

# Tubulopapillary Histomorphology in Renal Neoplasms: A Diagnostic Dilemma with Review of Literature

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## ABSTRACT

Conventional renal cell carcinomas have a straightforward diagnosis. However a different subset of renal neoplasms with prominent tubulopapillary histomorphology pose a diagnostic challenge due to significant overlap of microscopic features and very few points of differentiation between them. These constitute collecting duct carcinoma, renal medullary carcinoma, adenocarcinoma of renal pelvis; translocation associated renal carcinoma and mucinous tubular & spindle cell carcinoma. Hereby short case reports of three of these entities are presented with a comprehensive review of literature related to diagnostic and therapeutic inputs on renal neoplasms with tubulopapillary architecture.

**Key words:** Tubulopapillary, Carcinoma, Renal, Diagnosis

## INTRODUCTION

It is not rare to encounter tubulopapillary histomorphology while evaluating renal neoplasms microscopically, especially for those arising in medulla or at the confluence of medulla and renal pelvis. They have predominantly invasive tubulopapillary growth pattern and majority of them are classified as collecting duct carcinoma, medullary carcinoma or adenocarcinoma of renal pelvis. Other less frequently seen entities are translocation associated renal carcinoma and mucinous tubular and spindle cell carcinoma. <sup>(1)</sup> These have many overlapping features and fewer points of distinction, and thus pose a diagnostic dilemma. It is crucial to differentiate them for apt and timely management. We report here a series of three cases of renal neoplasms with tubulopapillary growth pattern and attempt

to classify them on the basis of clinical history, microscopy and immunohistochemistry.

## CASE

### Case One

A 48 years old male presented with left lumbar pain and flank mass since 6 months with hematuria and weight loss from last 3 months. CT scan showed well defined heterogenous lesion involving the pelvicalyceal system. Gross examination showed variegated growth appearance replacing whole renal parenchyma. Microscopy showed a malignant neoplasm predominantly with tubulopapillary architecture depicting hobnail shaped cells protruding in to glandular lumen accompanied by prominent desmoplastic stromal reaction with relative sparing of glomeruli. Immunohistochemistry of the

tumor cells showed strong positivity for High Molecular Weight Cytokeratin (HMWCK); Epithelial Membrane Antigen (EMA), Vimentin, CK 7 and CK 20 were weakly positive (Figure 1).

This pattern of expression was consistent in favour of Collecting duct

Carcinoma Kidney. Postoperative recovery was uneventful and patient was discharged with advice of regular follow up. However patient did not turn up for follow up and on enquiry it was found that he expired 3 months later at home. The cause of death was not established.

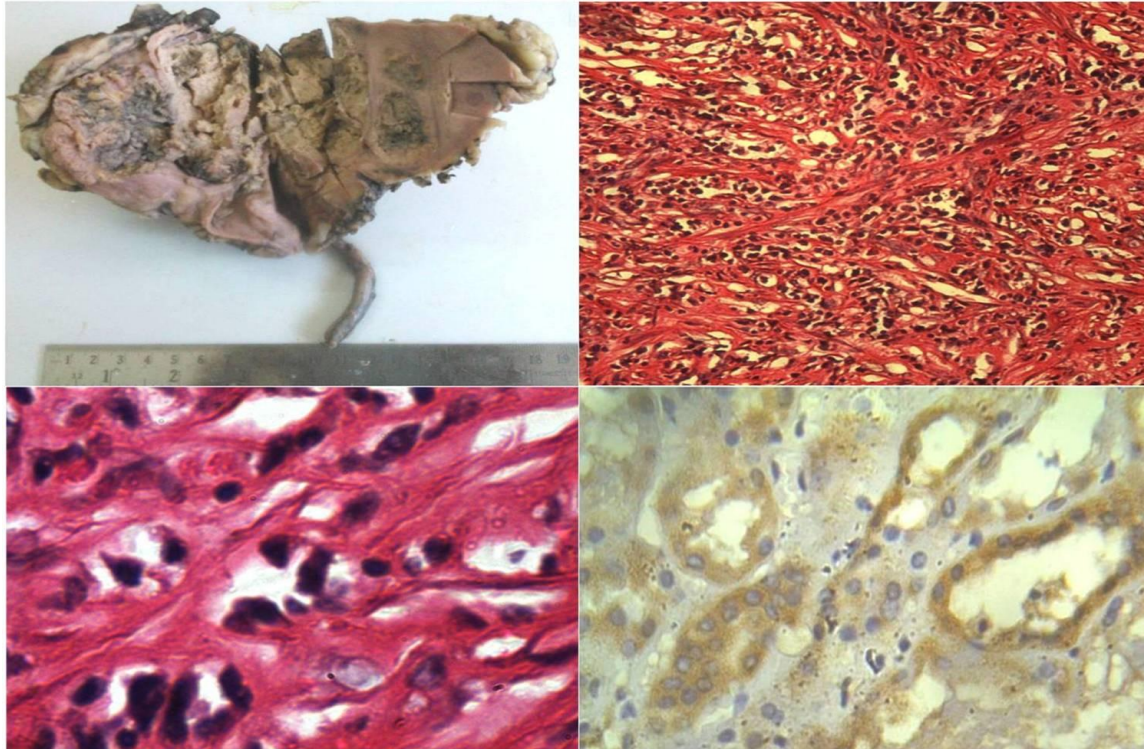


Figure 1: Collecting Duct Carcinoma kidney, prominent hobnailing with HMWCK positivity

### Case Two

A 22 years old female presented with palpable right lumbar mass, flank pain, gross hematuria and weight loss since 4 months, nonspecific body pain and anemia since childhood. CT scan as well as gross examination showed a well defined heterogenous mass measuring 8x7x6 cm involving most of the renal parenchyma with capsule infiltration in the right kidney. Histomorphology of the nephrectomy specimen revealed a renal neoplasm with prominent tubulopapillary architecture with characteristic presence of sickle shaped RBC's in traversing blood vessels across the tumor mass. The tumor cells were extending up to the capsule but not beyond it. This finding raised the suspicion for Renal Medullary Carcinoma and hence sickling test was performed, which turned to be

positive (Figure2). On immunohistochemistry CK 7, CK 20 were positive. HMWCK, EMA and Vimentin were negative. Additionally OCT 3/4 was also applied, which came positive, thereby confirming presence of Renal Medullary Carcinoma. Patient was discharged after one week. At 6 months follow up, her condition was satisfactory.

### Case Three

A 72 years old male patient presented with episodic hematuria, right lumbar pain, and loss of weight for 3 months. CT scan as well as gross examination revealed an ill defined heterogeneous mass measuring 8x5x3 cm involving renal pelvis and extending in to lower pole of right kidney. Microscopy revealed tubulopapillary architecture with glandular differentiation and presence of



signet ring cells with involved transitional epithelial lining and interstitial fibrosis. On immunohistochemistry CK 7 and CK 20 were positive (Figure 3). HMWCK, EMA and Vimentin were negative. Additionally Alcian blue and Uroplakin were also applied which turned positive and negative

respectively. Thereby by diagnosis of exclusion and clinicopathological correlation, the case was labelled as Adenocarcinoma of renal pelvis. Post-operative recovery was uneventful and on follow up at 6 months, the patient was disease free with no major complaints.

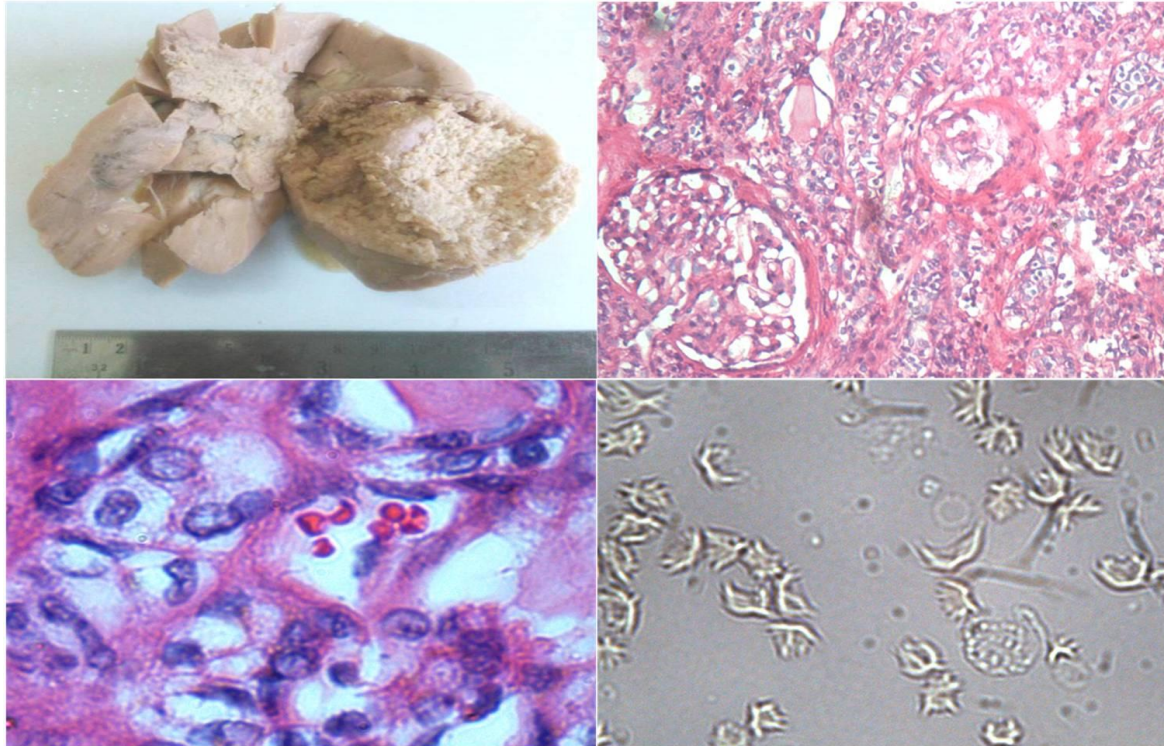


Figure 2: Renal medullary carcinoma sickled RBCs in neoplastic glands and on wet mount

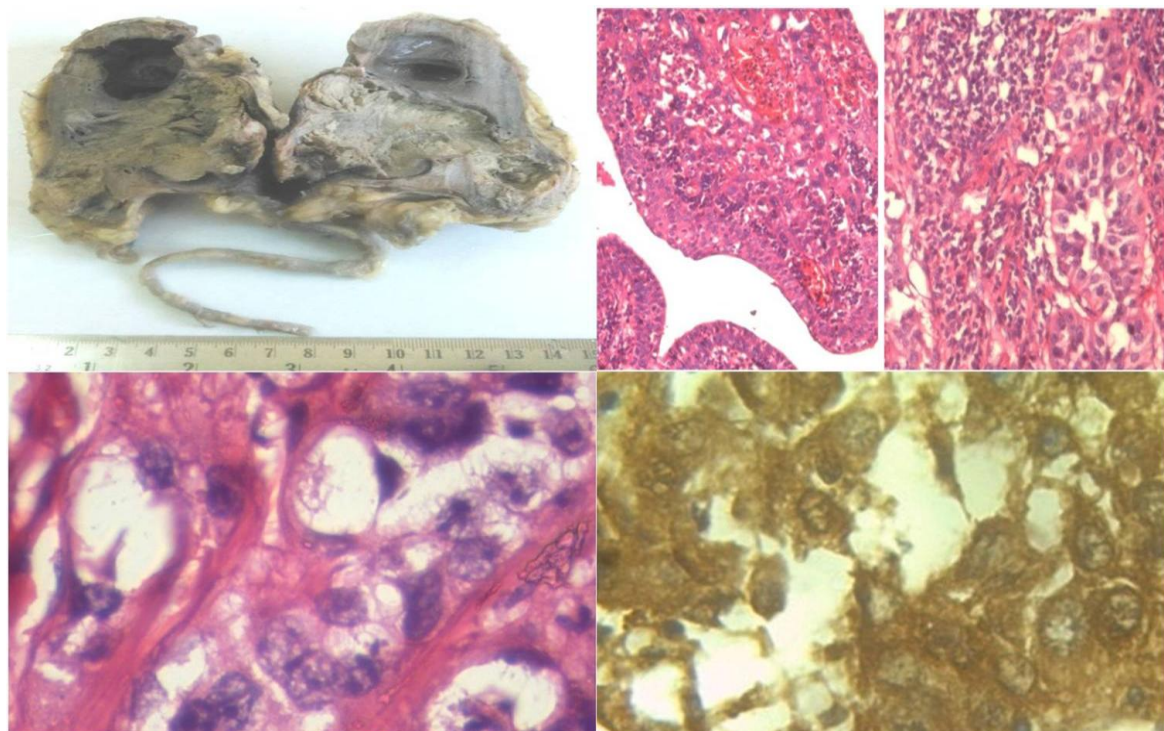


Figure 3: Adenocarcinoma of pelvis, prominent signet rings with CK7 positivity

## DISCUSSION

Renal neoplasms with clear cell or simple papillary histomorphology are easy to diagnose and fortunately these two entities form bulk of the subtypes diagnosed. However the other subtypes, most of them having their putative cell of origin in medulla, predominantly present with tubulopapillary histomorphology and require a meticulous correlation of clinical - histological-immunohistochemistry findings to label a precise diagnosis. The present manuscript is an attempt to define an algorithmic approach to accurately sub classifies such lesions.

Collecting duct carcinoma can be encountered in age group 13-84 years with mean age of 55. It is twice as common in males as compared to females. Renal medullary carcinoma is predominant in adolescents and young adults with most of cases reported from early third decade. Male female ratio is 1.9:1. Right kidney is more frequently involved as per published case reports. It has a strong association with sickle cell trait/disease and thus particularly more common in affected geographical belts and racial groups. Adenocarcinoma of renal pelvis is a rare tumor with very few reported cases. Majority of cases have been in adults with rare pediatric cases reported as well. Calculi, chronic inflammation and infection appear to be predisposing factors. Translocation associated carcinomas are more commonly encountered in younger age groups particularly in first and second decades, though rare cases have been reported in elderly population too. There is no significant sex predilection noted. However association with previous history of chemotherapy in about 15% cases has been found. Mucinous tubular and spindle cell carcinoma is reported in age from 13 to 82 years with a mean age of 53. Females are approximately four times more commonly involved as compared to males. <sup>(2-4)</sup>

Gross examination of the specimen helps, if the tumor is in early stage and has not extended to whole renal parenchyma. Collecting duct carcinoma has its nidus of

origin in medulla; those presenting in later stages are variegated and may also show “bubble wrap” appearance. Medullary carcinoma also originates from medullary portion of the collecting ducts. It has a variegated appearance too and only point of distinction on gross examination is frequent presence of “satellite nodules”. Adenocarcinoma of renal pelvis originates from pelvis and putative site of origin can be appreciated in early lesions. As the tumor outgrows, it acquires variegated appearance too. Translocation associated renal carcinomas too have nonspecific gross pathology and present with grayish yellow tanned appearance. Mucinous tubular and spindle cell carcinomas have a sharp circumscribed boundary with a glistening grayish yellow appearance. <sup>(2-4)</sup>

Microscopically all above mentioned entities present with baseline tubulopapillary architecture on histomorphology, though there are some additional specific features attributed by each subtype to be looked for a presumptive diagnosis. Collecting duct carcinoma depicts luminal structures lined by tumor cells with “hobnail appearance” and high nuclear grade, nuclear pleomorphism and prominent nucleoli. Medullary carcinoma presents with malignant tubules containing mucin with focally evident rhabdoid morphology of the tumor cells. The characteristic finding is presence of “sickled erythrocytes” in stroma or the traversing blood vessels across the tumor mass. Adenocarcinoma of renal pelvis should be differentiated from glandular variant of transitional cell carcinoma by demonstration of normal uroepithelium. The luminal structures show lining by high grade tumor cells often with a “signet ring appearance”. Translocation associated renal carcinomas show nested and papillary architecture lined by cells with wrinkled and irregular nuclei, often accompanied by numerous Psammomatous calcifications. Mucinous and tubular spindle cell carcinomas present with long tubular profiles lined by columnar cells with low grade nuclei, focally



vacuolated cytoplasm and spindling in a mucinous background. (2,4,5)

There is a significant overlap between the presenting gross and microscopic findings which necessitates employment of a baseline panel comprising of representative immunohistochemistry markers of each subtype for a definite diagnosis. A primary panel comprising of HMWCK, EMA, Vimentin, CK 7 and CK 20 works efficiently to categorize most of the doubtful cases. Strong HMWCK positivity favours collecting duct carcinoma. CK 7 / CK 20 positivity calls for employment of secondary panel consisting of OCT 3/4, Alcian blue and AMACR for designation as renal medullary carcinoma, adenocarcinoma of renal pelvis and mucinous tubular and spindle cell carcinoma respectively. Renal medullary carcinoma can also be confirmed by demonstrating positive sickling test. Translocation associated renal carcinomas express nuclear binding for TFE 3 / TFE B proteins other than under expressed / patchy classical renal cell carcinoma markers consisting of EMA and Vimentin. Definite diagnosis can also be established by genetic profiling. (4-6)

Tubulopapillary histomorphology in renal carcinomas commands a logical and systematic algorithmic approach to frame a definite diagnosis. Early detection and surgical resection offers the best modality for prolonged survival. It is crucial to identify the exact entity as all the possible differentials described above are potential candidates for post surgical chemo-, radio- or immunotherapy, the regimes being different in all of them. For collecting duct carcinomas, there have been few trials conducted recently with Sunitinib and Sorafenib, which have produced efficacious results but needs to be demonstrated on a broader cohort. (7) Renal medullary carcinomas are highly aggressive tumors with poor prognosis. Standard treatment modality at present comprises of platinum based chemotherapy with limited evidence of success. (8) With a preoperative suspicion

of adenocarcinoma of renal pelvis, the surgical approach should include a combined nephroureterectomy. Depending upon the stage of tumor presentation and patient's comorbidities, combined radiotherapy and cisplatin based chemotherapy may be offered which produces better outcome. (9) Mucinous tubular and spindle renal cell carcinomas are generally low pathological grade tumors and complete surgical excision appears to adequate treatment. There have been isolated case reports of responsive treatment to Sunitinib that requires validation at level of large cohort trials. (10) Cases of translocation associated carcinoma presenting with metastatic spread have been shown responsive to immunotherapy with cytokines such as interleukin 2 (IL-2), and interferon  $\alpha$  (IFN  $\alpha$ ). Recently there have been trials with targeted therapy (against VEGFR / mTOR) that produced better response as compared to immunotherapy. (11)

## CONCLUSION

Thus to conclude, a renal neoplasm presenting with tubulopapillary architecture should be assessed thoroughly and promptly with well-orchestrated clinicopathological correlation for a definitive diagnosis.

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