Subtypes of renal cell carcinoma with defined genomic alterations: diagnostic and prognostic significance

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Abstract

The World Health Organization (WHO) 2016 classification of renal neoplasia defines renal cell carcinomas (RCCs) with genomic alterations: (1) succinate dehydrogenase deficient (SDH) RCC, (2) hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome-associated RCC and (3) the MiT family translocation carcinoma (Xp11 translocation carcinoma and t(6;11) carcinoma). Genomic alterations also define two syndromes associated with RCC that have a varied histology; tuberous sclerosis complex and Birt-Hogg-Dube. This review will examine the WHO entities and the two aforementioned syndromes, and discuss a genomic alteration (TCEB1 mutation) that appears to define a subset of clear cell RCCs that histomorphologically overlap with clear cell tubulopapillary RCC. The focus will be on diagnostic considerations from the pathologic perspective, and include discussion of clinical features, prevalence, prognosis, common and uncommon immunohistochemistical stains and molecular testing.

Keywords diagnosis; genomic changes; prognosis; renal cell carcinoma

Introduction

All renal cell carcinomas (RCCs) have genomic alterations and many of these are well defined; however, it was not until the Vancouver modification of the World Health Organization (WHO) (published in 2013[1]) that RCC subtypes were defined by genomic alternations and The WHO Renal Neoplasia Classification of 2016 continued this trend (Tables 1a, 1b, 2a and 2b).

Seen within the context of pathology as whole, and with the move toward personalized medicine more generally, this shift is not surprising. In this review we will examine RCC defined by genomic alterations, and briefly touch on entities that are evolving. The focus will be predominantly on the diagnosis of these tumours, from the starting point of a clinical history and histomorphology. Diagnostic immunostains and molecular testing will be discussed; however, the focus will be on commonly available immunostains, so cases can be triaged appropriately at centres that have limited testing capabilities. Finally, the prognostic significance of these entities will be discussed.

The most common RCCs (clear cell renal cell carcinoma, papillary renal cell carcinoma and chromophobe renal cell carcinoma) may all be seen in the context of a syndrome and the genes involved have been identified. Familial clear cell RCC is associated with alterations in the *von Hippel–Lindau tumor suppressor (VHL)*, familial papillary RCC is associated with the *MET protooncogene (MET)*, and familial chromophobe RCC is associated with *folliculin (FLCN)*. It is worth noting that the three common RCC in the familial context are inherited as autosomal dominant. This review will not further discuss the common RCCs; however, BHD will be discussed in the evolving entities section.

Autosomal dominant inheritance likewise applies to succinate dehydrogenase deficient renal cell carcinoma (SDH-RCC), hereditary leiomyomatosis and renal cell carcinoma syndrome-associated renal cell carcinoma (HLRCC associated RCC) and the evolving tuberous sclerosis complex associated renal cell carcinoma (TSC associated RCC).

Subtypes of renal cell carcinoma with genomic alterations

Succinate dehydrogenase deficient renal cell carcinoma

Definition, genes and prevalence: succinate dehydrogenase deficient renal cell carcinoma (SDH-RCC) is a recently recognized renal cell carcinoma subtype that is defined by loss of the SDH (protein) complex in the tumour. It was added to the WHO classification in 2016. SDH is a tetramer that resides in the mitochondria, and is involved in both the citric acid cycle and electron transport chain. The subunits are named 'A', 'B', 'C' and 'D', and each subunit has a corresponding gene, i.e. SDHA, SDHB, SDHC and SDHD. In addition to this, there are helper genes that drive the assembly of the protein complex (e.g. SDHAF1, SDHAF2). All the preceding listed genes are required for the SDH complex to form. In SDH-RCC a mutation of one of the SDH genes can usually be proven. The most commonly described mutation is SDHB; both SDHA and SDHC mutations have been described. The largest series estimates that the prevalence of SDH-RCC may be as high as 0.2% of all all RCCs.[2]

Prognostic data is limited; however, a poor prognosis appears to be predicted by the nuclear grade and coagulative tumour necrosis. Individuals with a high grade tumour (ISUP nucleolar grade 3 or 4) had a high rate of metastases (7 of 10 individuals). Coagulative necrosis (seen in 4 individuals) was associated with metastatic disease in all four cases and three of the patients died of the disease.

Morphology: SDH-RCC tumours are typically solid. The histomorphology is characterized by a clumpy/flocculent and

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World health organization recognized entities - overview

Diagnosis	Clinical	Gross	Key histology	Other histology	Gene(s)
Succinate dehydrogenase deficient RCC	history or family history of paraganglioma(s)	solid	flocculent and vacuolated eosinophilic cytoplasm	cytoplasmic inclusion, intratumoural mast cells	reported: SDHA, SDHB (most common), SDHC; possible: SDHD
Hereditary leiomyomatosis and RCC-associated RCC	cutaneous leiomyomas — may be described as rash or few, uterine leiomyomas, esp. Requiring surgery before age 40	solid and/or cystic	prominent nucleoli (may be focal), presence of several morphologic patterns, esp. if including papillary or tubulopapillary	hyalinized fibrovascular cores, lack of foamy histiocytes in papillae	FH
Xp11 translocation RCC	typically young <50 years	solid and/or cystic	intratumoral calcifications, clear cells or eosinophilic cells	pseudopapillary structures	Translocation involving TFE3 — various partners (see text)
RCC with t(6;11)	typically young <50 years	solid, may be cystic	biphasic pattern: large cells (clear to eosinophilic cytoplasm) and small (lymphoid-like) cells	occasional rosette-like structures	MALAT1-TFEB

Table 1a

World health organization recognized entities—ancillary testing

Diagnosis	Common IHC with differential diagnosis	Specific IHC	Gold standard test
SDH-RCC	CD117- CK7- (ChRCC: CD117+, CK7+) (Oncocytoma: CD117+) (Eosinophilic solid and cystic RCC: CK20+)	SDHB-	sequencing SDH genes
HLRCC-associated RCC	CD10-, CK7- (Papillary RCC: CD10+, CK7+, AMACR+) (Tubulocystic RCC: CD10+, CK7+)	FH-, 2SC+	sequencing FH gene, clinical features of HLRCC syndrome
Xp11 translocation RCC	EMA (very focal or negative), AE1/AE3 (very focal) (CCRCC: EMA+, AE1/AE3+), melan A-/+	TFE3+ (most specific), cathepsin K	FISH breakapart probe, sequencing to determine specific translocation
RCC with t(6;11)	melan A+, HMB-45+, CD10+, PAX8±, CAM5.2+, RCC+	TFEB+, TFE3-	FISH fusion probe for t(6;11) or sequencing of fused genes

Table 1b

RCC with genomics alterations not specifically recognized by the WHO - Overview

Diagnosis	Clinical	Gross	Histology similar to or key features	Gene(s)
Tuberous sclerosis associated RCC	*SALSA HEART* — mnemonic see text	solid or cystic	Renal angioadenomatous tumour-like Eosinophilic solid and cystic RCC-like Chromophobe RCC-like	TSC1, TSC2
RCC associated with Birt-Hogg-Dube	skin lesions (face, neck anterior truck), lung cysts, pneumothorax	solid and/or cystic	chromophobe RCC, oncocytomas, hybrid oncocytic/chromophobe tumours, clear cell RCC	FLCN
Clear cell RCC with TCEB1 mutation	No specific clinical features known	solid with cystic areas	clear cells with cysts, leiomyomatous stroma without diffuse nuclear reverse polarization	TCEB1

Table 2a

vacuolated eosinophilic cytoplasm. (See Figure 1) Cytoplasmic inclusions may be seen. Mast cells may also be seen. In the largest series, the nuclear grade was low (ISUP nucleolar grade 1—2) in 72% of cases, and approximately 25% of patients had tumours bilaterally. The main histomorphologic differential diagnoses are oncocytoma and chromophobe RCC. A wider differential includes clear cell RCC and the large groups of renal tumours with eosinophilic cytoplasm.[3]

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