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CD138 Expression in Renal Tumors and Its Usage in the Differential Diagnosis

Böbrek Tümörlerinde CD138 Ekspresyonu ve Ayırıcı Tanıda Kullanımı

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ABSTRACT

Objective: The differential diagnosis of kidney tumors, especially those with eosinophilic cytoplasms, can be problematic due to overlapping morphologic features. CD138 is primarily a plasma cell marker but is known to be expressed in the proximal renal tubular epithelium as well. This study aims to investigate the possible contribution of CD138 expression in the differential diagnosis of kidney tumors with eosinophilic cytoplasm.

Material and Method: The case series consisted of 15 chromophobe (ChRCC), 5 eosinophilic variant (EoRCC), 10 clear cell (CCRCC) and 9 papillary (PRCC) renal cell carcinomas, and 13 oncocytomas. Sections obtained from representative paraffin blocks were stained against CD138 antibody.

Results: All CCRCC and PRCC showed membranous CD138 expression. In some of the other eosinophilic renal tumors, cytoplasmic CD138 labeling in varying degrees was detected. In CCRCC cases, CD138 expression was especially observed in low grade areas and areas showing cystic and pseudopapillary growth patterns. A similar pattern of cytoplasmic staining was seen in 3 of the EoRCC and the most of the PRCC cases (6/9).

Conclusion: Our findings suggest that CD138 may contribute to the differential diagnosis of renal tumors because of the membranous staining pattern in CCRCC and EoRCC cases and the cytoplasmic staining in CHRCC and oncocytoma cases. Its contributory role may be improved by combined usage with markers like Cytokeratin 7 and RCC marker.

Key Words: Renal neoplasms, Syndecans, Immunohistochemistry, Differential diagnosis

ÖZ

Amaç: Özellikle eozinofilik sitoplazmalı böbrek tümörlerinin ayırıcı tanısı, örtüşen morfolojik özellikleri nedeniyle sorunlu olabilmektedir. CD138 temelde bir plazma hücresi belirteci olmakla birlikte, proksimal renal tübüler epitelde de eksprese edildiği bilinmektedir. Bu çalışma eozinofilik sitoplazmalı böbrek tümörlerinin ayırıcı tanısında CD138 ekspresyonunun olası katkısını araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Olgu serisi 15 kromofob (KrRHK), 5 eozinofilik varyant (EoRHK), 10 berrak hücreli (BHRHK) ve 9 papiller (PRHK) renal hücreli karsinoma ile 13 onkositomadan oluşmaktadır. Seçilmiş bloklardan elde edilen kesitler CD138 belirteci ile boyanmış ve incelenmiştir.

Bulgular: BHRHK ve PRHK olgularının hepsinde membranöz CD138 ekspresyonu dikkati çekmiştir. Diğer eozinofilik sitoplazmalı böbrek tümörlerinin bir kısmında değişen oranlarda sitoplazmik işaretlenme saptanmıştır. CD138 ekspresyonu, BHRHK olgularının düşük dereceli, kistik ve psödopapiller alanlarında daha belirgin olarak izlenmiştir. EoRHK olgularının 3'ünde ve PRHK olgularının çoğunda (6/9) benzer paternde sitoplazmik boyanma saptanmıştır.

Sonuç: Bulgularımız, CD138'in, BHRHK ve PRHK olgularında membranöz; KrRHK ve onkositoma olgularında ise sitoplazmik boyanma paternleri göstermesi nedeniyle, renal tümörlerin ayırıcı tanısına katkıda bulunabileceğini düşündürmektedir. Sitokeratin 7 ve "RCC marker" gibi belirteçlerle birlikte kullanılması bu katkıyı arttırabilir.

Anahtar Sözcükler: Renal neoplaziler, Sindekanlar, İmmünohistokimya, Ayırıcı tanı

INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignant renal tumor. The 2004 WHO classification is used for the diagnosis (1). The differential diagnosis of renal tumors, and especially those with eosinophilic cytoplasm, can be difficult due to overlapping morphological features. This problem can become more acute with small biopsies and when metastases are being evaluated. Immunohistochemical and sometimes electron microscopic investigations are therefore frequently needed. Many immunohistochemical markers such as cytokeratin subtypes, CD10, VHL protein,

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epithelial membrane antigen (EMA), paralbumin, carbonic anhydrase, vinculin, CD24, hypoxia-induced factors (HIF 1α and 2α), "renal cell carcinoma marker antigen" (RCCM), "kidney-specific cadherin" (KSC), GLUT-1 and PAX-2 have been studied to this end (2-13). Most of these markers can be expressed in tumors other than RCC as well and their specificity is therefore limited. The contribution of RCCM and KSC has been found to be higher than other markers regarding a contribution to the diagnostic algorithm (8-11). Similarly, PAX-2 has been reported to be more sensitive than RCCM and KSC. Using these three markers together has also been reported to be potentially helpful (13).

CD138 (Syndecan 1) is a 220-kDa adhesion molecule that plays a role in the differentiation of B lymphocytes to plasma cells. Syndecan 1 is expressed in epithelial cells and Syndecan 2 in mesothelial and mesenchymal cells. CD138 is primarily a plasma cell marker but it has also been shown to be present in the proximal renal tubules (14). There are only a few studies showing the presence of CD138 expression in RCC (15,16). Our study aimed to investigate the contribution of CD138 expression in the differential diagnosis of renal tumors with eosinophilic cytoplasm.

MATERIAL and METHOD

The case series consisted of 15 chromophobe (CrRCC), 5 eosinophilic variant (EoRCC), 10 clear cell (CCRCC) and 9 papillary (PRCC) renal cell carcinomas and 13 oncocytomas. All cases were reviewed for diagnosis confirmation. Sections from the selected blocks were stained with the CD138 marker (Neomarkers, Labvision, Ab1, clone 5F7, 1:20, avidin-biotin-peroxidase) on an automatic device (Ventana, Benchmark XT).

The presence of membranous and/or cytoplasmic staining in at least 5% of tumor cells was interpreted as positive.

The staining intensity was graded and recorded semi-quantitatively as 0 (no staining), 1+ (weak), 2+ (moderate) and 3+ (strong). The proximal renal tubules in the kidney parenchyma neighbouring the tumor were used as positive control.

Data obtained from the staining were evaluated with the Chi square test. A p value <0.05 was accepted as statistically significant. SPSS for Windows, ver. 16.0 (SPSS Inc., IL, U.S.A.) was used for statistical evaluations.

RESULTS

The CD138 expression rates of the kidney tumors in our series are presented in Table I. Most cases had a dominance of membranous pattern and smaller rates of cytoplasmic staining pattern.

Membranous staining:

All CCRCC cases had typical diffuse and strong (2+/3+) membranous CD138 expression (Table I). CD138 expression varied in diffuseness (in 5-75% of tumor cells) in CCRCC cases. A stronger (3+) expression level in low-grade, cystic and pseudopapillary areas was noted in CCRCC cases (Figure 1A, B). One CCRCC case had no CD138 staining in the sarcomatous area while there was strong membranous staining in the low-grade clear cell areas. Most PRCC cases (6/9) and only 3 EoRCC cases showed membranous staining (Figure 2A, B, 3). The membranous CD138 expression in these cases was at varying rates between 5% of tumor cells and almost all. Only one PRCC case had type 2 morphology and almost all areas showed strong cytoplasmic and occasional membranous CD138 expression (Figure 2B).

Table I: CD138 expression and staining patterns in renal tumors

Histological Type	Staining Patterns	Expression Rate % (n)	Chi Square Test
CCRCC (n=10)	Membranous	100 (10)	p=0,003
PRCC (n=9)	Membranous	66 (6)	
EoRCC (n=5)	Membranous	60 (3)	
CrRCC (n=15)	Cytoplasmic	20 (3)	
Oncocytoma (n=13)	Cytoplasmic	53 (7)	

CCRCC: Clear cell renal cell carcinoma, **PRCC:** Papillary renal cell carcinoma, **EoRCC:** Eosinophilic variant renal cell carcinoma, **CrRCC:** Chromophobe renal cell carcinoma.

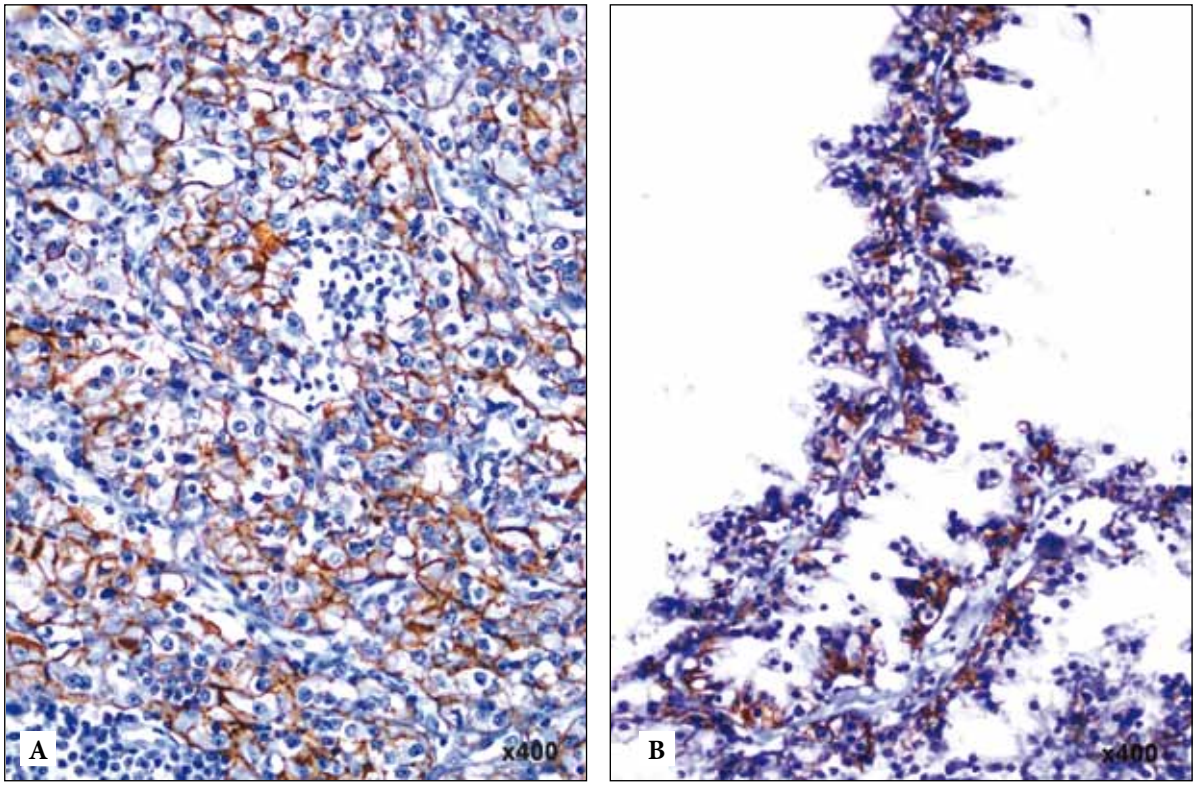

Figure 1: Membranous staining that is low-grade **(A)** and found in cystic and pseudopapillary **(B)** areas in a CCRCC case.

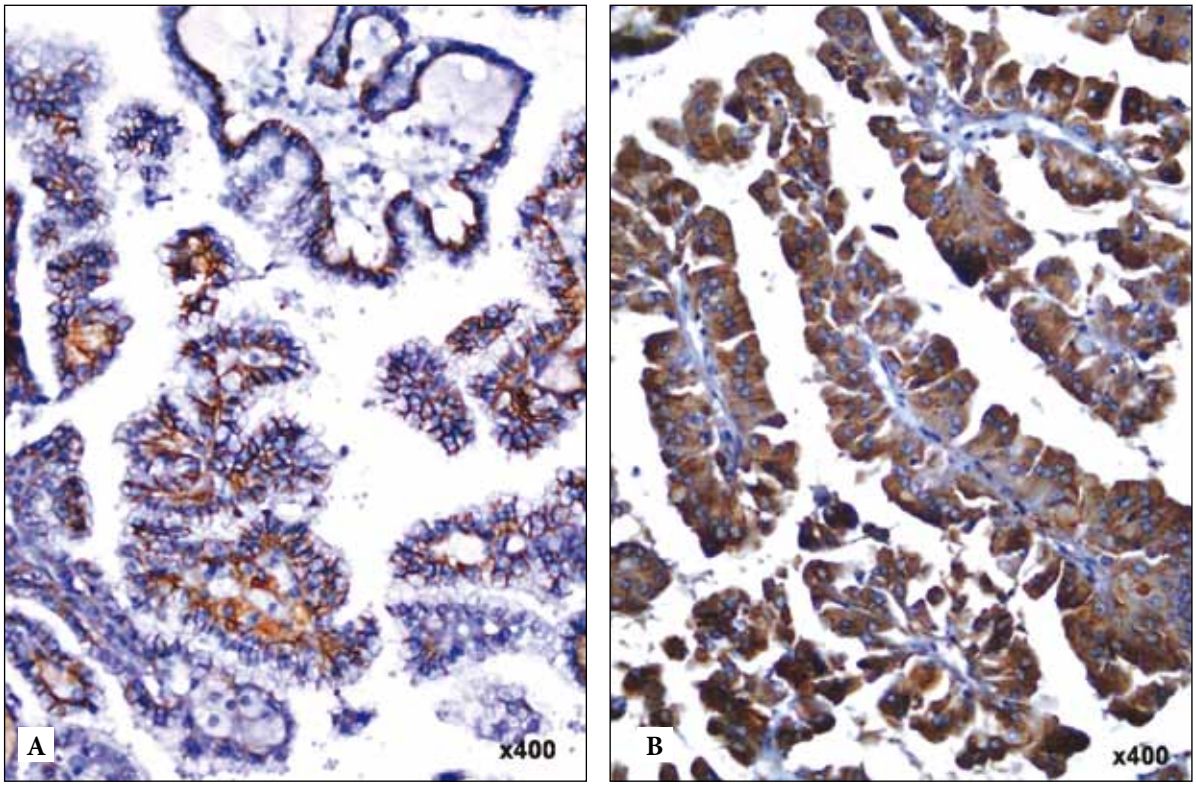

Figure 2: Membranous **(A)** and membranous and cytoplasmic CD138 expression **(B)** in PRCC.

Cytoplasmic staining:

Other renal tumors with eosinophilic cytoplasm (CrRCC and oncocytoma) showed cytoplasmic staining at varying rates (5-95% of tumor cells) and intensity (Table I). Cytoplasmic staining was generally more focal and weak in CrRCC and more diffuse and strong in oncocytomas (Figure 4, 5). However, membranous CD138 expression was not seen in any of these cases.

DISCUSSION

Renal cell carcinoma is the most common malignant tumor of the kidney. The morphological findings in Hematoxylin-Eosin stained sections are generally adequate for a categorical diagnosis. However, an overlap of these morphological findings may create a problem in the differential diagnosis in renal tumors with an eosinophilic cytoplasm. Many immunohistochemical markers have been studied to overcome this problem (2-13). However, the specificity and sensitivity of these markers vary. Markers such as CK7, RCCM and KSC have been reported to be more sensitive for differential diagnosis (8-11). There are still rare cases where the immunohistochemical panels containing these markers can prove to be inadequate. The need for the investigation of new immunohistochemical

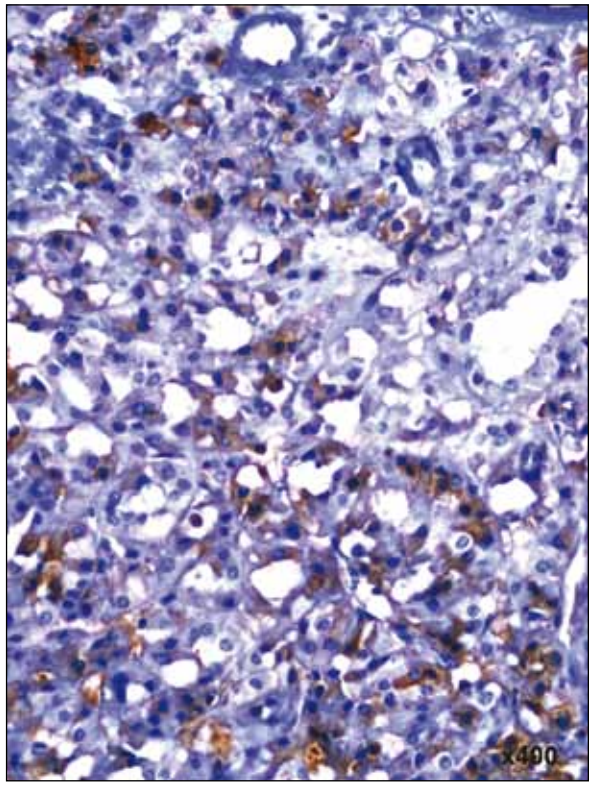

Figure 4: Example of cytoplasmic CD138 expression in CrRCC.

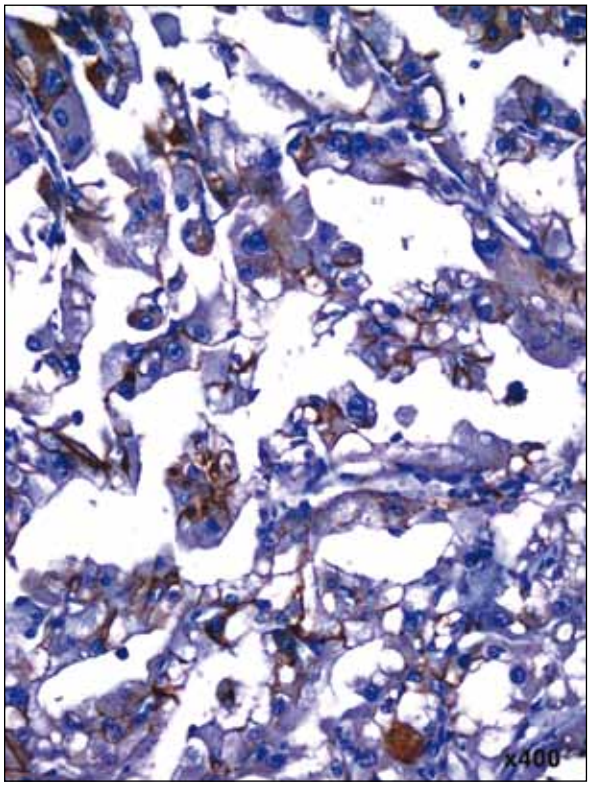

Figure 3: Example of membranous CD138 expression in EoRCC.

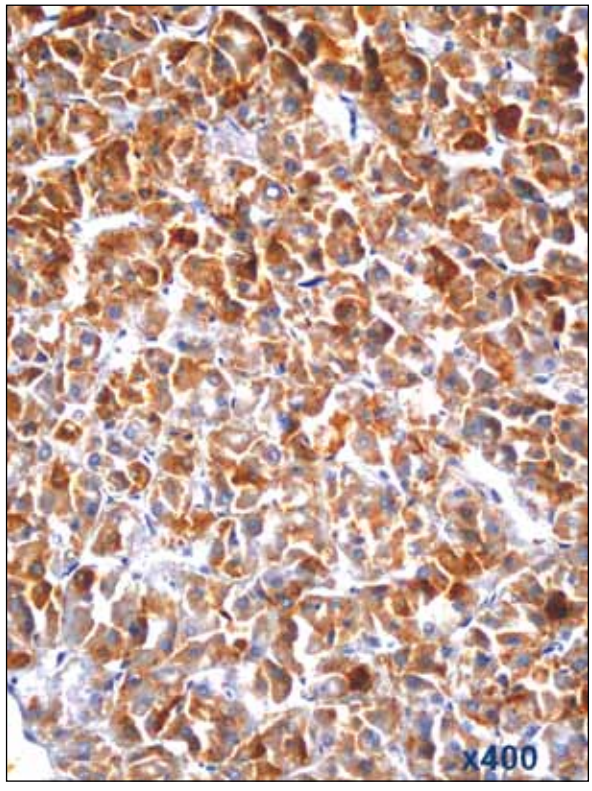

Figure 5: Example of cytoplasmic CD138 expression in oncocytoma.

markers and their usage in pathology practice therefore continues.

CD138 is a plasma cell marker and is mostly used in panels directed towards hematopoietic malignancies. It is known to be present in the proximal renal tubule epithelium (14). Our study results reveal the presence of CD138 expression in a membranous or cytoplasmic manner in various histological types of renal tumors with an eosinophilic cytoplasm. Various renal tumor studies have used various thresholds (such as 1%, 10%, 25%, 50%) for staining rates, often without providing a rationale, when evaluating immunohistochemical staining with various markers and disregarded any staining below these threshold values. However, the general tendency seems to be accepting any staining of 10% or more of the target cell population as positive (10-12). We found that more than 5% of tumor cells were stained with CD138 in almost all cases in our study. The staining was less than 5% in only a few cases. We therefore accepted 5% as the lower limit of significant staining.

Chu et al. have found a CD138 expression of 63% in renal cell carcinomas in a series consisting of a total of 447 hematopoietic and non-hematopoietic tumors (15). Similarly, O'Connell et al. have reported the expression of CD138 in one renal cell carcinoma case in their series of 238 hematopoietic and non-hematopoietic tumors (16). The number of renal cell carcinomas was low in both studies and there is no information on comment on the quality, quantity or morphological pattern of the staining. Our study found membranous and/or cytoplasmic staining in 74% (29/39) of renal cell carcinomas and only membranous CD138 expression in 49% (19/39). There was a cytoplasmic staining pattern with various rates (5-95% of tumor cells) and density (weak-strong) in CrRCC and oncocytoma cases. RCC cases other than CrRCC showed diffuse and strong membranous staining in tumor areas, especially in low-grade areas and those with a dominant cystic, pseudopapillary or papillary growth pattern. The sarcomatoid area in one of these cases did not show CD138 immunoreactivity, in contrast to the surrounding areas. The tumor cells with eosinophilic cytoplasm seen in CCRCC cases generally showed cytoplasmic and only focal CD138 immunoreactivity. Membranous staining was less common and discontinuous. Some EoRCC and one type 2 PRCC case in our series showed moderate to marked cytoplasmic staining despite the low rates of membranous staining.

The Chi-square test performed by taking into account whether the CD138 expression was mainly membranous or cytoplasmic revealed that this pattern difference was limited to some histological subtypes in general and that the difference was statistically significant (p=0.003) (Table I).

Our study aimed to show the expression of CD138, mainly a plasma cell marker, in renal tumors and its possible contribution to the differential diagnosis. It is the most comprehensive of similar studies in the current and accessible literature. CD138 mainly shows a membranous staining pattern in renal tumors while a cytoplasmic pattern is less frequent and more faint. Consideration of the histological subtypes revealed that CD138 showed a membranous staining in CCRCC, PRCC and EoRCC cases and a cytoplasmic staining pattern in CrRCC and oncocytoma cases. It is noteworthy that tumors with a membranous staining pattern are of proximal nephron origin while those with a cytoplasmic staining pattern are of distal nephron origin. This difference that has not been noted or emphasized in other studies may possibly be a reason for using CD138 for the differential diagnosis of renal tumors.

REFERENCES

1. ***Eble JN, Sauter G, Epstein JI, Sesterhenn IA:*** World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. In: Eble JN, Togashi K, Pisani P (Eds). Tumors of the Kidney. Lyon, IARCPress, 2004, 9-87
2. ***MacLennan GT, Farrow G, Bostwick DG:*** Immunohistochemistry in the evaluation of renal cell carcinoma: a critical appraisal. J Urol Pathol 1997, 6:195-203
3. ***Cochand-Priollet B, Molinié V, Bougaran J, Bouvier R, Dauge-Geffroy MC, Deslignières S, Fournet JC, Gros P, Lesourd A, Saint-André JP, Toublanc M, Vieillefond A, Wassef M, Fontaine A, Groleau L:*** Renal chromophobe cell carcinoma and oncocytoma. A comparative morphologic, histochemical, and immunohistochemical study of 124 cases. Arch Pathol Lab Med 1997, 121:1081-1086
4. ***Avery AK, Beckstead J, Renshaw AA, Corless CL:*** Use of antibodies to RCC and CD10 in the differential diagnosis of renal neoplasms. Am J Surg Pathol 2000, 24:203-210
5. ***Kim MK, Kim S:*** Immunohistochemical profile of common epithelial neoplasms arising in the kidney. Appl Immunohistochem Mol Morphol 2002, 10:332-338
6. ***Lee HJ, Kim DI, Kwak C, Ku JH, Moon KC:*** Expression of CD24 in clear cell renal cell carcinoma and its prognostic significance. Urology 2008, 72:603-607
7. ***Kim CM, Vocke C, Torres-Cabala C, Yang Y, Schmidt L, Walther M, Linehan WM:*** Expression of hypoxia inducible factor-1alpha and 2alpha in genetically distinct early renal cortical tumors. J Urol 2006, 175:1908-1914
8. ***McGregor DK, Khurana KK, Cao C, Tsao CC, Ayala G, Krishnan B, Ro JY, Lechago J, Truong LD:*** Diagnosing primary and metastatic renal cell carcinoma: the use of the monoclonal antibody 'Renal Cell Carcinoma Marker'. Am J Surg Pathol 2001, 25:1485-1492

9. ***Shen SS, Krishna B, Chirala R, Amato RJ, Truong LD:*** Kidney-specific cadherin, a specific marker for the distal portion of the nephron and related renal neoplasms. Mod Pathol 2005, 18: 933-940
10. ***Mazal PR, Exner M, Haitel A, Krieger S, Thomson RB, Aronson PS, Susani M:*** Expression of kidney-specific cadherin distinguishes chromophobe renal cell carcinoma from renal oncocytoma. Hum Pathol 2005, 36:22-28
11. ***Adley BP, Gupta A, Lin F, Luan C, Teh BT, Yang XJ:*** Expression of kidney-specific cadherin in chromophobe renal cell carcinoma and renal oncocytoma. Am J Clin Pathol 2006, 126:79-85
12. ***Ozcan A, Shen SS, Zhai QJ, Truong LD:*** Expression of GLUT1 in primary renal tumors: morphologic and biologic implications. Am J Clin Pathol 2007, 128:245-254
13. ***Ozcan A, Zhai J, Hamilton C, Shen SS, Ro JY, Krishnan B, Truong LD:*** PAX-2 in the diagnosis of primary renal tumors: immunohistochemical comparison with renal cell carcinoma marker antigen and kidney-specific cadherin. Am J Clin Pathol 2009, 131:393-404
14. ***Jenette JC, Olson JL, Schwartz MM, Silva FG:*** Heptinstall's Pathology of the Kidney. In:Monsib SM(Ed). Renal Anatomy and Histology. Volume I. 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2006, 1-70
15. ***Chu PG, Arber DA, Weiss LM:*** Expression of T/NK-cell and plasma cell antigens in nonhematopoietic epithelioid neoplasms. An immunohistochemical study of 447 cases. Am J Clin Pathol 2003, 120:64-70
16. ***O'Connell FP, Pinkus JL, Pinkus GS:*** CD138 (syndecan-1), a plasma cell marker immunohistochemical profile in hematopoietic and nonhematopoietic neoplasms. Am J Clin Pathol 2004, 121:254-263