Differentiation of Renal Oncocytoma from Renal Cell Carcinoma - A Mini-Review

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Abstract: *Renal oncocytomas (RO) are the small renal lesions that shared similar histological features with chromophobe renal cell carcinoma (chRCC). There are some hybrid tumors, renal oncocytosis and Brit-Hogg-Dube (BHD) syndrome that have shown the coexistence of both ROs and chRCCs. Presently, most of sporadic cases of ROs and chRCCs have been reported. The majority of ROs and chRCCs patients are asymptomatic, with no significant risk of metastatic ROs compared to chRCCs. However, incidental detection of small renal masses by cross section imaging has constituted an important diagnostic dilemma for their management. Therefore, it is important to differentiation ROs from chRCCs and other subtypes of RCCs for appropriate management. RO is a benign tumor and should be monitored and treated conservatively. For ROs more conservative treatment like nephron-sparing surgery should be considered but we are still on consistent effort of differentiating RO from chRCC. The more accurate diagnosis of ROs remained elusive until modern molecular biomarkers are determined. Even now the standard treatment for small renal tumors remained surgical resection. But recent studies of Cytochrome C oxidase subunit 1(CCO1) and Tc-MIBI SPECT/CT is appearing valuable in differentiating between these two entities. We suspect that in future the results of these experimental studies will favor us more towards conservative treatment of ROs. This review is focused on the differentiation of renal oncocytoma (RO) from renal cell carcinoma (RCC). It summarizes the introduction, epidemiology, clinical presentation of the renal neoplasms and describes the diagnostic dilemma, pathology, radiology, treatment of the renal neoplasms.*

Keywords: Renal Oncocytoma, Renal Cell Carcinoma

1. Introduction

First scientist to introduce renal oncocytoma (RO) as a neoplasm was Zippel [1]. RO is composed of eosinophilic granular cells called oncocytes. It is said that RO has its origin most likely from intercalated cells of collecting ducts [2]. It is also said that RO is a benign tumor and can be monitored and treated conservatively [3]. But a decade later, Theones et al. described chromophobe renal cell carcinoma (chRCC) as a distinct subtype from eosinophilic clear-cell renal cell carcinoma (ccRCC) and marked a question on the ROs, previously described as benign [4]. Both ROs and chRCCs shared similar morphological features and proper differentiation between two entities relies on H& E histochemistry of section, and experienced histopathologist to discern the characteristic histomorphological spectrum [5]. There are some hybrid tumors, renal oncocytosis and Brit-Hogg-Dube (BHD) syndrome that have shown the coexistence of ROs with chRCCs. Both ROs and chRCCs are small renal lesions that may also defer surgical treatment. Although it is said that chRCCs have good prognosis than others RCCs subtypes and active surveillance rather than surgical intervention should be considered, death can result from metastases due to its malignant nature. From past three decades incidence of renal tumors has been increasing in USA, Europe and Australia [6]. Same as, from decades widespread use of cross section imaging has been resulted in increase detection of incidental smaller renal tumors (lesions <4cm), with relatively constant incidence of advanced tumors [7, 8]. Therefore, it has become important to differentiation small renal masses like, ROs and chRCCs from other subtypes of RCCs, especially ccRCCs for appropriate management.

2. Epidemiology

Up to now, we know 16 subtypes of renal tumors. The four most common subtypes are ccRCC, papillary RCC, chRCC and collecting duct RCC [9, 10]. CcRCCs constituted 70-80% of RCC arising from proximal tubular epithelial cells, followed by papillary 10-15%, chRCCs 5% and collecting duct RCCs <1% [11, 12]. RO accounts for 3-7% of all renal tumors. The peak age of incidence for detecting ROs is in the seventh decade of life and men seem to affect twice than women. In contrast, peak age of incidence for detecting chRCCs is in sixth decade and both gender are affected equally [13]. So far, most of sporadic cases of ROs and chRCCs have been reported [14, 15]. Occasionally occurrence of familial renal cancers of oncocytoma with BHD syndrome has also been reported. Familial oncocytoma resulted from partial or complete loss of multiple chromosomes. Whereas Autosomal Dominant BHD syndrome is due to BHD gene locus located in the short arm of chromosome 17 [16, 17]. This syndrome is characterized by fibrofolliculomas, lung cysts leading to spontaneous pneumothoraxes and various subtypes of renal tumors including hybrid tumors, ROs, chRCCs and ccRCCs. Sometime in rare cases, patients can present with renal oncocytosis that is described as multiple and bilateral oncocytic nodules found diffusely throughout the renal parenchyma [18]. Hybrid development of ROs and chRCCs

was most commonly shown by a large series investigating renal oncocytosis [19].

Clinical presentation

The majority of ROs and chRCCs patients are asymptomatic. Rarely, chRCCs patients can present with symptoms of loin and flank pain, hematuria, weight loss and decrease appetite [14]. Occasionally, chRCCs patients can also present with paraneoplastic syndrome and metastatic disease to liver, but with better prognosis compared to other RCCs [20]. In contrast, ROs with no significant risk of metastases almost always follow benign clinical course. A few cases of metastatic ROs with initial presentation or following resection of ROs have been reported with no proper histopathological confirmation of metastatic deposits, except for one metastatic liver disease [3, 9, and 21]. Therefore, distinction of benign ROs from metastatic chRCCs is needed to guide management. If there is a suspicion of renal mass either clinically or via ultrasound, 4-phase CT scan should be performed immediately to describe its nature. Multiphase CT scans can outline the renal tumor with its extension to surrounding tissues and can also reveal metastases to other organs or regional lymph nodes. But generally speaking, we cannot differentiate benign renal lesions from malignant on CT scans. Similarly, a largest pool of biopsies have proven the growth rate of benign ROs similar to that of other subtypes of RCCs, highlighting the insignificancy of growth velocity to differentiate between the benign or malignant renal lesions [12]. That why, percutaneous biopsy of small renal masses has limited role in the clinical practice these days. The locality and size of tumors may also vary. An average size of ROs reported is around 4.9 ±2.7 cm, with one exception of large RO (25×15×12 cm) [22, 23]. ROs can be multifocal and bilateral, respectively, in 6-11% and 3-5% cases [24-26]. By comparison, size of chRCCs is larger than any other subtype of RCCs, of about 6.0 cm [14, 27]. Multifocality of chRCCs is around 10-12% [28].

Diagnostic dilemma

The increase use of CT scans has actually led to diagnostic dilemma for characterizing the nature of small renal masses and their treatment. RCCs such as ccRCCs, papillary and collecting ducts RCCs demonstrate heterogeneous or peripheral contrast enhancement on CT scans. Whereas chRCCs reveal homogenous contrast enhancement on CT scans. ChRCCs also demonstrate calcification on CT scans [29]. In contrast ROs demonstrate smooth, well defined, relative homogeneous enhancement with central stellate scarring on CT scans. Same as when renal angiography is performed on RO, it highlights the peripheral hypervascular area with relatively hypovascular central area, demonstrating the spoke-wheel pattern. Central stellate scar is said to be non-diagnostic hypoattenuated central area seems on CTscan in less than one-third of ROs [10, 16]. The 18-FDG PET/CT scan has limited role in detecting renal tumors [30]. Benign ROs are FDG-avid but has failed to separate them from other subtypes of RCCs due to high false negative rate [31]. So far, there are no consistently reliable pathognomic CT or alternative imaging technique features that can distinguish between ROs and chRCCs [32, 33]. Therefore, most ROs patients are treated by surgical resection due to suspicion of RCCs based on imaging. Recently, multiphasic multidetector CT scans with different enhancements at various phases of scan have been used to discriminate between RCCs subtypes [34]. This aids to distinguish ccRCCs from ROs but not ROs from chRCCs. Arterial phase enhancements >500% and washout values >50% in Hounsfield units obtained from multiphasic CT scans have been seen in ROs and aided to discriminate them from other subtypes of RCCs [35].

Pathology

As said above that renal mass biopsy is not widely used these days because pathologists have to face difficultly to diagnose renal tumor subtype from limited tissue biopsy samples, as an entire range of cytoarchitectural features is required to be examined for diagnosis [36]. Generally, the lesion looks like chRCCs on biopsy is declared with confidently as such. But lesion looks like RO may be incomplete sampled, merging with eosinophilic variant of chRCCs as a hybrid tumor or oncocytoma-like areas in a chRCC. Therefore, most pathologists did not diagnose RO on needle biopsy, and make a comment of having chRCCs elsewhere in the tumor. It is important to differentiate ROs from chRCCs based on histological characteristics. Below table 1 demonstrates the differences between these two entities.

Table 1: Comparison of macroscopic, microscopic and ultrastructural features of renal oncocytoma (RO) and chromophobe renal cell carcinoma (chRCC)

Features	RO	ChRCC
Macroscopic	Well circumscribed, mahogany brown with a central stellate scar [25].	Usually circumscribed, light brown or yellow color [37].
Microscopic	Cells arranged in a nested or organoid pattern, but tubular, trabecular or solid structure can also be seen [38]. Granular eosinophilic cytoplasm round, uniform nuclei [39].	Cells arranged in sheets, with distinct or accentuated cell borders [40]. Granular eosinophilic variant or pale, reticular and transparent appearing classic variant. Presence of perinuclear halos, wrinkled nuclei [41].
Ultrastructural	Many mitochondria with lamellar or focally stacked cristae but with absent or sparse microvesicles [39].	Less mitochondria with tubule-vesicular cristae but with abundant microvesicles [37].

Despite of distinguish histological features, there is also need to use histochemical and immunohistochemical (IHC) stains to differentiate between RO, chRCC and ccRCC subtypes. Up to now, none of the histochemical, IHC or cytogenetic features has been proven to be reliable and specific [42]. However, it is said that IHC markers may be helpful and cost-effective for disease monitoring, prognosis and treatment-plan regimens. Below table 2 demonstrates the difference between these three entities.
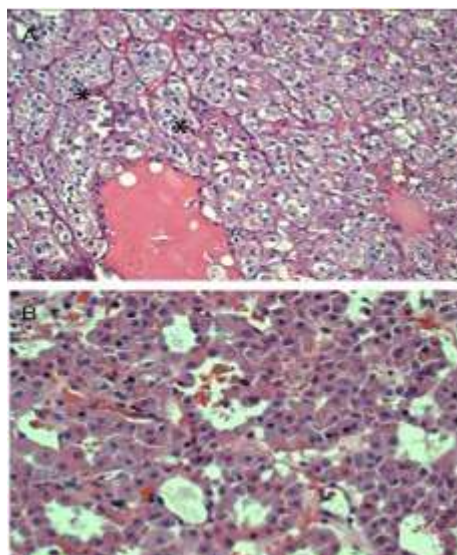
Figure 1, **(A)** H&E-stained section of an example of eosinophilic variant of chromophobe renal cell carcinoma, showing typical large, pale, polygonal cells with prominent cell membranes. Nuclei tend to be irregular and wrinkled, and cells are sometimes binucleated (asterisks). Perinuclear clearing can be prominent. **(B)** H&E stained section of an example of renal oncocytoma, showing large oncocytes with densely granular eosinophilic cytoplasm. Cells are round to polygonal and nuclei are round and monotonous. Nucleoli are small and inconspicuous.

Table 2: Histochemistry and immunohistochemistry (IHC) to differentiate clear cell renal cell carcinoma (ccRCC), chromophobe renal cell carcinoma (chRCC) and renal oncocytoma (RO)

Cancer Cell Type	Vimentin	Cytokeratin (CK) 7	CD10 and RCC Marker (RCCma)	Cyclin D1 Over-Expression	Cytochrome C, Oxidase Subunit1 (CCO1)	Hale's Colloidal Iron Stain
ccRCC	pos	neg	pos	not tested	not tested	neg
chRCC	neg	pos	neg	neg	perinuclear halo formation	diffuse reticular pattern with perinuclear halo[41]
RO	neg	neg or focal pos	neg	pos, mostly	neg	neg

positive (pos) and negative (neg)

Colloidal iron and CK7 positivity is used to discriminate chRCCs from ROs. Negative staining for vimentin and positive staining for CK7 versus negative staining for CK7 and positive staining for vimentin is used to distinguish chRCCs from ccRCCs [43]. All chRCCs are negative for cyclin D1 overexpression and CCND1 gene rearrangements. Whereas a large number of ROs are positive for cyclin D1 overexpresion and CCND1 rearrangements, suggesting that these two IHCs may be helpful to differentiate ROs from chRCCs [44]. A feature found in chRCC but not in RO is the predominance of a perinuclear halo when stained for CCO1.This describes for first time the formation of a perinuclear halo in CCO1 and suggests it as a highly specific marker for chRCC [45]. Apart from sharing similar histologic, cytologic features, ROs and chRCCs also shared IHC markers for S100A1 and CD117 (KIT) [46]. Several other studies with IHC markers, including kidney specific cadherin, CK7, EMA, CD10, RCC, c-KIT, and RON proto-oncogene have been used to discriminate chRCCs from ROs, but the results of these studies are not satisfactory [47].

Biomarker such as BCA2, a RING H2 finger protein RING E3 ligase, has potential to discriminate ROs from chRCCs [48]. Additionally, ROs also expressed higher cancer-testis antigens (CTAs), MAGE-A3/4 and NY-ESO-1, used to differentiate it from chRCCs [49].

Cadherins comprise of a transmembrane glycoprotein family that function as calcium-dependent homotypic adhesion molecules and are expressed by the epithelium. Currently, over 20 different tissue-specific cadherins have been identified [50], of which Kidney-specific cadherin (Ksp-cad), N & E-Cadherin, and Ep-CAM (epithelial cell adhesion molecule) have shown their promising evidence in differentiating chRCCs from ROs.

CKs are from intermediate filament family, the markers of epithelium differentiation. Currently, 20 distinct CKs have been identified. The CKs that have been tested to differentiate chRCCs from other RCCs and ROs, CK7 8 18 19 and 20, have not shown any major promising evidence. In contrast, Caveolin-1 encoded by the Cav-1 protein has shown better result in differentiating chRCCs from ROs than CK7 [51].

Radiology
Several studies have shown that the degree of enhancement is the most important parameter for discriminating between different subtypes of RCCs [52-55]. Absolute attenuation measurement is considered to be accurate for distinguishing different renal lesions, however, a large number of intrinsic and extrinsic factors such as organ perfusion and the quantity, time and rate of delivery of contrast material to organs like the kidneys, can influence the attenuation values

and the types of contrast enhancement of lesions in different contrast phases [56]. Therefore, An et al., in their study, used a ratio rather than an absolute enhancement in an attempt to correct the differences in each patient's body habitus and cardiac output. This study was focused on the ratio of lesion-to-cortex attenuation of CT enhancement for discriminating RO from ccRCCs. It has been corroborated that when differentiating benign renal lesions from malignant, on contrast-enhanced CT, ccRCCs and RO are greatly enhanced in the parenchymal phase, whereas chRCCs and angiomyolipoma moderately and papillary tumors slightly enhanced in the parenchymal phase [57]. RO can overlap with ccRCCs in terms of imaging features and the degree of enhancement. Therefore, the discrimination between RO and ccRCCs presents the greatest diagnostic challenge. This retrospective study included 46 patients with a solitary renal mass who underwent total or partial nephrectomy [58]. 14 patients were of RO and 32 were of ccRCCs. All patients were examined with contrast-enhanced CT. Area that demonstrates the greatest degree of enhancement, of the renal lesion, in the corticomedullary, nephrographic and excretory phase was selected. The ratios of lesion-to-renal cortex enhancement were calculated for all three phases. The results showed that all ccRCCs masses appeared to be better enhanced than RO on all contrast-enhanced phases of CT imaging, but there was no significant difference in absolute attenuation values between them ($P > 0.05$) [58]. The ratio of lesion-to-cortex attenuation in the corticomedullary phase revealed significantly different values between RO and ccRCCs. The degree of contrast enhancement in ccRCCs was equal to or greater than that of the normal renal cortex, but it was less than that of the normal cortex in RO in the corticomedullary phase. The ratio of lesion-to-cortex attenuation in the corticomedullary phase was higher than the cut off value of 1.0 in most ccRCCs (84%, 27/32) and lower than 1.0 in most RO (93%, 13/14) ($P < 0.05$). In the nephrographic phase, the ratio of lesion-to-cortex attenuation was higher than that in the corticomedullary phase in most RO (71%, 10/14), exhibiting a prolonged enhancement pattern and was lower than that in most ccRCCs (97%, 31/32), demonstrating an early washout pattern ($P < 0.05$) [58]. In the discrimination of RO from ccRCCs, the sensitivity was 93%, specificity 84%, positive predictive value 72%, negative predictive value 84%, and accuracy for RO was 87, if the ratio of lesion-to-cortex attenuation in a cortex phase was lower than the cutoff value of 1.0. The sensitivity was 71%, specificity was 97%, positive predictive value was 91%, negative predictive value was 91%, and accuracy for RO was 89%, if the ratio of lesion-to-cortex attenuation in nephrographic phase was higher than that in the corticomedullary phase. An et al. concluded that ratios of renal lesion-to-cortex attenuation may be helpful in differentiating RO from ccRCCs [58].

Recently, Rowe et al. explored the utility of Tc-MIBI SPECT/CT for the differentiation of renal oncocytoma from other subtypes of RCCs. It is based on the hypothesis that the large number of mitochondria in oncocytomas would lead to increased Tc-MIBI uptake. In this study, 6 patients, 3 with oncocytoma and 3 with RCC, were imaged with Tc-MIBI SPECT/CT [59]. The results of the study showed that all the 3 oncocytomas demonstrated, radiotracer uptake near or above the normal renal parenchymal uptake, whereas, the

3 RCCs were greatly photopenic relative to renal background. Rowe et al. concluded that Tc-MIBI SPECT/CT appears to be valuable in differentiating benign renal oncocytoma from RCC [59].

Treatment

So far, standard treatment of localize renal tumors remained surgical resection via complete or partial nephrectomy. Benatiya et al. described the management of 6 cases of ROs in their study [60]. The mean age of the patients was 53 ±9.7 years (range 34 to 61 years). At initial presentation, one patient was asymptomatic, 5 patients had flank pain and 2 had hematuria. The tumor was right sided in 4 cases and left sided in 2 cases. All patients underwent CT scan which showed central stellate area of low attenuation, only in 3 cases. The clinical suspicion of RO was made in 3 patients by cross-section imaging, preoperatively, but the suspicion of RCCs persisted and all patients underwent radical nephrectomy. Definitive diagnosis was made postoperatively, corroborating well circumscribed, unencapsulated tumors. Follow-up of patients for 3 years, revealed neither recurrence nor death from RO, with 100% progression free survival (PFS). This showed that RO has a benign clinical course with excellent long-term outcomes. Although, in this study, radical nephrectomy was the usual treatment, a conservative approach should be considered [60]. The precise preoperative or peri-operative diagnosis with signs of clinical and radiological findings, may possibly allow the frequent use of conservative surgery, such as partial nephrectomy or tumor excision. Currently, nephron-sparing surgery has been suggested as the standard care for ROs. These include nephron-sparing surgery with no chemo-radiotherapies afterward, cryoablation and radiofrequency ablation, high intensity focused ultrasound, microwave thermotherapy and interstitial photon irradiation. Actually, cryoablation and radiofrequency ablation have been the most studied. They have been performed laparoscopically and percutaneously [61]. After all, we suggested that benign ROs should be monitored closely and treated surgically or conservatively, if there is the evidence of coexisting RCC or rapidly growing tumor with destruction of the adjacent renal parenchyma [62, 63].

3. Conclusion

Small renal masses especially ROs, chRCCs and ccRCCs have revealed the diagnostic and management challenges for us. Ratio of lesion-to-cortex attenuation of CT enhancement for discriminating RO from ccRCCs has shown the results of ccRCCs masses, better enhanced in all contrast-phases of CT imaging than RO but with no significant difference for their absolute attenuation values [62]. Up to now, there are no reliable imaging features that can differentiate ROs from chRCCs and ccRCCs. Therefore, most of RO patients are treated with surgical resection due to suspicion of concurrent RCC subtypes rather than of conservative treatment. The more accurate diagnosis of ROs remained elusive until modern molecular biomarkers are determined. But a high level of confidence to diagnose with an improve use of preoperative diagnostic techniques can reduce the rate of interventions in RO patients. Recently, the use of Tc-MIBI SPECT/CT to distinguish ROs from other subtypes of RCCs

has shown a good result of differentiation. It demonstrates the radiotracer uptake nearly above the normal renal parenchymal uptake for ROs patients, with greatly photopenic relative to renal background for other RCCs subtype's patients [59]. Similarly, a feature found in chRCC but not in RO is the predominance of a perinuclear halo when stained for CCO1. This suggests a highly specific marker for chRCC that can be helpful to differentiate it from RO [45]. By these recent studies, we are getting close to differentiate ROs from other RCC subtypes like chRCCs and ccRCCs. So we suspect that in future more conservative treatment like nephron-sparing surgery for RO patients will be considered.

4. Financial Declaration

No author participating in this study has any financial conflict.

References

[1] Zippel . Zur Kenntnis der Oncocytome. Virchows Arch A Pathol Anat 1942;308:360–82.

[2] Storkel S, Pannen B, Thoenes W, et al. Intercalated cells as a probable source for the development of renal oncocytoma. Virchows Arch B Cell Pathol Incl Mol Pathol 1988;56:185–9.

[3] Oxley JD, Sullivan J, Mitchelmore A, et al. Metastatic renal oncocytoma. J Clin Pathol 2007;60:720–2.

[4] Thoenes W, Storkel S, Rumpelt HJ. Human chromophobe cell renal carcinoma. Virchows Arch B Cell Pathol Incl Mol Pathol 1985;48:207–17.

[5] Delongchamps NB, Galmiche L, Eiss D, et al. Hybrid tumour 'oncocytomachromophobe renal cell carcinoma' of the kidney: a report of seven sporadic cases. BJU Int 2009;103:1381–4.

[6] Ljungberg B, Campbell SC, Choi HY, et al.The epidemiology of renal cell carcinoma. Eur Urol 2011; 60:615–21.

[7] Duchene DA, Lotan Y, Cadeddu JA, et al. Histopathology of surgically managed renal tumors: analysis of a contemporary series. Urology 2003; 62:827–30.

[8] Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008; 34:193–205.

[9] Amin R, Anthony P. Metastatic renal oncocytoma: A case report and review of the literature. Clin Oncol (R Coll Radiol) 1999;11:277–9.

[10] Chawla SN, Crispen PL, Hanlon AL, et al. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. J Urol 2006;175:425–31.

[11] Kawaguchi S, Fernandes KA, Finelli A, et al. Most renal oncocytomas appear to grow: observations of tumor kinetics with active surveillance. J Urol 2011;186:1218–22.

[12] Kurup AN, Thompson RH, Leibovich BC, et al. Renal oncocytoma growth rates before intervention. BJU Int 2012;110:1444–8.

[13] Cindolo L, de lTA, Schips L, et al. Chromophobe renal cell carcinoma: comprehensive analysis of 104 cases from multicenter European database. Urology 2005;65:681–6.

[14] Vera-Badillo FE, Conde E, Duran I. Chromophobe renal cell carcinoma: a review of an uncommon entity. Int J Urol 2012;19:894–900.

[15] Lopez-Beltran A, Scarpelli M, Montironi R, et al. 2004 WHO classification of the renal tumors of the adults. Eur Urol 2006;49:798–805.

[16] Khoo SK, Bradley M, Wong FK, et al. Birt-Hogg-Dube syndrome: mapping of a novel hereditary neoplasia gene to chromosome 17p12-q11.2. Oncogene 2001;20:5239–42.

[17] Nickerson ML, Warren MB, Toro JR, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer cell 2002;2:157–64.

[18] Warfel KA, Eble JN. Renal oncocytomatosis. J Urol 1982;127:1179–80.

[19] Adamy A, Lowrance WT, Yee DS, et al. Renal oncocytosis: management and clinical outcomes. J Urol 2011;185:795–801.

[20] Tobias Klatte K-rH, Jonathan W. Said, Malte Bohm. Pathobiology and prognosis of chromophobe renal cell carcinoma. Urol Oncol-Semin Orig Investig 2008;26:604–09.

[21] PerezOrdonez B, Hamed G, Campbell S, et al. Renal oncocytoma: A clinicopathologic study of 70 cases. Am J Surg Pathol 1997;21:871–83.

[22] Akbulut S, Senol A, Cakabay B, et al. Giant renal oncocytoma: a case report and review of the literature. J Med Case Rep 2010;4:52.

[23] Romis L, Cindolo L, Patard JJ, et al. Frequency, clinical presentation and evolution of renal oncocytomas: multicentric experience from a European database. Eur Urol 2004;45:53–7; discussion 57

[24] Dechet CB, Bostwick DG, Blute MJ, et al. Renal oncocytoma: Multifocality, bilateralism, metachronous tumor development and coexistent renal cell carcinoma. J Urology 1999;162:40-2.

[25] Trpkov K, Yilmaz A, Uzer D, et al. Renal oncocytoma revisited: a clinicopathological study of 109 cases with emphasis on problematic diagnostic features. Histopathology 2010;57:893–906.

[26] Davis CJ MF, Sesterhenn IA, Ho CK. Renal Oncocytoma. Clinicopathological study of 166 patients. J Urogenital Pathol 1991;1:41–52.

[27] Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 2003;27:612–24.

[28] Yusenko MV. Molecular pathology of chromophobe renal cell carcinoma: a review. Int J Urol 2010;17:592–600.

[29] Kim JK, Kim TK, Ahn HJ, et al. Differentiation of subtypes of renal cell carcinoma on helical CT scans. AJR Am J Roentgenol 2002;178:1499–506.

[30] Aide N, Cappele O, Bottet P, et al. Efficiency of [(18)F]FDG PET in characterizing renal cancer and detecting distant metastases: a comparison with CT. Eur J Nucl Med Mol Imaging 2003;30:1236–45.

[31] Ramdave S, Thomas GW, Berlangieri SU, et al. Clinical role of F-18 fluorodeoxyglucose positron emission

tomography for detection and management of renal cell carcinoma. J Urol 2001;166:825–30.

[32] Choudhary S, Rajesh A, Mayer NJ, et al. Renal oncocytoma: CT features cannot reliably distinguish oncocytoma from other renal neoplasms. Clin Radiol 2009;64:517–22.

[33] Rosenkrantz AB, Hindman N, Fitzgerald EF, et al. MRI features of renal oncocytoma and chromophobe renal cell carcinoma. AJR Am J Roentgenol 2010;195:W421–7.

[34] Young JR, Margolis D, Sauk S, et al. Clear Cell Renal Cell Carcinoma: Discrimination from Other Renal Cell Carcinoma Subtypes and Oncocytoma at Multiphasic Multidetector CT. Radiology 2013;267:444–53.

[35] Bird VG, Kanagarajah P, Morillo G, et al. Response by authors re: Differentiation of oncocytoma and renal cell carcinoma in small renal masses (<4 cm): the role of 4-phase computerized tomography. World J Urol 2013;31:1011–2.

[36] Barocas DA, Rohan SM, Kao J, et al. Diagnosis of renal tumors on needle biopsy specimens by histological and molecular analysis. J Urol 2006;176:1957–62.

[37] Latham B, Dickersin GR, Oliva E. Subtypes of chromophobe cell renal carcinoma: a ultrastructural and histochemical study of 13 cases. Am J Surg Pathol 1999;23:530–5.

[38] Gudbjartsson T, Hardarson S, Petursdottir V, et al. Renal oncocytoma: a clinicopathological analysis of 45 consecutive cases. BJU Int 2005;96:1275–9.

[39] Tickoo SK, Amin MB. Discriminant nuclear features of renal oncocytoma and chromophobe renal cell carcinoma. Analysis of their potential utility in the differential diagnosis. Am J Clin Pathol 1998;110:782–7.

[40] Abrahams NA, MacLennan GT, Khoury JD, et al. Chromophobe renal cell carcinoma: a comparative study of histological, immunohistochemical and ultrastructural features using high throughput tissue microarray. Histopathology 2004;45:593–602.

[41] Crotty TB, Farrow GM, Lieber MM. Chromophobe cell renal carcinoma: clinicopathological features of 50 cases. J Urol 1995;154:964–7.

[42] Mazal PR, Exner M, Haitel A, et al. Expression of kidney-specific cadherin distinguishes chromophobe renal cell carcinoma from renal oncocytoma. Human pathology 2005;36:22–8.

[43] Ng KL, Rajandram R, Morais C, Yap NY, Samaratunga H, Gobe GC, Wood ST. Differentiation of oncocytoma from chromophobe renal cell carcinoma (RCC): can novel molecular biomarkers help solve an old problem? J Clin Pathol. 2014 Feb;67(2):97-104.

[44] Sukov WR, Ketterling RP, Lager DJ, Carlson AW, Sinnwell JP, Chow GK, Jenkins RB, Cheville JC.CCND1 rearrangements and cyclin D1 overexpression in renal oncocytomas: frequency, clinicopathologic features, and utility in differentiation from chromophobe renal cell carcinoma. Hum Pathol. 2009 Sep;40(9):1296-303.

[45] Adam AC, Scriba A, Ortmann M, Huss S, Kahl P, Steiner S, Störkel S, Büttner R. Immunohistochemical analysis of cytochrome C oxidase facilitates differentiation between oncocytoma and chromophobe

renal cell carcinoma. Appl Immunohistochem Mol Morphol. 2015 Jan;23(1):54-9.

[46] Bing Z, Lal P, Lu S, et al. Role of carbonic anhydrase IX, alpha-methylacyl coenzyme a racemase, cytokeratin 7, and galectin-3 in the evaluation of renal neoplasms: a tissue microarray immunohistochemical study. Ann Diagn Pathol 2013;17:58–62.

[47] Lee HW,Lee EH, Lee CH, et al. Diagnostic Utility of Caveolin-1 and MOC-31 in Distinguishing Chromophobe Renal Cell Carcinoma from Renal Oncocytoma. Korean J Urol 2011;52:96–103.

[48] Ehsani L, Seth R, Bacopulos S, et al. BCA2 is differentially expressed in renal oncocytoma: an analysis of 158 renal neoplasms. Tumour Biol 2013; 34:787–91.

[49] Demirovic A, Dzombeta T, Tomas D, et al. Immunohistochemical expression of tumor antigens MAGE-A3/4 and NY-ESO-1 in renal oncocytoma and chromophobe renal cell carcinoma. Pathol Res Pract 2010;206:695–9.

[50] Langner C, Ratschek M, Rehak P, et al. Expression of MUC1 (EMA) and E-cadherin in renal cell carcinoma: a systematic immunohistochemical analysis of 188 cases. Mod Pathol 2004;17:180–8.

[51] Liu L, Qian J, Singh H, et al. Immunohistochemical analysis of chromophobe renal cell carcinoma, renal oncocytoma, and clear cell carcinoma: an optimal and practical panel for differential diagnosis. Arch Pathol Lab Med 2007;131:1290–7.

[52] Kim JK, Kim TK, Ahn HJ, Kim CS, Kim KR, Cho KS. Differentiation of subtypes of renal cell carcinoma on helical CT scans. AJR Am J Roentgenol 2002;178:1499-506.

[53] Dyer R, DiSantis DJ, McClennan BL. Simplified imaging approach for evaluation of the solid renal mass in adults. Radiology 2008;247:331-43.

[54] Sheir KZ, El-Azab M, Mosbah A, El-Baz M, Shaaban AA. Differentiation of renal cell carcinoma subtypes by multislice computerized tomography. J Urol 2005;174:451-5.

[55] Ueda T, Mori K, Minami M, Motoori K, Ito H. Trends in oncological CT imaging: Clinical application of multidetector-row CT and 3D-CT imaging. Int J Clin Oncol 2006;11:268-77.

[56] Bae KT, Heiken JP, Brink JA. Aortic and hepatic peak enhancement atCT: Effect of contrast medium injection rate-pharmacokinetic analysis and experimental porcine model. Radiology 1998;206:455-64.

[57] Zhang J, Lefkowitz RA, Ishill NM, Wang LO, Moskowitz CS, Russo P, *et al*. Solid renal cortical tumor: Differentiation with CT. Radiology 2007;244:494-504.

[58] Ren A, Cai F, Shang YN, Ma ES, Huang ZG, Wang W, Lu Y, Zhang XZ. Differentiation of Renal Oncocytoma and Renal Clear Cell Carcinoma Using Relative CT Enhancement Ratio. Chin Med J (Engl). 2015;128(2):175-9.

[59] Rowe SP, Gorin MA, Gordetsky J, Ball MW, Pierorazio PM, Higuchi T, Epstein JI, Allaf ME, Javadi MS. Initial Experience Using 99m Tc-MIBI/CT for the Differentiation of Oncocytoma From Renal Cell Carcinoma. Clin Nucl Med. 2015 Jan 20.

[60] Benatiya MA, Rais G, Tahri M, Barki A, El sayegh H, Iken A, Nouini Y, Lachkar A, Benslimane L, Errihani H, Faik M. Renal oncocytoma: experience of Clinical Urology A, Urology Department, CHU Ibn Sina, Rabat, Morocco and literature review. Pan Afr Med J. 2012;12:84. Epub 2012 Jul 24.

[61] Ponholzer A, Reiter WJ, Maier U. Organ sparing surgery for giant bilateral renal oncocytoma. J Urol. 2002 Dec;168(6):2531-2.

[62] Chao DH, Zisman A, Pantuck AJ, Freedland SJ, Said JW, Belldegrun AS. Changing concepts in the management of renal oncocytoma. Urology. 2002 May;59(5):635-42.

[63] Neuzillet Y, Lechevallier E, Andre M, Daniel L, Nahon O, Coulange C. Follow-up of renal oncocytoma diagnosed by percutaneous tumor biopsy. Urology. 2005 Dec;66(6):1181-5.