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CD10 Expression in Bladder Papillary Urothelial Carcinoma is Linked to Both High Tumor Grade and Late Stage

Mesane Papiller Ürotelyal Karsinomunda CD10 Ekspresyonu Hem Yüksek Tümör Derecesi Hem De Geç Evre ile Bağlantılıdır

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ABSTRACT

Objective: Bladder papillary urothelial carcinoma remains a significant issue with a high recurrence rate, necessitating close patient follow-up despite advances in treatment. Bladder cancer recurrence following initial resection in patients with pTa and pT1 tumors can reach rates as elevated as 80%. This study aims to examine CD10 immunohistochemical expression in urothelial carcinoma of the bladder and evaluate its relationship with histopathological parameters. Materials and Methods: 56 papillary urothelial carcinoma cases taken from the bladder were included in our study. Histopathologically, hematoxylin-eosin (HE) stained sections of each case were re-evaluated and classified according to the current World Health Organization (WHO) grading system. Within the scope of the study, 57.4% of the cases were high-grade and 42.9% were low-grade urothelial carcinoma. Results: Positive CD10 expression was detected in 80.4% of cases. A significant correlation was found between CD10 expression and tumor invasion and high histological grade ($p<0.001$). Significantly higher CD10 expression was detected in invasive pT1, pT2, and pT3 tumors compared to non-invasive pTa tumors ($p=0.003$; 0.004, and 0.01, respectively). A significant positive correlation was also found between pT and CD10 ($r=0.43$, $p=0.001$). No relationship was found between CD10 immunoexpression and overall survival, disease-free survival, and other clinicopathological criteria. Conclusion: The analysis revealed a robust correlation between CD10 expression and high tumor grade, invasion, and pathological stage in urothelial carcinoma of the bladder. Considering these collective findings, it was deduced that CD10 might play a role in tumor progression within the pathogenesis of bladder cancer.

Keywords: *Bladder, Urothelial carcinoma, Immunohistochemistry, CD10*

ÖZ

Amaç: Mesane papiller ürotelyal karsinomu, tedavideki gelişmelere rağmen yüksek tekrarlama oranına sahip önemli bir sorun olmaya devam etmekte olup, hastanın yakın takibini gerektirmektedir. pTa ve pT1 tümörlü hastalarda ilk rezeksiyon sonrası mesane kanseri nüksü %80'e varan oranlara ulaşabilmektedir. Bu çalışmanın amacı mesanenin ürotelyal karsinomunda CD10 immünohistokimyasal ekspresyonunu incelemek ve bunun histopatolojik parametrelerle ilişkisini değerlendirmektir. Materyal ve Metot: Çalışmamıza mesaneden alınan 56 ürotelyal karsinom vakası dahil edildi. Histopatolojik olarak her vakanın hematoksilen-eozin (HE) boyalı kesitleri yeniden değerlendirildi ve mevcut Dünya Sağlık Örgütü (DSÖ) derecelendirme sistemine göre sınıflandırıldı. Çalışma kapsamında vakaların %57,4'ünün yüksek dereceli, %42,9'unun ise düşük dereceli ürotelyal karsinom olduğu görüldü. Bulgular: Vakaların %80,4'ünde pozitif CD10 ekspresyonu tespit edildi. CD10 ekspresyonu ile tümör invazyonu ve yüksek histolojik derece arasında anlamlı bir korelasyon bulundu ($p<0,001$). İnvaziv pT1, pT2 ve pT3 tümörlerinde, invaziv olmayan pTa tümörlerine kıyasla anlamlı derecede yüksek CD10 ekspresyonu tespit edildi (sırasıyla $p=0,003$; 0,004 ve 0,01). pT ile CD10 arasında da anlamlı bir pozitif korelasyon bulundu ($r=0,43$, $p=0,001$). CD10 immün ekspresyonu ile genel sağkalım, hastalıksız sağkalım ve diğer klinikopatolojik kriterler arasında herhangi bir ilişki bulunamadı. Sonuç: Analiz, mesanenin ürotelyal karsinomunda CD10 ekspresyonu ile yüksek tümör derecesi, invazyon ve patolojik evre arasında güçlü bir korelasyon olduğunu ortaya çıkardı. Bulgular bir arada değerlendirildiğinde CD10'un mesane kanseri patogenezinde tümör ilerlemesinde rol oynayabileceği sonucuna varıldı.

Anahtar Kelimeler: *Mesane, Ürotelyal karsinom, İmmünohistokimya, CD10*

INTRODUCTION

CD10 is a cell surface metalloprotease that is responsible for the enzymatic hydrolysis of peptides and plays a role in the signal transduction pathway that regulates cell apoptosis and tumor progression. For this reason, its role in different malignancies has been evaluated (1,2). This marker, which was used to distinguish hematological malignancies, was later identified to be expressed in many tissues and was reported to be highly expressed in various malignancies, including malignant melanoma. CD10 has been reported to be associated with clinicopathological parameters such as tumor size and grade in papillary urothelial carcinoma (PUC) and may be a poor prognostic indicator. However, it has been reported that the relationship between CD10 immune expression and survival is limited (3-8).

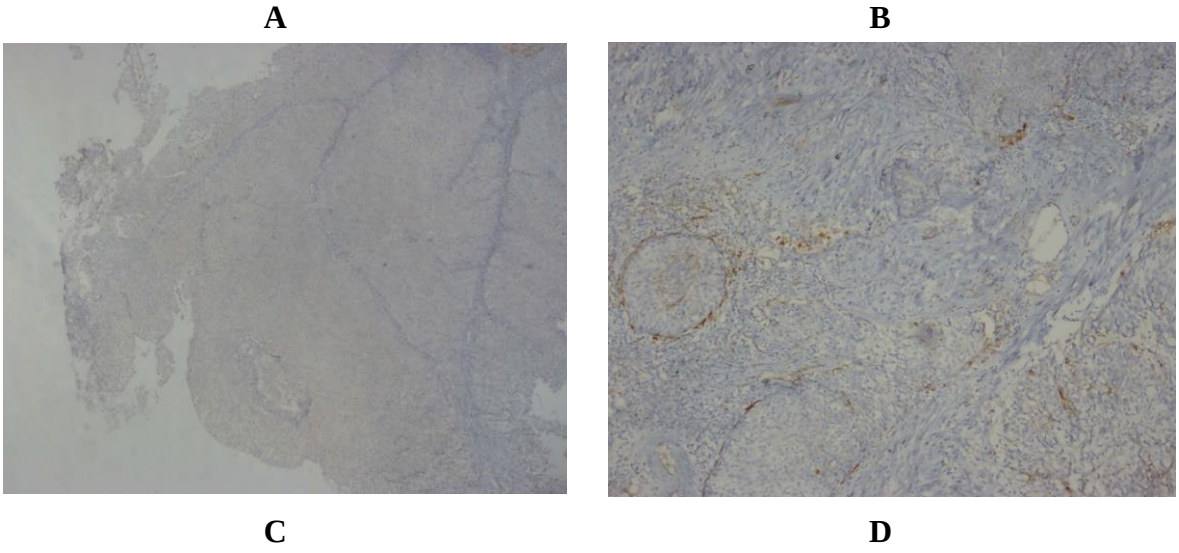
This study aimed to examine the immune expression of CD10 in PUC and to determine the relationship of this marker with histological grade, pathological stage and survival, and to evaluate the role of CD10 in the prognosis of PUC.

MATERIAL and METHOD

56 bladder cases diagnosed with PUC were included in the study. The study complied with the *Declaration of Helsinki* and was approved by *the Kirikkale University Non-Interventional Research Ethics Committee (REC No. 2019/09/03)*. Histopathological samples included both transurethral resection tissue and radical cystectomy samples. Each case was re-evaluated according to the current (WHO 2016) grading system and reclassified as low- or high-grade PUC. We employed an automated immunostaining apparatus (Benchmark, Ventana, USA) to perform CD10 immunohistochemical staining on specific tumor samples. The staining utilized the clone 56C6 antibody at a dilution of 1:10 from CELL MARQUE. Tonsil tissue served as the positive control for CD10. The stained cells were categorized into four scores based on the percentage: score 0 (no staining), score 1 (1-5% staining), score 2 (5-50% staining), and score 3 (>50% staining). Statistical analysis was carried out using the SPSS statistical software program (SPSS 20.0). Significance was evaluated using the $\chi 2$ test and Mann-Whitney U test, with a significance level set at $p<0.05$ and a 95% confidence interval.

RESULTS

Regarding CD10, positive staining was detected in 45 (80.4%) PUC cases and negative staining was detected in 11 PUC cases (19.6%). 1+ staining in 13 of the CD10 positive cases (23.2%); 2+ staining was detected in 10 cases (17.9%) and 3+ staining was detected in 22 cases (39.3%) (Figure 1).



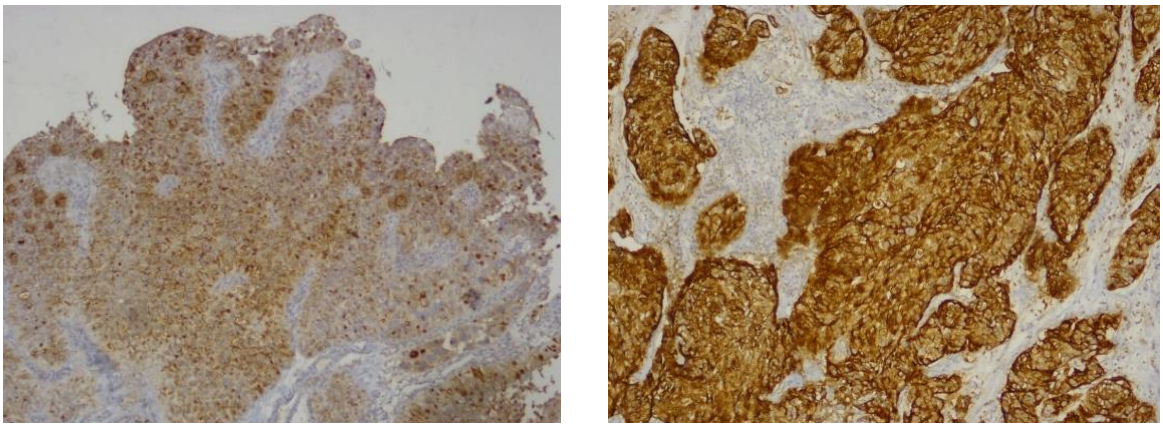


Figure 1: Increase in CD10 Expression with İnvasion and Grade in Papillary Urothelial Carcinoma. A: Low-grade non-invasive (pTa) (x100); B: Low-grade invasive (pT1) (x100), C: High-grade non-invasive (pTa) (x100) and D: High-grade invasive (pT1) (x100).

Among the 56 cases, 23 (41.1%) were female, and 33 (58.9%) were male. Of those, 24 cases (42.9%) were identified as low-grade PUC, while 32 cases (57.1%) were designated as high-grade PUC. While 45 PUC cases (80.4%) were stained positively with CD10, no staining was detected in 11 PUC cases (19.6%). CD10 expression was significantly correlated with high histological grade ($p<0.001$) and invasion ($p<0.001$) (Table 1).

Table 1: Relationship of CD10 Score with Histological Grade and Invasion

	CD10 Immunoreactivity Score				***p***
	0	**1**	**2**	**3**	
Histological grade					
LGPUC	9 (16%)	10 (17,8%)	4 (7.1%)	1 (1.7%)	*<0.001*
HGPUC	2 (3.5%)	3 (5,3%)	6 (10.7%)	21 (37.5%)	
Invasion histological grade					
Invasive histological grade	8 (14.2%)	9 (16%)	3 (5.3%)	3 (5.3%)	*<0.001*
Non- invasive	3 (5.3%)	4 (7.1%)	7 (12.5%)	19 (33.9%)	

*LGPUC: Low-grade papillary urothelial carcinoma, HGPUC: High-grade papillary urothelial carcinoma.

Overall, CD10 expression was significantly higher in pT1, pT2 and pT3 tumors than in non-invasive pTa tumors ($p=0.003$; 0.004 and 0.01, respectively) (Table 2).

Table 2: Relationship of CD10 Score with Pathological Stage

Pathological Stage	**CD10 immunoreactivity score**			
	0	**1**	**2**	**3**
pTa	8 (14.2%)	9 (16%)	3 (5.3%)	3 (5.3%)
pT1	1 (1.7%)	1 (1.7%)	0	8 (14.2%)
pT2	2 (3.5%)	3 (5.3%)	4 (7.1%)	9 (16%)
pT3	0	0	3 (5.3%)	2 (3.5%)

Additionally, a significant positive correlation was detected between pT and CD10 (r=0.43, p=0.001). No relationship was detected between CD10 immunoexpression and age and gender. CD10 immunoexpression did not correlate with either overall survival (long-rank test, p=0.067) or disease-free survival (long-rank test, p=0.550) (Figures 2 and 3).

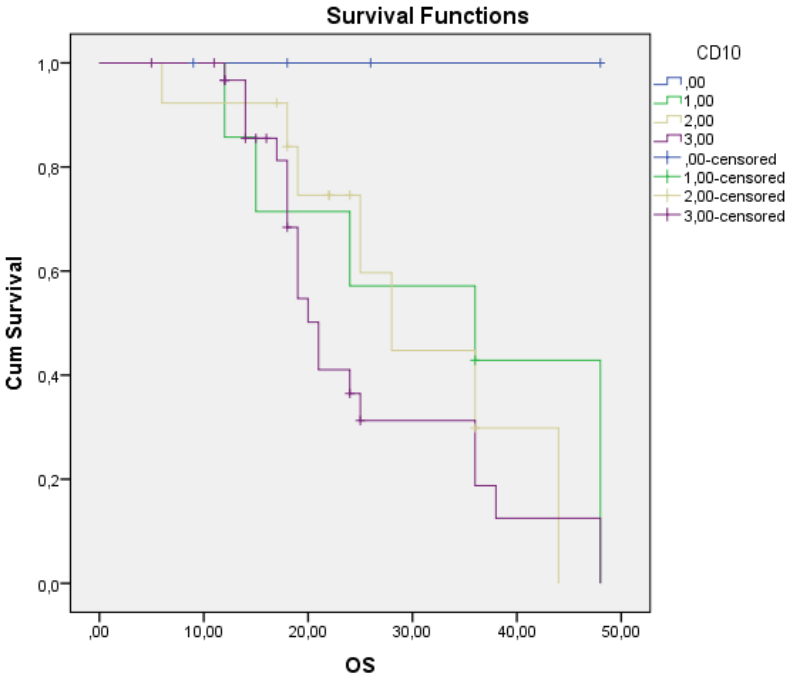


Figure 2: Relationship of CD10 Expression with Survival.

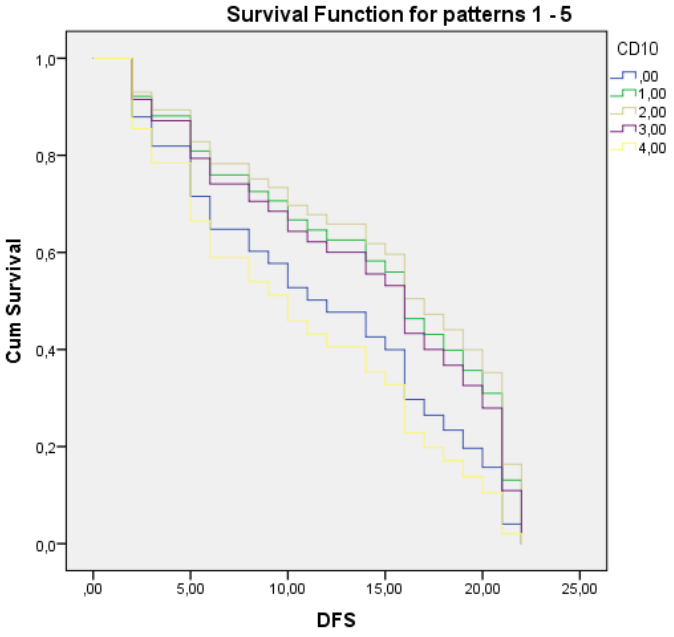


Figure 3: Relationship of CD10 Expression with Disease-Free Survival.

DISCUSSION and CONCLUSION

CD10 is a peptidase found on cell membranes, playing a role in breaking down peptides and linked to cancer development. This study examined CD10 expression in bladder urothelial carcinoma using immunohistochemistry. Previous studies have reported various results. Shukla et al. (2021) found positive CD10 expression in 68.6% of their studies, which included 78.4% high-grade urothelial carcinoma. Another study reported a statistically significant difference in CD10 prevalence between low- and high-grade tumors (8). In addition to these two studies, which express findings consistent

with our study, Kumagai-Togashi et al. (2019) also found a significant difference between CD10 expression and histological grade, consistent with our study. Bahadir et al. (2009) detected a high score in 58.6% of CD10-positive cases in urothelial carcinoma cases and reported a significant relationship between CD10 expression and high histological grade. Furthermore, studies are increasingly highlighting a statistically significant distinction between pathological tumor grade and

CD10 expression levels (9-11). In line with the referenced studies, this study also identified a significant correlation between CD10 expression and grade as well as stage. This correlation is likely explained by the role of CD10 as a cell surface metalloprotease. CD10 expression can create a microenvironment conducive to tumor aggressiveness and invasion in PUC.

Al-Maghrabi (2023) found CD10-positive staining in 49% of UC cases and reported a significant relationship between positive CD10 immunostaining and muscularis propria invasion (3). Another study reported a positive correlation between CD10 expression and muscle invasion in PUC (12). Additionally, studies are reporting a statistically significant difference between pathological tumor stage and CD10 expression (1,9-11,13-16). In this study, consistent with the aforementioned studies, CD10 expression was found to be significantly related to higher tumor stage and worse prognosis. Additionally, Bahadir et al. Similar to (2009), higher CD10 expression was detected in invasive (pT1, pT2 and pT3) tumors than in non-invasive pTa tumors (5).

In our study, consistent with Al-Maghrabi (2023) and Shukla et al. (2021) we did not detect a relationship between CD10 immunoexpression, overall survival, or disease-free survival (1,3). Conversely, another study demonstrates a noteworthy correlation between tumor CD10 positivity and a shorter mean survival time (16,17). Our findings show that CD10 expression is strongly related to higher tumor stage and grade in bladder PUC, and further studies with more patients and longer follow-up periods may shed light on the relationship with survival.

In our study, similar to findings by Al-Maghrabi (2023) and Shukla et al. (2021), we did not observe a correlation between CD10 immunoexpression and disease-free survival overall survival (1,3). Our results suggest a strong association between CD10 expression and anvanced stage and higher tumor grade in bladder PUC. Further investigations involving longer follow-up periods and more patients may provide insight into the relationship between CD10 expression and survival outcomes.

Although we used all related cases in our hospital, the sample size was a limitation for this study. Future studies with a larger number of cases will confirm the data in this study and strengthen the findings. Since CD10 expression increases with tumor grade in bladder PUC, it is thought that it can be used to distinguish low and high-grade tumors. However, it was not evaluated to be associated with survival and other clinicopathological parameters. The observation of heightened CD10 expression as the tumor grade and stage advance led to the conclusion that CD10 might play a role in the progression of bladder cancer during its pathogenesis.

Declaration of Ethical Code: In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out. The study complied with the Declaration of Helsinki and was approved by the Kirikkale University Non-Interventional Research Ethics Committee (REC No. 2019/09/03).
Conflict of interest: The author have no conflicts of interest to declare.
The status of the study outcome being previously included in scientific platforms: This study was partially presented at the 3rd International Hippocratic Congress of Medicine and Health Sciences (6-7 March 2020; Ankara, TURKEY).

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