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Immunohistochemical Markers in Renal Tumors and Findings in Non-Tumoral Renal Parenchyma

Renal Tümörlerde İmmünohistokimyasal Belirleyiciler ve Tümör Dışı Renal Parankim Bulguları

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ABSTRACT

Objective: Renal epithelial cells comprise distinct pathological and physiological differences. Renal epithelial neoplasms derived from these cells may show overlapping morphological features, and differential diagnosis requiring the use of ancillary methods. The purpose of this study was to determine the diagnostic utility of the immunohistochemical expression patterns of a wide range of markers in renal epithelial cells.

Material and Method: Normal renal cortical parenchyma and renal pelvis were immunostained for cytokeratin (CK) subtypes (CK7, CK19, CK34βE12), vimentin, RCCMa, CD10, CD117, AMACR, WT-1, EMA and p63. The immunohistochemical expression patterns were examined in 10 cases.

Results: Although there is some overlap, subtypes of epithelial cells showed distinctive CK and CD expression profiles. Proximal tubular cells showed CD10, RCCMa, AMACR expression. Distal tubular cells and collecting ducts showed CK7, CK19 and EMA expression. Urothelial cells showed CK7, CK19, CK34βE12, and p63 expression. CD117 and vimentin selectively stained intermittently in some cells lining the tubules. Endothelial cells and visceral epithelial cells stained with WT-1. Glomerular epithelial cells stained with CD10, but focal and intermittent staining with AMACR, CK7, CK 19, and RCCMa was found in parietal cells.

Conclusion: In conclusion, a panel of cytokeratins, CDs and other markers are helpful in distinguishing epithelial cells and urothelial cells. The expression patterns of these markers may be helpful in the differential diagnosis of epithelial neoplasms.

Key Words: Kidney, Immunohistochemistry, Renal cell carcinoma, Tumor markers

ÖZ

Amaç: Renal epitelyal hücreler belirli patolojik ve fizyolojik farklılıklar içerir. Bu hücrelerden köken alan renal epitelyal neoplazmlar çakışan morfolojik özellikler gösterebilir ve ayırıcı tanı yardımcı yöntemlerin kullanımını gerektirir. Bu çalışmanın amacı, üropatolojide kullanılan geniş bir belirleyici grubunun renal epitel hücrelerinde ekspresyon paternlerini araştırarak tümörlerin ayırıcı tanısındaki yararını belirlemektir.

Gereç ve Yöntem: Normal renal kortikal parenkim ve renal pelvis, immünohistokimyasal olarak sitokeratin alt tipleri (SK7, SK19 ve SK34βE12), vimentin, RCCMa, CD10, CD117, AMACR, WT-1, EMA ve p63 ile boyandı. İmmünohistokimyasal ekspresyon özellikleri 10 olguda araştırıldı.

Bulgular: Bazı çakışmalar olmakla birlikte epitel hücre alt tipleri belirli sitokeratin ve CD ekspresyon profili gösterdi. Proksimal tübüler hücrelerde CD10, RCCMa, AMACR ekspresyonu izlendi. Distal tübüler hücreler ve toplayıcı duktuslar ise SK7, SK19 ve EMA; ürotelyal hücreler ise SK7, SK19, SK34βE12, ve p63 ekspresyonu gösterdi. CD117 ve vimentin tübülleri döşeyen bazı hücrelerde fokal olarak boyandı. Endotel hücreleri ve viseral epitel hücreleri WT-1 ile glomerüler epitelyal hücreler CD10 ile boyandı. Parietal hücrelerde ise AMACR, SK7, SK19 ve RCCMa ile fokal ve kesintili boyanma izlendi.

Sonuç: Sonuç olarak sitokeratinler, CD'ler ile diğer belirleyicilerin yer aldığı panel, epitel ve ürotelyal hücrelerin ayrımında yardımcıdır. Bu belirleyicilerin ekspresyon paternleri epitelyal tümörlerin ayırıcı tanısında yardımcı olabilir.

Anahtar Sözcükler: Böbrek, İmmünohistokimya, Renal hücreli karsinom, Tümör belirleyicileri

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INTRODUCTION

The classification and differential diagnosis of renal tumors have been defined in detail in the recent WHO classification (1). Most malignant tumors derived from renal epithelial cells (REC) are collected under the header of renal cell carninomas (RCC) with some subtypes. However, this classification based on the the cytoplasmic and structural features and morphological appearance of tumor cells can sometimes cause difficulties in the differential diagnosis and immunohistochemical (IHC) investigation is required (2-46). Similarly, metastatic lesions inwhich the history of the primary renal tumor is unknown can also cause problems. The IHC panel used in such cases may help in the differential diagnosis and localization of REC-derived tumors. The current IHC markers that are frequently emphasized in the uropathology literature are presented in Table I.

IHC is used more and more commonly in the differential diagnosis of RCC, especially for neoplasms that contain cells with an eosinophilic, granular cytoplasm. However, the varied features and endogenous activity of REC may cause problems in the interpretation of IHC findings and determining their specificity. The location of many different antibodies in RCC differential diagnosis has been emphasized in the literature. The presence of a large number of commercial antibodies produced by various companies can lead to differences between study results and make it difficult to access reliable information. Knowing the staining features and patterns of the antibodies used in the normal renal parenchyma may help to predict the staining features and patterns of RCC that develop from these cells and be useful in the differential diagnosis. We investigated the staining features of 11 antibodies used frequently in uropathology in the non-tumoral renal parenchyma and tried to define their location in RCC differential diagnosis using the current literature.

MATERIAL and METHOD

This retrospective study was performed on cases that had undergone partial or radical nephrectomy. The surgical materials had been assessed at our department and IHC had been performed for the differential diagnosis. The general information of the cases was obtained from the Ege University Medical Faculty Hospital records and the macroscopic and microscopic data from the Ege University Medical Faculty Department of Pathology archival records. Evaluation was performed for each variable in a retrospective and randomized manner in the peritumoral normal renal parenchymal areas in 10 cases.

We investigated the locations and features of IHC expressions detailed below, used frequently for uropathology routine, in non-tumoral renal tissues with normal histological features using the light microscope.

Table II presents the characteristics of immunohistochemical markers employed in the study.

A demonstrative block from each case that contained normal renal parenchyma adjacent to the tumor was chosen from the paraffin-embedded formalin-fixated blocks. 4-5 microns thick sections were put onto electrostatic-charged slides (X-traTM, Surgipath Medical Industries, Richmond, Illinois, USA) and dried for at least two hours at 60°C. All the IHC staining processes including deparaffinization and antigen exposure steps were performed on the BenchMark XT fully automatic IHC staining device. The sections were counter-stained in the device with hematoxylin and blue dye solution and the process was finished with section dehydration, xylene clarification and coverslip closure by hand.

The cellular staining features and patterns of IHC markers in normal renal parenchyma were defined. The staining features were evaluated in glomerular parietal epithelial cells (PEC) and visceral epithelial cells (VEC), and in the proximal tubule cells (PTC) and distal tubule cells (DTC) in the cortical tubules. The collecting tubule cells (CTC) in the medulla and pyramid and the urothelial epithelial cells in the renal pelvis were also evaluated, in addition to other areas when available. Staining features were graded for each cell group as negative, focal positive (less than 10%) and diffuse positive. The staining patterns in the epithelial cells were defined as apical, basal, cytoplasmic and nuclear if they showed such features. Urothelial epithelial staining in the renal pelvis was noted in five cases.

RESULTS

All cases were adults except 7 cases where WT-1 was studied. The findings associated with each marker have been defined separately below. Table III summarizes the staining features of all markers and Figures 1A-F and 2A-F show the typical staining patterns.

Renal cell carcinoma marker (RCCMa): The PTC stained prominently with RCCMa in all cases. Staining was especially prominent at the apical "brush border". Variable focal staining of PEC in some glomerules was noted. There was no staining of DTC or CTC. No urothelial epithelium staining was found.

CD10: There was marked staining in PTC, especially in the apical section, in all cases. There was positivity in both

Table I: The immunohistochemical markers used for the diagnosis and differential diagnosis of renal adenocarcinomas in uropathology with their frequency of use and reference studies

Usage	Immunohistochemical marker	Abbreviations	References
Most frequent	RCC marker Common acute lymphoblastic leukemia antigen Cytokeratin 7 Vimentin Alpha methyl CoA racemase CD117	RCCMa CD10 CK7 Vim AMACR C-kit	2-10 11-13, 9,12-27 8,12-15,24,28,29 9,21,30-33 7,9,12,34-35
Quite frequent	Cytokeratin 19 Epithelial membrane antigen Cytokeratin 1,5,10,14 P63	CK19 EMA-MUC1 CKhmw, 34βE12	13,14,15 9,24,28,36 9,13,14,27,37-39 37-38
Frequent	Kidney-specific cadherin Wilms' tumor 1 protein TFE	Ksp-cad WT-1	16,40,41 42 43
Current	Parvalbumin Caveolin 1 Glutathione S transferase alpha Epithelial cell adhesion molecule	 GST-α EpCAM	11,28 44 12 12
Not important	Cytokeratin 14 Cytokeratin 20 Cytokeratin 10	CK14 CK20 CK10	12-14,44,45 13-15,20 14,15,20
Others	Melanoma tumor associated antigen LeuM1 Syndecan-1	CD63 CD15 CD138	44

Table II: The immunohistochemical markers used in the study

Antibody	Clone	Dilution	Company	Catalog no
RCC marker (RCCMa)	PN-15	1: 100	Neomarkers	MS-409-P
CD10	56C6	1: 100	Novo Castra	NCL-L-CD10-270
Cytokeratin 7	OV-TL 12/30	1: 500	Neomarkers	MS-1352-P
Cytokeratin 19	A53-B/A2.26	1: 150	Neomarkers	MS-198-P
AMACR	13H4	1: 100	Dako	M3616
Vimentin	Vim 3B4	1: 100	Dako	M7020
Epithelial membrane antigen	E29	1: 400	Thermo Scientific	MS-741-P
C-kit (CD117)	Poliklonal	1: 250	Dako	A4502
Cytokeratin HMW (keratin 1,4,10,14)	34ßE12	1: 100	Dako	M0630
p63	4A4	1: 500	Dako	M7247
Wilms' tumor 1	6F-H2	1: 100	Dako	M3561

glomerular PEC and VEC. We did not find staining in CTC or urothelial epithelium.

Vimentin: Although it was difficult to determine the exact localization in the renal parenchyma, there was generally focal and irregular vimentin positivity that was usually more pronounced in the basal portions of the tubular cells. Most of these cells were interpreted as DTC. There was more marked positive staining that was still marked together with chronic tubuloinstersitial changes and distalization in one case. Glomerular VEC were positive. Peritubular capillaries and vessel walls were also vimentin positive. No positivity was found in the urothelial epithelium.

Table III: Staining features of immunohistochemical markers in normal renal parenchyma

	Glomerular epithelium		Tubular epithelium			Urothelium
	Visceral	Parietal	Proximal	Distal	Collecting	
RCC Ma	-	-/+	+	-	-	-
CD10	+	+	+	-	-	-
CK7	-	-/+	-	+	+	+
CK19	-	-/+	-	+	+	+
CK	-	-	-	-	+	+
Vimentin	-	-	-/+	-/+	-/+	-
AMACR	-	-/+	+	-	-	-
CD117	-	-	-	-/+	-/+	-
EMA	-	-/+	-	+	+	?
P63	-	-	-	-	-	+
WT-1	+	-	-	-	-	-

Cytokeratin (CK) 7: Both DTC and CTC were positive. The staining was stronger in the collecting ducts. Weak and focal positivity in some PEC was seen in 7 cases. There was positivity in the urothelial epithelium while no positivity was seen in PTC.

CK19: We observed the same staining pattern as CK7.

High molecular weight cytokeratin (CKhmw): There was no staining of DTC, PTC or glomerular cells except for minimal and irregular focal positivity consistent with CTC in the cortex. Three cases had increased CKhmw positive cortical tubule cells together with chronic tubulointerstitial changes. Cytoplasmic positivity that was more marked in basal cells was noted in the urothelial epithelium.

p63: No positivity was found in the PTC, DTC and epithelial cells in the cortex. There was nuclear positivity in basal urothelial epithelium in 6 cases.

CD117: There was focal and irregular positivity that was more marked in the basal section of the cells in the DTC and CTC in general in the cortex. We found no positivity in the glomerular epithelial cells or the urothelial epithelium.

EMA: Positivity was found in DTC and CTC and there was PEC positivity as well in 5 cases.

AMACR: There was prominent cytoplasmic positivity in the PTC of all cases. There was faint focal staining of glomerular PEC in 8 cases. There was no staining of collecting tubules or urothelial epithelium.

WT-1: No positivity was found in PTC, DTC, CTC and glomerular PEC or urothelial epithelium. We found cytoplasmic positivity in glomerular VEC and endothelial cells in all cases.

DISCUSSION

We demonstrated the staining features in normal renal parenchyma with a wide IHC marker panel in this study. These IHC markers can roughly be grouped as cytokeratins, CDs and the others. Renal parenchymal distribution of IHC markers regarding the histologic type of epithelial cells can shortly be defined as PTC, DTC, CTC and urothelial epithelium. Some IHC markers showed positivity in proximal tubules, some in distal and collecting ducti and some in urothelial epithelium. Tumors that derive from these cells can be expected to show the same IHC staining with normal epithelium. However, the possibility of antigen expression loss and/or gain during the carcinogenesis should not be forgotten.

IHC markers RCCMa, CD10 and AMACR in this study defined the proximal tubules and were not expressed in DTC, CTC or urothelial epithelium. Similar features have been reported in other publications (3,4,8,9,12,30).

CK 7, CK 19 and EMA defined DTC, CTC and the urothelial epithelium; this feature has also been roughly defined in other publications (3,4,8,9,12,30).

However CK7, CK19, RCCMa and AMACR can at times be seen focally in some glomerular PEC. It is interesting that these markers are not present in all glomerules and PEC. The glomerular PEC staining characteristics have not been emphasized in other publications (4,8,14,30). We sometimes see that PTC line Bowman's space and take the place of PEC in kidney needle biopsies performed for various reasons. This finding as relates to CK7 and CK19 can be accepted to be an indicator of PTC present in Bowman's space or roughly metaplasic epithelium or aberrant synthesis. This

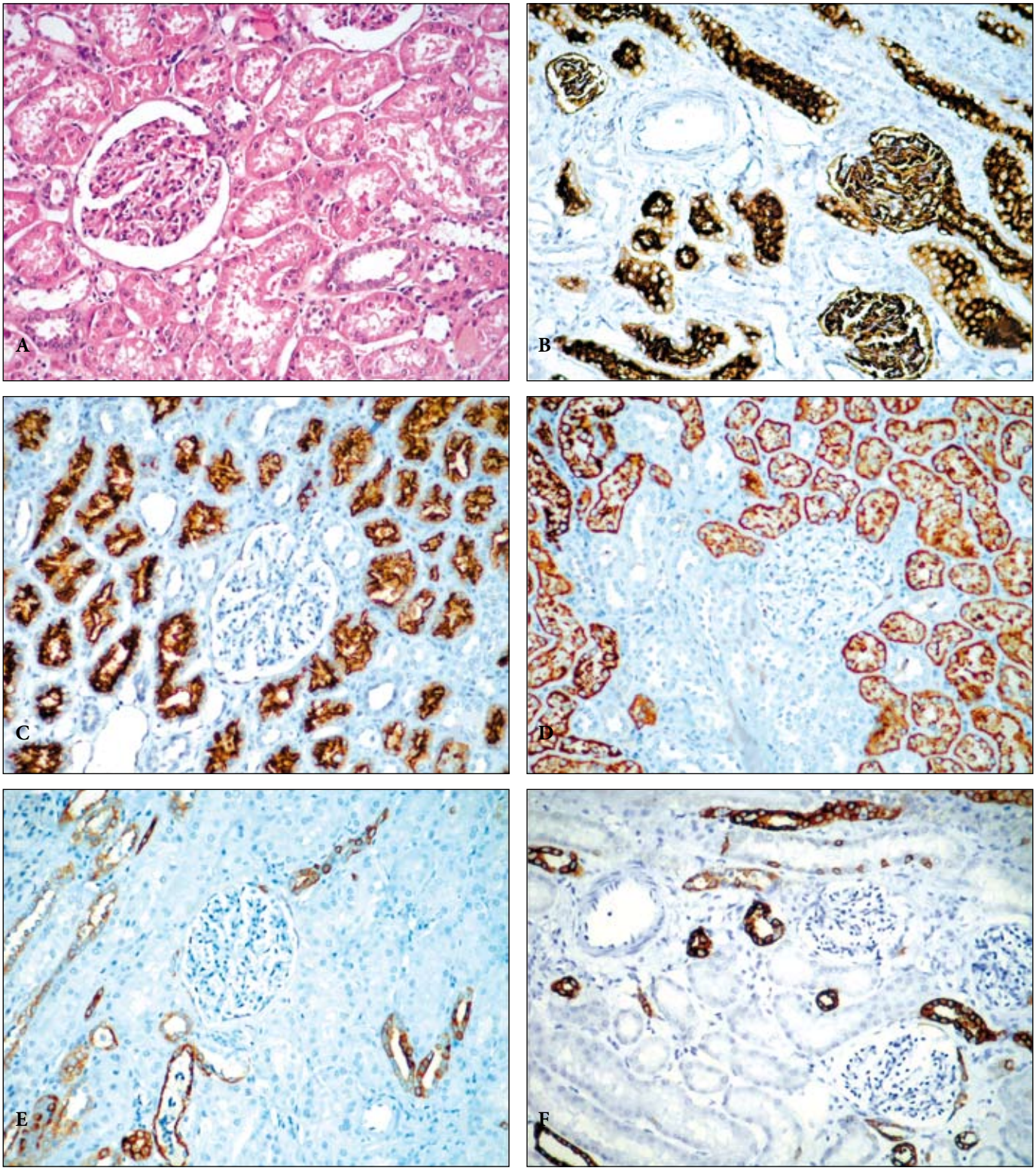

Figure 1: Glomerular and tubular structures with different immunohistochemical markers in the normal renal parenchyma. **A)** H&E, **B)** CD10, **C)** Renal cell carcinoma marker (RCCMa), **D)** AMACR, **E)** CK7, **F)** CK19 (DAB, x200).

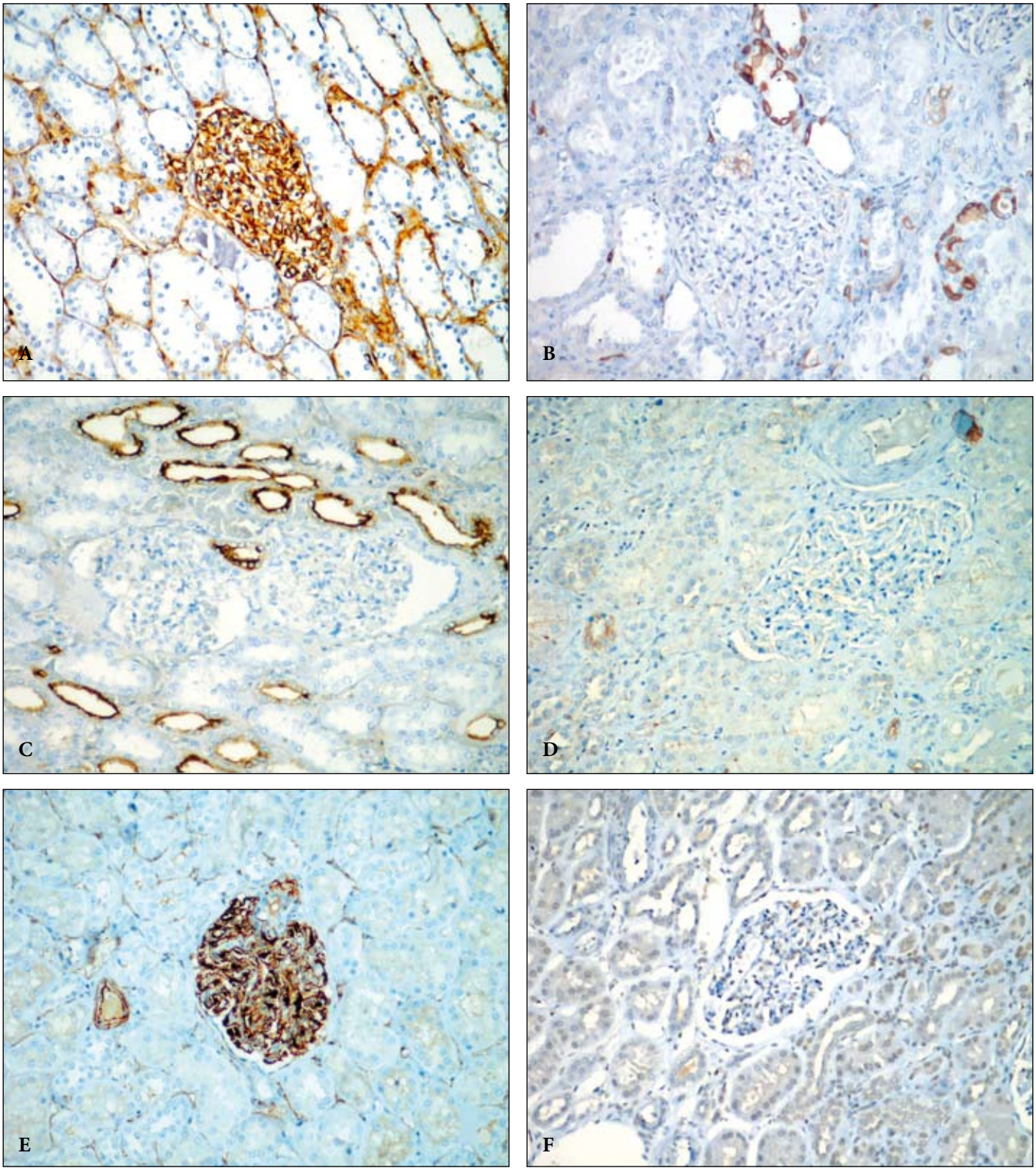

Figure 2: Glomerular and tubular structures with different immunohistochemical markers in the normal renal parenchyma. **A)** Vimentin, **B)** C kit (CD117), **C)** EMA, **D)** CKhmw, **E)** WT-1, **F)** p63 (DAB, x200).

finding can also explain the positivity of these markers in clear cell tumors.

Vimentin and CD117 interestingly showed an interrupted staining pattern as focal and generally single or multiple cell groups in the renal cortical tissue. It is therefore probable that these cells are intercalated cells. These markers were also seen more intensely in the basal section of the cells. These CD117 findings have also been reported by others (12). Vimentin positivity in peritubular capillaries can be interpreted as basal staining of tubular epithelial cells. Reports generally state that tubular epithelial cells are negative (8,12,14). There are no reports on positive tubular epithelial cells.

CKhmw and p63 are generally positive in urothelial epithelium. CKhmw can show minimal CTC positivity in the cortex but the staining of tubular epithelial cells increases in areas of inflammatory infiltration and atrophy. There are various findings regarding CKhmw in renal tumors (14,15). CKhmw and p63 are used for the diagnosis of urothelial carcinoma together with CK7 (14, 46).

WT-1 is only cytoplasmic positive in glomerule VEC and has not been detected in other REC. Endothelial cells also show cytoplasmic WT-1 staining.

We need to shortly remember the histopathogenesis of renal tumors before discussing the use of these data in routine uropathological procedures in light of these findings. Clear cell RCC (RCCclear) develops from PTC while papillary RCC (RCCpap) is said to originate from DTC (14). The less frequently seen chromophobe cell RCC (RCCchro) that can cause differential diagnosis problems with clear cell RCC "eosinophilic variant", and oncocytoma that is accepted as its benign variant have been said to originate from CTC intercalated cells (1). Although some articles have emphasized the Henle loop relation for mucinous tubular spindle cell carcinoma (MTSCC), one of the newly-defined tumors, its origin is said to be the distal nephron (1). The medullary collecting tubule is said to give rise to medullary carcinoma, collecting ductus carcinoma (CDC) and tubulocystic carcinoma (46).

When compared with normal histology, tumors of PTC origin can be expected to be positive for CD10, RCCMa and AMACR. CD10 and RCCMa are highly positive in both primary and metastatic RCCclear cases in the literature (4-8, 10). CK7, CK19 and vimentin positivity is also seen at varying rates and in an aberrant manner in these tumors (13-15).

RCCpap and MTSCC of distal tubule origin would be expected to be positive for CK7, CK19 taking the normal histology into account. These tumors show a high degree of CK19 and CK7 positivity (9,14,15). The differential diagnosis between RCCpap and metanephric adenoma can sometimes be difficult. CKhmw negativity and CK19 positivity are important for the diagnosis of metanephric adenoma (42). EMA has been reported negative at times in metanephric adenoma (47). However, although RCCpap and MTSCC originate distally, they show a high rate of AMACR positivity, normally demonstrated at the proximal tubule (9,30). This may indicate aberrant expression in tumors originating from the distal nephron. CD10 and RCCMa positivity can also be found in RCCpap in an aberrant manner (4,8,14). We interestingly did not observe CD10 expression in MTSCC while the RCCMa positivity was not as marked as in RCCpap (48). This may help in the differential diagnosis of both tumors but one article has found markedly positive CD10 expression in 3 cases (%15) (9). CD117 expression can also rarely be seen in this tumor (9).

The differential diagnosis of RCCchro and oncocytoma said to originate from intercalary cells from RCCclear eosinophilic variant is often difficult. CD117 positivity would be expected in these tumors if they show their normal cell features. Vimentin stains with a similar pattern in the normal renal parenchyma so it may be showing the intercalated cells. However, the vimentin negativity in both tumors is interesting (8,12,14,46). CD117 is said to be definitive for oncocytoma (7, 12) but a high rate of positivity has been reported in RCCchro as well (7, 12). These tumors are rich in mitochondia and have endogenous biotin activity that may lead to false interpretation, requiring the utmost care (14). Incorrect results have been defined for CK14 in accordance (14). The membranous CK7 positivity of RCCchro is valuable for the diagnosis. It is difficult to say whether this expression is aberrant or not as there is no clear information for CK7 positivity in intercalary cells. It is possible that these cells are normally CK7-positive as well.

Tumors defined as of collecting tubule origin are quite rare and these can be expected to show CKhmw, CK7, CK19 positivity accordingly. However, only CKhmw and CK19 for CDC have been reported in this group (13,46). No specific immunohistochemical features have been defined for medullary carcinoma.

Urothelial carcinomas (UC) derived from renal pelvis urothelial epithelium may be expected to show CKhmw, P63, CK7, and CK19 positivity. This feature is important regarding CDC that can cause problems in the differential diagnosis. UC do show a high rate of CKhmw, CK7 and p63 positivity. There may be a problem in the differential diagnosis

of highly invasive UC with squamous differentiation from nonkeratinized SCC in tumors that do not contain papillary structures or squamous metaplasia and are seen together with in situ carcinoma in the urothelial epithelium. The importance of CK7 negativity in the in situ areas for in situ SCC should be investigated, as CK7 is positive in urothelial carcinoma if in situ. Both in situ tumors should be CKhmw and p63 positive. The possibility of nonkeratinized SCC should be investigated for urothelial epithelial tumors that are CK7 negative. No CKhmw positivity has been seen in RCCclear cases. Various staining features have been described for MTSCC (9).

We did not find WT-1 positivity in the adult kidney except for the glomeruli. The only use of this marker outside pediatric Wilms' tumor is therefore the differential diagnosis of metanephric adenoma and RCCpap (42, 46). WT-1 positivity helped in the differential diagnosis in a similar case of ours with metanephric adenoma. The WT-1 positivity of metanephric adenoma supports its relation with Wilms' tumor (42). WT-1 expression seems to be limited to nephroblastic tumors in the kidney, indicating that metanephric adenoma is within the spectrum of Wilms' tumor, one of the nephroblastic tumors.

Needle biopsies contain only a limited amount of material that makes IHC investigation very important (2). Table IV presents the main IHC markers and panels according to the predominant cell type for RCC differential diagnosis in such biopsies and surgical material. The presence of extratumoral normal renal parenchyma in addition to the tumor during these investigations will provide reliable information as internal control during the IHC evaluation.

REC shows positivity with more than one IHC marker, as summarized in Figure 3. Knowing the defined features of normal renal parenchyma and the normal and aberrant positivity in tumors in relation will facilitate differential diagnosis. It is important to select a suitable panel and evaluate the normal renal parenchyma adjacent to the tumor as an internal control during IHC investigation for tumors. The findings may help the differential diagnosis according to the cell type of tumor origin but the possibility of aberrant expression or loss of expression must also be taken into account.

Table IV: Renal tumors according to the cell of origin and the immunohistochemical features

		Degree of positivity		Negative
Neoplasm origin		**High probability (more than 75%)**	**Moderate probability**	**Less than 25%**
Proximal tubule				
	RAC clear cell	CD10, RCCMa	Vimentin, CKhmw	CK7, parvalbumin, CD117, Ksp-cad, p63
Distal tubule				
	RAC papillary	CD10, RCCMa, CK7; CK19, AMACR	Vimentin, EMA, CKhmw, Ksp-cad	WT-1, p63
	Mucinous tubular spindle cell carcinoma	CK7, CK19, AMACR	RCCMa, EMA, Vimentin, CKhmw	CD10, p63, Ksp-cad
	Metanephric adenoma	WT-1, CK19,	CD57	AMACR, CK7, EMA, CD57, p63, CD56
Intercalated cells				
	RAC, chromophobe	CK7, CD117, parvalbumin, Ksp-cad, EpCAM	CD10,	RCCMa, Vimentin, p63, GST-α
	Onkocytoma	CD117, Ksp-cad,	CD10, CK7,	Vimentin, p63, GST-α
Collecting tubule				
	Collecting duct carcinoma		CKhmw, vimentin	CD10, RCCMa, AMACR, p63
Urothelial epithelium				
	Urothelial carcinoma	CK7, CKhmw, p63	CD10, CK20, vimentin	RCCMa
	Squamous cell carcinoma	CKhmw, p63		

Abbreviations: RCCMa; Renal adenocarcinoma marker, bs-cadherin; kidney specific cadherin, CK7; cytokeratin 7, CK19; cytokeratin 19, CKhmw; High molecular weight cytokeratin, CK20; cytokeratin 20, WT-1; Wilms' tumor-1.

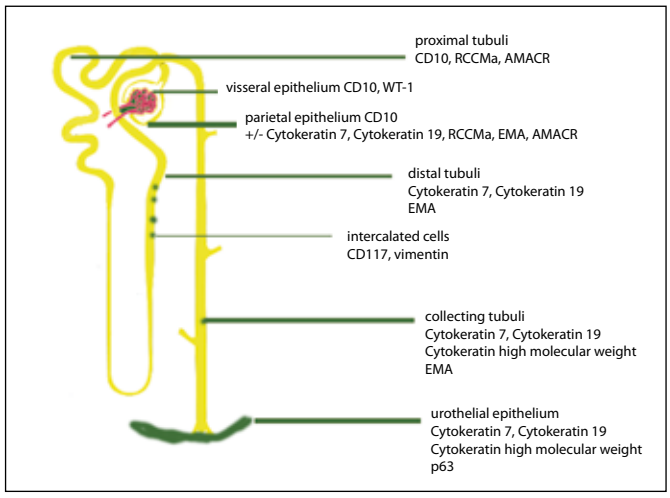

Figure 3: Nephron findings with the antibodies used in the study.

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