The remarkable advances in our understanding of renal tumor pathogenesis, driven by the widespread application of molecular testing, are reflected in the latest 2022 World Health Organization classification. This updated classification categorizes renal cell carcinoma (RCC) into morphologically and molecularly defined RCCs. It includes updates to existing entities and introduces newly established and provisional entities. A standard macroscopic and microscopic evaluation is typically sufficient for diagnosing morphologically defined RCCs and serves as the initial step in the identification of molecularly defined entities. In cases where classification based solely on histologic examination is challenging, a limited panel of immunohistochemical stains can be employed to aid in the diagnosis, with molecular testing for validation if necessary. Therefore, this review explores the key clinical, pathological, and molecular features essential for classifying both the commonly encountered morphologically defined RCCs and the less common but clinically significant molecularly defined RCCs. The goal is to increase awareness of these RCC subtypes among clinicians and promote a deeper understanding of the pathological diagnostic process, ultimately improving patient care.

**Key Words:** Renal cell carcinomas, World Health Organization, Classification, Histology, Immunohistochemistry, Diagnostic molecular pathology

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**INTRODUCTION**

The classification of kidney tumors has evolved significantly over time. Modern understanding now extends beyond a purely morphology-based system to an integrated approach that encompasses clinical, histologic, immunohistochemical, cytogenetic, and molecular findings. Previously, renal cell carcinoma (RCC) classifications were primarily based on histologic characteristics, including predominant cytoplasmic features (e.g., clear cell RCC [CCRCC], chromophobe RCC [ChRCC]), architectural features (e.g., papillary RCC [PRCC]), and anatomical location. Additional factors such as underlying renal disease (e.g., acquired cystic disease-associated RCC) and familial syndromes (e.g., hereditary leiomyomatosis and RCC syndrome-associated RCC) also played a role in classification [1].

With the widespread adoption of next-generation sequencing (NGS) in clinical settings, the genomic land-
scape of RCC has been more clearly defined. This advancement has led to the introduction of a molecular-driven renal tumor classification in the new 2022 World Health Organization (WHO) classification. Alongside the established morphologically defined RCC entities, a new family of molecularly defined RCCs has been introduced (Table 1) [1]. Molecular tests play a crucial diagnostic role in these molecularly defined RCCs; however, routine histologic and immunohistochemical examinations remain essential. Additionally, molecular tests can provide valuable diagnostic insights for morphologically defined RCCs, particularly in cases with difficult-to-classify or undifferentiated histologic features.

Therefore, this review explores recent updates in RCC pathology, covering both the frequently encountered, morphologically defined RCCs and the newly introduced, molecularly defined RCCs. Based on the extensive information available on RCCs, the intention was to concisely summarize the key histologic, immunohistochemical, and molecular features useful for patient management.

### MORPHOLOGICALLY DEFINED RENAL CARCINOMAS

The pathological diagnosis of morphologically defined RCCs is typically made through histologic examination, often complemented by immunohistochemistry (IHC). Subtype-specific genetic alterations, which are well-documented in morphologically defined RCCs, can be used as ancillary tests for accurate classification.

#### 1. Clear Cell RCC

CCRCC can be identified by its golden yellow cut surface during macroscopic examination, clear cells with fine arborizing vascularity observed under microscopic examination, positive carbonic anhydrase IX (CA9) IHC, and biallelic von Hippel-Lindau (VHL) inactivation as determined through molecular pathology (Fig. 1A-C) [1].

In most cases, the pathological diagnosis of CCRCC is straightforward. High-grade CCRCC often exhibits

<table>
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<tr>
<th>Family (class)</th>
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<tr>
<td>Clear cell renal tumors</td>
<td>Clear cell renal cell carcinoma</td>
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<td>Multilocular cystic renal neoplasm of low malignant potential</td>
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<td>Papillary renal tumors</td>
<td>Renal papillary adenoma</td>
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<td>Papillary renal cell carcinoma*</td>
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<td>Oncocytic and chromophobe renal tumors</td>
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<td>Chromophobe renal cell carcinoma</td>
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<td>Other oncocytic tumors of the kidney</td>
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<td>Collecting duct tumors</td>
<td>Collecting duct carcinoma</td>
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<td>Other renal tumors</td>
<td>Clear cell papillary renal cell tumor</td>
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<td>Mucinous tubular and spindle cell carcinoma</td>
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<td>Tubulocystic renal cell carcinoma</td>
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<td>Acquired cystic disease-associated renal cell carcinoma</td>
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<td>Eosinophilic solid and cystic renal cell carcinoma</td>
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<td>Renal cell carcinoma, NOS</td>
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<td>Moleculary defined renal carcinomas</td>
<td>TFE3-rearranged renal cell carcinoma</td>
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<td>TFEB-altered renal cell carcinoma</td>
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<td>ELOC (formerly TCEB1)-mutated renal cell carcinoma</td>
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<td>FH-deficient renal cell carcinoma</td>
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<td>SDH-deficient renal cell carcinoma</td>
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<td>ALK-rearranged renal cell carcinoma</td>
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<td>SMARCB1-deficient renal medullary carcinoma</td>
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NOS, not otherwise specified; FH, fumarate hydratase; SDH, succinate dehydrogenase; SMARCB1, SWI/SNF related, matrix-associated, actin-dependent regulator of chromatin subfamily B member 1.

*Several emerging/provisional entities are introduced and include papillary renal neoplasm with reversed polarity, biphasic hyalinizing psammomatous renal cell carcinoma, biphasic squamous/alveolar renal cell carcinoma, thyroid-like follicular renal cell carcinoma, and Warthin-like papillary renal cell carcinoma. †Two provisional entities low-grade oncocytic renal tumor and eosinophilic vacuolated tumor are included.

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sarcomatoid or rhabdoid features and tumor necrosis, which are characteristics that may also appear in other subtypes. When extensive sarcomatoid changes complicate classification, revisiting the macroscopic examination and looking for the typical golden yellow tumor areas for microscopic confirmation can aid in diagnosing CCRCC. This approach is useful because the classification of malignant tumors depends on the identification of well-differentiated areas.

CA9 is an enzyme encoded by the CA9 gene, playing a role in the hypoxia pathway. It is upregulated in CCRCC due to dysregulation of the VHL pathway. Diffuse membranous immunopositivity for CA9 can aid in diagnosing CCRCC [2-5]. However, similar mechanisms may also occur in areas of ischemia and necrosis in other RCC subtypes, which could lead to CA9 positivity through activation of the hypoxia pathway. Therefore, CA9 positivity must be interpreted with caution.

Given that the biallelic VHL inactivation is identified in >90% of CCRCC cases, molecular tests can facilitate the diagnosis in challenging cases [6-10]. These tests include detecting chromosome 3p loss in one allele and either inactivating mutations (73%–89%) or promoter region methylation (8%–16%) in the second VHL allele [6-11].

2. Papillary RCC

PRCC is characterized by its papillary and tubular structures visible under microscopic examination, AMACR positivity on IHC, and genetic changes, including gains of chromosomes 7 and 17, as well as loss of the Y chromosome (Fig. 1D-F). Low-grade tumors frequently display a MET
mutation [12,13].

In low-grade PRCC, the histologic features are very similar to those observed in papillary adenoma, making them challenging to distinguish. Consequently, a size criterion (≥15 mm) is utilized to classify such tumors as PRCC [1]. Conversely, high-grade tumors, particularly those with a mixed morphological pattern, can display histologic characteristics that overlap with those of other molecularly defined RCCs, such as fumarate-hydratase (FH)-deficient RCC. It is therefore essential to exclude the possibility of FH-deficient RCC to confirm the diagnosis of high-grade PRCC [1].

Traditionally, PRCC was divided into low-grade PRCC type 1 and high-grade PRCC type 2. However, the 2022 WHO classification no longer makes this distinction [1,13,14]. This update is due to the frequent observation of PRCC cases exhibiting mixed or overlapping characteristics of both types. Additionally, advancements in clinical understanding and molecular pathology have shown that type 2 PRCC is not a homogeneous group but consists of various entities with unique molecular profiles. Some tumors previously categorized under PRCC are now recognized as distinct entities, including FH-deficient RCC, tubulocystic RCC, and TFE3/TFEB-altered RCC [15-17]. As a result, the 2022 WHO classification for PRCC now includes what was formerly known as type 1 PRCC and the remaining type 2 tumors, excluding those newly identified entities. With the elimination of subtyping in PRCC, the WHO/International Society of Urological Pathology histological grading system may provide additional prognostic information for PRCC.

Currently, the PRCC includes emerging or provisional entities for which the accumulated clinicopathologic data are considered insufficient to determine whether they should be classified as distinct new entities. These entities are papillary renal neoplasm with reversed polarity (PRNRP), biphasic hyalinizing psammomatous RCC (BHP RCC), biphasic squamoid/alveolar RCC, thyroid-like follicular RCC (TLF RCC), and Warthin-like PRCC [18-24]. They exhibit specific molecular alterations, including KRAS mutations in PRNRP, NF2 mutations in BHP RCC, and EWSR1::PATZ1 fusions in TLF RCC [23,25,26].

3. Oncocytic and Chromophobe Renal Tumors

The oncocytic renal tumor category includes 2 well-established entities: oncocytoma and ChRCC. In the revised classification, ChRCC retains its original characterization, marked by large pale cells with wrinkled nuclei, perinuclear haloes, and distinct cell membranes upon microscopic examination. Additionally, it demonstrates clusters of cytokeratin 7 (CK7)-positive cells on IHC and exhibits losses of multiple chromosomes (Fig. 1G-I) [27,28].

The 2022 WHO classification includes 2 provisional entities: low-grade oncocytic renal tumor and eosinophilic vacuolated tumor. Although data are limited, these tumors appear to exhibit indolent behavior and are associated with either inactivating mutations of the TSC1/2 genes or activating mutations of the MTOR gene [27,29].

The remaining sporadic oncocytic tumors are classified as other oncocytic tumors of the kidney in the 2022 WHO classification and are diagnosed as “oncocytic renal neoplasms of low malignant potential, not otherwise specified (NOS)” [27,30]. This category is specifically applied to sporadic, nonfamilial cases and serves more for clinical management purposes than for defining a distinct entity [27]. Considering the generally indolent nature of these tumors, it is crucial to differentiate them from high-grade unclassified RCC or RCC NOS, which are typically characterized by aggressive behavior.

4. Eosinophilic Solid and Cystic RCC

Eosinophilic solid and cystic RCC (ESC-RCC) was introduced as a new entity in the 2022 WHO classification. It predominantly affects women and is characterized by a solid and cystic macroscopic appearance. Microscopically, it features voluminous eosinophilic cytoplasm with coarse basophilic stippling. It frequently shows positivity for CK20 on IHC and exhibits biallelic losses or mutations in the TSC1/TSC2 genes (Fig. 1J-L) [16,31-33].

ESC-RCC was first described in patients with tuberous sclerosis complex; however, recent data indicate that sporadic cases are more common [34,35]. Most ESC-RCC cases exhibit indolent clinical behavior, though rare instances of metastasis have been reported [32]. The inactivation of TSC1/
TSC2 leads to hyperactivation of the mammalian target of rapamycin (mTOR) pathway. One study has documented the clinical benefit of mTOR inhibitors in patients with ESC-RCC [32].

MOLECULARLY DEFINED RENAL CARCINOMAS

Molecularly defined RCCs often exhibit diverse histologic features, making them challenging to classify based on histologic examination alone. Although these cancers are characterized by specific molecular alterations, ideally confirmed by fluorescent in situ hybridization (FISH) or NGS, most can also be diagnosed using IHC, except for ELOC-mutated RCC. The efficacy of IHC, compared to various genetic testing methods, has been recognized and termed “next-generation IHC” in multiple cancers for detecting or inferring the presence of mutations. Thus, the value of cost-effective IHC-based diagnosis should not be underestimated, especially when highly sensitive and specific assays are available [36,37]. Consequently, molecularly defined RCCs should initially be suspected from histologic examination and diagnosed via IHC, with molecular tests employed for confirmation when necessary.

1. TFE3-Rearranged RCC

TFE3-rearranged RCC is defined by chromosomal rearrangements involving the fusion of the TFE3 gene with various partner genes. It is characterized by mixed histologic patterns, often featuring voluminous clear cells, papillary architecture, and psammoma bodies on microscopic examination, along with strong nuclear positivity for TFE3 on IHC (Fig. 2A-C) [38].

The most commonly observed fusions partners include ASPSCR1 (also called ASPL) via t(X;17)(p11.2;q25), PRCC via t(X;1)(p11.2;q21), and SFPQ (also called PSF) via t(X;1)(p11.2;p34) [39-41]. TFE3-rearranged RCC is relatively common in childhood, accounting for up to 50% of RCC cases in children and 5% of adult RCC cases [39,42,43]. However, since RCC is more frequent in adults, the absolute number of patients with TFE3-rearranged RCCs is larger in adults than in children [44].

2. TFEB-Altered RCC

TFEB-altered RCC is characterized by TFEB gene fusion for TFEB-rearranged RCC and amplification of the 6p21 locus, which harbors TFEB, for TFEB-amplified RCC, along with nuclear positivity for TFEB on IHC [45]. Formerly categorized as MiT family translocation RCC along with TFE3-rearranged RCC, TFEB-altered RCC is now classified as a new entity, encompassing TFEB-rearranged RCC and TFEB-amplified RCC. TFEB-rearranged RCC commonly involves fusion with MALAT1 (also called alpha) via a t(6;11)(p21;q12) translocation [46,47].

TFEB-rearranged RCC exhibits a characteristic biphasic pattern on microscopic examination, with larger epithelioid cells surrounding smaller cells clustered around eosinophilic spheres of basement membrane material [46,47]. The histologic features of the TFEB-amplified RCC are less distinctive but often present as high-grade tumors (Fig. 2D-F) [48,49]. A definitive diagnosis requires demonstrating TFEB rearrangement or amplification through break-apart FISH or RNA sequencing. Immunoreactivity for TFEB is highly specific, particularly for TFEB-rearranged RCC. Additionally, immunoreactivity for melanocytic markers, particularly Melan-A IHC, can be used as a sensitive, though not highly specific, marker for TFEB-rearranged and TFEB-amplified RCC [48,50].

TFEB-rearranged RCCs tend to be more indolent than TFE3-rearranged RCCs, whereas TFEB-amplified RCCs are more aggressive and often present at an advanced stage or as metastatic disease [48].

A retrospective combined cohort analysis of translocation RCCs, predominantly comprising TFE3- and TFEB-rearranged RCCs, revealed uniformly elevated activity of NRF2, a transcription factor that regulates the cellular antioxidant...
Fig. 2. Pathologic features of molecularly defined renal cell carcinomas (RCCs). TFE3-rearranged RCC shows papillary architecture (A), voluminous clear cytoplasm (B), and diffuse strong nuclear immunopositivity for TFE3 (C). TFEB-altered RCC shows a tubulocystic pattern (D), high-grade atypia (E), and nuclear immunopositivity for TFEB (F). ELOC-mutated RCC shows prominent thick intervening fibromuscular septae (G), abundant clear cytoplasm (H), and immunopositivity for CK7 (I). Fumarate-hydratase (FH)-deficient RCC shows tubulopapillary and solid patterns (J), prominent large eosinophilic nuclei (K), and immunonegativity (loss) for FH (left) and immunopositivity for S-(2-succino)-cysteine (right) (L). Succinate dehydrogenase-deficient RCC shows compact eosinophilic cell nests (M), eosinophilic cytoplasm with pale flocculent inclusions (N), and immunonegativity (loss) for succinate dehydrogenase complex iron sulfur subunit B. ALK-rearranged RCC shows tubules and nests (P), intracytoplasmic mucin (Q), and immunopositivity for anaplastic lymphoma kinase (R). SMARCB1-deficient renal medullary carcinoma shows a tubuloglandular pattern (S), high-grade nuclear atypia (T), and immunonegativity (loss) for integrase interactor 1 (INI1) (U). (A, D, M, P, S, hematoxylin and eosin staining (H&E), ×200 magnification; G and J, H&E, ×50 magnification; B, E, H, K, N, Q, and T, H&E, ×400 magnification; C, F, I, L, O, R, and U, IHC, ×400 magnification) *Authors express sincere gratitude to Gyung Chul Moon from Seoul National Hospital, Department of Pathology for sharing the images of a rare case of SDHB-deficient renal cell carcinoma (M-O).
response. Immune checkpoint inhibitors (ICI) demonstrated greater clinical benefit than vascular endothelial growth factor receptor (VEGFR)-targeted therapies [39].

3. ELOC-Mutated RCC

Elongin-C (ELOC)-mutated RCC is characterized by the biallelic inactivation of ELOC, presenting as a clear cell neoplasm with thick fibromuscular bands observed microscopically and positivity for CK7 on IHC [51]. Mutations in ELOC, a crucial component of the VHL complex, occur exclusively at its VHL binding site Y79 or A100 and are accompanied by the loss of the other allele on chromosome 8 [11,52]. Consequently, the binding of ELOC with VHL is abolished, leading to impaired ubiquitination and the subsequent accumulation of HIF, an oncogenic mechanism comparable to that observed in CCRCC [11].

Microscopically, tumor cells in ELOC-mutated RCC exhibit low-grade nuclear atypia and voluminous clear cytoplasm, resembling features seen in CCRCC. However, ELOC-mutated RCC often presents with prominent thick fibromuscular bands and positivity for CK7 in addition to CA9 positivity on IHC (Fig. 2G-I). Owing to these pathological characteristics, it has previously been referred to as “CCRCC with fibromyomatous or leiomyomatous stroma” [11,52]. This tumor is distinct among molecularly defined RCCs in requiring molecular testing, as mutation of the ELOC gene is an essential criterion for its diagnosis [51]. In cases where molecular testing for ELOC mutations is unavailable, it is suggested that the condition be referred to as clear cell RCC with prominent fibromuscular septations and CK7 positivity, and to provide a differential diagnosis of ELOC-mutated RCC [53].

In cases with low-grade nuclei and no additional oncogenic mutations, ELOC-mutated RCC typically exhibits an indolent clinical course. Therefore, an accurate diagnosis of this tumor is crucial to avoid unnecessary adjuvant treatments in patients who undergo radical resection [15,52].

4. FH-Deficient RCC

FH-deficient RCC is characterized by the biallelic mutation/inactivation of the FH gene. It typically shows FH immunonegativity (loss) and/or S-(2-succino)-cysteine (2SC) immunopositivity on IHC, along with mixed histologic patterns and prominent eosinophilic macronucleoli observed under the microscope (Fig. 2J-L) [54-56].

Previously designated as hereditary leiomyomatosis and RCC (HLRCC) syndrome-associated RCC, this condition is an autosomal dominant disorder related to germline FH mutations. It may also be associated with a family history of skin and uterine leiomyomas [57-59]. However, since somatic biallelic alterations of the FH gene have been identified in patients with no family history of HLRCC, the term “FH-deficient RCC” has been designated in the 2022 WHO classification [60,61]. Similarly, in cases where the family history is unavailable, and the genetic status is unknown at the time of diagnosis, FH-deficient RCC is the preferred terminology. Nonetheless, the designation “HLRCC syndrome-associated RCC” remains acceptable for familial cases [55,60].

On microscopic examination, FH-deficient RCC is characterized by mixed histologic patterns, including tubulocystic and papillary architectures and high-grade nuclei with viral inclusion-like eosinophilic macronucleoli [54-56]. Owing to its heterogeneous high-grade histology, this entity has previously been described as “unclassified high-grade RCC,” “tubulocystic carcinomas with dedifferentiated foci,” “type 2 PRCC,” and “collecting duct carcinomas” [54-56].

The demonstration of germline/somatic mutation in FH is essential for diagnosing FH-deficient RCC. However, immunohistochemical evidence of FH deficiency, indicated by FH negativity and/or 2SC positivity on IHC, is also diagnostic. The histologic features mentioned above may be subtle or focal. Therefore, it is recommended that the immunohistochemical screening for FH and/or 2SC be used generously with a low threshold in any difficult-to-classify RCC cases [56]. FH IHC is highly specific (100%) but incompletely sensitive (87.5%–91%), while 2SC IHC is highly sensitive (97.7%–100%) but incompletely specific (91.7%) [56,62].

Owing to the possible germline FH mutations and its aggressive behavior with high metastatic potential, appropriate genetic counseling, and germline testing may be necessary for the patient and their family members [56]. This entity may respond better to combination therapy with the
epidermal growth factor receptor blocker erlotinib and anti-VEGF antibody bevacizumab or ICI monotherapies than to standard treatment [15,63].

5. SDH-Deficient RCC

Succinate dehydrogenase (SDH)-deficient RCC is characterized by the biallelic inactivation of SDH and negativity for succinate dehydrogenase complex iron sulfur subunit B (SDHB) on IHC. It typically shows bland cells with eosinophilic cytoplasm and pale, flocculent cytoplasmic inclusions on microscopic examination (Fig. 2M-O) [64,65].

SDH-deficient RCC involves the inactivation of any component of the SDH complex, typically owing to germline mutations. While SDHB is the most commonly mutated gene, mutations in SDHC, SDHA, and SDHD are also observed [64]. Germline mutations in SDH subunit genes are often associated with syndromic neoplasms, including pheochromocytoma-paraganglioma, gastrointestinal stromal tumor, and pituitary adenoma [64]. Negativity for SDHB on IHC is a reliable surrogate marker for SDH mutations, but it should only be interpreted as negative if there is strong, granular cytoplasmic staining in non-tumoral internal control cells [64]. Low-grade tumors have a low risk (11%) of metastasis, with surgery being curative, while high-grade tumors have a high risk (70%) of metastasis [64].

6. ALK-Rearranged RCC

ALK-rearranged RCC is characterized by ALK gene fusion, ALK positivity on IHC, and heterogeneous histology, featuring polygonal cells with eosinophilic cytoplasm, often showing striking vacuolization and intracytoplasmic mucin on microscopic examination (Fig. 2P-R) [66,67].

ALK-rearranged RCCs involve chromosomal translocations that result in ALK gene fusions at chromosome 2p23 with various partners, such as VCL, TPM3, EMLA, and STRN [67,68]. Positivity for ALK on IHC is a useful screening test, and confirmation of ALK rearrangement via break-apart FISH or sequencing can be diagnostic [69]. ALK-rearranged RCCs have been documented in young patients with sickle cell trait [66,67]. It is extremely rare; however, an accurate diagnosis is important because ALK-rearranged RCC may potentially benefit from ALK inhibitors [70,71].

7. SMARCB1-Deficient Medullary Carcinoma

SMARCB1-deficient medullary carcinoma is characterized by an infiltrative mass centered in the renal medulla on macroscopic examination, high-grade adenocarcinoma with extensive inflammatory cell infiltration on microscopic examination, SMARCB1 (INI1) negativity on IHC, and loss/inactivation of the SMARCB1 gene by molecular testing [72-74].

Formerly known as “renal medullary carcinoma,” this condition is commonly related to inactivation of the SMARCB1 gene at 22q11.23, typically through concurrent hemizygous loss and translocation or by homozgyous loss [72,74]. It is a rare entity, mainly occurring in young adults of African ancestry and sickle cell trait or sickle cell disease [72,74,75]. When there are no associated hemoglobinopathies, it is regarded as a subtype and designated as SMARCB1-deficient medullary-like RCC (Fig. 2S-U) [73].

Secondary SMARCB1 (INI1) deficiency has been observed in CCRCC with sarcomatoid and rhabdoid differentiation, collecting duct carcinoma, or FH-deficient RCC with secondary SMARCB1 loss. These cases should be diagnosed according to their underlying subtype [76-78]. SMARCB1-deficient medullary RCC is frequently metastatic at presentation, with a dismal prognosis. Patients with metastasis are typically treated with platinum-based chemotherapy as first-line therapy. However, alternative strategies are emerging, such as combining chemotherapy with proteasome and EHZ inhibitors [15,79,80].

CONCLUSIONS

The 2022 WHO classification of renal tumors may offer better precise prognostic insights, influencing appropriate management decisions across different RCC entities. Achieving this relies heavily on accurately classifying RCC pathologically. Most morphologically defined RCC cases can be diagnosed directly through macroscopic and microscopic examination, but molecularly defined RCCs pose challenges in classification. However, in most instances, these can be diagnosed through IHC analysis, with the exception
of ELOC-mutated RCCs. In cases of molecularly defined RCC, the selection of the panel of IHC assays to be tested should be based on the histologic features. It is important to understand that the interpretation of IHC follows a hierarchy of importance, considering not only the biological relevance but also the sensitivity and specificity of each antibody. When necessary, molecular tests, including FISH, NGS, and RNA sequencing, can be utilized for a definitive diagnosis.

A schematic diagram has been provided for cases where the diagnosis is challenging based on histologic findings alone and those that require further testing (Fig. 3). This diagram presents only key diagnostic factors; however, additional IHC stains or molecular diagnostics can be used as needed.

**NOTES**

- **Author Contribution:** Conceptualization: BA, CS, YMC; Data curation: JJ, YIL, JMP, SYY; Formal analysis: YIL; Funding acquisition: YMC; Methodology: YIL; Project administration: JMP, SYY; Visualization: JJ; Writing - original draft: BA, YMC; Writing - review & editing: BA, CS.

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