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*Case Report*

# Differential diagnosis of renal tumors with tubulopapillary architecture in children and young adults: a case report and review of literature

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**Abstract:** Background: Tumors of the kidney are uncommon in children and young adults. Accurate classification is crucial for both prognostication and therapeutic intervention. However, majority of the tumors in this age group have unusual morphology that renders classification challenging. Tubulopapillary architecture is one of the most common morphological patterns observed in renal tumors of children and young adults. Methods: A patient with epithelial predominant Wilms tumor was reported. Differential diagnosis of renal tumors with tubulopapillary morphology was discussed with an emphasis on the histological and immunohistochemical features, and the literature was reviewed. Results: A 25 year-old female patient presented with bilateral multilocular cystic masses. She underwent right radical nephrectomy and left partial nephrectomy. The pathological examination revealed a tumor with tubulopapillary architecture which was lined with low columnar epithelial cells. During the work-up of this case, several entities were considered and ruled out by careful gross, microscopic examination and prudent use of immunohistochemistry. The tumor cells were positive for WT-1, and variably positive for cytokeratin AE1/3, CD56, CD57, and negative for cytokeratin 7 and EMA. Fluorescent in-situ hybridization revealed no gain of chromosome 7 and 17. A diagnosis of epithelial predominant adult Wilms tumors was rendered for both kidneys. The patient received systemic chemotherapy and radiation to the remnant left kidney and was free of disease three years after the initial surgery. Conclusion: The differential diagnosis of renal tumors with tubulopapillary features in children and young adults include papillary renal cell carcinoma, metanephric adenoma, epithelial predominant Wilms tumor, translocation renal cell carcinoma and metastatic adenocarcinoma to the kidney. An accurate classification relies on careful examination of clinical and pathological features and immunohistochemical characteristics.

**Keywords:** Kidney, renal tumor, children, young adults, tubulopapillary, differential diagnosis, Wilms tumor, papillary renal cell carcinoma, metanephric adenoma

## Introduction

Majority of the tumors in children and young adults are Wilms tumor. Renal cell carcinomas that are derived from the renal tubular epithelial cells are rare [1-4]. The most common subtypes are the translocation-associated renal cell carcinomas, papillary renal cell carcinoma, renal medullary carcinoma, and oncocytic renal cell carcinoma following neuroblastoma [3]. The classification is often challenging as many of them have unusual morphology and considerable heterogeneity within and overlap between each of the above subtypes and by similarities to other pediatric renal neoplasms. Tubulopapillary architecture is one of the most common morphological patterns observed in renal tumors of this age group. Accurate classification is crucial for both prognostication and therapeutic intervention.

## Case report

A 25 year-old female with back pain and urinary tract infection was found to have bilateral renal masses. An abdominal CT scan demonstrated complex cystic lesions with multiple enhancing septations and peripheral calcifications in both kidneys. Work-up revealed normal lung, GI and GYN tract. She underwent right radical nephrectomy.

Her right kidney was largely replaced by a multilocular cystic mass. The wall of the cysts varied

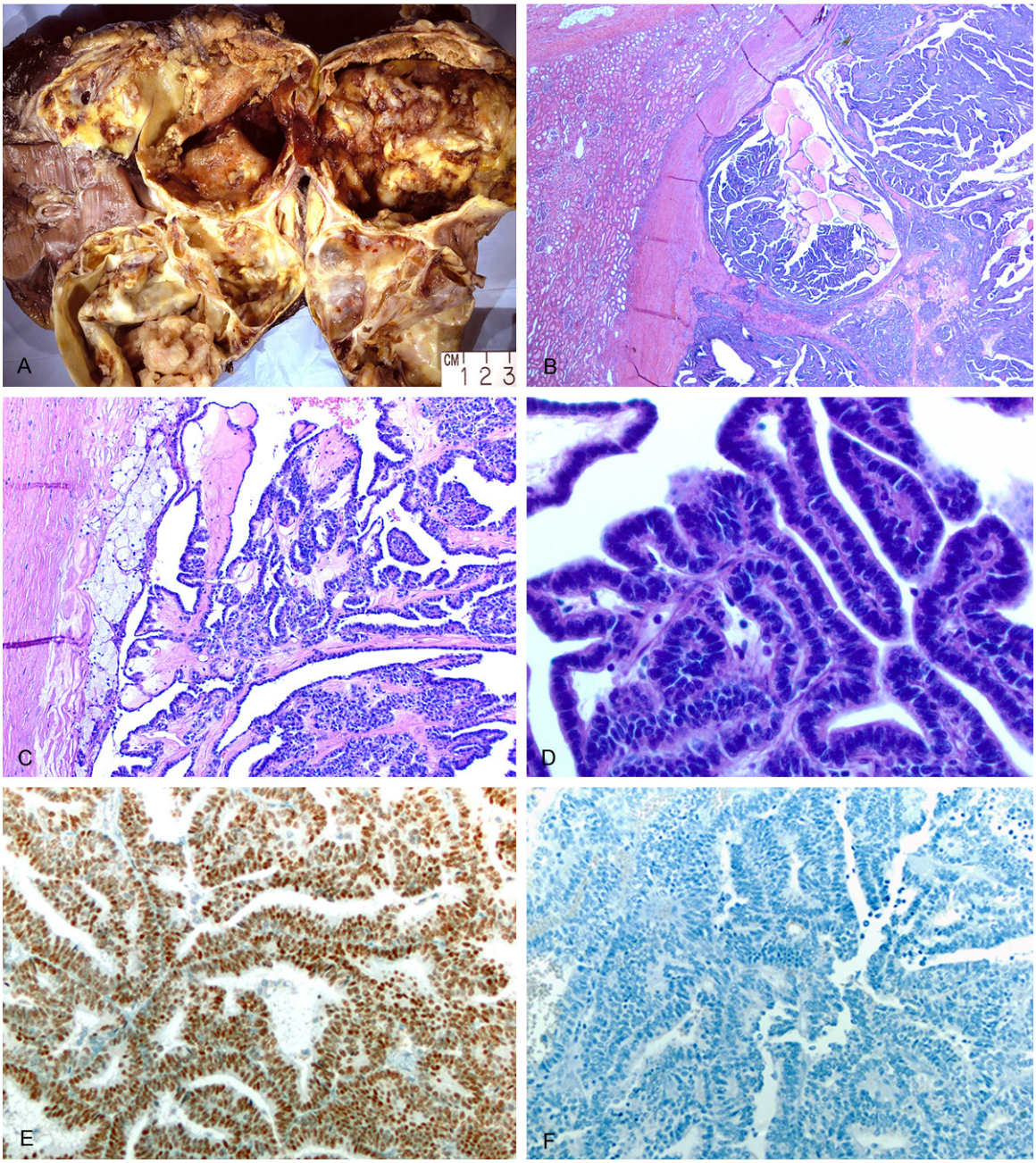


**Figure 1.** Epithelial predominant adult Wilms tumor. The kidney was largely replaced by a multilocular cystic mass with multiple mural nodules (A). The tumor had a thick fibrous capsule with multifocal invasion into/through the capsule (B). The tumor cells formed complex papillary structures (B) that were lined with low columnar cells (D). Clusters of histiocytes were also present in the cystic septa (C). Tumor cells were positive for WT-1 (E) and negative for cytokeratin 7 (F).

in thickness. The inner surface of the cysts was varied with some white-tan, smooth and glistening areas and other areas with necrotic friable yellow-brown material. Many expansible polypoid white-grey tumor nodules were noted in the wall of the cysts (**Figure 1A**).

Microscopically, the tumor had a thick fibrous capsule with multifocal invasion into/through the capsule (**Figure 1B**). The tumor cells formed complex papillary structures (**Figure 1C**) that were lined with low columnar cells (**Figure 1D**). Clusters of histiocytes are also present within

**Table 1.** Renal Tumors with Tubulopapillary Architecture in Children and Young Adults

| |
|---|
| Renal cell carcinoma, papillary type |
| Renal cell carcinoma associated with Xp11.3/TFE3 translocation |
| Metanephric tumors, including metanephric adenoma |
| Wilms tumor, differentiated type (epithelial predominant Wilms tumor) |
| Metastatic adenocarcinoma |

the cystic septa (**Figure 1C**). Vascular invasion was also present. The tumor has basophilic appearance as the tumor cells have scant cytoplasm and the nuclei were oval and relatively uniform with open chromatin and inconspicuous nucleoli. No nuclear anaplasia or atypical mitosis was seen. Tumor cells were positive for WT-1 (**Figure 1E**), and variably positive for cytokeratin AE1/3, CD56, CD57, and negative for cytokeratin 7 (**Figure 1F**) and EMA. Fluorescent in-situ hybridization revealed no gain of chromo some 7 and 17.

A diagnosis of Wilms tumor, differentiated type (epithelial predominant Wilms tumor), was rendered. She was referred to pediatric oncology for further management. She received chemotherapy which included dactinomycin, vincristine and doxorubicin. She continued to have persistent renal mass in her left kidney and underwent left partial nephrectomy 7 months after the initial surgery. The same diagnosis, Wilms tumor, differentiated type, was rendered on the left partial nephrectomy specimen. She then had radiation to the left remnant kidney. She had no evidence of disease 3 years after the initial surgery.

## Discussion

In children, the most common renal tumor is Wilms tumor (WT) [5]. 98% of them occur in patients younger than 10 years of age. It is exceedingly rare in adolescents and adults. The incidence of adult WT is difficult to determine, and a recent study estimated the WT in patients older than 16 years accounts for <3% of WTs [6-8]. The clinical manifestation of adult WT differs from childhood WT. The main symptom in adults is flank pain, and majority of the patients have weight loss and abrupt decrease in performance status [7, 9]. In contrast, children with WT are mainly asymptomatic and present with painless swollen abdomen. The stage of the adult patients at diagnosis is in general higher than in childhood, and may account for the worse prognosis reported for adult WT compared with the pediatric counterparts. However, adult WT is a curable disease if multimodality treatment according to the pediatric regimen, including chemotherapy, radiation and surgery [7, 8].

The pathological features of adult WT have been rarely studied. Huser *et al* studied 11 such cases [9] and found these cases were similar to pediatric cases with a classic triphasic pattern (including blastemal, epithelial and mesenchymal components) in 7 (66%) and biphasic in 4 (34%) cases. None of the tumor had anaplasia. Large tumor size and high mitotic rate were associated with a poor prognosis. However, no nephrogenic rests were seen in any of the study cases, suggesting that the pathogenic pathways in adult WT may not be identical to its pediatric counterpart.

Epithelial predominant WT with tubules, glands and papillae accounting for the majority of the tumor mass, similar to the case reported in this study, is even rarer. The tumor nuclei are cuboidal or columnar shaped and have stippled chromatin. Mitosis may be brisk. Foamy histiocytes and psammomatous calcification may also be seen. WT-1 is expressed in blastemal and epithelial cell types but may be absent in the differentiated epithelial and stromal elements. The blastemal cells frequently express CD56 and vimentin. Pan-cytokeratin and cytokeratin 7 are expressed focally and weakly in 1/3 tumors.

Metanephric adenoma (MA) is a benign lesion derived from the metanephric blastema [10]. It has a wide age range of presentation but is the most common renal epithelial neoplasm of children and young adults. There is a 2:1 female predominance. The clinical findings are generally not specific to metanephric adenoma, but 10 to 15% of patients have polycythemia, which usually disappears after resection of the tumor. Grossly, MAs are well-circumscribed, non-encapsulated masses with a homogenously grey to tan and yellow cut surface [10]. Microscopically, MA lacks a pseudocapsule in the majority of cases. The tumor forms a sharp interface with non-neoplastic kidney parenchyma. Typically, MAs are densely cellular neo-

**Table 2.** Histological Features of Papillary Renal Cell Carcinoma, Epithelial Predominant Wilms Tumor and Metanephric Adenoma

| | Papillary RCC | Wilms Tumor | Matanephric Adenoma |
|---|---|---|---|
| Prominent tumor pseudocapsule (fibrous and compressed kidney tissue) | + | + | - |
| Cytology | Vesicular chromatin with variably prominent nucleoli | Columnar with large overlapping nuclei and fine chromatin | Oval and bland nuclei that lack prominent nucleoli |
| Mitosis | Rare | + | - |
| Foamy histiocytes | ++ | + | + |
| Psammomatous calcification | + | + | + |
| Other components in non-neoplastic parenchyma | Tubulopapillary hyperplasia | Nephrogenic rests | May have stromal component |

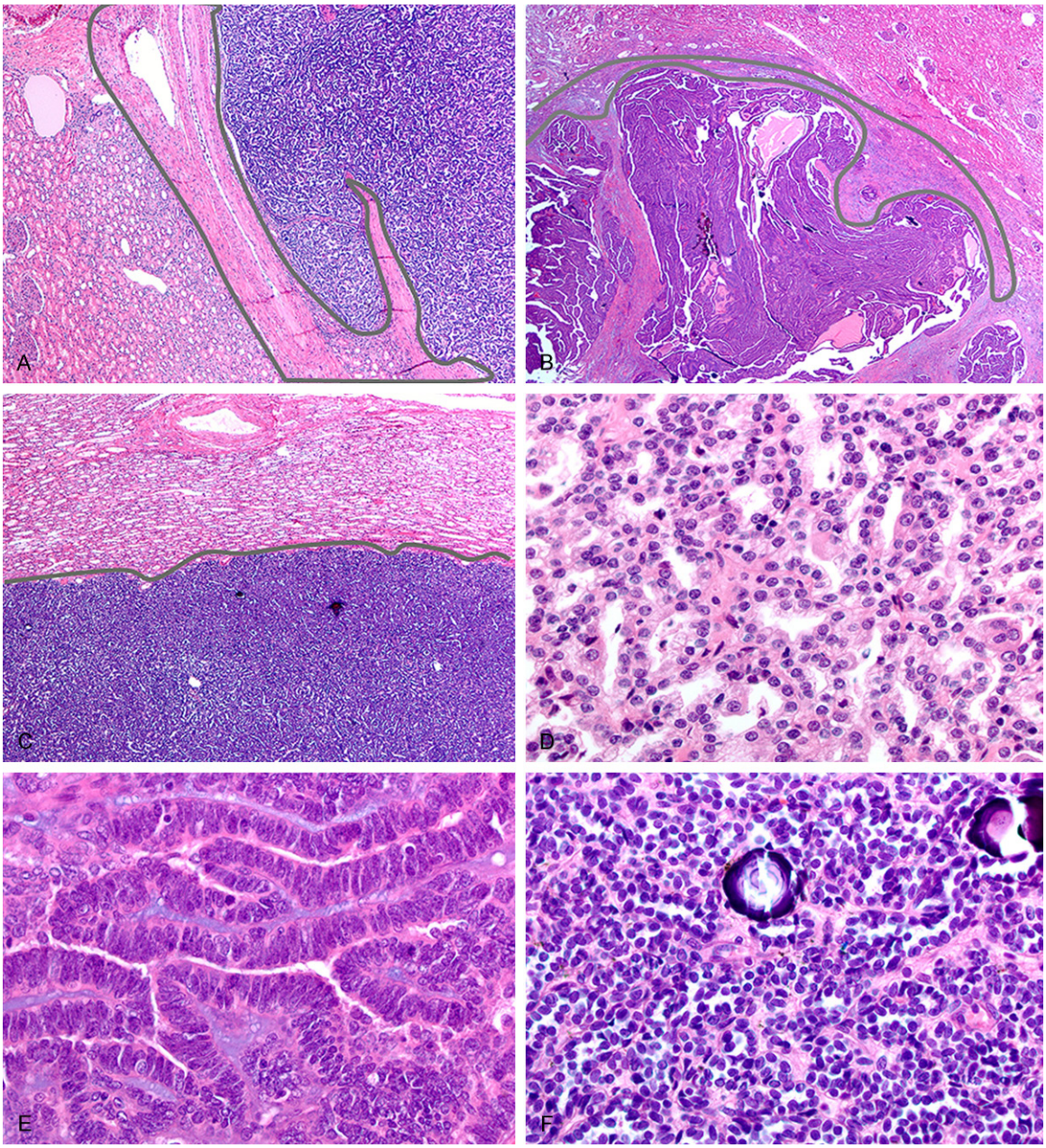


**Figure 2.** Morphological features discriminatory of papillary renal cell carcinoma, epithelial predominant Wilms tumor and metanephric adenoma. Thick tumor pseudocapsule of irregular thickness is present in papillary renal

cell carcinoma (A) and Wilms tumor (B), but not in MA which directly interfaces with normal renal parenchyma to form a sharp and distinct border (C). Grey lines outline the tumor capsules or tumor-parenchymal interface. Papillary renal cell carcinoma has variable amounts of cytoplasm and nuclei with vesicular chromatin and variably prominent nucleoli (D). Tumor cells in both Wilms tumor (E) and metanephric adenoma (F) have little cytoplasm and more primitive nuclei with finely disperse chromatin and inconspicuous nucleoli. Wilms tumor has columnar nuclei with frequent mitosis while metanephric adenoma has uniform oval nuclei with scant or no mitosis.

**Table 3.** Immunohistochemical profiles of Papillary Renal Cell Carcinoma, Epithelial Predominant Wilms Tumor and Metanephric Adenoma

| | PRCC | WT | MA |
|---|---|---|---|
| AE1/3 | 100% | 29% | 50% |
| Cytokeratin 7 | 78% | 30% | 7% |
| CD15 | 100% | 0 | 0 |
| EMA | 63% | 44% | 7% |
| CD56 | 0 | 100% | 0 |
| CD57 | 70% | 7% | 89% |
| AMACR | 98% | 10% | 10% |
| WT-1 | 10% | 81% | 82% |

plasms composed of tightly packed small round acini or small branching tubules. Foci of papillary architecture are common, often consisting of stubby papillae reminiscent of immature glomeruli. The stroma is often inconspicuous, but sometimes is hyalinized or edematous. Psammoma bodies are common. The epithelial tumor cells are uniform, small and cytologically bland with oval, hyperchromatic nuclei without visible nucleoli. Mitotic figures are absent or rare. Immunohistochemically WT-1 is frequently detectable in the nuclei of MAs. The tumor cells are positive for PAX2, PAX8 and CD57, frequently negative for EMA, CK7, cytokeratin AE1/AE3, CD56 and AMACR [10, 11]. A recent study identified BRAF mutations in majority of MAs [12].

Renal cell carcinoma (RCC) in children and young adults is rare, accounting for <2% of childhood renal tumors [2, 3]. Several recent studies [1, 13] found that the common RCC histologic subtypes detected in adults can also be found in children and young adults. RCC associated with Xp11.2 translocation and TFE3 overexpression constitutes the majority of RCCs in this age group. Furthermore, RCC in childhood tends to have an unusual morphology and is more likely to have tubulopapillary architecture and unclassifiable morphology using the 2004 WHO classification. Papillary RCC accounts for a sizable proportion of RCCs in children [1, 3]. The pathological and genetic features are similar to its adult counterpart [1, 3].

RCC associated with Xp11.2 translocation/TFE3 gene fusion is defined by chromosomal translocation involving *TFE3* gene on chromosome Xp11.2 that results in overexpression of the TFE3 protein [14-16]. These carcinomas typically affect children and young adults. Although RCC accounts for <5% of pediatric renal tumors, Xp11.2 associated RCCs make up a significant proportion of these cases. This tumor has been increasingly diagnosed in adults and may constitute 1-4% of adult renal cell carcinomas [17]. Unlike other types of RCC, Xp11.2 RCCs are not defined by their histologic feature. However, papillary architectures lined with clear cells are perhaps the most distinctive feature. A nested pattern made up of cells with ample acidophilic cytoplasm is most common. Tumors with different chromosomal translocations may exhibit somewhat different morphological features. The morphological features are distinct from the aforementioned three tumors, *i.e.*, papillary RCC, metanephric adenoma and epithelial predominant Wilms tumor. This tumor under-expresses epithelial markers including cytokeratins and EMA. CD10, RCC Ma, PAX2 and PAX8 are consistently expressed [18]. Melanocytic markers such as HMB-45 and Melan A are positive in some tumors. Nuclear immunoreactivity for TFE3 gene product is confirmatory [14-16].

Metastatic adenocarcinoma to the kidney is rare. In a recent radiological study, tumors metastatic to the kidney accounted for 0.9% of all radiologically detected renal tumors [19]. The most common primary tumors are lung squamous cell carcinoma and adenocarcinoma, and melanoma, although other primary tumors are also observed, including gastrointestinal adenocarcinoma, seminoma, thyroid papillary carcinoma, cervical squamous cell carcinoma, small cell carcinoma and adenosqumous carcinoma. Metastasis to the kidney is more likely in patients with higher primary tumor stage or if other visceral sites are also affected. A diagno-

sis should be considered and ruled out when patients have a prior history of malignancy involving other body sites, or the renal tumor has an unusual pathological features.

Thyroid carcinoma metastatic to the kidney should always be included in the differential diagnosis of renal tumors with tubulopapillary architecture in children and young adults. It is rare with 30 such cases reported in the literature [20]. However, metastasis of thyroid carcinoma to the kidney has been reported in two young adults [21]. If it is suspected based on clinical history, the diagnosis is often straightforward and can be confirmed by positive stains for TTF-1 and thyroglobulin in metastatic thyroid carcinoma. The use of PAX-8 should be avoided as it is positive in both RCC and thyroid carcinoma [22].

A renal tumor with tubulopapillary architecture in children and young adults should elicit a differential diagnosis to include the renal tumors mentioned above (**Table 1**). However, the most important differential diagnosis should include epithelial predominant WT, MA and papillary RCC when a renal tumor with basophilic tubulopapillary morphology is encountered. The histological features discriminatory of these 3 tumors are summarized in **Table 2**. Tumor pseudocapsule composed of fibrous and compressed kidney tissues is present in papillary RCC and WT, but not in MA which directly interfaces with normal renal parenchyma to form a sharp and distinct border (**Figure 2A-C**). Papillary RCC may have abundant cytoplasm and nuclei with vesicular chromatin and prominent nucleoli. Tumor cells in both WT and MA have little cytoplasm and more primitive nuclei with finely disperse chromatin and inconspicuous nucleoli. WT have columnar nuclei with frequent mitosis while WT and MA have uniform oval nuclei (**Figure 2D-F**). Foamy histiocytes and psammomatous calcification are of little use as it can be found in all three lesions. The presence of blastemal cells supports a diagnosis of WT.

In difficult cases, prudent use of immunohistochemistry can help establish a correct diagnosis (**Table 3**) [10, 11, 23-25]. Papillary RCC is in general positive for epithelial markers, including AE1/3, cytokeratin 7 and EMA. AMACR, a marker expressed in the distal convoluted tubules, and CD15, a pan-renal tubular marker, is positive in almost all PRCCs. WT-1 is usually negative in papillary RCC. MA and WT are negative for AMACR and CD15, variably positive for epithelial markers, while positive for WT-1. Muir et al [11] found CD56 and CD57 were quite useful in the differential diagnosis. CD56 is positive only in WT, and CD57 positive in the majority of MA and PRCC and rarely in WT. A panel of markers that include cytokeratin 7, CD15, CD56, CD57, AMACR and WT-1 should result in clear separation of papillary RCC, WT and MA [10, 11, 26].

## Conclusions

For a renal tumor with tubulopapillary morphology in children and young adults, one should always consider papillary RCC, MA and epithelial predominant Wilms tumor. Attention to characteristic histological features (tumor pseudocapsule and nuclear features) and judicious use of immunohistochemical markers (CK7, CD56, CD57, WT-1) should help achieve a clear separation of these 3 tumors.

## Disclosure of conflict of interest

None.

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