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Assessment of Immuno-histochemical Expression of CD44 in Renal Tumors

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ABSTRACT

Background: Cluster of differentiation 44 (CD44) is the most commonly reported immune marker of the cancer stem cells in renal cell carcinoma.
Objectives: To assess the frequency of CD44 expression in renal tumors, to assess the expression of CD44 in different histological types, and to detect its association with variable clinicopathological parameters.
Materials and methods: In this retrospective case series study, 76 cases of primary renal tumors were obtained by nephrectomy, and a study of CD44 was done by using the immunohistochemical technique.
Results: The age of the patients ranged from 29–82 years with a mean of 54.8 ± 11.96 with a male to female ratio of 1.05:1. Tumor size ranged from 2–17 cm with a mean of 6.2 ± 3.23. Clear cell renal cell carcinoma was forming 61.83% of the cases. Among all cases, a positive CD44 expression was observed in 35 (46.05%) cases; among the malignant cases, CD44 was positive in 32 (45.71%). CD44 immunohistochemical stain showed significantly higher expression in cases with higher nuclear grade and tumor stage (P-value of 0.0376 and 0.0075, respectively). CD44 cannot differentiate between benign and malignant renal tumors.
Conclusion: CD44 immune marker can be used as a prognostic factor to predict the aggressive behavior of renal tumors. It can also be used with standard prognostic markers to add prognostic information for subgrouping cases within the same grade and stage.
Keywords: Renal cell carcinoma; CD44; Immunohistochemical; Expression; Prognosis.

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INTRODUCTION

Kidney tumors are considered one of the most heterogeneous neoplasms [1]. Malignant renal tumors form about 3% of all malignant cases in adults [2–4]. Clear cell renal cell carcinoma (ccRCC), papillary RCC (pRCC), chromophobe RCC (chRCC), and oncocytoma represent more than 90% of renal tumors [5, 6]. Although the grading and staging are the best markers to predict overall survival, (OS) and disease-free survival; still the prognosis of the patients with RCC and within the same grade and stage differs widely [2]. Recent studies showed that cancer stem cells (CSCs) are responsible for cancer heterogeneity and control the cancer's initiation, progression, spread, and even its recurrence [3]. Multiple CSCs had been reported, and the CD44 emerged as the most commonly detected CSC marker in RCC [3].

A cluster of differentiation 44) CD44(is a transmembrane adhesion glycoprotein that possesses multiple structures and functions [7]. CD44 is encoded by the CD44 gene, which is placed on chromosome 11p13 [3, 7]. Newly found that cancer cells expressed CD44 [1, 7, 8] and it is considered a molecular marker for CSC [1, 7]. Several isoforms of CD44 have been reported [3, 9]. The CD44 standard (CD44s) is the main form, other isoforms of CD44 are named CD44 variants (CD44v) [3]. In normal renal tissue, CD44 expression can be detected in small mononuclear cells and some vessel walls [10]. In RCC, still, there are contradictory results [11] and the majority of research concentrated on the biological behavior of CD44 in ccRCC subtype while few studies are exploring its role in the other histological types [11]. Hence, we aimed to assess the frequency of CD44 expression in cases of primary renal tumors, assess its expression in different histological types, and

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detect its association with variable clinicopathological parameters.

MATERIALS AND METHODS

In this retrospective case series study, during a period from January 2023 to March 2024, 76 cases of primary renal tumor were collected from labs of Al-Jumhori and Al Salam Teaching Hospitals in Mosul City and Rizgary Teaching Hospital in Hawler City, Iraq. Demographic data (age of the patient, sex, tumor side, and size) were obtained from medical records. As RCC is usually diagnosed in older adults (the median age of diagnosis is 64 years), and in young adults shows variability in clinical presentations and prognosis, for statistical analysis, the patients in this study were divided into two groups, those aged 60 years and below and those older than 60.

The Hematoxylin and Eosin slides were prepared to determine the histological type, nuclear grades for ccRCC and pRCC, and tumor stage. The immunohistochemical (IHC) study for CD44 was done according to the protocol of the manufacturer using "CD44s Dako Monoclonal Mouse AntiHuman CD44 protein, code M7082". Intratumoral lymphocytes were considered as an internal positive control, while slides treated with buffer solution instead of primary antibody were used as a negative control.

Evaluation of immunostaining

The percentage of the positive cells was determined by counting at least 1000 tumor cells at ×400 magnification, and cases with ≥ 5% tumor cells showing brown membranous ± cytoplasmic stain were considered positive for CD44 expression. As shown in Table 1, studies adopted by earlier researchers [2, 12–14] demonstrated the validity of using 5% and higher as a cut-off value for the interpretation of CD44.

The sample size was calculated according to the prevalence of renal tumors in Iraq (2.3/100 000) [15] with a confidence interval (80%) and absolute precision (5%) by using G power statistical software. A sample size of 165 cases was estimated. The sample size was larger than that of this study; this may be attributed to the fact that the sample included only nephrectomy specimens to obtain a comparison with pathological features. Those cases with only percutaneous biopsy, those with missing information, those with the unavailability of their tissue blocks, and those with preoperative treatment for downstaging, were excluded from the sample.

Ethics approval

This study was approved by the Medical Research Ethics Committee, College of Medicine, University of Mosul, with a reference number (UOM/COM/MREC/23-24/APLS on 21/4/2024).

Table 1. The scoring of CD44 immune staining [2, 13]

Negative	Score 0	Immune staining of < 5% of tumor cells
Positive	Score 1+ (Weak positive)	5–24% of tumor cells show CD44 positivity
	Score 2+ (Moderate positive)	25–75% of tumor cells show CD44 positivity
	Score 3+ (Strong positive)	>75% of tumor cells show CD44 positivity

Statistical analysis

The collected data were entered and analyzed using SPSS (Statistical Package for the Social Sciences). The age of patients and tumor size were expressed as a range with mean. Categorical variables were presented in tables as frequencies and percentages. When indicated, the Chi-square (χ^2) test or Fisher exact test was used to analyze the relationship between CD44 and variable clinicopathological parameters (patient's age, sex, tumor side, size, histological type, in addition to nuclear grade and pathological stage). The differences were considered statistically significant when the P-value < 0.05.

RESULTS

In this retrospective case series study, 76 cases of primary renal tumors were included, 70 cases were malignant, and 6 benign tumors of oncocytoma, (Figure 1).

The age of patients ranged from 29-82 years, with a mean of 54.8 ± 11.96 years and the male to female ratio was 1.05:1. In 47.37% of cases, the tumor was located in the right kidney. The tumor size ranged from 2–17 cm with a mean of 6.2 ± 3.23. Among ccRCC and pRCC, grade II was the most common grade (61.67%). Stage I was the most common stage, which formed 67.14% of all malignant tumors (Table 2).

Normal renal parenchyma showed a negative CD44 expression. Positive CD44 staining was observed in 35 (46.05%) cases (Table 3).

The CD44 expression showed a statistically significant association with nuclear grading and T stage. No significant association was detected with the patient's age, sex, tumor side and size. No significant association was detected between CD44 and histological types and between the benign and malignant cases (Table 4).

Figure 2 illustrates negative CD44 expression in the normal renal tissue and renal tumor (score 0), while Figure 3 shows positive CD44 expression in renal tumors with different scores (scores 1–3).

DISCUSSION

RCC is considered a highly aggressive cancer with an increasing rate of metastasis [1]. Over the last decades, several studies have been done to find prognostic markers for kidney

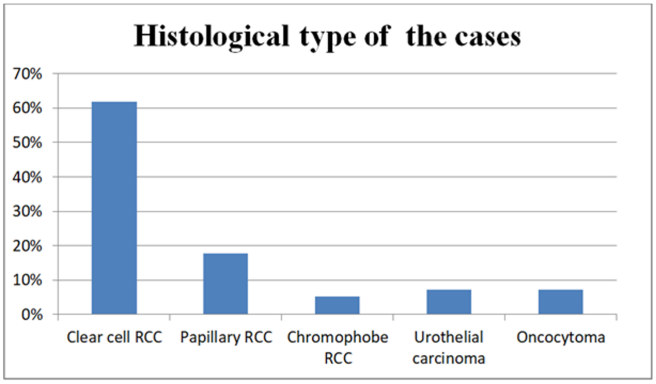

Figure 1. The frequency of histological types of renal tumors included in the study.

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Table 2. Demographic, clinical, and pathological characteristics of the 76 cases with renal tumors.[*†]

Clinicopathological parameters	Number	Percentage
Age in years		
≤ 60	50	65.79
> 60	26	34.21
Sex		
Male	39	51.32
Female	37	48.68
Side		
Right	36	47.37
Left	26	34.21
Unspecified	14	18.42
Size		
≤ 7 cm	53	69.74
> 7 cm	23	30.26
Histological type		
ccRCC	47	61.84
pRCC	13	17.10
chRCC	4	5.26
Urothelial carcinoma	6	7.90
Oncocytoma	6	7.90
Benign versus malignant tumors		
Benign	6	7.90
Malignant	70	92.10
[†]Nuclear grading of ccRCC and pRCC		
I	10	16.66
II	37	61.67
III	9	15
IV	4	6.67
[†]T stage of malignant tumors		
I	47	67.14
II	16	22.86
III	6	8.57
IV	1	1.43

[*] The clear cell renal cell carcinoma = ccRCC, Papillary RCC = pRCC, Chromophobe RCC = chRCC, and T stage = Tumor stage.

[†] The total number of cases was 76 but only 60 and 70 cases were included in nuclear grading and tumor pathological staging respectively.

tumors [16]. CD44 is the most commonly reported marker of the CSC in RCC [11]. In this study, CD44 expression showed a significant relation with the most important prognostic factors (nuclear grade and T stage), CD44 can be used as a prognostic marker in RCC.

In the current study, immunohistochemical evaluation of CD44 showed a negative expression in normal renal parenchyma. Other studies also found a significant upregulation of CD44 expression in cancer tissues compared to normal renal parenchyma, this indicates that CD44 may play an important role in the pathogenesis of renal tumors [17–20].

The CD44 expression was positive in 46.05% of all cases and among the malignant cases in 45.71%. This result was near to that of Noroozinia et al. [12], where the CD44 expression was positive in 46.9% of malignant tumors. CD44 was positive in 61.8% and in 66% of RCC cases in a study done by Papanastasiou et al. [21] and Gupta et al. [13] respectively, while in a study done by Kabiri et al. [14], the CD44 was positive in 32.6%. However, all these results are within the range of 16.4%–87.5% which was detected in a meta-analysis done on 18 researches that studied CD44s expression in malignant renal tumors [3]. This wide range of CD44 positivity may be due to the interpretations scoring system or cut-off point used to define CD44 expression varied across the studies [20]. In addition to the variability in populations included in the studies and different CD44 antibody clones used. This indicates that there is a demand for acquiring a uniform cut-off value and standardizing the detection method used. In this study, although more CD44 negativity was detected among patients ≤ 60 years and female cases, no significant association was detected between CD44 with patients' age and sex, this may be attributed to the relatively small sample size and a few numbers of cases of both extreme of ages included in this study, however, this result is similar to that of other studies [2, 8, 9, 12, 20, 22, 23]. Another study with many cases is indicated to confirm this result. In the current study, no significant association was detected between CD44 expression and tumor side, up to our knowledge no other researchers studied this relation.

Previous researchers found a significant association of CD44 expression with tumor size, that CD44 expression increased with the increase in tumor size [2, 18, 22, 24]. In this study, although more negative CD44 expression was seen in cases with smaller tumor sizes, no significant association was detected. This may be due to the relatively small sample size; however, the result of this study agreed with other studies [8, 9, 12, 20].

In a comparison of CD44 expression in benign versus malignant cases, no significant association was detected. The majority of studies of CD44 in renal carcinomas concentrated on ccRCC subtypes, and few studies included; other histological types [11]. In this study, in addition to ccRCC type, pRCC, chRCC, and urothelial carcinoma cases were included, the more negative cases of CD44 expression were detected among ccRCC, while all cases of chRCC were positive for CD44. However, no significant association was detected between CD44 and histological types. This finding aligns with other studies [13, 25]. This may indicate that CD44 as an immune marker cannot be used to differentiate between the different histological types. However, in this study, the difference in the size of the ccRCC cases compared to other histological types and few benign cases, was due to the rarity of these histological types when compared to ccRCC type, another study including a larger number of non-ccRCC and benign renal tumors is needed to confirm the result of this study.

CD44 expression was significantly related to tumor nuclear grade, that the expression increased with the increase of nuclear grade; this result was similar to the previous investigations [2, 8, 9, 13, 18–24]. While Noroozinia et al [12] found no significant association of CD44 with nuclear grade. The significant relation between high CD44 expression and the high grade reflects a functional role of CD44 as CSC in preserving a more dedifferentiated and embryonic state of renal tumor cells [22], probably by maintaining the tumor-initiating cells in renal cancer. Prior investigations found no significant association of CD44 with the T stage [8, 9, 13]. In the current study, the cases with high T stage (T3 and T4) were positive for CD44, while the majority of cases with low stage (T1 and T2) were negative for CD44, that the expression of CD44 increased with the increasing of T stage, this association was highly significant, this result was similar to other

Table 3. The CD44 expression in different histological types of renal tumors.*

Histological type of tumors	Negative	Positive			Total Number(%)
	Score 0	Score 1+	Score 2+	Score 3+	
ccRCC	30 (39.47)	2 (2.63)	5 (6.58)	10 (13.16)	47 (61.84)
pRCC	5 (6.58)	0 (0.00)	0 (0.00)	8 (10.52)	13 (17.10)
chRCC	0 (0.00)	2 (2.63)	0 (0.00)	2 (2.63)	4 (5.26)
Urothelial carcinoma	3 (3.95)	0 (0.00)	0 (0.00)	3 (3.95)	6 (7.90)
Oncocytoma	3 (3.95)	0 (0.00)	3 (3.95)	0 (0.00)	6 (7.90)
Total (%)	41 (53.95)	4 (5.26)	8 (10.53)	23 (30.26)	76 (100)

* The clear cell renal cell carcinoma = ccRCC, Papillary RCC = pRCC, and Chromophobe RCC = chRCC.

Table 4. Relation of CD44 expression with variable clinicopathological parameters of renal tumor cases.*†

Variable clinicopathological parameters		CD44 Expression		Total Number(%)	P -value
		Negative Number(%)	Positive Number(%)		
Age in years	≤ 60	29(38.16)	21(27.63)	50 (65.79)	
	> 60	12(15.79)	14(18.42)	26 (34.21)	0.325
	Total	41(53.95)	35(46.05)	76(100)	
Sex	Male	18(23.69)	21(27.63)	39(51.32)	
	Female	23(30.26)	14(18.42)	37(48.68)	0.16167
	Total	41(53.95)	35(46.05)	76(100)	
Side	Right	19(25)	17(22.37)	36(47.37)	
	Left	14(18.42)	12(15.79)	26(34.21)	0.9620
	Not specified	8(10.53)	6(7.89)	14(18.42)	
	Total	41(53.95)	35(46.05)	76(100)	
Size	≤ 7 cm	29(38.16)	24(31.58)	53(69.74)	
	> 7 cm	12(15.79)	11(14.47)	23(30.26)	0.83809
	Total	41(53.95)	35(46.05)	76(100)	
Histological types	ccRCC	30(39.47)	17(22.37)	47(61.84)	
	pRCC	5(6.58)	8(10.52)	13(17.10)	
	chRCC	0(0.00)	4(5.26)	4 (5.26)	0.0896
	Urothelial carcinoma	3(3.95)	3(3.95)	6(7.90)	
	Oncocytoma	3(3.95)	3(3.95)	6(7.90)	
	Total	41(53.95)	35(46.05)	76(100)	
Benign versus malignant tumors	Benign	3(3.95)	3(3.95)	6(7.90)	
	Malignant	38(50)	32(42.10)	70(92.10)	0.83982
	Total	41(53.95)	35(46.05)	76(100)	
Nuclear grading of ccRCC and pRCC	I	8(13.33)	2(3.33)	10(16.66)	
	II	22(36.67)	15(25)	37(61.67)	
	III	4(6.67)	5(8.33)	9(15)	0.0376†
	IV	0(0.00)	4(6.67)	4(6.67)	
	Total	34(56.67)	26(43.33)	60(100)	
T stage of malignant tumors	T1	30(42.86)	17(24.28)	47(67.14)	
	T2	8(11.43)	8(11.43)	16(22.86)	
	T3	0(0.00)	6(8.57)	6(8.57)	0.0075†
	T4	0(0.00)	1(1.43)	1(1.43)	
	Total	38(54,29)	32(45.71)	70(100)	

* The clear cell renal cell carcinoma = ccRCC, papillary RCC = pRCC, chromophobe RCC: chRCC, and T stage = Tumor stage.
† Statistical significance (P-value < 0.05), Chi-square (χ^2) test, and Fisher exact test used when indicated.

studies [2, 17, 18, 20–22].

In the present study, the higher CD44 expression is associated with high grade and high T stage indicating that CD44 can be used as a marker of poor prognosis in renal cancers. Jeong et al [9] found that the CD44 is an independent prognostic factor for tumor recurrence and patient survival in ccRCC. Qin et al. [22] and Chrabańska et al. [25] reported that the CD44 can be used as an independent prognostic fac-

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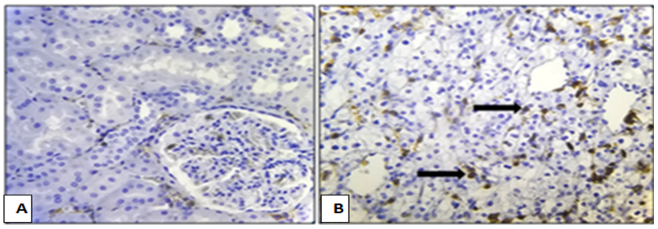

Figure 2. Negative CD44 expression (score 0) A: Normal renal tissue. B: Renal tumor (clear cell renal cell carcinoma) with the internal positive control, lymphocytes (black arrow). Magnification X 400.

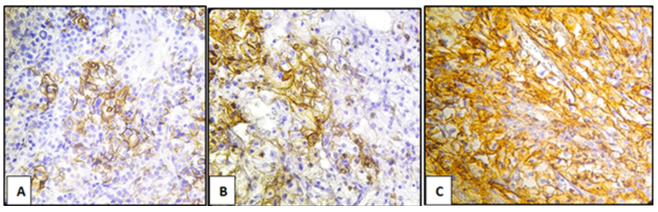

Figure 3. Positive CD44 expression in renal tumors. A: Score 1+ (weak positive), B: Score 2+ (moderate positive), C: Score3+ (strong positive). Magnification X 400.

tor of shorter OS. Besides, the study also found that cases with increased CD44 expression had a significantly higher risk of death than those with low expression.

The essential limitations of this study were its retrospective nature, a relatively small sample size with few benign cases, and only nephrectomy cases with available clinical data collected from selected labs, which may not reflect the true prevalence of renal tumors and their subtypes. The other limitation was the limited number of prior research studies concentrated on non-ccRCC. Lastly, this study was done using the standard isoform of CD44 (CD44s), the variant forms of CD44 may be studied in the future.

CONCLUSION

CD44 cannot be used to differentiate benign from malignant renal tumors. CD44 can be used as a prognostic factor to predict the aggressiveness of RCC, and it can be used with standard prognostic markers to add additional prognostic information for subgrouping of the cases within the same grade and stage.

ETHICAL DECLARATIONS

Acknowledgments

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Ethics Approval and Consent to Participate

This study was approved by the Medical Research Ethics Committee, College of Medicine, University of Mosul with a reference number of UOM/COM/MREC/23-24/APLS on 21-4-2024. Owing to the retrospective nature of this study, informed consent was waived.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All listed authors contributed significantly, directly, and intellectually to the work. All authors read and approved the final version to be published.

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