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Pediatric Renal Cell Carcinoma

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Abstract

Renal cell carcinomas are rare in children, and they show significant differences in their histology and pathogenesis when compared to those common in adults. The most common subtypes seen preferentially in children are the translocation-associated tumors, papillary renal cell carcinoma, renal medullary carcinoma, and oncocytic renal cell carcinoma following neuroblastoma. The histological diagnosis of renal cell carcinoma is made difficult by the considerable heterogeneity within and overlap between each of the above subtypes and by similarities to other pediatric renal neoplasms. While no effective therapies have yet been identified, there is considerable promise that the new Children's Oncology Group protocol will provide knowledge that will guide the future therapy of these lesions.

Keywords

renal; carcinoma; pediatric; children

Introduction

Pediatric renal cell carcinomas (RCC) account for approximately 2% of all new pediatric renal tumors^{1,2}. Within three large studies analyzing a total of 87 unselected cases, pediatric RCC differed in histologic appearance and genetic features from those of adults.^{3–5} The most common are the Xp11 (TFE3) translocation-RCC (20–40% of total), an entity recognized in the 2004 World Health Organization's classification.⁶ While TFE3 translocations involving a multitude of variant partners have been reported, by far the most common are those involving chromosome 17 [t(X;17)(p11.2;q25), ASPL-TFE3 fusion] and chromosome 1 [t(X;1)(p11.2;q21), PRCC-TFE3 fusion]. Translocation-RCC may occur following chemotherapy for other diseases.⁷ Closely following it in frequency is papillary RCC, which comprises approximately 30% of total and includes both type 1 and type 2 lesions. Papillary RCC in children may arise in the setting of pre-existing neoplasms, including Wilms tumor, metanephric adenoma, and metanephric adenofibroma. Conventional clear cell RCC comprises 6–20% of the total in these large studies; however, many cases are histologically atypical or have morphologic features of translocation-RCC, and these seldom have genetic abnormalities of 3p21.^{3,4} In the experience of the Children's Oncology Group (COG) Renal Tumor Pathology Center (RTPC), true clear cell RCC are extraordinarily rare in childhood. In addition to the above categories, there are two extremely rare tumors that most commonly present in

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childhood. Renal medullary carcinoma is a highly aggressive tumor arising in patients with the sickle cell gene.⁸ Lastly, a rare oncocytic RCC had been identified in patients previously diagnosed with neuroblastoma.⁹ Importantly, up to 25% of pediatric RCC cannot be readily classified due to atypical features. These may represent additional entities that have yet to be adequately characterized.

Gross Features

Most translocation-RCC and papillary RCC are circumscribed, single lesions that do not significantly differ in their gross features from those in adults or from other pediatric renal neoplasms. Multifocality in pediatric RCC is unusual and when present may point toward an underlying syndrome, such as tuberous sclerosis or von Hippel-Lindau disease. However, patients with genetic syndromes associated with RCC typically develop renal tumors in adulthood. Renal medullary carcinomas have a strikingly infiltrative growth pattern typically involving the medulla. This infiltrative pattern may be so extreme that a dominant mass is not radiographically or grossly apparent, resulting in the appearance of a severe infectious process.⁸ Lastly, the neuroblastoma-associated oncocytic RCCs are often multifocal or bilateral.⁹ It should be noted that tumor size, as measured in greatest dimension, is a critical feature of the TNM staging system most commonly utilized in the evaluation of RCC.¹⁰

Microscopic Features

Translocation-RCCs are composed of cells architecturally arranged in nests, tubules, papillae, and pseudopapillae. The cells often contain large amounts of clear to variably eosinophilic cytoplasm and possess distinct cell borders separated by thin fibrovascular septa (Figures 1, 2). The majority have a Furman nuclear grade of 3, with easily identified nucleoli.¹¹ Small psammomatous calcifications are variably present. An infiltrative border is present in most cases, with entrapment of native renal tubules and vascular invasion. The histologic features do not reliably differ depending on the translocation variant, although some differences have been suggested. Tumors containing the *ASPL-TFE3* phenotype tend to have abundant, voluminous cytoplasm that often contains cytoplasmic granules and eosinophilic bodies (Figure 1). Those with *PRCC-TFE3* gene fusion often have less abundant cytoplasm, are arranged more compactly, contain fewer calcifications, and display lower nuclear grades (Figure 2).^{3;12} In the experience of the COG-RTPC, such trends may be seen but are not reliable. Furthermore, the histologic spectrum that may be seen in all the translocation variants is quite broad, even within individual tumors (Figure 2). Quite rarely, the related *TFEB* gene may also be involved in a translocation RCC, resulting in a histologic appearance that is similar to TFE3-RCC but often shows more nesting.¹³ They also may contain infrequent clusters of small cells clustered around hyaline material (Figure 3).

Papillary RCCs are composed of cells arranged in tubular and papillary configurations, often containing foamy macrophages. Two types of papillary RCC are identified within the WHO classification. Type 1 tumors are composed of cuboidal cells with little cytoplasm arranged in a single layer, whereas type 2 tumors contain pseudostratified cells with higher nuclear grade and typically more eosinophilic cytoplasm (Figure 4). Rare tumors may show regions with clear cell features. Papillary RCCs are typically encapsulated, although the tumor often penetrates its fibrous pseudocapsule.

Renal Medullary Carcinomas are usually composed of high-grade epithelial cells with acidophilic cytoplasm, arranged in a tubular, often cribriform architecture; they occasionally are solid or sarcomatoid.⁸ Characteristic microscopic features include desmoplasia and an acute inflammatory reaction (Figure 5). The nuclei are large with prominent nucleoli in most cases. Cytoplasmic inclusion reminiscent of those seen in rhabdoid tumors are often seen. Drepanocytes are commonly seen coincident with formalin fixation.

Post-neuroblastoma renal cell carcinomas are single, bilateral, or multifocal masses composed⁹ of solid and occasionally papillary cells with oncocytoid features and cellular heterogeneity. Many cells contain copious eosinophilic cytoplasm with high nuclear grade, but others may lack these features (Figure 6).

Differential Diagnosis

While many pediatric RCC demonstrate a characteristic appearance that immediately prompts an accurate diagnosis, an uncomfortably large number are not easily categorized without immunohistochemistry, and many escape precise classification entirely. There is considerable histologic overlap among many of the different types of pediatric RCC and between some types of pediatric RCC and other renal neoplasms. The differential diagnosis will be considered below within four broad histologic categories.

The majority of pediatric RCC belong to a category of tumors that show moderate to large amounts of clear and variably eosinophilic cytoplasm with nested, solid, acinar, and/or tubulopapillary architectural growth patterns. The intra- and inter-tumoral heterogeneity of this group is evident by the above description. This group contains the translocation-associated RCCs, whose histologic spectrum varies from areas indistinguishable from clear cell RCC to areas similar to type 2 papillary RCC (Figure 2). Translocation-RCCs may also have a histologic appearance that is remarkably similar to epithelioid angiomyolipomas. Many lesions in this category escape precise classification and are given the WHO classification of “Renal Cell Carcinoma, Unclassified”.

Next in frequency are the basophilic tubulopapillary renal lesions. The differential diagnosis for these may be quite difficult and includes type 1 papillary RCC, well-differentiated epithelial Wilms tumor, and metanephric adenoma. Both metanephric adenoma and epithelial Wilms tumors are more common than type 1 papillary renal cell carcinoma in childhood.³ The most valuable histologic clues for distinguishing these often similar lesions include 1) the presence of a fibrous pseudocapsule surrounding epithelial Wilms tumor and papillary RCC, whereas by definition metanephric adenoma directly interfaces with the adjacent kidney; 2) the presence of mitotic activity (albeit at times sparse) within Wilms tumor and papillary RCC, but the virtual absence of mitoses in metanephric adenoma; 3) the definitional absence of nucleoli in metanephric adenoma, whereas nucleoli may be present in papillary RCC.¹⁴ Features that do not distinguish these three tumors include foamy macrophages within papillary cores and calcospherites, which may be a prominent feature in each.

The third histologic group includes a variety of eosinophilic tubulopapillary lesions, most commonly represented by type 2 papillary RCC. However, some TFE3/PRCC translocation-associated RCC contain relatively little cytoplasm and demonstrate a more consolidated, homogeneous histology that may overlap with that of type 2 PRCC. Renal medullary carcinomas also fall into this category. Because of their highly invasive growth pattern, characteristic cytology, and desmoplasia, these seldom provide diagnostic challenge once they are considered, and drepanocytes and/or history of sickle cell trait/disease should be helpful in this distinction.

Lastly (and quite uncommonly) renal tumors with oncocytic features may be seen in childhood. These include those tumors arising following neuroblastoma, as well as oncocytoma, a benign renal lesion seldom seen in childhood. The characteristic gross appearance, the low-power nested architecture, and the monotonous nuclear cytology with absence of mitoses easily distinguishes oncocytoma from the post-neuroblastoma oncocytic RCC. It should be noted that the COG-RTPC has experienced a handful of unencapsulated, multifocal, and often bilateral oncocytic tumors displaying epithelial markers and lacking the nuclear features of oncocytoma. These have escaped current classification and are of unknown biologic potential.

Diagnosis

The diagnosis of pediatric RCC is made by considering pertinent clinical features and the histologic appearance (discussed above), supplemented by immunohistochemistry when needed and genetic analysis when available. The ancillary studies that aid in the diagnosis of each entity are provided below.

Translocation-RCCs demonstrate an immunohistochemical profile that differs from the common types of RCC found in adults by the formers' paucity of staining for vimentin and epithelial markers [including epithelial membrane antigen (EMA), Cam 5.2, cytokeratin 7 (CK7), and AE1/AE3]. In common with the common adult forms of RCC, translocation-RCCs are positive for CD10, RCC antigen, and Alpha-methylacyl coenzyme-A racemase (AMACR); translocation-RCCs are negative for CD117. Nuclear expression for the retained C-terminal portion of the TFE3 protein (Santa Cruz biotechnology) may be documented by immunohistochemistry, a test that has been shown to be both sensitive and specific regardless of the variant TFE3 translocation.¹⁵ However, immunohistochemistry with anti-TFE3 may be difficult to perform and to interpret, due to ubiquitous expression of TFE3 and variable tissue immunoreactivity; negativity does not exclude the diagnosis of translocation-RCC. TFEB-RCC consistently expresses melanocytic markers HMB-45 and Melan-A, which thus may be useful to screen for this rare variant translocation. It should be noted, however, that TFE3-RCC may also show positivity for melanocytic markers.^{4,11}

All evidence currently available suggests that pediatric papillary RCC show the same genetic and immunohistochemical features as those found in adults. Cytokeratin 7 is positive in 87% of type 1 and 20% of type 2 lesions¹⁶; EMA is typically positive in both types. Because epithelial differentiated Wilms tumor and metanephric adenoma typically show cytokeratin 7 and EMA positivity limited to a very small number of individual or small clusters of cells, these markers are quite useful for detecting papillary RCC within Wilms tumors and metanephric adenomas and for differentiating papillary RCC from these entities. Lastly, papillary RCC is negative for WT1, a marker commonly positive in both Wilms tumor and metanephric adenoma. Papillary RCC is commonly (but not always) positive for both vimentin and EMA, which may aid in its distinction from some translocation-RCC.

The diagnosis of renal medullary carcinoma of the kidney rarely requires immunohistochemistry. However, because this tumor not uncommonly presents as a tumor of unknown origin with distant metastasis, it is useful to be aware that it is positive for AE1/AE3 and EMA (although to a lesser extent) and negative for high molecular weight cytokeratin. Most show nuclear accumulation of p53 protein.⁸ Because of its histologic similarities with rhabdoid tumor, it is of interest that this tumor shows similar loss of nuclear INI-1 protein (BAF47).¹⁷ The diagnosis of post-neuroblastoma oncocyctic RCC likewise rarely depends on ancillary studies. These tumors have been shown to be positive for EMA, vimentin, and cytokeratins 8, 18 and 20, and negative for cytokeratins 7, 14, and 19.⁹

Treatment and outcome of pediatric renal cell carcinomas

Little is known about the outcome or the optimal treatment of the different subtypes of childhood RCC. While it is difficult to compare the outcomes of childhood RCC to those in adults, they appear to be similar stage-for-stage, although it has been suggested that the presence of lymph node metastases alone may be less ominous in children.² Neither chemotherapy nor radiation therapy have demonstrated significant activity in adult or pediatric patients with metastatic or residual RCC, regardless of the histologic type. For this reason, adjuvant therapy is not currently recommended for children with translocation-RCC and papillary RCC and no residual tumor. Renal medullary carcinomas typically present with distant metastasis at diagnosis, and survival seldom exceeds a year regardless of adjuvant

therapy.⁸ The evidence currently available regarding the prognosis of the two most common subtypes of pediatric RCC are summarized below.

Translocation-RCC

Six series of unselected pediatric translocation-RCC consistently showed an incidence of lymph node metastases at the time of diagnosis of 33–50%, an incidence that is higher than that seen in common adult forms of RCC.^{4;11;18–20} There is less consistency concerning the prognosis of translocation-RCC, with some of these studies reporting a good prognosis even with lymph node metastasis, and others reporting a poor outcome regardless of stage. Potential sources of discrepancy include the ability for these tumors to recur quite late¹⁸ and the relatively short follow-up available in many of these studies. Combining the above studies, approximately 45% of tumors with either nodal or distant metastasis at the time of diagnosis will show tumor progression, whereas approximately 15% of tumors without lymph node or distant metastasis at diagnosis will progress.

Papillary RCC

Two large pediatric series provide the outcome of 32 patients with papillary RCC.^{4;5} Seventy-five per cent (24/32) presented with disease limited to the kidney, and 22 of the 24 were free of disease; death from disease occurred in one T2N0MX tumor and the other died from other causes. . Of the remaining eight patients with higher stage disease, three (T4N0MX, T3N1M0, T2,N2,M0) died of their disease. In a large study of adult papillary RCC, type 2 lesions resulted in a significantly higher progression risk and shorter disease-free survival.²¹

Until recently, pediatric RCC has not been targeted for by European or North American Cooperative groups, which has hampered progress. The Children's Oncology Group now provides a protocol for registration of pediatric RCC. Therefore, it is hopeful that in the next decade more accurate knowledge will accrue regarding epidemiology, pathogenesis, and prognosis, and that this will be coupled with the identification of therapeutic targets.

Pathologic Differential Diagnosis Box

a. Clear and eosinophilic, nested, solid, acinar and/or tubulopapillary lesions

- i. Translocation-Renal Cell Carcinoma
- ii. Clear Cell Renal Cell Carcinoma
- iii. Epithelioid Angiomyolipoma
- iv. Renal Cell Carcinoma, Unclassified

b. Basophilic tubulopapillary lesions

- i. Metanephric Adenoma
- ii. Epithelial Differentiated Wilms Tumor
- iii. Papillary Renal Cell Carcinoma

c. Eosinophilic tubulopapillary lesions

- i. Papillary Renal Cell Carcinoma Type 2
- ii. t(X;1) translocation- Renal Cell Carcinoma
- iii. Renal Medullary Carcinoma

d. Oncocytic lesions

- i. Post-neuroblastoma Oncocytic Renal Cell Carcinoma
- ii. Oncocytoma
- iii. Renal Cell Carcinoma, Unclassified

Key Pitfalls Box

a. Translocation- Renal Cell Carcinoma

- i. The histologic spectrum of translocation-RCC is quite broad.
- ii. While translocation-RCC characteristically show paucity of EMA and Vimentin staining, exceptions occur.
- iii. Currently available antibodies for TFE3 and TFEB are often not reliable.

b. Papillary RCC

- i. The histologic overlap between type 1 PRCC, metanephric adenoma, and well-differentiated epithelial Wilms tumor is considerable. The diagnosis is often difficult with significant therapeutic implications.
- ii. The distinction between type 2 papillary RCC and some translocation-RCC, particularly those involving t(X;1), may be difficult.

c. Renal Medullary Carcinoma

- i. These highly aggressive tumors commonly present as enlarged cervical lymph nodes with an unknown primary site.
- ii. The cytology may resemble rhabdoid tumors, and renal medullary carcinoma may also show loss of nuclear INI-1 protein.

Key features Box

a. Translocation-associated renal cell carcinoma

- i. Abundant clear to variably eosinophilic cytoplasm arranged in nests, acini, tubules, papillae, and pseudopapillae
- ii. Prominent nucleoli common
- iii. Minimal positivity for EMA, vimentin and cytokeratin 7
- iv. Nuclear positivity for TFE3 in most
- v. Positive for CD10, AMACR, RCC-antigen common
- vi. Positivity for melanocytic markers (TFEB translocations).

b. Papillary renal cell carcinoma

- i. Tubular, papillary, or tubulopapillary architecture
- ii. positivity for EMA, RCC antigen, AMACR, CD10
- iii. negativity for TFE3
- iv. Type 1: Low-grade nuclear cytology, scant cytoplasm; diffuse positivity for cytokeratin 7.

- v. Type 2: Higher grade nuclear cytology with pseudostratification, eosinophilic cytoplasm is common; cytokeratin 7 often negative.
- c. Post-neuroblastoma oncocyctic RCC**
 - i. Abundant eosinophilic cytoplasm
 - ii. Variability in cell and nuclear size and shape
 - iii. Positivity for EMA, vimentin
 - iv. negativity for cytokeratin 7.
- d. Renal medullary carcinoma**
 - i. Infiltrative tubular, reticular, and solid nests of cells with prominent nucleoli
 - ii. Prominent desmoplasia and neutrophils
 - iii. Drepanocytes often observed
 - iv. Loss of INI-1 nuclear protein
 - v. Positivity for EMA, cytokeratin 7, vimentin
 - vi. Negativity for high molecular weight cytokeratin

References

1. Pastore G, Znaor A, Spreafico F, Graf N, Pritchard-Jones K, Steliarova-Foucher E. Malignant renal tumours incidence and survival in European children (1978–1997); report from the ACCIS project. *Eur J Cancer* 2006;42:2103–2114. [PubMed: 16919774]
2. Geller JI, Dome JS. Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. *Cancer* 2004;101:1575–1583. [PubMed: 15378495]
3. Bruder E, Passera O, Harms D, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. *Am J Surg Pathol* 2004;28:1117–1132. [PubMed: 15316311]
4. Rao Q, Chen YJ, Wang DJ, et al. Renal cell carcinoma in children and young adults: Clinicopathological, immunohistochemical, and VHL gene analysis of 46 cases with follow-up. *Int J Surg Pathol*. 2009
5. Selle B, Furtwangler R, Graf N, Kaatsch P, Bruder E, Leuschner I. Population-based study of renal cell carcinoma in children in Germany, 1980–2005. *Cancer* 2006;107:2906–2914. [PubMed: 17109448]
6. Eble, JN.; Sauter, G.; Epstein, JI.; Sesterhenn, IA. World Health Organization Classification of Tumours; Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press; 2004.
7. Argani P, Lae M, Ballard ET, et al. Translocation carcinomas of the kidney after chemotherapy in childhood. *J Clin Oncol* 2006;24:1529–1534. [PubMed: 16575003]
8. Swartz MA, Karth J, Schneider DT, Rodriguez R, Beckwith JB, Perlman EJ. Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. *Urology* 2002;60:1083–1089. [PubMed: 12475675]
9. Medeiros LJ, Palmedo G, Krigman HR, Kovacs G, Beckwith JB. Oncocytoid renal cell carcinoma after neuroblastoma: a report of four cases of a distinct clinicopathologic entity. *Am J Surg Pathol* 1999;23:772–780. [PubMed: 10403299]
10. Guinan P, Sobin LH, Algaba F, et al. TNM staging of renal cell carcinoma. *Cancer* 1997;80:992–993. [PubMed: 9307205]
11. Camparo P, Vasiliu V, Molinie V, et al. Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. *Am J Surg Pathol* 2008;32:656–670. [PubMed: 18344867]

12. Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. *Am J Pathol* 2001;159:179–192. [PubMed: 11438465]
13. Argani P, Hawkins A, Griffin CA, et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t (6;11)(p21.1;q12) chromosome translocation. *Am J Pathol* 2001;158:2089–2096. [PubMed: 11395386]
14. Pins MR, Jones EC, Martul EV, Kamat BR, Umlas J, Renshaw AA. Metanephric adenoma-like tumors of the kidney: report of 3 malignancies with emphasis on discriminating features. *Arch Pathol Lab Med* 1999;123:415–420. [PubMed: 10235500]
15. Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE, Ladanyi M. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. *Am J Surg Pathol* 2003;27:750–761. [PubMed: 12766578]
16. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Mod Pathol* 1997;10:537–544. [PubMed: 9195569]
17. Cheng JX, Tretiakova M, Gong C, Mandal S, Krausz T, Taxy JB. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. *Mod Pathol* 2008;21:647–652. [PubMed: 18327209]
18. Wu A, Kunju LP, Cheng L, Shah RB. Renal cell carcinoma in children and young adults: analysis of clinicopathological, immunohistochemical and molecular characteristics with an emphasis on the spectrum of Xp11.2 translocation-associated and unusual clear cell subtypes. *Histopathology* 2008;53:533–544. [PubMed: 18983462]
19. Altinok G, Kattar MM, Mohamed A, Poulik J, Grignon D, Rabah R. Pediatric renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions and clinicopathologic associations. *Pediatr Dev Pathol* 2005;8:168–180. [PubMed: 15747097]
20. Ramphal R, Pappo A, Zielenska M, Grant R, Ngan BY. Pediatric renal cell carcinoma: clinical, pathologic, and molecular abnormalities associated with the members of the mit transcription factor family. *Am J Clin Pathol* 2006;126:349–364. [PubMed: 16880148]
21. Antonelli A, Tardanico R, Balzarini P, et al. Cytogenetic features, clinical significance and prognostic impact of type 1 and type 2 papillary renal cell carcinoma. *Cancer Genet Cytogenet* 2010;199:128–133. [PubMed: 20471516]

Figure 1. Translocation-Renal Cell Carcinoma involving t(X;17)

A) Within an overall tubular or nested architecture, cells with clear or eosinophilic cytoplasm protrude into the luminal area and result in a pseudopapillary appearance. Nucleoli are commonly evident at low power. Microcalcifications may be identified. The nests, acini, and tubules are separated by fine fibrovascular septae. **B)** Extensive cytoplasmic eosinophilia may occur, and cytoplasmic granules are not uncommon. **C)** Nuclear staining for the TFE3 protein is seen in this RCC metastatic to the liver. Cytoplasmic staining may occasionally be evident but should not be interpreted as positivity.

Figure 2. Translocation-Renal Cell Carcinoma involving t(X;1)

The morphologic appearance of all translocation-RCC may be heterogeneous. Shown are three different areas from the same tumor containing the t(X;1). A) Areas are more compact, with less cytoplasm, resembling type 2 papillary renal cell carcinomas. B) All translocation-RCC may show areas with striking clear cell features that may result in an erroneous diagnosis of clear cell carcinoma of the kidney. C) Regions devoid of overt epithelial differentiation may resemble epithelioid angiomyolipoma.

Figure 3. Translocation-Renal Cell Carcinoma involving t(6;11), *TFEB/ALPHA*

A) TFEB-RCC also show a spectrum of histologic appearance varying from tubulopapillary to solid. Many lack overt epithelial differentiation and resemble epithelioid angiomyolipomas. This is complicated by the fact that both entities express melanocytic markers. B) TFEB-RCC may show clusters of small cells surrounding hyaline bodies composed of basement membrane material. Such foci may be quite infrequent and are not always identified in these tumors.

Figure 4. Papillary Renal Cell Carcinoma

A) Type 1 lesions most commonly have cuboidal nuclei that lack pleomorphism and lack prominent nucleoli. Foamy histiocytes within the papillae are common. Type 1 lesions show diffuse positivity for cytokeratin 7. B) Type 2 lesions often contain eosinophilic cytoplasm with pseudostratification and prominent nucleoli. Type 2 lesions are often negative for cytokeratin 7.

Figure 5.
Renal Medullary Carcinomas are composed of a tubular and cribriforming growth pattern accompanied by significant desmoplasia. The cells contain prominent eosinophilic cytoplasm, occasionally with rhabdoid-like inclusions. Nucleoli are often prominent.

Figure 6. Oncocytic Renal Cell Carcinoma following Neuroblastoma

Such tumors are identified a median of 8 years following the diagnosis of neuroblastoma and contain cells which have a highly variable amount of eosinophilic cytoplasm. The nuclei are characteristically irregular and often contain prominent nucleoli.