The diagnostic value of immunohistochemistry in the typing of renal tumors with eosinophilic cytoplasm

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ABSTRACT

AIM: In this study, we aimed to review the diagnostic approach to eosinophilic cell renal neoplasms by light microscopy and immunohistochemical techniques.

METHOD: In this study, 23 of these tumors were eosinophilic variant classic RCC, 15 eosinophilic variant papillary RCC, 13 eosinophilic variant chromophobe RCC and 13 oncocytoma cases. These tumors were immunohistochemically treated with CK7, CD117, EpCAM, Vimentin, RCCm (Renal cell carcinoma marker) and GST-α.

RESULTS: In our study, contrary to the general literature on Vimentin, 65.2% negativity was found in our patients with eosinophilic variant classic RCC. However, when compared with other tumor types in our study, vimentin expression was highest in eosinophilic variant classical RCC with 34.8%. Statistically, RCCm, GST-α, EpCAM, CD117, CK7 were found to be significantly associated with tumor types, while no significant relationship was found between Vimentin and tumor types. RCCm positivity and CK7 and CD117 negativity were in favor of eosinophilic variant papillary RCC. CD117 positivity and Vimentin, CK7 and GST-α negativity were found to support oncocytoma.

CONCLUSIONS: The panel with RCCm, GST-α, EpCAM, CD117, CK7 will contribute to the differentiation of eosinophilic cytoplasm renal tumors that cannot be determined by morphological findings and to reach the correct diagnosis (Tab. 3, Fig. 4, Ref. 54). Text in PDF www.elis.sk

KEY WORDS: RCC, oncocytoma, immunohistochemistry.

Introduction

Following the prostate and bladder carcinomas, the RCC is the third most frequent urological malignancy; it is the most lethal urological cancer with poor prognosis and constitutes 2% of all the types of cancer (1–7). RCC might remain asymptomatic until advanced/metastatic phase. Metastatic diseases constitute approximately one-third of RCC patients and 50% of them are detected by coincidence in imaging tests performed because of unrelated reasons (7). After the surgical resection, metastases are observed in one-third of RCC patients and recurrence in 40% (1–10). The incidence of RCC increases in 6th and 7th decades and the male/female ratio is 2–2.5:1 (10–15).

It is generally known that RCC is resistant to chemotherapy (6, 7). Although many renal tumors are morphologically diagnosed, there are certain overlapping morphological characteristics such as benign masqueraders and newly emerging tumor types. Such diagnostic problems are especially observed in small biopsies, metastatic RCC (7), eosinophilic variants of RCC as in the present study, and in oncocytoma cases. Because of its prognostic importance, these tumors should be distinguished and the immunohistochemical panels must be utilized in the differential diagnosis (1–3). In the present study, the primary antibodies CK7, CD117, EpCAM, vimentin, RCCm, and GST-α were immunohistochemically applied to the eosinophilic variant renal tumors that cannot be determined by morphological findings and to reach the correct diagnosis. The accurate histological diagnosis and classification gained more importance than before (6). Although many renal tumors are morphologically diagnosed, there are certain overlapping morphological characteristics such as benign masqueraders and newly emerging tumor types. Such diagnostic problems are especially observed in small biopsies, metastatic RCC (7), eosinophilic variants of RCC as in the present study, and in oncocytoma cases. The diagnostic value of these markers was investigated for these tumors.

Methods

Study design and data collection

Sixty-four nephrectomy materials obtained from the archive of the Pathology Department of Medical Faculty, Fatih University, were retrospectively involved in the present study. Of these tumors, 23 were eosinophilic variant classic RCC, 15 eosinophilic variant papillary RCC, 13 eosinophilic variant chro-
mophobe RCC, and 13 oncocytoma cases. Regardless of the previous diagnoses, their slides were reviewed and the final diagnoses were taken as basis in this study. The tumor blocks selected for immunohistochemical staining process were cut into 4-micron thickness and taken to the glasses coated with polylysine. The primary antibodies used were CD117 (lab vision, USA), CK7 (Invitrogen, DAKO), USA, EpCAM (Thermo, USA), GST-α (Novacastra, USA), vimentin (Thermo, USA), and RCCm (Thermo, USA). In immunohistochemical staining process, the sections were kept in a drying oven at 37°C for 15 minutes and then passed through xyol and alcohol series for 5 minutes each. Then, they were rinsed with distilled water. The sections were kept in 3% hydrogen peroxide for 10 minutes in order to prevent endogen peroxidase activity and then rinsed again with distilled water for 1 minute. Then, for antigen retrieval process, the sections were boiled in 10% citrate buffer at 750 MW. Then, they were left for cooling at room temperature for 20 minutes. Following this step, they were rinsed in PBS for 5 minutes. Then, the sections were dried and the tissues were circumscribed using pap-pen. For the protein blockage, Blocking Reagent-Ultra V Blok (Thermo, USA) was dripped and kept in a bain-marie for 10 minutes. The fluid in the sections was removed when using RCCm stain in 23 eosinophilic variant classic RCC cases, 14 (60.9%) diffuse, 4 (17.4%) medium, 2 (8.7%) focal and 3 (13%) negative staining were observed (Fig. 1a). Among fifteen eosinophilic variant papillary RCC cases, there were 12 (80%) diffuse and 2 (13.3%) medium staining (Fig. 3a). Of thirteen eosinophilic variant chromophobe RCC cases, only 1 (7.7%) was diffusely stained and there was no medium or focal staining (Fig. 2a). Moreover, none of the 13 oncocytoma cases was observed as positive (Fig. 4a). A statistically significant relationship was found between RCCm and tumor types (p = 0).

**Statistical analysis**

The statistical analyses were performed using SPSS-12.0 software by calculating the Chi-Square and Correlation tests. The statistical significance was set at p < 0.05.

**Results**

**Immunohistochemical staining characteristics**

**RCCm**

When using RCCm stain in 23 eosinophilic variant classic RCC cases, there was 1 (4.3%) medium staining, but no staining was observed in 22 cases (95.7%) (Fig. 1b). Of fifteen eosinophilic variant papillary RCC cases, 9 (60%) were diffusely stained, 2 (13.3%) were stained at medium level, 1 (6.7%) was stained focally, but no staining was observed in 3 (20%) of cases (Fig. 3b). Of thirteen eosinophilic variant chromophobe RCC cases, 10 (76.9%) cases were stained diffusely and 2 (15.4%) at medium level, but no staining was observed in 1 (7.7%) case (Fig. 2b). Of thirteen oncocytoma cases, there was 1 (7.7%) with medium level staining, but no staining was observed in twelve (92.3%) cases (Fig. 4b). A statistically significant relationship was found between CK7 and tumor types (p = 0).

**CK7**

When using CK7 stain in 23 eosinophilic variant classic RCC cases, there was 1 (4.3%) medium staining, but no staining was observed in 22 cases (95.7%) (Fig. 1b). Of fifteen eosinophilic variant papillary RCC cases, 9 (60%) were diffusely stained, 2 (13.3%) were stained at medium level, 1 (6.7%) was stained focally, but no staining was observed in 3 (20%) of cases (Fig. 3b). Of thirteen eosinophilic variant chromophobe RCC cases, 10 (76.9%) cases were stained diffusely and 2 (15.4%) at medium level, but no staining was observed in 1 (7.7%) case (Fig. 2b). Of thirteen oncocytoma cases, there was 1 (7.7%) with medium level staining, but no staining was observed in twelve (92.3%) cases (Fig. 4b). A statistically significant relationship was found between CK7 and tumor types (p = 0).

**CD117**

When using CD117 stain in 23 eosinophilic variant classic RCC cases, it was observed that one (4.3%) case was diffusely stained and 2 (8.7%) cases were focally stained, but no staining was observed in 20 (87%) cases (Fig. 1b). Among fifteen eosinophilic variant papillary RCC cases, there were 1 (6.7%) diffuse, 1 (6.7%) medium, and 1 (6.7%) focal staining but no staining was observed in 12 (80%) cases (Fig. 3b). Among thirteen eosinophilic
Fig. 1a. Eosinophilic variant classic RCC; left eosinophilic variant of the classic RCC histopathological image (H & Ex400) on the left, RCCm positivity in the upper right corner and EpCAM positivity in the lower right corner (immunoperoxidase, x400).

Fig. 1b. Eosinophilic variant classic RCC; vimentin positivity of classic RCC in upper left corner, GST-α positivity in upper right corner, CD117 negativity in lower left corner, CK7 negativity in lower right corner (immunoperoxidase, x400).

Fig. 2a. Eosinophilic variant chromophobe RCC; histopathological image of eosinophilic variant chromophobe RCC (H & Ex400) on the left, negativity of RCCm in the upper right corner, and EpCAM positivity in the lower right corner (immunoperoxidase, x400).

Fig. 2b. Eosinophilic variant chromophobe RCC; vimentin negativity in the upper left corner, GST-α negativity in the upper right corner, CD117 positivity in the lower left corner, CK7 positivity in the lower right corner (immunoperoxidase, x400).

Fig. 3a. Eosinophilic variant papillary RCC; histopathological appearance of eosinophilic variant papillary RCC (H & Ex400) on the left, positivity of RCCm in the upper right corner, and EpCAM positivity in the lower right corner (immunoperoxidase, x400).

Fig. 3b. Eosinophilic variant papillary RCC; vimentin negativity in the upper left corner, eosinophilic variant papillary RCC, GST-α negativity in the upper right corner, CD117 negativity in the lower left corner and positivity of CK7 in the lower right corner (immunoperoxidase, x400).
variant chromophobe RCC cases, there were 6 (46.2%) diffuse, 4 (30.8%) medium, and 1 (7.7%) focal staining, but no staining was observed in 2 (15.4%) cases (Fig. 2b). Of thirteen oncocytoma cases, 8 (61.5%) were stained diffusely and 4 (30.8%) were stained at medium level, but no staining was observed in 1 (7.7%) case (Fig. 4b). A statistically significant relationship was found between CD117 and tumor types (p = 0).

EpCAM
When using EpCAM stain in 23 eosinophilic variant classic RCC cases, it was determined that 2 (8.7%) of cases were diffusely stained, 5 (21.7%) at medium level and 6 (26.1%) at focal level, whereas no staining was observed in 10 (43.5%) cases (Fig. 1a). Of fifteen eosinophilic variant papillary RCC cases, 6 (40%) were stained diffusely, 2 (13.3%) at medium level and 2 (13.3%) at focal level but no staining was observed in 5 (33.3%) cases (Fig. 3a). The staining was observed in all 13 eosinophilic variant chromophobe RCC cases (Fig. 2a). Among thirteen oncocytoma cases, there were 3 (23.1%) medium level and 2 (15.4%) focal staining, but no staining was observed in 8 (61.5%) cases (Fig. 4a). A statistically significant relationship was found between EpCAM and tumor types (p = 0.009).

GST-α
When using GST-α stain in 23 eosinophilic variant classic RCC cases, it was observed that there were 7 (30.4%) diffuse, 4 (17.4%) medium level, and 2 (8.7%) focal staining, but no staining was observed in 10 (43.5%) cases (Fig. 1b). Among fifteen eosinophilic variant papillary RCC cases (Fig. 3b) and thirteen eosinophilic variant chromophobe RCC cases (Fig. 2b), there was no staining. Among thirteen oncocytoma cases, there was 1 (7.7%) diffuse staining but no staining was observed in 12 (92.3%) cases (Fig. 4b). A statistically significant relationship was found between GST-α and tumor types (p = 0).

Vimentin
When using Vimentin in 23 eosinophilic variant classic RCC cases, it was determined that there were 7 (30.4%) diffuse staining, 2 (8.7%) medium level staining, and 3 (13%) focal staining, but no staining was observed in 15 (65.2%) cases (Fig. 1b). Among fifteen eosinophilic variant papillary RCC cases, there were 2 (13.3%) diffuse, 2 (13.3%) medium level, and 2 (13.3%) focal staining, but no staining was observed in 9 (60%) cases (Fig. 3b). One (7.7%) of thirteen eosinophilic variant chromophobe RCC cases was focally stained, but no staining was observed in 12 (92.3%) cases (Fig. 2b). No staining was observed in thirteen oncocytoma cases (Fig. 4b). No statistically significant relationship was found between Vimentin and tumor types (p = 0.21).

Discussion
Given the difficulties in differential diagnosis of eosinophilic cytoplasmic epithelial renal tumors, the difficulty of diagnosis becomes more prominent in cases with limited cellular specimens such as “tru-cut” biopsy and fine-needle aspiration cytology, as well as intraoperative (frozen section) examinations (7, 19–31). In such cases, the use of “oncocytic tumor” term is recommended (19–31).

Rather than the expensive and specific methods such as molecular, genetic, and immunohistochemical (IHC) methods in diagnosing the eosinophilic/granular cytoplasmic epithelial tumors of kidney, the macroscopic and microscopic examination is considered to be the golden standard. The macroscopic characteristics of tumor in nephrectomy specimens are useful in diagnosis, as well as it allows multiple specimens from different locations. However, the fine-needle and tru-cut biopsy methods and cytological specimens do not offer this option. These methods necessitate making a diagnosis with minimum one tissue/cell in the hand (7, 29–32). Given the fact that oncocytoma and eosinophilic variant chromophobe RCC might have similar nuclear, cytoplasmic, and...
The monoclonal cytokeratins such as CK7 and CK20 stain different components of renal tubular system and are useful in defining the origins of different tumors that might be observed in kidneys. It was claimed that CK7 might be used in the differential diagnosis of oncocytoma and eosinophilic variant chromophobe RCC. CD117 is secreted in normal adult renal parenchyma. The negativity of this antibody in classic RCC cases is useful in distinguishing from the other RCCs. However, because of the positivity of this marker in both oncocytoma and eosinophilic variant chromophobe RCC, it is useless in distinguishing these two tumors (10, 30, 33). In studies carried out using CD117, up to 100% positivity was found in chromophobe RCC and oncocytoma cases, whereas no staining was observed in classic and papillary RCC cases (17, 30, 33–35). In the present study, although there are certain differences with literature in terms of eosinophilic variant classic and papillary RCC cases, the staining percentages of other tumor subtypes overlap in the literature.

The monoclonal cytokeratins such as CK7 and CK20 stain different components of renal tubular system and are useful in defining the origins of different tumors that might be observed in kidneys. It was claimed that CK7 might be used in the differential diagnosis of oncocytoma and eosinophilic variant of RCC (30, 36, 37). Although it is generally negative in classic RCC, CK7 was reported to be positive in 11% in some studies. Extensive positivity was reported in papillary and chromophobe RCCs (30, 33, 34, 38). The positivity in oncocytoma is focal/cytoplasmic and not strongly membranous staining as in chromophobe RCC. Kurenlji et al reported that the CK7 immune staining density decreases as the nuclear level increases in chromophobe RCC, papillary RCC, and classic RCC cases (12). The results obtained in the present study corroborate with the literature. In the present study, a high level of negativity was detected in eosinophilic variant classic RCC and oncocytoma cases (95.7% and 92.3%, respectively), but an immune-reactivity was detected in 84.6% of eosinophilic variant chromophobe RCC cases.

Significant immune-reactivity was reported with glutathione S-transferase (GST) in the proximal tubule, classic RCC, and RCC cases, and negativity was found to be 92.3% in oncocytoma cases, whereas positivity detected in eosinophilic variant classic RCC cases was 56.5%. EpCam is immune-reactive in high levels of chromophobe RCCs, whereas it is positive in lower levels of classic RCCs and single/small group oncocytoma cases. It is very useful especially in distinguishing chromophobe RCC and oncocytoma (30, 40–42). However, EpCam is negative in sarcomatoid chromophobe RCC (30). In the present study, although there are similarities between EpCam positivity in eosinophilic variant chromophobe RCC cases and literature, there also are significant differences between the positivity percentages in tumor subtypes.

Vimentin is positive especially in classic and papillary RCC cases. It is not expected to be positive in chromophobe RCC and oncocytoma cases (43). Liu et al claimed that vimentin is the most sensitive and most specific marker for classic RCC (30). In various studies, the vimentin positivity was reported to be 51–85% in classic RCC, 21% in chromophobe RCC, 80–86% in papillary RCC, and 0–20% in oncocytoma (34, 38, 43–46). In the present study, the positivity of vimentin was found to be 35% in eosinophilic variant classic RCC, 40% in eosinophilic variant papillary RCC, and 8% in eosinophilic variant chromophobe RCC, whereas no immune-reactivity was observed in oncocytoma cases. No statistically significant relationship was found between tumor types and vimentin (p > 0.05) and, on the contrary with many studies in literature, a high rate of negativity (65%) was determined in eosinophilic variant classic RCC. Similar to the present study, Williams et al reported the negativity of vimentin in classic RCC to be 61% (47).

RCCm is secreted from the brush borders of renal proximal tubules and has high specificity primarily for classic RCC (48–51). Wang et al reported staining with RCC marker in 80% of the granular-eosinophilic variant of classic RCC and immune-reactivity in oncocytoma and chromophobe RCC cases (17). Allozy et al however, reported positivity at 37% in classic RCC, 53% in papillary RCC, and 2% in oncocytoma, whereas they reported no positivity in chromophobe RCC (34). In the present study, the immune-reactivity was reported in 89.3% of chromophobe RCC, 70.6% of papillary RCC, and 57.1% of oncocytoma cases. The positivity detected in eosinophilic variant chromophobe and papillary RCC cases was 93.3% and 86.7%, respectively.

In summary, the present study corroborates with the literature in terms of eosinophilic variant classic and papillary RCC cases, whereas positivity detected in eosinophilic variant classic RCC cases was 56.5%. EpCam is immune-reactive in high levels of chromophobe RCCs, whereas it is positive in lower levels of classic RCCs and single/small group oncocytoma cases. It is very useful especially in distinguishing chromophobe RCC and oncocytoma (30, 40–42). However, EpCam is negative in sarcomatoid chromophobe RCC (30). In the present study, although there are similarities between EpCam positivity in eosinophilic variant chromophobe RCC cases and literature, there also are significant differences between the positivity percentages in tumor subtypes.

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activity was detected in 87% in the eosinophilic variant of classic RCC, 93.3% in eosinophilic variant papillary RCC, 7.7% in eosinophilic variant chromophobe RCC, and 23.1% in oncocyoma.

The difference between the studies is related to the differences in laboratory staining procedures and the use of different antibodies (30). The diagnosis of typical oncocyoma is generally using H&E staining and no differential diagnosis problem is observed (22–27, 52). However, there may be differential diagnosis problems between atypical oncocyoma, chromophobe RCC, classic RCC's eosinophilic variant, and eosinophilic variant of papillary RCC. The IHC method is very useful in distinguishing these cases (22–26).

Similarly, Liu et al. claimed that the diagnosis would be in favor of chromophobe RCC or oncocyoma in vimentin and GST-α negativity. It was also reported that CK7 positivity and vimentin and GST-α negativity are useful in diagnosis of chromophobe RCC. Even if CD117 can be added to the panel, it was determined in the experiments on radical nephrectomy cases that CK7 positivity and vimentin and RCCm negativity in oncocyoma. It was also reported that in the experiments on radical nephrectomy cases that CK7 positivity and vimentin and GST-α negativity in oncocyoma. In eosinophilic variant of classic RCC, CK7 was reported to be negative. In conclusion, Sen et al. recommended the use of a panel containing vimentin, CK7, and CD117 in the accurate diagnosis of needle biopsy of kidney (31).

Similarly, Liu et al. claimed that the diagnosis would be in favor of chromophobe RCC or oncocyoma in vimentin and GST-α negativity and CD117 positivity and in favor of classic RCC in vimentin positivity and GST-α and CD117 negativity. It was reported that in differential diagnosis of oncocyoma and chromophobe RCC, the CK7 positivity and EpCAM positivity support chromophobe RCC and CK7 and EpCAM negativity supports the oncocyoma (30).

In conclusion, the results obtained in the present study are as follows (Tab. 3):

1. The combination of RCCm positivity and CK7 and CD117 negativity is in favor of eosinophilic variant classic RCC.
2. The combination of EpCAM, CK7, and CD117 positivity and vimentin, GST-α, and RCCm negativity is in favor of eosinophilic variant chromophobe RCC.
3. The combination of CK7 and RCCm positivity and CD117 and GST-α negativity is in favor of eosinophilic variant papillary RCC.
4. The combination of CD117 positivity and vimentin, CK7, and GST-α negativity supports the oncocyoma.
5. The panel as the primary step in RCC with diagnosis problem should include RCCb, CK7, and CD117. In cases, in which the diagnosis cannot be made using this trio, adding vimentin, EpCAM, and GST-α would be very useful.
6. Nowadays, in cases in which the diagnosis cannot be made using morphological results in eosinophilic cytoplasmic cell renal carcinomas with differential diagnosis problem, immunohistochemistry is a very useful diagnostic instrument.

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