Original Article

Tubulocystic oncocytoma of the kidney: a case study and review of literature with focus on implications for differential diagnosis

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Abstract: Renal oncocytoma (RO) can rarely present with a multilocular or tubulocystic growth pattern that may cause significant diagnostic difficulties with a variety of cystic renal cell carcinomas (RCC). Distinguishing these RO variants from their many RCC mimickers is critical because of its typical benign clinical course. Herein, we report a case of RO with extensive tubulocystic architectures on a 42-year-old female patient and discuss the clinicopathologic characterizations of this unusual RO variant with an emphasis on the wide spectrum of differential diagnoses of a variety of primary or secondary renal tumors that are featuring of both oncocytic cell changes and tubulocystic growth patterns.

Keywords: Renal tumor, oncocytoma, tubulocystic carcinoma, differential diagnosis

Introduction

Renal oncocytoma (RO) is an uncommon, benign renal epithelial tumor with distinct gross, histomorphologic, ultrastructural and cytogenetic features [1]. It accounts for 3-9% of all adult renal epithelial neoplasms in most series [2-4]. Microscopically, classic RO is composed of dense eosinophilic monotonous tumor cells with bland cytologic features in solid, nest, or tubular growth patterns, separated by a variable degree of edematous or hyprocellular stroma [1]. Morphologic variants and unusual features, such as small cell or oncoblastic variant, focal clear cell change, chromophobe-like appearance, presence of mitoses, and cystic transformation, have rarely been documented in RO in the literature [5, 6], which could cause significantly diagnostic confusions. Foci of microcystic change is not uncommon seen in RO and is generally considered as a degenerative process related to the central scar of this entity [2, 3, 6], but oncocytoma with a multilocular cystic presentation is very rare [3, 6-9], and is often misdiagnosed as renal cell carcinoma (RCC) with a cystic component, particularly when limited tissue sample is available for assessment. In this report, we present a case of RO with extensive tubulocystic architectures and emphasize the wide spectrum of differential diagnoses of a variety of primary or secondary renal tumors that are featuring of both oncocytic cell changes and tubulocystic architectural patterns.

Case presentation

A previously healthy 42-year-old female was incidentally identified to have a mass in her right kidney by ultrasonic scan for annual physical examination. Subsequent computed tomography (CT) scan revealed a low-density, round, 3.5-cm partially cystic and solid mass located in the upper pole of the right kidney (Figure 1). The mass was circumscribed and abutting the capsular region. With the suspicion of RCC, the patient underwent a right laparoscopic partial nephrectomy. Both the intraoperative impression and a postoperative ultrasonography confirmed that gross total tumor resection had been achieved. She was discharged a week later after the surgery. Recently at a 10-month
follow-up, the patient was in a good status with no evidence of renal tumor relapse.

Materials and methods

The resected specimen was fixed in 10% buffered formalin and routinely processed and stained with hematoxylin and eosin. Immunohistochemical analyses were performed using avidin-biotin-complex immunoperoxidase technique with a panel of commercially available primary antibodies to the following antigens: PAX8 (polyclonal, Proteintech, USA), cytokeratin 7 (CK7) (OV-TL12/30, Dako), high molecular weight cytokeratin (HWCK) (34βE12, Dako), vimentin (V9, Dako), epithelial membrane antigen (EMA) (E29, Dako), CD10 (56C6, Dako), alpha methylacyl-CoA racemase (AMACR) (p504s, Dako), renal cell carcinoma marker (RCCma) (gp200, Dako), E-cadherin (polyclonal, Dako), c-kit (polyclonal, Dako), thyroid transcription factor 1 (TTF1) (8G7G3/1, Dako), thyroglobulin (TG) (2H11, Dako), melan-A (A103, Dako), HMB45 (HMB45, Dako) and Ki67 (MIB-1, Dako). Appropriate positive and negative controls were run concurrently for all the markers tested.

Results

Gross examination showed that the tumor was well-defined and encapsulated with the maximum diameter measuring up to 3.5-cm. Cut surface showed that the tumor was predominantly cystic and partially solid of a spongy consistency; the cysts were multilocular and separated by thick-walled and smooth septa, some of which were filled with blood or clear fluid. No central scar was grossly evident, necrosis was not identified. Microscopically, the tumor was well-demarcated and separated from the surrounding renal parenchyma by a thick fibrotic capsule (Figure 2A). It was composed of variable-sized cysts ranging from cystic dilated tubules, microcysts to large cystic spaces that were covered by a single layer of cuboid to low-columnar epithelial cells (Figure 2B). The smaller cystic spaces were empty whereas the larger ones were filled with serosanguinous fluid, or blood fluid (Figure 2C). Not frequently, delicate papillae-like formations, typically forming isolated protrusions within the dilated cysts, were noted (Figure 2D). Between the cysts and cystic tubules were usually scant delicate edematous stroma with occasional solid tumor cells nests and islands present. A small area of classic solid oncocytoma was identified at the periphery of the tumor. The tumor cells were cuboid to low-columnar and contained abundant, granular eosinophilic cytoplasm, no hobnail or clear cells were found. The nuclei were round with one or several small nucleoli corresponding to Fuhrman nuclear grade 2, no mitosis or significant nuclear atypia or cytologic pleomorphism was found (Figure 2E, 2F). Focal hemosiderin deposits or hemosiderin-laden macrophages were noted.

On immunohistochemistry (IHC), the tumor cells showed patchy nuclear expression of PAX8, diffuse membranous expression of EMA, c-kit (Figure 3A), and E-cadherin (Figure 3B). Less than 5% of the tumor cells expressed CK7 (Figure 3C), they were negative for all the other markers detected including vimentin (Figure 3D), AMACR, CD10, RCCma, HMB45, melan-A, TTF1, and TG. Ki67 labeled approximately 1% tumor cells. A diagnosis of tubulocystic oncocytoma was rendered on the basis of the unique architectural patterns, classic cytological features as well as the typical immunohistochemical profiles supportive of RO.

Discussion

RO is the second commonly seen benign renal epithelial tumor after papillary adenoma, which
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comprises 3-9% of all renal tumors and has excellent prognosis [1-4]. Although single case reports of its malignant behavior have been documented in the older literature [10, 11], contemporary large series studies using standardized diagnostic criteria have consistently confirmed the benign nature of RO [6].

Figure 2. Microscopic examination showed that (A) the tumor was well-demarcated and encapsulated and (B) composed of variable-sized cysts ranging from cystic dilated tubules, microcysts to large cystic spaces. (C) These cystic spaces were filled with serosanguinous fluid, or blood fluid. (D) Depicting papillae-like formations, typically forming isolated protrusions within the dilated cysts. (E, F) The lining cells were cuboid to low-columnar and contained finely granular eosinophilic cytoplasm with bland-appearing nuclei, arranged in a single row pattern.

RO is histologically known for its variations in architecture and cytology, which may show a spectrum of atypical morphology, such as vascular or adipose tissue extension, presence of small oncocytic cells, microscopic necrosis, pleomorphic nuclei, or rare mitoses, accounting for its well-known ability to mimic malignant
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Several growth patterns have been documented in RO with nested and solid patterns being the two most commonly seen ones, less uncommon architectures include cystic, tubular, and trabecular. Most ROs demonstrate a combination of these growth patterns, and less frequently, prominence with one architectural pattern [1, 3]. RO with prominent tubulocystic features is very unusual and comprises 3-7% of all RO in the latest large series studies [3, 6, 9]. Similar tumors have been designated as “cystic renal oncocytoma” [9], “telangiectatic oncocytoma” [4], or “multilocular cystic renal oncocytoma” [8] in the literature. To date, less than forty such RO case have been reported in the English language literature.

Clinically, the mean age of patients with tubulocystic RO is 68.7 years (range, 51 to 85 y) with male-to-female ratio of 2.4:1. Preoperative imaging studies show that tumors usually present as an hypervascular heterogeneous mass, consistent with or suspicious for RCC, and no distinction with other cystic renal tumors is possible, in particular, no central scar is seen and these tumors may be classified as suspected cystic tumors corresponding to Bosniak’s class 3 [4, 8]. Grossly, the mean size is 2.5 cm, displaying brown cut surface with numerous small to large, often hemorrhagic cysts; necrosis is uniformly absent. Histologically, tubulocystic RO is composed of an admixed proliferation of variable-sized cystic tubules and cysts separated by a background of loose or hypocellular stroma. A variable component of cell islands and solid areas are consistently present in all cases of tubulocystic RO [9]. The cystic spaces are typically empty, or filled with serosanguinous or pure blood fluid resembling a cavernous hemangioma [4]. Rarely, isolated, delicate papillary projections can be noted in the dilated microcysts [6]. The lining cells of the tubules and cysts are a single row of cuboid to columnar epithelium.
nar shaped oncocytic cells with a finely granular and eosinophilic cytoplasm and small, round, bland-appearing nuclei. Necrosis and mitosis are uniformly not noted. Histochemical and immunohistochemical studies show that tubulocystic RO demonstrates the same expression profile to conventional RO, with tumor cells strongly and diffusely positive for c-kit and E-cadherin and usually negative for CK7, CD10, vimentin, AMACR, and colloid iron stain [9, 12].

The differential diagnosis of tubulocystic RO is broad and includes a variety of common and not-so-common, primary or secondary renal tumors that are featuring of both tubulocystic growth pattern and oncocytic cell changes. These include eosinophilic variant chromophobe RCC, tubulocystic RCC, oncocytic papillary RCC, and metastatic thyroid carcinoma. Although careful histomorphologic investigation and identification of foci of typical solid RO areas is critical in distinguishing tubulocystic RO from its many mimickers, IHC, and occasionally molecular genetic analysis will prove decisive.

Eosinophilic chromophobe RCC typically shows a densely packed nested or broad alveolar growth pattern, and rarely, it may adopt a predominance of tubular or cystic growth pattern mimicking tubulocystic RO [13]. In contrast to the finely granular cytoplasm and uniform, round nuclei of RO, the cytoplasm in chromophobe RCC is more pale, and the nuclei is more irregular and usually takes on a “raisinoid” shape with perinuclear clearing. By IHC, both entities show diffuse and strong membranous expression of c-kit and E-cadherin, and these two markers alone are unhelpful in distinguishing oncocytoma from chromophobe RCC [12, 14]. However, diffuse staining for CK7, seen in the majority of chromobobe RCC, is in contrast with negative staining or staining restricted to only rare clustered cells in oncocytoma [12]. Tubulocystic RCC, which has been recently recognized by the International Society of Urological Pathology (ISUP) of Vancouver Classification as a distinct subtype of RCC [15, 16], shares many features with tubulocystic RO including both have a spongy imaging or gross appearance, extensive tubulocystic growth pattern, and eosinophilic lining cells. However, tubulocystic RCC occurs predominantly in male patients with a male-to-female ratio being more than 7:1 [16], and the cyst lining cells are usually elongated and often hobnail with prominent nuclei and atypia, arranged in a single row or in a pseudostratified pattern contrasting to that of tubulocystic RO which are relatively uniform, bland-appearing, cuboidal arranged in a single row. Moreover, the septa between the cysts in tubulocystic RCC are usually fibrotic whereas that in RO are typically edematous and hypocellular. Mitoses can also be found more frequently in tubulocystic RCC. By IHC, in comparison to RO, tubulocystic RCC marks more frequently for vimentin, CD10, AMACR, and CK7 and has a higher proliferative index by ki67 [9]. C-kit is consistently negative in tubulocystic RCC but it is usually positive in RO [9, 14]. Oncocytic papillary RCC is a recently identified subtype of papillary RCC [17], but RO can be confidently excluded if a tumor demonstrates a dominant or significant papillary growth pattern because papillary formations can only rarely be noted in the dilated cysts of tubulocystic RO [6]. However, if oncocytic papillary RCC exhibits mainly solid and tubular growth that it could cause diagnostic confusions with tubulocystic RO [18]. In this scene, immunohistochemical studies can help arriving at accurate diagnosis, briefly, the presence of immunoexpression primarily of CK7, CD10, vimentin, and AMACR and negativity for c-kit and E-cadherin may favor the diagnosis of oncocytic papillary RCC, and tubulocystic RO if conversely. Lastly, thyroid neoplasms, both papillary and follicular carcinomas, can rarely metastasize to kidney and histologically demonstrate a cystic and follicular growth pattern resembling tubulocystic RO [19], the absence of intracystic colloidal materials and immuno-negative of TTF1 and TG can easily rule out this possibility [20].

In summary, we present a rare case of tubulocystic RO and discuss the clinicopathologic, immunohistochemical features as well as the broad spectrum of differential diagnoses of this entity. Currently with a growing trend in many institutions to establish the initial diagnosis of renal tumors on needle biopsies, the presence of unusual and problematic findings in these scenes can also pose additional diagnostic challenges. Recognizing the spectrum of morphological features of oncocytoma may help to establish a final diagnosis on core biop-
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sy, possibly allowing surgeons and patients to avoid unnecessary treatment [6].

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Disclosure of conflict of interest

None.

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