

The Evaluation of CD10 and HER2 Immunohistochemical Markers in Urothelial Carcinoma of Urinary Bladder

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Abstract

Background: Urothelial carcinoma (UC) has been considered the most frequent bladder tumor. Although the degree of bladder wall invasion and grade of the tumor are the essential prognostic factors in bladder carcinoma, there is no dependable parameter predicting patients' outcomes. **Objectives:** To assess the frequency of CD10 expression (in tumor cells and tumor stroma) and HER2 (in tumor cells) in primary UC of the urinary bladder and to assess their relation with patients' age, gender, grade, lympho-vascular invasion, and muscle invasion. **Materials and Methods:** In this retrospective case series study, 50 cases of primary bladder UC were obtained through a transurethral resection, and a study for CD10 and HER2 was done by immunohistochemical (IHC) technique. **Results:** The age of patients ranged from 34 to 90 years (mean = 59.9 years) with male to female ratio was 7.33:1. CD10 expression in tumor cells was positive in 60% of cases while in the stromal cells, it was only positive in 38% of the cases. HER2 IHC stain was positive in 20 cases (40%). A significant association was detected between stromal CD10 expression with the gender of patients, tumor grade, and muscle invasion ($P = 0.0244$, $P = 0.004115$, and $P = 0.0378$, respectively). HER2 IHC stain showed a significantly higher expression in higher grade and muscle invasion cases ($P = 0.00875$ and $P = 0.0445$, respectively). No significant association was detected between tumorous CD10 expression and any clinicopathological parameters. **Conclusion:** CD10 expression in stromal cells (not in tumor cells) and HER2 IHC stain can be used as prognostic markers in primary bladder UC.

Keywords: CD10, HER2, immunohistochemical stain, urothelial carcinoma

INTRODUCTION

Cancer is considered an important global health problem regarding the morbidity and rate of death,^[1] as each year the reported cancer cases continue to increase^[2] and particularly it is common in developing areas, whereas regarding the cause of death, cancer comes third, after the cardiovascular diseases and trauma.^[1] The malignant tumors of the urinary bladder are the ninth most common cancer worldwide.^[3] About 90% of bladder tumor cases are urothelial carcinoma (UC)^[3-5] and greater than 90% of UC is situated in the bladder.^[3] In general, for all patients with UC, the survival rate is rather high; however, the outcome is worse for those who have bladder wall invasion at diagnosis or have distant metastases.^[4] The finding of new markers, may enhance the therapeutic approaches of cases and decrease the danger of progression and mortality.^[3,5]

The CD10 is a zinc-dependent cell surface metalloendoprotease,^[5-7] it was initially detected as a tumor-specific antigen of leukemia cells,^[7] it arrests various bioactive neuropeptides^[3] and further to its enzymatic function, it regulates cell growth and apoptosis by having a direct role in signal transduction pathways.^[3,5,6] CD10 expression has been noticed in some cancers such as gastric, breast, prostate, lung, and colorectal^[7], and significant association was observed between CD10 expression level in tumor cells and larger size, higher differentiation, vascular invasion,

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and survival rate.^[7] The expression of CD10 in stromal cells has been identified in endometrium, normal bone marrow, and stromal cells of some tumors.^[8] In breast cancer, pancreatic cancer, and nonsmall cell lung carcinoma, stromal CD10 expression was correlated with poor outcomes.^[8] In UC, the CD10 expression was evaluated in several studies and most of these studies focused on tumorous CD10^[9] and found that CD10 expression in tumor cells is connected with tumor advancement and an unfavorable prognosis, while other studies found that high tumorous CD10 expression is a favorable factor in patients with lymph node-positive UC.^[9] So the exact role of CD10 in UC is still doubtful.

In addition to HER1/EGFR, HER3, and HER4, HER2 is a part of the human epithelial growth factor receptors family,^[10] it is transmembrane receptor tyrosine kinases, they share in multiplication, mobility, and survival of cells through the reduction of the function of variable signaling pathways inside the cell.^[10] HER2 is a proto-oncogene placed at the long arm of chromosome 17(17q12), codes for the HER2 protein, and its mutation and amplification lead to HER2 overexpression,^[10] which is considered as predictive in addition to be prognostic marker in breast, gastric, and gastroesophageal malignancies. The HER2 test becomes a routine clinical investigation and guidelines for breast and gastric cancer treatment.^[4] New studies have observed a similar HER2 protein change in UC, but its clinical significance has not been studied well and the available literature show a broad range for the ratio of patients with UC showing HER2 expression and the exact range of it is still not determined.^[11]

This study aimed to assess the frequency of immunohistochemical (IHC) expression of CD10 (in tumor cells and tumor stroma) and HER2 (in tumor cells) in primary UC of the urinary bladder and to assess their relation to variable clinicopathological parameters such as the age of the patients, gender, grade, lympho-vascular invasion, and muscle invasion.

MATERIALS AND METHODS

Patients and sample collection

In this retrospective case series study, during a period from January 2021 to April 2023, 50 cases (paraffin-embedded tissue blocks) of primary UC obtained through a transurethral resection, were collected from a lab of a single private hospital in Mosul city, North of Iraq. The data regarding the patients' age and gender were obtained from medical records. A 4 µm thickness sections were obtained from paraffin blocks of cases included in this study then hematoxylin and eosin (H&E) slides were prepared and examined for histopathological reevaluation of each case regarding the grade, the presence or absence of lympho-vascular and muscle invasion.

IHC study

For each case, two tissue sections from paraffin block with adequate nonnecrotic tumor tissue were chosen then stained with mouse monoclonal antibodies, one against the CD10 and the other against HER2 (Dako). IHC studies were done using Labeled Streptavidin-Biotin System-Horseradish Peroxidase (LSAB2 System-HRP) which is dependent on a modified labeled Avidin-Biotin (LAB). The antibody complex is became visible by the addition of substrate chromogen reagent, diaminobenzidine (DAB) produced by Dako, which appears as brown precipitation at the antigen site in tissue. Sections treated with distilled water instead of primary antibodies were used as negative controls. While sections from normal endometrium and sections from breast carcinoma which were previously known to be positive for HER2 immune stain were used as a positive control for CD10 and HER2, respectively.

IHC interpretation

For CD10 expression, the cytoplasm and/ or cell membrane staining was evaluated and the interpretation score was done as shown in Table 1.^[3,5,6,12,13] Score 0 was interpreted as negative, on the other hand, score 1+ and 2+ were considered positive.^[12,13] For HER2 expression, only membranous staining was regarded as positive and the interpretation was done as shown in Table 2.^[3,5] Scores 2+ and 3+ were considered as positive for HER2, scores 0 and 1+ were considered as negative.

Statistical analysis

Results were statistically analyzed using the Chi-square test. Fisher exact test was used when indicated. *P* value which was <0.05 regarded statistically significant.

Ethical approval

This study was conducted based on the principles of ethics that have their origin in the Declaration of Helsinki and it was approved by the Medical Research Ethics Committee,

Table 1: Scoring system for CD10 expression (the cytoplasm and/or cell membrane staining)

Score 0	No staining or <5% of tumor cells were positive
Score 1+	5–50% of tumor cells were positive
Score 2+	>50% of tumor cells were positive

Table 2: Scoring system for evaluation of HER2 expression (membranous staining)

Score 0	No staining or membrane staining observed in <10% of tumor cells
Score 1+	Partial faint membrane staining in >10% of tumor cells
Score 2+	Circumferential weak to moderate staining observed in >10% of tumor cells
Score 3+	Circumferential strong membrane staining observed in >10% of tumor cells

College of Medicine, University of Mosul with a reference number [UOM/COM/MREC/22-23(33)] on May 21, 2023, to get this approval.

RESULTS

This study included 50 cases of primary UC, the age of patients ranged from 34 to 90 years (mean = 59.9 years) with 54% of them were ≤60 years of age. Regarding the gender, 44 cases (88%) were males with a male-to-female ratio was 7.33:1. The majority of cases, 31 cases (62%) were of low grade, 34 cases (68%) showed no lympho-vascular invasion and 38 cases (76%) showed no muscular

invasion. IHC study of all the cases included in this study revealed that 30 cases (60%) were positive for CD10 in tumor cells and CD10 showed positive stain in stromal cells in 19 cases (38%). HER2 immune stain was positive in 20 cases (40%) Table 3.

CD10 expression in tumor cells

In this study, 30 cases showed positive CD10 expression in tumor cells. No significant association was detected with patients' age ($P = 0.23$). Regarding the gender, the tumor cell CD10 expression was more in males, that 27 cases (54%) of 44 (88%) cases were positive, but also no significant association was detected between CD10 and gender with ($P = 0.6723$). Although 13 (26%) out of 19 (38%) of high-grade cases were positive for tumorous CD10, no significant association was detected ($P = 0.3413$). Also, no significant association was found with lympho-vascular invasion and muscle invasion ($P = 0.80449$ and $P = 0.3168$, respectively) [Table 4].

CD10 expression in tumor stroma

In the current study, the expression of CD10 in tumor stroma was detected in 38% of the cases. Significant association was detected with female gender ($P = 0.0244$),

Table 3: The IHC expression of CD10 in tumor cells, in tumor stroma, and HER2 expression in the cases included in the study

IHC markers	Expression	Total no.	Percentage
CD10 expression in tumor cells	Positive	30	60%
	Negative	20	40%
CD10 expression in tumor stroma	Positive	19	38%
	Negative	31	62%
HER2	Positive	20	40%
	Negative	30	60%

Table 4: The association of CD10 expression in tumor cells with variable clinicopathological parameters of the cases included in the study

Clinicopathological parameters	CD10 expression in tumor cells		Total	P value
	Positive, No. (%)	Negative, No. (%)	No. (%)	
Age in years				
31–40	2 (4)	1 (2)	3 (6)	0.23
41–50	2 (4)	7 (14)	9 (18)	
51–60	10 (20)	5 (10)	15 (30)	
61–70	11 (22)	4 (8)	15 (30)	
71–80	3 (6)	2 (4)	5 (10)	
81–90	2 (4)	1 (2)	3 (6)	
Total	30 (60)	20 (40)	50 (100)	
Gender				
Male	27 (54)	17 (34)	44 (88)	0.6723
Female	3 (6)	3 (6)	6 (12)	
Total	30 (60)	20 (40)	50 (100)	
Grade				
Low grade	17 (34)	14 (28)	31 (62)	0.3413
High grade	13 (26)	6 (12)	19 (38)	
Total	30 (60)	20 (40)	50 (100)	
Lympho-vascular invasion				
Absent	20 (40)	14 (28)	34 (68)	0.80449
Present	10 (20)	6 (12)	16 (32)	
Total	30 (60)	20 (40)	50 (100)	
Muscle invasion				
Absent	21 (42)	17 (34)	38 (76)	0.3168
Present	9 (18)	3 (6)	12 (24)	
Total	30 (60)	20 (40)	50 (100)	

Table 5: The association of CD10 expression in tumor stroma with variable clinicopathological parameters of the cases included in the study

Clinicopathological parameters	CD10 expression in tumor stroma		Total	P value
	Positive, No. (%)	Negative, No. (%)	No. (%)	
Age in years				
31–40	1 (2)	2 (4)	3 (6)	0.9318
41–50	3 (6)	6 (12)	9 (18)	
51–60	6 (12)	9 (18)	15 (30)	
61–70	5 (10)	10 (20)	15 (30)	
71–80	2 (4)	3 (6)	5 (10)	
81–90	2 (4)	1 (2)	3 (6)	
Total	19 (38)	31 (62)	50 (100)	
Gender				
Male	14 (28)	30 (60)	44 (88)	0.0244*
Female	5 (10)	1 (2)	6 (12)	
Total	19 (38)	31 (62)	50 (100)	
Grade				
Low grade	7 (14)	24 (48)	31 (62)	0.004115*
High grade	12 (24)	7 (14)	19 (38)	
Total	19 (38)	31 (62)	50 (100)	
Lympho-vascular invasion				
Absent	12 (24)	22 (44)	34 (68)	0.5655
Present	7 (14)	9 (18)	16 (32)	
Total	19 (38)	31 (62)	50 (100)	
Muscle invasion				
Absent	11 (22)	27 (54)	38 (76)	0.0378*
Present	8 (16)	4 (8)	12 (24)	
Total	19 (38)	31 (62)	50 (100)	

*Significant *P* value <0.05

high-grade tumors ($P = 0.004115$), and muscle invasion ($P = 0.0378$). Neither patients' age nor lympho-vascular invasion showed a significant association with the expression of CD10 in stromal cells of UC ($P = 0.9318$ and $P = 0.5655$, respectively) [Table 5].

HER2 expression in tumor cells

In this study, the immune stain for HER2 in tumor cells of UC was positive in 40% of cases. HER2 immune stain was significantly associated with high-grade tumors ($P = 0.00875$). Also, HER2 expression showed significant association with muscle invasion with ($P = 0.0445$). No significant association was detected with age of the patients, gender, and lympho-vascular invasion ($P = 0.9531$, $P = 0.7223$, and $P = 0.3221$, respectively) [Table 6].

The association of stromal CD10/HER2 phenotype of the cases included in the study showed a significant relationship between tumor grade and muscle invasion ($P = 0.00978$ and $P = 0.0337$, respectively), that low-grade tumors and absence of muscle invasion were more detected in cases that showed negativity of both stromal CD10 and HER2 expression. No association was detected with patients' age, gender, and lympho-vascular invasion [Table 7]. Representative photomicrographs of the cases included in this study are

shown in Figures 1 and 2. Figure 1 shows a negative and positive CD10 expression in tumor and tumor stromal cells, Figure 2 shows variable scores of HER2 expression.

DISCUSSION

UC of the urinary bladder is the most prevalent histological type of primary urinary bladder carcinoma.^[12] Different parameters had been used to assess the prognosis of this tumor, like TNM staging system, histological grade, age of the patients, and lymph node involvement,^[3] however, still there are no definite markers that can expect the likelihood of tumor relapse or progression^[3] and even the patients with the same stage and grade may show a different outcomes.^[14] Recently, many IHC markers have been evaluated to determine UC prognosis.^[15]

In the current study which included 50 cases of primary UC, CD10 expression in tumor cells was seen in 60% of cases, this result is similar to that of Abdou^[8] who found that tumorous CD10 was positive in 55% of all bladder carcinoma types and was positive in 60% of UC subtype. Also, the result of this study was near to the results detected by Ramzan *et al.*,^[6] Mohamed,^[5] and Shukla,^[15] that the CD10 expression in tumor cells was positive in 54.67%, 63%, and 68.6%, respectively. While Al-Maghrab^[12] and

Table 6: The HER2 expression in tumor cells and its association with variable parameters of cases included in the study

Clinicopathological parameters	HER2		Total	P value
	Positive, No. (%)	Negative, No. (%)	No. (%)	
Age in years				
31–40	1 (2)	2 (4)	3 (6)	0.9531
41–50	3 (6)	6 (12)	9 (18)	
51–60	6 (12)	9 (18)	15 (30)	
61–70	6 (12)	9 (18)	15 (30)	
71–80	3 (6)	2 (4)	5 (10)	
81–90	1 (2)	2 (4)	3 (6)	
Total	20 (40)	30 (60)	50 (100)	
Gender				
Male	18 (36)	26 (52)	44 (88)	0.7223
Female	2 (4)	4 (8)	6 (12)	
Total	20 (40)	30 (60)	50 (100)	
Grade				
Low grade	8 (16)	23 (46)	31 (62)	0.00875*
High grade	12 (24)	7 (14)	19 (38)	
Total	20 (40)	30 (60)	50 (100)	
Lympho-vascular invasion				
Absent	12 (24)	22 (44)	34 (68)	0.3221
Present	8 (16)	8 (19)	16 (32)	
Total	20 (40)	30 (60)	50 (100)	
Muscle invasion				
Absent	12 (24)	26 (52)	38 (76)	0.0445*
Present	8 (16)	4 (8)	12 (24)	
Total	20 (40)	30 (60)	50 (100)	

*Significant *P* value <0.05**Table 7: The stromal CD10/HER2 phenotypes and their relation with variable clinicopathological parameters**

Variable clinicopathological parameters		Stromal CD10+/HER2+	Stromal CD10–/HER2–	Stromal CD10–/HER2+	Stromal CD10+/HER2–	Total (%)	P value
Age in years	31–40	1 (2%)	2 (4%)	0 (0%)	0 (0%)	3 (6%)	0.7077
	41–50	3 (6%)	6 (12%)	0 (0%)	0 (0%)	9 (18%)	
	51–60	3 (6%)	6 (12%)	3 (6%)	3 (6%)	15 (30%)	
	61–70	2 (4%)	6 (12%)	4 (8%)	3 (6%)	15 (30%)	
	71–80	1 (2%)	1 (2%)	2 (4%)	1 (2%)	5 (10%)	
	81–90	1 (2%)	1 (2%)	0 (0%)	1 (2%)	3 (6%)	
	Total	11 (22%)	22 (44%)	9 (18%)	8 (16%)	50 (100%)	
Gender	Male	9 (18%)	21 (42%)	9 (18%)	5 (10%)	44 (88%)	0.0507
	Female	2 (4%)	1 (2%)	0 (0%)	3 (6%)	6 (12%)	
	Total	11 (22%)	22 (44%)	9 (18%)	8 (16%)	50 (100%)	
Grade	Low	4 (8%)	19 (38%)	5 (10%)	3 (6%)	31 (62%)	0.00978*
	High	7 (14%)	3 (6%)	4 (8%)	5 (10%)	19 (38%)	
	Total	11 (22%)	22 (44%)	9 (18%)	8 (16%)	50 (100%)	
Lympho-vascular invasion	Absent	6 (12%)	16 (32%)	6 (12%)	6 (12%)	34 (68%)	0.7421
	Present	5 (10%)	6 (12%)	3 (6%)	2 (4%)	16 (32%)	
	Total	11 (22%)	22 (44%)	9 (18%)	8 (16%)	50 (100%)	
Muscle invasion	Absent	5 (10%)	20 (40%)	7 (14%)	6 (12%)	38 (76%)	0.0337*
	Present	6 (12%)	2 (4%)	2 (4%)	2 (4%)	12 (24%)	
	Total	11 (22%)	22 (44%)	9 (18%)	8 (16%)	50 (100%)	

*Significant *P* value <0.05

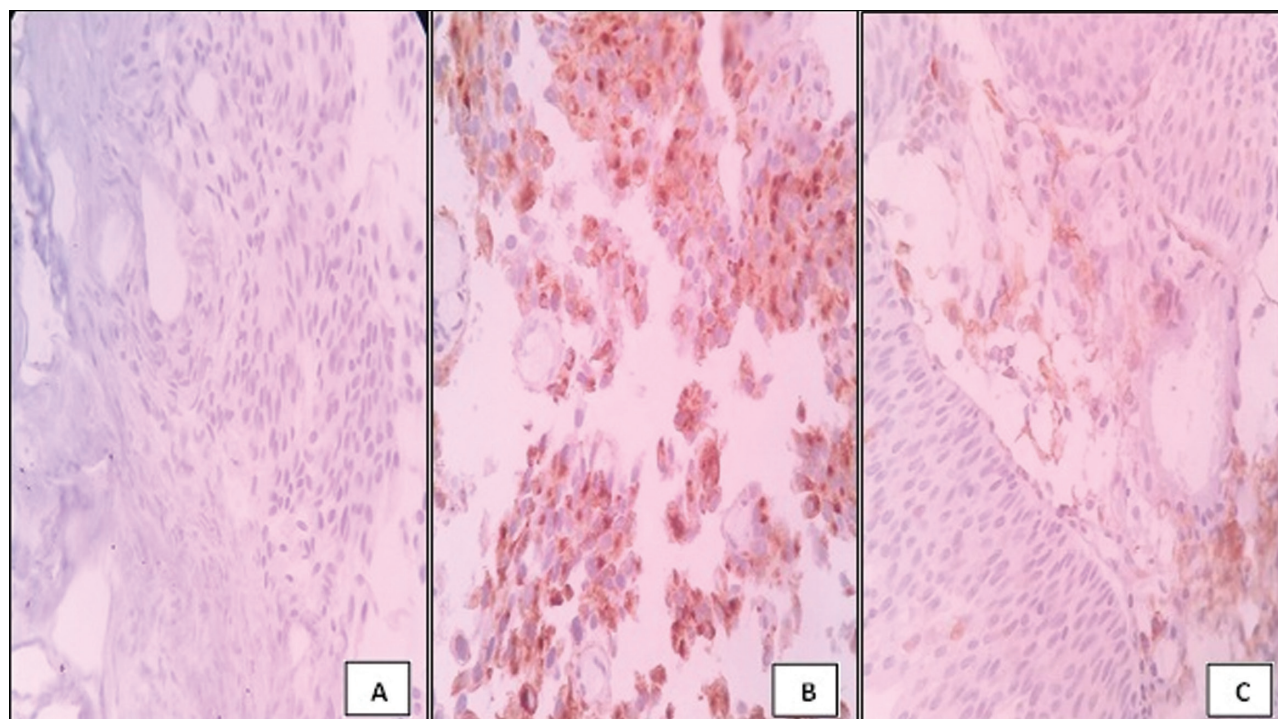


Figure 1: Urinary bladder UC, CD10 expression (membranous and cytoplasmic): (A) score (0), negative CD10 immune stain in tumor cells and stromal cells; (B) score (2+), positive CD10 immune stain in > 50% of cells tumor; (C) score (2+), positive CD10 immune stain >50% of tumor stromal cells (magnification 100×)

Abdelhalim Salem^[3] found that CD10 was positively expressed in 49% and 50%, respectively, the last two results were lower than that of this study. This variability may be related to variability in study populations and the heterogeneity between kits, protocols, antibodies, cutoff values, or interpretations.^[16] The wide variability in the results reported in these researches indicates that there is a need for standardized laboratory methods and adapting a uniform cut of value. Regarding the association between tumor cells' CD10 expression and patients' age and gender, no significant association was detected, this result is similar to that of Abdelhalim Salem,^[3] Mohamed,^[5] Abdou,^[8] Kumagai-Togashi,^[9] and Al-Maghrab.^[12]

Abdelhalim Salem,^[3] Mohamed,^[5] and others^[9,13,17] in their studies found that the CD10 expression in tumor cells was more commonly expressed in UC with high grade. In the current study, although 13 (26%) out of 19 (38%) of high-grade tumor showed CD10 expression, no significant association was detected, and this may be due to the small size of the cases sampled and statistical bias. Abdelhalim Salem,^[3] Mohamed,^[5] Kumagai-Togashi,^[9] and Hussien,^[17] found a statistical association between the tumor CD10 with lympho-vascular invasion and muscle invasion, these results disagreed with that of the current study which showed no significant association among CD10 in urothelial neoplastic cells and these prognostic factors. However, Al-Maghrab,^[12] in his study found neoplastic cell CD10 is significantly associated with grade and muscle invasion but not with lympho-vascular

invasion and distant metastasis. Abdou^[8] found that the tumorous CD10 is not statistically associated with grade, or muscle invasion, while it is associated with vascular invasion and tumor stage. This variation may be attributed to variations in patient population and tumor stage included in these studies.

The expression of CD10 in stromal cells of the tumor was found to be associated with a bad prognosis and advanced stage in a number of solid cancers originating from colorectum, breast, and pancreas in addition to nonsmall cell carcinoma of the lung.^[15] Although in UC, CD10 was studied in several studies, they emphasized CD10 evaluation in tumor cells^[8] while stromal CD10 was disregarded apart from few studies.^[8,9,18]

In the current study, a significant association was detected between stromal CD10 and gender, that the stromal CD10 was more detected in females, this result is similar to the findings by Abdou,^[8] although in her study no significant association was detected between CD10 stromal expression and the gender in bladder cancer cases in general, in UC subtype, the high score of stromal CD10 significantly correlated with females gender, while Kumagai-Togashi^[9] in their study failed to find this association.

Regarding the stromal CD10 and grades of tumor, the tumor stromal cells with positive CD10 expression were detected more in cases with high grade in comparison with low-grade cases, this association was significant. The same result was detected by Hussien^[17] and Omran,^[18]

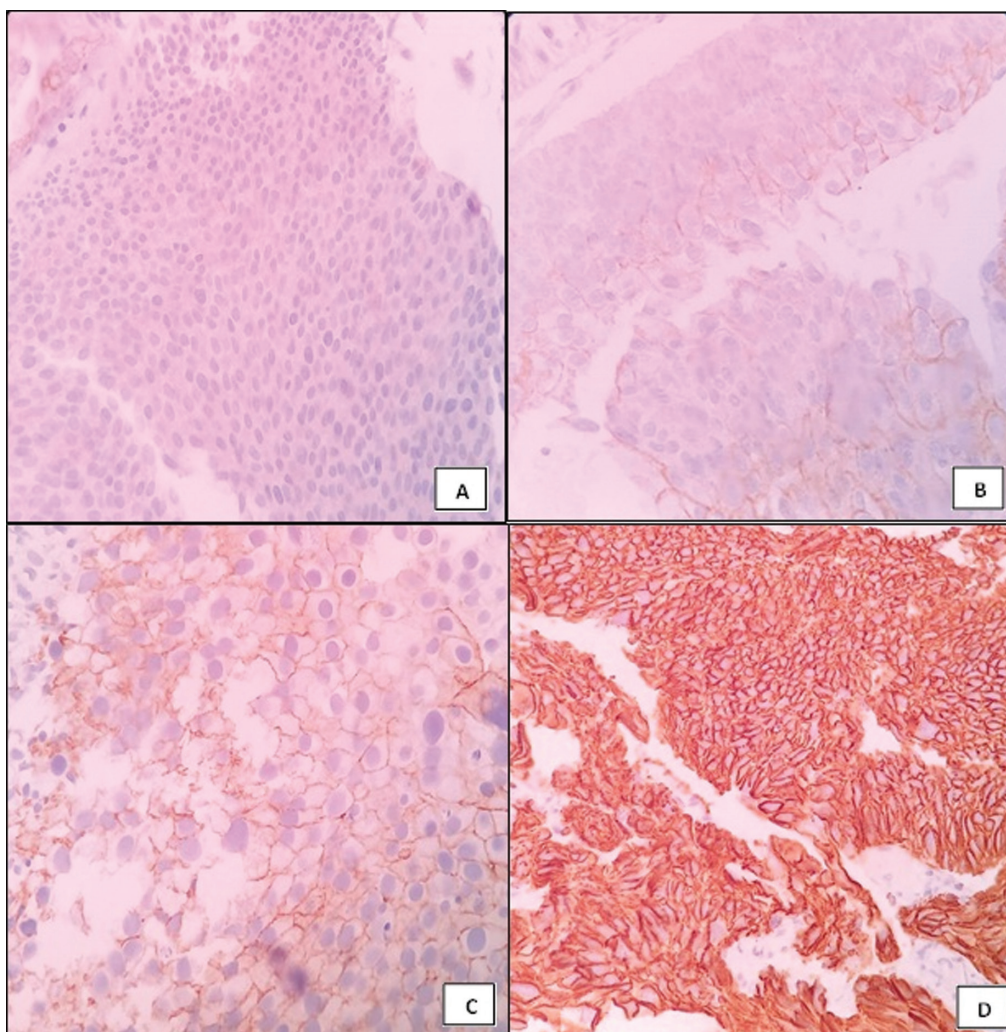


Figure 2: Urinary bladder UC, HER2 expression: (A) score (0): negative HER2 immune staining; (B) score (1+): partial faint membrane staining in >10% of tumor cells; (C) score (2+): circumferential weak to moderate staining observed in >10% of tumor cells; (D) score (3+): circumferential strong membrane staining observed in >10% of tumor cells (magnification 100×)

but it disagreed with that of Abdou^[8] and Kumagai-Togashi.^[9] Stromal CD10 expression was more detected in the cases showing muscle invasion than in the cases with no muscle invasion, this association was statistically significant. Kumagai-Togashi,^[9] Hussien,^[17] and Omran^[18] found that stromal CD10 is significantly associated with the stage, this may be the result of a similar structure of CD10 to the stromal matrix metalloproteases and its proteolytic function that lead to a microenvironment enhancing the invasiveness and distant metastasis of malignant tumor cell.^[6] No significant association with lympho-vascular invasion was detected and this is similar to the findings by Abdou,^[8] but in disagreement with that of other studies.^[9,17]

The major factors that detect the prognosis of cases with bladder malignant tumors are the extent of malignant cell invasion into the bladder muscle wall and the differentiation of tumor cells.^[3] As the tumor stromal CD10 expression, not tumor cell CD10 appeared to

be significantly associated with these two important prognostic parameters, it indicates there is a difference in the function of CD10 between tumor and stromal cells and stromal CD10 can be regarded as a prognostic marker that helps to predict the outcome of tumor and to subclassify the patients regarding the prognosis.

In bladder cancers, HER2 is a commonly amplified oncogene, associated with high tumor grade and stage,^[14,19] so it has had prognostic properties in addition it offers a chance for treatment with drugs targeting HER2 to improve the overall survival of the patients.^[14] However, other studies have found no such association.^[14,19] So the exact benefit of HER2 in UC is still unknown.

HER2 overexpression and/or amplification in the UC is still controversial with a wide range from 23% to 80% for overexpression and from 0% to 32% for amplification.^[16] In the current study, the HER2 protein overexpression was only studied and it was detected in 40% of all cases,

this result is within this range and near to that of the studies done by Sebina Asmi,^[20] Abdelhalim Salem,^[3] and Abdou Hassan,^[21] which were 36%, 44%, and 49%, respectively, while the result was lower than that detected by Bai *et al.*,^[18] which showed HER2 expression in 57.4% of cases and that detected by Ibrahim,^[22] which was 63.35%. El Ochi *et al.*,^[14] and Rosli,^[23] in their study, found HER2 expression was present in 11.7% and 18.8%, respectively. The variability of HER2 expression level presented in different studies may be attributed to UC heterogeneity,^[23] in addition to variable grades and stages, the variable patient number included, in addition to the different laboratory tests, and the use of different antibody clones and different criteria for definition of positivity.^[20]

About the predictive value of HER2, some researches showed that HER2 overexpression was linked to a worse prognosis, while other researches suggested that HER2 status was not predictive.^[17] In the current study, the association of HER2 protein IHC expression with the grade of bladder carcinoma was statistically significant, this result is similar to that of Abdelhalim Salem,^[3] Mohamed,^[5] El Ochi *et al.*,^[14] Bai *et al.*,^[19] Sebina Asmi,^[20] and Abdou Hassan.^[21] In a study done by Rosli,^[23] HER2 was only significantly associated with tumor grade and concluded that in patients with higher-grade UC, HER2 may be a useful IHC marker. Histopathology is the gold standard for the staging of UC, according to WHO classification, the invasion to submucosal connective tissue is considered as pT1 while invasion to muscularis propria is pT2.^[23] In comparison between muscle invasive versus noninvasive UC regarding IHC expression of HER2 in the current study, the expression was more detected in the cases that showed muscle invasion and this association was statistically significant. Mohamed,^[5] El Ochi *et al.*,^[14] Sebina Asmi,^[20] and Abdou Hassan,^[21] in their study they found that tumor stage and HER2 have a substantial correlation. In agreement with Abdelhalim Salem,^[3] Mohamed,^[5] El Ochi *et al.*,^[14] Bai *et al.*,^[19] and Ibrahim,^[22] HER2 in this study did not show any association with patients' age; however, in a study was done by Abdou Hassan,^[21] patients under 60 years of age showed a strong correlation with HER2 expression. No significance between HER2 expression and patients' gender in the current study, this result was similar to that of Abdelhalim Salem,^[3] Mohamed,^[5] El Ochi *et al.*,^[14] Bai *et al.*,^[19] Abdou Hassan,^[21] and Ibrahim.^[22] To our knowledge, this is the first research studying the dual stromal CD10/HER2 phenotype of UC and comparing them with clinicopathological parameters, this study showed that negative expression of both stromal CD10/HER2 may help to predict good prognosis in UC of the bladder since the majority of cases which showed negativity for both stromal CD10 and HER2 expression more commonly appeared to be of low grade and with no muscle invasion.

CONCLUSION

This study revealed that expression of CD10 is more common in tumor cells than in tumor stromal cells of UC. HER2 expression and stromal CD10 expression are associated with higher grade and muscle invasion, so they may have an important role in UC pathogenesis and progression and could be used as prognostic factors to predict the outcome of the cases in addition, the detection of HER2 expression may help to choose those who will most likely benefit from anti-HER2-targeted treatment. Large prospective studies in the future are required to validate these results.

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Conflicts of interest

There are no conflicts of interest.

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