Section: Pathology

Original Research Article

EXPRESSION OF PROGNOSTIC BIOMARKERS (HER2/NEU, CD10) IN URINARY BLADDER NEOPLASMS AND ITS ASSOCIATION WITH MORPHOLOGY

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ABSTRACT

Background: A variety of biomarkers have been used to assess the prognosis of urinary bladder neoplasm (UBN). In the present study role of two novel biomarkers (HER2/neu and CD10) were studied by immunohistochemistry (IHC) as prognostic markers for UBN.

Materials & Methods: This prospective study included 30 newly diagnosed cases of UBN. Bladder cystoscopy was performed in patients clinico-radiologically suspected of UBN; cytological and biopsy samples were taken from the suspicious area. Cytomorphological features and diagnosis was correlated with histopathology on biopsy, resected specimen and typing and grading of tumor. Expression of HER2/ neu and CD10 were correlated with grade and stage of the tumor. Complete routine urine examination including cytospin smear for malignant cells were also studied.

Results: Overall HER2 /neu expression was present in 14 cases (46.7%) with 2+ and 3+ immunoreactivity in 13(43.3%) and 1(3.3%) case respectively. CD10 expression was noted in 13 (43.3%) patients, +1 in 11 (36.7%) and +2 in two cases (6.7%) cases, there was no +3 expression. The remaining 17 (56.7%) patients were negative for CD 10 expression.

Conclusion: A significant direct association was observed between HER2/neu over expression with both increasing grade of carcinoma (p=0.00), and depth of tumor invasion (0.042). CD10 expression with histologic grade and stage (p=0.05) was not statistically significant.

Keywords: Urinary bladder neoplasm, HER2/neu, CD10, Prognostic biomarkers, immuno-histochemistry, urinary bladder cytology.

INTRODUCTION

Urinary bladder neoplasm (UBN) is one of the most common malignancies affecting the genitourinary tract, is the 10th most common cancer in the world, and its incidence is steadily rising worldwide, especially in developed nations.[1] The incidence is higher as compared to mortality which is due to the higher frequency of the UBN with favourable prognosis (superficial, non-muscle invasive) compared to the poor prognostic types (muscle invasive and metastatic).[2] Most newly diagnosed patients of UBN are well-differentiated superficial papillary tumors, most of these patients have prolonged survival followed by transurethral resection (TUR) with or without intra-vesical chemotherapy (CT). However, patients with risk factors have more recurrences following initial resection. According to the molecular genetics, superficial and invasive lesions develop along distinct molecular pathways. Low grade papillary tumors (LGPT) harbour constitutive activation of the receptor- tyrosine kinase-Ras signal transduction pathway and a high frequency of fibroblast growth factor receptor 3 (FGFR3) mutations. In contrast, Carcinoma-in-situ (CIS) and invasive tumors have a higher frequency of p53 and RB gene alterations.[3] Most bladder cancers occur due to exposure to

environmental and occupational chemicals, the largest of which is tobacco smoke. Greater tobacco smoke and occupational exposure in men may help explain the 4-fold gender predisposition in urinary bladder cancer incidence.[1] The major prognostic factors include the depth of invasion into the bladder wall and the degree of differentiation of the tumor. However, there is no reliable parameter predicting the risk of recurrence or progression. Molecular markers are therefore required to estimate the individual prognosis of patients as well as for diagnosis and effective treatment. A few molecular markers e.g., bladder tumor antigens, tumor suppressor gene (p53), cell cycle regulator proteins (p27, cyclin E, E-cadherin, CD44) are reported to be of prognostic value.[4]

In the present study the association of two novel biomarkers HER2/neu and CD10 with the morphology, grade, and stage of UBN were studied.

MATERIAL AND METHODS

The study was conducted in the Departments of Pathology and Surgery, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi.

Study Period: July 2014 to April 2016

Study Population: patients presenting with painless hematuria and diagnosed with urinary bladder malignancy were included in the study

Study design: Prospective study

Inclusion Criteria: Newly diagnosed cases of Urinary Bladder Neoplasm were included in the study

Exclusion Criteria: Patients with past history of Chemo/ radiotherapy for Urinary Bladder Neoplasm were excluded.

Methodology: Relevant clinical details and investigations were recorded and tabulated. Cystoscopy guided cytology smears and biopsy samples were taken from the suspected areas / growth for diagnostic confirmation. Multiple smears were prepared; two of them air dried methanol fixed Giemsa stained smear for cytological diagnosis and histological correlation. Rest were used for ICC as and when possible. The smears were studied for detail for following cytomorphology features: cellularity, pattern, shape and size of cells, cytoplasmic features, nuclear details (grooves, inclusions, pleomorphism, mitosis) and background. An attempt was made to type and grade the tumor on cytological smears. Extra slides were used for the panel of ICC, wherever possible.

Immunochemical staining:(ICC/IHC)

HER 2/ neu and CD10 immunohistochemical stains were applied on sections as well as cytology smears in diagnosed cases of UBN. The smears/ sections were processed by strept ABC method using diaminobenzidine (DAB) as a chromogen.

Staining pattern for neoplastic cells: Two authors independently graded on a semiquantitative basis, percentage (%) of the cells stained and the intensity of staining.

HER2/neu scoring: cell membrane stain was considered as positive expression and only cytoplasmic staining were considered negative, irrespective of the staining intensity. Scores of 0,1,2 (negative, focal, diffuse positivity) were recorded when <10% of cells were positive, 10-50% of cells /weak, >50% of cells/ strong positivity is seen.

The cells positive for CD10 showed positivity for cytoplasm and membrane staining.

The cells positive for HER2/neu showed membrane staining.

Scoring for HER2/neu; 1 (negative): faint and focal membrane stain in 10% of neoplastic cells; 2 (positive): weak but definitive stain of the entire membrane in 10% of neoplastic cells; 3 (strongly positive): strong stain of the entire membrane in 10% of neoplastic cells.

Scoring for CD 10: cytoplasm and membrane staining was considered as positive expression, CD 10 scored as 1-3; 1(Negative): no stain in neoplastic cells; 1+ (minimal): < 5% of neoplastic cells stain positive; 2 (moderate): 5-50% of neoplastic cells stain positive; 3 (strong): > 50% of neoplastic cells stain positive.

RESULTS

The cases were statistically analysed using Chi square test, P value < 0.05 was taken as significant.

A Cytohistological correlation was available in 20 cases, cytological diagnosis in 15 cases (75%) could be correctly correlated with the histological diagnosis; however, the remaining cases (5) were over diagnosed by one grade. Four cases diagnosed as papilloma / PUNLMP and, five cases diagnosed as LGPUC on cytology were correlated correctly on biopsy. Out of 10 cases diagnosed as HGPUC on cytology, five were diagnosed as TCC LGPUC and five as HGPUC on biopsy. One case diagnosed as Malignant NOS on cytology was diagnosed as HGPUC on biopsy. [Table 1]

Major prognostic significance exist between high grade and low grade lesions. Papillomas, PUNLMP and LGPUC have a better survival rates regardless of the number of recurrences. Only a few patients experience progression of their disease to higher grade in contrast, about 40 % individuals with high grade UBN survive to 10 years, the tumor is progressive in 65 % of cases. Hence grading the lesion as high grade

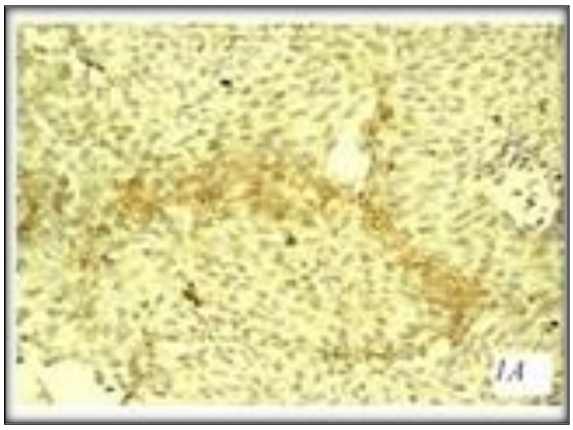
carries amore prognostic significance than grading it as low grade. Therefore, in case of discrepancy between cytology and histology, the histological diagnosis being the gold standard will be considered the final diagnosis to be conveyed to the clinician for the appropriate management of patients.

Histomorphological parameters: microscopic features assessed were presence of necrosis, presence

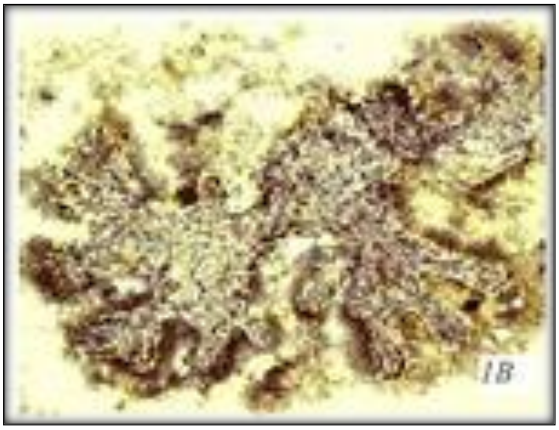
and grade of inflammatory infiltrate and lympho vascular invasion [Table 2]

TUMOR MARKERS EXPRESSION WITH CLINICAL AND MORPHOLOGICAL PARAMETERS

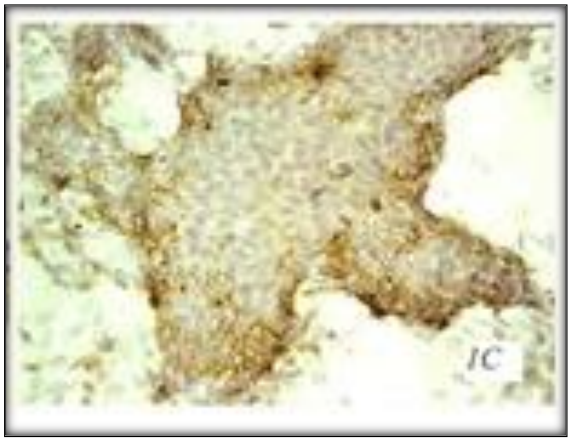
HER2/neu: Among the 30 investigated bladder carcinomas, HER2/neu membranous staining was observed in 14 cases (46.7%); Scores of 2+ and 3+ were considered positive and was found in 13 (43.3%) and 1 (3.3%) cases respectively. (Figure 1 and 2).



1A. IHC, 1+ positive (400x)

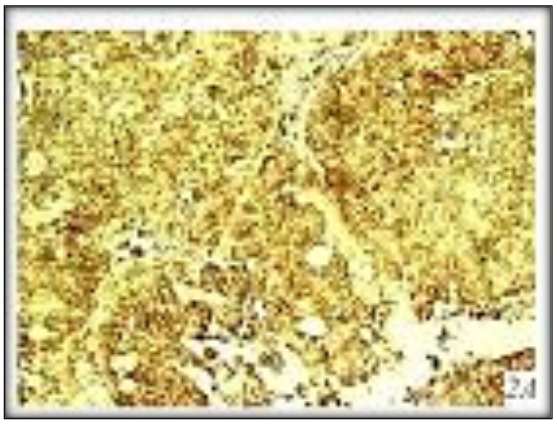


1B. ICC, 1+ positive (400x)



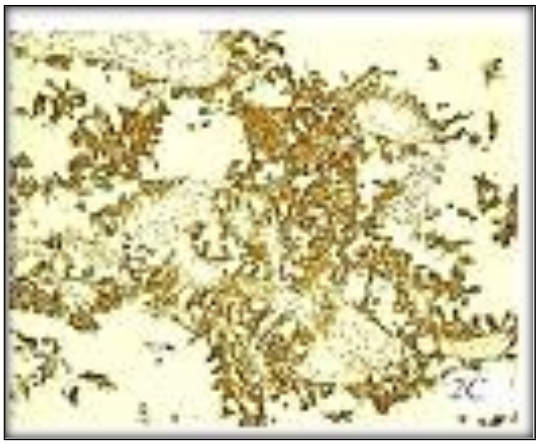
1C. ICC, focal positive (400x)

Figure 1: HER2/neu Immunohistochemistry (Photomicrographs)



2A.ICC positive 3+ (400x)

2B.IHC showing membranous positivity 3+ (400x)



2C.IHC positive 3+ Honeycomb pattern (400x)

Figure 2: HGUC: HER2/neu immunohistochemistry (Photomicrographs)

Correlation between HER2/neu expression and pathologic stage of UBC.A significant direct association was observed between increased HER2/neu expression with depth of tumor invasion and increased stage of UBN with *p value 0.042. [Table 3]

A significant direct association was observed between HER2/neu expression and increasing grade of UBN (*p value = 0.00). [Table 4]

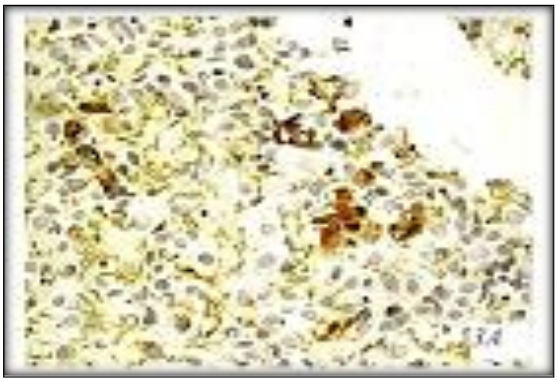
CD 10 EXPRESSION WITH CLINICOPATHOLOGICAL FEATURES

CD 10 immunostaining, positivity was considered by membranous and cytoplasmic golden- brown staining in tumor cells with a 1% cut off point. The extent of immunoreactivity was scored semi quantitatively according to the following criteria:

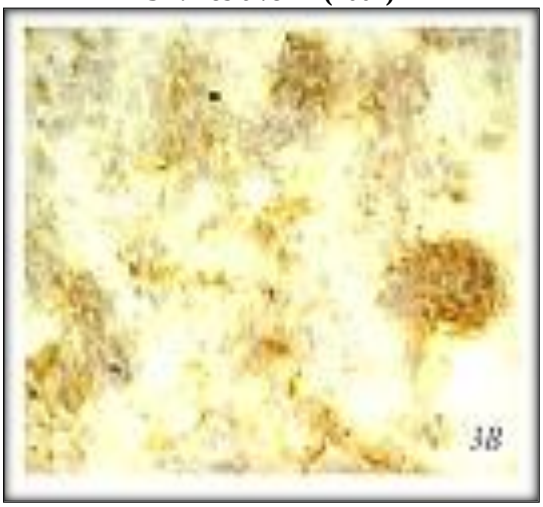
CD 10 scoring (Table 6). In the present study thirteen out of 30 (43.3%) patients demonstrated positive CD 10 staining. 1+ and 2+ staining was observed in 11 (36.7%) and 2 (6.7%) cases respectively. the remaining cases 17 (56.7%) were negative for CD 10. There was no + 3 expression.

Overall CD 10 expression was seen in 13/30 (43.3%) cases. (Figure 3 and 4)

There was no significant association with CD 10 expression with the pathological stage and histological grade of UBN(p value = > 0.05) as shown in Table 7 and 8 respectively.



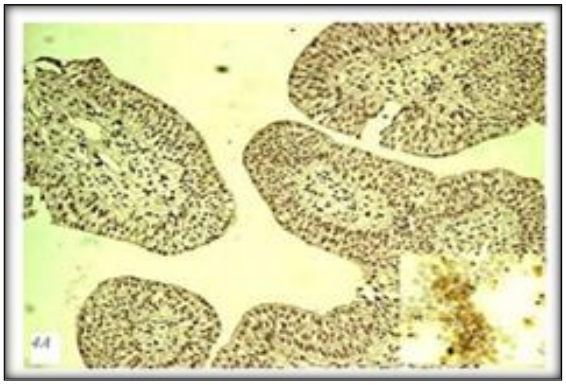
3A. Positive 1+ (400x)



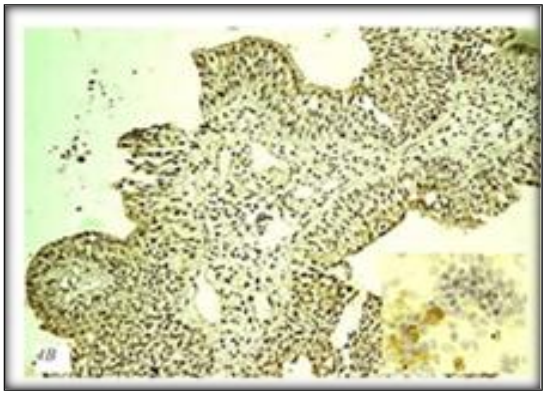
3B. Positive 2+ (400x); inset cytoplasmic positivity

3CPositive 3+ (400x)

Figure 3: LGPUC: CD10 immunohistochemistry



4A.CD 10 (IHC) negative (400x); inset (ICC) focal positive



4B. HER2/neu (IHC) negative, (400x); inset (ICC) negative

Figure 4: PAPILLOMA; CD 10 IHC&ICC

Table 1: Showing Cyto-histological correlation

Cytological diagnosis		Histological diagnosis			
	No. of cases (20)	Papilloma / PUNLMP	LGPUC	HGPUC	SCC
Equivocal	0	0	0	0	0
Papilloma /PUNLMP	4	4	0	0	0
LGPUC	5	0	5	0	0
HGPUC	10	0	5	5	0
Malignant NOS	1	0	0	1	0

Table 2: Showing Histomorphological features

Histomorphological features	Present No. of cases (%)	Absent No. of cases (%)
Necrosis	4 (13.3%)	26 (86.7%)
Inflammatory infiltrate	3 (10%)	27 (90%)
Lympho-vascular invasion	1 (3.3%)	29 (96.7%)

Table 3: HER2/neu Expression with pathological stage

	HER2/neu Expression (N=30 cases)				
STAGE	0	1+	2 +	3+	
0a	3	0	1	0	*P VALUE = 0.042
I	0	5	7	0	
II	0	7	4	1	
III	0	0	1	0	
IV	0	1	0	0	

Table 4: HER2/neu Expression with the grade of UBN

	HER2/neu Expression (N=30 cases)				
GRADE	0	1+	2+	3+	
PAPILLOMA	2	0	0	0	
PUNLMP	1	0	1	0	
LGPC	0	8	6	0	
HGPC	0	5	6	1	

Table 5:CD 10 scoring criteria

Negative	**1% or fewer positive cells**
1+	2%-10% positive cells
2+	11%-50% positive cells
3+	>50% positive cells.

Table 6: CD 10 Expression

CD 10 Expression	Number of cases (percentage) (N=30 cases)
Negative	17(56.7%)
1+	11(36.7%)
2+	2(6.7%)
3+	0

Table 7: CD 10 Expression with pathological stage

	CD 10 Expression (N= 30 cases) Number			
STAGE	**0**	**1+**	**2+**	**3+**
0a	2	2	0	0
I	7	3	2	0
II	7	5	0	0
III	0	1	0	0
IV	1	0	0	0

Table 8: CD 10 expression with histological grade

	CD 10 Grades				
UBN Grades	0	1	2	3	
Papilloma	1	1	0	0	P value=0.83
PUNLMP	1	1	0	0	
LGPC	8	2	2	0	
HGPC	7	0	0	0	

DISCUSSION

About 60% of UBN, when first discovered are single and grossly purely papillary (70%), nodular (10%), mixed (20%), sessile, infiltrating and flat intraepithelial type with lateral and posterior regions of bladder are involved the most.[5] In the present study, solitary growth was seen in 25 cases (83.3 %) and more than one /multiple sites were seen in five cases (16.7%). In the gross morphology pattern, papillary growth pattern was the most common, seen in 21 cases (70 %), followed by sessile growth pattern in five (16.7 %), nodular in three (10.0%) and thickened wall in a single case (3.3 %). Lateral wall was the most common site of involvement in the present study. Voided urinary cytology (UC) is a useful non-invasive adjunct to cystoscopy, it has overall high specificity to identify exfoliated malignant cells in urine. The specificity of UC is >90%,[6] while the sensitivity for high- grade and CIS can be as high as 80-90%.[7] In the present study urine cytology was suspicious in 16 (53.3%), positive for malignant cells in 2 (6.7%) and negative in 12 (40%) cases.A Cytohistological correlation was obtained in 20 cases. Cytological diagnosis in 15 cases could be correctly correlated with the histological diagnosis; however, the remaining five cases were over-diagnosed by one grade. Four cases that were

diagnosed papilloma/PUNLMP on cytology; were diagnosed the same on biopsy. Out of 10 cases that were diagnosed as HGPUC on cytology, only 5 were diagnosed as HGPUC, remaining five were down staged as LGPUC on biopsy. Rest five cases diagnosed as LGPUC on cytology, were diagnosed same on biopsy. Single case diagnosed as Malignant NOS on cytology was diagnosed as HGUC with squamous differentiation on histology.

Major prognostic differences exist between high grade (HG) and low grade (LG) lesions. Papilloma's, PUNLMP and LGPUC have a better survival rate regardless of the number of recurrences. Only a few patients experience progression of their disease to HG lesion in contrast, about 40% individuals with HG-TCC survive up to 10 years, the tumor is progressive in 65% of cases.[8] Hence, grading the tumor as HG carries a poor prognosis as compared to LG. Therefore, in cases of cyto-histological discrepancy, the histological diagnosis being the gold standard should be considered as final diagnosis which is helpful in appropriate management of patient.

Among the 30 cases of UBN in the present study, HER2/Neu membranous staining was observed in 14 (46.7%), 2+ and 3+ immunoreactivity was observed in 13(43.3%) and 1(3.3%) case respectively. There was a positive Her-2 status in 23 (59%) cases of bladder cancer in a study by Gehani et al.[9] Of the 39 bladder carcinomas studied by Shawky et al, 16 (41%) were considered negative, whereas 23 (59%) were considered positive.[10] A significant direct association was observed between HER2/neu over expression with both increasing grade of carcinoma ($p = 0.00$), and depth of tumor invasion ($p=0.042$). This agrees with study by Kolla et al where the HER2/neu status was significantly related to the tumor stage ($p =0.001$) and the grade of the disease.[11]

Also, it is agreement with study by Shawky et al where HER2/ Neu overexpression was significantly associated with tumor differentiation grade ($p = 0.001$) as well as the depth of tumor invasion ($p \leq 0.001$) with the overexpression more prevalent in the high grade and deeply invasive specimens reflecting the aggressiveness of the tumor cells.[10] HER2 expression was invariably negative in the normal urothelium. Study by Gehani et al revealed a significant correlation between HER2 expression and the tumor stage ($p= 0.011$).[9] Although there was no statistically significant association ($p=0.21$) between HER2 and tumor grade, HER2/neu showed over-expression more often in high-grade (8/12, 66.6%) than in low-grade tumors (12/27 44.4%). In a study by Ismail et al revealed a significant correlation between HER2/neu expression and the tumor grade (p value =<0.001),[12] though there was statistically insignificant association n between HER2/neu positivity and tumor stage ($p=0.16$).[10]

In contrast in a study by Osman et al,[13] found no significant association between HER2/NEU over-expression and tumor grade ($p=0.06$).

In a study by Eissa et al, Tommasi et al, no significant association was found between HER2/neu and either pathological stage or tumor grading. [14,15] Gehani et al reported that the variations in HER2/neu expression in UBN may be the result not only of true biological variations but also of several confounding variables in these studies e.g., use of different antibodies for IHC, different criteria for IHC positivity (i.e., cytoplasmic/membrane staining) and different scoring criteria.[9]

Differences in the HER2/neu expression and its prognostic significance in UBN could be due to different pathways (gene amplification vs. protein overexpression) and different antibodies applied for IHC, in addition to the inconsistent criteria set for detecting IHC positivity.[10] Despite the inconclusive data on the prognostic value of HER2neu as an independent marker of tumor progression, there may be a therapeutic role for an anti HER2 agent such as trastuzumab in cancer treatment.[9]

In the present study, 13 (43.3%) cases demonstrated CD10 expression; however, it didn't reveal any correlation with histologic grade and pathologic stage (*p value=> 0.05). This was in concordance with the study by Kandemir et al,[16] whereas Bircan et al found an inverse correlation between CD10 expression and tumor stage without any association with histologic grade.[17] Murali et al detected CD10 expression in 50% of non-neoplastic mucosal samples and in 67% of UBN, they concluded that CD10 expression is associated with high histologic grade, but independent of tumor stage.[18] In contrast, Atique et al reported statistically significant ($p<0.001$) CD 10 expression in different grade of tumors.[19] Jang et al also reported similar findings on CD10 expression and found significant correlation with tumor grade ($p=0.004$) and tumor invasion ($p=0.003$).[20] Bahadir et al has reported CD10 had a strong correlation with both histologic grade and pathologic stage.[21] However, conflicting results for CD10 expression in normal bladder epithelium have been reported; in some reports by Koiso K et al and Chu P, Arber DA et al CD10 was not observed in normal bladder urothelium,[22,23] however some studies by Kandemir NO et al have reported CD10 expression in 50% of normal bladder urothelium and was successively lost from normal urothelium to TCCs.[18] These conflicting results suggest that normal bladder mucosa is exposed to different microenvironments and differed in their molecular profiles. As per several studies on CD10 expression on normal bladder urothelium, it may prevent mucosa from carcinogenesis through degradation of molecules delivering antiapoptotic signals and growth- promoting signals. The present study did not demonstrate a significant correlation of CD10 expression with tumor grade and tumor invasion; this may be due to small sample size;the improper staging of the specimens due to subjective errors in assessing the stage or improper transurethral resection technique in which deeper tissues including the muscular layer had not been taken may contribute to

under/over staging and affecting the number of cases in each stage. Further studies with large number of cases are needed to confirm our results and to elucidate the role and significance of CD 10 in urothelial carcinoma.

CONCLUSION

The present study demonstrates a statistically significant association between HER2/neu expression and grade and stage of UBN (p=0.00 & 0.042) respectively. Assessment of HER2/neu status can be helpful in identifying patients at high risk of disease progression who may benefit from adjuvant HER2 targeted therapy after radical cystectomy. Future studies on HER2 expression with chemosensitivity and efficacy of HER2 targeted therapies in UBN is warranted. To date only few comparative IHC studies have assessed CD 10 expression was seen in both high grade and stage of UBN. In the present CD 10 expression was seen in both high grade and low grade UBN. However, CD 10 staining of malignant cells didn't reveal any correlation with histologic grade and pathologic stage (p= >0.05). Therefore to conclude, this study can be considered as pilot study and further studies with larger sample sizes are required to substantiate the role of HER2/neu and CD 10 as prognostic biomarker in Urinary bladder neoplasms.

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