Kidney Tumors

New and Emerging Kidney Tumor Entities

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KEYWORDS

• Kidney • Renal cell carcinoma • Unclassified renal tumor
• Unclassified renal cell carcinoma • Novel entities • Pathology • WHO • GUPS

KEY POINTS

- Several novel and emerging renal entities have been recently characterized, owing to the rapid acquisition of new evidence and knowledge.
- This review summarizes the current state of the art on several new and emerging renal entities, including eosinophilic solid and cystic renal cell carcinoma, renal cell carcinoma with fibromyomatous stroma, anaplastic lymphoma kinase-rearranged renal cell carcinoma, low-grade oncocytic renal tumor, eosinophilic vacuolated tumor, thyroid-like follicular renal cell carcinoma, and biphasic hyalinizing psammomatous renal cell carcinoma.
- Pathologists played a key role in characterizing these new and emerging tumors; importantly the diagnosis of most of them rests primarily on recognizing their morphologic features with the aid of immunohistochemistry.
- We hope that this updated review will promote awareness of these entities, and will stimulate additional studies for their further characterization, resulting in more accurate diagnosis and improved patient prognostication and management.

EOSINOPHILIC SOLID AND CYSTIC RENAL CELL CARCINOMA

Introduction

Eosinophilic solid and cystic renal cell carcinoma (ESC RCC) is a recently characterized renal cell neoplasm demonstrating a unique set of clinical, microscopic, immunohistochemical, and molecular features.[1,2] Such tumors were likely designated previously as "unclassified RCC" or "unclassified renal neoplasm/RCC with oncocytic/eosinophilic features."

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Clinical Features

ESC RCC is typically sporadic and solitary tumor, found in patients of broad age range; most tumors are identified in females.[1–3] A subset has been documented in patients with tuberous sclerosis complex (TSC).[4,5] Although a great majority of ESC RCCs have indolent behavior, rare tumors with metastatic disease have also been reported, warranting the designation of "carcinoma" for this entity.[6–8]

Gross

As the descriptive name implies, solid and cystic components are the main gross features of ESC RCC. The tumors are well delineated, but nonencapsulated, and show a variable mix of solid parts and macrocysts. The cysts range from few millimeters to few centimeters. Rare cases have predominantly solid growth, with only rare microcysts. Tumor cut section is yellow, gray, and tan. Reported size varied broadly, but most tumors are less than 5 cm in size.[1,2]

Microscopy

The solid parts are composed of eosinophilic cells exhibiting diffuse, compact acinar, or nested growth (**Fig. 1**A–B).[1,2] Scattered foamy histiocytes and lymphocytes are also common, as are psammoma bodies. A characteristic feature is the presence of coarse, basophilic to purple, cytoplasmic granules (stippling). The nuclei are round to oval with focally prominent nucleoli. Focal papillary growth, clear cell areas, focal insular or tubular growth, and clusters of multinucleated cells can also be found.

Immunohistochemistry

ESC RCC shows either diffuse or focal CK20 expression (see **Fig. 1**C), although rare cases may be CK20 negative.[1,2] CK7 is typically negative or very focally positive. At least focal cathepsin K expression has been documented in a great majority of cases. Other positive stains include PAX8, AE1/AE3, CK8/18, and vimentin. Negative stains include CD117 and CAIX; HMB45 and melan-A are also negative in a great majority of cases, although rare cases show focal reactivity.

Molecular and Genetic Findings

Most sporadic ESC RCCs have recurrent, somatic biallelic losses or mutations in *TSC2* and *TSC1*. A subset of tumors has been identified in patients with TSC. These genetic changes result in dysregulation of the mammalian target of rapamycin (mTOR) signaling pathway.[6,9,10]

Differential Diagnosis

1. Oncocytoma: Typically lacks large cysts; cells have homogeneous oncocytic cytoplasm, without coarse granules. Immunohistochemistry (IHC): CD117+/CK20−/vimentin− (vs ESC RCC: CD117−/CK20+/vimentin+).
2. Chromophobe RCC, eosinophilic: Typically lacks large cysts, and cells lack coarse granules; irregular (raisinoid) nuclei with perinuclear halos are typical. IHC: CD117+/CK7+/CK20−/vimentin− (vs ESC RCC: CD117−/CK7−/CK20+/vimentin+).
3. SDH-deficient RCC: Cells have more flocculent cytoplasm and intracytoplasmic vacuoles. IHC: SDHB−/CK20−.
4. Epithelioid angiomyolipoma: Typically lacks large cysts (although smaller cysts can be present in some cases); cells lack coarse granules. IHC: PAX8−/CK20− (vs ESC RCC: PAX8+/CK20+).

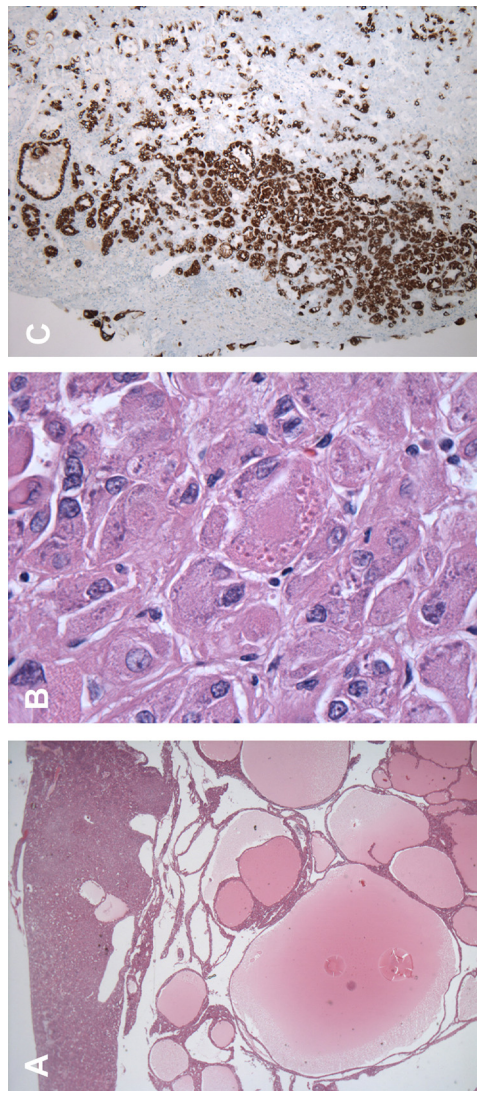

Fig. 1. ESC RCC. (*A*) At low power, it is an eosinophilic tumor that shows solid and cystic components; the cysts vary in size from macroscopic to microscopic. (*B*) The cells have voluminous eosinophilic cytoplasm with characteristic coarse cytoplasmic granules (stippling). (*C*) ESC RCC is typically CK20 positive (either diffuse or focal).

RENAL CELL CARCINOMA WITH FIBROMYOMATOUS STROMA

Introduction

Renal cell carcinoma with fibromyomatous stroma (RCC FMS) was described by Canzonieri and colleagues[11] in 1993, named as *mixed renal tumor with carcinomatous and fibroleiomyomatous components*. Over the years, various names were used in the literature to describe this entity, including: *RCC with prominent smooth muscle stroma*, *mixed renal tumor with carcinomatous and fibroleiomyomatous components*, *RCC associated with prominent angioleiomyoma-like proliferation*, *clear cell RCC with smooth muscle stroma*, and *RCC with clear cells, smooth muscle stroma, and negativity for 3p deletion*.[12] The name renal cell carcinoma with fibromyomatous stroma was officially endorsed by the Genitourinary Pathology Society (GUPS) in 2021, based on a broad consensus.[14] Recently published fifth edition of World Health Organization (WHO) classification of genitourinary tumors refers to this tumor as "renal cell carcinoma with prominent leiomyomatous stroma."[13]

Clinical Features

RCC FMS occurs more frequently in women (male:female [M:F] = 1:2) and is seen in adults of broad age range. The tumor is usually sporadic, but rare cases had familial association with TSC.[15] The prognosis is generally good and a great majority of cases had an indolent clinical course.[14,16,17] One case has been reported with lymph node metastasis in a patient with tuberous sclerosis and multifocal tumors.[18]

Gross

RCC FMS is a well-circumscribed, solid tumor, usually of small size (mean: 2.7 cm). Cut surface has a tan-brown color, often with lobulated appearance due to fibromyomatous septae.[12,19,20]

Microscopy

RCC FMS is typically composed of an epithelial neoplastic component, often forming nodules, separated by and admixed with a fibromuscular stromal component (**Fig. 2**A). The epithelial component consists of cells with voluminous clear cytoplasm, arranged in solid sheets, nests, branching tubules, and focal papillary structures (see **Fig. 2**B–C). The nuclei are WHO grade 2 or 3 (equivalent). The fibromyomatous stromal component can be variable and often appears more prominent at the periphery of the tumor.[12,14,19]

Immunohistochemistry

The characteristic IHC profile for RCC FMS includes diffuse positivity for CK7 (see **Fig. 2**D), as well as CAIX and CD10.[14,16,21] CAIX staining is usually diffuse membranous, but focally it can be cup shaped. Other positive stains include vimentin and high-molecular-weight cytokeratin. AMACR is typically negative. CK20 has been found positive in an apical pattern in some cases.[22]

Molecular and Genetic Findings

Molecular studies have provided evidence of association of RCC FMS with mutations involving the TSC/MTOR pathway.[14,16,22] A subset of tumors has shown mutations of *ELOC* (previously known as *TCEB1*) and monosomy of chromosome 8.[23] Unlike conventional clear cell RCC, these tumors are not associated with loss of heterozygosity (LOH) in chromosome 3p or *VHL* mutations.[14,24] Fibromyomatous stroma has been shown to be polyclonal and nonneoplastic.[24]

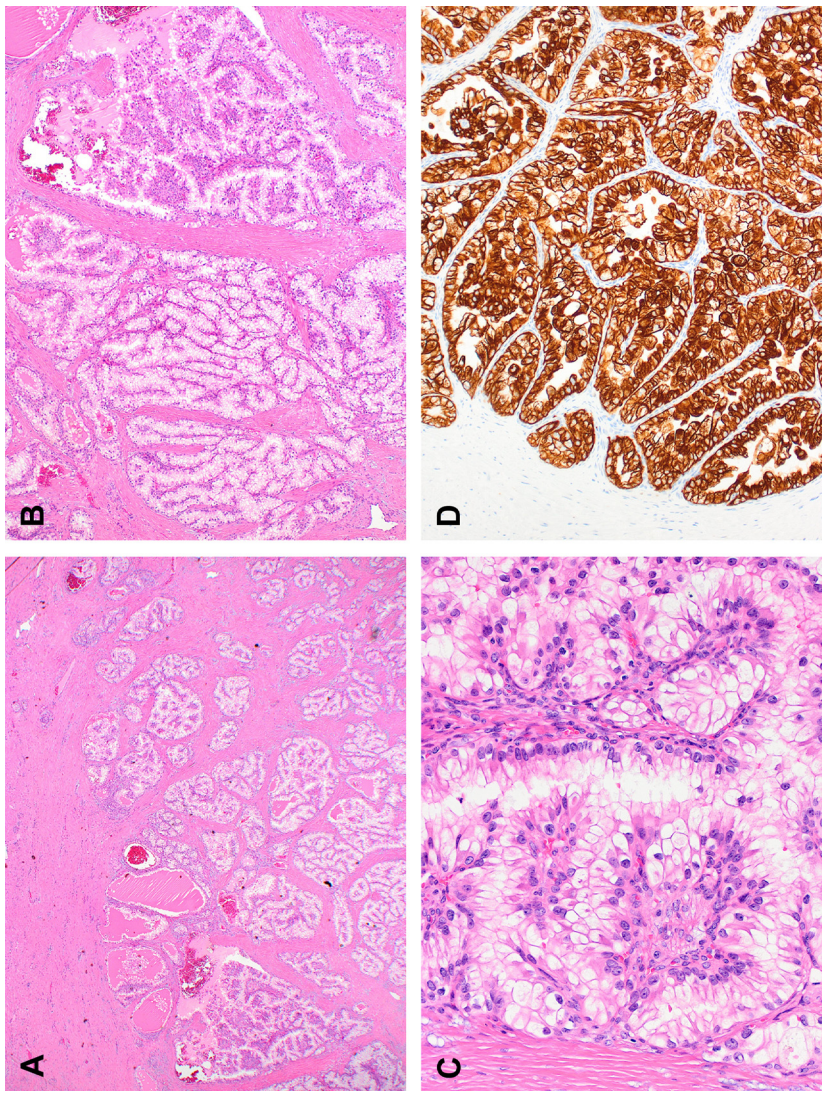

Fig. 2. RCC FMS. (*A*) RCC FMS has a clear cell morphology, with epithelial cells organized in lobules, separated by fibromuscular stroma. (*B*) The epithelial component often forms compact branching tubules (left) and focal papillary formations (*right*). (*C*) At high power, the nuclei are enlarged and may show more prominent nucleoli. (*D*) CK7 is typically diffusely positive.

Differential Diagnosis

1. Clear cell RCC: Typically lacks fibromyomatous stroma (although rare cases may show focally prominent stroma). Focal papillary structures are not usually present. IHC: CK7 is negative (or only focally positive); CD10 and AMACR are usually positive.
2. Clear cell papillary renal cell tumor: Cells have scant clear cytoplasm and form tubular and focal papillary structures. The nuclei are of lower grade (WHO/ISUP grade1 equivalent) and have a linear arrangement along the luminal surface. IHC: diffuse positivity for CAIX (cup shaped, not box shaped) and CK7, but CD10 is negative, as is AMACR.

ANAPLASTIC LYMPHOMA KINASE-REARRANGED RENAL CELL CARCINOMA

Introduction

Anaplastic lymphoma kinase-rearranged renal cell carcinoma (ALK RCC) is a renal entity first described in 2011.[25,26] ALK RCC is listed in the 2022 fifth edition of WHO classification of genitourinary tumors as a molecularly defined entity.[13] ALK RCC is characterized by an *ALK* gene fusion with various partner genes, leading to aberrant *ALK* activation. *ALK* rearrangement can be identified either by ALK protein expression on IHC, fluorescence in situ hybridization (FISH), or by sequencing methods. ALK RCC is a clinically important diagnosis because targeted therapies with ALK inhibitors are available and can be used as in other *ALK* rearrangement-associated neoplasms.[27,28]

Clinical Features

ALK RCCs have been reported in patients of wide age range, including pediatric and adolescent patients with sickle cell trait, as well as adult patients who typically did not harbor a sickle cell trait.[29] ALK RCC is not associated with other extrarenal tumors harboring ALK rearrangement. ALK RCC is slightly more common in males (M:F = 1.5:1). Patients had a diverse racial background, including African American, Caucasian, and Asian. ALK RCCs are indolent in most cases, although some may show aggressive clinical course, including metastasis and death.

Gross

ALK RCC usually presents as a solitary and circumscribed tumor, often less than 5 cm in size; it may be solid or solid-cystic, with tan-gray or variegated cut surface. Pseudocapsule of varying thickness can also be found.

Microscopy

ALK RCC typically demonstrates variable and diverse morphology with no characteristic or specific morphologic features. The growth patterns may include papillary, solid, tubular, trabecular cystic, cribriform, signet-ring, single cells, "mucinous tubular and spindle cell RCC-like" and "metanephric adenoma-like" (**Fig. 3**A–C).[14,29] However, mucinous or myxoid component (intracellular or interstitial) has been commonly found. Thus, a diagnostic consideration of ALK RCC and screening for ALK should be done in all difficult-to-classify renal tumors with variable and admixed patterns, unusual morphologies, or containing a mucinous component. Psammoma bodies and tumor necrosis are also common.

Immunohistochemistry

ALK protein expression by IHC, typically diffuse cytoplasmic and membranous, is a defining feature of ALK RCC (see **Fig. 3**D). Remaining immunoprofile is nonspecific

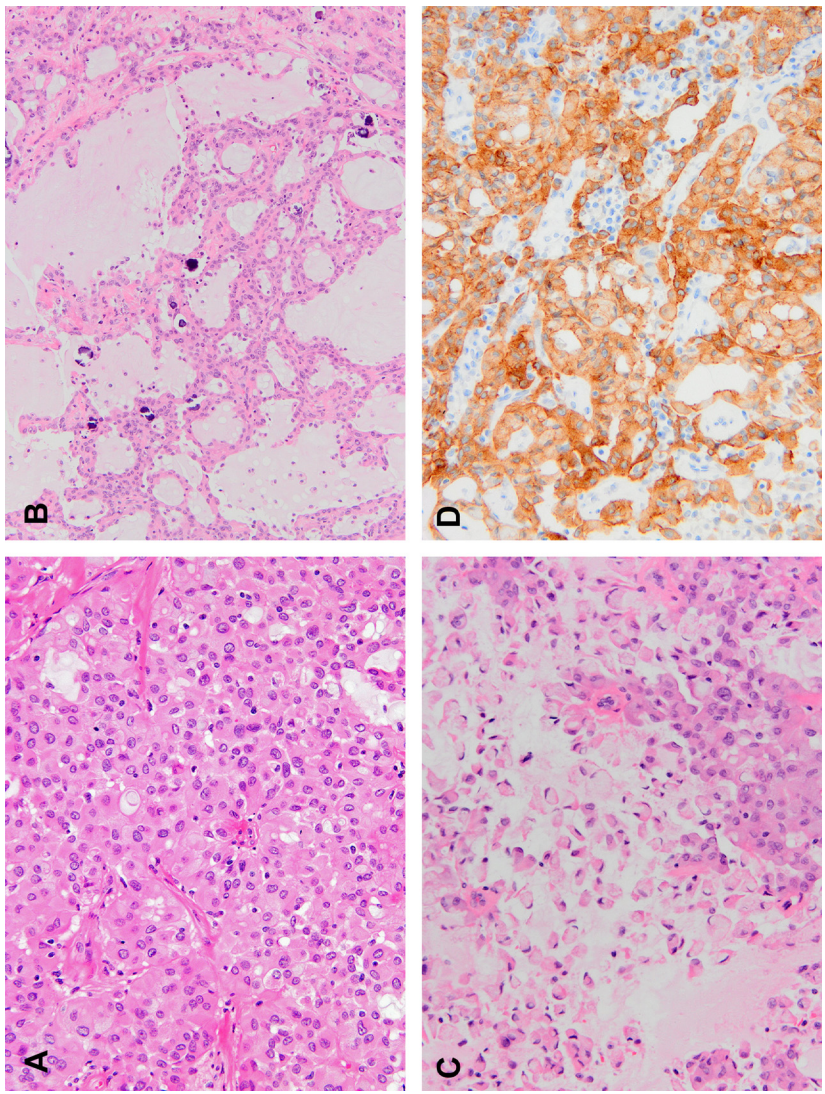

Fig. 3. ALK RCC. (*A–C*) ALK RCC shows mixed and variable patterns occurring in the same tumor, including, for example, solid areas (*A*); papillary, trabecular and tubulocystic areas, often with scattered psammomatous calcification (*B*); and focal single signet-ring cells (*C*). Note the extracellular mucinous background (*B*) and intracellular mucin in the signet-ring cells (*C*). (*D*) ALK expression is uniformly positive.

and includes reactivity for PAX8, CK7, vimentin, INI1 (retained), 34βE12, and AMACR. Negative IHC stains include CK20, GATA3, melan-A, HMB45, S100, and cathepsin K.[14,29] TFE3 reactivity by IHC was reported in some cases, but without evidence of *TFE3* rearrangement by FISH.[30]

Molecular and Genetic Findings

Several *ALK* fusion partners were identified in ALK RCC, including *VCL, HOOK1, STRN, TPM3, EML4,* and *PLEKHA7*.[14] A recent multi-institutional study reported 3 additional fusion partners *CLIP1, KIF5B,* and *KIAA1217*.[29]

Differential Diagnosis

The differential diagnosis of ALK RCC is broad, because its heterogeneous morphology may mimic a wide spectrum of other renal tumors, including SMARCB1-deficient renal medullary carcinoma (in children and adolescents), papillary RCC, MiTF RCC (TFE3 and TFEB), rhabdoid RCC (or clear cell RCC with rhabdoid features), collecting duct carcinoma, metanephric adenoma, mucinous tubular and spindle cell RCC, or unclassifiable RCC/tumor. A negative ALK IHC along with more specific immunomarkers for certain entities may help rule out ALK RCC.

EOSINOPHILIC VACUOLATED TUMOR

Introduction

Eosinophilic vacuolated tumor (EVT) is a recently described renal entity that emerged from the group of eosinophilic/oncocytic tumors with shared features between renal oncocytoma and chromophobe RCC.[31–33] EVT was described by He and colleagues[34] (as high-grade oncocytic tumor [HOT])[34] and by Chen and colleagues[35] (as sporadic RCC with eosinophilic and vacuolated cytoplasm). The recent GUPS consensus proposed the name *eosinophilic vacuolated tumor* for this entity.[14] EVT was also identified in some patients with TSC.[22,36–38] The 2022 fifth edition of WHO classification regards this tumor as one of the two emerging entities within the broader category of "other oncocytic tumors."[13]

Clinical Features

EVT is found in patients of broad age range and occurs more frequently in women (M:F = 1:2.5).[14,34,35,39] All reported EVT cases had benign behavior, without evidence of recurrence or metastatic disease.[14,39,40]

Gross

EVT is mostly a solitary and sporadic tumor of smaller size, about 3 to 4 cm in greatest dimension, although rare EVTs have been documented exceeding 10 cm.[34,35,38,39] EVT is typically solid, gray, or tan to brown tumor.[14,34,35,38,39]

Microscopy

EVT has a diffuse and solid growth, often admixed with nested and tubulocystic foci. Thick-walled vessels are virtually always present at the periphery, but a well-formed capsule is lacking. The cells have an eosinophilic cytoplasm and prominent intracytoplasmic vacuoles (**Fig. 4**A). The nuclei are round to oval, with prominent nucleoli that focally can be quite large and resemble viral inclusion.[34,35]

Immunohistochemistry and Electron Microscopy

EVT is positive for CD117 (KIT), CD10, antimitochondrial antigen antibody, and cathepsin K, in some cases focally (see **Fig. 4**B); CK7 is typically expressed only in

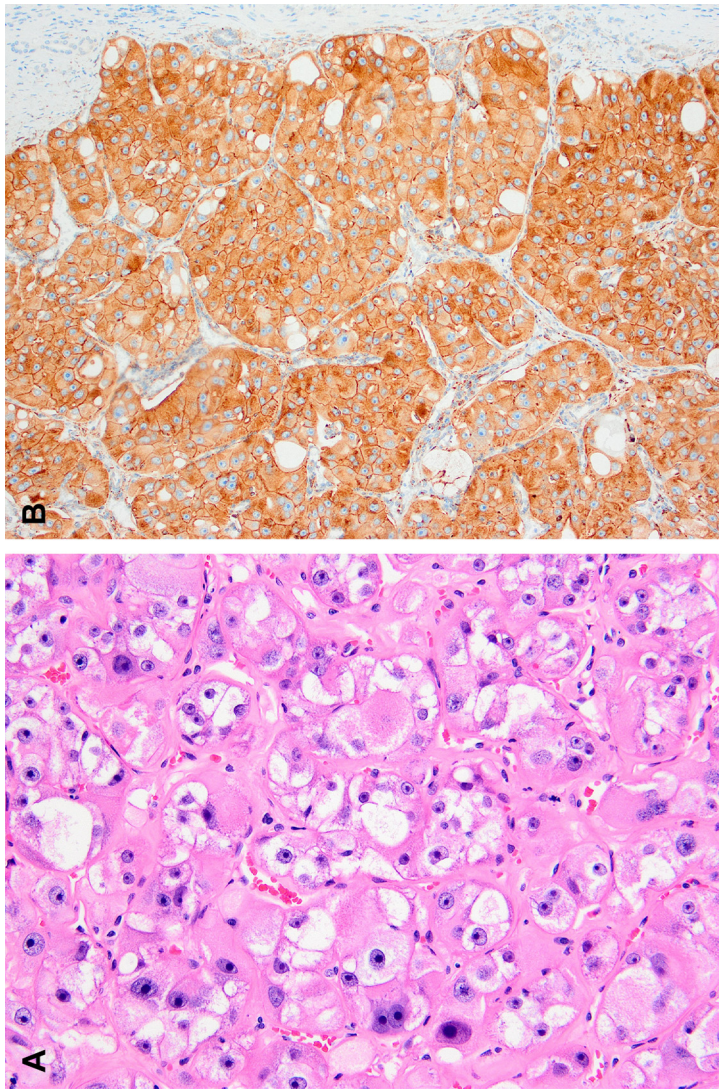

Fig. 4. EVT. (*A*) EVT is composed of eosinophilic cells with voluminous cytoplasm, typically showing prominent intracytoplasmic vacuoles, and enlarged, round to oval nuclei, often with very prominent nucleoli, imparting a "high-grade" appearance. (*B*) Cathepsin K is typically positive.

rare, scattered cells.[34,39] The immunoprofile "CD117+ and CK7+ only in rare cells" resembles that of an oncocytoma. EVT is negative for vimentin. Fumarate hydratase (FH) and succinate dehydrogenase B (SDHB) are retained. p-S6 and p-4EBP1, markers associated with mTOR pathway activation, have also been found to be expressed in EVT.[35]

On electron microscopy, EVT demonstrated numerous intracytoplasmic mitochondria, as well as dilated cisterns of rough endoplasmic reticulum.[38,40]

Molecular and Genetic Findings

Losses of chromosomes 1 and 19p were frequently found in EVT, along with loss of heterozygosity at 16p11 and 7q31.[34] However, complete losses or gains of other chromosomes, as in chromophobe RCC, have not been found. *TSC/mTOR* mutations seem to be consistent molecular findings in EVT[35,38] In a recent study, Farcas and colleagues[39] demonstrated nonoverlapping mutations in *MTOR*, *TSC2*, and *TSC1* in all evaluated cases, associated with low mutational burden. Thus, EVT is associated with either germline or somatic mutations leading to mTORC1 activation.[38]

Differential Diagnosis

1. Hybrid oncocytic tumor (Birt-Hogg Dubé syndrome): Typically multiple/bilateral tumors with hybrid (oncocytoma/chromophobe RCC-like) look; no stromal areas; often scattered cells with clear cytoplasm (mosaic pattern); the nuclei are typically low-grade and without prominent nucleoli; may show perinuclear halos. IHC: CD117+, CK7+ only focally, cathepsin K+/− (limited data).
2. Oncocytoma: Can show tubulocystic growth; cells lack perinuclear halos; stromal archipelaginous areas are present containing larger cell aggregates. IHC: CD117+, CK7+ only in scattered cells, but cathepsin K− and often CD10−.
3. Chromophobe RCC, classic: Cells usually have more prominent membranes and show irregular (raisinoid) nuclei with uniform perinuclear halos. IHC: CD117+, CK7+, but cathepsin K− and often CD10−.
4. SDH-deficient RCC: Cells have more flocculent cytoplasm and intracytoplasmic vacuoles; lack perinuclear halos. Edematous stromal areas with individual cells (as in LOT) can be seen. IHC: SDHB−/CD117−/CK7−.

LOW-GRADE ONCOCYTIC TUMOR

Introduction

Low-grade oncocytic tumor (LOT) is another recently described renal tumor that emerged from the spectrum of eosinophilic/oncocytic tumors with shared features between renal oncocytoma and chromophobe RCC.[12,41] Rare examples have been found in patients with TSC.[42] LOT is another emerging entity included within the broader category of "other oncocytic tumors" in the fifth edition of the 2022 WHO classification.[13]

Clinical Features

LOT is typically found as a single and incidental tumor, but multiple LOTs have also been documented, either in patients with end-stage kidney disease[43] or in patients with TSC.[42] Lerma and colleagues[37] recently reported four patients, in whom LOT was associated with other recently described renal tumors, typically found in patients with TSC, including eosinophilic solid and cystic ESC RCC, EVT, RCC FMS, as well as angiomyolipoma and papillary adenoma.[37]

LOT was identified in patients of broad age range, but usually older patients. Overall, LOT is slightly more frequent in females (M:F = 1:1.3). All reported LOTs with available

follow-up have behaved in a benign fashion, without evidence of disease progression and metastatic disease.[41–46]

Gross

LOT is usually a smaller tumor with median size between 3 and 4 cm, but similar to EVT; larger tumors have also been reported, exceeding 10 cm.[41,43,44] Grossly, LOT is a solid and compact tumor, without necrosis or cysts. Cut surface is tan-yellow to mahogany-brown, similar to oncocytoma.[41] Hemorrhagic areas may also be seen, usually more centrally.

Microscopy

LOT has a diffuse and solid growth, typically showing compact nests, and focal tubular, tubuloreticular, or trabecular growth. LOT lacks a well-formed capsule, and entrapped tubules may be seen at the periphery.[14,41] The neoplastic cells are eosinophilic with round to oval nuclei, lacking significant irregularities, and may show focal perinuclear halos or clearings (**Fig. 5**A–B). An important finding is that of sharply delineated, edematous stromal areas with scattered individual cells that can be elongated, and may form cordlike formations ("boats in a bay"), or may have an irregular "tissue culture" arrangement.[14,41] Edematous areas often contain fresh hemorrhage. Small lymphocytic collections can also be often seen in the solid areas.[14,41] Adverse features, such as coagulative necrosis, nuclear pleomorphism, cell atypia, multinucleation, and mitotic activity are typically absent.

Immunohistochemistry and Electron Microscopy

LOT is diffusely positive for CK7 (see **Fig. 5**C) and is negative, or in rare cases, very focally and weakly positive for CD117. LOT is also positive for PAX8, e-cadherin, BerEP4, and MOC31.[41] Negative stains include CAIX, CK20, CK5/6, p63, CD15, HMB45, melan-A, cathepsin K, and vimentin. CD10 and AMACR can be either negative or focally positive. FH and SDHB are retained. LOT is consistently positive for GATA3. LOT also expresses, at least focally, p-S6 and p-4EBP1, both markers associated with mTOR pathway activation.[42,45] Another novel marker FOXI1, typically expressed in both oncocytoma and chromophobe RCC, has been recently found to be negative or with very low reactivity in LOT.[47,48] In the normal kidney, FOXI1 is positive in the intercalated cells.[48]

On electron microscopy, LOT exhibits abundant, closely packed cytoplasmic mitochondria, similar to oncocytoma.[40]

Molecular and Genetic Features

LOT shows frequent deletions at 19p13, 1p36, and 19q13, or may show a disomic chromosomal status.[41] No other complete chromosomal gains or losses were found. *CCND1* rearrangements are not found in LOT (unlike in oncocytoma, in which they are frequent).[43]

Recent studies demonstrated common involvement of the mTOR pathway genes in LOT. In one study, abnormalities in mTOR pathway genes were found in 80% (8 of 10) of evaluated LOTs, including *mTOR* (7 of 8) and *TSC1* (1 of 8).[45] Another study found somatic, likely activating, mutations in *mTOR* (4 of 6) and *RHEB* (1 of 6) in 6 evaluable LOTs; one additional patient with multiple bilateral LOTs had a pathogenic germline mutation in *TSC1* (1 of 6).[42] *TSC1* germline mutations were also found in 2 patients with *TSC* mutations who had multiple LOTs.[37]

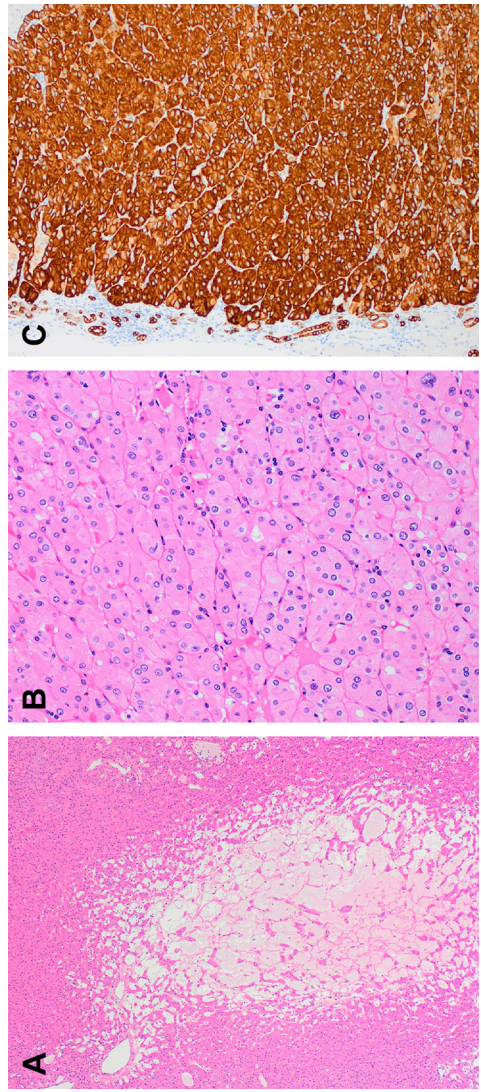

Fig. 5. LOT. (*A*) At low power, LOT is an eosinophilic solid tumor, often exhibiting sharply delineated, edematous areas with scattered individual cells ("boats in a bay"). (*B*). Higher magnification reveals eosinophilic cells with "low-grade" round to oval nuclei, and occasional perinuclear clearings. (*C*) EVT is diffusely positive for CK7 (shown) and negative for CD117 (not shown).

Differential Diagnosis

1. Oncocytoma: Can show tubulocystic growth, cells lack perinuclear halos, and archipelaginous areas are present containing larger cell aggregates. IHC: CD117+, CK7+ only in scattered cells.
2. Chromophobe RCC, eosinophilic: Lacks hypocellular stromal areas, cells usually have irregular (raisinoid) nuclei with uniform perinuclear halos. IHC: CD117+, CK7+.
3. SDH-deficient RCC: Cells have more flocculent cytoplasm and intracytoplasmic vacuoles, lack perinuclear halos. Edematous stromal areas with individual cells (as in LOT) may be present. IHC: SDHB−, CD117−, CK7−.

THYROID-LIKE FOLLICULAR RENAL CELL CARCINOMA

Introduction

Thyroid-like follicular renal cell carcinoma (TLF RCC) is a rare tumor with less than 50 cases described in the literature, mostly published as individual case reports. TLF RCC has also been considered an emerging renal entity in the recent GUPS update[14] and is listed in the 2022 fifth edition of WHO as an "emerging entity."[13]

Clinical Features

The sex distribution of TLF RCC has a slight female predominance (M:F = 1:1.8). Age range is broad (from 10 to 83 years).[49–51] No specific clinical features have been associated with TLF RCC. The clinical behavior was usually indolent in most reported cases, but lymph node and distant metastases were documented in about 10% of the patients.[52–55] Some reports have documented associations in individual patients with a family history of hereditary leiomyomatosis-associated RCC but without *FH* mutation, with mixed epithelial stromal tumor of the kidney, nephrolithiasis, and polycystic kidney disease.[14,54,56–59]

Gross

TLF RCC is a solitary, solid, well-circumscribed, and nonencapsulated tumor. The reported size range was wide (from 0.8 to 16.5 cm).[14,49–51]

Microscopy

TLF RCC resembles thyroid gland morphology (**Fig. 6**A–B). The tumors demonstrated follicular pattern, but focal branching and papillary structures were also reported. The size of the follicles was variable, and they were typically lined by a single layer of cuboidal or low columnar epithelial cells. The reported WHO grade was 2 or 3 (equivalent).[12,14,49–52,60–63] Sarcomatoid differentiation has been reported in one case.[64]

Immunohistochemistry

TLF RCC is usually positive for CK7, vimentin, and PAX8, and less frequently for RCC, AMACR, CD10, and CK20. An important finding is the negative staining for TTF1 and thyroglobulin, in contrast to true metastatic carcinomas of the thyroid.[14,58]

Molecular and Genetic Features

An association of TLF RCC and *EWSR1* gene abnormality has been recently reported by Al-Obaidy and colleagues,[58] documenting a fusion of *EWSR1-PATZ1* genes in 3 cases. The reported copy number variations have been variable, but neither consistent copy number changes nor other recurrent gene alterations have been found in TLF RCC.[49,55,60,64–66]

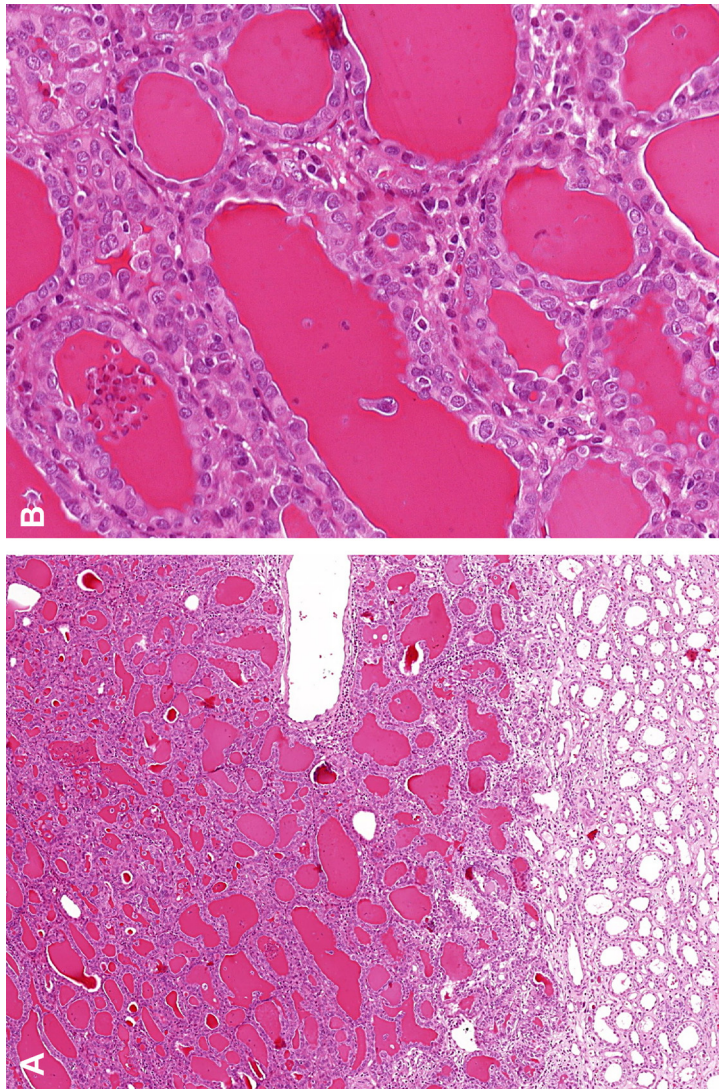

Fig. 6. TLF RCC. (*A*) This tumor shows a morphology resembling a thyroid gland, and is composed of back-to-back arranged, variable-sized follicles, with "colloid-like" luminal content. (*B*) At high power, the follicles are lined by a single layer of cuboidal to low columnar epithelial cells.

Differential Diagnosis

1. Metastasis of thyroid gland carcinoma to the kidney: This is the most important differential diagnosis that can be easily ruled out by IHC, because TTF1+ and thyroglobulin+ are found in a thyroid metastasis, in contrast to TLF RCC, which is negative for both. Caution: metastatic thyroid carcinoma is PAX8+, which may be a pitfall, because PAX8+ is found in almost all thyroid gland tumors.
2. Atrophic kidney-like lesion: Rare, well-demarcated, brown, tumor-like mass; considered nonneoplastic and likely reactive. This lesion is composed of atrophic renal tubules admixed with rare collapsed glomeruli. The key morphologic findings are the atrophic tubules and the collapsed glomeruli, which are not found in TLF RCC.

BIPHASIC HYALINIZING PSAMMOMATOUS RENAL CELL CARCINOMA

Introduction

Biphasic hyalinizing psammomatous renal cell carcinoma (BHP RCC) is a recently proposed renal tumor entity, invariably demonstrating neurofibromin 2 (*NF2)* mutations.[67] However, it is unclear whether *NF2* abnormalities represent a specific feature or a genetic driver in a group of related tumors that may represent an entity, or if they are a nonspecific finding, because they have been found in other RCC subtypes with various morphologies.[67–69] For example, in one recent study, 2 tumors described as BHP RCC did not show *NF2* abnormality.[70] In contrast, *NF2* abnormalities have been identified in some advanced papillary RCCs.[69] Thus, further study is necessary to validate whether BHP RCC represents a distinct renal entity sharing *NF2* gene abnormalities.[14,68,71]

Clinical Features

No specific clinical features were identified in the initial series of 8 cases,[67] and in a subsequent series of 6 cases.[72] There were 6 males and 1 female (1 unknown gender) in the study by Argani and colleagues,[67] and 3 males and 3 females in the study by Wang and colleagues.[72] Age range was broad (39–82 years), and no hereditary/syndromic or other associations were reported. Approximately half of the cases reported in the literature demonstrated metastatic disease.[70,71]

Gross

BHP RCC is a well-demarcated, solid, solitary tumor, occasionally demonstrating a peripheral capsule. Size ranged from 0.9 to 7.5 cm.[67,70–73]

Microscopy

BHP RCC is a solid tumor, with variable architecture, often including papillary and tubular growth. The tumors were typically composed of biphasic neoplastic cells, with smaller cells clustering around basement membrane material forming pseudorosettes and resembling the classic morphology of TFEB RCC (**Fig. 7**A–B). The second cell population consisted of larger cells with pale cytoplasm. Some reported tumors resembled a gonadoblastoma and formed solid pseudotubules or pseudoresettes, composed of cuboidal to cylindrical cells with pale to eosinophilic cytoplasm. Another morphologic variation was the presence of focal tubulopapillary growth, associated with basement membrane material, resulting in a glomeruloid appearance. The stromal component was typically sclerotic and focally hyalinized and scattered psammoma bodies were common.[67,71–73]

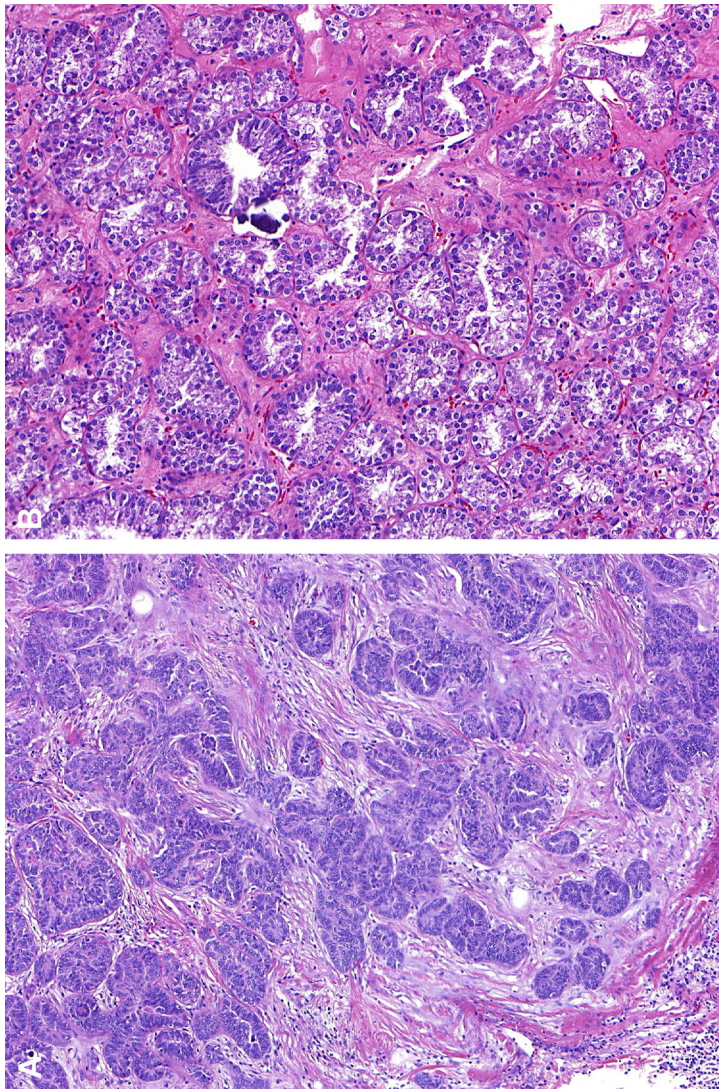

Fig. 7. BHP RCC. (*A*) BHP RCC is a solid tumor composed of glandlike structures, embedded in a fibrous, focally hyalinized stroma. These tumors typically show biphasic cell composition with smaller cells forming pseudorosettes. (*B*) Some areas show tubular morphology, and scattered psammoma bodies are common.

Table 1
Features of novel and emerging renal entities

Type	Clinical Features	Morphology	Immunohistochemistry	Molecular Features
ESC RCC	Mostly in females, mostly sporadic and solitary, rare cases in patients with TSC, indolent (great majority)	Solid and cystic, voluminous eosinophilic cells, cytoplasmic stippling	CK20+ CK7− CD117−v imentin+c athepsin K+ (focal)	Somatic biallelic loss or mutations of *TSC1* and *TSC2*
RCC FMS	Mostly sporadic and solitary, rare cases in patients with TSC, indolent (great majority)	Solid, smaller tumor, tan to brown, frequent lobulated appearance; clear cells with voluminous cytoplasm forming nodules, separated and encircled by fibromuscular stroma	CK7+ CAIX+ (membranous) CD10+ AMACR−	Frequent mutations in TSC/mTOR pathway genes, *ELOC* (*TCEB1*) mutation in some cases; some lack *VHL* mutations, or LOH/ deletion of chromosome 3
ALK RCC	Broad age range, solitary tumor, some in patients with sickle cell trait	Diverse (variable admixed patterns), often mucinous/myxoid background; medullary carcinoma-like morphology in children	ALK+ Other IHC nonspecific Rare cases TFE3+ (without translocation)	*ALK* rearrangement Fusion partners: *VCL*, *HOOK1*, *STRN*, *TPM3*, *EML4*, *PLEKHA7*, *CLIP1*, *KIF5B,* and *KIAA1217*
EVT	Broad age range, sporadic and solitary, rare cases in patients with TSC, indolent	Solid, smaller tumor, tan to brown or gray, large vessels often found at the periphery; eosinophilic cells with frequent and prominent intracytoplasmic vacuoles, large nucleoli	cathepsin K+ CD117+ CD10+ CK7− (only rare cells +) CK20−v imentin−	*TSC/mTOR* mutations virtually in all cases, deletions of chromosome 19 and 1 also found

(*continued on next page*)

Table 1
(*continued*)

Type	Clinical Features	Morphology	Immunohistochemistry	Molecular Features
LOT	Older patients, sporadic and solitary, rare cases in patients with TSC, indolent	Solid, smaller tumor, tan to mahogany brown; sharp transition to edematous areas with scattered individual cells; round to oval nuclei without irregularities and prominent nucleoli, often with perinuclear halos	CK7+ (diffuse) CD117− (rarely weak +) GATA3+ (limited data) FOXI1− CK20−v imentin−	Frequent *TSC/MTOR* mutations, lacks multiple chromosomal losses, deletions of chromosomes 19p, 19q and 1p also found, no *CCND1* rearrangements
TLF RCC	Broad age range including children, solitary, mostly indolent	Thyroid-like follicular arrangement, follicles of variable size with eosinophilic luminal content, lining cells cuboidal to cylindrical	CK7+ PAX8+ Vimentin− TTF1−t hyroglobulin−	Fusion of *EWSR1-PATZ1* found in 3 cases No other specific findings
BHP RCC	Adult patients, about half of tumors with aggressive clinical course	Tubulopapillary architecture, prominent fibrotic to hyalinized stroma, and microcalcifications Heterogeneous morphology	CK7+ PAX8+ CD10+ HMB45−m elan A−	*NF2* abnormalities , loss of chromosome 22 found in some cases

Immunohistochemistry

The neoplastic cells were usually reactive for PAX8, CD10, and CK7, but were negative for GATA3, cathepsin K, melan-A, inhibin, SF1, and WT1. All tested cases were also negative for *TFE3* and *TFEB* rearrangements by break-apart FISH.

Molecular and Genetic Features

A typical molecular feature identified in all analyzable cases of BHP RCC was a mutations of the *NF2* gene.[67,71,72] In a recent study, two tumors described as BHP RCC lacked *NF2* abnormalities.[70] Additional mutations in *PBMRT1, BAP1, ARID1A, DNMT3A, TERT*, and *SMARCB1* were also found in some cases. The copy number variation pattern was not uniform and showed multiple chromosomal gains and losses, most commonly a loss of chromosome 22. Coalteration of *NF2* and *PBMRT1* was found in some cases with aggressive clinical course.[71]

Differential Diagnosis

BHP RCC represents a heterogeneous group of renal tumors with a limited number of reported cases, usually demonstrating prominent fibrotic and hyalinized stroma, microcalcification, and tubulopapillary architecture. The differential diagnosis of BHP RCC is broad and may include papillary RCC, MiTF family RCC (often demonstrating cathepsin K or melanotic marker expression, as well as *TFE3*/*TFEB* rearrangements), *ALK*-rearranged RCC (typically showing ALK rearrangements), and metastatic sex core stromal tumor, such as gonadoblastoma (which can be ruled out by the absence of gonadal primary and inhibin and SF1 immunoreactivity). However, without genetic testing for *NF2*, the diagnosis of BHP RCC remains virtually impossible.

SUMMARY

This article provides an overview of several new and emerging renal entities. The summary of their key features is shown in **Table 1**. The awareness of these renal neoplasms is essential for practicing pathologists because the navigation through this evolving field is a challenging task, even in places with large volumes of renal tumors. Such cases can, however, be seen in practices of any scope, and their correct classification requires diagnostic awareness among general pathologists, because they can be often diagnosed, or at least suspected, on morphology in combination with IHC. The recognition of such novel renal entities will guide both pathologists and clinicians in translating these developments into more accurate diagnosis and better patient management.

DISCLOSURE

Authors have no conflicts of interest to declare that are relevant to the content of this article.

DEDICATION

We dedicate this paper to our friend and colleague Dr. Ondřej Hes - Ondra, who passed away suddenly on July 2, 2022. We acknowledge and salute his many contributions that shaped the contemporary field of renal tumor pathology and resulted in recognition of many renal entities and subtypes included in this review and in the WHO 2022 classification (5th edition) of urinary and male genital tumors. We dedicate this paper to Dr. Hes to honor his memory, friendship, and scientific legacy.

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