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Review - Kidney Cancer

2004 WHO Classification of the Renal Tumors of the Adults

Antonio Lopez-Beltran [a,*], *Marina Scarpelli* [b], *Rodolfo Montironi* [b], *Ziya Kirkali* [c]

[a] *Department of Pathology, Reina Sofia University Hospital and Cordoba University Medical School, Cordoba, Spain*
[b] *Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region, Ancona, Italy*
[c] *Department of Urology, Dokuz Eylul University School of Medicine Izmir, Turkey*

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Abstract

Background: The recently introduced 2004 World Health Organisation (WHO) classification of the adult renal epithelial neoplasms is meant to replace the previous 1998 WHO classification.
Methods and results: The 2004 WHO classification is based on pathology and genetic abnormalities. The description of categories has been expanded to improve their recognition and new diagnostic categories are included. Emphasis has been placed on defining familial renal cancer, carcinoma associated with Xp11 translocations, carcinoma associated with neuroblastoma, multilocular cystic renal cell carcinoma, tubular, mucinous and spindle cells carcinoma; and mixed epithelial and stromal tumour. The potentially aggressive epithelioid angiomyolipoma is recognised.
Conclusions: Recognising these categories may have important implications in patients' clinical management.

* Corresponding author. Unit of Anatomical Pathology, Faculty of Medicine, Avda. Menendez Pidal s/n, E-14004, Cordoba, Spain. Tel. +34 957 218993; Fax: +34 957 218229.
E-mail address: em1lobea@uco.es (A. Lopez-Beltran).

1. Introduction

The 2004 World Health Organisation (WHO) classification is adopted in the book *Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs*, i.e., one of the ''Blue Books'' of the new series of WHO Classification of Tumors (Table 1) [1]. This classification summarises the achievements and contributions of previous classificationsly, in particular the Mainz (1986) and Heidelberg (1997) classifications [2,3]. It describes categories and entities based on pathological and genetic analyses [1].

This review, based on presentations made in recent meetings, gives an overview on the latest WHO classification of adult kidney tumors.

2. Familial renal cancer

Inherited or familial predisposition to renal neoplasia is present in less than 4% of renal tumors [1]. Table 2 lists known inherited syndromes that predispose to renal tumors as presented in the 2004 WHO classification [4–11]. Each of these

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Table 1 – WHO classification of kidney tumors [1]

- Familial renal cancer
  - Renal cell tumors
    - Malignant
      - Clear cell renal cell carcinoma
      - Multilocular clear cell renal cell carcinoma
      - Papillary renal cell carcinoma
      - Chromophobe renal cell carcinoma
      - Carcinoma of the collecting ducts of Bellini
      - Renal medulary carcinoma
      - Xp11 translocation carcinomas
      - Carcinoma associated with neuroblastoma
      - Mucinous tubular and spindle cell carcinoma
      - Renal cell carcinoma unclassified
    - Benign
      - Papillary adenoma
      - Oncocytoma
  - Metanephric tumors
    - Metanephric adenoma
    - Metanephric adenofibroma
    - Metanephric stromal tumors
  - Mixed mesenchymal and epithelial tumors
    - Cystic nephroma
    - Mixed epithelial and stromal tumor
    - Synovial sarcoma
  - Nephroblastic tumors
    - Nephrogenic rests
    - Nephroblastoma
    - Cystic partially differentiated nephroblastoma
  - Neuroendocrine tumors
    - Carcinoid
    - Neuroendocrine carcinoma
    - Primitive neuroectodermal tumor
    - Neuroblastoma
    - Phaeochromocytoma
  - Other tumors
    - Mesenchymal tumors
    - Haematopoietic and lymphoid tumors
    - Germ cell tumors
    - Metastatic tumors

syndromes predispose to a distinct histologic type of renal cell carcinoma (RCC) or other kidney tumor. From the clinical point of view hereditary renal cancers show a tendency to be multiple and bilateral, may have a family history, and present at an earlier age than the non familial and non hereditary renal neoplasms [1].

3. Malignant renal cell tumors

3.1. *Clear cell RCC*

All kidney tumors of the clear cell type of any size are considered malignant according to 2004 WHO classification, a proposal also found in the 1998 WHO classification [1,12]. Most clear cell RCC are solitary cortical neoplasms that occur with equal frequency in either kidney. Multicentricity (4%) and bilaterality (0.5 to 3.0%) may be seen [1,13]. The size is variable, but the frequency of small lesions increases due to imaging techniques [15]. Clear cell RCC is typically golden yellow. Necrosis, cystic degeneration, hemorrhage, calcification, ossification, extension into the renal vein and sarcomatoid change may occur [14,15]. The term ''granular cell'' indicates RCC with acidophilic cytoplasm, a specific tumor category in the 1998 WHO classification [12]. RCCs with this morphology are now included among the clear cell type based in the absence of genetic and clinical differences between both types [1]. Microvascular invasion might be a relevant clinical prognostic parameter for low clinical stage RCC and could be the only independent predictor of disease-recurrence after radical surgery [16,17]. Sarcomatoid change may be seen in all types of RCC with no evidences supporting that RCC develops ''de novo'' as sarcomatoid carcinoma, therefore the 2004 WHO classification by contrary to the previous WHO classification does not consider it as an entity [12,18] but rather as a progression of any RCC [18,19]. Clear cell RCC has a worse prognosis when compared with chromophobe or papillary subtypes. However, the response

Table 2 – Familial RCC: syndromic and non-syndromic presentation

Syndrome	Gene	Tumor
Von Hippel-Lindau (VHL) [4]	VHL (3p25)	Clear cell
Tuberous Sclerosis [5]	TSC1, TSC2	Angiomyolipoma, clear cell, other
Constitutional chromosome 3 translocation [6]	Responsible gene not found*	Clear cell
Familial renal carcinoma [7]	Gene not identified	Clear cell
Hereditary PRCC [8]	c-MET	Papillary type 1
Birt-Hogg-Dube (BHD) [9]	BHD	Chromophobe**
Familial oncocytoma [10]	Partial or complete loss of multiple chromosomes	Oncocytoma
Hereditary leiomyoma-RCC [11]	FH	Papillary type 2

* VHL gene mutated in some families.
** Renal oncocytomas, hybrid oncocytic and clear cell carcinomas may occur.

Table 3 – Main clinico-pathologic and genetic features of adult RCC according to the 2004 WHO classification

RCC subtype	Incidence	Development	Cell/tissue characteristics	Growth pattern	Prognosis	Genetic
Clear cell	75%	Solitary, rare multicentric or bilateral	clear cytoplasm; cells with eosinophilic cytoplasm occassionaly	Solid, tubular, cystic, rare papillae	Aggressiveness according to grade, stage and sarcomatoid change	−3p, +5q22, −6q, −8p, −9p, −14q
Multilocular cystic	Rare	Solitary, rare bilateral	clear cytoplasm, small dark nuclei	Cystic, no solid component	No progression or metastases	VHL gene mutation
Papillary	10%	Multicentric, bilateral or solitary	Type 1 (basophilic) or type 2 (eosinophilic)	Tubulo-papillary, solid	Aggressiveness according to grade, stage and sarcomatoid change	+3q, +7, +8, +12, +16, +17, +20, −Y
Chromophobe	5%	Solitary	Pale or eosinophilic granular cytoplasm	Solid	10% mortality	−1, −2, −6, −10, −17, −21, hypodiploidy
Collecting ducts of Bellini	1%	Solitary	Eosinophilic cytoplasm	Irregular channels	Aggressive, 2/3 of patients die within two years	−1q, −6p, −8p, −13q, −21q, −3p (rare)
Medulary	Rare	Solitary	Eosinophilic cytoplasm	Reticular pattern	Mean survival of 15 weeks after diagnosis	Unknown
Xp11 translocation	Rare	Solitary	Clear and eosinophilic cells	Tubulo-papillary	Indolent	t (X; 1) (p11.2; q21), t (X; 17) (p11.2; q25), Other
After neuroblastoma	Rare	Solitary	Eosinophilic cells with oncocytoid features	Solid	Related to grade and stage	Allelic imbalance at 20q13
Mucinous tubular and spindle cell	Rare	Solitary	Tubules, extracellular mucin and spindle cells	Solid	Rare metastases,	−1, −4, −6, −8, −13, −14, +7, +11, +16, +17
Unclassified	4%-to-6%	Solitary	Variable, sarcomatoid	Solid	High mortality	Unknown

rate to systemic therapy is higher than other histological types [1,17].

Fuhrman nuclear grade after stage is the most important prognostic predictor in RCC [14,15,19]. Sporadic clear cell RCC displays frequent chromosome 3p losses (Table 3) [1].

3.2. *Multilocular cystic renal cell carcinoma (MCRCC)*

This is a tumor with excellent outcome and entirely composed of cysts of variable size separated from the kidney by a fibrous capsule (Fig. 1) [1]. The cysts are lined by a single layer of clear to pale cells but occasionally shows a few small papillae [1]. The septa are composed of fibrous tissue that may have epithelial cells with clear cytoplasm that resemble those lining the cysts. Cases with expansive nodules are excluded [1]. VHL gene mutations in MCRCC supports its classification as a type of clear cell RCC. There is a male predominance of 3:1 with age ranging 20 to 76 years [1]. No progression of MCRCC has been observed. MCRCC was considered a type of cyst-associated RCC in the previous WHO classification, but the diagnostic criteria and its good prognosis has been noticed in the current WHO classification that consider it a specific entity.

3.3. *Papillary renal cell carcinoma (PRCC)*

PRCC has a less aggressive clinical course than clear cell RCC [1–20]. PRCC has variable proportions of papillae and may be bilateral or multifocal with frequent hemorrhage, necrosis and cystic degeneration. The papillae contain a fibrovascular core with aggregates of foamy macrophages, calcified concretions and frequent hemosiderin granules [1–20]. Cellular type 1 and type 2 tumors have been recognised with papillae covered by small cells with scanty cytoplasm arranged in a single layer in type 1, and tumor cells of higher nuclear grade, eosinophilic cytoplasm and pseudostratified nuclei in type 2 (Fig. 1) [20]. This terminology is preferred in the current WHO classification, to previous terms such as basophilic (type 1) or eosinophilic (type 2) chromophilic PRCC in previous classifications. Prognostic differences between type 1 and 2 categories and a better definition of higher grade lesions (type 2) characterize the 2004 WHO classification. Associated sarcomatoid change is rare. Trisomy or tetrasomy 7, trisomy 17 and loss of chromosome Y are the earliest karyotypic change.

Fuhrman's tumor grade, stage, tumor proliferation and sarcomatoid change being correlated with outcome. Type 1 tumors have longer survival. Age

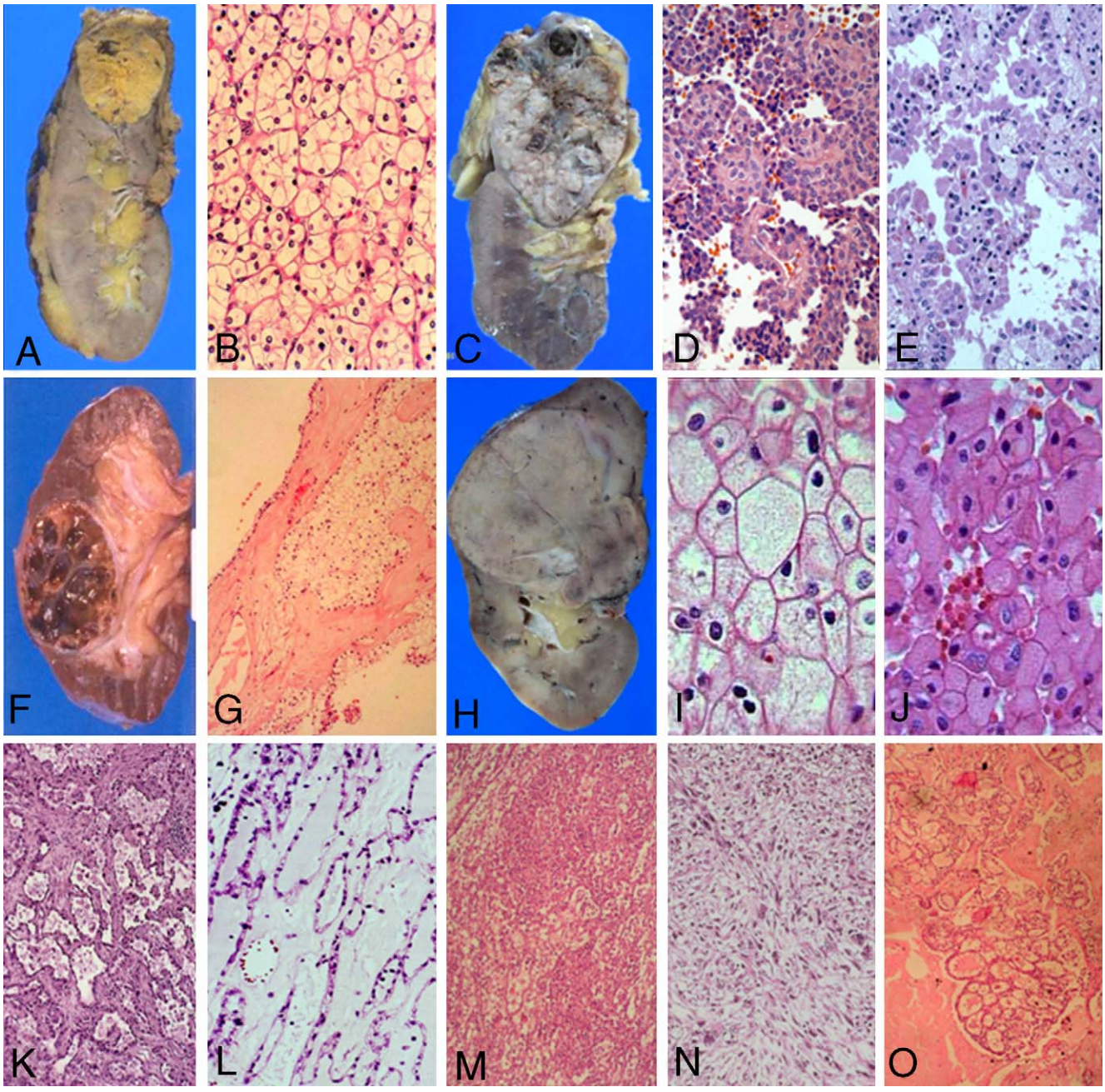

Fig. 1 – Clear cell RCC (A) gross and (B) microscopic features; PRCC (C) gross and microscopic features of (D) type 1 and (E) type 2; MCRCC (F) gross and (G) histological features; chromophobe RCC (H) gross and microscopic features of (I) the usual and (J) the eosinophilic types; unusual types of RCC including (K) CDC, (L) tubular, mucinous and spindle cell carcinoma and (M) medullary carcinoma; unclassified RCC showing pure (N) sarcomatoid carcinoma or (O) unrecognizable cell types.

and sex distribution of PRCC is similar to clear cell RCC [1–20].

3.4. *Chromophobe RCC*

Less aggressive than other RCCs, the chromophobe type is characterised by huge pale cells with reticulated cytoplasm and prominent cell membrane [1]. It accounts for 5% of renal epithelial tumors. Chromophobe RCC is solid and appears orange turning grey or sandy after fixation. The eosinophilic variant needs to be differentiated from oncocytoma. Sarcomatoid transformation is associated to aggressive disease [1]. Diffuse cytoplasmic Hale's iron colloid stain is characteristic. The relationship between oncocytoma and chromopho-

beRCC is still under investigation. Both are considered to be derived from the intercalated cell of the collecting duct, both have alterations of mitochondria, that is, rearrangement of mitochondrial DNA and increased mitochondria in oncocytoma and numerous mitochondria-derived microvesicles in chromophobe RCC, and both are frequently observed in the oncocytosis with or without BHD syndrome. In addition, there are reports of hybrid tumor composed of oncocytic and chromophobe elements. Therefore, oncocytoma might be the benign counterpart of chromophobe RCC. Loss of several chromosomes characterises chromophobe RCC (Table 3) [21–24]. Recognising occassional occurrence of metastases and 10% mortality rate represents an advance over the 1998 WHO classification. At diagnosis most patients are in the sixth decade, stage T1 or T2 (86%) and similar gender incidence [21–24].

3.5. *Carcinoma of the collecting ducts of Bellini*

Collecting duct carcinoma (CDC) is centraly located in the kidney, ranges 2.5 to 12 cm and typically shows a firm grey-white appearance. When small, origin within a medullary pyramid may be seen [1,25,26]. Most tumors are in advanced stage with metastasis at diagnosis [25,26]. The cells of CDC display Fuhrman 3 and 4 nuclear features. The immunophenotype has been expanded in the current WHO classification as compared with the previous one. CDC is positive for keratins of low (LMW) and high molecular weight (HMW) and vimentin, but molecular alterations of CDC are poorly understood [1]. The main differential diagnoses of CDC include type 2 PRCC, renal pelvic adenocarcinoma or urothelial carcinoma with glandular differentiation.

CDC accounts for <1% of renal malignancies and derives from the ''principal cells'' of the collecting duct. Mean patient age is 55 years with a slight male predominance. Upper tract imaging often suggests urothelial carcinoma and patients may have positive urine cytology [1,25,26].

3.6. *Renal medullary carcinoma*

It is a rapidly growing rare tumor of the renal medulla regarded as an aggressive variant of CDC [1] that was considered of renal pelvis origin in the 1998 WHO classification [12,27].

With few exceptions this tumor is seen in young male blacks with sickle cell trait (mean age 22 years), presenting with hematuria, flank pain, weight loss and palpable mass. Metastatic deposits may be the initial clinical evidence. Prognosis is poor [1].

3.7. *Renal carcinoma associated with Xp11.2 translocations/TFE3 gene fusions*

This type of RCC is defined by different translocations involving chromosome Xp11.2, all resulting in gene fusions involving the TFE3 gene (Table 3) [1,28]. This carcinoma predominantly affects children and young adults. The ASPL-TFE3 translocation carcinomas characteristically present at an advanced stage associated with lymph node metastases [28]. RCC associated with Xp11.2 translocations resemble clear cell RCC on gross examination and seems to have an indolent evolution, even with metastasis. The histopathologic appearance is that of a papillary carcinoma with clear cells and cells with granular eosinophilic cytoplasm (Fig. 2); [28]. These cells display nuclear immunoreactivity for TFE3 protein (Fig. 2) [28]. This group of tumors was not recognized in the previous WHO classification.

3.8. *Renal cell carcinoma associated with neuroblastoma*

A few cases of RCC arise in long term survivors of childhood neuroblastoma [1,29]. This group is heterogeneous, shows oncocytoid features and was not recognized in the previous WHO classification [1,12]. Allelic imbalances occur at the 20q13 locus. The prognosis is similar to other RCC [29]. Males and females are equally affected with a mean age of 13.5 years, being uni- or bilateral.

3.9. *Mucinous, tubular and spindle cell carcinoma*

This entity, included by the first time in the current WHO classification, is a low-grade carcinoma composed of tightly packed tubules separated by pale mucinous stroma and a spindle cell component. It seems to derive from the distal nephron [1,30]. This tumor has a combination of losses involving chromosomes 1, 4, 6, 8, 13 and 14 and gains of chromosome 7, 11, 16 and 17 [1]. There is a female predominance and the mean age is 53 years. It presents as circumscribed asymptomatic mass on ultrasound examination. One case had metastases [1].

3.10. *Renal cell carcinoma, unclassified*

In surgical series, it represents 4–6% of renal tumors and at presentation, most are of high grade and stage with poor survival [31]. Features which might place a carcinoma in this category include: (i) composites of recognised types, (ii) pure sarco-

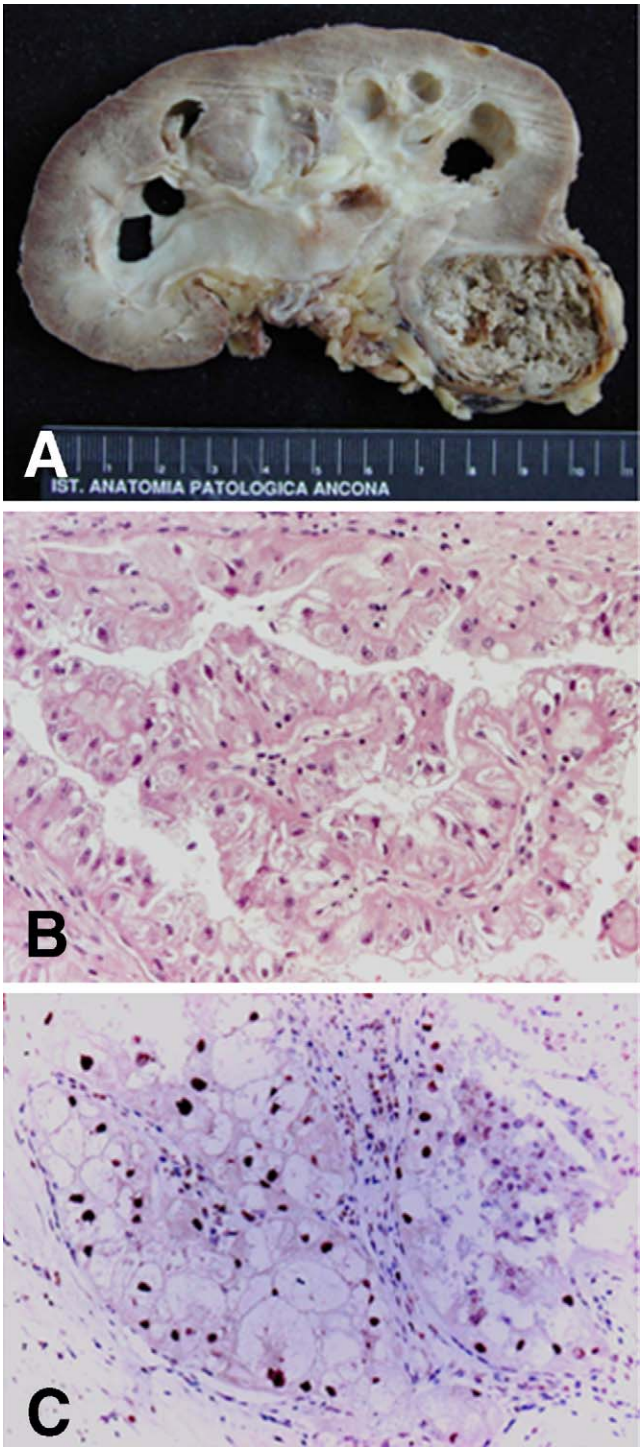

Fig. 2 – Renal cell carcinoma in a case of Xp.11 translocation showing (A) gross and (B) histological features with papillary architecture; (C) nuclear immunorreactivity for TFE-3 protein is characteristic.

matoid morphology without recognisable epithelial elements, (iii) mucin production, (iv) rare mixtures of epithelial and stromal elements, and (v) unrecognisable cell types [1].

4. Benign tumors

4.1. *Papillary adenoma*

Papillary adenoma (0.5 cm or smaller) is usually solitary, well circumscribed, greyish or white lesion in the renal cortex [1] that shows a tubulo-papillary architecture similar to cellular types 1 and 2 in PRCC (Fig. 3). Papillary adenoma is the most common neoplasm of the epithelium of the renal tubules. It is found in 10% to 40% of specimens and shows genetic alterations similar to PRCC [32].

''Renal adenomatosis'' refers to the occasional occurrence of multiple and/or bilateral papillary adenomas [1,32].

4.2. *Oncocytoma*

Oncocytoma is a benign renal epithelial neoplasm that derives from the intercalated cells [1,33]. It is well circumscribed, non-encapsulated, mahogany-brown or pale yellow with a central stellate scar (Fig. 3). The ''oncocyte'' has densely granular eosinophilic cytoplasm and round and regular nuclei. Mitotic activity and necrosis are uncommon [33]. Chromosomes 1 and/or 14 loss and alterations of mitochondrial DNA are frequent [23]. Oncocytoma comprises 3% to 9% of all primary renal neoplasms. Males are affected twice as often as females. Most are incidental and sporadic but few are symptomatic.

The term oncocytosis (oncocytomatosis) refers to a small subset of oncocytic tumors removed surgically because of a dominant mass that microscopically has the features of oncocytoma, although some may have either chromophobe RCC or hybrid features [33,34].

5. Metanephric neoplasms

This group includes metanephric adenoma, metanephric adenofibroma, and metanephric adenofibrosarcoma and represents a novelty in the current WHO classification [1,32].

Metanephric adenoma is an epithelial neoplasm that occurs in children and adults (fifth and sixth decades). There is a female preponderance, half are incidental but may present with polycythemia [32]. An exceptional case with metastasis has been reported. Patients range 5 months to 36 years and may coexist with Wilms tumor or RCC. A case of high grade sarcoma arising in association with metanephric adenoma (metanephric adenosarcoma) has been described [1,32]. Metanephric

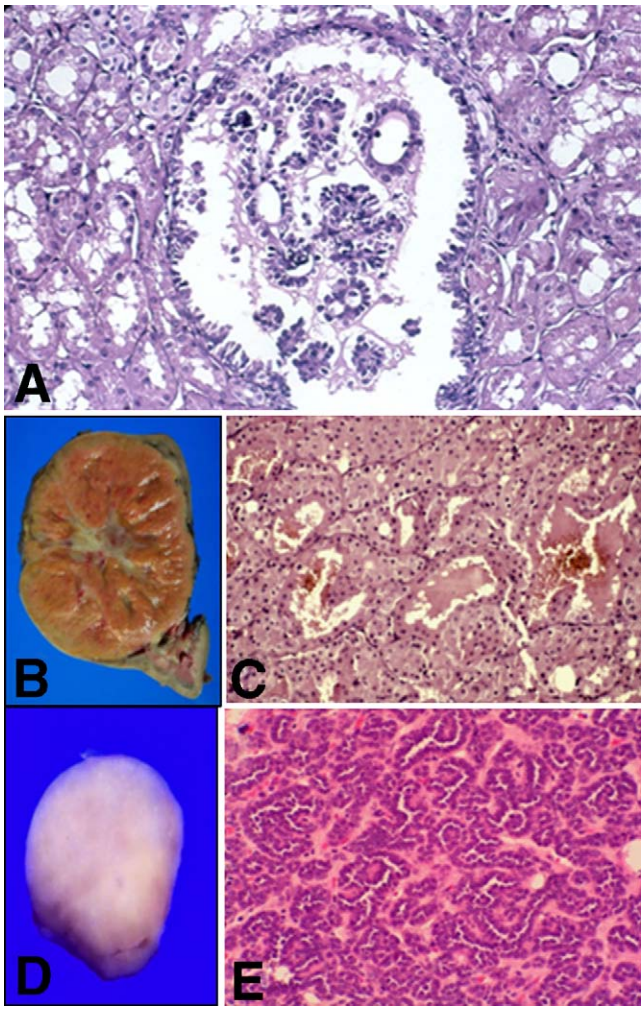

Fig. 3 – Benign renal cell tumors including papillary adenoma (A), oncocytoma (B) gross and (C) microscopic features and metanephric adenoma (D) gross and (E) microscopic features.

adenomas are 3 to 6 cm, usually solitary and not encapsulated (Fig. 3). Metanephric adenofibroma shows an epithelial component identical to that of metanephric adenoma which is embedded in a fibroblast-like stroma [1]. Metanephric adenoma has a normal karyotype [1,32].

6. Mixed epithelial and mesenchymal tumors

Cystic Nephroma is a benign mixed epithelial and stromal neoplasm frequently unilateral, solitary and multilocular. It is encapsulated with no solid areas or necrosis [1].

Adult cases present after age of 30 with female predominance. Some are associated with pleuropulmonary blastoma [35]. Nonrandom X chromosome inactivation supports its neoplastic nature.

Mixed epithelial and stromal tumor of kidney is a rare renal neoplasm composed of a mixture of stromal solid areas and epithelial (mostly cystic) elements known as cystic hamartoma of renal pelvis or adult mesoblastic nephroma in the 1998 WHO classification [12]. Some stromal cells react with antibodies to estrogen and progesterone. There is a female predominance with history of estrogen therapy [36]. All cases have been seen in adults. Some are incidental but others have flank pain or hematuria. Surgery is curative.

Synovial sarcoma (embryonal sarcoma) may arise in the kidney.

7. Other adult tumors

Other uncommon neoplasms may be observed in the adult kidney as seen in Table 1. The potentially aggressive epithelioid angiomyolipoma deserves mention. Half of published cases have history of tuberous sclerosis, some show metastatic potential [1].

8. Conclusions

Unlike our knowledge of RCC a decade ago, we now know that it is not a single disease. As acknowledged by the 2004 WHO classification of adult kidney tumors, biological and clinical properties define a number of entities whose recognition is of value in daily clinical practice. Different subtypes have different clinical outcomes and show different response to therapy.

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