Renal Cell Carcinoma: Recent Types and Challenges in Certain Tumor Typing

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Abstract

Background: Most histopathological variants of renal cell carcinomas (RCC) are showing distinct morphological patterns. However, there are some overlaps between some variants, which in turn, affect the prognosis. The aim of this review articleis to distinguish the recently described variants of RCCs and to illustrate the role of immunohistochemistry and genetic study in diagnosis of confusing cases.

Conclusions: Applying immunohistochemical and moleculartests in addition to routine staining allow better classification of different variants of RCCs.

Key words: Renal cell carcinoma, Oncocytic renal neoplasms**,** Immunohistochemistry.

Introduction

Renal cell carcinoma is the 6th leading cause of cancer-related deaths in Western world and comprises 2-3% of all newly diagnosed malignancies in adults. It represents about 85% of all renal neoplasms. The peak incidence is the6th decade of life with male to female ratio about 2:1 and incidence of bilaterality about 1%. Incidence rates are higher in Europe, North America, and Australia thanin India, Japan, Africa, and China(**Aurilio et al., 2019).** There are several well-established risk factors for RCC; some are modifiable as smoking, obesity and hypertension, while others are non-modifiable as genetic and racial factors **(Maher, 2018).**Thisstudy aims to discuss recent forms of RCCs and highlight the role of immunohistochemistry and genetic study in distinguishing similar forms of RCCs.

Pathological Variants of RCCs

Clear cell RCC (ccRCC):

It is the most common type of RCCs accounting for about 65-70% of all renal cancers. In 90% of cases, these tumors exhibit alterations in VHL tumorsuppressor gene on chromosome3. Most tumors are sporadic, but multiple bilateral tumors are seen in VHL syndrome**(Aurilio et al., 2019).**Multifocal sporadic tumors are rare and a recent study has shown that apparent multifocality may be due to retrograde venous invasion from a single tumor**(Taneja et al., 2018).**

Grossly, ccRCCs characteristically contain solid yellow areas with variable amounts of cystic change, hemorrhage and necrosis**(Leibovich et al., 2010).**

Microscopically, tumor cells of ccRCCare relatively large, the appearance of cytoplasm ranging from optically clear to deeply granular with many transional forms. Such clear cytoplasm due to lipid and glycogen accumulation. The nuclei are generally centrally located. The typical architectural pattern is mainly solid with occasional alveolar and acinar patterns on the stroma showing prominent, thin-walledblood vessels**(Leibovich et al., 2010).**

Immunohistochemically (IHC)ccRCCs co-express pan-cytokeratin (CK) and vimentin, a feature not present in normal tubular cells.Also,ccRCCs are carbonic anhydrase IX (CA-IX) positive, but are usually CK7 negative**(Taneja et al., 2018).**

Papillary RCC:

It is the 2nd common subtype accounting for 15-18% of all RCCs. It is more often multifocal and bilateral than the other common tumor types, as seen in approximately 10% of cases **(Modiand Singer, 2016).**Papillary RCCs are also more frequent in acquired cystic kidney disease. It is subdivided into two types; type1 in which the papillae are covered by a single layer of cells with scanty pale cytoplasm, Collections of foamy macrophages are often present within the papillary fibro-vascular cores and calcifications (psammoma bodies) and intracellular hemosiderin are common. They may also show solid growth, with very compact papillary structures. IHC; type1 RCC is positive to CK7 and Alpha-methyl CoA racemase(AMACR)**(Delahunt et al., 2001).**Type2, on the other hand, represents heterogenous collections of high grade RCC with papillary architecture. Recent molecular studies have shown that MiT family translocation RCC and RCC associated with hereditary leiomyomatosis are frequently misclassified as type2 papillary RCC **(Flippot et al., 2018).**

Microscopically; type2 papillary RCC is characterized by papillae coveredby pseudostratified epithelium composed of cells with abundant eosinophilic cytoplasm **(Flippot et al., 2018).**

Chromophobe RCC:

Chromophobe RCC consists about 5% of all cases of RCCs. It is usually sporadic and generally has a good prognosis. Most of these tumors are confined to the kidney at diagnosis, though they may be large at the time of presentation. They are characteristically

tan in color, similar to the benign renal oncocytoma that is the main differential diagnosis **(Shuch et al., 2015).**

On microscopy, chromophobe RCCs characteristically consists of large cells with prominent cell membranes, pale cytoplasm with nuclei showing irregular nuclear membrane, hyperchromasia and frequent binucleation with perinuclear halos. An eosinophilic variant also occurs, where the cells have an oncocytic cytoplasmic appearance and the nuclear features described are often less apparent.IHC; chromophobe RCCs usually express epithelial membrane antigen (EMA), CD117 in addition to CK7 **(Tan et al., 2010).**

The multilocular cystic renal neoplasm of low malignant potential:

Multilocular cystic renal neoplasm of low malignant potential was formerly included in the clear cell carcinoma category, but is now known to have indolent behavior and an excellent prognosis, regardless of its size, with no reported metastases. It is rare (< 1% of renal tumors). These cystic tumors characteristically have thin fibrous septae containing low-grade clear cells, but there isno solid expansile clear cell nodules that are seen in ccRCC. They have been shown to have chromosome 3p deletions and VHL gene mutations similar to clear cell RCCs. Correct pathological diagnosis of these tumors is important, as they may be managed conservatively**(Bhatt et al., 2016).**

Fumarate-Hydratase-Deficient-RCC(Hereditaryleiomyomatosis and RCC -associated RCC):

Patients with RCC associated with hereditary leiomyomatosis and renal cancer syndrome have an autosomal dominant inherited germline mutation in fumaratehydratase (FH) gene on chromosome1. This syndrome is also associated with cutaneous and uterine leiomyomata, occurring at greater frequency than the associated RCCs**(Maher, 2018).**These tumors are high grade and often have a papillary architecture, with tumor cells having eosinophilic cytoplasm. However, the morphology may be very variable and lead to misdiagnosis**(Chen et al., 2014).**A characteristic histological feature is the presence of distinctive prominent nucleoli with peri-nucleolar halos, exhibiting an appearance reminiscent of cytomegalovirus inclusions **(Merino et al., 2007).**

IHC; combination of a lack of FH expression and overexpression of *S*-2-succino cysteine suggests a diagnosis of FH-deficient RCC, which can then be confirmed with molecular studies. These are highly aggressive tumors,

even when of small size, and show frequent distant metastases **(Maher, 2018).**

Collecting duct carcinoma:

Collecting duct carcinomais a rare; 1-2%and a highly aggressive type of RCC arising in the renal medulla. It may be difficult to distinguish histologically from urothelial carcinoma of the renal pelvi-calyceal system, due to similar infiltrative high-grade variable morphology and their overlapping immunohistochemistry (IHC) profiles. **(Ohe et al., 2018).**

Renal medullary carcinoma:

Renal medullary carcinoma has similar morphologyofcollecting duct carcinoma and occurs in association with sickle cell trait or disease. This is rare, aggressive and occurs more often in younger adults. In contrast to collecting duct carcinomas, these tumors may express Octamer-binding transcription factor 3/4 (OCT3/4) on IHC and show loss of expression of SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member (SMARCB1)**(Ohe et al., 2018).**

MiT family translocation RCCs:

MiT family translocation RCCs are rare and should be considered particularly in children and young adults presenting with RCC, although they also occur in the adult population **(Calio et al., 2019).**They result from gene fusions involving the MiTtranscription factor genes; Transcription factor E3 (TFE3) and Transcription factor EB(TFEB), with differing fusion partners. Some correlations exist between type of gene fusion and tumor morphology**(Cutruzzula et al., 2016).**

Microscopically, the overall features are typically veryheterogenous. Papillary structures maybe prominent. Tumor cells may have either clear or markedly granular eosinophilic cytoplasm. Psammoma bodies may be abundant. IHC; these tumors usually express Paired box protein 2 and 8 (PAX2 and PAX8) but do not usually express MiT**(Argani, 2015).**

Succinate dehydrogenase-deficient RCC:

Succinate dehydrogenase-deficient RCCis rare and results from inherited germline mutations in the succinate dehydrogenase (SDH) gene, most commonly SDHB but also in SDHA, SDHC and SDHD. Affected patients may also present with paragangliomas and GISTs. The associated RCCs may be multifocal and bilaterality occurs in around 25% of cases **(Williamson et al., 2015).**

On microscopy, succinate dehydrogenase-deficient RCC are

usually solid and are composed of cells with eosinophilic cytoplasm with distinctive cytoplasmic vacuolation and inclusions. Intra-tumoral mast cells are also a common feature**(Smith et al., 2016).**

IHC for demonstration of SDHB is available, as loss of staining is indicative of a mutation in the SDHB (most common), SDHC or SDHD genes. SDHA gene mutation can be demonstrated by additional absence of staining for SDHA. **(Williamson et al., 2015).**

Tubulo-cystic RCC:

Tubulo-cystic RCCis another rare, indolent tumor with relatively good prognosis. It is slightly common in men. It was thought to be related to papillary RCCs, but is now accepted as a separate entity. It has a characteristic "bubble wrap" gross appearance, due to the presence of fibrotic stroma separating cystic spaces**(Amin et al., 2009).**

Microscopically, it is formed of small tubules present within the stroma and are lined by cells with eosinophilic cytoplasm with round nuclei and nucleoli of variable prominence. Tumor cells may also have a 'hobnail' appearance **(Srigleyand Delahunt, 2009).**Tubulo-cystic RCC express AMACR and CK7 on IHC. On molecular analysis, there is a suggested relationshipto papillary RCC,but this remains controversial. Currently, there is no known distinct genetic signature for tubulo-cystic RCC**(Srigleyand Delahunt, 2009).**

Acquired cystic disease-associated RCC:

This neoplasm is seen only in patients with acquired cystic renal disease due to dialysis. Microscopically, such tumor has prominent macrocystic growth, with occasional solid and papillary architectural patterns. Two characteristic features include intra-tumoral oxalate crystals and a unique sieve-like architectural pattern resulting from inter and intracellular lumina. IHC; such tumor is often negative toCK7 but still express AMACR**(Przybycin et al., 2018).**

Clear cell-papillary RCC:

Clear cell-papillary RCC was first described by Tickooand Reuter. within a series of RCCs arising in end stage kidney disease**(Tickooand Reuter, 2011).**Now, it seems to be more common to occur sporadically. It acquired its importance because when it is diagnosed by strict histological criteria, no recurrence or metastasis has been reported**(Zhou et al., 2014).**

Grossly, clear cell-papillary RCC is circumscribed and often capsulated,

with solid or more often cystic cut section.Microscopically, cystic areas get lined by a single layer of low cuboidal clear cells, with areas of papillary tufts lined by similar cells. More solid areas have admixture of architectural patterns including tubular, acinar and nesting. There is frequently reversed polarity with sub-nuclear clearing and linear arrangement of the nuclei. The tubular pattern almost always shows branching. Solid and nested areas may show a significant overlap with clear cell carcinoma. Tumor cell necrosis and invasion of renal vessels should be absent.IHC;clear cell-papillary RCC is immunoreactive to CK7. While CD10 and AMACR are typically negative in clear cell-papillary RCC(**Zhou et al., 2014).**

Unclassified RCC:

Approximately 5% of tumors remain difficult to categorize after thorough sampling andimmunohistochemical (IHC) assessment because the tumor is purely sarcomatoid or the immunoprofile is not definitive or there is even overlapping morphological features. **(Perrino et al., 2018).**

Challenges in Certain Tumor Typing

Most RCCs exhibit a characteristic morphology that enables their easy categorization, with or without using IHC. However, it is not uncommon to face a difficulty in assigning certain tumors particularly in separating oncocytic tumors which are further classified into three categories; classic prototypical oncocytoma, classic prototypical chromophobe RCCs and oncocytic tumors difficult to classify **(Kryvenko et al., 2014).**Despite its distinct gross and microscopic features, oncocytoma may show confusing gross features as multicentricity and bilaterality**(Williamson et al., 2017).**

Microscopically, invasion of peri-renal tissue and renal vein may be encountered in oncocytoma. Oncocytoma cells sometimes are bi-nucleated and psammoma bodies may be seen in intraluminal location**(Kryvenko et al., 2014).**

IHC; oncocytoma cells express low molecular weight keratin, CD117. It is usually negative or focal positive for CK7. Cytogenetically; it lacks 3p abnormalities as in ccRCCs. Instead, oncocytoma shows different chromosomal alterations especially loss of chromosome1 **(Williamson et al., 2017).**The main differential diagnosis of renal oncocytoma is eosinophilic variant of RCC, succinate dehydrogenase-deficient RCC and chromophobe RCC. The presence of irregular nuclear membrane with

frequent binucleation and perinuclear halo are sufficient to classify the questionable renal tumor as chromophobe RCC **(Kryvenko et al., 2014).**

Conclusions:

In the recent years, there was great advances in diagnosis of RCCs. However, there are some variants that show confusing histological patterns, which in turn generate diagnostic and prognostic difficulties. Applying immunohistochemical and available molecular tests allowing accurate diagnosis of RCCs.

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