

ORIGINAL PAPER

The diagnostic value of cytokeratins expression in the renal parenchyma tumors

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Abstract

Renal carcinomas are a heterogeneous group of tumors, difficult to classify and identify precisely. Since their prognosis depends very much upon their type, precise diagnosis might mean the difference between therapeutic success and patient death. Cytokeratins are particularly useful for the identification of the epithelial nature of the tumors, because their expression is maintained even in poorly differentiated tumors. Monoclonal cytokeratins such as CK7 and CK20 stain different components of the renal tubular system and are a useful duo for the identification of the origin of the different tumors that might arise in the kidney. Along with polyclonal cytokeratins such as AE1/AE3 and high molecular weight cytokeratin antibodies (34betaE12, Cam 5.2), epithelial membrane antigen (EMA) and vimentin, they are included in every diagnostic panel for renal tumors. We have selected 138 renal parenchyma tumor specimens, performed morphological diagnosis and then stained them with polyclonal cytokeratin antibody AE1/AE3, and monoclonal antibodies to CK7 and CK20. AE1/AE3 was expressed in 61.7% of the renal parenchyma tumors, with high intensity and percentage of positive cases in the papillary carcinomas (100%), and with rare and weakly positive cells in chromophobic cells carcinomas, clear cells carcinomas and sarcomatous carcinomas. CK7 was positive in 68% of the renal parenchyma tumors, with positive reaction in 100% of the cases of chromophobic cells and sarcomatous carcinomas. Clear cells carcinomas had the less percentage of positive cells, whereas papillary carcinomas were positive in seven out of eight cases. No difference in the staining pattern was noticed between type I and type II papillary carcinomas. CK20 was negative in all cases studied.

Keywords: cytokeratins, renal carcinomas, immunohistochemistry, AE1/AE3, cytokeratin 7, cytokeratin 20.

✉ Introduction

Cytokeratins are intermediate filaments proteins that form the cytoskeleton of the epithelial cells, which maintain their expression in tumors of epithelial origin. Since the differential diagnosis between the different subtypes of renal carcinomas is very difficult in plain morphology, especially in poorly differentiated tumors, immunohistochemistry might prove useful as well as histochemistry. For example, the chromophobic carcinomas are typically negative for vimentin, and positive to Halls staining method with colloidal iron [1]. The expression of cytokeratins in the tumors of the renal parenchyma is very useful for the differential diagnosis between different types of renal parenchyma tumors, having an important influence on their classification and the patient prognosis. The polyclonal cytokeratins are a constant presence in the primary immunophenotyping antibody panels, highlighting the epithelial origin for the tumor if they are positive. The monoclonal antibodies against certain cytokeratins might prove useful for the specific diagnosis of tissue origin of the tumor. The peculiarity of the renal tumors is the fact that the carcinoma cells are positive for a high variety of markers, which reflects their heterogeneity. Typically, some antigens that might be detected in a group of patients are usually negative in another group. The most frequently expressed monoclonal cytokeratins in the

renal parenchyma tumors are cytokeratin 7 (CK7) and cytokeratin 20 (CK20), whereas the polyclonal cytokeratin AE1/AE3 (also referred as pan-cytokeratin) is useful for specifying the epithelial origin of the tumor cells in difficult cases.

CK7 is a low molecular weight cytokeratin, which is expressed in a vast variety of epithelia in both normal and malignant conditions. There are a high number of studies in the literature in which CK7 was useful in the diagnosis of several tumors, such as those of the gastrointestinal tract [2–4], lung [2–4] and genital tract [5]. As for the usefulness of CK7 immunostaining in renal parenchyma tumors, the literature data is still controversial. Some studies published so far argue that CK7 is typically negative for renal carcinomas, without precisely establishing the subtype of the tumor studied [2–4, 6, 7].

The expression of CK20 in renal carcinomas has been studied only by few researchers. One of these studies performed on archival blocks from 11 cases of chromophobic renal carcinomas from 1984–2000 has found the tumors negative for CK20 in all cases [8].

The conventional renal carcinoma is usually positive for low molecular weight cytokeratins, CK18, AE1/AE3, EMA and vimentin, but negative for CK7, CK20, high molecular weight cytokeratins (34betaE12), carcino-embryonal antigen [6], S-100 protein [9], HMB456 and inhibin [10]. The difficulties posed by the morpholo-

gical diagnosis are usually resolved by immunohistochemistry.

☞ Material and Methods

Hundred and thirty-eight renal parenchyma tumors specimens from patients admitted between 1999 and 2004 were selected from the archive of the Urology Clinic of the Emergency County Hospital in Timișoara, were primary processed, performed morphological diagnosis and pretreated for immunohistochemistry. Briefly, the specimens were fixed in 4% buffered formalin, embedded in paraffin and sectioned at 3–5 μ m. The slides were then dewaxed and rehydrated and either stained with the usual HE staining for the morphological diagnosis or pretreated for immunohistochemistry. The antigen retrieval for immunohistochemistry was performed by microwave heating of the slides submerged in citrate buffer at pH 6 for 15 minutes for CK7 and 20 minutes for CK20 immunostaining, respectively. The next step was blocking of the endogenous peroxidase with hydrogen peroxide, followed by the incubation with the primary antibody for 30 minutes, then by the application of the LSAB2 system: secondary antibody and the

Streptavidin–Biotin Complex for 10 minutes each. The reaction was visualized by activated Diaminobenzidine (DAB), and then the slides were counterstained with Lillie's Hematoxylin. After staining, the slides were dehydrated and mounted with Canada balsam.

☞ Results

Polyclonal cytokeratin expression

AE1/AE3 cytokeratin was positive in 29/47 of renal parenchyma tumors (61.70%), and negative in 14 of the 33 cases of clear cells carcinomas; in positive slides, it had low intensity and stained few cells; was intensely positive in all cases of papillary and chromophobic cells carcinomas; and was negative in all cases of sarcomatous carcinoma.

The internal positive control was represented by collecting ducts and connective tubes, as well as the parietal layer of the Bowman capsule and the urothelium. All these elements were constant positive in all cases where normal renal parenchyma was present on the section (Figure 1, a–d). The final reactions were strictly cytoplasmic, granular or diffuse, with high intensity.

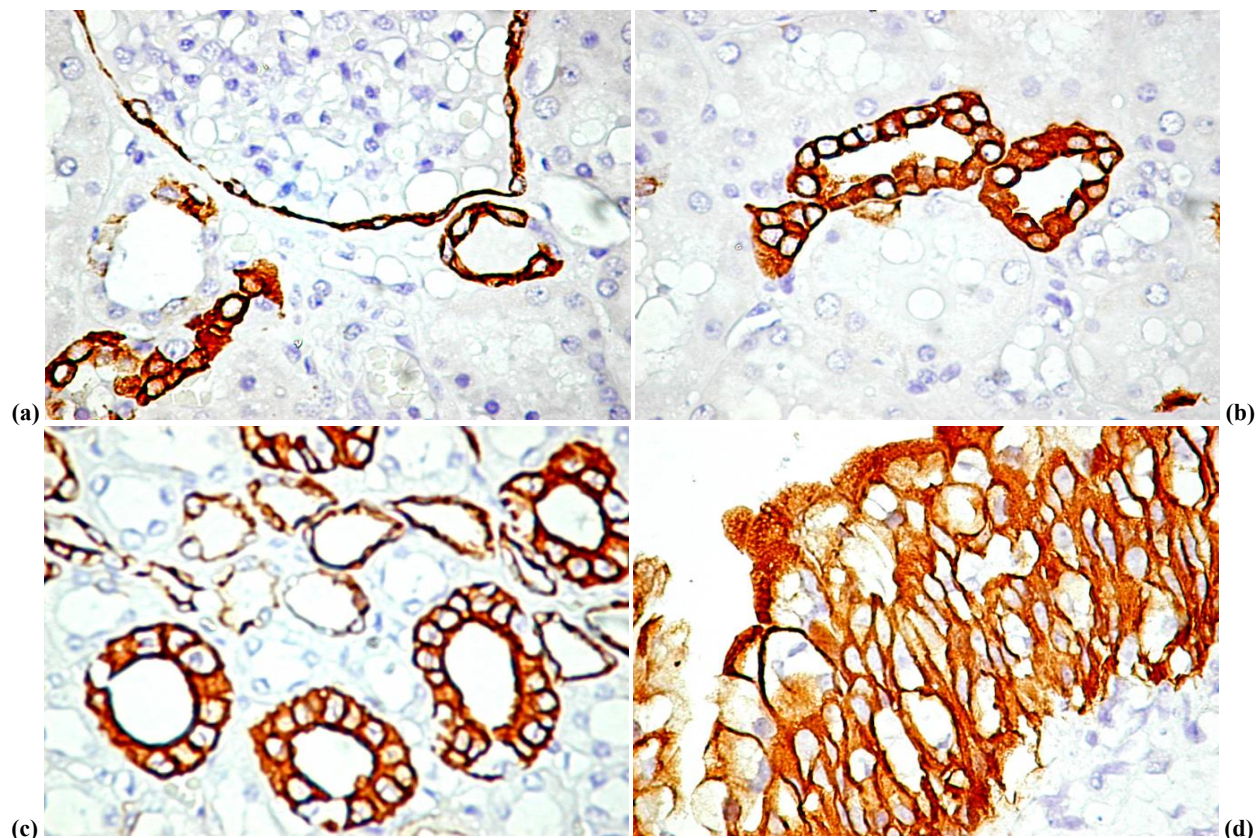


Figure 1 – (a) Internal positive control for AE1/AE3 ($\times 400$). Parietal layer of the Bowman capsule. (b) Internal positive control for AE1/AE3 ($\times 400$). Connecting tubules. (c) Internal positive control for AE1/AE3 ($\times 400$). Collecting ducts. (d) Internal positive control for AE1/AE3 ($\times 400$). Urothelium.

The intensity of the reaction was compared with control slides. The reaction was assessed qualitatively, following the protocol: -, negative, +/-, rare positive cells, either isolate or in small groups, +, less than 33% positive cells, ++, 33 – 66% positive cells and +++, over 66% positive cells.

Out of the 33 cases of clear cell carcinoma, only 19

were positive (11 labeled +/-, seven labeled + and two labeled ++). The fact that this cytokeratin, although mentioned by the majority of the studies published in the literature, had not yielded the expected results in clear cells carcinoma (Figure 2, a and b). The most frequent distribution pattern of this cytokeratin in clear cells carcinoma was that with rare moderately positive

cells, arranged usually isolated, in tumor cells nests (Figure 2c). In five cases, we have noticed the presence of intensely positive collecting tubules caught into the proliferation (Figure 2d).

The areas of clear cells from chromophobic cells carcinomas have been also negative (Figure 3).

The intravascular emboli of tumor cells were also negative or weakly positive (Figure 4). In contrast, the invasion of the neighboring structures was formed of intensely positive cells (Figure 5a). Similar areas with intensely positive and negative cells were identified in the tumor origin area as well (Figure 5b).

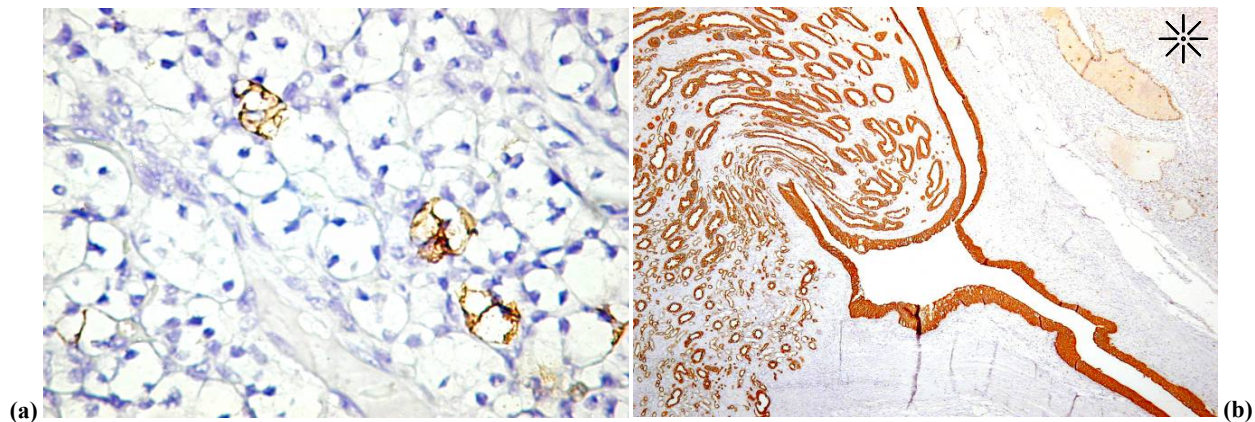


Figure 2 – (a) Clear cells carcinoma. Rare moderately positive cells. AE1/AE3 immunostaining ($\times 400$). (b) Clear cells carcinoma. Intensely positive collecting tubules of the medulla and urothelium, negative tumor (*) (low magnification). AE1/AE3 immunostaining.

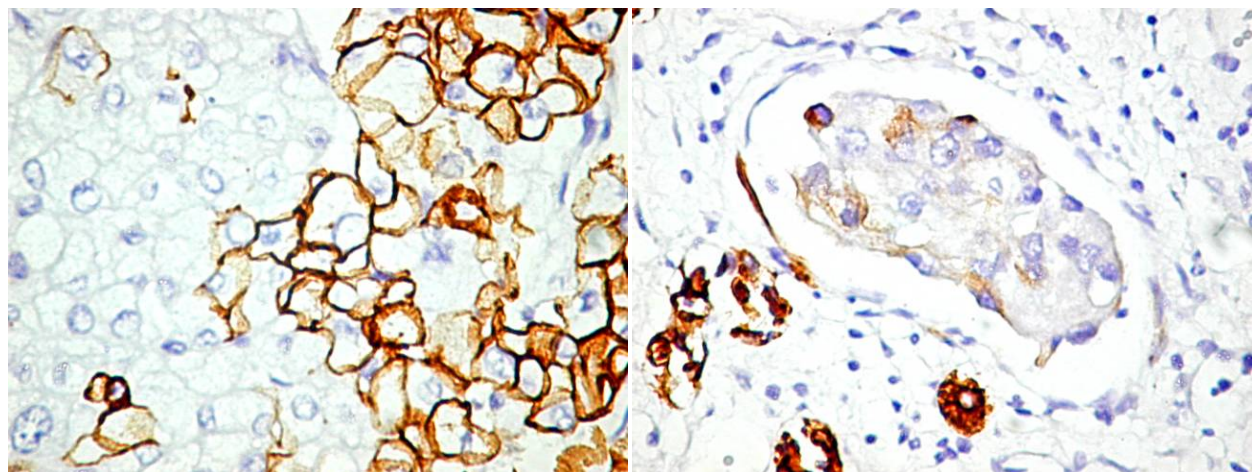


Figure 3 – Negative clear cells area in a chromophobic carcinoma. AE1/AE3 immunostaining ($\times 400$).

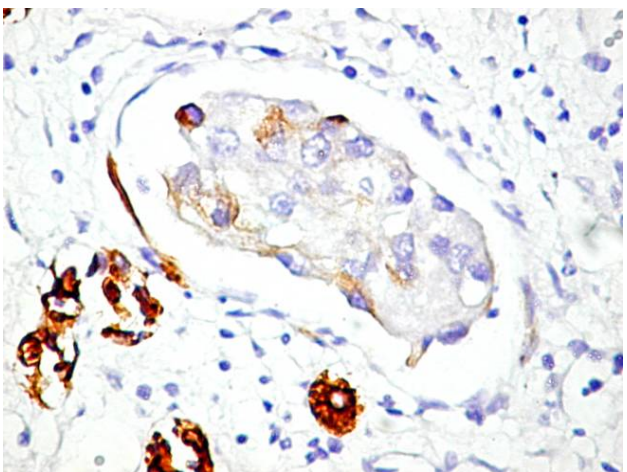


Figure 4 – Weakly positive or negative tumor cells embolus. AE1/AE3 immunostaining ($\times 400$).

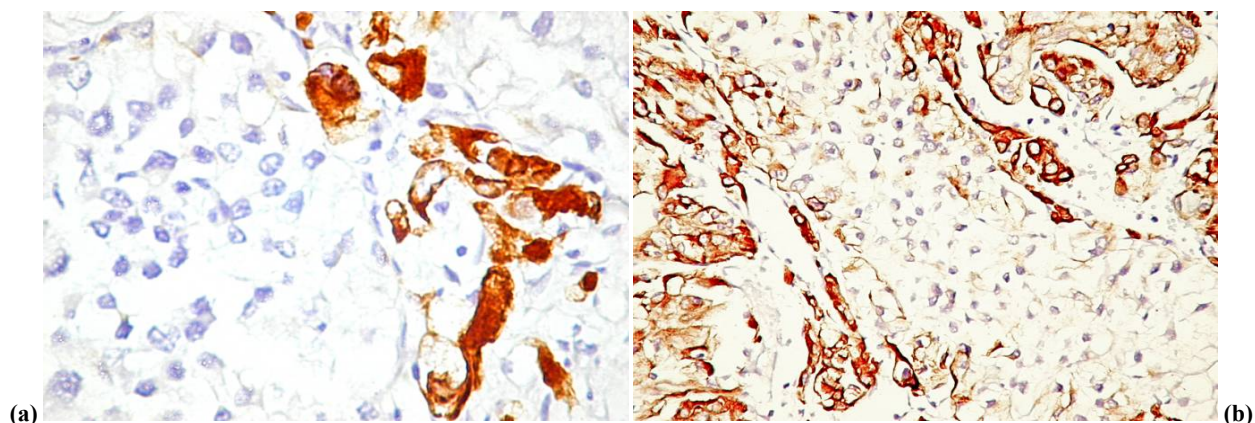


Figure 5 – (a) Negative tumor cells embolus and intensely positive tumor cells invading the stroma. AE1/AE3 immunostaining ($\times 400$). (b) Tumor mass, with positive and negative areas. AE1/AE3 immunostaining ($\times 200$).

The eight cases of papillary carcinoma were intensely positive, noted in six of the cases with +++ and in two of the cases with ++. Basically, all of the papillae were intensely stained, with negative

immunostaining in the connective axes (Figure 6a). The reaction had the same pattern in both types of papillary carcinoma (Figure 6b), and was the most constant in expression in all of the cases studied.

All the epithelial cells were intensely stained, homogenous, with cytoplasmic pattern, and the axis with macrophages (Figure 7a) or calcifications (Figure 7b) was negative. Chromophobic cells carcinomas (n=2) had a peculiar distribution pattern of the final reaction product. The ectocyttoplasm of the majority of the malignant cells was intensely positive (+++); but the chromophobic nuclear halo was not stained with AE1/AE3, the same pattern as in usual HE staining (Figure 8a). In comparison with the papillary carcinoma, the staining pattern was significantly

heterogeneous, although there were no significant intensity differences (Figure 8b).

All of the three sarcomatous carcinomas were negative for AE1/AE3, only rare weakly positive cells were noted between anaplastic malignant cells (Figure 9a). In some areas, we have noticed the presence of small groups of positive cells, with mild or moderate staining intensity, between the severe anaplastic negative cells (Figure 9b). We take these cells as collecting tube cells caught between malignant cells due to the rapid tumor proliferation.

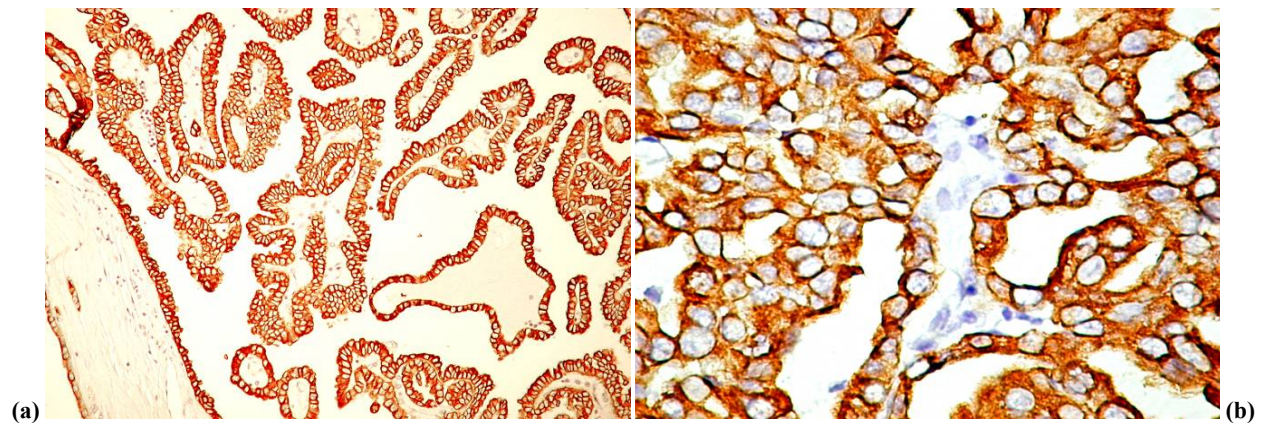


Figure 6 – (a) Papillary carcinoma, the papillae have negative connective axis, and positive epithelium. AE1/AE3 immunostaining (×40, low magnification). (b) Type II papillary carcinoma, with +++ intensity. AE1/AE3 immunostaining (×400).

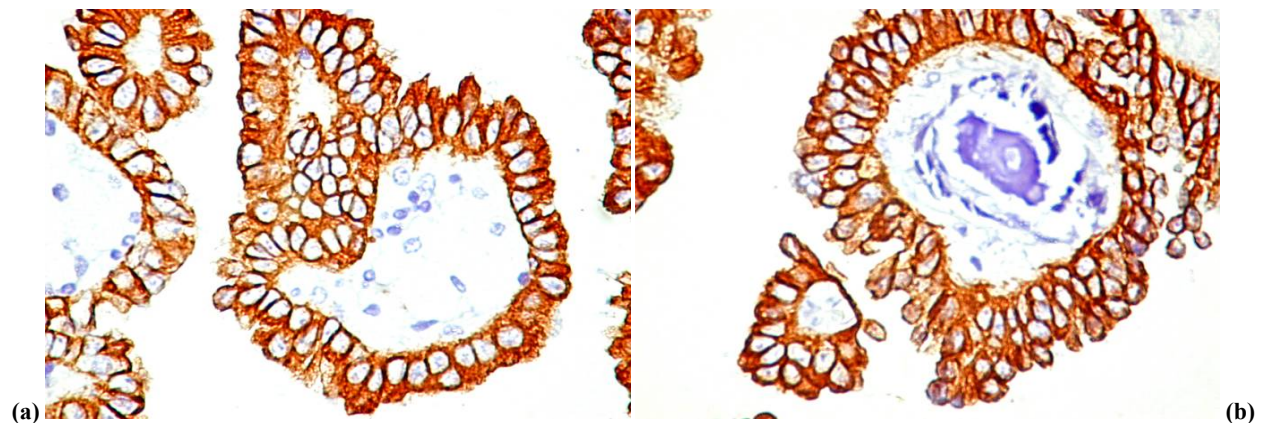


Figure 7 – (a) Papillary carcinoma with intensely stained epithelial cells and axis macrophages negative. AE1/AE3 immunostaining (×400). (b) Papilla with positive epithelium and negative calcification. AE1/AE3 immunostaining (×400).

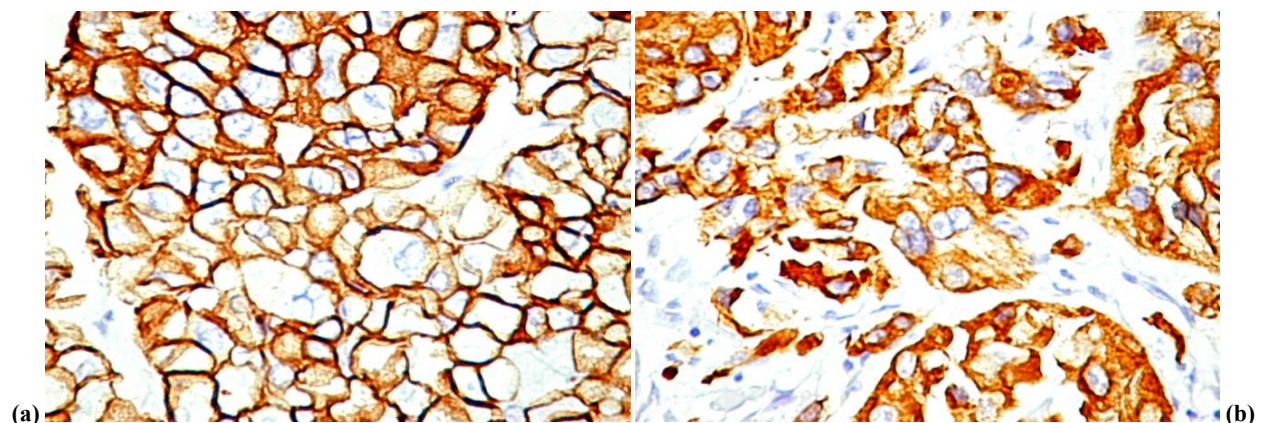


Figure 8 – (a) Chromophobic cells carcinoma with chromophobic nuclear halo. AE1/AE3 immunostaining (×400). (b) Heterogeneous distribution of the final reaction product. AE1/AE3 immunostaining (×400).

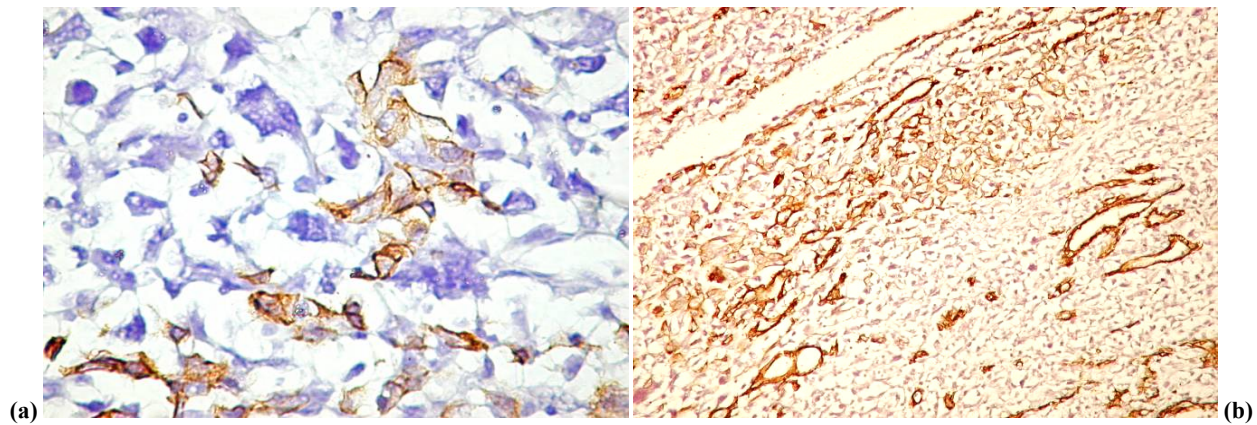


Figure 9 – (a) Sarcomatous carcinoma. Rare weakly positive cells, arranged between monstrous malignant cells. AE1/AE3 immunostaining (×400). (b) Sarcomatous carcinoma. The intensely positive tubules were trapped into the tumor proliferation. AE1/AE3 immunostaining (×100).

Expression of cytokeratins 7 and 20

All of the cases studied were negative for cytokeratin 20. This result is especially useful for the differential diagnosis with urothelial carcinoma, which is constantly positive to this marker. Cytokeratin 7 was expressed in the remaining renal parenchyma in the collecting and connecting tubules, with diffuse cytoplasmic pattern and

high intensity (Figure 10a). The calyces' urothelium was intensely positive, and, unlike EMA, stained all of the cells with the same intensity (Figure 10b). These elements were the internal positive control. A peculiar aspect was noticed in the connecting tubules, in which the intensely positive cells alternate regularly with negative cells (Figure 10c).

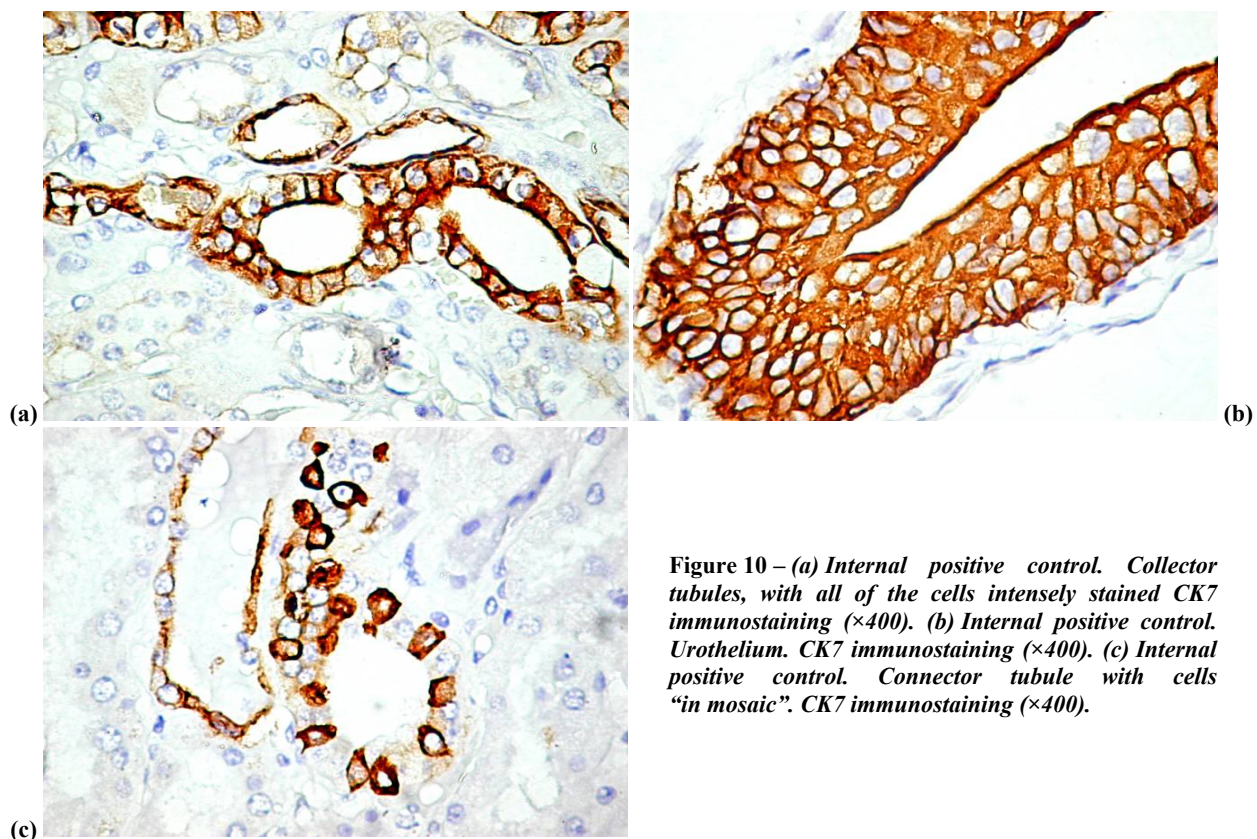


Figure 10 – (a) Internal positive control. Collector tubules, with all of the cells intensely stained CK7 immunostaining (×400). (b) Internal positive control. Urothelium. CK7 immunostaining (×400). (c) Internal positive control. Connector tubule with cells "in mosaic". CK7 immunostaining (×400).

Out of the 47 cases stained for cytokeratin 7, 32 were positive (68%). Chromophobic cells and sarcomatous carcinomas were 100% positive. Only 20 of the 33 cases of clear cells carcinomas and seven of the papillary carcinomas were positive (Table 1).

In clear carcinoma cases, the intensity of the staining was weak or focally moderate. None of the cases were labeled ++ or +++, due to the fact that the intensity of

the staining was low and limited to the cellular membrane and/or due to the reduced number of stained cells (Figure 11a). In addition, the staining was weakly positive or negative in undifferentiated cells, with obvious nuclear anaplasias (Figure 11b). Although the majority of the cases of clear cells carcinoma had presented a few positive cells, isolated or in small groups and intensely stained, most of the malignant

cells were negative (Figure 11c). In the proliferation front, remaining tubular cells, intensely positive, were frequent, and contrasting with weakly positive or negative malignant cells (Figure 11d). This aspect reflects the partial lose of the phenotype regarding CK7 expression.

Papillary carcinoma was positive in seven of the eight cases, and in six of the positive cases, the staining had high intensity and stained almost all of the malignant cells. In some areas, the staining was more intense towards the connective axis of the papillae (Figure 12a). In three cases, the staining was heterogeneous, with intensely, moderately and weakly stained

cells in the same microscopic field (Figure 12b). No significant differences of the staining patterns were noticed between type I and type II papillary carcinomas (Figure 12, c and d).

Table 1 – The incidence of the cases with positive CK7 immunostaining

Type	No. of positive cases	%
Clear cells carcinoma (n=33)	20	42.5
Papillary carcinoma (n=8)	7	87.5
Chromophobic cells carcinoma (n=2)	2	100
Sarcomatous carcinoma (n=3)	3	100
Mixed tumor (n=1)	0	0

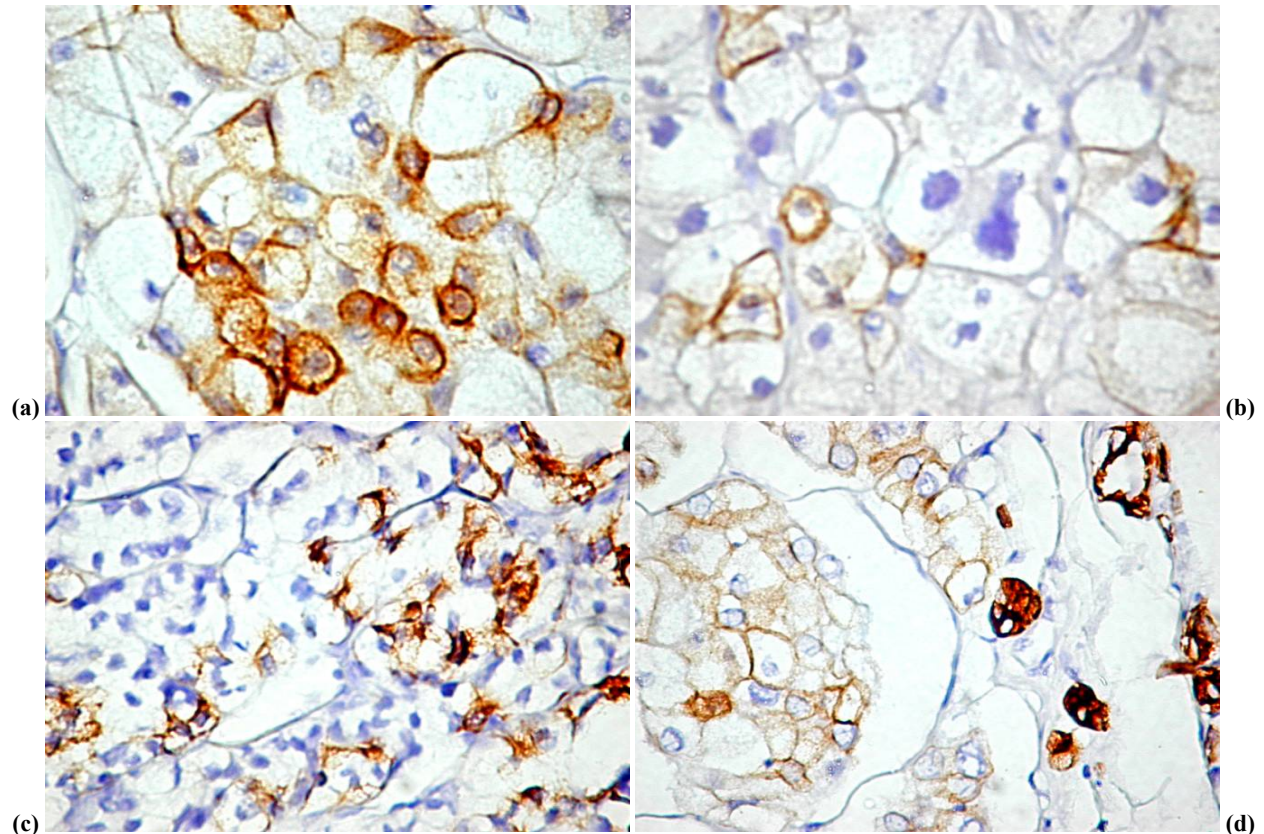


Figure 11 – (a) Clear cells carcinoma. Heterogeneous cellular population. CK7 immunostaining ($\times 400$). (b) Clear cells carcinoma. Negative cells with nuclear anaplasia. CK7 immunostaining ($\times 400$). (c) Clear cells carcinoma. Mostly negative cells. CK7 immunostaining ($\times 400$). (d) Clear cells carcinoma. Remaining tubular cells, intensely positive, malignant cells with weak membranous staining. CK7 immunostaining ($\times 400$).

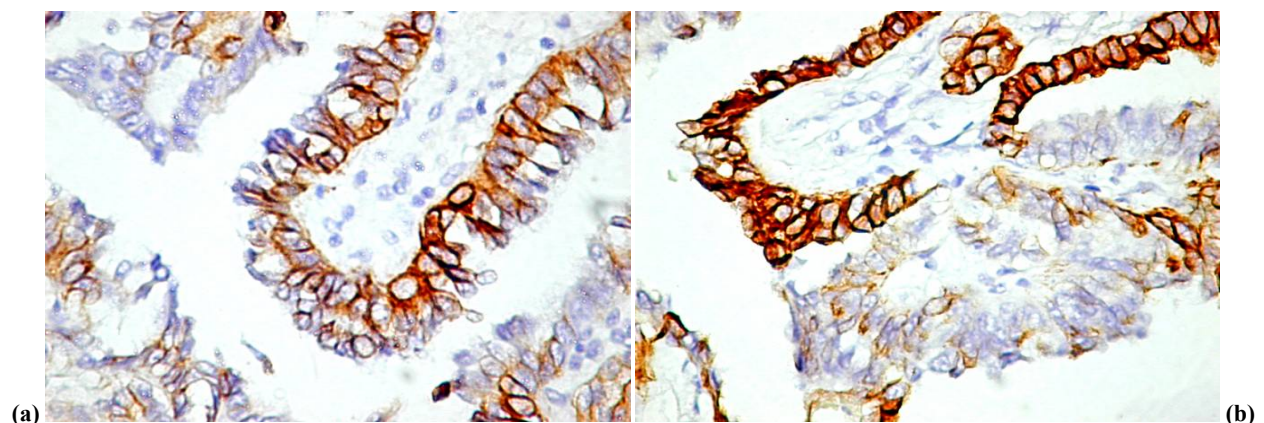


Figure 12 – (a) Papillary carcinoma. Predominantly positive staining of the cells near the connective axis. CK7 immunostaining ($\times 400$). (b) Papillary carcinoma. Heterogeneous staining pattern. CK7 immunostaining ($\times 400$).

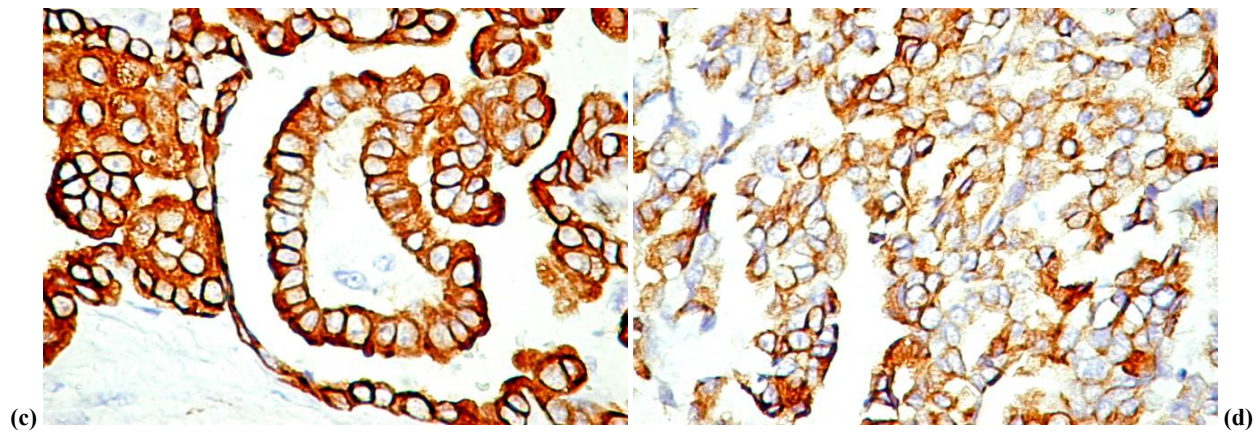


Figure 12 – (c) Papillary carcinoma. Type I papillary carcinoma, intensely positive. CK7 immunostaining ($\times 400$). (d) Papillary carcinoma. Type II papillary carcinoma. CK7 immunostaining ($\times 400$).

The two cases of chromophobic cells carcinomas were positive, one with high intensity and in all tumor cells, and the other with medium intensity and density (Figure 13a). All of the three sarcomatous carcinomas

were positive, two of them were intensely positive with diffuse pattern (+++). Unlike the other two cytokeratins used, CK7 stained most of the tumor cells, including the monstrous ones (Figure 13b).

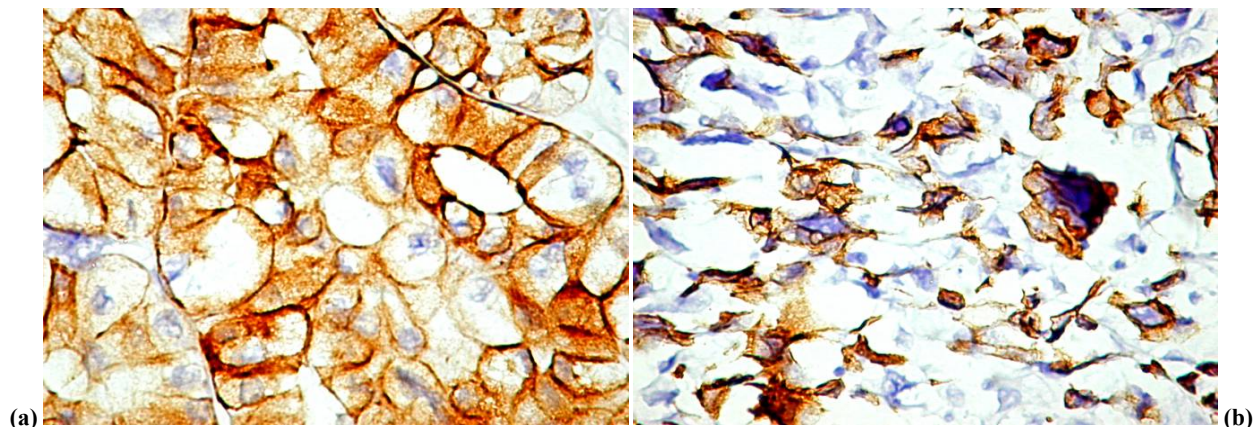


Figure 13 – (a) Chromophobic cells carcinoma, with intensely positive staining. CK7 immunostaining ($\times 400$). (b) Sarcomatous carcinoma with monstrous positive cells. CK7 immunostaining ($\times 400$).

Discussion

The literature studies show the importance of the cytokeratin expression profile in the differential diagnosis between the different subtypes of renal carcinoma [11–14], but the results obtained so far are controversial.

In our study, 43 out of the 80 cases stained with cytokeratin AE1/AE3 were positive (53.75%). Some authors, on a series of 55 clear cells renal carcinomas, had found 48 cases with positive expression of cytokeratins. Out of these cases, 84% were positive for Cam 5.2 antibody and 67% ($n=37$) were positive to AE1/AE3. AE1/AE3 cytokeratin was also positive in two Cam 5.2 positive tumors [10].

Papillary renal carcinomas are a rare subtype of kidney epithelial tumors, with particular macroscopic, microscopic and cytogenetic features. Macroscopically, these tumors are not homogenous, and in microscopy, they are composed of cells with central nucleus and weakly basophilic cytoplasm. The immunohistochemical profile of this type of tumor is not well characterized yet.

In 1997, Renshaw AA *et al.* [15] have studied 36 papillary renal carcinomas, using a panel of antibodies that included anti-cytokeratin and anti-EMA, and found AE1/AE3 positive in 100% of the cases, Cam 5.2 positive in 92% (33) of the cases, whereas only 3% (1) of the cases was positive for 34betaE12. In the same study, 11% of the cases were positive for CEA [10]. In the present study, AE1/AE3 expression was positive in all of the papillary carcinomas, in concordance with the literature data, which show an immunostaining over 80% [16].

Although in general CK7 expression is inconstant in renal carcinomas [3, 4], there are some studies, along with ours, which show positive expression of CK7 in renal tumors. It is a constant presence in papillary carcinomas [13, 17]. Strong expression of CK7 in type I, relatively benign, papillary carcinoma, unlike weak expression in type II, considered much more aggressive, was shown by other authors as well [1].

Literature data show positive immunostaining for CK7 in 100% of the papillary carcinomas, and our study the percent is of 88%, with high staining intensity. This

is the main reason why we consider CK7 as a useful marker for the differential diagnosis of this tumor type, along with other authors [15, 18, 19, 20, 21].

A small number of studies have found that chromophobic cells carcinomas are positive for CK7 [13], which is consistent with our results.

Recently, some authors [14, 17] have recommended CK7 as a marker for chromophobic cells carcinomas and renal oncocytomas.

In our study, CK7 was positive in 68% of the cases, results similar with the ones obtained by other authors [1, 8]. In addition, CK7 was expressed by all of the cells of sarcomatous carcinomas. Our results differ from the ones reported by other studies [22], which found positive expression of CK7 only in 39% of the tumor cells.

Depending on the subtype of renal carcinomas, some authors [11, 17, 22] identify a positive reaction only in 8% of the conventional carcinomas, compared to our results (61%), in 77% of the papillary carcinomas, which is close to our findings (88%), and 88% of the chromophobic cells carcinomas (100% in our study).

It must be pointed out that we have not found any differences between final reaction in type I and type II papillary carcinomas, as other authors [11, 22]. Taking into account the data presented, we have reached the same conclusion as other authors [11, 22]: CK7 immunostaining might be useful for the differentiation of the chromophobic cells carcinomas from other types of renal tumors.

In our study, the sarcomatous carcinomas were also positive to CK7, so we conclude that it might be useful for their diagnosis as well. For CK20 expression, our results confirm all of the data from the literature for the chromophobic cells carcinomas, with the mention that the reaction was negative in all of the tumor types. Our results were negative even in conventional carcinomas, close to the results obtained by Ohta Y *et al.* [23], which showed a negative CK20 expression in 20 out of the 24 cases of conventional carcinomas studied.

☐ Conclusions

Polyclonal cytokeratin AE1/AE3 was predominantly expressed in papillary and conventional carcinomas. AE1/AE3 was 100% positive in papillary carcinomas.

Cytokeratin 7 was 100% positive in chromophobic cells and sarcomatous carcinomas.

Cytokeratin 7 was positive in 87.5% of the cases in papillary carcinomas, with no staining pattern differences between type I and type II.

Cytokeratin 20 was negative in all of the cases.

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