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Review

WHO 2022 Classification of Kidney Tumors: what is relevant? An update and future novelties for the pathologist

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Summary
Classification systems reflect our technical abilities in the investigation of tumors and our current theories on tumor development. Herein, by providing a historical perspective on the evolution of classifying renal tumors, we assess the current WHO classification highlighting the novelties and the implications of these changes in daily clinical practice.

Key words: classification, WHO, renal cell carcinoma, molecular, clinical relevance, therapy, management

Historical perspective

The classification of renal cell tumors has changed in the last five decades. The previous classifications have been based on various clinical-pathological findings, including cytological (clear cell and chromophobe renal cell carcinoma) or architectural (papillary renal cell carcinoma) characteristics, tumor location (collecting duct and renal medullary carcinomas), correlations with underlying renal disease (acquired cystic disease-associated renal cell carcinoma), the similarity of tumors to embryological structures (metanephric adenoma), or a specific hereditary background (hereditary leiomyomatosis and renal cell carcinoma syndrome associated renal cell carcinoma) [1-3] (Fig. 1).
While the two most important categories of renal tumors in adults were only carcinoma and angiomyolipoma acknowledged in the second series of Armed Forces Institute of Pathology fascicle (AFIP) published in 1975 [4], the modern era of renal tumor classification started in 1996 with a consensus of an expert group held in Heidelberg [5]. It was the first time that genetic alterations were considered with morphological criteria and that the sarcomatoid features were recognized as dedifferentiation of all types of renal cell carcinoma with prognostic implication rather than a histotype *per se*. Moreover, the introduction in this consensus of unclassified renal cell carcinoma as a diagnostic category has afterward led to the recognition of specific entities initially belonging to it. In fact, the result of this process was evident in the 2004 World Health Organization (WHO) [1] classification in which several important different tumors were introduced such as mucinous tubular and spindle renal cell carcinoma, medullary renal cell carcinoma, epithelioid angiomyolipoma and, for the first time, a tumor defined based on a specific molecular alteration: Xp11 translocation renal cell carcinoma.

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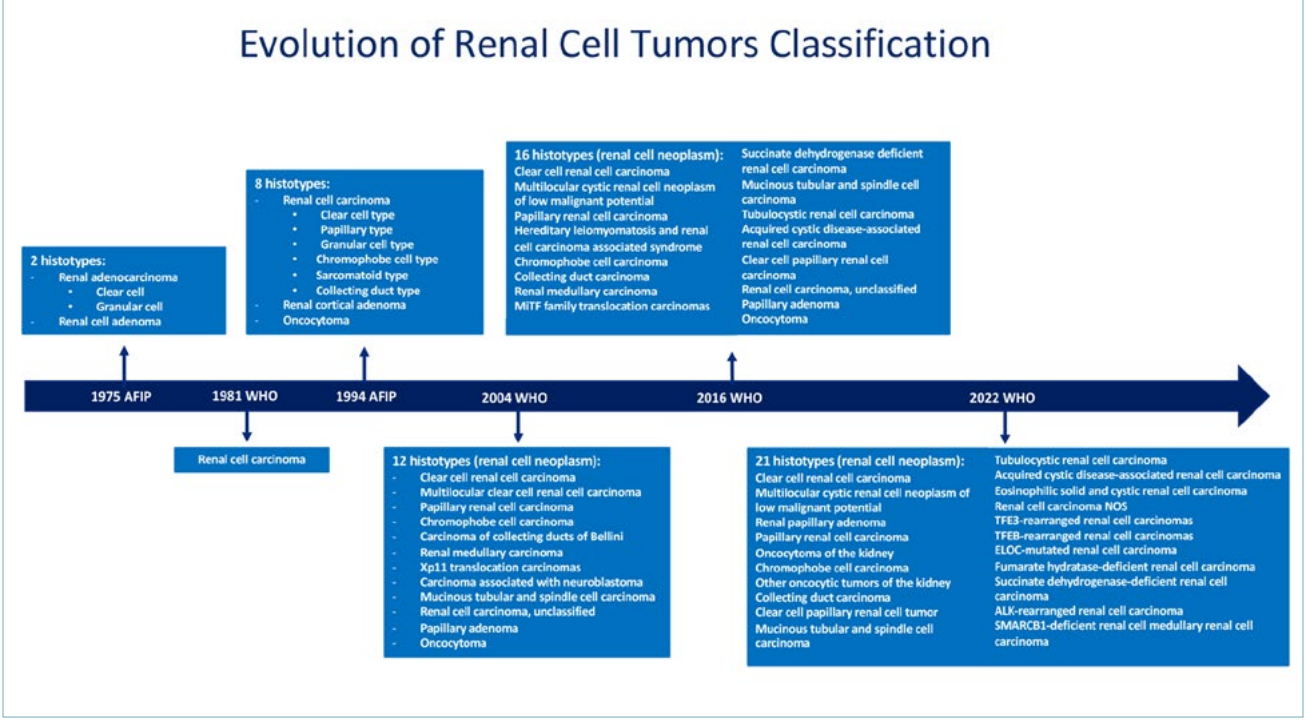

Figure 1. Flow diagram showing the evolution of the classification of renal cell tumor, with progressive implementation of newly recognized entities in the different editions of the AFIP and WHO blue books.

The recognition of peculiar tumors in end-stage renal disease is one of the main novelties in the 2016 WHO classification [2]. While acquired cystic disease renal cell carcinoma arose only in this clinical setting [6], clear cell papillary renal cell carcinoma has been observed in sporadic scenarios [7] and became the fourth kind of carcinoma occurring in the kidney [8]. On the other hand, new molecular-driven histotypes were introduced such as MiTF family translocation carcinoma, succinate dehydrogenase (SDH)-deficient renal cell carcinoma, and hereditary leiomyomatosis and renal cell carcinoma syndrome associated renal cell carcinoma [2]. The relevance of molecular data for the improvement of the kidney tumor classification has been confirmed in the last WHO classification in which a category of molecularly defined renal cell carcinoma has been introduced, including TFE3-rearranged renal cell carcinoma, TFEB-rearranged, and TFEB-amplified renal cell carcinoma, FH-deficient renal cell carcinoma, SDH-deficient renal cell carcinoma, ALK-rearranged renal cell carcinoma, ELOC (formerly TCEB1)-mutated renal cell carcinoma and SMARCB1 (INI1)-deficient renal cell carcinoma [3]. Finally, recent studies have described several renal tumors with oncocytic features and *mTOR* gene pathway alterations. Among those, eosinophilic solid and cystic renal cell carcinoma is the only one nowadays recognized as a nosographic entity [9].

Since the qualities of a good classification system are based on clinical relevance, histopathological clues to guide the differential diagnosis, inter- and intraobserver reliability, and ultimately feasibility of the diagnosis in different worldwide laboratories [10], the question is: what is relevant in the WHO 2022 classification of renal tumors?

We are aware that expanding a classification is important from a biological point of view for academic advancement; however, in daily routine practice, the relevance mainly concerns the following aspects: prognosis, clinical management of patients and their families, and therapy.

Changes relevant in prognosis

Clear cell papillary renal cell tumor

Firstly recognized in end-stage kidney disease [6], clear cell papillary renal cell carcinoma was later described in the sporadic setting as well [7]. After the identification of this entity in the sporadic scenario, it was initially chosen to designate this neoplasm as a carcinoma for several reasons: 1) in 2006, Tickoo and coauthors

named the tumor as carcinoma in end-stage kidney disease; 2) two years later, when it was observed in the sporadic setting, the data regarding of follow-up and knowledge of biology underling were limited; 3) the distinction with low-grade clear cell renal cell carcinoma was subtle, especially when a tubular pattern was observed [11]. However, the absence of *VHL* mutation and 3p loss by gene expression profiling analysis in those tumors supported their distinction from low-grade clear cell renal cell carcinoma [12,13].

Grossly, these neoplasms are usually small well-circumscribed encapsulated masses sometimes with cystic changes. Conversely to clear cell renal cell carcinoma, when the cystic changes are prominent the color is not yellow but grayish and translucent. Morphologically, the tumor is made up of clear cells arranged in a variable mixture of cystic, branched tubular, solid, and papillary components (Fig. 2). Characteristically, the nuclei are oriented towards the lumen of the tubules and papillae. The immunohistochemical phenotype, characterized by diffuse cytokeratin 7 staining, "cup-shaped" expression of carbonic anhydrase 9, GATA3 immunolabelling, and negativity for AMACR and CD10, is distinctive and helpful to properly identify this tumor, even in biopsy samples [6,7,14,15]. Based on the indolent behavior without, to date, evidence of any recurrent or metastatic case, it was decided to change the name of this neoplasm to tumor rather than carcinoma[3].

TFE3 and TFEB-rearranged renal cell carcinoma

Previously known as MiT family translocation renal cell carcinomas, TFE3-rearranged and TFEB-rearranged renal cell carcinomas are separate entities in the current classification. Despite both being initially recognized in childhood [16,17], they can occur in

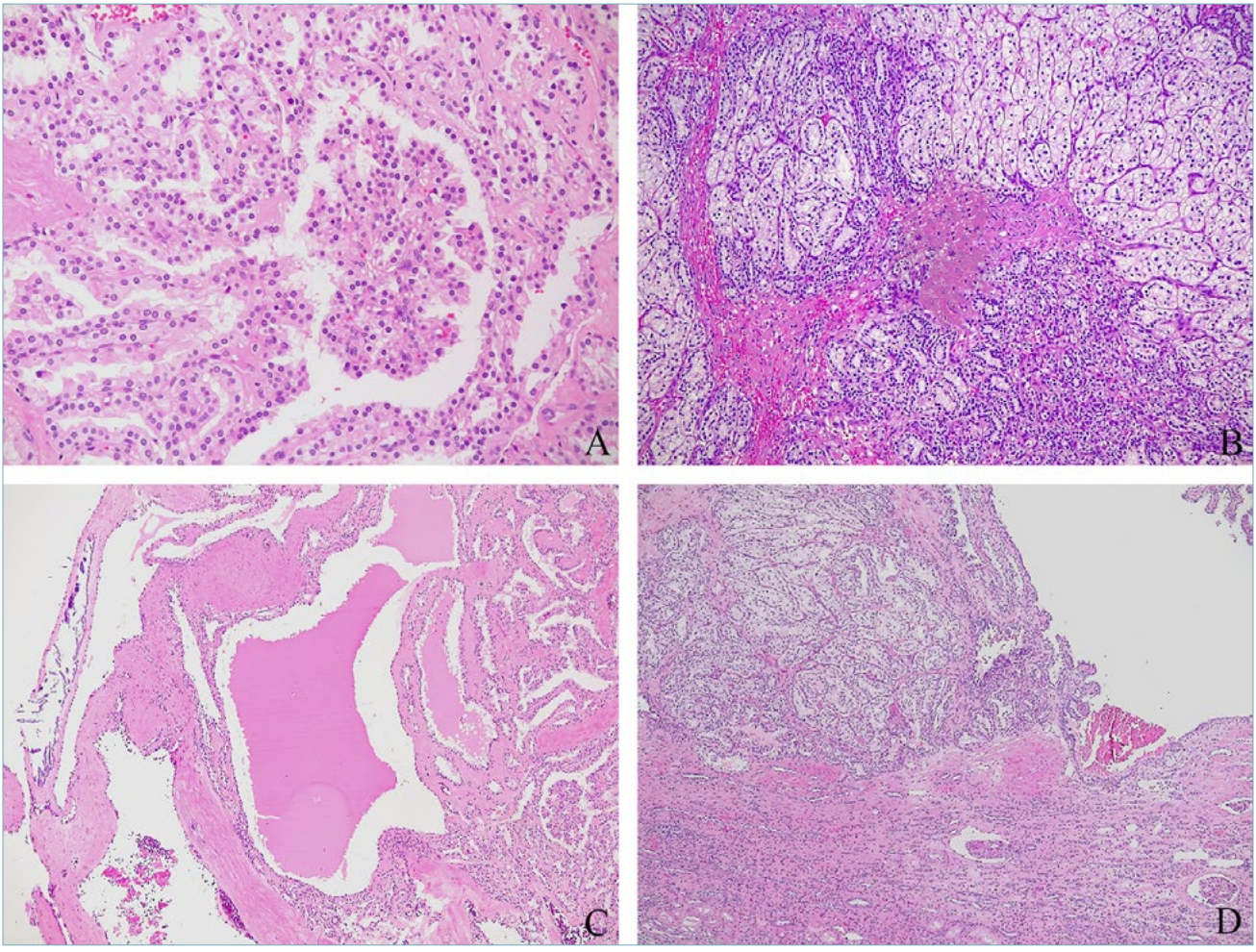

Figure 2. Several possible growth pattern of clear cell papillary renal cell tumor: papillary (A), tubular (B), cystic (C), tubular and cystic (D).

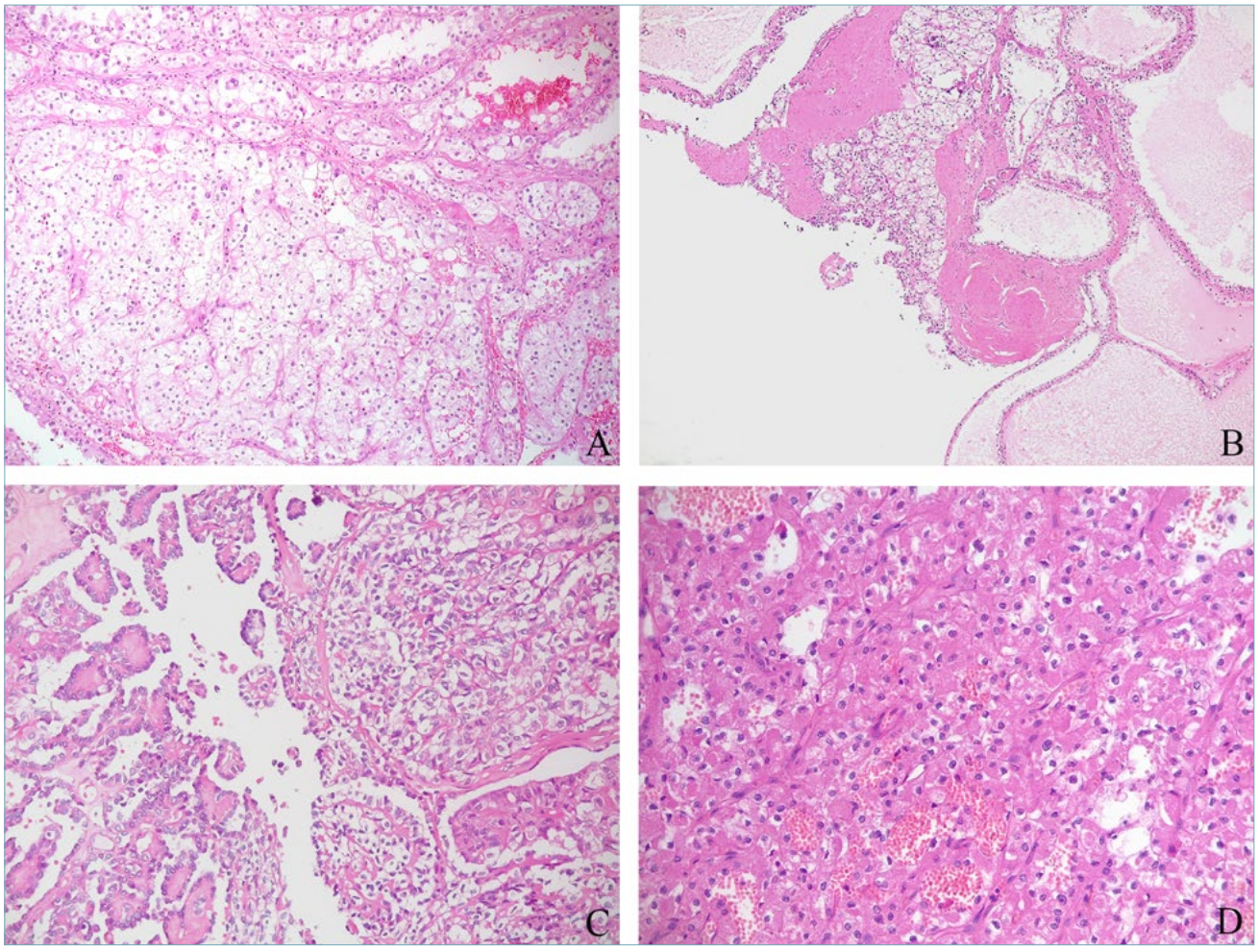

Figure 3. Various challenging morphological appearances of *TFE3* and *TFEB*-rearranged renal cell carcinoma, respectively mimicking clear cell renal cell carcinoma (A), clear cell papillary renal tumor (B), papillary renal cell carcinoma (C), and renal oncocytoma (D).

adults as well [18]. These neoplasms harbor molecular rearrangements involving different genes including the melanocytic inducing transcription factor (MITF), *TFE3* gene, and *TFEB* gene, respectively. Although a spectrum of morphological features has been reported in both entities (Fig. 3), TFE3-rearranged renal cell carcinoma is more commonly a papillary tumor with epithelioid clear cells and psammoma bodies [18], whereas TFEB-rearranged renal cell carcinoma is usually characterized by a distinctive biphasic appearance made up of larger epithelioid cells and smaller cells clustered around eosinophilic spheres formed by basement membrane material [19]. By immunohistochemistry, both tumors generally underexpress epithelial markers,TFE3-rearranged renal cell carcinoma stains for cathepsin K in roughly half of the cases, and occasionally for melanogenesis markers (Melan-A and HMB45) [20]. On the other hand, these latter markers and cathepsin K are constantly positive in TFEB-rearranged renal cell carcinoma [21-23]. In either TFE3 or TFEB-rearranged renal cell carcinoma, the identification of gene rearrangement by FISH assays or RNA-sequencing [24,25] is considered the gold standard to confirm diagnosis. Concerning clinical behavior, TFE3-rearranged renal cell carcinomas are aggressive in up to 50% of cases, while TFEB-rearranged renal cell carcinoma often displays an indolent clinical course. Furthermore, among renal cell carcinoma with *TFEB* gene alteration, TFEB-amplified renal cell carcinoma is a high-grade renal cell carcinoma characterized by an aggressive clinical course [26-28].

In conclusion, due to different translocation genes involved, different morphology, and most important different behavior, TFE3-rearranged and TFEB-rear-

ranged renal cell carcinomas are currently considered separate entities.

Changes relevant for clinical management of patients and their family

SDH deficient renal cell carcinoma

Succinate dehydrogenase (SDH)-deficient renal cell carcinoma is a rare neoplasm characterized by a favorable prognosis [29]. Germline mutations of any one of the *SDH* genes are found in the majority of the patients harboring those tumors. Conversely to the paradigm of hereditary tumors, which are usually multiple and bilateral masses where the radiologist is the first to suggest the diagnosis, SDH-deficient renal cell carcinoma is more commonly a solitary tumor and, for this reason, the pathologist could be the first to suspect a hereditary form. Histologically, the tumor is composed of low-grade eosinophilic cells arranged in a nested growth pattern with frequent eosinophilic flocculent cytoplasmic inclusions (Fig. 4a). Loss of immunohistochemical label of SDH, as a surrogate of *SDH* gene mutation, has been demonstrated to be a useful stain to screen for SDH deficiency [30]. Patients with a germline mutation can also develop other tumors such as pituitary adenoma, gastrointestinal stromal tumor (GIST), and paraganglioma/pheochromocytoma [31]. Therefore, the role of pathologists to properly recognize these tumors is crucial for patients and their relatives to encourage genetic counseling. Because of the indolent behavior, rather than looking for metastasis the follow-up of this condition mainly deals with early identification of the other neoplastic conditions characterizing the syndrome. To note, SDH-deficient

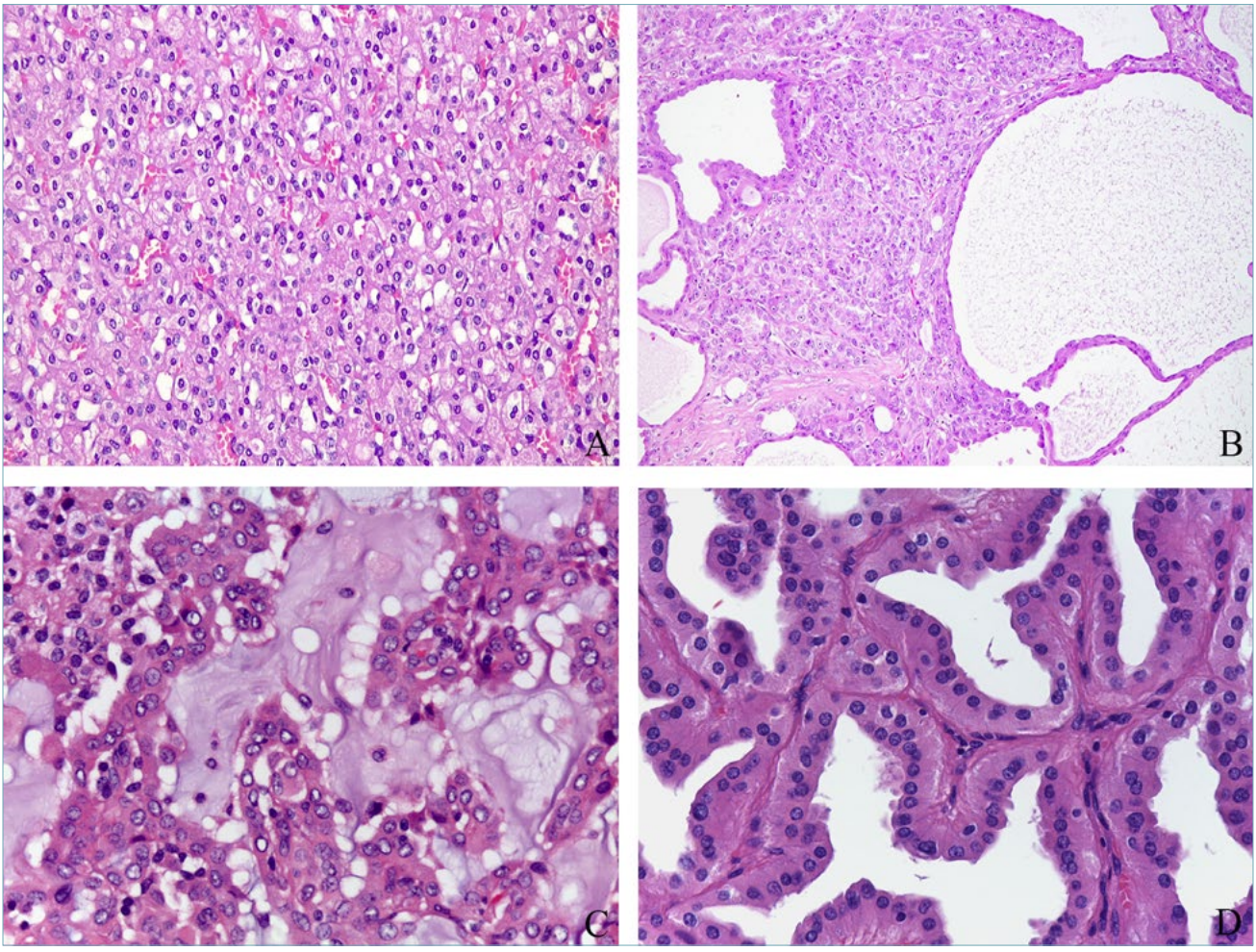

Figure 4. Molecularly defined renal cell tumors: succinate dehydrogenase deficient renal cell carcinoma (A), fumarate hydratase deficient renal cell carcinoma (B), ALK-rearranged renal cell carcinoma (C), papillary neoplasm with inverted polarity (D).

renal cell carcinoma may be misinterpreted with low-grade FH-deficient renal cell carcinoma, representing a challenging differential diagnosis.

FH deficient renal cell carcinoma

Fumarate hydratase (FH) - deficient renal cell carcinomas are highly aggressive early metastasizing tumors carrying mutations, mainly germline, in the *FH* gene located at chromosome 1q42. In the beginning, in the 2004 WHO classification [1] they were included among papillary renal cell carcinoma type 2. They were then recognized as a distinctive entity in the 2016 WHO classification where they were designated as hereditary leiomyomatosis and renal cell carcinoma syndrome associated renal cell carcinoma [2], highlighting the hereditary setting. The decision to change the denomination in the current WHO classification is the result of the awareness that roughly 20% of these tumors are sporadic [32]. As SDH-deficient renal cell carcinoma, loss of FH protein expression by immunohistochemistry allows the pathologist to identify this entity in the majority of cases.

Microscopically, FH-deficient renal cell carcinoma was originally described as a tumor characterized by a papillary architecture. However, actually, multiple admixed architectural patterns (papillary, solid, tubulocystic, and cystic) have been observed (Fig. 4b). Voluminous eosinophilic cells with high-grade nuclear and nucleolar features are characteristic features. Nevertheless, recently, low-grade FH-deficient renal cell carcinoma cases have been reported [33]. Those tumors are composed of cytologically low-grade cells with homogeneous architectural patterns mimicking SDH-deficient renal cell carcinoma, oncocytoma, and, in general, low-grade oncocytic tumors. Conversely to FH-deficient renal cell carcinoma characterized by an aggressive outcome, the low-grade patterns show a more favorable prognosis.

As SDH-deficient renal cell carcinoma, FH-deficient renal cell carcinoma is usually a single solitary mass in the kidney even in the hereditary setting. In these latter cases, cutaneous and uterine leiomyomas are often associated with renal tumors and the role of pathologists to properly recognize them is crucial to encourage genetic counseling of patients and their relatives.

Generally speaking the recommendations for genetic counseling according to the American Urological Association Guidelines are testing all patients ≤ 46 years of age with renal cancer, those with multifocal or bilateral renal masses, or whenever: 1) the personal or family history suggests a familial renal cancer syndrome; 2) there is a first or second-degree relative with a history of renal cell carcinoma (even if a kidney cancer has not been observed); or 3) whenever pathological examination demonstrates histology suggestive for such a syndrome. (https://www.auanet.org//membership/publications-overview/auanews/all-articles/2022/may-2022/aua-guidelines-renal-mass-and-localized-renal-cancer-evaluation-management-and-followup).

Changes relevant for therapy

ALK-rearranged RCC

Anaplastic lymphoma kinase (ALK) - rearranged renal cell carcinoma is a tumor harboring chromosomal translocations of the *ALK* gene located at chromosome 2p23 [9,34]. It is a rare tumor, as roughly 40 cases have been reported so far without any gender predominance, in both children and adults. Numerous gene fusion partners have been reported: when vinculin (VCL)-ALK gene fusion occurs, they affect young patients with sickle cell trait, and show distinctive morphology. For this reason, this tumor has been proposed as the "eighth sickle cell nephropathy." Since several morphologies can be observed in this type of tumor, the definitive diagnosis requires the demonstration of *ALK* gene rearrangement by FISH or immunohistochemistry. However, mucinous background, intracytoplasmic mucin, and myxoid changes have been reported in a subset of cases and can be helpful clues in recognizing these rare tumors (Fig. 4c).

Follow-up of the reported cases is limited to date; however, as 30% of patients demonstrated an aggressive clinical course, they may benefit from targeted ALK inhibitors as a potentially effective treatment [35].

Changes that are biologically relevant but less relevant for prognosis, therapy, and clinical management

Papillary renal cell carcinoma

Papillary renal cell carcinoma is the second most common neoplasm arising in the kidney. It is a molecularly heterogeneous entity, ranging from low-grade to high-grade tumors. Traditionally regarded as type 1 and type 2 papillary renal cell carcinoma [36], the former is a quite uniform subgroup on both morphological features and molecular findings (*MET* gene alterations). On the other hand, the latter is characterized by different genetic alterations so that it has been hypothesized that different tumor entities were included in this initially designed category. For this reason, the diagnostic criteria for type 2 papillary renal cell carcinoma need to be re-evaluated and the subclassification into type 1 and type 2 is no longer recommended [37].

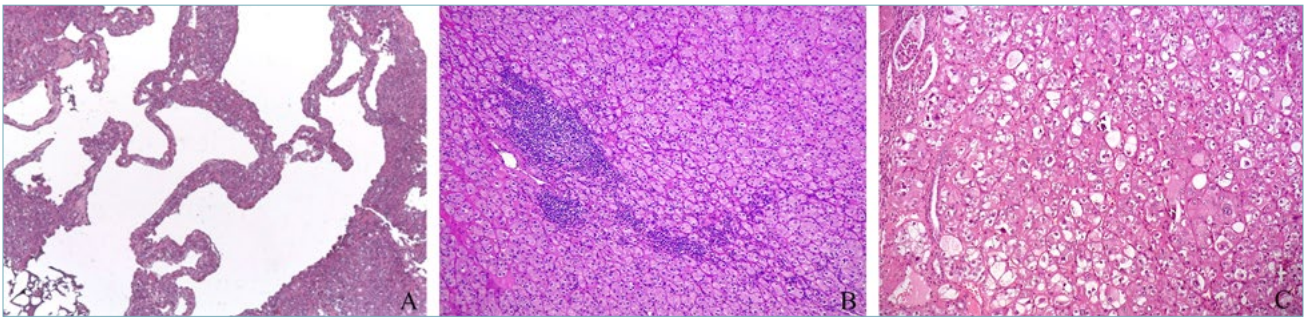

Figure 5. Oncocytic renal tumors: eosinophilic solid and cystic renal cell carcinoma (A), low-grade oncocytic tumor (LOT) (B), eosinophilic vacuolated tumor (EVT) (C).

Papillary neoplasm with inverted polarity

Papillary neoplasm with inverted polarity is a proposed entity in the new WHO classification currently included as a subtype of papillary renal cell carcinoma with pathogenic mutations of the *KRAS* gene [38]. It is characterized by papillary or tubulopapillary structures covered by a single layer of eosinophilic cells with finely granular cytoplasm and apically located round nuclei with inconspicuous nucleoli [39] (Fig. 4d). Immunohistochemically the expression of GATA3 and, variably, of AMACR suggest that these neoplasms show a differentiation toward distal nephron rather than the proximal tubules [40]. The low-grade nuclear feature is reflected in the indolent clinical behavior.

Oncocytic tumors

We are aware that the current classification of oncocytic tumors is complex, difficult either for clinicians or pathologists to adopt.

Among these neoplasms, eosinophilic solid and cystic renal cell carcinoma has been introduced in the current WHO classification as a new entity [3]. As the name states, it is made up by cells with eosinophilic cytoplasm arranged in a solid and cystic architecture [41] (Fig. 5a). Focal or diffuse immunostaining for cytokeratin 20 and cathepsin K is a characteristic feature [42]. Although biallelic losses or mutations in the *TSC1*/*TSC2* genes have been identified in the majority of cases, only a few are associated with tuberous sclerosis [43]. This molecular data was interesting one since it was the first renal epithelial tumor identified to harbor *mTOR* gene pathway alteration [44]. Moreover, this finding may open new possible therapeutic approaches (mTOR inhibitors), even though only few metastatic cases have been recorded so far.

Other tumors with eosinophilic cells and somatic inactivating mutations of *TSC2* gene or activating mutations of mTOR as the primary molecular alteration have been subsequently described. Low-grade oncocytic tumor (LOT) [45,46] and eosinophilic vacuolated tumor (EVT) [47-49] share eosinophilic cells with regular nuclear membranes mainly arranged in an alveolar pattern (Figs. 5b, 5c). While the the former is characterized by few nuclear features, the latter typically display nucleolar prominence. Both neoplasms are usually small and solitary, arising in a sporadic setting with an indolent clinical behavior. These tumors show morphological, molecular, and clinical overlaps and, albeit the distinction is biologically relevant, in the daily routine practice their accurate distinction does not seem to imply any different management. Therefore, in the current WHO classification they are designated as "oncocytic renal neoplasms of low malignant potential NOS".

Conclusions

In conclusion, the new WHO classification reveals an increasing complexity. The changes and novel implications include: i) distinguishing clear cell papillary renal cell tumor from clear cell renal cell carcinoma due to the indolent behavior of the former; ii) identifying FH-deficient and SDH-deficient renal cell carcinoma for the hereditary implications; iii) recognizing ALK-rearranged renal cell carcinoma for possible targeted therapy.

Finally, the low-grade eosinophilic neoplasia group includes several biologically different tumors but so far sharing the same indolent clinical outcome. On the other hand, the academic position should avoid "lumping" category for better comprehension of oncocytic renal tumors using the descriptive term oncocytic renal neoplasm of low malignant potential EVT type or LOT type.

Conflicts of interest

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization: AC and GM. Methodology: AC and GM. Formal analysis and investigation: AC and SM. Writing/original draft preparation: AC and GM. Writing/review and editing: SM and MB. Supervision: GM.

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