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Review

Imaging findings of hereditary renal tumors, a review of what the radiologist should know

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ABSTRACT

It is estimated that up to 8% of currently diagnosed renal cancers are part of a hereditary syndrome. The radiologist may be the first person to associate a renal tumor presenting during an imaging study to other manifestations of a hereditary syndrome. This diagnosis can have broad implications for the patient but also for other family members. This update reviews the current known associations and emerging mutations of hereditary renal cancers from a radiologist's perspective. Renal manifestations, as well as associated radiological findings and pitfalls are discussed. Additionally, screening and surveillance recommendations are also discussed to aid radiologists in the decision-making process for patient management.

1. Introduction

Renal cell carcinoma is the 6th most common type of cancer, with an estimated incidence of 63,990 cases in 2017 in the United States alone [1]. It is currently estimated that 5–8% of these patients are non-sporadic and have a hereditary component, but the number may be higher as further genetic predispositions are identified. One population-based study estimated that a hereditary component may be part of up to 58% of cases [2,3]. Germline genetic mutations may play a pivotal role in future management and treatment strategies, so patients with a possible hereditary component should be referred for genetic evaluation. The findings have direct implications for first degree relatives of the patient. Recently, it has been found that genetic testing is beneficial in individuals with a family history of renal cancer or an unusual personal history, as well as patients presenting in childhood or as young adults [4]. The radiologist may be the first to suspect a possible hereditary syndrome.

In this review, we have organized the current known mutations associated with hereditary renal cancer (HRC) into renal-epithelial syndromes and emerging mutations that are still not completely characterized (Table 1). We will describe the renal and systemic manifestations of von Hippel-Lindau (VHL) syndrome, tuberous sclerosis complex (TSC), Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC), hereditary papillary renal carcinoma syndrome (HPRCC), and hereditary non-polyposis colorectal cancer syndrome (HNPCC) which have been previously well described. Many of the radiological features present in the described syndromes are not distinct, and require a thorough review of the associated findings which may help the radiologist to identify the syndrome. Additionally, a review of the current recommended follow-up and management strategies will also be discussed.

Additionally, there is an increasing list of newly discovered mutations which are still not as well described or taxonomized as the ones mentioned above. Currently, the non-syndromic mutations associated with renal cancer include chromosome 3 translocations, PTEN mutation, BAP1 predisposition syndrome, MiTF-associated cancer syndrome, succinate dehydrogenase complex subunit B-associated renal cell carcinoma (RCC), and Xp11.2 translocation/TFE3 gene fusion. These will also be discussed from a radiologist's perspective, based on imaging appearances and any known associations.

2. Characterized renal-epithelial syndromes

2.1. von Hippel-Lindau syndrome

The most commonly identified HRC is von Hippel-Lindau syndrome. It is estimated that 1 in 35,000 people are carriers of this autosomal dominant hereditary disease caused by a mutation in the *VHL* tumor suppressor gene, with about 20% of cases being due to sporadic mutation [5]. The most common manifestations include neuroendocrine tumors of the pancreas, CNS hemangioblastomas, pancreatic cysts, retinal angiomas, papillary cystadenomas of the epididymis, as well as

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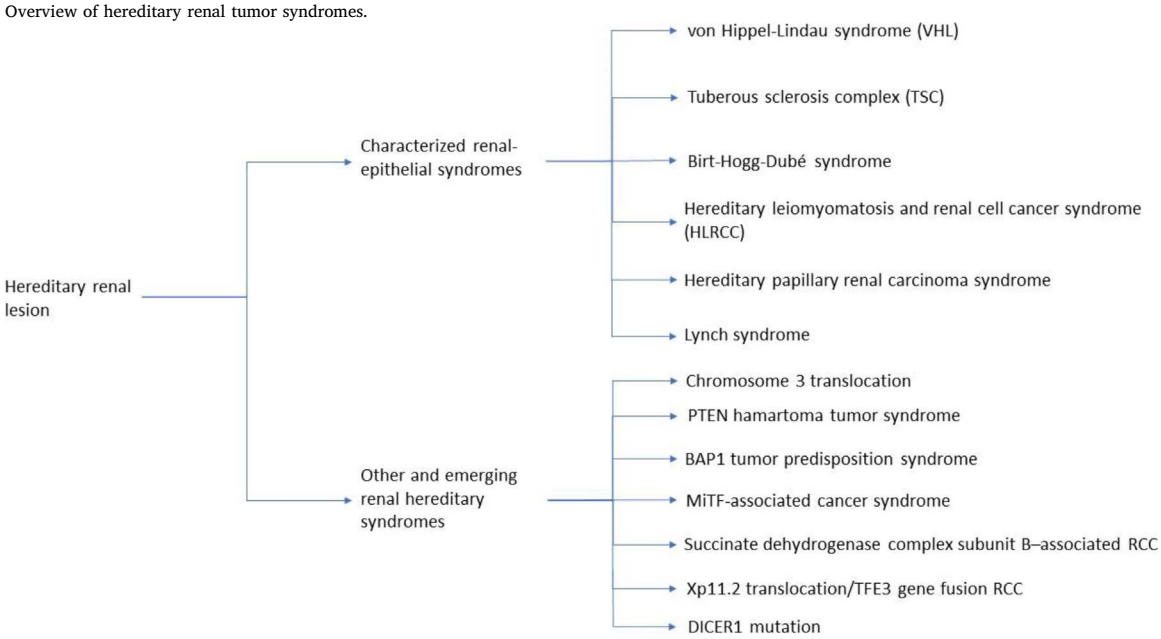
Table 1
Overview of hereditary renal tumor syndromes.



clear cell solid and cystic renal cell carcinoma (ccRCC). These manifestations cause significant morbidity, but ccRCC is associated with the highest mortality, with 24–45% of patients being affected and a 70% lifetime risk [6,7].

2.1.1. Renal imaging findings

Patients with the *VHL* tumor suppressor gene mutation develop multiple renal cysts, which are lined by clear cells that can give rise to neoplasia. For this reason, all cysts can be considered premalignant and warrant follow-up. Clear cell RCC represents nearly 100% of the subtypes of VHL-associated renal cancer, but the pathogensis in not fully understood [8,9].

On MRI, the lesions are T1-hypointense and T2-hyperintense due to their cystic nature. On CT, the cysts usually have a water attenuation. With progression, septations can develop, as well as solid components consisting of mural nodular enhancement and hypervascularity can be seen on contrast enhanced images (Fig. 1). These nodules can eventually overtake the cystic component leading to completely, or near completely-solid renal masses. Compared to other RCC subtypes, ccRCC shows a stronger enhancement in the cortico-medullary phase with a more persistent enhancement in the excretory phase. The pattern of enhancement has previously been shown to be the best predictor of tumor subtype [10]. This finding requires careful inspection to differentiate with minimally complex type 2F Bosniak cysts. Once multiple septations and/or mural enhancement develop, the lesions should be considered Bosniak 3 cysts.

2.1.2. Extra-renal manifestations

Except for the described predisposition for renal cysts and ccRCC, abdominal studies may show pancreatic cysts, solid pancreatic neuroendocrine tumors (PNETs) and pheochromocytomas/paragangliomas. Like the kidney, pancreatic cysts are often multiple and distributed throughout the pancreas. Pancreatic serous cystadenoma is the most common histological subtype which has a benign natural history [11]. These lesions are seen on cross-sectional imaging as polycystic with cysts typically measuring < 10 mm (Fig. 2) and often arranged in a rosette pattern around a central scar. The cysts are often surrounded by a dense fibrous septum in addition to a central scar, making them hard on palpation during surgery. Calcification is frequent. Serous cystadenomas are characterized by larger, multiple cysts as opposed to the more commonly seen isolated cyst. Similar findings are seen in males with multiple cysts in the epididymis, with up to 40%

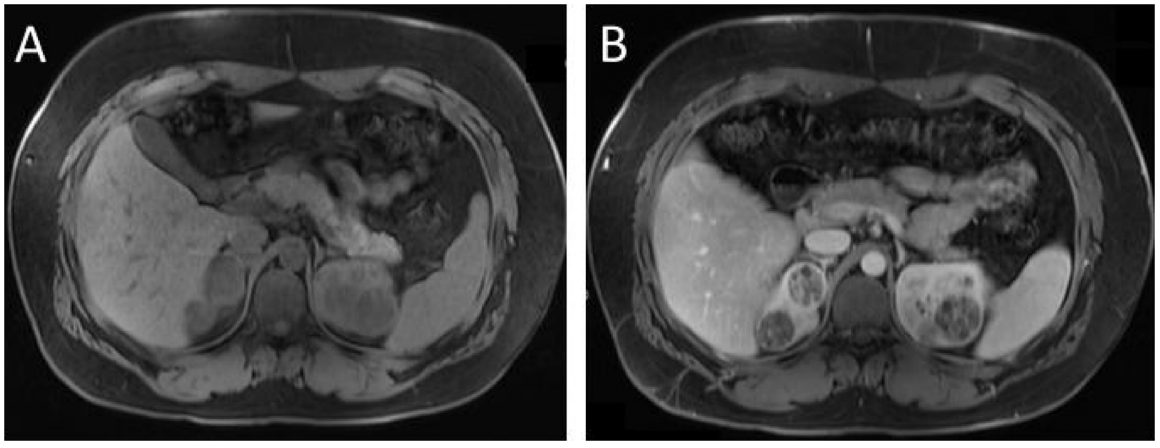


Fig. 1. Pre (A) and post-contrast (B) T1 weighted fat saturated MR images in a patient with VHL disease with bilateral renal lesions. Pre-contrast image shows heterogeneous lesions in both kidneys (A); whereas post-contrast image shows mixed solid-cystic lesions with heterogeneous enhancement (B). Biopsy confirmed clear cell renal cell carcinoma.