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Papillary Renal Cell Carcinoma Mimicking Metanephric Adenoma: Features Enabling Differential Diagnosis in Two Cases

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Abstract

Numerous histologic similarities exist between the solid variant of type 1 papillary renal cell carcinoma, monophasic Wilms tumor, and metanephric adenoma. Distinguishing these entities is crucial, because patient management varies drastically based on which diagnosis is made. Patient demographic information, the presence of a fibrous capsule separating neoplastic tissue from uninvolved tissue, and immunohistochemical staining can be utilized to help differentiate these lesions. In particular, CK7 immunohistochemical staining must be performed before a diagnosis of metanephric adenoma can be rendered. If CK7 is diffusely positive, the diagnosis of metanephric adenoma has been excluded. Here we report two surgical pathology cases of papillary renal cell carcinoma that mimicked metanephric adenoma and emphasize important features enabling differential diagnosis.

Keywords: Solid papillary renal cell carcinoma; metanephric adenoma; Wilms tumor; nephroblastoma; CK7; WT1; CD57; AMACR

Introduction

Renal cell carcinomas (RCCs), primary malignant epithelial tumors arising from the kidney, comprise approximately 2% of new cancer diagnoses and deaths worldwide each year [1]. Papillary RCC (pRCC) is the second most common RCC and represents 11%-15% of all RCCs [2]. pRCCs are divided into three main categories: pRCC type 1, pRCC type 2, and pRCC oncocytic variant [2,3]. Type 1 tumors are defined by a single layer of low nuclear grade tumor cells (International Society of Urologic Pathologists/World Health Organization nuclear grade 1 or 2) with scanty amphophilic cytoplasm. Type 2 tumors are characterized by pseudostratified or stratified tumor cells of high nuclear grade (nuclear grade 3 or 4) with abundant eosinophilic cytoplasm. The pRCC oncocytic variant has oncocytic tumor cells of low nuclear grade (grade 1 or 2) with inverted nuclear polarity [4,5]. pRCC type 1, in particular, displays a wide variety of histologic features [5]. As a result, pRCC can mimic other neoplasms complicating diagnosis. In addition to classic pRCC type 1 histologic features, solid variants of pRCC type 1 tumors lack true papillae and display solid sheets of cells and micronodules that resemble glomeruloid bodies [6]. These tumors also commonly have psammoma bodies and foamy macrophages. Though this neoplasm has clear and identifiable characteristics, its diagnosis is complicated by its close resemblance to both metanephric adenoma (MA) and monophasic Wilms tumor (mWT).

MAs are rare neoplasms consisting of primitive blue cells forming crowded acini with minimal associated peritumoral stroma. Like solid variants of pRCC type 1, MAs can form papillae, glomeruloid structures, and solid sheets of cells with minimal supporting stroma. Additionally, MAs are associated with psammomatous calcifications and foamy macrophages. Unlike pRCC, however, MAs are benign tumors that carry an excellent prognosis [7-9]. Wilms tumors (WTs), also known as nephroblastomas, are malignant neoplasms originating from embryonal nephrogenic blastema cells. WTs occur almost exclusively in children (98%) with classical triphasic differentiation consisting of mitotically active blastemal cells, epithelial cells, and stromal cells. It is not uncommon, however, for these tumors to display only one or two of these triphasic components. mWTs consisting entirely of epithelial cells display a wide variety of architectures including poorly formed tubules, well-formed tubules, glomeruloid structures, and papillary structures [10]. As such, these tumors can share significant histologic overlap with pRCC type 1 and MA. Distinguishing these entities is crucial, as patient management varies drastically based on which diagnosis is made. Here, we present two cases of pRCC initially misdiagnosed as MAs. We review the major differences between these entities and emphasize the utility of diagnostic tools, namely CK7

immunostaining, to differentiate pRCC variants from MA and mWT.

Materials and Methods

We queried the surgical pathology database and identified two cases of pRCC mimicking MA or mWT. We reviewed pathology reports and clinical histories from both patients and evaluated hematoxylin and eosin (H&E)-stained slides for routine evaluation. We then performed CK7, AMACR, WT1, and CD57 immunostaining on a representative tumor block from each case (Table 1). Because it involved less than three cases, this study did not require IRB approval.

Antibody	Clone	Dilution	Control	Vendor	Platform
CK7	RN7	RTU	Skin	Leica	Bond
AMACR	13H4	1:200	AMACR	DAKO	Bond
WT1	6F-H2	RTU	WT-1	DAKO	Bond
CD57	NK-1	RTU	Tonsil	Leica	Bond
RTU: ready to use					

Table 1: Antibodies used in this study.

Results

Using a retrospective surgical database query, we identified two patients with pRCC mimicking MA or mWT. The first patient was a 66-year-old female with a history of breast cancer and a 5-cm centrally cystic mass in the lateral interpolar region of the right kidney that was identified during routine imaging. This mass was surrounded by a thick peripheral rind measuring up to 7 mm in thickness. Differential diagnosis included RCC, cystic nephroma, mixed epithelial and stromal tumor, and hemorrhagic cyst. Right partial nephrectomy was performed to remove and further characterize the lesion. Grossly, the resected specimen showed a well-encapsulated, partially cystic, and solid mass. Sectioning of the tumor revealed low-grade neoplastic cell proliferation with some areas showing papillary architecture or glomeruloid structure, and other areas forming primitive tubules. Tumor cells were separated from the non-neoplastic renal parenchyma by a thick, fibrous capsule (Figures 1A-B, 2A). No necrosis, foamy histiocytes, or psammomatous calcifications were seen. The main differential diagnosis was pRCC, MA, and mWT. Immunohistochemical (IHC) stains were performed to classify the tumor. The neoplastic cells were positive for CK7 (Figure 2B) and AMACR, and negative for WT1 and CD57. The tumor was diagnosed as a pRCC type 1.

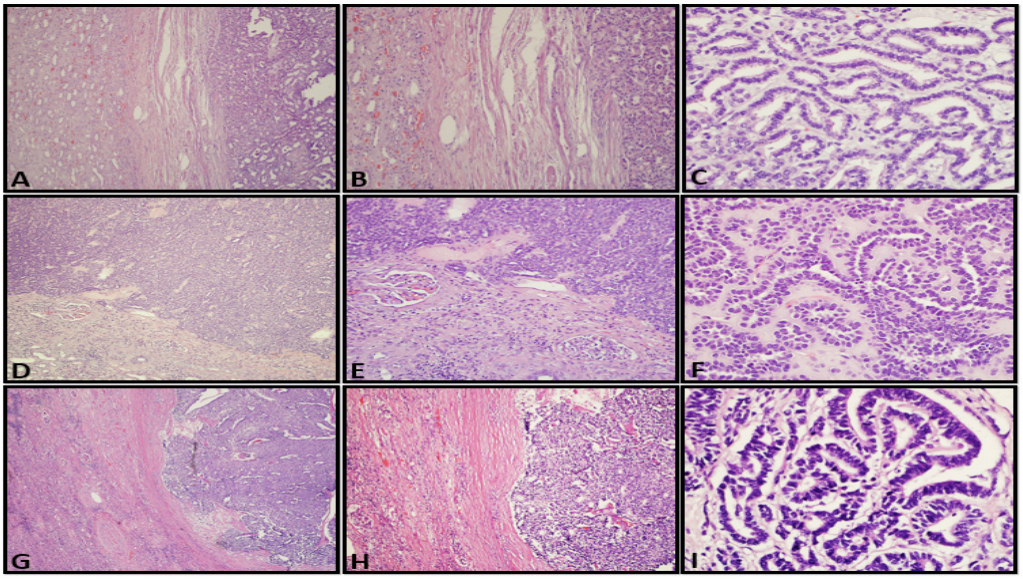

Figure 1: Hematoxylin and eosin (H&E) staining of solid variant papillary renal cell carcinoma (pRCC), type 1 (A, 40x; B, 100x; C, 200x), metanephric adenoma (D, 40x; E, 100x; F, 200x), and Wilms tumor (G, 40x; H, 100x; I, 200x). The medium-power views demonstrate the presence of a thick capsule separating neoplastic from non-neoplastic kidney in both the pRCC and Wilms tumor. In contrast, the metanephric adenoma has no fibrous capsule and instead immediately transforms from non-neoplastic tissue to tumor. The high-power views demonstrate the architectural patterns between these tumors.

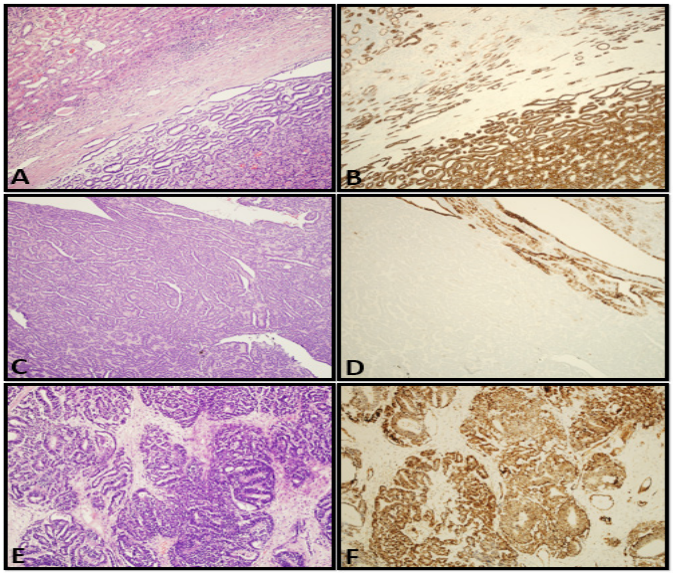

Figure 2: Medium-power views of hematoxylin and eosin (H&E)-stained sections of a solid variant type 1 papillary renal cell carcinoma (pRCC) (A, 100x), metanephric adenoma (C, 100x), and Wilms tumor (E, 100x) demonstrate hyperchromatic, low-grade cells forming poorly defined tubules. Immunohistochemical staining with CK7 shows strong CK7 staining within the non-neoplastic and pRCC neoplastic cells (B, 100x). The neoplastic cells are negative for CK7 in metanephric adenoma (D, 100x). Immunohistochemical staining of Wilms tumor demonstrates the neoplastic cells to be WT1 positive.

The second patient was a 51-year-old male with a history of polycystic kidney disease who presented with an incidental 1.5-cm mass in the anterolateral mid-pole of the right kidney. The mass was partially exophytic and demonstrated cortical-based enhancement overtly concerning for malignancy. This patient underwent a right partial nephrectomy to remove the mass. The resected specimen showed a well-encapsulated, tan-yellow, and hemorrhagic mass. Sectioning of the mass revealed a well-circumscribed proliferation of neoplastic cells that formed predominantly small tubules. The tumor cells had small nuclei that lacked nucleoli and scant cytoplasm. No cytologic atypia, tumor necrosis, or mitoses were seen. A thick fibrous capsule separated the tumor from the non-neoplastic kidney tissue. IHC stains were performed to determine if the tumor was a pRCC, MA, or mWT. The neoplastic cells were positive for CK7 and AMACR, and negative for WT1 and CD57. This tumor was diagnosed as a pRCC type 1.

Discussion

pRCC type 1, MA, and mWTs with a predominantly epithelial cell component all demonstrate low-grade nuclei and can form small tubular, glomeruloid, papillary, and solid structures (Figure 1). These histologic similarities can complicate accurate diagnosis. Notably, there are several key differences between these tumors that can prevent misdiagnosis to ensure proper patient care. IHC profiling is a critical step in distinguishing these tumors. CK7, AMACR, WT1, and CD57 immunostaining is recommended for all adult cases of renal neoplasms histologically resembling MA [11]. A CK7-, AMACR-, WT1+, and CD57+ immunophenotype is diagnostic of MA (Figure 2). Notably, initially ordering all four stains may be excessive. CK7 is the only stain necessary to determine if a patient has an MA; CK7 positivity indicates the tumor is pRCC or mWT, while CK7 negativity (or weak and focally positive CK7) suggests MA. If these results are ambiguous, additional immunostaining for AMACR, WT1, and CD57 should be pursued. Further, because MA is never strongly positive for CK7, we strongly recommend that the diagnosis of MA not be made without first performing IHC staining for CK7. When interpreting IHC results, it is also necessary to consider the possibility of mWT, as these tumors have overlapping histological and immunohistochemical profiles with pRCC and MA. mWTs that predominantly consist of epithelial cells generally stain positive for CK7 and WT1, and negative for CD57 and AMACR (Table 2).

Antibody	pRCC	MA	mWT
CK7	+	-	+
AMACR	+	-	-
WT	-	+	+
CD57	-	+	-
BRAF	-	+	-

pRCC: papillary renal cell carcinoma; MA: metanephric adenoma; mWT: monophasic Wilms tumor

Table 2: Immunohistochemical findings of pRCC, MA, and mWT.

In addition to their IHC profiles, MAs can be distinguished by their uniform nuclei and lack of mitotic activity. Though IHC stains are important for accurate diagnosis, traditional H&E findings may also aid in diagnostic discrimination. In particular, the presence of a fibrous capsule separating neoplastic cells from the background renal parenchyma is more commonly seen in pRCC and Wilms tumor. In MA, neoplastic cells simply blend into the non-neoplastic kidney without any significant demarcation. Mechanistically, capsule formation depends on whether the body ignores a benign process (as in MA) or tries to wall-off a malignant process from normal tissue (as in pRCC). Ultimately, the etiology of these findings remains unclear. Patient demographic information can also aid in diagnostic discrimination. pRCC is approximately two to four times more common in men, MA is approximately twice as prevalent in women, and WT almost exclusively occurs in children [12,13]. While diagnoses should not be made solely based on demographic information, correlating this data with tumor morphology can be helpful. Some cases will inevitably

present with discordant morphologies and immunophenotypes. In these situations, further workup with ancillary studies is essential. Cytogenetic studies have demonstrated that >90% of MAs have mutations in BRAFV600E, and MAs lack the trisomy 7 and 17 traditionally seen in pRCC [14,15]. Recent studies have demonstrated KANK1-NTRK3 fusion in BRAF wildtype cases, providing even greater power to diagnose MA [16]. The causes underlying the morphological resemblance of pRCC type 1 to MA are unknown. While most likely multifactorial, genes such as ALK have been shown to be notably overexpressed in RCCs with MA morphology [17]. Whether or not ALK plays a key role in tumor morphology remains unknown, and further studies are needed to fully understand the architectural pathogenesis.

Conclusion

The solid pRCC type 1 variant, MA, and mWT share many histologic features, which complicates accurate pathological diagnosis. Correctly distinguishing these entities is crucial for pathologists, as patient management varies considerably depending upon which diagnosis is rendered. Fortunately, several key features exist to aid in this process. First, the presence of a fibrous capsule separating neoplastic cells from the uninvolved renal parenchyma is highly suggestive of malignancy. MAs rarely demonstrate this growth pattern and observing such architecture should prompt the pathologist to consider pRCC and mWT in their differential. Next, IHC staining for CK7 should be performed. If tumor cells are positive for CK7, MA can be ruled out. At this point, with a single IHC stain, the important distinction of benign versus malignant can be made. To further characterize the neoplasm, immunostaining with AMACR, WT1, and CD57 can be performed. These results, together with patient demographic information, should render a diagnosis in most cases. However, if the diagnosis remains elusive, ancillary testing can be performed. With these tools, pathologists should feel comfortable differentiating between solid variants of type 1 pRCC, MA, and mWT with epithelial cell predominance.

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