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Review Article

Clear cell papillary renal cell carcinoma, renal angiomyoadenomatous tumor, and renal cell carcinoma with leiomyomatous stroma relationship of 3 types of renal tumors: a review☆,☆☆

Ondrej Hes, MD, PhD *, Eva Maria Compérat, MD, PhD, Nathalie Rioux-Leclercq, MD, PhD

Department of Pathology, Charles University in Prague, Faculty of Medicine in Plzeň, Pilsen, Czech Republic
Department of Pathology, Hôpital La Pitié Salpêtrière, Faculty of Medicine UPMC Paris VI, France
Department of Pathology, CHU Pontchaillou, Université de Rennes 1, Rennes, France

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ABSTRACT

Renal angiomyoadenomatous tumor has been described in 2000, followed by description of clear cell papillary renal cell carcinoma in 2006. Discussions about possible relationship of both tumors were published since their description. The main differential diagnostic feature was considered presence/absence of fibroleiomyomatous stroma-relationship of renal angiomyoadenomatous tumor in stroma-rich tumors. However, it was shown that stroma is reactive and nonneoplastic by its nature and that all other histologic, immunohistochemical, and molecular-genetic features of both entities are identical. In upcoming World Health Organization classification of renal tumors (2016), both lesions are considered as a single entity (clear cell papillary renal cell carcinoma [CCPRCC]). Most published cases followed the benign/indolent clinical course. In addition, most tumors has normal status of *VHL* gene (methylation, LOH 3p, mutations); however, CCPRCC was referred in patients with VHL syndrome. Another issue covered by this review is possible relationship of CCPRCC and "renal cell carcinoma with leiomyomatous stroma" (RCCLS). Renal cell carcinoma with leiomyomatous stroma shows clear cell cytology and abundant leiomyomatous stroma. Some of RCCLS are positive for cytokeratin 7; some are negative. Similar situation exists for relation of RCCLS and *VHL* gene abnormalities. It is so far unclear whether any relation between CCPRCC and RCCLS exists. From all published studies, it seems that these tumors are less likely related to each other.

1. Introduction

Renal angiomyoadenomatous tumor (RAT) has been described by Michal et al [1] in 2000 in the form of a case report and later in 2009 as series of 5 cases. Since initial description, several reports describing this distinct renal tumor have been published [1-4] (Fig. 1). Morphologically, RATs are composed of tubules, small compact nests, and abortive papillae lined by neoplastic columnar epithelial cells with optically clear cytoplasm, frequently with an apical "blister" quality and low-grade (Fig. 2), basally located nuclei, a well-developed peritubular capillary network and slightly open, variably angulated tubules which have been likened to the "shark smile" (Fig. 3) and variable presence of a leiomyomatous/myofibroblastic stroma (Fig. 4). Immunohistochemically, the neoplastic epithelial cells of RAT express carbonic anhydrase 9 (CANH-9) (cup-shaped pattern), cytokeratin 7 (CK-7), and PAX8, whereas expression of vimentin, CD10, and racemase (AMACR) is variable.

Clear cell papillary renal cell carcinoma (CCPRCC) has been introduced in 2006 by Tickoo et al [5] in end-stage kidney disease. Most cases reported since initial description have been recognized in nonatrophic kidney [5-8]. Numerous studies were addressed to further characterization of this relatively common, previously underrecognized renal tumor.

According to the International Society of Urological Pathology (ISUP) Vancouver Classification 2012, CCPRCC is well circumscribed and well encapsulated. The cut surface is whitish to tan. Tumors are composed of clear cells of low nuclear grade, variable papillary, tubular/acinar, and cystic architecture and a characteristic linear arrangement of nuclei away from the basal aspect of cells (Fig. 5). Immunohistochemical profile is nearly identical with RAT; that is, tumors are positive for CK-7 (Fig. 6), CANH-9, high-molecular-weight cytokeratin positive, and CD10 and AMACR negative [9]. Coexpression of CK-7, which is, by definition diffuse and strong, and CANH-9 is usually consider as immunohistochemical landmark of CCPRCC. Expression of CANH-9 is mostly diffuse with characteristic cup-like shape pattern [7]. Such pattern corresponds with shape of neoplastic cells. Typically, they are cylindrical with elongated blister-shaped snouts in luminal aspect of neoplastic

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* Corresponding author at: Department of Pathology, Charles University, Medical Faculty and Charles University Hospital Plzen, Alej Svobody 80, 304 60 Pilsen, Czech Republic.
E-mail address: hes@medima.cz (O. Hes).

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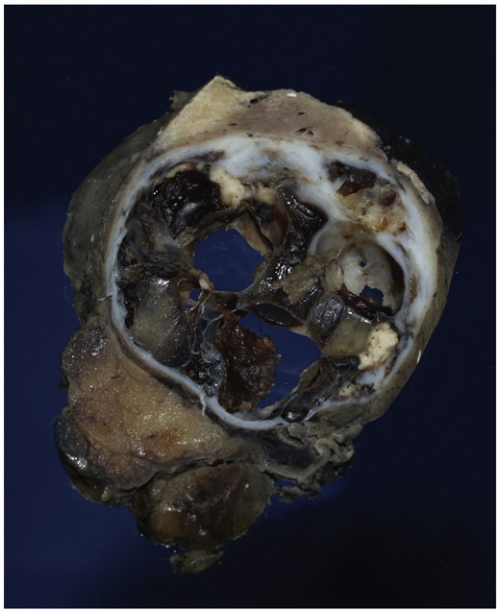

Fig. 1. Typical CCPRCC (RAT). Tumor is encapsulated by thick whitish tissue with prominent septa crossing neoplastic mass.

glands. Apical portion of such cells is negative for CANH-9; thus, "cup shape" of the membranous positivity is obvious.

1.1. Relationship of CCPRCC and RAT

Renal angiomyoadenomatous tumor and CCPRCC share almost equal morphology and immunophenotype. Both types are characterized by the presence of fibroleiomyomatous stroma and CK-7 positivity; they also bear similar molecular genetic attributes (lack of *VHL* gene abnormalities) [10,11]. Presumably, the difference between them inheres in stromal component, in the sense that RAT exhibits a voluminous stromal component and CCPRCC, in contrast, usually features a much less prominent smooth muscle stroma.

There is no strict line between CCPRCC and RAT. Minimum volume/amount of stroma has never been defined. Thus, it is a very subjective issue without exact criteria for differential diagnostic process.

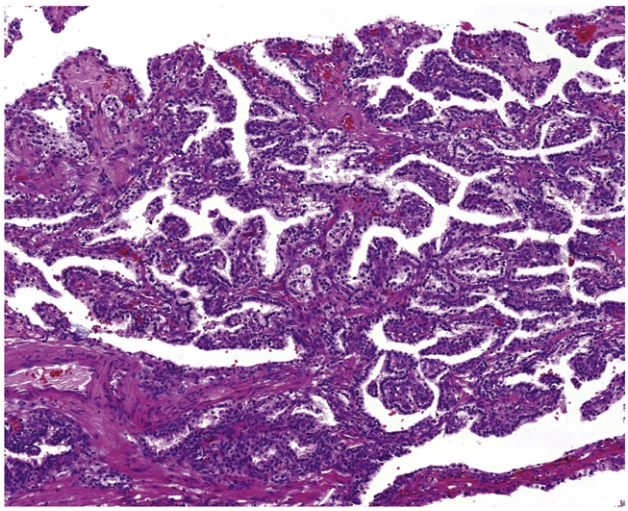

Fig. 2. Clear cell papillary renal cell carcinoma (RAT) is composed of tubules, small compact nests, and abortive papillae lined by neoplastic columnar epithelial cells with optically clear cytoplasm, with an apical "blister" quality and low-grade, basally located nuclei.

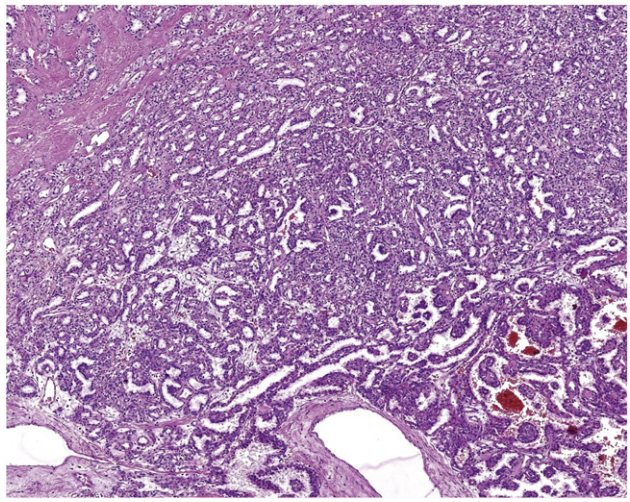

Fig. 3. Angulated tubules that have been likened to the "shark smile" seen scattered in neoplastic mass.

However, the presence of the abundant fibroleiomyomatous stroma has been becoming as an important mark of distinction between RAT and CCPRCC, and hence, these 2 entities are regarded as related tumors and viewed as 2 ends of the spectrum of 1 nosologic entity in ISUP 2012 [9].

Two multicentric studies have been published recently [7,8]. As conclusion of both articles is obvious, that RAT and CCPRCC are 2 morphologic ends of 1 etiologic entity. Similar view will be expressed in upcoming World Health Organization classification 2016.

1.2. Clear cell papillary renal cell carcinoma/RAT differential diagnosis

Most cases are easily recognizable tumors with characteristic morphology. There are several issues that should be addressed.

Morphologic changes resembling CCPRCC can be seen within "typical" clear cell renal cell carcinoma (CCRCC). Such changes can produce tubopapillary architecture, "shark smiles," and even blister-like proliferation within lumens of cystic or tubular changes. In typical CCRCC, such areas are mostly CK-7 negative.

However, CCRCC are considered as CK-7–negative tumor, but it is possible to find cases with strong CK-7 positivity. Expression of CK-7 in CCRCC (albeit not strong and diffuse) has been documented by Gatalica et al [12] as early as 1995. The authors described immunoreactivity for

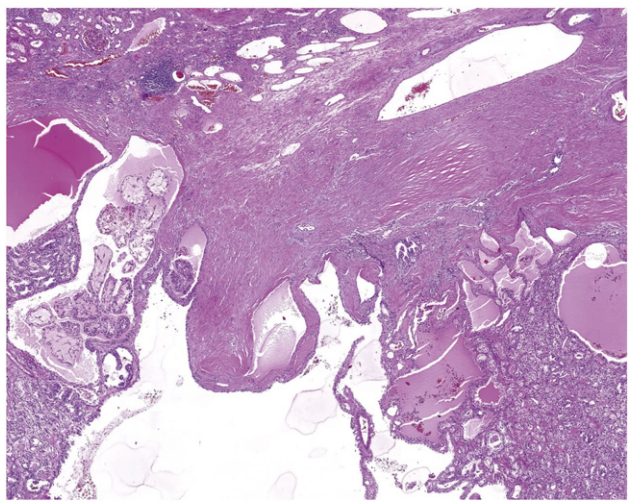

Fig. 4. Capsule and leiomyomatous stroma is clearly visible in histotopogram of CCPRCC (RAT).