Tubular epithelium abutting the tumour or layering adjoining collecting ducts may appear dysplastic.

Focal lymphatic invasion, vascular invasion and incrimination of regional lymph nodes is common. Stroma surrounding neoplastic lobules is prominently infiltrated by an inflammatory infiltrate comprised of neutrophils (Figure 1) [3,4].

Ultrastructural examination exhibits cellular features of adenocarcinoma such as intracellular and extracellular

lumina. Besides, congruous cellular junctions, prominent basal lamina and abridged apical microvilli are observed (Figure 2 and Table 1) [3,4].

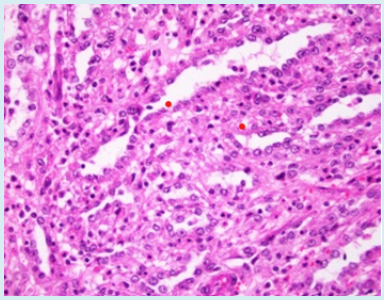

**Figure 1:** Collecting duct carcinoma enunciating nests, cords, papillae and tubules lined by pleomorphic epithelial cells pervaded with enlarged, high grade nuclei, coarse nuclear chromatin and prominent nucleoli. Surrounding stroma is desmoplastic and inflamed [5].

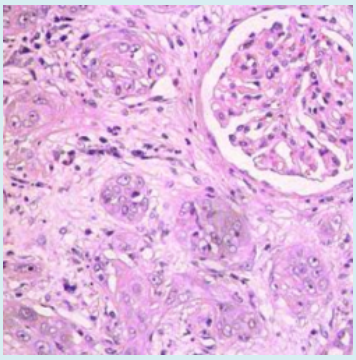

**Figure 2:** Collecting duct carcinoma delineating nests, cords, tubules and papillae layered by pleomorphic epithelial cells incorporated with eosinophilic cytoplasm, pleomorphic nuclei with coarse chromatin and prominent nucleoli. Surrounding stroma is desmoplastic and inflamed [6].

| 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 1:** Molecular Characterization of Renal Cell Carcinoma [4].

Neoplastic cells appear immune reactive to PAX8, PAX2, high molecular weight cytokeratin CK 34βE12, CK7, Ulex europaeus lectins (Ulex1), peanut lectin agglutinin (PNA), mucin, vimentin, CK8/18, CK19, epithelial membrane antigen (EMA), S100A1, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1(SMARCB1) or integrase interactor 1(INI1) and fumarate hydratase (FH).

Tumour cells appear immune non-reactive to p63, uroplakin II, GATA3, CD10, alpha-methylacyl-CoA racemase (AMACR), E-cadherin, carbonic anhydrase IX(CAIX), OCT 3/4 or CD117 [7].

Collecting duct carcinoma requires segregation from neoplasms such as metastatic carcinoma, urothelial carcinoma with glandular differentiation, cystic renal cell carcinoma, fumarate hydratase (FH) deficient renal cell carcinoma, hereditary leiomyomatosis and renal cell carcinoma associated renal carcinoma syndrome, papillary renal cell carcinoma, SMARCB1 deficient renal medullary carcinoma, mucinous tubular spindle cell carcinoma or tubulo-cystic carcinoma [7].

Collecting duct carcinoma may be appropriately discerned with histological evaluation of formalin fixed paraffin embedded sections (FFPE). Adequate sampling of incriminated renal parenchyma, especially adjacent renal pelvis is necessitated. Cogent evaluation of major criterion, minor criterion and designated criterion is beneficial and diagnostic [7].

Classic component of diverse neoplasms as clear cell renal cell carcinoma, papillary renal cell carcinoma or mucinous tubular and spindle cell carcinoma appears indicative of malignant metamorphosis into collecting duct carcinoma or pleomorphic, high grade morphology.

Appropriate assessment of clinical history, preceding cytological or histological evaluation and radiographic concurrence is advantageous in discerning distant metastasis or occurrence of urothelial carcinoma. Immunohistochemistry with PAX8, CK34βE12, GATA3, SMARCB1, OCT 3/4 and fumarate hydratase may be advantageous for tumour detection [7].

Computerized tomography (CT) exhibits concordance with morphological features. Tumefaction is confined to renal medulla and incriminates renal sinus. Nearly 50% of neoplasms demonstrate a cystic component. Perinephric stranding, regional lymphadenopathy, vascular invasion and distant metastases may be encountered.

The infiltrative tumour frequently demonstrates preservation of renal contour, in contrast to an expansible neoplastic growth or exophytic configuration observed within various renal cell carcinomas [7].

Collecting duct carcinoma can be appropriately subjected to surgical procedures as nephrectomy. Adjuvant cytotoxic chemotherapy may be employed, along with or in the absence of radiation therapy. Chemotherapeutic agents as gemcitabine or cisplatin may be accompanied by median overall survival of ~11 months. Neoplasms demonstrating CDKN2A homozygous deletion and distant metastasis may be treated with palbociclib [7].

Adoption of tyrosine kinase inhibitors, immune checkpoint inhibitors, anti-programmed death 1 antibody or cytotoxic T lymphocyte associated antigen 4 antibodies for curative intent remains debatable. Besides, immunotherapy regimens as neo-antigen based vaccination or neo-antigen reactive T cells necessitate additional evaluation.

Collecting duct carcinoma manifests a median survival of 7.6 months to 11 months wherein two thirds (~67%) of subjects delineate disease associated mortality within initial 2 years [7].

Nearly 40% of incriminated individuals manifest with distant metastasis. Majority of subjects exhibit distant metastases upon initial disease representation or following surgical manoeuvers as nephrectomy.

Commonly, metastases into regional or distant lymph nodes, hepatic parenchyma, pulmonary parenchyma, bone, adrenal gland or contralateral kidney may ensue.

Factors contributing to superior prognostic outcomes emerge as

- Absence of regional lymph node involvement
- Absence of distant metastasis
- Absent foci of sarcomatoid differentiation
- Preliminary tumour stage [7].

Neoplasms with focal sarcomatoid differentiation and tumours lacking therapeutic surgical intervention are associated with significant disease associated mortality.

Collecting duct carcinoma demonstrating median neutrophil to lymphocyte ratio ≥ 4 is accompanied by inferior cancer specific survival [7].

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