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Review

Renal tumors with clear cells. A review

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ABSTRACT

The spectrum of primary renal tumors in which clear cells may appear is revisited in this review. The pathologist's viewpoint of this topic is pertinent because not all the tumors with clear cells are carcinomas and not all renal cell carcinomas with clear cells are clear cell renal cell carcinomas. In fact, some of them are distinct entities according to the new WHO classification. The morphological approach is combined with genetics. Renal cell carcinoma related to von Hippel–Lindau disease is reviewed first because many of the genetic disorders underlying this disease are also present in sporadic, conventional renal cell clear cell carcinomas. Subsequently, conventional renal cell clear cell carcinomas, familial, non von Hippel–Lindau-associated renal cell carcinomas, translocation carcinomas, hereditary papillary renal cell carcinomas, carcinomas associated to tuberous sclerosis and to Birt–Hogg–Dubé syndrome, chromophobe renal cell carcinomas, carcinomas associated with end-stage renal disease, and clear cell tubulopapillary carcinomas are reviewed. Finally, epithelioid angiomyolipoma is also considered in this review.

Contents

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Introduction

As pathologists, we have a clear idea of what we are talking about when we refer to clear cells. "Clear cell", like "small cell", "round cell" and other "cells", is an expression that becomes part of the pathologists' jargon. The term refers to cells with characteristic clear or "washed out" cytoplasm due to rich cytoplasm glycogen or fat content that are lost during tissue processing and therefore not stained with hematoxylin–eosin. Generally, the cytoplasm is also delineated by a very well-defined membrane. A broad range of neoplasms, and sometimes non-neoplastic conditions, may contain clear cells. A glance at the alphabetical index of any book on current surgical pathology [38,69], or keying in "clear cell carcinoma" on PubMed will be enough to discover how long and varied the list can be.

Occasionally, a clear cell can make a tumor exclusive, giving it a life of its own with a built-in prognosis. Other times, its clear cell appearance is only a secondary change, a mere circumstance with no implications for diagnosis or prognosis. It is important, therefore, to distinguish a carcinoma *with* clear cells from a clear cell carcinoma, because the two terms are not necessarily synonymous.

Renal cell carcinoma associated with von Hippel–Lindau disease

VHLD is a hereditary neoplastic syndrome characterized by retinal and central nervous system hemangioblastomas, clear cell renal carcinomas, and pheochromocytoma. It affects around one out of 35,000 people in an autosomal dominant manner. It was described in 1894 by Treacher Collins, when he described vascular lesions in the retinas of a pair of twins. However, the disease took its name from the German ophthalmologist Eugene von Hippel and the Swedish pathologist Arvid Lindau, who each studied the disease's retinal and cerebellar lesions on their own more than a decade after Dr. Collins' first report.

Later, a series of lesions associated with the disease have been described, particularly visceral cysts (pancreatic and renal) and a broad range of tumors (clear cell renal carcinomas, adrenal pheochromocytomas, endolymphatic sac tumors, broad ligament tumors, epididymis tumors and tumors of the pancreatic islets) [53].

Genetics

The gene responsible for VHLD was located and described for the first time in 1988 by Seizinger et al. [76] on the short arm of chromosome 3 (3p25–26). It consists of 3 exons and it is ubiquitous, not limited to the organs that are affected by the disease.

Germline inactivation in one of the alleles of the *VHL* gene is the cause of the neoplastic syndrome, which manifests when a somatic mutation occurs in the other allele. *VHL* gene mutations are extremely heterogeneous, and they are distributed throughout the gene sequence. To date, around 150 different mutations have been described [91]. A list of them is to be found at http://www.umd.necker.fr:2005 and http://web.ncifcrf.gov.

The *VHL* gene is a suppressor gene [15,55,58]. It encodes a protein with two isoforms, $pVHL_{30}$ and $pVHL_{19}$, which are responsible for the gene's anti-tumoral function. Under normoxic conditions, the protein targets the hypoxia-inducible factors (HIFs) to proteosomes for degradation; therefore HIF protein levels are kept low. Lack of its function, either by gene mutation or promoter hypermethylation, causes HIFs to become accumulated within the cell and induces the transcriptional activation of a broad range of factors that regulate angiogenesis (vascular endothelial growth factor, VEGF), cell cycles and cell growth (platelet-derived growth factor, PDGF), pH balance (carbonic anhydrase CAIX), and erythropoietin [48,79].

However, pVHL also plays a role in the regulation of metalloproteinases and other enzymes. The absence of pVHL, for instance, increases the levels of carbonic anhydrases IX and XII, substances that increase the level of acidification in the microenvironment, which in turn enhances invasive properties and tumoral growth, and up-regulate cyclin D1. The presence of carbonic anhydrase IX (CAIX) and cyclin D1 can be studied by immunohistochemical staining in paraffin sections, which is important for pathologists in their daily work, as will be discussed later in this review.

CCRCC associated with VHLD tends to be multifocal, bilateral and cystic, and has an early age onset. Therefore, the pathologist should consider VHLD when we encounter renal tumors with these characteristics in people who are younger than expected and have other stigmata of VHLD [43].

Pathology

In general, these tumors are limited to the kidney (pT1/2). The affected kidney may contain multiple cysts. The walls of the cysts are lined with one or more layers of malignant clear cells. However, the cystic wall may be denuded or covered by fibrinous-hemorrhagic material. Sometimes the malignant cells are flattened and may be difficult to visualize. Cystic regions alternate with solid nests of clear cells. There may be multiple patterns of cell growth, including trabecular, tubular, cystic or microcystic, and pseudopapillary, accompanied by a thin arborizing capillary network. The cells are polygonal and contain a hyperchromatic nucleus, and often with no apparent nucleolus (Fig. 1). The immunohistochemical signature is similar to sporadic clear cell carcinomas, as will be detailed in the paragraphs below. CCRCC associated with VHLD should be distinguished from the multilocular subtype of CCRCC, which is typically entirely cystic and without solid regions. Additionally, multilocular CCRCC grossly shows a thick fibrous capsule and no solid clear cell nests microscopically.