Demirović A., Cesarec S., Spajić B., Tomas D., Bulimbašić S., Milošević M., Marušić Z., Krušlin B. (2010) ***Can renal oncocytoma be distinguished from chromophobe renal cell carcinoma by the presence of fibrous capsule?*** **Virchows Archiv, 456 (1). pp. 85-9. ISSN 0945-6317**

http://www.springer.com/journal/428/

http://www.springerlink.com/content/0945-6317/

http://dx.doi.org/10.1007/s00428-009-0868-x

CAN RENAL ONCOCYTOMA BE DISTINGUISHED FROM CHROMOPHOBE RENAL CELL CARCINOMA BY THE PRESENCE OF FIBROUS CAPSULE?

Alma Demirović[1], Sanja Cesarec[2], Borislav Spajić[3], Davor Tomas[1,2], Stela Bulimbašić[4], Milan Milošević[5], Zlatko Marušić [1], Božo Krušlin[1,2]

[1]Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Zagreb, Croatia

[2]School of Medicine, University of Zagreb, Zagreb, Croatia

[3]Department of Urology, Sestre milosrdnice University Hospital, Zagreb, Croatia

[4]Department of Pathology, University Hospital Dubrava, Zagreb, Croatia

[5]School of Public Health Andrija Štampar, Zagreb, Croatia

Correspondence:

Božo Krušlin, MD, PhD

Ljudevit Jurak University Department of Pathology

Sestre Milosrdnice University Hospital

Vinogradska cesta 29

Zagreb, Croatia

Email: bkruslin@kbsm.hr

Phone: +385 1 37 87 177

Fax: +385 1 37 87 2

ABSTRACT

The most important differential diagnosis of chromophobe renal cell carcinoma is renal oncocytoma. Due to overlapping morphological characteristics of renal oncocytoma and chromophobe renal cell carcinoma, particularly its eosinophilic variant, making a correct diagnosis can be challenging. To date no data are available on the presence of the tumor fibrous capsule as a diagnostic feature in differentiating these tumors. The main purpose of this study was to establish the presence and compare the thickness of the tumor fibrous capsule between two tumor groups. A total of 37 tumors-18 cases of chromophobe renal cell carcinoma (3 eosinophilic and 15 classic) and 19 cases of renal oncocytoma-were analyzed. Four slides of each tumor stained with hematoxylin and eosin were first scanned at low-power magnification (X40) to assess the presence of the capsule. If present, capsule was measured in three different, thickest areas at higher magnification (X200). The mean value of capsule thickness was calculated and taken into consideration. Capsule was present in 12 (66.7%) cases of CRCCs and in only 2 (10.5%) cases of renal oncocytomas. Statistical analysis showed significant difference between the presence of fibrous capsule in these two observed tumor groups (P=0.001). Average thickness of capsule in CRCCs was 337.7 μm, and 115.4 μm in renal oncocytomas, but the median was not statistically significant (P=0.198). Studies with a larger number of cases are needed to conclude if this characteristic could be a low-cost, reliable microscopic feature in differentiating between chromophobe renal cell carcinoma and renal oncocytoma.

Key words: chromophobe renal cell carcinoma, renal oncocytoma, capsule, morphometry

INTRODUCTION

In the current World Health Organization (WHO) classification of renal tumors, chromophobe renal cell carcinoma (CRCC) is recognized as a malignant renal cell neoplasm derived from the intercalated cell of the collecting duct, which accounts for 5% of renal epithelial tumors [1]. Two main variants are classic and eosinophilic CRCC. Although considered less aggressive than other renal cell carcinomas, CRCC has a metastatic potential and may undergo sarcomatoid transformation, which is associated with more aggressive behavior [1]. Renal oncocytoma is a benign tumor, which shares a common cellular origin with CRCC and represents 3% to 9% of all primary renal tumors [1]. Due to overlapping morphological characteristics of renal oncocytoma and CRCC, particularly its eosinophilic variant with the abundant granular eosinophilic cytoplasm, making a correct diagnosis can be challenging. In recent years, much effort has been made to identify immunohistochemical markers that could be useful in differentiating between CRCC and renal oncocytoma [2-6]. However, final decision about the appropriate panel of immunohistochemical markers for the differential diagnosis of CRCC and renal oncocytoma is still being discussed. Hale's iron stain can be particularly useful in differentiating these tumors but many laboratories have found this stain to be technically challenging and present with variable results [3]. Other authors have attempted to make the distinction on account of nuclear morphometric measurements and features, with the conclusion that a combination of hyperchromatic wrinkled nuclei and perinuclear halos is more often associated with CRCC [7-10]. CRCC is, like cases of clear cell renal carcinoma, according to our experience, in the majority of cases surrounded by a fibrous capsule, which separates the tumor tissue from the surrounding renal parenchyma. Unlike CRCC, renal oncocytoma, despite being a benign tumor, lacks the fibrous capsule in a number of cases. The main purpose of this study was to establish the presence and compare

the thickness of the tumor fibrous capsule between two tumor groups. According to the English literature there are no data on similar research in this field.

PATIENTS AND METHODS

Patients

The files from two Departments of Pathology (Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital and Department of Pathology, University Hospital Dubrava, Zagreb) from the period between 1999-2008 were searched for cases of histologically confirmed CRCC and renal oncocytoma. All cases were reviewed and diagnosis of CRCC and renal oncocytoma was established according to the criteria proposed by 2004 WHO for classification of renal tumors [11]. There were 37 cases in total: 18 (3 eosinophilic and 15 classic) CRCCs and 19 renal oncocytomas. Four slides of each tumor, stained with hematoxylin and eosin were analyzed. Among patients with CRCC, 10 were females, and 8 males. Patients' age ranged from 34-76 years (mean 56.9). Tumor size ranged from 1.7-17 cm (mean 7.9). Nuclear grade for CRCC was assessed according to the Fuhrman classification system (12). There were 10 CRCCs with G2, 7 with G3 and 1 with G4 nuclear grade. Among patients with renal oncocytoma, 12 were females, and 7 males. Patients' age ranged from 47-80 years (mean 65.2). Tumor size ranged from 0.9-8 cm (mean 3.6).

Methods

We analyzed the presence of the tumor fibrous capsule and measured its thickness in the cases of CRCCs and renal oncocytomas. Four slides of each tumor were first scanned at low-power magnification (X40) to assess the presence of tumor fibrous capsule. If present, capsule was measured in three different, thickest areas at higher magnification (X200). Morphometric

measurements of capsule were done by computerized morphometry system with an Olympus microscope BX51, QuickPHOTO Pro software and an Olympus Camedia C-5050 camera and were expressed in micrometers (μm). The mean value of capsule thickness was calculated and taken into consideration**.** All samples were examined independently by three observers and any difference was resolved by a joint review. Statistical analysis was performed using Chi-Square test, Spearman's correlation test, Fisher's exact test and Mann-Whitney test. The level of statistical significance was set as $P<0.05$.

RESULTS

The main clinical and morphometric findings are summarized in Tables 1 and 2. Capsule was present in 12 cases (66.7%) of CRCCs and in only 2 cases (10.5%) of renal oncocytomas (Figure 1). Statistical analysis showed significant difference between the presence of fibrous capsule in these two observed tumor groups (P=0.001). The capsule in CRCCs was found to encompass the whole tumor circumference on the examined slides, while in cases of ROs with capsule it was formed only partially. Seven cases (36.8%) of ROs featured a grossly visible star-shaped central scar, but there was no surrounding fibrous capsule in any of them. Average thickness of capsule in CRCCs was 337.7 μm, and 115.4 μm in renal oncocytomas but the median was not statistically significant (P=0.198). The correlation between tumor size, nuclear grade and capsular presence in CRCCs showed no statistically significant differences (P=0.616, P=0.091, respectively). When comparing capsule thickness with tumor size, and nuclear grade in CRCCs, no statistically significant differences were found (P=0.688, P=0.533, respectively). Mean tumor size was higher in CRCCs (7.9 cm) than in renal oncocytomas (3.6 cm). Patients with renal oncocytoma were significantly older compared to

patients with CRCC (P=0.021). Significant difference in distribution of these two tumor types between male and female was not found (P=0.743).

DISCUSSION

The most important differential diagnosis of CRCC is renal oncocytoma. Their distinction is essential since CRCC has malignant potential whereas renal oncocytoma is a benign tumor. Moreover, cases of sarcomatoid transformation of CRCC emphasize the importance of making the accurate diagnosis due to more aggressive behavior of this type of CRCC [1,13-15]. CRCCs and renal oncocytomas have overlapping morphologic, immunohistochemical, histochemical and ultrastructural characteristics. Preoperative physical and radiographic examinations are not reliable in distinguishing renal oncocytoma from CRCC, which makes the accurate diagnosis for pathologists even more complicated [16,17]. Also, the conclusions of studies concerning fine-needle aspiration biopsy results in differentiating these tumors are inconsistent [18-20]. Thus, in the majority of cases the final diagnosis is made after a histopathological evaluation. Under the light microscope the most important discriminating characteristics are nuclear and cytologic features. Renal oncocytoma has homogeneous nuclear size, round nuclear contours, common binucleation and discrete nucleoli. However, CRCC in some cases can also have similar appearance although more often with hyperchromatic wrinkled nuclei and perinuclear halos [10]. Entrapped normal tubules in the central or peripheral parts of the tumor could also be the clue to the diagnosis of renal oncocytoma [2]. In the majoritiy of cases, however, a definitive diagnosis can still not be rendered based on these criteria under the light microscope evaluation only. Much effort has been made to identify immunohistochemical markers that could be useful in differentiating between CRCC and renal oncocytoma, such as caveolin-1, CD63, anti-mitochondrial

antibody, cytokeratin 14, cytokeratin 7, vimentin, glutathione S-transferase α, CD10, CD117, claudin-7, claudin-8 and kidney-specific cadherin [2-6]. Antimitochondrial antibodies and parvalbumin are considered to be excellent markers for differentiating between these tumors [21-23]. Also the combination of three immunohistochemical markers: vimentin, glutathione S-transferase α and epithelial cell adhesion molecule is highly sensitive and specific for the differential diagnosis of CRCC and renal oncocytoma [4]. Hale's iron stain continues to be a useful histochemical marker in differentiating between these tumors but many laboratories have found it technically challenging and with variable results [3]. Brunelli et al. [24] analyzed a group of 10 renal oncocytomas and 19 CRCCs by fluorescence in situ hybridization to clarify the genetic lesions of these tumors and revealed that detection of losses of chromosomes 2, 6, 10 and 17 could support the diagnosis of CRCC over a renal oncocytoma. These conclusions will hopefully lead to a better understanding of different patterns of genetic anomalies and facilitate the differential diagnosis between CRCC and renal oncocytoma. According to our experience, in a number of cases, CRCC was found to be surrounded by a fibrous capsule, which separates the tumor tissue from adjecent renal parenchyma. When compared with renal oncocytoma statistically significant difference in the presence of the fibrous capsule in the two observed tumor groups was striking. Even though the capsule in oncocytomas, when present, was less thick than in CRCCs, the median was not statistically significant due to a small number of cases. In somewhat older literature, surrounding capsule of variable thickness was reported to be a feature of typical oncocytoma [25]. However, in the last World Health Organization classification of kidney tumors, oncocytomas are defined as well-circumscribed, nonencapsulated neoplasms [11]. Interestingly, no data are available on the presence of the tumor fibrous capsule as a diagnostic feature in differentiating these tumors. Shimasaki et al. [26] studied the participation of myofibroblasts in the capsular formation of renal cell carcinomas, with only

two cases of CRCC, and concluded that myofibroblasts may participate in the capsular formation of conventional and CRCC. To date there are no data on similar research regarding renal oncocytoma and comparative analysis with CRCC. Our results show that the capsule is significantly more common and thicker in chromophobe renal cell carcinomas compared to renal oncocytomas. Studies with a larger number of cases are needed to conclude if this characteristic could be a low-cost, reliable microscopic feature in differentiating between CRCC and renal oncocytoma.

ACKNOWLEDGMENT

This work was supported in part by the Ministry of Science, Education and Sports, Croatia, project number 108-1081870-1884 and 134-0000000-3381.

CONFILCT OF INTEREST

The authors declare that they have no conflict of interest.

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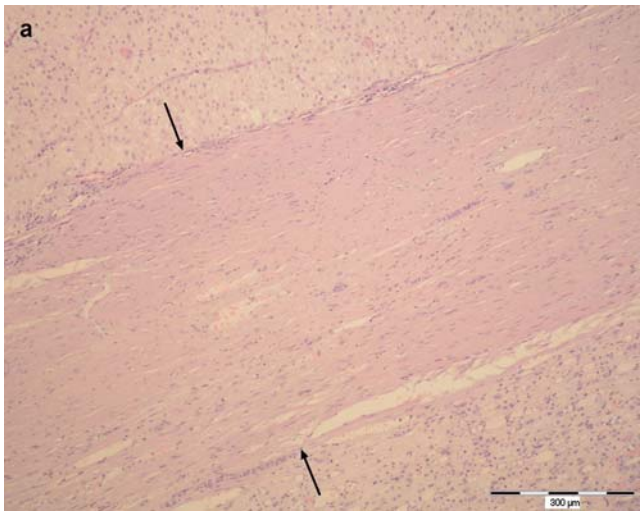
Table 1. Clinical, histological and morphometric findings in chromophobe renal cell carcinoma

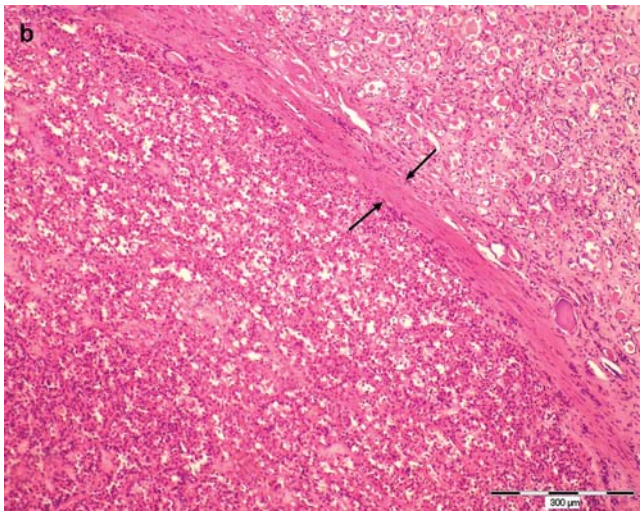
Case	Age	Gender	Tumor size (cm)	Type	Nuclear grade	Capsule	Capsule thickness (μm)
1	55	F	6.5	classic	G2	+	83.2
2	53	F	12	classic	G2	+	295
3	60	F	12	classic	G2	+	175.7
4	63	M	10	eosinophilic	G2	+	85.1
5	47	F	1.7	classic	G3	+	380.4
6	46	M	5.5	classic	G3	+	218.4
7	60	F	7	eosinophilic	G2	+	507.9
8	47	F	17	eosinophilic	G4	+	562.2
9	58	M	3	classic	G2	+	551.4
10	51	F	8	classic	G2	-	
11	66	M	6.2	classic	G3	+	238.5
12	76	M	4.5	classic	G2	-	
13	49	F	7.5	classic	G3	+	565.5
14	75	M	11	classic	G3	+	623.6
15	34	F	12	classic	G3	-	
16	52	M	6	classic	G2	-	
17	56	F	5.5	classic	G2	-	
18	76	M	7.2	classic	G3	-	

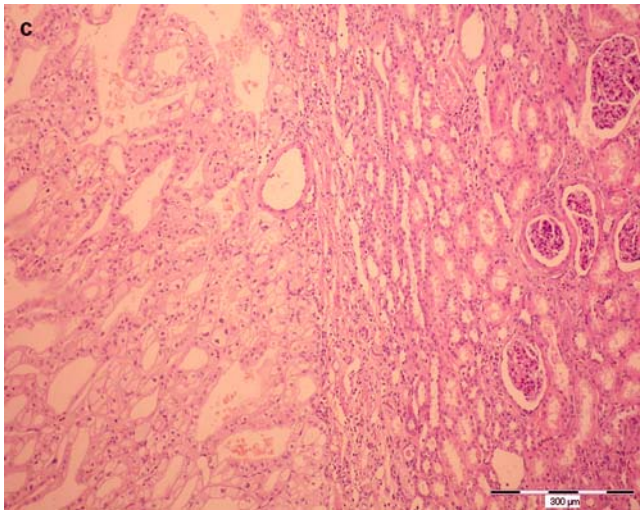
Table 2. Clinical and morphometric findings in renal oncocytoma

Case	Age	Gender	Tumor size (cm)	Capsule	Capsule thickness (μm)
1	70	F	1.5	+	120.7
2	54	F	3	+	110.1
3	79	F	2.5	-	
4	57	M	4	-	
5	68	F	2.2	-	
6	62	F	3	-	
7	68	M	3	-	
8	70	F	6.5	-	
9	77	M	0.9	-	
10	61	F	1.7	-	
11	55	F	8	-	
12	80	F	6	-	
13	47	M	4.3	-	
14	74	F	2.6	-	
15	52	M	6	-	
16	72	M	3.5	-	
17	69	F	2	-	
18	66	M	3	-	
19	58	F	4.2	-	

Figure 1 Chromophobe renal cell carcinoma (a) and renal oncocytoma (b) surrounded by fibrous capsule. Chromophobe renal cell carcinoma (c) and renal oncocytoma (d) without fibrous capsule (X100, HE).



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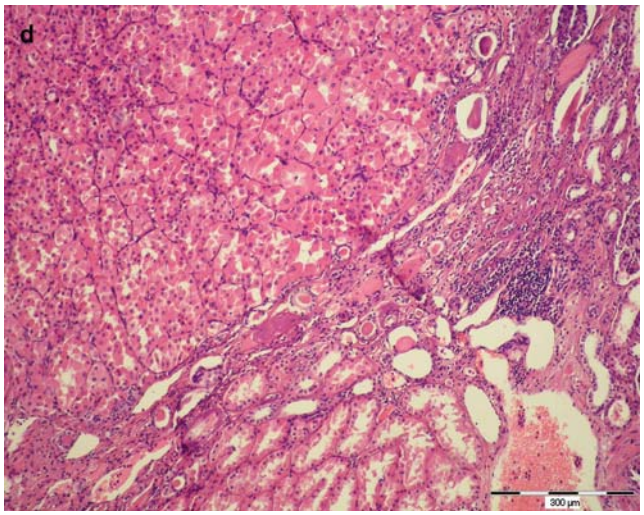
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