High-Grade Carcinomas Involving the Renal Sinus
Report of a Case and Review of the Differential Diagnosis
and Immunohistochemical Expression

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We report the case of a high-grade carcinoma involving the kidney in a young male with renal vein thrombosis and review the differential diagnosis and immunohistochemical workup. High-grade neoplasms involving the renal sinus include collecting duct carcinomas (CDCs), renal medullary carcinomas (RMCs), invasive high-grade urothelial carcinoma (UC) of the upper urinary tract, clear cell renal cell carcinoma, and type 2 papillary renal cell carcinoma. Distinguishing UC from CDC and RMC is problematic in small biopsy samples. The diagnosis of CDC (a rare, aggressive subtype of renal cell carcinoma) is challenging and requires the exclusion of UC. Renal medullary carcinoma is characterized by an appropriate clinical setting and consistent loss of nuclear expression of integrase interactor 1 (INI-1). A panel consisting of p63, paired box gene 8 (PAX8), and INI-1 is most optimal in distinguishing UC from CDC and RMC. A subset of urothelial carcinoma of upper urinary tract may be positive with PAX8.


REPORT OF A CASE

A 34-year-old male patient underwent a renal biopsy for the workup of renal vein thrombosis. The right kidney biopsy specimen showed an invasive carcinoma composed of variably sized nests infiltrating between glomeruli. The surrounding stroma was mildly desmoplastic. The tumor cells contained moderate amounts of eosinophilic cytoplasm and had high-grade nuclear atypia. No clear cells, racemose vascular pattern, or prominent papillary architecture was noted.

The critical differential diagnosis in this case includes invasive high-grade urothelial carcinoma involving upper urinary tract (favored morphologically) versus a high-grade renal cell carcinoma (collecting duct carcinoma of the kidney versus renal medullary carcinoma). Immunohistochemistry was performed to rule out renal cell carcinoma (RCC) owing to the presence of renal vein thrombosis. Renal medullary carcinoma entered into consideration owing to the young age of the patient. The tumor cells strongly expressed cytokeratin 7 (CK7), p63, paired box gene 8 (PAX8), and integrase interactor 1 (INI-1), and lacked vimentin expression. The biopsy specimen was diagnosed as a high-grade carcinoma, favoring urothelial carcinoma (Figure 1, A through F). The patient underwent a radical nephrectomy, which confirmed the diagnosis of high-grade urothelial carcinoma of the upper urinary tract involving the renal pelvis and extending into the renal sinus fat, renal parenchyma, and into perinephric adipose tissue (pT4). In addition, presence of tumor within the thrombosed renal vein was confirmed. Tumor cells in the excision specimen were strongly positive with p63 and INI-1, and weakly positive with PAX8. This case will be used to discuss the differential diagnosis of high-grade carcinoma involving the renal sinus and to review the immunoprofile of such tumors.

COMMENT

The differential diagnosis of high-grade carcinomas involving the renal sinus includes those arising from the renal pelvis and medulla as well as those that extend into it. While urothelial carcinoma (UC) of the upper urinary tract, collecting duct carcinoma (CDC), and renal medullary carcinoma (RMC) are usually centered in the renal medullary/sinus region, clear cell type renal cell carcinoma (clear cell type RCC) and papillary RCC (commonly, type 2 papillary RCC), may extend to involve the renal sinus fat. High-grade UC of the upper urinary tract frequently presents as an infiltrative mass that may extensively involve the renal parenchyma, mimicking high-grade RCCs. Distinguishing UC from subtypes of RCC, notably CDC and RMC, is often problematic, especially with small biopsy samples (Figure 2, A through F).

Urothelial carcinoma arising in the renal pelvis is uncommon, accounting for approximately 5% of all urothelial tumors. The average age of presentation is 70 years and the condition occurs slightly more often in men. Most patients (80%) present with painless hematuria and up to one-third with flank pain. Most often, invasive urothelial carcinoma that is stage pT2 or above is nonpapillary and has conventional morphologic features, with infiltrating nests of varying size, tumor cells with a moderate amount of eosinophilic cytoplasm, and enlarged hyperchromatic nuclei with variable pleomorphism (Figure 2, A). However, similar
to invasive UCs arising in the bladder, a significant minority shows variant/divergent differentiation in which the carcinoma takes on a unique histomorphologic phenotype.\textsuperscript{4,5} In 1 large series of UC of the upper urinary tract, 40% of cases exhibited divergent differentiation including glandular, squamous, rhabdoid, and micropapillary forms,\textsuperscript{4} among others, as such significant morphologic heterogeneity occurs (Figure 2, B).

Figure 1. Renal biopsy from a 34-year-old man with renal vein thrombosis. A, The biopsy specimen shows a high-grade carcinoma composed of variably sized nests infiltrating between glomeruli. B, Tumor cells are strongly positive with cytokeratin 7. C, Tumor cells are negative with vimentin. D, Tumor cells show moderate to strong nuclear positivity with PAX8. E, Tumor cells show strong nuclear positivity with p63. F, Tumor cells show strong nuclear positivity with INI-1 (hematoxylin-eosin, original magnification ×200 [A]; original magnifications ×200 [B through F]).

Figure 2. Representative images from urothelial carcinoma, collecting duct carcinoma, and renal medullary carcinoma highlight the morphologic overlap between these tumors. A, Urothelial carcinoma with solid nests and high-grade nuclei. B, Collecting duct carcinoma with solid architecture and high-grade nuclei. C, Renal medullary carcinoma with solid growth pattern. D, Urothelial carcinoma with glandular features and high-grade nuclei. E, Collecting duct carcinoma with glandular architecture, high-grade nuclei, and desmoplastic stroma. F, Renal medullary carcinoma with glandular architecture, high-grade nuclei, and desmoplastic stroma (hematoxylin-eosin, original magnifications ×200 [A through F]).
Collecting duct carcinomas and RMCs are rare but biologically, they are extremely aggressive subtypes of RCC, with most patients presenting with metastatic disease. 

Both tumors arise in the renal medulla and are located in the central region of the kidney. Collecting duct carcinomas are primarily high-grade adenocarcinomas with glandular architecture and occur predominantly in adults (mean age, 55 years). The major diagnostic criteria for the diagnosis of CDC include location of the tumor in the medullary pyramid (for small tumors), typical histology, and desmoplastic stroma with prominent inflammation including granulocytes, as well as exclusion of UC of upper urinary tract. These tumors usually show a tubular/glandular and tubulopapillary architecture, infiltrating renal parenchyma between intact glomeruli, and are typically associated with a desmoplastic stroma; however, a spectrum ranging from solid sheets to rhabdoid morphology has been described in these tumors. The tumor cells are frequently high grade (Fuhrman nuclear grade 3–4) with eosinophilic cytoplasm and may show hobnail morphology (Figure 2, B and E). Although immunohistochemical reactivity of CDC with high-molecular-weight cytokeratin and Ulex europaeus agglutinin lectin has been included in the criteria for diagnosis of CDC, the utility of these stains is limited as UCs also express these markers.7,8

Renal medullary carcinoma is a distinctive clinicopathologic entity occurring almost exclusively in young African American men with a sickle cell trait. Patients’ age mostly ranges between 10 and 40 years (mean, 22 years); presentation in persons older than 40 years is extremely unusual. The tumor can show a diverse morphology with cribriform, tubular, reticular, or solid architecture with prominent intratumoral infiltrate (usually neutrophils) and extensive desmoplasia. The tumor cells have amphophilic cytoplasm, and vesicular nuclei are prominent (Figure 2, C and F). Loss of nuclear expression of SNF1 (IN1-1 protein), a marker commonly showing positivity in almost all other tumors including UCs and other subtypes of RCCs, is a consistent finding in RMCs.8

We recently evaluated the utility of an optimal immunohistochemistry panel to accurately differentiate high-grade RCCs (clear cell type RCC, type 2 papillary RCC, CDC, and RMC) involving the renal hilum from UC of the upper urinary tract/renal pelvis. We found that a select panel consisting of CK7, p63, vimentin, PAX8, and IN1-1 offers the greatest sensitivity, specificity, and predictive value, and defined our select optimal panel for sorting out this differential diagnosis.7 Our results show that RCCs can be distinguished from UCs as a result of lack of p63 expression, along with predominant expression of vimentin and PAX8 and predominant lack of expression of CK7. Strong, diffuse expression of p63 in UC is most valuable in distinguishing UC from RCC, including CDC and RMC, and supports the utility of p63 as a sensitive and specific marker of UC with diffuse nuclear expression.7,8 No p63 expression was noted in any RCCs, including CDCs or RMCs, in our cohort.

A panel consisting of PAX8, p63, and IN1-1 is most optimal in distinguishing UC from CDC and RMC, as all 3 tumors show similar staining pattern with CK7 and vimentin. The utility of CK7 and vimentin is mainly in excluding clear cell RCC and papillary RCC (negative with CK7 and positive with vimentin) from UC, RMC, and CDC, which are commonly positive with CK7 and negative with vimentin. PAX8 is a member of the PAX gene transcription family and shows strong expression within nuclei of normal kidney and most RCCs.10 IN1-1 is most useful in the distinction of RMC from UC and other subtypes of RCC.

An immunoprofile consisting of PAX8+/p63+/IN1-1+ supports the diagnosis of UC involving upper urinary tract (sensitivity 83%, specificity 100%); a PAX8+/p63−/IN1-1+ immunoprofile supports a diagnosis of CDC (sensitivity 88%, specificity 100%); while an immunoprofile consisting of PAX8+/p63−/IN1-1 supports a diagnosis of RMC in the correct clinical setting.

The unusual scenario of PAX8+/p63+ immunoprofile was seen in our study case. A recent unpublished abstract,12 which analyzed 12 cases of RMC, found PAX8 and p63 positivity in 100% and 58% of cases, respectively, and postulated that PAX8+/p63+ immunoprofile supports the diagnosis, with a sensitivity of 58% and specificity of 89%. However, the diffuse, strong IN1-1 expression in our study case, in conjunction with clinical history (lack of sickle cell trait and Spanish ancestry), conclusively ruled out RMC in our index case.

In our experience,7 PAX8 is a sensitive marker of CDC and stains most CDCs (83%), and most often shows negativity in UCs (77–91%).13,14 A recent study15 analyzed a large series of CDCs (21 cases) and found all CDCs to be positive with PAX8. This study found p63 positivity in a small subset (3 of 21, 14%) of CDCs, a finding not noted in our cohort of CDCs. However, interestingly, several studies, including those of Albadine et al13 (3 of 34 UCs of upper urinary tract [9%]), Tong et al11 (4 of 17 UCs of upper urinary tract [23%]), and Carvalho et al10 (our study; 3 of 18 UCs of upper urinary tract [17%]), found that a small subset of UCs, especially UCs involving the upper urinary tract, can be positive with PAX8. Our experience with p63 in UC involving upper urinary tract supports previous studies,9 which show that p63 is a useful marker in distinguishing UC from high-grade RCC including CDC (100% specificity for UC with no staining of any RCC, including poorly differentiated tumors with p63).

CONCLUSIONS

Distinguishing urothelial carcinomas of the upper urinary tract from collecting duct carcinomas and renal medullary carcinomas is problematic especially in small biopsy samples. The study case showed a high-grade carcinoma morphologically resembling urothelial carcinoma in a kidney biopsy specimen of a young male with renal vein thrombosis. The tumor cells were strongly positive with CK7, IN1-1, PAX8, and p63, and negative with vimentin. The diffuse, strong IN1-1 expression, in conjunction with clinical history (lack of sickle trait and Spanish ancestry), conclusively ruled out renal medullary carcinoma. Additional clinical information including positive urine cytology findings and the presence of urothelial carcinoma in situ along the renal pelvis, which may be useful features to support a diagnosis of urothelial carcinoma, was not present in this case. A panel consisting of p63, PAX8, and IN1-1 is most optimal in distinguishing UC from CDC and RMC. Our study case showed an unusual immunoprofile, as the tumor cells were positive with p63 and PAX8. However, several studies have shown that a subset of urothelial carcinomas of upper urinary tract can be PAX8 positive. Hence, in conjunction with morphology, we rendered a diagnosis of high-grade carcinoma, favoring urothelial carcinoma (on the basis of strong p63 expression, which in our experience is not observed in RCCs). Subsequent excision of the kidney...
confirmed the diagnosis of urothelial carcinoma involving the renal pelvis and extending into renal parenchyma.

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References