Alpha-Methylacyl-CoA Racemase Expression in Invasive and Non-Invasive Bladder Urothelial Carcinomas

İnvaziv ve Noninvaziv Mesane Karsinomalarında Alfa-Metalasil-CoA Rasemaz Ekspresyonu

Nil CULHACI, MD,[a]
Zeliha ÇETİN, MD,[a]
Mehmet DÜNDAR, MD[b]

Departments of
[a]Pathology,
[b]Urology,
Adnan Menderes University
Faculty of Medicine, Aydın

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Yazışma Adresi/*Correspondence:*
Nil ÇULHACI, MD
Adnan Menderes University
Faculty of Medicine,
Department of Pathology, Aydın,
TÜRKİYE/TURKEY
nculhaci@adu.edu.tr

ABSTRACT Objective: α-methylacyl-CoA racemase (AMACR) is a useful diagnostic marker for prostatic adenocarcinoma with a high sensitivity and specificity. Although originally viewed as a marker preferentially expressed in prostatic carcinoma, further studies showed its expression in other tumors. The aim of this study is to explore the pathologic significance of AMACR expression in non-invasive and invasive urothelial carcinomas (UCs) of the bladder. **Material and Methods:** A total of 160 UCs of the bladder and 77 adjacent tissues with carcinoma in situ were investigated for AMACR expression immunohistochemically. Positive AMACR expression was defined as cytoplasmic staining with granular pattern. Staining intensity was graded as 0 (negative), 1+ (weak), 2+ (moderate), or 3+ (strong). Positivity was further classified as focal or diffuse. **Results:** Non-neoplastic urothelium revealed no expression of AMACR. There was a statistically significant positive correlation between AMACR expression and grade ($p = 0.021$). AMACR expression was significantly higher in high-grade UCs than low-grade ones. AMACR expression was also correlated with the stage which was significantly higher in invasive tumors ($p < 0.001$). Although nonsignificant, diffuse staining was prominent in high grade tumors. **Conclusion:** In the present study, AMACR was found to be expressed in a significant number of urothelial carcinomas of the bladder. AMACR expression was shown to be correlated with advanced tumor grade and stage. Our data suggest that AMACR expression may be used as an additional prognostic indicator in urothelial carcinomas. Evaluation of AMACR expression may also be useful in determining the aggressive capacity of these tumors in transurethral resection specimens.

Key Words: Urinary bladder neoplasms; carcinoma, transitional cell; alpha-methylacyl-coa racemase

ÖZET Amaç: α alfa metalasil CoA rasemaz (AMACR) prostate adenokarsinomu için yüksek sensitivite ve spesifisiteye sahip yararlı bir tanısal belirleyicidir. İlk başlarda başlıca prostat karsinomalarında eksprese edilen bir belirleyici olarak görülmüşse de, sonraki çalışmalar diğer tümörlerde ekspresyonunu göstermiştir. Bu çalışmanın amacı AMACR ekspresyonunun non invaziv ve invaziv mesane kanserlerinde patolojik önemini araştırmaktır. **Gereç ve Yöntemler:** Yüz altmış mesane kanseri ve 77 adet komşuluğunda karsinoma in situ bulunan dokularda immünohistokimyasal olarak AMACR ekspresyonu araştırıldı. Pozitif AMACR ekspresyonu granüler paternli sitoplazmik boyanma olarak tanımlandı. Boyanma yoğunluğu 0 (negatif), 1+ (zayıf), 2+ (orta), or 3+ (güçlü) olarak derecelendirildi. Boyanma daha sonra diffüz ve fokal olarak sınıflandırıldı. **Bulgular:** Neoplastik olmayan ürotelyumda AMACR ekspresyonu izlenmedi. AMACR ekspresyonu ve derece arasında istatiksel olarak pozitif korelasyon vardı ($p= 0.021$). AMACR ekspresyonu yüksek dereceli üroteliyal karsinomlarda düşük derecelilere göre anlamlı ölçüde yüksekti. AMACR ekspresyonu invaziv tümörlerde anlamlı olarak yüksek olan evre ile de korrele idi ($p< 0.001$). Anlamlılığı olmamasına rağmen, diffüz boyanma yüksek dereceli tümörlerde belirgindi. **Sonuç:** Bu çalışmada, AMACR'ın üroteliyal mesane kanserlerinin anlamlı kısmında eksprese edildiği bulunmuştur. Ayrıca AMACR ekspresyonunun tümor derecesi ve evre ile de korrele olduğu gösterilmiştir. Verilerimiz üroteliyal karsinomlarda AMACR ekspresyonun ilave bir prognostik gösterge olarak kullanılabileceğini de düşündürmektedir. Transüretral rezeksiyon örneklerinde tümörlerin agresiflik kapasitesini saptamak için AMACR ekspresyonun değerlendirilmesi yararlı olabilir.

Anahtar Kelimeler: Mesane tümörleri; karsinom, değişici hücreli; alpha-methylacyl-coa racemase

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The incidence of bladder tumors has been increasing recently. Urothelial carcinoma (UC) comprises approximately 90% of all primary malignant tumors of this organ.[1] Currently, identification of patients with aggressive UC and determination of their treatment are mainly based on the tumor grade and stage. A number of tumor markers have been studied for their potential role in the prognosis of UC. Nevertheless, there is stil a need for biomarkers that can identify cancers with a high risk of progression.

P504S, a cytoplasmic protein which has been identified as human α-methylacyl-CoA racemase (AMACR), is a peroxisomal and mitochondrial enzyme that plays an important role in the beta oxidation of branched-chain fatty acids and fatty acid derivatives.[2] This protein has been detected immunohistochemically in both prostatic carcinoma and prostatic intraepithelial neoplasia, but not in benign prostate tissues. Interestingly, immunohistochemical expression of AMACR has also been detected in a significant proportion of other carcinomas. However, studies on AMACR expression in the other carcinomas are limited unlike in prostatic carcinoma. The aim of this study is to explore the pathologic significance of AMACR expression in non-invasive and invasive UC of the bladder.

MATHERIAL AND METHODS

A total of 237 specimens obtained from 160 patients (39 females, 121 males) who underwent transurethral surgical resection and diagnosed as urothelial carcinoma, and 77 adjacent tissues with carcinoma in situ (CIS) between the years 2000 and 2008 were analysed and included in the study. The patients who were receiving any therapy had not been included in the study. The histological diagnosis of each specimen was provided by standard light microscopic evaluation of the routinely processed and paraffin embedded tissues. The hematoxylin eosin (H&E) stained slides of each case were taken from the pathology archives and reviewed by two pathologists. Grading was performed according to the WHO grading system, corresponding to the WHO/ISUP consensus classification.[1] TNM classification system based on AJCC/UICC 2005 was used for staging.[3] Noninvasive papillary carcinoma was defined as pTa; flat carcinoma in situ was defined as pTis; tumor invading subepithelial connective tissue (lamina propria) was defined as pT1; tumor invading muscularis propria (detrusor muscle) was defined as pT2. Staging was based on the information at the time of diagnosis.

IMMUNOHISTOCHEMISTRY

Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded sections. The tissue block that represented tumor tissue the best was chosen for each case and 5 μm sections were taken to poly-L lysin coated slides for immunuhistochemical staining. Standard streptavidin biotin immunperoxidase method was used for immunostaining. The tissue sections were deparaffined, and antigen retrieval conditions included 0.1M citrate buffer (pH 6.0) in an 800-W microwave oven for 15 minutes. The sections were incubated in 3% hydrogen peroxidase to quench endogenous tissue peroxidase for five minutes. The tissue sections were then incubated with a monoclonal antibody against p504s/AMACR for 60 minutes at room temperature (E 4401, Spring, Fremont, CA, Bioscience). Immunohistochemical reactions were developed with diaminobenzidine as the chromogenic peroxidase substrate, and slides were counterstained with hematoxylin. Prostatic carcinoma served as the positive control. Positive signal stained brown. Negative controls included omission of the primary antibody. No positive staining was found in the negative control slides.

ASSESSMENT OF IMMUNOHISTOCHEMICAL STAINING

Positive AMACR expression was defined as cytoplasmic staining with either a finely stippled or coarsely granular pattern. Staining intensity was graded as 0 (negative), 1 + (weak), 2 + (moderate), or 3 + (strong).[4] Positivity was further divided into focal (5% – 50% positive cells) and diffuse (> 50% positive cells).[5]

STATISTICAL ANALYSIS

Data were analyzed by computer software SPSS for Windows 10.0. A p value < 0.05 was considered as statistically significant. Immunohistochemical sco-

res were compared with tumor grade and stage using Kendall's tau-b and Spearman correlation tests, respectively.

RESULTS

The clinicopathologic features of the patients are shown in Table 1. The median age of the patients was 72 (range, 31-92) years. Stage pTa was present in 26 (11%), pTis in 77 (32.5%), pT1 in 102 (43%), and pT2 in 32 (13.5%) cases. There were 70 (43.8%) low-grade and 90 (56.3%) high-grade cases among 160 UC specimens. Among 237 tumor samples included in the final analysis, distinct cytoplasmic AMACR staining was detected in 151 (63.7%) of the cases (Figure 1a-d). Non-neoplastic urothelium revealed no expression of AMACR. Sixty-nine cases (45.7%) had only focal staining whereas 82 (54.3%) showed diffuse staining. Although statistically nonsignificant, diffuse staining was more prominent in high grade tumors (Figure 2). There was a statistically significant positive correlation among AMACR expressions in terms of grade (Table 2, Figure 3). The frequency of AMACR expression was significantly higher in high-grade UCs than the low-grade ones ($p = 0.021$). AMACR expression was also correlated with the stage (Table 3, Figure 4). The frequency of AMACR expression was significantly higher in invasive tumors ($p < 0.001$).

TABLE 1: Clinicopathological features.

Age (years)	
Median (range)	72 (31-92)
Sex	
Male	121 (75.6%)
Female	39 (24.4%)
Pathologic tumor stage	**Number of patients (%)**
Ta	26 (11%)
Tis	77 (32.5%)
T1	102 (43%)
T2	32 (13.5%)
Noninvasive tumors (Ta+Tis)	103 (43.5%)
Invasive tumors (T1+T2)	134 (56.5%)
Pathological tumor grade	
Low grade	70 (43.7%)
High grade	90 (56.3%)

DISCUSSION

AMACR has been extensively investigated in prostatic carcinoma and has been established as a valuable diagnostic marker for prostate adenocarcinoma with a high sensitivity and specificity.[2,6] Initial studies suggested that AMACR was strongly positive in 97% to 100% of prostate cancers.[7-9] Certain variants such as foamy gland, pseudohyperplastic and atrophic carcinomas were even less frequently positive for AMACR expression, with 60-80% positivity.[10,11] Although it was originally viewed as a marker preferentially expressed in prostatic carcinoma, further studies showed its expression in other tumors, including renal cell carcinoma, intestinal adenocarcinoma, lung carcinoma, hepatocellular carcinoma, endometrial carcinoma, breast carcinoma, pancreatic carcinoma, neuroen- docrine tumors, Sertoli cell tumor, and even in extramammary Paget disease.[4,12-20] Limited number of studies are available describing the role of AMACR in UC.[13,21,22] In Jiang et al.'s[13] study, 761 cases of different tissues and cancers were evaluated and overexpression of AMACR was found in 31% of UCs, both low-grade and high-grade. Beach et al.[23] and Zhou et al.[14] found in their studies with small sample sizes (six and four cases respectively) that invasive UC had at least focal AMACR staining. In the study of Beach et al [23] five of six (83%) specimens had 2+ staining and one specimen had 1+ staining. In the present study, we report that AMACR is overexpressed in 63.7% of the bladder UCs.

Immunohistochemically, moderate to strongly positive staining with AMACR has been demonstrated in a wide variety of normal human tissues, including liver, kidney, breast, and salivary glands, and benign lesions.[24,26] Weak, partial AMACR staining was found in 15.9% of benign prostatic glands, in 4% of foci of atrophy.[27] Although the percentages were not high, positive staining for AMACR was found in prostatic benign lesions in various studies.[28-30] The expression is occasional, and the level of expression is significantly lower than in the malignant counterpart. This can cause interpretation problems especially when the amo-

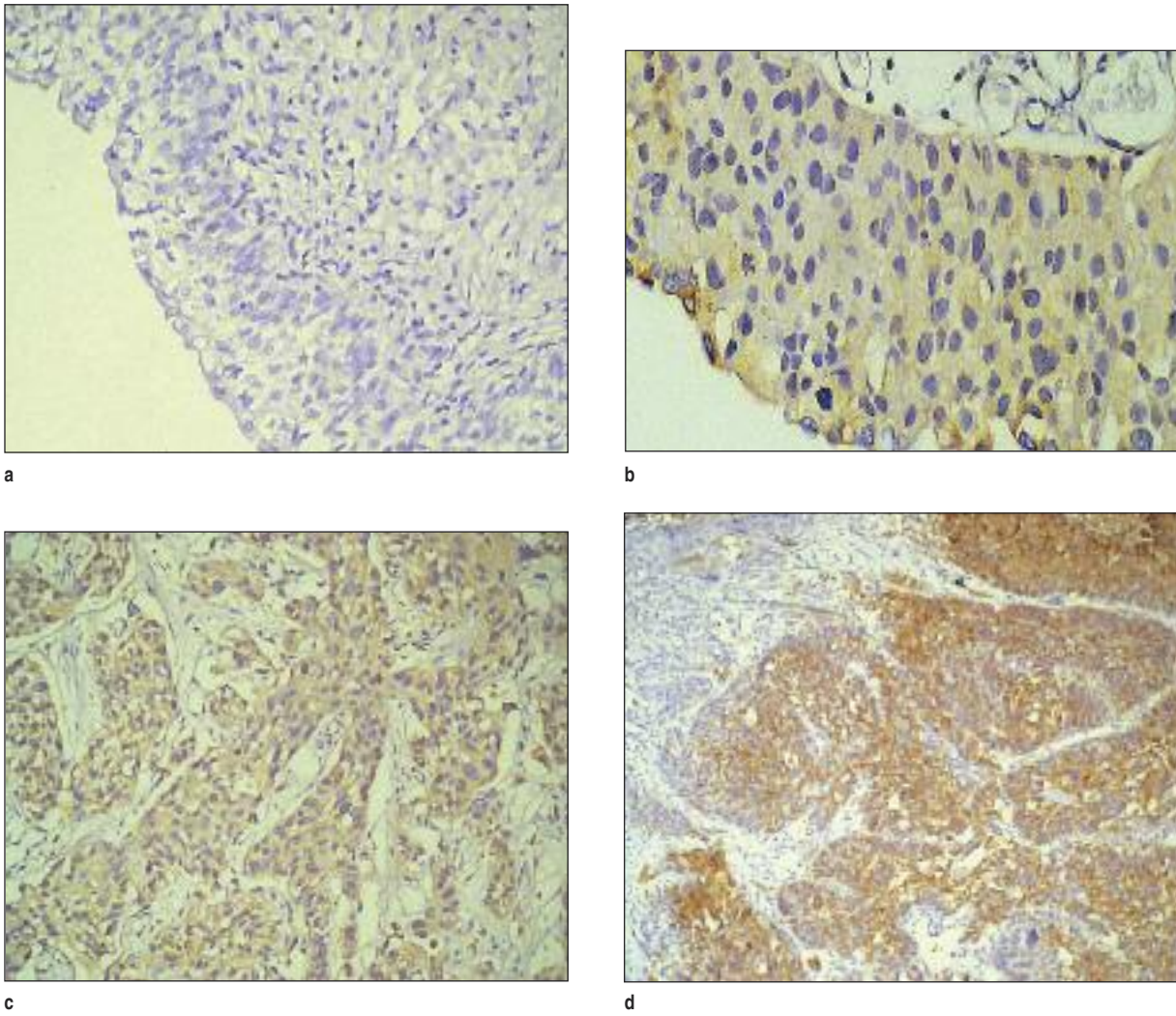

FIGURE 1: Immunohistochemical staining for AMACR showing; **a.** negative immunoreactivity in non-neoplastic urothelium (original magnification, x200), **b.** weak staining in carcinoma in situ (original magnification, x200), **c.** moderate (original magnification, x200), and **d.** strong cytoplasmic AMACR immunostaining in UC (anti-AMACR, original magnification, x100).

unt of tissue is limited, as in needle biopsies.[31] The levels of AMACR expression in both benign and malignant glands may vary in response to local changes in the concentration or metabolism of branched chain fatty acids. On the other hand, increased AMACR expression in benign glands may indicate a preneoplastic change at a biochemical level. AMACR immunoreactivity was also found in a significant number of precursor lesions such as high-grade prostatic intraepithelial neoplasia, ductal carcinoma in situ, and colonic adenomas.[24,27,32,33] AMACR immunostaining distinguished nondysplastic benign hepatocytes from dysplastic and malignant hepatocytes, and high grade dysplasia from reactive atypia in Barret esophagus.[34,35] In the present study, normal urothelium did not show positive staining with AMACR as in the previous studies.

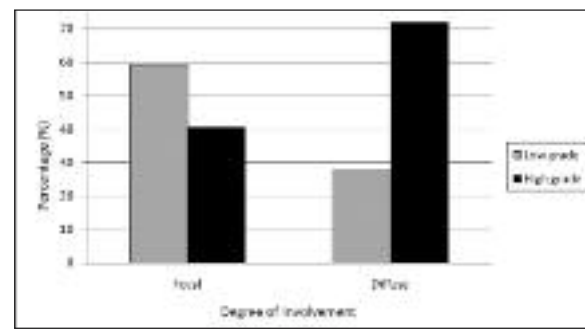

FIGURE 2: Degree of involvement in terms of tumor grade.

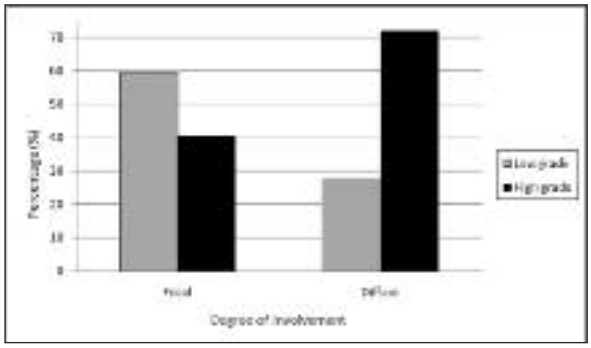

FIGURE 2: Degree of involvement in terms of tumor grade.

TABLE 2: Tumor grade and immunohistochemical staining.

	Negative	*Weak*	*Moderate*	*Strong*	*p*
Low grade	43 40.2%	38 35.5%	21 19.6%	5 4.7%	0.021
High grade	43 33.1%	35 26.9%	33 25.4%	19 14.6%	

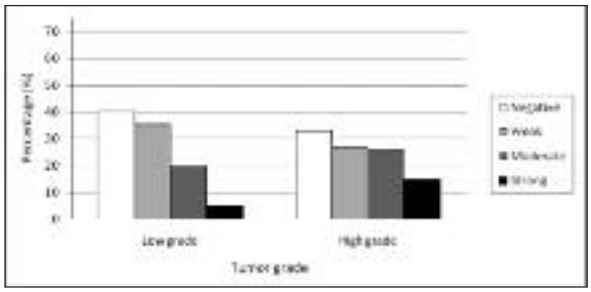

FIGURE 3: Distribution of immunohistochemical staining scores in terms of tumor grade.

TABLE 3: Tumor stage and immunohistochemical staining.

	Negative	**Weak**	**Moderate**	**Strong**	**p**
Ta	7 26.9%	11 42.3%	6 23.1%	2 7.7%	<0.001
Tis	45 58.4%	25 32.5%	5 6.5%	2 2.6%	
T1	25 24.5%	30 29.4%	33 32.4%	14 13.7%	
T2	9 28.1%	7 21.9%	10 31.2%	6 18.8%	

In the study of Went et al.,[20] normal urothelium was not stained with AMACR, but AMACR expression was found in 15% of 41 invasive UC and 11% of 44 non-invasive UC. AMACR may help us to distinguish normal from malignant urothelium.

The role for AMACR in tumor differentiation has been suggested by previous studies on various carcinomas. Li et al.[25] did not find a significant correlation between AMACR expression and grade in hepatocellular carcinomas. Well-differentiated and moderately-differentiated colonic adenocarcinomas expressed moderate to high levels of AMACR protein whereas poorly differentiated carcinomas had a lower intensity.[36] In the study of Witkiewicz et al.,[24] the authors found that AMACR expression was inversely related to the degree of tumor differentiation in breast cancer. They suggested that this intriguing role of AMACR may be tissue specific. AMACR expression was found more likely associated with the early stages of gastric cancer rather than advanced stages.[5] Gunia et al.[22] found a significant positive correlation between AMACR expression and higher tumor grades in UC. In all 60 randomly selected tumor samples, cytoplasmic expression of AMACR was found to be evenly distributed throughout the entire tumor tissue in a fairly homogeneous pattern. There was no focal or patchy staining pattern. In the series of Langner et al.[21] AMACR was expressed in about 50% of upper urinary tract tumors with 20% of cases showing extensive immunostaining. Extensive AMACR expression was detected predominantly in high-stage and high-grade tumors. Herein, we demonstrated a significant association of AMACR expression with grade and stage in transurethral resection specimens. Although nonsignificant, diffuse AMACR expression was notable in high grade UCs. These results are similar to those of previous studies. Strong AMACR staining may alert us for a higher tumor

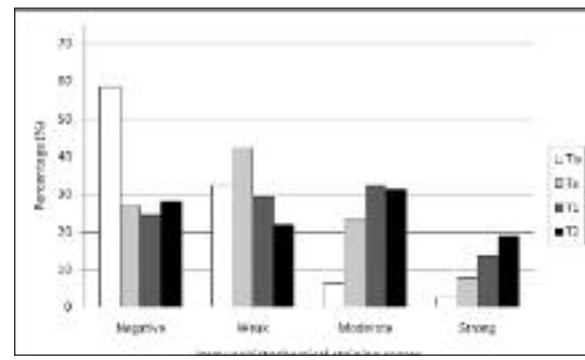

FIGURE 4: Distribution of tumor stage in terms of immunohistochemical staining scores.

stage, as well as strong and diffuse staining may reflect a high grade tumor. Close follow-up should be beneficial when strong AMACR staining of tumors in transurethral surgical resection materials were observed in early periods. Therefore this may show us that AMACR may be used as an additional indicator of unfavourable prognosis. Since bladder cancer has high recurrence rate and requires life-long treatment, early detection of the aggressive nature will allow us to initiate the appropriate therapy.

CONCLUSION

In summary, in this study we demonstrated that AMACR was expressed in a significant number of UCs. Its expression seems to be associated with certain pathologic characteristics such as tumor differentiation and stage. These results indicate that the AMACR expression may play an important role in urothelial cancer progression and may be used as an additional prognostic indicator of unfavourable prognosis in UC. Evaluation of AMACR expression might be useful in determining the aggressive capacity of these tumors at an earlier stage. It is not known yet whether AMACR could act as a future serum or urinary marker for UC. Further investigations may provide new insights for AMACR in UC.

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