
EDITORIAL NOTE

Cannulated and metamorphosed-renal cell carcinoma

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EDITORIAL

Previously designated as hepatocellular carcinoma, Grawitz tumour or hypernephroma, adult renal cell carcinoma enunciates diverse histological subtypes and incriminates renal parenchyma. As per modified WHO classification 2016, renal cell carcinoma is categorized into clear cell renal cell carcinoma, multilocular cystic renal neoplasm of low malignant potential, papillary renal cell carcinoma, hereditary leiomyomatosis renal cell carcinoma, chromophobe renal cell carcinoma, collecting duct carcinoma, renal medullary carcinoma, MiT family translocation carcinomas, succinate dehydrogenase deficient renal cell carcinoma, mucinous tubular and spindle cell carcinoma, tubulocystic renal cell carcinoma, acquired cystic disease-associated renal cell carcinoma, clear cell papillary renal cell carcinoma and unclassified renal cell carcinoma.

Hereditary renal cell neoplasms are encountered in von Hippel-Lindau syndrome, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis and renal cell carcinoma, familial papillary thyroid carcinoma, hyperparathyroidism-jaw tumour syndrome, Birt-Hogg-Dube syndrome, tuberous sclerosis or constitutional chromosome 3 translocation [1, 2]. Paraneoplastic syndromes such as Cushing's syndrome, gynaecomastia, hypercalcemia, hypertension, leukemoid reaction, polycythaemia, Stauffer syndrome comprised of hepatomegaly with hepatic dysfunction, systemic amyloidosis or polyneuropathy may concur [1, 2].

Generally, Caucasian individuals >50 years or populations with enhanced socioeconomic status are incriminated. A male predominance is observed with a male-to-female proportion of 2:1. Individuals with distinct genetic susceptibility exhibit the emergence of renal cell carcinoma along with the activation of diverse molecular pathways. Factors contributing to the emergence of renal cell carcinoma appear as obesity, cigarette smoking, hypertension, acquired cystic renal disease occurring due to end-stage renal disease, occupational exposure to trichloroethylene or therapeutic intervention of neuroblastoma. Clinically, characteristic manifestatio

ns of costovertebral pain, palpable mass and haematuria may appear [1,2].

Upon gross examination, factors such as invasion of renal sinus, perinephric adipose tissue, the periphery of renal vein, uninvolved renal parenchyma or regional lymph nodes require evaluation. Tumefaction is well circumscribed, centred upon the renal cortex and frequently extends towards the renal vein or inferior vena cava. Enlarged tumours depict infiltration of the renal sinus. Renal contour can be distorted. The neoplasm may exhibit satellite tumour nodules. Focal areas of haemorrhage, necrosis, calcification or cystic change are frequently encountered [1, 2].

Cytological examination exemplifies tumour cells imbued with abundant, vacuolated, fluffy or granular cytoplasm and indistinct cellular boundaries. Cells of chromophobe renal cell carcinoma depict distinct cellular outlines. Tumour cell nuclei demonstrate varying atypia, irregular contour, haphazard orientation, aberrant chromatin and prominent nucleoli. Renal tubular epithelial cells delineate well-defined cellular outlines, homogenous cytoplasm and uniform, spherical, orderly nuclei. Exceptionally, heterogeneous cell populations, miniature cytoplasmic vacuoles or hemosiderin pigment deposits may be discerned. Upon microscopy, renal cell carcinoma exhibits distinct architectural patterns as solid, alveolar (nested), acinar (tubular), micro-cystic with red cell extravasation or impacted eosinophilic fluid or an occasional, macro-cystic configuration [1, 2].

Characteristically, renal cell carcinoma configures compact nests and sheets of tumour cells incorporated with clear to granular eosinophilic cytoplasm and distinct cytoplasmic membrane. Tumour cell aggregates demonstrating granular, eosinophilic cytoplasm are intermingled with a network of arborizing, miniature, thin-walled vascular articulations. Tumour cell magnitude is roughly twice the diameter of a normal epithelial tubule cell. Intervening stroma is nondescript and devoid of desmoplastic reaction or an inflammatory cell infiltrate [1,2]. Focal areas of haemorrhage or necrosis may ensue.

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Additionally, fibromyxoid stroma, focal calcification or ossification may be discerned. Neoplasms of advanced grade exhibit distinctive features as rhabdoid differentiation configured of enlarged, malignant cells incorporated with abundant, homogeneous, eosinophilic cytoplasm and an eccentric nucleus demonstrating globular, eosinophilic intracytoplasmic inclusions [3, 4]. Sarcomatoid differentiation enunciates a fibrotic, spindle-shaped cellular stroma. The feature may appear in designated subtypes of renal cell carcinoma (Figures 1 and 2). Infrequently discerned histologic variants with undetermined prognostic significance articulate cystic or pseudo-papillary tumour configuration, heterotopic bone formation, intracellular or extracellular hyaline globules, basophilic cytoplasmic inclusions, abundant multinucleated giant cells, sarcoid-like granulomas or myospherulosis [1, 2] (Table 1).

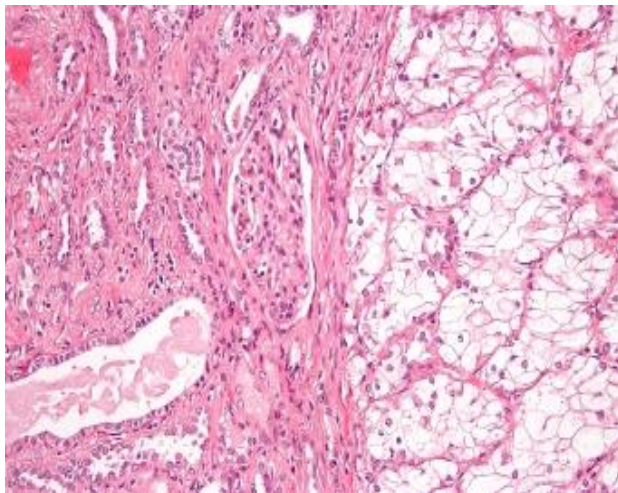


Figure 1) Renal cell carcinoma depicting tubules and glandular articulations layered with neoplastic cells admixed with aggregates of clear cells with clear cytoplasm, uniform, vesicular nuclei and prominent nucleoli [5]

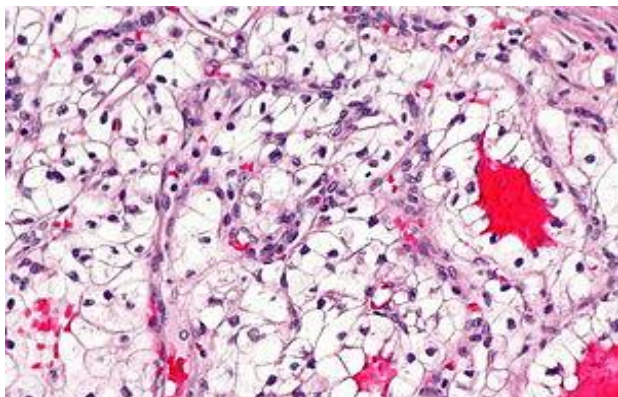


Figure 2) Renal cell carcinoma delineating clusters of clear cells imbued with clear cytoplasm, regular, vesicular nuclei with prominent nucleoli traversed by fibrous tissue septa [6].

TABLE 1
TNM classification of renal cell carcinoma [2,3]

Tumour	Node	Metastasis
–	NX: Lymph nodes cannot be assessed	–
T0: No evidence of primary tumour	N0: No regional lymph node metastasis	M0: Distant metastasis absent
T1: Tumour ≤ 7 cm, confined to kidney •T1a: Tumour ≤ 4 cm confined to the kidney	N1: Regional lymph node metastasis present	M1: Distant metastasis present
•T1b: Tumour between 4 cm to 7 cm, confined to the kidney	–	–
T2: Tumour > 7 cm confined to kidney •T2a: Tumour >7cm & ≤10cm confined to the kidney	–	–
•T2b: Tumour >10cm confined to kidney	–	–
T3: Tumour extends to major veins or perinephric tissues. Extension into the ipsilateral adrenal gland or beyond Gerota's fascia is absent. •T3a: Tumour invades renal vein or segmental branches, pelvicalyceal system, peri-renal & renal sinus adipose tissue. •T3b: Tumour extends into vena cava below the diaphragm. •T3c: Tumour extends to vena cava above the diaphragm or invades the wall of vena cava	–	–
T4: Tumour extends beyond Gerota's fascia with contiguous spread to the ipsilateral adrenal gland	–	–

Contingent to nucleolar prominence, World Health Organization categorizes papillary and clear cell renal cell carcinoma into

- G1 where tumour cell nucleoli are absent or inconspicuous and basophilic at 400X magnification.
- G2 where nucleoli appear conspicuous and eosinophilic at 400X magnification or visible and inconspicuous at 100X magnification.
- G3 where nucleoli are conspicuous and eosinophilic at 100X magnification.
- G4 where tumour cells depict significant nuclear pleomorphism, multinucleated giant cells or foci of rhabdoid or sarcomatoid differentiation [3, 4].

Renal cell carcinoma is immune reactive to PAX8, PAX2, CAIX, CD10, RCC, vimentin, cytokeratin AE1/AE3, CAM5.2 or EMA. Renal cell carcinoma is immune nonreactive to CK20, inhibin, Melan A/MART1, calretinin, TTF1 or CEA [3, 4]. Cystic renal epithelial neoplasms require segregation from tumours such as multilocular cystic renal neoplasm of low malignant potential, cystic clear cell papillary renal cell carcinoma, clear cell renal cell carcinoma with cystic degeneration, clear cell renal cell carcinoma originating in a benign cyst, acquired cystic disease-associated renal cell carcinoma, tubulocystic renal cell carcinoma or adult cystic nephroma. Renal epithelial and stromal tumours may emerge as mixed epithelial

and stromal tumours.

Subjects demonstrating renal tumefaction upon pertinent clinical examination require demarcation from peri-renal or renal abscess, angiomyolipoma, renal oncocytoma, renal adenoma, renal lymphoma, renal cyst, renal infarction, sarcoma or metastasis from distant primary lesions as metastatic malignant melanoma. Besides, a distinction is mandated between acute or chronic pyelonephritis, carcinoma urinary bladder, non-Hodgkin lymphoma or adult type Wilm's tumour. Image-guided surgical tissue sampling or Tru-Cut needle biopsy can be adopted to appropriately evaluate solitary, miniature renal tumefaction and associated, cogent therapeutic strategies. The majority of enlarged neoplasms are detected incidentally or upon radiographic imaging [3, 4].

Contingent to the tumour subtype, renal cell carcinoma can be appropriately treated with surgical extermination procedures such as partial or radical nephrectomy. Traditionally, adjuvant chemotherapy or radiation appears inefficacious. However, agents such as interferon, cytokine interleukin 2, diverse antiangiogenic drugs or immunotherapy with sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib or nivolumab can be advantageously adopted. Prognostic outcomes and therapeutic response of stage IV, metastatic renal cell carcinoma is assessed.

- Memorial Sloan Kettering Cancer Centre (MSKCC) system comprised of elevated serum Lactate Dehydrogenase (LDH) elevated serum calcium anaemia systemic therapy as targeted therapy, immunotherapy or chemotherapy required within <one year from tumour detection poor performance status.
- International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) system comprised of elevated leucocyte count with neutrophilia thrombocytosis elevated serum calcium anaemia systemic therapy as targeted therapy, immunotherapy or chemotherapy required within <one year from tumour detection poor performance status.

Incriminated subjects are categorized as

- Low risk demonstrating an absence of aforesaid factors and superior prognosis.
- Intermediate risk delineating 2 aforesaid factors and an intermediate prognosis.
- High risk exemplifying ≥ 3 aforesaid factors and an inferior prognosis. Prognostic outcomes are contingent on TNM tumour staging. In contrast to papillary or chromophore renal cell carcinoma, clear cell renal cell carcinoma depicts an unfavourable prognosis. Tumefaction exhibiting an identical stage with enhanced histological grade or sarcomatoid or rhabdoid differentiation demonstrates an inferior prognosis. Focal coagulative tumour necrosis >10% is associated with decimated overall survival [3, 7].

5-year survival following nephrectomy is 70% and 10% in renal cell carcinoma demonstrating metastasis. 5-year survival is decimated in carcinoma of the renal pelvis [3,7].

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