Knowledge of hereditary renal cancer syndromes: a pending issue for oncologists

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Renal cell cancer (RCC) is a rare disease that accounts for 2–3% of all solid malignancies. Although its etiology is not known, approximately 4% of RCC occurs in the context of complex hereditary syndromes in which the kidney lesions are associated with other manifestations. Therefore, clinical suspicion is essential for proper diagnosis and management. In this review a practical summary to aid treating physicians in the identification of hereditary RCC syndromes, including von Hippel–Lindau syndrome, hereditary papillary RCC, Birt–Hogg–Dubé syndrome, and hereditary leiomyomatosis RCC, is provided. Early recognition of these specific populations will lead to better care, correct surveillance, and, in the near future, to personalized treatment taking advantage of underlying genetic defects. *Anti-Cancer Drugs* **22 (suppl 1):S15–S20**

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Introduction

Renal cell cancer (RCC) is a rare disease that accounts for 2–3% of all solid malignancies. Although its etiology is not known, approximately 4% of RCC occurs in the context of complex hereditary syndromes in which the kidney lesions are associated with other manifestations. Overall, hereditary tumors accounted for 2300 of the total 57 760 patients diagnosed with RCC in the United States in 2009 [1]. Despite the relatively small numbers, the clinical and familial repercussions of these entities are enormous. Thus, proper identification and management of these rare forms of renal cancer are critical for physicians treating patients with this disease.

Recent genetic studies have enlarged our knowledge of hereditary renal cancer syndromes by identifying the key genetic abnormalities that cause the disease. In addition to providing important clues for diagnoses and genetic counseling, some of these mutations are indeed bonafide therapeutic targets. This knowledge is now allowing more effective and personalized treatment in an analogous manner to what has been proposed for example, for BRCA mutation carriers [2].

Despite the difficulties in understanding the complexities of the genetic alterations and the molecular implications of such abnormalities, physician awareness of these syndromes and their manifestations plays an important role from the clinical perspective. It is likely that practicing oncologists or urologists treating RCC will face, at some point in their careers, one of these syndromes. Clinical suspicion is essential for proper diagnosis and management.

In this review a practical summary to aid treating physicians in the recognition of hereditary RCC syndromes is provided. To that end, the discussion focuses on the clinical aspects of the presentation, diagnoses, and management rather than a detailed review of the epidemiology and molecular data. Each section begins with a presentation of the clinical picture in which the cardinal manifestations of these syndromes are presented in a succinct and schematic manner. This is followed by a more formal description of each of the syndromes. The goal is to provide physicians with an easy-to-remember list of diagnostic clues that can help to select patients for an in-depth genetic analysis.

Von Hippel–Lindau syndrome

Clinical picture

(1) Patient with multiple (often bilateral) clear RCC plus renal cysts [3]
(2) Patient with clear RCC and personal or familial history of pheocromocytoma [4]
(3) Hemangioblastomas (retinal, brain, or spinal) [5]
(4) Clear cell renal cancer and pancreatic cysts or neuroendocrine islet cell tumors [6]
(5) Key, but rare, lesions such as epididymis (male) or broad ligament (female) cystoadenomas and endolymphatic sac tumors [7] (Fig. 1).

Description

The von Hippel–Lindau (VHL) syndrome is an inherited multisystem disorder characterized by abnormal growth of blood vessels and is the most frequent hereditary RCC syndrome. It is inherited in an autosomal dominant manner with an incidence of 1 in 36 000 births [8]. Renal tumors are uniformly of clear cell histology and, on average, the kidneys of individuals affected with this condition contain up to 600 microscopic neoplasms and 1100 cystic lesions [3,9]. Individuals affected

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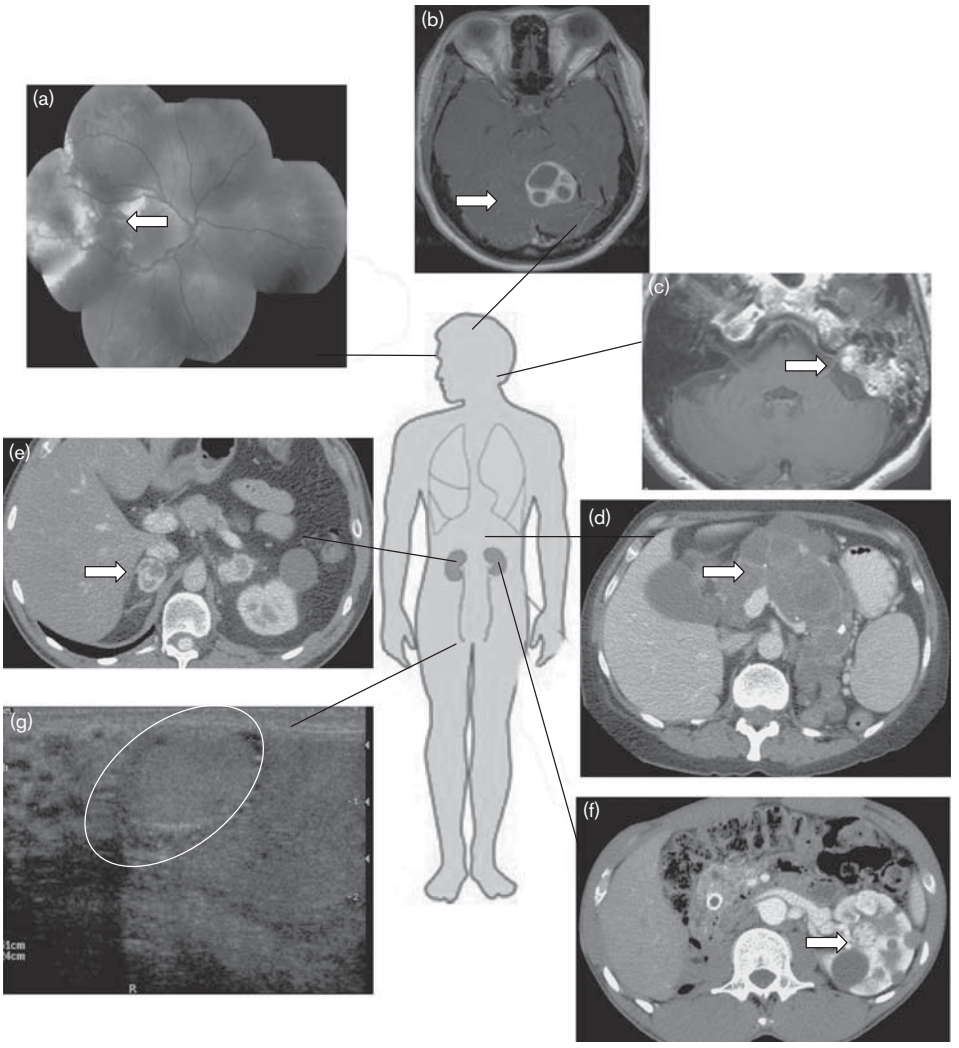
Fig. 1



von Hippel–Lindau syndrome: most common clinical pictures (a) retinal hemangioblastoma; (b) brain hemangioblastoma; (c) endolymphatic sac tumors; (d) pancreatic cysts; (e) pheocromocytoma; (f) multiple clear-cell renal carcinoma; (g) papillary cystadenoma of the epididymis. Adapted with permission from Leung *et al.* (2008) and Chan *et al.* (2007) [13,14].

with the VHL syndrome often present with other, albeit less-frequent, abnormalities as summarized in the clinical picture above in a well-established genotype–phenotype correlation [9–11].

Molecular aspects

The *VHL* gene, located on the short arm of chromosome 3, is a tumor suppressor gene. Through the formation of a complex with elongin B and C and Cul2, VHLp (*VHL* gene product) targets the hypoxia-inducible factors (HIFs), HIF-1α and HIF-2α for ubiquitin-mediated degradation. When there is a mutation of the *VHL* gene, HIF is not degraded and accumulates leading to increased transcription of HIF downstream genes involved in angiogenesis [vascular endothelial growth factor (*VEGF*); platelet-derived growth factor], cell proliferation (transforming growth factor), glucose uptake (glucose transporter 1 or GLUT-1) and acid–base balance (carbonic anhydrase-IX) [10,11]. VHL somatic mutations are also frequent, up to 75%, in sporadic renal clear cell cancer, which is the rationale for the success of antiangiogenic therapy in this setting. Although different VHL germ line mutations have been described, current comprehensive genetic analysis yields a sensitivity of approximately 100% in their detection [12].

Management

Renal cancer is the leading cause of death in individuals affected with the VHL syndrome and therefore, close follow-up and management of renal lesions are critical. In addition, screening and appropriate early management

of other manifestations of the syndrome may avoid severe sequelae, such as loss of vision and neurological damage. As a guidance, these individuals need to undergo complete physical and ophthalmological examinations annually; computed tomographic scan of the abdomen every 2 years, alternating with abdominal ultrasound every other year; magnetic resonance imaging of the brain and assessment of metanephrines and plasma catecholamines annually (depending on the risk conferred by each specific mutation) and finally, an audiology examination every 2 years. Small renal tumors can be followed without resection up to a size of 3 cm. This approach has been shown to be safe and represents the best option for preserving renal function as long as possible [15]. Larger tumors have a higher risk of invading and disseminating and therefore, should be removed. The surgical procedure of choice is a nephron-sparing nefrectomy aiming to preserve as much renal function as possible.

Targeted therapies

As discussed above, the loss of the *VHL* gene product results in high levels of HIF-1α, which, in turn, increases the transcription of several genes including *VEGF*. VEGF is a well-known mediator of angiogenesis and has been a key target for the development of antiangiogenesis agents. The understanding of the basic biology of RCC has prompted the testing of angiogenesis inhibitors in this disease. A series of well-designed phase II and III clinical trials have shown that targeting the VEGF pathway by either monoclonal antibodies against the growth factor itself, such as bevacizumab, or small molecule inhibitors of the VEGF tyrosine kinase receptor, such as sorafenib, sunitinib, and pazopanib results in objective responses and increases patient survival [16–18]. In addition, HIF-1α levels are not only altered by reduction in protein degradation but also by an increase in protein production. Similar to patients with sporadic RCC, these agents are the frontline treatment for hereditary RCC. Furthermore, anecdotal data suggest that these drugs may also be effective in other complications resulting from *VHL* gene defects and are currently being investigated [19–21].

Hereditary papillary renal cell carcinoma

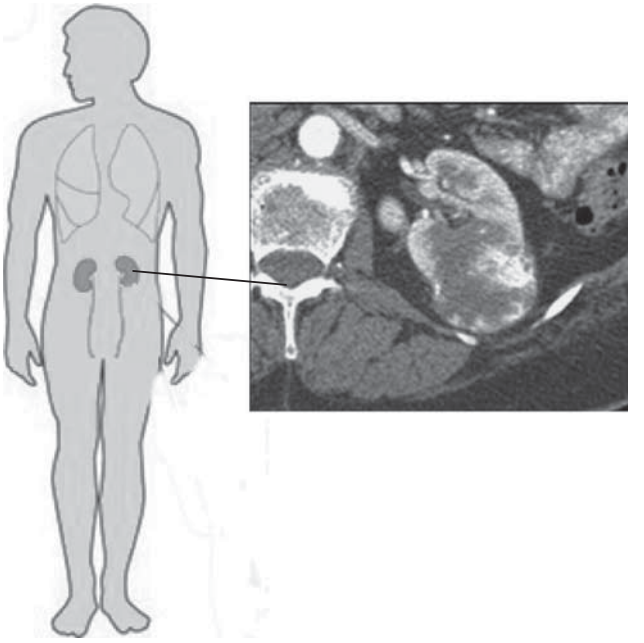
Clinical picture

Patients with bilateral, multifocal papillary type 1 RCC (PRCC) are shown in Fig. 2.

Description

Hereditary PRCC is an infrequent autosomal dominant hereditary syndrome, highly penetrant with, typically, a late onset. Kidney cancer is uniformly type 1 PRCC and affected individuals are at high risk of developing bilateral, multifocal tumors [22]. No other manifestation has been linked to this particular syndrome.

Fig. 2



Hereditary papillary renal cell carcinoma. Clinical picture, papillary type 1 renal cell carcinoma. Adapted with permission from Vikram *et al.* (2009) [25].

Molecular aspects

c-MET is the gene responsible for hereditary PRCC and encodes the cell surface receptor for hepatocyte growth factor. MET presents somatic mutations or amplifications in many sporadic papillary cancers [23].

Management

As no extra renal manifestation has been described in this syndrome, every effort must be made to concentrate in preventing excessive growth of kidney tumors. As in the VHL syndrome, nephron-sparing excision is preferred for lesions reaching more than or equal to 3 cm of diameter.

Targeted therapies

The hepatocyte growth factor/c-MET axis is one of the most attractive targets in anticancer drug development. Like in other ligand–receptor systems, therapeutic interventions range from antibodies directed to the extracellular domain of the receptor to small molecule inhibitors of the tyrosine kinase receptor as already discussed in other papers of this supplement. There is a significant number of new agents in this category undergoing clinical development in different cancer types including hereditary PRCC, with promising results. One of such agents is GSK1363089, a small molecule inhibitor of c-MET. In a phase I study of this c-MET inhibitor, two patients with PRCC achieved a partial response [24]. These data led to a phase II study of this agent in patients with histologically proven PRCC stratified in two groups based on c-MET activation. In a

preliminary analysis of these groups, there are two confirmed partial responses of 25 patients evaluated so far [26].

Birt–Hogg–Dubé syndrome

Clinical picture

(1) Patients with RCC (any histology including oncocytoma) and cutaneous lesions (fibrofolliculomas) [27]
(2) Patients with RCC (any histology including oncocytoma) and lung cysts or spontaneous pneumothorax
(3) Multiple cromophobe, hybrid or oncocytic RCC (Figs 3 and 4).

Description

Birt–Hogg–Dubé (BHD) syndrome is an autosomal dominant hereditary syndrome with a variable phenotype and a large spectrum of clinical manifestations. The most typical are skin lesions that can be easily missed in some cases. Some patients present with familial pneumothorax as the only manifestation of the disease. A high level of suspicion is therefore needed to properly diagnose this syndrome. RCC in patients with BHD is often multifocal and bilateral and presents diverse histology. Fifty percent of tumors are hybrid oncocytic, 38% are cromophobe carcinomas, and 9% clear cell subtype [28]. Oncocytosis is a common finding in nontumoral renal parenchyma [29].

Molecular aspects

The *BHD* gene is localized at the short arm of chromosome 17 and encodes a protein known as foliculin [30]. Although not completely characterized, foliculin seems to downregulate the mammalian target of rapamycin pathway and could therefore function as a tumor suppressor gene [31].

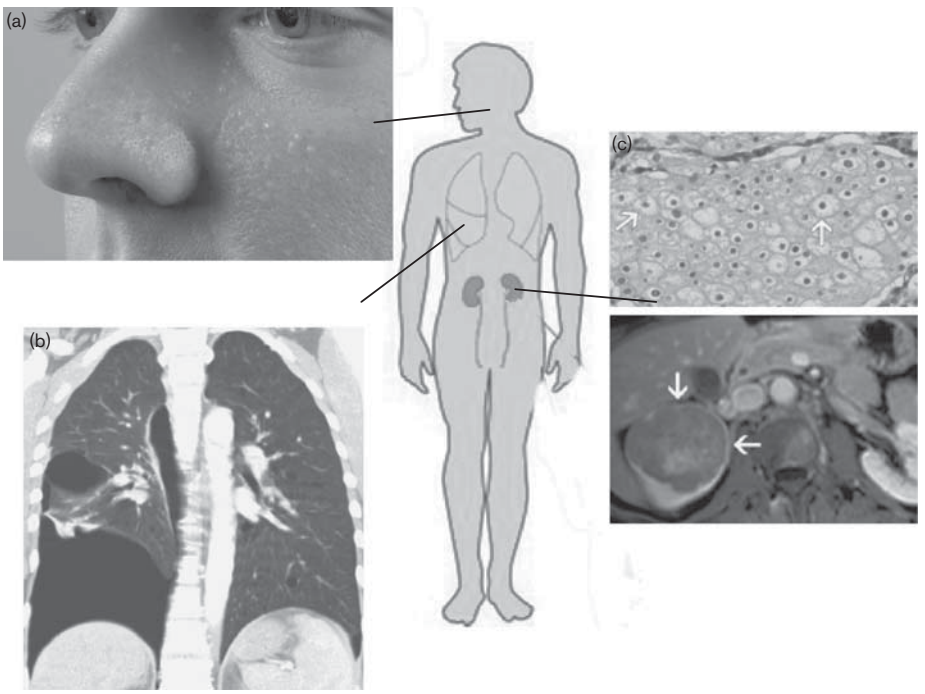
Management

Kidney cancer is the most threatening condition in patients with the BHD syndrome. As it is usually recommended for patients with inherited RCC, close follow-up of lesions of less than 3 cm is recommended whereas larger tumors will require nephron-sparing surgery.

Targeted therapies

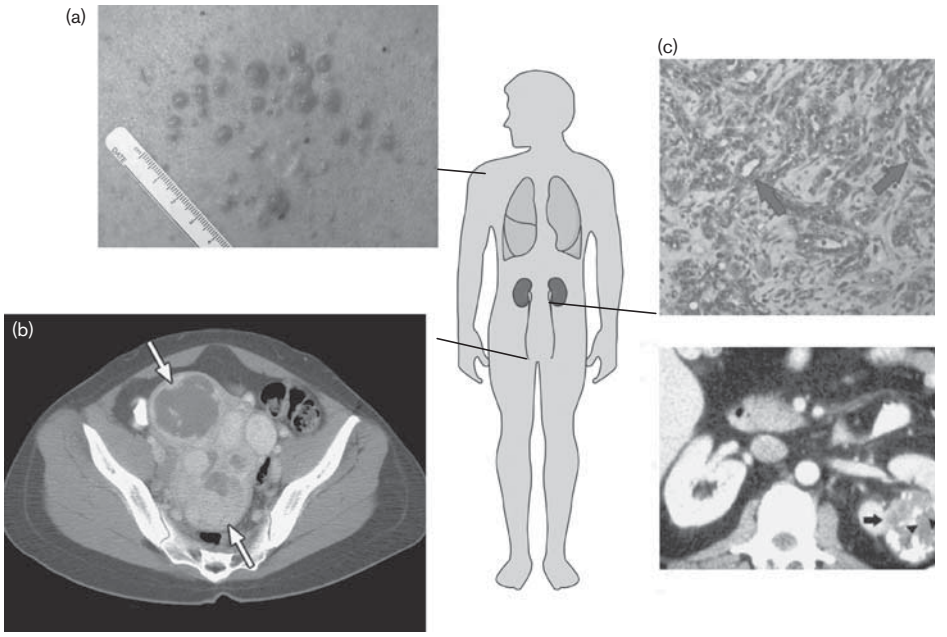
BHD disease is a rare condition that affects approximately 200 families worldwide. No specific therapy has been established for this disease [32]. Despite the fact that the molecular functions of foliculin could provide the basis for a theoretical use of mammalian target of rapamycin inhibitors, this hypothesis has not yet been validated, and subsequently, general recommendations for kidney cancer apply.

Fig. 3



Birt–Hogg–Dubé syndrome: most common clinical pictures (a) fibrofolliculomas; (b) pneumothorax; (c) cromophobe renal cell carcinoma (radiological and pathological views). Adapted with permission from Menko *et al.* (2009) and Prasad *et al.* (2006) [32,33].

Fig. 4



Hereditary leiomyomatosis renal cell carcinoma: most common clinical picture (a) cutaneous lesions leiomyonas; (b) uterine leyomiomas; (c) collecting duct carcinoma (radiological and pathological views). Adapted with permission from Prasad *et al.* (2006) and Grubb *et al.* (2007) [33,39].

Hereditary leiomyomatosis renal cell carcinoma

Clinical picture

(1) Patients with cutaneous lesions (leiomyomas) and RCC
(2) Patient with renal carcinoma who performed a hysterectomy for benign tumors (uterine leyomiomas) at young age
(3) Collecting duct carcinoma of the kidney
(4) PRCC type 2 plus some of the former conditions.

Description

Hereditary leiomyomatosis renal cell carcinoma (HLRCC) is an autosomal dominant inherited syndrome and represents a variant of the so-called multiple cutaneous and uterine leiomyomatosis syndrome [34]. Despite its relatively low incidence, renal carcinoma is the most lethal entity in 2–15% of the patients. Histologically, the tumors are characterized by prominent orangiophilic nucleoli that can be reported as collecting duct or papillary type 2 carcinoma [35].

Molecular aspects

The germ line mutation of HLRCC is localized at the long arm of chromosome 1 and encodes for fumarate hydratase (FH), a Krebs cycle enzyme [36]. Physiologically, FH converts fumarate to malate in the mitochondria level. When damaged, fumarate overaccumulates leading to overexpression of HIF, a proposed mechanism of tumorigenesis in this syndrome [37]. Moreover, FH deficiency is known to upregulate expression of HIF-1α by enhancing the stability of an HIF transcript.

In other way lactate dehydrogenase-A, also a HIF-1α target, promotes fermentative glycolysis (conversion of pyruvate to lactate), a step essential for regenerating NAD^+. It has been shown that lactate dehydrogenase-A inhibition results in increased apoptosis in cells with FH deficiency suggesting that this could be another therapeutic target for these tumor types [38].

Management

HLRCC acts quite differently compared with other hereditary tumors. Thus, the tumor typically rises as a unique mass at an early age and must be resected without delay because of its aggressiveness and trend to metastasize [39].

Targeted therapies

Similar to other rare syndromes, traslational investigation in HLRCC is still lacking. Although current molecular knowledge, once again, points out the possible role of antiangiogenic therapies, no clinical data have confirmed this rationale so far.

Conclusion

It has been shown that hereditary RCC cannot be considered a single entity. Thus, each syndrome owns particular features that must be, at least partially,

known to the attending oncologists and urologists. Early recognition of these specific populations will lead to better care, correct surveillance, and in the near future, personalized treatments taking advantage of the underlying genetic defects.

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