

CD10 and CA19.9 Immunohistochemical Expression in Transitional Cell Carcinoma of the Urinary Bladder

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Author's Contribution

^{1,2,5}Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, data collection, manuscript writing, Final approval of the version to be published, ^{3,4,6}Active participation in active methodology, ⁷Literature review, data analysis

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ABSTRACT

Objectives: To determine the frequency of immunohistochemical expression of CD10 and CA19.9 in patients with papillary urothelial carcinoma of the bladder in accordance with the WHO 2004 grading of the tumor.

Methodology: This descriptive cross-sectional study was conducted at the Foundation University Medical College Islamabad, from October 2017 to October 2018. Seventy-five patients from both genders, aged 40 to 80 years, undergoing trans urethral resection of bladder tumors to diagnose papillary urothelial bladder were included in our study. The data were analyzed with SPSS version 17. Immunohistochemical processing was performed and the results were interpreted by the consultant pathologist for the expression of CD10 and CA19.9 on transitional cell carcinoma with respect to the 2004 grading of the tumor.

Results: age range in this study was from 40 to 80 years with a mean age of 52.60 ± 7.60 years. Out of these 75 patients, 39 (52.0%) were male and 36 (48.0%) were female, with a male-to-female ratio of 1.1:1. The frequency of positive expression of CD10 and CA19.9 on immunohistochemistry in patients with papillary urothelial carcinoma of the bladder was found in 41 (54.67%) and 39 (52.0%) cases, respectively. It was seen that positive CD10 expression was found in 12 (31.58%) low grade tumors and in 24 (63.16%) high grade tumors. Positive CA19.9 expression was found in 29 (78.38%) low grade tumors and 15 (40.54%) high grade tumors.

Conclusion: The study concluded that there was a slightly increased expression of CD10 in transitional cell carcinoma of the urinary bladder compared with CA19.9. However, high-grade urothelial carcinomas showed increased expression of CD10 in contrast to low-grade urothelial carcinomas, which revealed increased positive expression of CA19.9.

Keywords: CA19.9, CD10, Urothelial Carcinoma, Immunohistochemistry

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Introduction

Urinary bladder urothelial carcinoma is the most frequently diagnosed cancer in the world, coming in at number seven.¹ Genitourinary tract cancers in men are most commonly diagnosed after prostate carcinoma.² Males are diagnosed at a rate of 4%, and females at a rate of 9%, with this cancer in the United States. Males outnumber females by a ratio of 3:1. Every 100,000

Pakistani men and women, 8.9 will develop urothelial carcinoma.³ Urothelial carcinoma is caused by a combination of genetic and environmental factors, including smoking and occupational exposure to carcinogens.⁴

There are two types of papillary urothelial carcinomas in the bladder: high-grade (HG) and low-grade (LG). Long-term monitoring of low-grade papillary urothelial

carcinoma is common. In most cases, when it does penetrate the bladder wall, it recurs in the same place.⁵ Papillary carcinomas with higher grades are more likely to invade the bladder wall and have a high mortality rate.⁶ Most patients with urinary bladder carcinoma have low-grade urothelial carcinoma rather than high-grade cancer. At the time of diagnosis, the prognosis for a particular tumor type and stage can vary greatly.

CD10, a zinc-dependent metalloprotease, inhibits the activity of a number of bioactive neuropeptides. Consequently, it has a significant impact on cell growth and apoptosis. Because of its structural resemblance to the stromal matrix metalloproteases 1, altering the microenvironment of tumor cells may influence their invasion and metastatic potential.

CA19.9 is a blood type-specific antigen (carbohydrate antigen). CA19.9, a cancer-related phenomenon, cannot occur without the expression of Lewis, a blood group antigen. Additional benefits include activation of ELAM-1, an important cell adhesion protein involved in cell extravasation from the bloodstream, as well as increased adhesion of human epithelial cancer cell lines to the blood vessel endothelium. Because of this adhesion, hematogenous cancer cell spread is made easier. The expression of CA19.9 and CD10 in urothelial bladder carcinomas is not well studied in Pakistan.⁷

CD10 and CA19.9 expression in the previously diagnosed low and high-grade papillary urothelial carcinomas was the primary goal of this study. The study's goal was to aid doctors in the early detection and treatment of carcinomas, reduce the risk of developing high-grade papillary urothelial carcinoma, and detect tumor recurrence through routine follow-up cystoscopy.

Methodology

This descriptive, cross-sectional study was done at Foundation University Medical College Islamabad between October 2017 and October 2018. Seventy five individuals were chosen for the study using the WHO calculator based on a 95% confidence level, and the anticipated population proportion was 26% with a 10% absolute precision level.¹ The approach of consecutive non-random sampling was applied with patients presented between specific period of one year was selected unbiased.

Patients from both genders, age groups 40 to 80 undergoing TURBT to diagnose papillary urothelial

bladder were included in our study. Patients who received chemotherapy or radiotherapy before having their tumors removed, as well as those with insufficient specimens to make a diagnosis, were excluded from our study.

Data collection was done after ethical approval was obtained from Foundation University Medical College, Islamabad & patient's consent. 75 tumors have were removed by transurethral resection from the urinary bladder & from the available histopathological reports, we could obtain various parameters, such as age, gender, and histological grade.

A rotator microtome was used to cut three 4–5 nm thick sections. For histopathological evaluation of tumor grade, one section was stained with eosin and hematoxylin stain. While CD10 and CA19.9 monoclonal antibodies were stained using the streptavidin method in the other two sections. For CA19.9 immunohistochemical expression, cytoplasmic brown staining was a positive result. The percentage of stained cells and the intensity of the staining were used in the evaluation.

The percentage of stained cells indicates that 0 represents when the coloration was negative, +1 represent less than 25% of positive cells, +2 represents 25% of positive cells between 50% and 75%, and +3 represents more than 50% of positive cells.

There are four different levels of intensity in the staining: 0 if the coloration is negative, +1 if it is weak, +2 if it is moderate, and +3 if the coloration is intensely positive, which can be seen even at low levels of increase. The maximum number of stained cells in ten high-power spots was evaluated as 0/Negative showing less than 5% of cells, +1 showing low expression or 5 to 50% positive cells, +2 showing high expression or more than 50% positive cells as CD10 immunohistochemistry showed brown staining of the cell membrane and/or cytoplasm as positive1.

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Analysis of the data was done by using the software SPSS version 17. A quantitative variable like age was measured as mean SD. Qualitative variables like gender, tumor grade (low, high), CD10 and CA19.9 expression were measured as frequency and percentage. To compare the proportion of CD10 and CA19.9 expression among low and high grade papillary urothelial carcinomas of the urinary bladder, Chi-square test was applied. P value of less than 0.05 was considered statistically significant.

Results

Age range in this study was from 40 to 80 years with mean age of 52.60 ± 7.60 years. Out of those 75 patients, 66 (88%) were between 40-60 years and 09 (12%) were between 61-80 years with mean \pm SD of 52.60 ± 7.60 years. 39 (52%) patients were males and 36 (48%) were females with male to female ratio 1.1 :1. Out of 39 male patients, 19 (48.71%) showed positive expression of CD10 and 20 (51.28%) showed negative expression. However, CA19.9 showed positive expression in 18 (46.15%) and negative expression in 18 (46.15%) of male patients.

In females, out of 36 patients 22 (61.11%) showed positive expression and 14 (38.89%) showed negative expression of CD10 immunohistochemical marker respectively. However, for CA19.9, 21 (58.33%) patients had positive expression while 15 (41.67%) had negative expression on immunohistochemistry.

Keeping in view the age of patients and immunohistochemical expression of CD10, positive expression was found in 37 (56.06%) of patients with age between 40-60 years and 29 (43.93%) patients of same age group. 32 (48.48%) and 34 (51.51%) patients of same age group showed positive and negative expression of CA19.9 respectively.

However, for age group ranging 61-80 years, 04 (44.44%) showed positive and 55.55% (05) revealed negative expression of CD10 on immunohistochemistry. For CA19.9 04 (44.44%) showed positive and 05 (55.55%) revealed negative expression in patient with same age group.

Overall, frequency of positive expression of CD10 and CA19.9 on the immunohistochemistry in patients of papillary urothelial carcinoma (both low grade and high grade) of the urinary bladder was found in 41 (54.67%) & 39 (52.0%) cases respectively as shown in Table I.

Stratification of the expression of CD10 and CA19.9 on immunohistochemistry with respect to the grade of tumor is shown in Table-II. It is seen that positive CD10 expression was found in 12 (31.58%) low grade tumor while 24 (63.16%) high grade tumors. However, positive CA19.9 expression was found in 29 (78.38%) low grade tumors and 15 (40.54%) high grade tumors.

Table I: Frequency of expression of CD10 and CA19.9 on immunohistochemistry in patients of papillary urothelial carcinoma of the urinary bladder

| | Positive | Negative |
|--------|-------------|-------------|
| CD10 | 41 (54.67%) | 34 (45.33%) |
| CA19.9 | 39 (52.0%) | 36 (48.0%) |

Table II: Stratification of the expression of CD10 and CA19.9 on immunohistochemistry with respect to the grade of tumor.

| | | Low grade (n=38) | High grade (n=37) | P-value |
|---------------|----------|------------------|-------------------|---------------|
| CD10 | Positive | 31.58% (12) | 78.38% (29) | 0.0001 |
| | Negative | 68.42% (26) | 21.62% (08) | |
| CA19.9 | Positive | 63.16% (24) | 40.54% (15) | 0.050 |
| | Negative | 36.84% (14) | 59.46% (22) | |

Discussion

This study is directed toward the expression of two important markers, CD10 and CA19.9 in the urothelial carcinoma of the urinary bladder. CD10 expression occurs in 43%–67% of urothelial neoplasms. In most reports, CD10 expression shows an inverse correlation with the tumor grade, while a positive correlation with the grade has been noted in others.⁸ Reports show the expression of carbohydrate antigens CA 19.9 correlates with the atypical grade and clinical stage of cancer in some carcinomas.^{9,10} Recently, a relationship between CA19.9 and urothelial cancers has been found.¹¹ However, in the literature, only a few studies have been published evaluating the expression of CA19.9 in transitional cell carcinoma of the bladder. This study was conducted to determine the frequency of expression of CD10 and CA19.9 on immunohistochemistry in patients with papillary urothelial carcinoma of the urinary bladder. The age range in this study was from 40 to 80 years, with a mean age of 52.60 ± 7.60 years. Out of these 75 patients, 39 (52.0%) were male and 36 (48.0%)

were female, with a male-to-female ratio of 1.1:1. A study was conducted in Norway which revealed 72.8 years as median age of patients, which is against the median age of our study and is most probably due to environmental and genetic factors.¹² In concordance with Ferlay.J et al., urinary bladder carcinoma has more incidence in males compared to females in the Asian population but has more incidence in females of the African population, which is most probably due to genetic differences.¹³ The frequency of the positive expression of CD10 and CA19.9 on immunohistochemistry in the patients with papillary urothelial carcinoma of the urinary bladder was found in 41 (54.67%) and 39 (52.0%) cases. Respectively positive CD10 expression was found in 12 (31.58%) low-grade tumors and 24 (63.16%) high-grade tumors. Positive CA19.9 expression was found in 29 (78.38%) low-grade tumors and 15 (40.54%) high-grade tumors. According to Kandemir et al.⁸, higher expression of CD10 was found in urothelial carcinomas compared to non-neoplastic urothelium, and in high-grade carcinomas compared to low-grade carcinomas. Another study by Atique M et al also suggested a strong correlation between CD10 with the high tumor grade.¹⁴ In contrast with Murali et al¹⁵ who detected expression of CD10 in 50% of non neoplastic urothelium samples and in 67% of the urothelial carcinomas in his study, took large samples of non neoplastic lesions while Bircan et al¹⁶ found CD10 expression in 9.9% of non-neoplastic urothelium and in 43% of the urothelial carcinomas. The first study assessing CD10 activity in the bladder was performed by Koiso et al (1994).¹⁷ They found that both the enzyme activity and IHC expression were higher in the superficial cancers than the invasive cancers and normal urothelium. They concluded that CD10 was expressed at a certain stage of differentiation in the course of neoplastic process.

In 2000, Chu and Arber¹⁸ reported positive cytoplasmic staining in 54% (13/24) of the urothelial carcinomas, while there was no reaction in non-neoplastic tissues. However, the correlation of CD10 expression with the pathologic stage or histologic grade was not investigated in that study. These results suggested that neoplastic tissues rather than non-neoplastic epithelium have a propensity for CD10 expression. Conversely, Murali and Delprado¹⁹ demonstrated CD10 staining in 50% (5/10) of non-neoplastic urothelium. Despite the small number of cases, they found CD10 expression in 80% of the invasive carcinomas and also proved that the staining

intensity for the high- grade group (including the invasive carcinoma, high-grade papillary urothelial carcinoma, and carcinoma in situ) was statistically higher than that of the low grade group (including low-grade papillary urothelial carcinoma, papillary urothelial neoplasm of low malignant potential and normal urothelium). Bircan et al.¹⁶ Discovered an inverse relationship between CD10 expression and tumor stage, but no relationship with histological grade or staining score was detected. The authors proposed that a higher level of CD10 expression in the noninvasive carcinomas appears to inhibit the invasion. In a more recent series of 49 cases by Abdou et al., CD10 expression significantly correlated with some parameters, including advanced stage, the tumor size, and shorter mean survival, but not with the grade.¹⁹ The authors suggested that CD10 appears to be associated with tumor progression and that it could play a pivotal role in bladder cancer pathogenesis, a proposal also supported by our findings. Apparently, our study, in which CD10 staining increased with the grade of the tumor, bears some similarities with and shows some differences from these previous reports.

CA 19.9 is a cancer-related carbohydrate antigen that is recognized using a monoclonal antibody against colorectal cancer. Structurally, it is a Sialyl-Lewis with sialic acid combined with lea antigen, a blood group carbohydrate. It is useful as a tumor marker mainly for cancers of the digestive system.^{20,21} The clinical usefulness of monitoring CA19.9 in urothelial carcinoma is less commonly described. The reports so far published have provided significant opinions on the CA 19.9 expression in urothelial carcinoma. Muhammad et al. stated the higher expression of CA19.9 in low-grade urothelial carcinomas compared to high grade, which correlates with the findings of our study, but no significant correlation was found with the stage.¹ Another study published stated CA19.9 as a promising marker in the detection and monitoring of low-grade urothelial carcinoma.²² A study published by Kajiwara et al. reveals inverse expression of CA19.9 with grade of atypia and stated that the lack of expression of CA19.9 implies higher malignant potential 22 which is also in support of our study findings.

Conclusion

According to the findings of this study, patients with papillary urothelial carcinoma of the urinary bladder have significantly higher rates of immunohistochemical expression of CD10 and CA19.9. High levels of CD10

expression are found in high-grade urothelial carcinomas, while low levels of CA19.9 expression are common. Hence, it is revealed that CD10 and CA19.9 expression could be of valuable importance in the differentiation between high grade and low grade urothelial carcinomas and in determining the prognosis in such cases. These immunohistochemical markers (CD10 and CA19.9) can be used for early diagnosis and timely management in high-risk patients in order to reduce mortality and morbidity, as well as the risk of tumour recurrence or progression.

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