Adult Renal Cell Carcinoma

A Review of Established Entities from Morphology to Molecular Genetics

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KEYWORDS

• Renal cell carcinoma • Clear cell • Papillary • Chromophobe
• Mucinous tubular and spindle cell carcinoma • Translocation • Xp11.2 • Collecting duct

ABSTRACT

According to the current World Health Organization (WHO), renal cell carcinomas (RCCs) that primarily affect adults are classified into 8 major subtypes. Additional emerging entities in renal neoplasia have also been recently recognized and these are discussed in further detail by Mehra et al (Emerging Entities in Renal Neoplasia, Surgical Pathology Clinics, 2015, Volume 8, Issue 4). In most cases, the diagnosis of a RCC subtype can be based on morphologic criteria, but in some circumstances the use of ancillary studies can aid in the diagnosis. This review discusses the morphologic, genetic, and molecular findings in RCCs previously recognized by the WHO, and provides clues to distinction from each other and some of the newer subtypes of RCC. As prognosis and therapeutic options vary for the different subtypes of RCC, accurate pathologic distinction is critical for patient care.

OVERVIEW

Primary cancers of the kidney are a heterogeneous group of neoplasms that account for approximately 4% of newly diagnosed malignancies in men and women annually.[1] In the United States, this translates into approximately 65,000 new cases annually, approximately one-fifth (23%) of which will result in death from disease (~2.6% of all cancer deaths).[1] Renal epithelial neoplasms account for most renal tumors (80%–85%), and in 2004, the World Health Organization (WHO) recognized the following 8 adult renal epithelial malignancies: clear cell (conventional) renal cell carcinoma (CCRCC), multilocular CCRCC, papillary RCC (PRCC), chromophobe RCC (ChRCC), Xp11.2 translocation RCC, mucinous tubular and spindle cell carcinoma (MTSCC), collecting duct carcinoma, and unclassified RCC.[2] Overall, renal epithelial tumors occur more frequently in men than women, but some of the newer subtypes affect women more frequently than men. Renal epithelial neoplasms can be associated with a lack of early warning signs (based on their protected location in the retroperitoneum) and diverse clinical signs, and are frequently found incidentally with imaging studies for other clinical reasons. Accordingly, the average age of a patient with a renal epithelial neoplasm is now likely younger than originally thought (classically RCCs are thought to occur most frequently in the seventh to eighth decades). Although the overall 5-year survival for all renal malignancies has shown a trend toward improvement over the past 3 decades,[1] the actual prognosis based on RCC subtype can vary significantly with CCRCC, collecting duct carcinoma, unclassified RCC, and those with sarcomatoid differentiation having the worst survival rates.[3–7] For this reason, accurate subtyping of renal epithelial neoplasms is paramount to defining the most appropriate treatment options and predicting prognosis[8] (see also

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Albiges et al., Diagnosis of Renal Cell Carcinoma: A Clinician's Perspective, Surgical Pathology Clinics, 2015, Volume 8, Issue 4).

CLEAR CELL (CONVENTIONAL) RENAL CELL CARCINOMA

CLINICAL PRESENTATION, GROSS FEATURES, AND PROGNOSIS

CCRCC is the most common variant of RCC, accounting for more than 70% of kidney malignancies. It can present as a small solitary lesion confined to the kidney or can grow quite large beyond the confines of the renal capsule (**Fig. 1**). Tumors can also be multifocal or bilateral; however, this is a less common occurrence. CCRCC has the highest propensity for renal vein involvement and can present with metastatic disease. Grossly, the tumors are often well circumscribed and may be surrounded by a thin fibrous pseudocapsule. The cut surface of CCRCC is typically golden yellow to tan (see **Fig. 1**); the former of which is due to lipid and glycogen within the cells. It is important to sample fleshy white appearing areas of a CCRCC as this may represent sarcomatoid differentiation, which is associated with a worse prognosis.[3,5,9] As CCRCC is derived from cortically based tubules (thought to be the proximal convoluted tubules), the renal cortex is often the epicenter of the tumor, and growth typically occurs with a "pushing" front, displacing non-neoplastic renal parenchymal elements (nephrons) to the periphery (**Fig. 2**). However, high-grade tumors may demonstrate small satellite nodules or infiltrate between renal tubular structures beyond the confines of the main mass.[10] Areas of cystic change and hemorrhage within CCRCCs are frequently present. Necrosis has been shown to be associated with a worse prognosis,[11,12] and the presence should be mentioned in the final pathology report. Approximately half of CCRCCs are confined to the kidney at the time of surgery (pT1-pT2); nevertheless, approximately 30% of CCRCCs will recur or metastasize and this is not restricted to high-grade, high-stage disease. Although patients with von Hippel Lindau (VHL) disease may develop CCRCC, most CCRCCs are associated with a sporadic mutation on the short arm of chromosome 3 (3p), including the site of the *VHL* gene[13] (see below for more details).

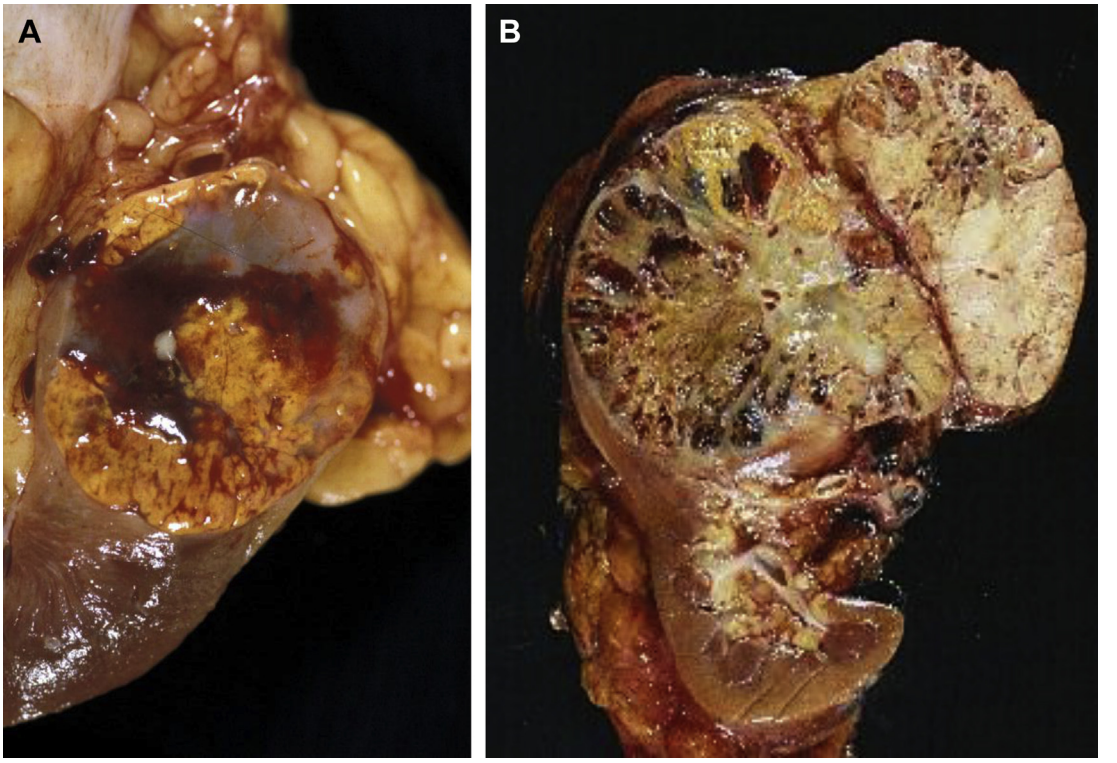

Fig. 1. Clear cell renal cell carcinoma. The gross appearance of a CCRCC is characteristically golden yellow, and it may be associated with variable amounts of hemorrhage and necrosis. Tumors arise from cortical tubules and can be (*A*) confined to the renal parenchyma or (*B*) extend beyond the capsule into perinephric soft tissue.