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Original Research Article

Evaluation of COX-2 expression in renal cell carcinoma and its correlation with clinicopathological factors: a tissue microarray study.

Ashour G.A.R.[1], Said, W.M.[1].*
1Department of Pathology, Faculty of Medicine, University of Benghazi, Benghazi, Libya
** Corresponding Author: E-mail: guheina.ashour@uob.edu.ly, Tel: +218917242599*

ABSTRACT:

Objectives: This study, aimed to evaluate the expression of COX-2 in renal cell carcinoma, and correlate it with different patient clinicopathological data, emphasizing on the role of COX-2 as a prognostic factor for renal cell carcinoma and to decide which cases more likely benefit from the targeted therapy later on.

Patients and Methods: The present series consisted of tissue samples obtained from 47 patients (30 patients were males and 17 were females). All the tumor samples were collected from the Pathology Department, Faculty of Medicine, Alexandria University during the period from July 2009 to November 2010. Archival paraffin-embedded renal cell carcinoma tissue samples were used to prepare tissue microarray blocks for immunohistochemical staining with COX-2 antibody. Marker expression was categorized for statistical analysis then correlated to clinicopathological variables.

Results: The histological types was significantly associated with COX-2 expression, with higher expression being more common in papillary and chromophobe renal cell carcinoma, the majority of these two types were in score 1 and 2 while majority of clear cell renal cell carcinoma had score 0 and 1.

Conclusion: The association of COX-2 marker was related to the histologic type of tumor; COX-2 expression study might provide prognostic information regarding tumor aggressiveness. These findings suggested a potential impact of COX-2 targeted therapy in the treatment of renal cell carcinoma with overexpressed COX-2 that needs further investigation.

Key words: renal cell carcinoma, COX-2 expression, immunohistochemistry, tissue microarray, prognosis.

INTRODUCTION

Renal cell carcinomas (RCC) represent 2-3% of all cancers and account for more than 90% of cancers in the kidney (guidelines 2017). Over the last two decades the incidence of RCC increased by about 2% worldwide, accompanied by an improved 5 year survival [1].

Patients' prognosis depends on several clinicopathologic parameters including tumor, size, stage, microscopic grade, distant metastasis, RCC subtype, and sarcomatoid features [2], but it is important to identify indicators of biological aggressiveness of RCCs.

RCCs are resistant to chemotherapy and radiation therapy, so nephrectomy stays the treatment of choice even in patients with disseminated tumor. For this reason molecular targeted therapy in these tumors has received more attention in recent years. One of these attention-grabbing targets is cyclooxygenase 2 (COX-2), an enzyme in the arachidonic acid pathway leading to production of Prostaglandin E_2 (PGE_2) [3].

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In the human kidney, COX-2 is detected under certain conditions, such as aging and physiological stress, in both the cortex and medulla [4]. The COX-2 levels have been shown to increase in several types of human cancers; this suggests that the COX-2 may play an important role in the cancer progression [5] and an inhibition of COX-2 has been shown to be a promising anti-tumour and antiangiogenic strategy in several tumour types including RCC [6].

In this study, the association of COX-2 protein expression with clinicopathological and histopathological parameters was investigated with emphasis on the prognostic value of COX-2 expression.

MATERIALS AND METHODS

Specimens and clinical data

This study was carried out on 47 consecutive cases of RCC. Specimens were submitted to the Pathology Department, Faculty of Medicine, Alexandria University, during the period from July 2009 to November 2010. Specimens included radical nephrectomy (36 cases) and partial nephrectomy (11 cases). Ten cases had preaortic and/or para-aortic lymphadenectomy. The clinical and radiological data were collected from the archives of the Pathology and Urosurgery Departments, Faculty of Medicine, Alexandria University. The outcome was determined after a follow-up period from the date of diagnosis to the date of death or the last follow-up before study closure (minimum follow-up period: 12 months).

Histopathological examination

The histopathology of all cases was reviewed on complete tissue sections to determine the histological type and grade of the tumor, presence/absence of invasion of the capsule, perinephric fat, renal sinus, Gerota's fascia and renal vein, and also for the detection of lymph node involvement.

The histological type of RCC was determined according to the Heidelberg and UICC/AJCC classification [7]. Tumor grading was performed according to the Fuhrman grading system [8] and staging was carried out according to the 2009 TNM staging system [9].

Tissue microarray construction [10].

H&E-stained sections of RCC were used for the selection of morphologically representative regions of each tumor for tissue microarray (TMA) study. Two tumor spots were chosen under microscopy for each case and the corresponding spots were marked on the tissue block. A manual tissue arrayer punch (Beecher Instruments Inc., Sun Prairie, Wisconsin, USA) was used to remove tissue cores 1 mm in diameter in the marked area on the donor block. These tissue cores were then transferred to corresponding receiver pores in the recipient paraffin block, arranged in a precisely spaced array pattern in order to eventually construct a TMA block according to a predetermined scheme. The block was heated at 40 °C for 15 minutes and the surface was flattened. Sections from this block were cut using a microtome. An H&E-stained section of each TMA block was used to establish the adequacy of sampling by ensuring representative selection for the histological type and Fuhrman grade of RCC. Other sections were mounted on charged slides for immunohistochemical staining [10].

A ninety four tumor spots representing the 47 cases of RCC studied were performed (two spots per case). In addition, four spots of normal kidney were used as control spots. Results wereinterpreted with reference to a map of the TMA, with labelled rows and columns and their corresponding case number.

Immunohistochemical staining

Immunohistochemical staining was performed on 5 mm thick sections cut from the tumor TMA block. The TMA paraffin sections were deparaffinized in xylene, rehydrated in descending grades of alcohol, and then immersed in 0.3% hydrogen peroxide in methanol for 20 min to inhibit endogenous peroxidase activity. Antigen retrieval was performed by placing the TMA slides in citrate buffer (0.01 mol/l, pH 6.0) in a 700 W microwave oven for 8 minutes. Slides were allowed to cool to room temperature, and then an ultra V block was applied for 3–5 minutes to block nonspecific background staining.

The following primary antibody was applied: anti-COX-2 (RB-9072-PO, 1:40 dilution). The sections were incubated overnight at 41 °C in a humidity chamber. The TMA slides were then washed twice for 5 minutes with 10 mM phosphate-buffered saline (PBS) and incubated with biotinylated rabbit anti-goat immunoglobulin (Ig) G (1:200 dilution; Dako, Carpinteria, CA, USA) for 1 hour at room temperature, and then in peroxidase-conjugated steptavidin for 20 minutes at room temperature. After a final washing,

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the colour reaction was developed using 0.5% diaminobenzidine and 0.01% hydrogen peroxide for 10 min. The TMA slides were counterstained with H&E stain, dehydrated in ascending grades of alcohol, cleared in xylene, and mounted. The positive control used was a case of colorectal carcinoma and normal kidney tissue. Sections where the primary antibody has been omitted served as negative controls.

Evaluation of COX-2 immunohistochemical staining

COX-2 immunostaining was evaluated using a Nikon i50 microscope at the magnification of x40, blinded by the information on tumor grade, stage or clinical outcome. The COX-2 expression was semi-quantitatively estimated based on the presence of the cytoplasmic staining.

Two different grading systems (A and B) were applied to assess the pattern of COX-2 expression in tumor cells on the basis of the percentages of immunopositive cells. In system A, Specimens showing at least 10% staining of tumor cells were assumed as positive [11]. In system B, the data were subdivided into five categories according to the methods described by Sinicrope et al. [12] as follows: (0) 10%; (1) 11-25%; (2) 26-50%; (3) 51-75%; and (4) >75% positive cells. The immunointensity was also subclassified into four categories: (0) negative; (1) weak; (2) moderate; and (3) strong. The immunoreactive scores for each case were generated by multiplying the values of the two parameters, which were then stratified into three groups: weak (scores 0-4), moderate (scores 5-8), and strong (scores 9-12) COX-2 expression for the survival analysis. For statistical purposes, weak score categorized (0), moderate score categorized (1) and strong score categorized (2) [12].

STATISTICAL ANALYSIS

Statistical analysis was carried out using the SPSS software package, version 20.0 (SPSS, Chicago, Illinois, USA). Continuous variables were expressed as mean± SD, whereas categorical variables were expressed as numbers and percentages. Statistical correlations between two categorical variables were assessed using the Chi-square or the Fisher exact test. Statistical correlations between categorical and continuous variables were assessed using the Mann–Whitney U-test. The level of significance was set at a $P<0.05$

RESULTS

Clinicopathological data

This study included 47 cases of RCC. Patient ages ranged from 18 to 95 years (mean 50.64±15.19 years). Thirty patients (63.8%) were men and 17 (36.2%) were women (Table 1).

The size of the tumor ranged from 4 to 21 cm (mean 17.77±10.08 cm); Multicentric tumor masses were seen in four cases (8.5%). Invasion of the renal capsule and perinephric fat was detected in 9 cases (19%), renal sinus invasion in four cases (8.5%), Gerota's fascia invasion in one case (2%), adrenal gland invasion in one case (2%), and invasion of the collecting system in two cases (4%). Lymph node metastases were found in five out of the 10 patients (50%) who had undergone lymphadenectomy.

In the present study, five histological types of RCC were recognized (according to Heidelberg and UICC/AJCC classification): 30 cases (63.8%) were clear cell RCC (CCRCC); 11 cases (23.4%) were papillary RCC (PRCC); three cases (6.4%) were chromophobe RCC (chRCC); one case (2.1%) was collecting duct RCC (CDRCC); and two cases (4.3%) were RCC with sarcomatoid change (SRCC). Six cases (12.8%) were Fuhrman grade 1; 19 cases (40.4%) were grade 2; 18 cases (38.3%) were grade 3; and four cases (8.5%) were grade 4. According to the TNM staging system 2009, 15 cases (31.9%) were stage I; 8 cases (17%) were stage II; 9 cases (19.1%) were stage III; and 15 cases (31.9%) were stage IV. Fifteen cases (31.9%) were metastatic. Venous invasion was found in fifteen cases (31.9%). In terms of the outcome, 28 patients (59.6%) showed no evidence of disease, 15 patients (31.9%) were alive with disease, and four patients (8.5%) died of their disease.

Immunohistochemical staining of TMA

The tissue microarray technique was applied in this study. The total number of spots performed was 98; 94 spots represented the 47 studied cases of RCC (two spots per case) and four spots of normal kidney represented the control spots. A total of 94 tissue spots were informative for immunohistochemistry analysis including 60 CCRCC, 22 PRCC, six chRCC, two CDRCC, four SRCC, and four normal kidney tissue.

Expression patterns of COX-2

In normal renal tubular epithelium, COX-2 immunostaining was always cytoplasmic (Figure 1 a &

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b). The expression pattern of COX-2 in tumor cell was mainly cytoplasmic and occasionally membranous. The expression patterns of COX-2 in RCC lesions are illustrated in following figures respectively (Figures 2, 3, 4, 5, 6, and 7; a & b).

The frequencies of expression patterns of COX-2 protein receptors evaluated by IHC technique were: weak expression in 12 cases (scores 0-4, 25.5%), moderate in 21 case (scores 5-8, 44.7%), strong expression in 14 cases (scores 9-12, 29.8 %).

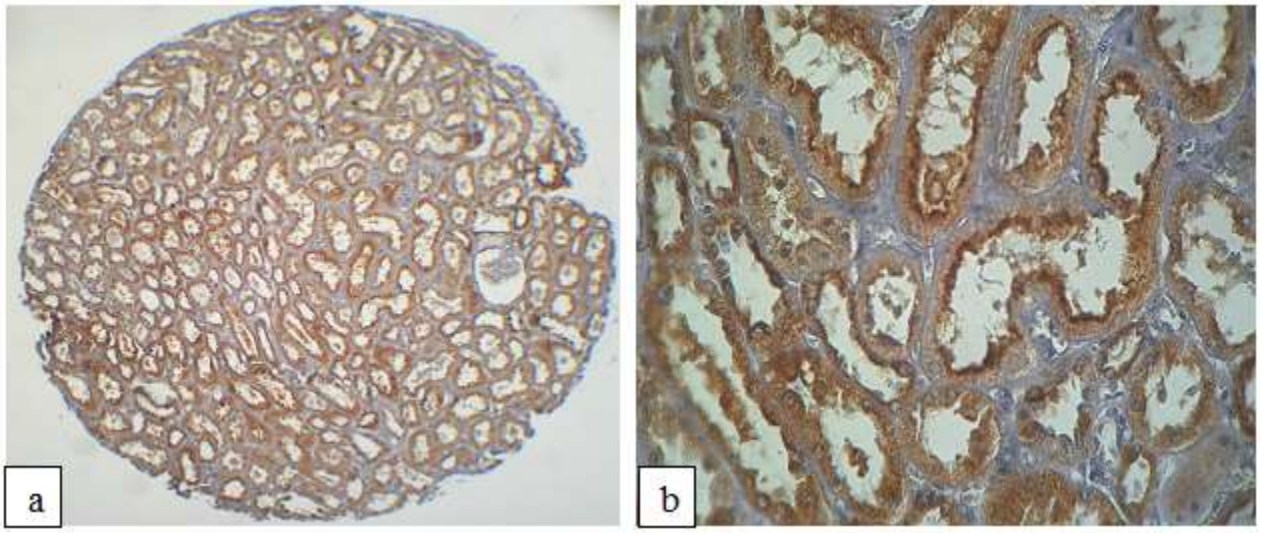

Figure 1: (a) Representative normal renal tissue core array showing strong COX-2 cytoplasmic immunostaining of tubular epithelium; (original magnification: x100). (b) Normal renal tissue showing strong COX-2 cytoplasmic immunostaining of tubular epithelium; (original magnification: x400).

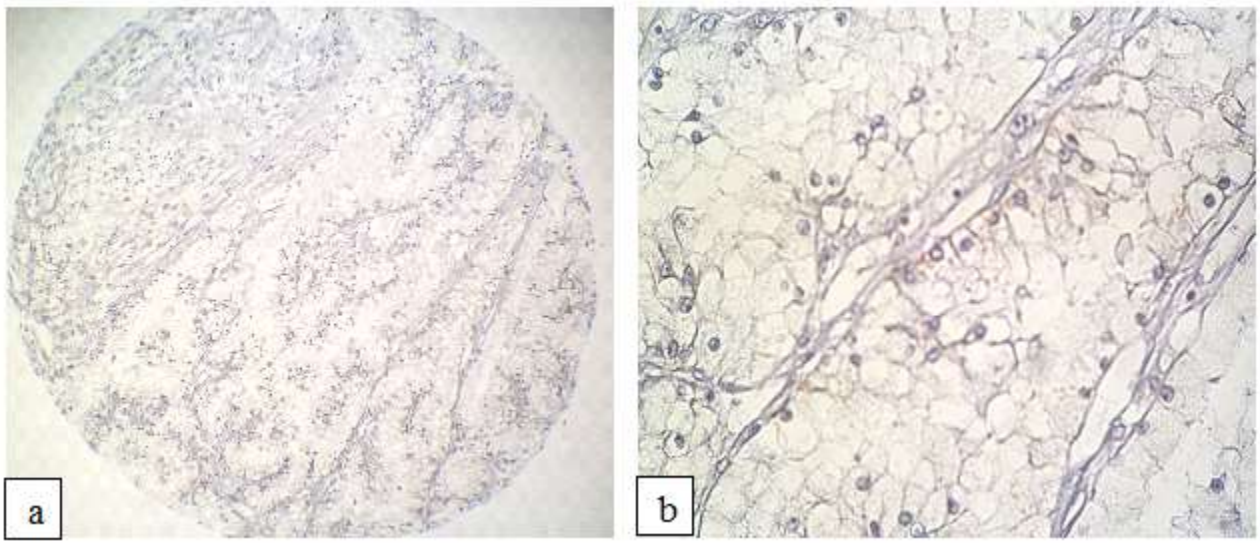

Figure 2: (a) Representative tissue core array of CCRCC showing weak COX-2 cytoplasmic immunostaining (score 0) (original magnification: x100). (b) CCRCC showing weak COX-2 cytoplasmic immunostaining (score 0) (original magnification: x400).

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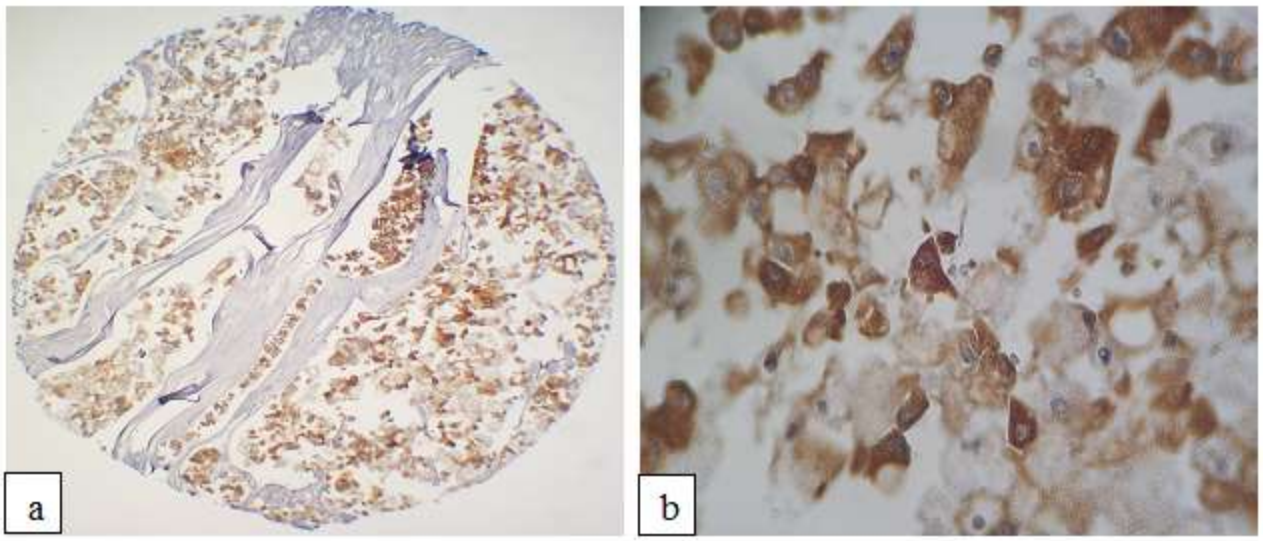

Figure 3: (a) Representative tissue core array of High-grade CCRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x100). (b) High grade CCRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x400).

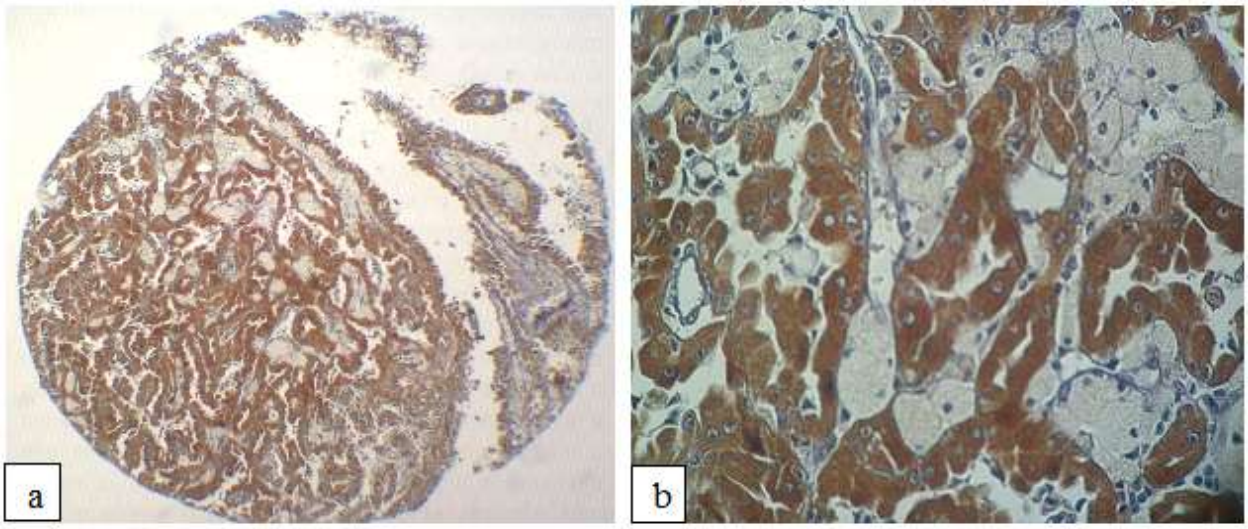

Figure 4: (a) Representative tissue core array of PRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x100). (b) PRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x400).

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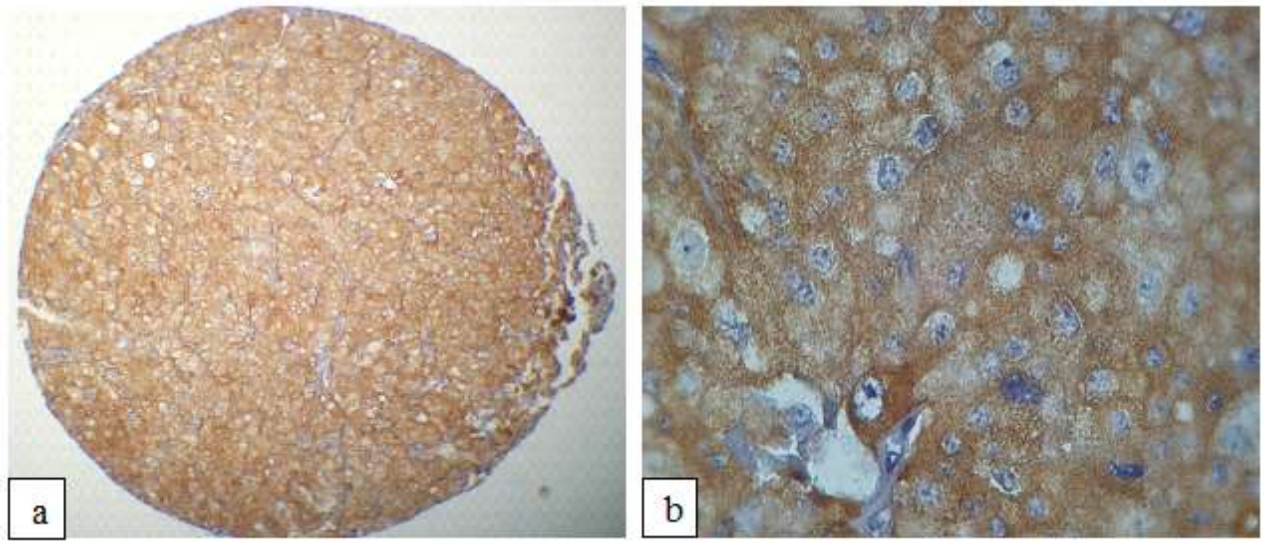

Figure 5: (a) Representative tissue core array of chRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x100). (b) chRCC showing strong COX-2 cytoplasmic immunostaining (score 2) (original magnification: x400).

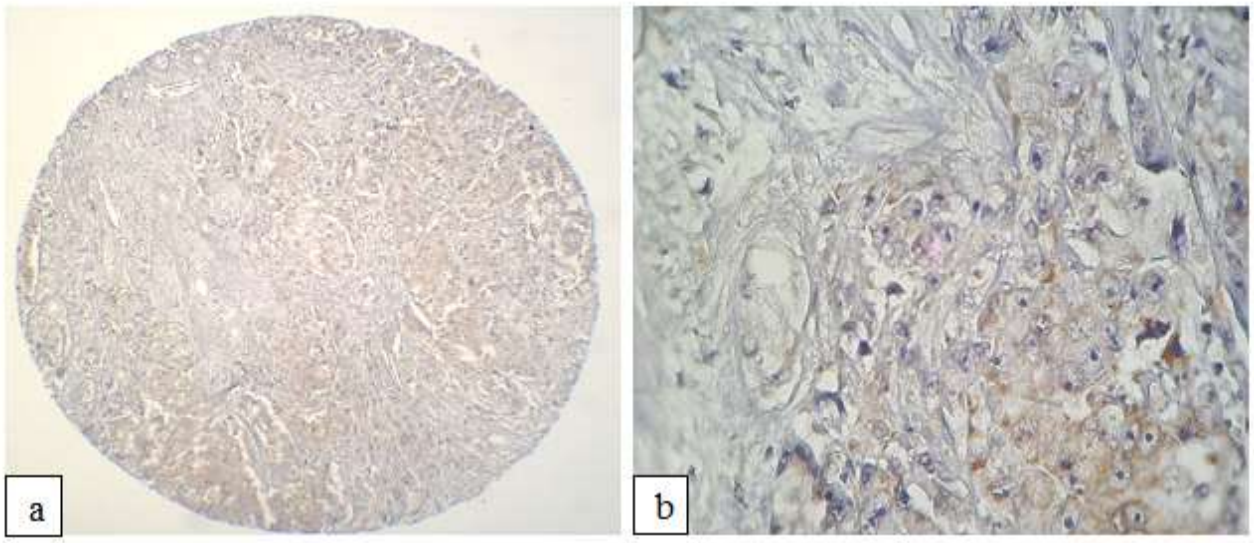

Figure 6: (a) Representative tissue core array of CDRCC showing moderate COX-2 cytoplasmic immunostaining (score 1) (original magnification: x100). (b) CDRCC showing moderate COX-2 cytoplasmic immunostaining (score 1) (original magnification: x400).

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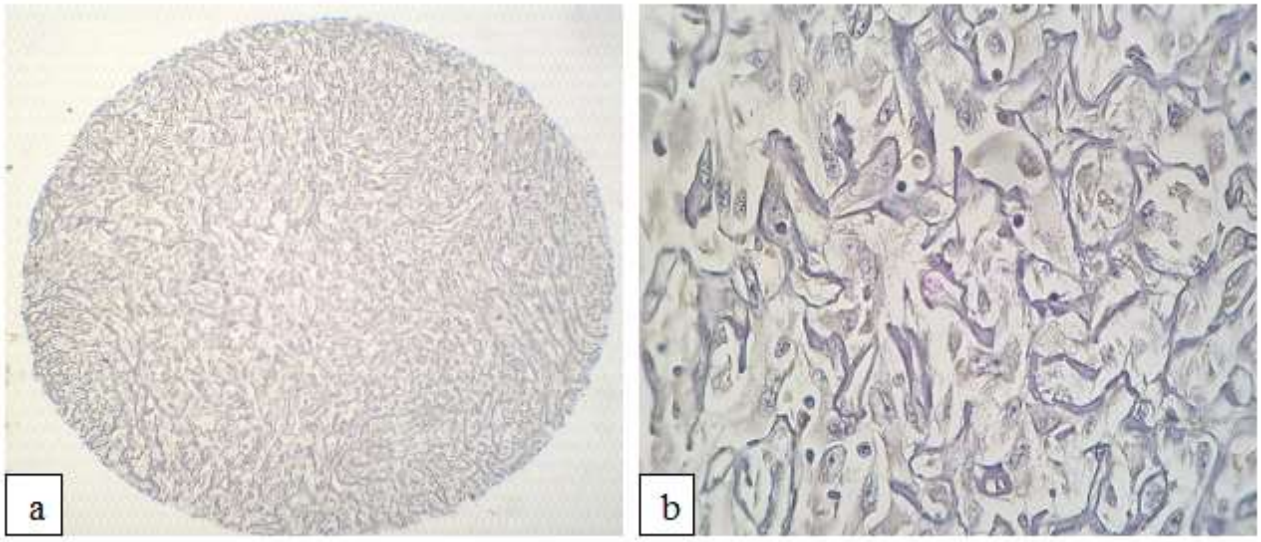

Figure 7: (a) Representative tissue core array of SCRCC showing weak COX-2 cytoplasmic immunostaining (score 0) (original magnification: x100). (b) SCRCC showing weak COX-2 cytoplasmic immunostaining (score 0) (original magnification: x400).

The histological types was significantly associated with COX-2 expression (Table 1), with higher expression being more common in papillary RCC and chromophobe RCC, the majority of this two type was in score 1 and 2 while majority of clear cell RCC had score 0 and 1 (P<0.01). As a result of the few number in both histopathological types; collecting duct RCC and sarcomatoid change RCC, the two types had no significant value. On the other hand, there was no statistically significant difference in COX-2 immunoexpression in regards to patient age, patient sex, tumor size, TNM staging, Fuhrman Grading, metastasis, invasion, thromboembolism, and the disease outcome of patients (Table 1 & 2).

Table 1: Relation between COX-2 immunostaining and characteristics of the 47 RCC patients studied

	COX-2 Immunostaining score				
	0	1	2	Total [N (%)]	*P* value
AGE (YEARS)					
< 50	3(25)	12(57)	7(50)	22 (46.81)	0.197
≥ 50	9(75)	9(43)	7(50)	25 (53.19)	
SEX					
Male	6(50)	12(57.1)	12(85.7)	30 (63.8)	0.116
Female	6(50)	9(42.9)	2(14.9)	17 (36.2)	
SIZE (CM)					
≤ 7	4(33.3)	10(47.6)	4(28.6)	18 (38.3)	0.482
> 7	8(66.7)	11(52.4)	10(71.4)	29 (61.7)	

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Table 2: Relation between COX-2 immunostaining and characteristics of the 47 RCC patients studied

	COX-2 Immunostaining score				
	0	1	2	Total [N (%)]	*P* value
HISTOLOGICAL SUBTYPES					
CCRCC	10(83.3)	14(66.7)	6(42.9)	30(63.8)	0.011*
PRCC	0(0)	6(28.6)	5(35.7)	11(23.4)	
chRCC	0(0)	0(0)	3(21.4)	3(6.4)	
CDRCC	0(0)	1(4.8)	0(0)	1(2.1)	
SCRCC	2(16.7)	0(0)	0(0)	2(4.3)	
GRADE					
Grade1	1(8.3)	3(14.3)	2(14.3)	6(12.8)	0.389
Grade2	4(33.3)	9(42.9)	6(42.9)	19(40.4)	
Grade3	4(33.3)	9(42.9)	5(35.7)	18(38.3)	
Grade4	3(25)	0(0)	1(7.1)	4(8.5)	
STAGE					
Stage1	3(25)	8(38.1)	4(28.6)	15(31.9)	0.690
Stage2	2(16.7)	3(14.3)	3(21.4)	8(17)	
Stage3	1(8.3)	4(19)	4(28.6)	9(19.1)	
Stage4	6(50)	6(28.6)	3(21.4)	15(31.9)	
METASTATIC STATUS					
Non Metastatic	5(41.7)	16(76.2)	11(78.6)	32(68.1)	0.07
Metastatic	7(58.3)	5(23.8)	3(21.4)	15(31.9)	
VENOUS INVASION					
Negative	6(50)	15(71.4)	11(78.6)	32(68.1)	0.375
Positive	6(50)	6(28.6)	3(21.4)	15(31.9)	
OUTCOME					
NED	5(41.7)	13(61.9)	10(71.4)	28(59.6)	0.317
AWD	6(50)	5(23.8)	4(28.6)	15(31.9)	
DOD	1(8.3)	3(14.3)	0(0)	4(8.5)	

AWD, alive with disease; DOD, died of disease; NED, no evidence of disease. *Significant at *P*<0.05.

Discussion

COX-2 is the key enzyme catalyzing prostaglandin synthesis that plays an important role in the pathogenesis of many cancer types including RCC [13 & 14]. In RCC, the clinical significance of COX-2 proteins remains under-investigated and poorly linked to the patients' clinico-pathological features and survival status. Kanaoka et al. reported that overexpression of COX-2 contributes to carcinogenesis via increasing cell proliferation, suppressing apoptosis, augmenting

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invasiveness, and inducing chronic activation of immune responses and angiogenesis [15].

In this study, we examined the expression and localization of COX-2 protein in a subset of RCC and a number of adjacent histological normal tubular epithelium. The results showed that COX-2 expressed in normal renal tissues adjacent to RCC. A similar finding had been reported by other investigators [16 & 17].

The result showed that a membranous and cytoplasmic expression was well observed in 74.5% of cases. These results are in general agreement with those of previous studies [3 & 18].

An interesting finding in our immunohistochemical study was the correlation between COX-2 expression and histological type. COX-2 overexpression occurs mainly in cases belonged to papillary subtypes (all cases are of score 1, 2), and chromophobe subtypes (all cases are of score 2), while majority of clear cell RCC had score 0 and 1. This finding consistent with finding of Tabriz et al. who observed that COX-2 expression was more than others in papillary subtype and has the minimum incidence rate in clear subtype [3]. A similar finding has been reported by Sun et al., [19].

In the present work, no relationship was seen between the COX-2 expression and the age of the patients; this was similar to the results of the studies done by Tabriz et al. [3] and Tuna et al., [20].

In the present study, the relation between the COX-2 expression and sex of RCC patients was statistically insignificant that was similar to the results of Tabriz et al. [3] and Tuna et al., [20]. However, positive COX-2 expression (score1, 2) was seen more in male gender. A study conducted by Lee et al. that comes in agreement with finding but reached the conclusion that there is relation between the COX-2 expression and male gender [21].

In the current work, COX-2 expression (score 1, 2) was more in nuclear grade 2 and 3. Tumors of grade 4 were mostly negative for COX-2 expression; one case of CCRCC grade 4 shows high COX-2 expression (score2 see Figure 3), but the relationship between the increase of COX-2 expression and the microscopic grade was statistically insignificant, that was similar to the results of Tabriz et al. [3]. A different from this result, a study by Miyata et al. shows COX-2 expression was associated significantly with tumor grade and none of the tumors negative for COX-2 was from patients with tumor grade 3 or 4 [21]. Hashimoto et al.'s study, the result was; increased COX-2 expression with higher tumor grade [18]. In the present study, no association between COX-2 and tumor stage was found, similar to the results of Tabriz et al. [3], but different from Hashimoto et al.'s study, the results were the opposite, with increased COX-2 expression with higher tumor stage [18].

COX-2 positive expression scores were more in non-metastatic RCC than in metastatic RCC. COX-2 positive expression scores were more in RCC without venous invasion than in RCC with venous invasion. However, these findings were not significant, similar to the results of Tabriz et al., [3] and the study of Cho etal [5].

There is evidence for and against the notion that COX-2 expression is associated with distant metastasis. Kankuri-Tammilehto *et al.* [11] proposed that COX-2 expression is associated with a slower development of metastases and also maintained that COX-2 expression is a favorable prognostic factor in metastatic RCC, while Miyata et al. [22] showed that positive COX-2 expression correlated significantly with metastasis but was not an independent factor of metastasis.

Our study did not show significant statistical correlation with COX-2 expression, and the disease outcome of patients. However, COX-2 positive expression scores were more in patients with no evidence of disease than in patients who alive with disease or died of the disease. The findings of the present study are in keeping with the results of Cho et al., [5] and Tabriz et al., [3] who found that no significant relation was observed between COX-2 expression the survivability of the patients. However, a study by Lee et al. [21] confirmed a significant correlation between higher degree of COX-2 expression and shorter cancer-specific and progression-free survival in CCRCC.

CONCLUSION

In conclusion, our results demonstrated that COX-2 overexpression was related to histologic type of tumor; it was expressed with maximal positivity in papillary and chromophobe subtypes, other than histological types.

LIMITATION OF THE STUDY

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The discrepancy between our results and other may be attributed to differences in the methodologies employed for samples collection, fixation and protocol used for immunohistochemical staining. Moreover, the low number of patients as total and low number of patients in subgroups under study may have affected the results we obtained.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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ملخص باللغة العربية

تقييم ظهور انزيم كوكس-2 في سرطان الخلايا الكلوية وعلاقة ذلك بالعوامل السريرية والمرضية: دراسة بأستخدام تقنية الصف النسيجي الدقيق.

جهينة عبدالله رجب عاشور، وردة محمد مصباح سعيد
قسم علم الامراض، كلية الطب البشري، جامعة بنغازي، بنغازي، ليبيا.
المؤلف المسؤول: جهينة عاشور، البريد الالكتروني: guheina.ashour@uob.edu.ly

الملخص

الأهداف: تهدف هذه الدراسة إلى تقييم ظهور إنزيم كوكس-2 في سرطان الخلايا الكلوية، وعلاقته مع بيانات المرضى السريرية والمرضية المختلفة، مع التركيز على دور أنزيم كوكس-2 كعامل تنبؤي بمصير مريض سرطان الخلايا الكلوية ولتقرير أي الحالات قد تستفيد من العلاج المستهدف في وقت لاحق.

المرضى وطرق الدراسة: تتكون السلسلة الحالية من عينات الأنسجة التي تم الحصول عليها من 47 مريض (30 مريضا كانوا من الذكور و 17 من الإناث). تم جمع جميع عينات الورم من قسم علم الأمراض، بكلية الطب، بجامعة الإسكندرية خلال الفترة من يوليو 2009 إلى نوفمبر 2010. استخدمت عينات سرطان الخلايا الكلوية المحفوظة في البارافين لإعداد عينات الصف النسيجي الدقيق و عمل الصبغة المناعية الهستوكيميائية باستخدام الأجسام المضادة لـ كوكس-2، ثم تصنيف ظهور التعبير للتحليل الإحصائي و علاقته بالمتغيرات السريرية و المرضية.

النتائج: ترتبط الأنواع النسيجية لسرطان الخلايا الكلوية بشكل ملحوظ مع ظهور تعبير كوكس-2، حيث ان ظهور التعبير العالي أكثر شيوعا في سرطان الخلايا الكلوية الحليمي والكروموفوب، وكانت الغالبية العظمى من هذين النوعين في النقاط 1 و 2 , في حين أن غالبية سرطان الخلايا الكلوية ذو الخلية الصافية كانت في النقاط 0 و 1.

الخلاصة: يرتبط ظهور تعبير كوكس-2 بالنوع النسيجي للورم. و دراسة ظهور تعبير كوكس-2 قد توفر معلومات تنبؤية بشأن عدوانية الورم. هذه النتائج تشير إلى تأثير محتمل من كوكس-2 في العلاج المستهدف لسرطان الخلايا الكلوية ذات التعبير العالي لهذا الإنزيم والتي تحتاج إلى مزيد من البحث.

الكلمات المفتاحية: سرطان الخلايا الكلوية، ظهور تعبير كوكس-2، الصبغة المناعية الهستوكيميائية، الصف النسيجي الدقيق، التنبؤ.

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