Seminars in Diagnostic Pathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Morphological clues to the appropriate recognition of hereditary renal neoplasms

Holger Moch[a,*], Riuko Ohashi[b,c], Jatin S. Gandhi[d], Mahul B. Amin[d,e]

[a] Department of Pathology and Molecular Pathology, University and University Hospital Zurich, Switzerland
[b] Histopathology Core Facility, Niigata University Faculty of Medicine, Niigata, Japan
[c] Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[d] Department of Pathology and Laboratory Medicine, University of Tennessee Health Sciences, Memphis, USA
[e] Department of Urology, University of Tennessee Health Sciences, Memphis, USA

ARTICLE INFO

Keywords:
Hereditary
Renal cell carcinoma
Familial
VHL
Tuberous sclerosis
HLRCC
Immunohistochemistry
Cowden syndrome
HRPT2
Eosinophilic
Solid and cystic renal cell carcinoma

ABSTRACT

An important emerging role of the surgical pathologist besides the traditional tasks of establishment of the diagnosis and documentation of prognostic and predictive factors, is to recognize the possibility of a hereditary condition in cases where the histology is suggestive for a familial cancer syndrome. In recent years, the knowledge regarding all of the above roles, including the role of recognition of familial cancer, has particularly expanded in renal neoplasms with the close scrutiny to morphology, molecular correlates and clinical features of the different sub-types of renal cell carcinoma. Awareness of these clinically distinctive sub-types and their associated histologic clues will prompt the pathologist for further immunohistochemical or molecular work up, to look for clinical information to support the suspected diagnosis of familial cancer, to alert managing physician/s to look for stigmata of history of familial cancer, which will permit triaging patients and their families for appropriate genetic counseling. This review provides a comprehensive review of the known sub-types of renal cell carcinoma that have a predilection to occur in the setting of hereditary disease; examples include renal cancers occurring in the background of von Hippel Lindau disease, hereditary leiomyomatosis and renal cell carcinoma syndrome, tuberous sclerosis, Birt Hogg Dube syndrome and succinate dehydrogenase deficiency. Herein we focus on diagnostic clues for renal tumors occurring in a non-pediatric setting that should prompt their correct recognition and reiterate the importance of the correct diagnosis.

Introduction

Most renal cell carcinomas (RCC) are sporadic, but it is estimated that 2–4% of RCC are associated with inherited tumor syndromes.[1] Many tumor syndromes predispose patients to develop a specific histological type of RCC (Table 1). The von Hippel Lindau (VHL) disease is the most common familial renal cancer syndrome and is associated with clear cell renal carcinoma, associated with mutations in the *VHL* gene and loss of the wild-type *VHL*-allele.[2] Patients with hereditary papillary renal carcinoma syndrome (HPRCC) have a germline activating mutation in the *MET*-proto-oncogene, which can cause renal cancers with papillary type 1 histology.[3,4] The hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC), which is caused by germline loss-of-function mutations in the *Fumarate-Hydratase* (*FH*) gene are associated with a specific renal tumor type and uterine smooth-muscle tumors.[5,6] The hyperparathyreoidism-jaw tumor (HPT-JT) syndrome is associated with parathyroid adenomas, fibro-myalgious tumors of the jaw and renal tumors. This syndrome is caused by germline mutations in *HRPT2*.[7] The Birt-Hogg-Dubé syndrome (BHD) is associated with an increased risk for renal cancers of various histological types, such as chromophobe RCC and hybrid oncocytic tumors.[8] Other hereditary tumor syndromes with development of renal cancers include succinate dehydrogenase (SDHB)-deficient renal cell carcinoma,[9] tuberous sclerosis (TS)[10] and Cowden's disease,[11] caused by alterations of *SDHB*, *TSC1*, *TSC2* and *PTEN*. Familial pediatric renal tumor syndromes include the familial nephroblastoma, the WAGR-syndrome with *W*ilms tumor, *A*niridia, *G*enitourinary malformations and mental *R*etardation, the Denys-Drash-syndrome, characterized by Wilms tumor, mesangial sclerosis and pseudohermaphroditism. The Beckwith Wiedemann-syndrome is characterized by Wilms tumor, hemihypertrophy, macroglossia, omphalocele and visceromegaly. Herein we focus on tumors occurring in the non-pediatric setting, although some of the tumor types we discuss may occur in young patients. Awareness of clinically distinctive renal neoplasms and their associated histologic clues will

* Corresponding author.
E-mail address: holger.moch@usz.ch (H. Moch).

https://doi.org/10.1053/j.semdp.2018.01.005

Table 1
Hereditary Conditions and Associated renal neoplasms.

Syndrome	Gene Protein	Chromosome	Kidney	Skin	Other Tissue	Syndrome	Gene Protein	Chromosome
von Hippel-Lindau	*VHL* pVHL	3p25	Multiple, bilateral clear-cell renal cell carcinoma (CCRCC), renal cysts	–	Retinal and CNS haemangioblastomas, phaechromocytoma, pancreatic cysts	von Hippel-Lindau	*VHL* pVHL	3p25
Hereditary papillary renal cancer	*c-MET* HGF-R	7q31	Multiple, bilateral papillary renal cell carcinomas (PRCC), Type 1	–		Hereditary papillary renal cancer	*c-MET* HGF-R	7q31
Hereditary leiomyomatosis and RCC	FH *FH*	1q42–43	Papillary renal cell carcinoma (PRCC), non-Type 1	Nodules (leiomyomas)	Uterine leiomyomas and leiomyosarcomas	Hereditary leiomyomatosis and RCC	FH *FH*	1q42–43
Birt-Hogg-Dubé	*BHD* Folliculin	17p11.2	Multiple chromophobe RCC, conventional RCC, hybrid oncocytoma, papillary RCC, oncocytic tumors	Facial fibrofolliculomas	Lung cysts, spontaneous pneumothorax	Birt-Hogg-Dubé	*BHD* Folliculin	17p11.2
Constitutional chromosome 3 translocation	unknown		Multiple, bilateral clear-cell renal cell carcinomas (CCRCC)	–	–	Constitutional chromosome 3 translocation	unknown	
Hyperparathyroidism-jaw tumor (HP-JT)	*HRTP2*	1q25–32	Mixed epithelial and stromal tumors, papillary RCC: cysts	–	Parathyroid tumors, fibro-osseous mandibular and maxillary tumors	Hyperparathyroidism-jaw tumor (HP-JT)	*HRTP2*	1q25–32
Familial papillary thyroid cancer (FPTC)	Unknown gene	1q21	Papillary RCC, oncocytoma	–	Papillary thyroid cancer, nodular thyroid disease	Familial papillary thyroid cancer (FPTC)	Unknown gene	1q21
Tuberous sclerosis	*TSC1* Hamartin*TSC2*Tuberin	9q34 16p13	Multiple, bilateral angiomyolipomas, lymphangioleiomyomatosis	Cutaneous angiofibroma ('adenoma sebaceum') *peau chagrin*, subungual fibromas	Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, lung and kidney cysts, cortical tubers and subependymal giant cell astrocytomas (SEGA)	Tuberous sclerosis	*TSC1* Hamartin*TSC2*Tuberin	9q34 16p13
BAP1 inactivated RCC	BAP1 proteins	3p21	clear cell RCC	uveal melanoma, cutaneous melanoma, and melanocytic BAP1-mutated atypical intradermal tumors	*meso*thelioma,	BAP1 inactivated RCC	BAP1 proteins	3p21