

Expression of CD44s in Advanced Stage Esophageal Squamous Cell Carcinomas and Other Clinicopathological Prognostic Factors

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ABSTRACT

CD44s is an adhesion molecule which is a member of the cell adhesion molecules family hyaladherins. CD44s has some effects including tumor-endothel interaction, cell motility and migration, cell adhesion and tumor invasion, tumor progression, and metastasing. In this study, we aimed to evaluate the CD44s expression and some other prognostic factors in patients with esophageal squamous cell carcinoma.

Between 1999 and 2004, pathological specimens of 35 patients were examined by the Yuzuncu Yıl University (YYU) Medical Faculty, Pathology Department and other clinical and laboratory findings were collected from Oncology Department patient files.

CD44s staining was positive in 32 patients and negative in 3. The intensity of stained CD44s was positive in 30 and negative in 5 patients. Thirteen patients were well-differentiated, 18 were mid-differentiated, and 4 were poorly differentiated. Inflammatory reactions were observed in 23 cases. The median survival was 5.3 months and the one year, two year and five year survival rates were 34.2%, 8.6% and 2.9% respectively. Treatment modality, clinical stage and tumour size at the diagnosis time was significant at univariate analysis and only treatment modality was significant in multivariate analysis.

Very high CD44s expression was observed in sq cell esophageal cancer patients. CD44s may be an important marker in prognosis. Treatment modality was found as an independent factor on prognosis of esophageal cancer.

Key Words: Esophageal squamous cell carcinoma, CD44s, Immunohistochemistry, Prognosis

ÖZET

İleri Evre Özefagus Yassı Epitelyum Hücreli Karsinomlarında CD44s Ekspresyonu ve Diğer Klinikopatolojik Prognostik Faktörler

CD44s bir adezyon molekülüdür ve hyaladherinler olarak adlandırılan hücre adezyon molekülleri ailesinin bir üyesidir. CD44'ün tümör-endothel etkileşiminde, hücre motilitesi ve migrasyonunda, hücre adezyonunda ve tümör invazonu, progresyonu ve metastazında etkisi olduğu kabul edilmektedir. Bu çalışmada özefagus yassı epitelyum hücreli karsinomu olan hastalarda CD44s ekspresyon durumu ve diğer prognostik faktörlerin incelenmesi amaçlandı.

Yüzüncü Yıl Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı tarafından 1999 - 2004 yılları arasında raporlanmış 35 vakaya ait patoloji preparatları değerlendirildi ve hastalara ait klinik ve laboratuvar bulguları Onkoloji Bilim Dalı dosyaları taranarak elde edildi.

CD44s boyanma oranı 32 hastada pozitif, 3 hastada negatif, CD44s boyanma yoğunluğu 30 hastada pozitif, 5 hastada negatif olarak bulundu. Vakaların 13'ü iyi diferansiye, 18'i orta derecede diferansiye, 4'ü az diferansiye idi. İltihabi reaksiyon 23 olguda var, 12 olguda yoktu. Toplam 35 hastanın medyan genel sağ kalım süresi 5.3 ay olup, bir ve beş yıllık genel sağ kalım oranları ise %34.2 ile %2.9 idi. Tek değişkenli analizlerde sağkalımı tedavi modalitesi, klinik evre ve tanı anındaki tümör boyutu istatistiksel anlamlı olarak etkiliyordu. Çok değişkenli analizde ise yalnızca tedavi modalitesi istatistiksel olarak anlamlı bulundu.

Bu çalışmada ileri evre özefagus yassı epitelyum hücreli karsinomu olan hastalarda CD44s ekspresyonu çok yüksek bulundu. CD44s ekspresyonu önemli bir prognostik marker olabilir. Tedavi modalitesi ise özefagus kanserli hastalarda bağımsız bir prognostik faktör olarak bulundu.

Anahtar Kelimeler: Özefagus yassı epitelyum hücreli karsinomu, CD44s, İmmunohistokimya, Prognoz

INTRODUCTION

Esophageal cancer is an aggressive disease with a generally very poor prognosis and fatal outcome. The principal treatment is surgery alone or in combination with radiochemotherapy. Surgical cure rates are compromised by the fact that most patients are diagnosed at a late stage of disease because of the delayed onset of symptoms, by which time metastases and organ infiltration may have already occurred.¹ The propensity of Esophageal cancer for early metastatic dissemination is well known; even patients with the earliest stage disease are at risk.²

Adhesion processes are involved in all levels of the metastatic cascade. The overexpression of various adhesion molecules is associated with advanced stages of tumour growth, increased metastatic potential and a shortened disease-free and overall survival in various types of human malignancy.³ The CD44 cell-surface adhesion molecules form a family of transmembrane glycoproteins, including several isoforms mostly via hyaluronic acid.^{4,5} CD44 plays an important role in normal cell-cell adhesion, extracellular-matrix adhesion, lymphocyte homing, leukocyte activation, lymphopoiesis, embryogenesis, angiogenesis, wound healing, cell motility and migration, proliferation, inflammation and tumor metastasis.⁵⁻⁹ Related studies have shown that the expression of CD44 isoforms correlates with tumour progression and metastatic capability in human malignant diseases, such as head and neck cancer¹⁰, thyroid cancer¹¹ gastrointestinal cancer¹²⁻¹⁴, lung cancer¹⁵⁻¹⁷, cervical cancer¹⁸, endometrial cancer¹⁹, vulvar cancer²⁰, renal cancer^{21,22}, non-Hodgkin's lymphoma^{23,24} and malign melanoma.²⁵

In this study, we retrospectively evaluated the relationship between survival rates and immunohistochemically detected CD44s expression and other clinicopathologic data in 35 patients with esophageal squamous cell carcinoma (ESCC).

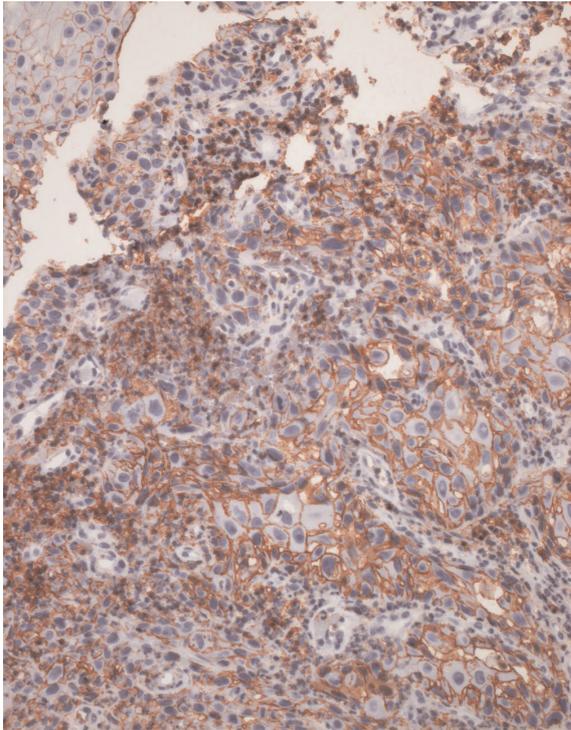
PATIENTS AND METHODS

Patients

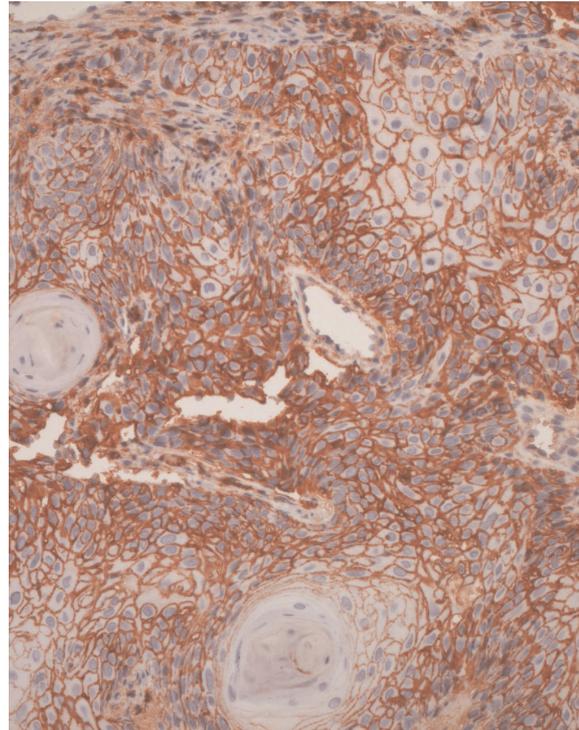
Between 1999 and 2004, 35 patients which were reported as advanced stage ESSC were included. Age, sex, performance status, tumor location, size and histological type of tumor, depth of tumor invasion to nearby structure/organ, and lymph node involvement and metastases, chemotherapy, radiotherapy applications and last control dates were recorded archives of Yüzüncü Yıl University Medical Faculty Pathology Department and Oncology Department patient files. All patients were inop thus tumour localization, size, invasion depth, lymph nodes and distant metastasis state were evaluated according to endoscopy reports, and MR and CT results.

Microscopic Characteristics

Hematoxylin-eosin stained archived preparations were re-examined. Tumors' histological grades and inflammatory infiltrations were studied. Each lesion was graded histologically according to the World Health Organization classification.²⁶ Beside inflammatory infiltration was also evaluated and noted as present or absent.



Picture 1. CD44 standard form was visualised upon immunohistochemistry (reddish, brown) in esophageal squamous cell carcinoma: CD44s staining intensity (+++) (Immunoperoxidase X 200)



Picture 2. CD44 standard form was visualised upon immunohistochemistry (reddish brown) in esophageal squamous cell carcinoma: The percentage of positive tumor cells staining with CD44s (+++) (Immunoperoxidase X 200)

CD44s Application and Evaluation

For immunohistochemical study, one paraffin block which is the best representative of the tumor without any necrosis or artefacts for each case were chosen, and sections of 4 μ were prepared for CD44 standard (CD44s) study. Sections were cut for CD44s, deparaffinized in xylene and dehydrated through a graded series of ethanols. They were then incubated in 3% H₂O₂ for 10 minutes and rinsed with distilled water. Antigen was applied for a total of 20 minutes with intervals after dilution with Target Retrieval Solution (1/10 diluted) at 750W. After waiting at room temperature for 20 minutes washed with distilled water, remained in PBS for 5 minutes and incubated with 1/50 diluted CD44s antibody (HCAM Ab-4 (Clone 156 3C 11) Mouse Anti-Human CD44s Antigen, LSAB, DAKO) for one hour antibody was washed in PBS for 10 minutes. Incubated with biotin solution for 15 minutes and remained in PBS 10 minutes. Incubated with Streptavidin peroxidase and again in PBS for 10 minutes, after that remained in AEC (3 amino-9-ethylcarbazole)

chromogen for 5 minutes, washed with distilled water. For contrast staining remained in Mayer's Hematoksilen, after all washed with tap water and closed with ultramound.

Immunohistochemical evaluation with the light microscope revealed red membranous staining with CD44s primary antibodies. Stainings were evaluated in two subgroups according to their intensity and amount of stained cells. For intensity of staining, no staining (0) and poor staining (+) were accepted as negative, moderate staining (++) and strong staining (+++) were accepted as positive (Picture 1). For amount of stained cells, 5% or less of tumor cells stained (0) and 5-25% stained (+) were accepted as negative, while 25-50% stained (++) and >50% stained (+++) were accepted as positive (Picture 2).

Statistical Analysis

Statistical analyses were done with the SPSS for Windows program. The primary determinant in this

Table 1. Analysis results of clinical, histopathological and immunohistochemical parameters related with general survival and prognosis.

Parameters	n (%)	Median Survival	1 year Survival%	2 Year Survival%	5 Year Survival %	P
Total Patients	35 (100)	5.3	34.2	8.6	2.9	
CD44s staining rate						
Negative	3 (8.6)	3.7	33.3	0	0	
Positive	32 (91.4)	5.3	34.4	9.4	3.1	0.4218
CD44s Staining intensity						
Negative	5 (14.3)	8.4	20.0	0	0	
Positive	30 (85.7)	5.2	36.7	10.0	3.3	0.4430
Histological Differentiation						
Well	13 (37.1)	5.2	23.1	7.7	7.7	
Moderate	18 (51.4)	3.7	38.9	11.1	0	
Poor	4 (11.5)	10.4	50.0	0	0	0.8367
Inflammatory reaction						
No	12 (34.3)	3.7	33.3	0	0	
Yes	23 (65.7)	5.3	34.9	13.0	4.3	0.4916
Sex						
Male	14 (40.0)	2.77	50.0	7.14	0	
Female	21 (60.0)	5.27	23.8	9.52	4.8	0.8195
Age (Median/ Range)	(53 / 35-69)					
<50	14 (40.0)	3.7	42.8	7.1	0	
≥50	21 (60.0)	8.1	28.6	9.5	4.8	0.9651
Performance Status						
0-1	12 (34.3)	16.0	58.3	16.7	8.3	
2-3	23 (65.7)	3.7	21.7	4.4	0	0.0530
Treatment Modality						
Best supportive care	3 (8.6)	1.8	0	0	0	
Chemotherapy	21 (60.0)	3.7	23.8	0	0	
Chemoradiotherapy	11 (31.4)	17.0	63.6	27.3	9.1	0.0065
						0.018*
Depth of Invasion						
T3	14 (40.0)	8.1	35.7	14.3	7.1	
T4	17 (48.6)	8.4	41.2	5.9	0	0.5634
Clinical Stage						
Stage III	19 (54.3)	12.5	52.6	15.8	5.3	
Stage IV	16 (45.7)	2.3	12.5	0	0	0.0191
						0.746*
Tumor size						
≤5 cm	9 (25.7)	16.0	66.7	22.7	11.1	
>5 cm	26 (74.3)	3.7	23.0	3.8	0	0.0210
						0.092*

* Cox proportional regresyon

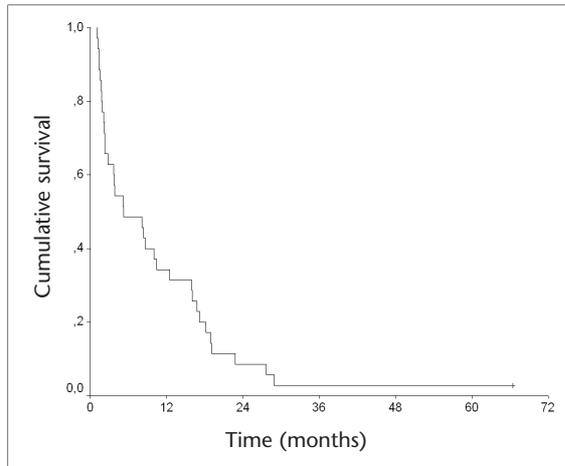


Figure 1. Overall survival curve of 35 patients with esophageal squamous cell carcinoma.

study was survival time, as measured from the date of biopsy until the time of the last follow up visit or death. Survival curves for 35 patients were constructed according to the Kaplan-Meier method²⁷, and curves were drawn and the effect of parameters with potential prognostic importance on survival was estimated by the log-rank test in univariate analysis. The prognostic significance of individual parameters in multivariate analysis was determined by using Cox's proportional-hazards model.²⁸ A p value of less than 0.05 were considered significant.

RESULTS

Thirty five patients with squamous cell carcinomas of the esophagus were included in this study. Patients were treated from 1999 through 2004. The median age was 53 (range: 35-69 years), with 14 male (40.0%) and 21 female (60.0%). Table 1 summarizes the clinical, histopathological and immunohistochemical parameters of the 35 patients. Nineteen patients (54.3%) were clinical stage III and 16 patients (45.7%) were stage IV. Median tumor size was 7 cm in diameter (range between 4-11 cm). Nine tumors (25.7%) were smaller than 5 cm, 26 (74.3%) were larger than 5 cm. Thirteen patients with (37.1%) well-differentiated, 18 patients (51.4%) with moderate differentiated, and 4 patients (11.5%) with poor differentiated tumors. Inflammatory reactions were present in 23 cases (65.7%).

Immunohistochemical Staining Results

CD44s was evaluated regarding the both of amount of staining and intensity of staining. Besides, it was seen that there was no or very little staining with CD44s in "glob korne" structures in the middle of solid areas of ESCC. According to CD44s staining 32 cases (91.4%) were positive and 3 cases (8.6%) were negative, according to CD44s staining intensity 30 cases (85.7%) were positive and 5 cases (14.3%) were negative.

Prognosis

The median follow-up of 35 patients was 5.3 months (range: 1-66 months). At the last control only one patient was alive, all of the remaining were died. The one year, two year and five year survival rates were 34.2%, 8.6% and 2.9% respectively (Figure 1). Univariate analysis results of clinical, histopathological and immunohistochemical parameters related with overall survival were shown in the Table 1.

Median overall survival for CD44s negative patients was 3.7 months, survival rates at 1 year and 5 years were 33.3% and 0% respectively, For positive patients these results were 5.3 months, 34.4% and 3.1% respectively (p= 0.4218).

Median overall survival for CD44s intensity negative patients was 8.4 months, survival rates at 1 year and 5 years were 20% and 0% respectively. For positive patients these results were 5.2 months, 36.7% and 3.3% respectively (p= 0.4430).

Median overall survival for patients, that was received only best supportive care, was 1.8 months, survival rates at 1 year and 5 years were 0% and 0% respectively. Patients who were treated only by chemotherapy, these results were 3.7 months, 23.8% and 0% respectively. For chemoradioterapy patients, these results were 17 months, 63.6% and 9.1% respectively (p= 0.0065) (Figure 2).

Treatment modality, clinical stage and tumour size at the time of diagnosis were statitically significant in univariate analysis and only treatment modality (p= 0.018) was significant in cox regression multivariate analysis (Table1).

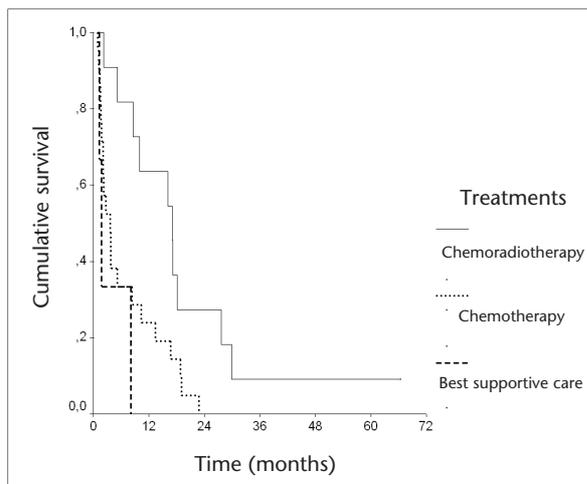


Figure 2. Relation between treatment modality and overall survival curves of 35 patients with esophageal squamous cell carcinoma (p: 0.0065).

DISCUSSION

Role of CD44 and variants on cancer cells, were evaluated in many studies. When compared to control equivalents, there was increased expression of CD44 and its isoform in malign tissues of these diseases; thyroid cancers (CD44s and v6), lung cancer (squamous cell carcinoma CD44v5 and v6, adenocarcinoma CD44v6, small cell carcinoma CD44v10), hepatocellular carcinoma (CD44s, v5, v7, v8, v10), renal cell carcinoma (CD44s), ovary carcinoma (CD44s, v3, v4, v5, v6, v10), endometrial cancer (CD44v6) and malign melanoma (CD44v5).^{10-12,17,18,21,25} But there are very limited data regarding esophageal cancer and CD44s expression. In a Japanese study CD44 was observed in 99% of esophageal squamous cell cancer patients (n= 233).²⁹ Castella et al³⁰ reported that ratio for esophageal adenocancers as 75% (n= 20). In our study we also observed the very high expression of CD44s in esophageal squamous cell cancers just like as Japanese study. There was no statistically significant difference both in CD44s amount (p= 0.4218) and intensity (p= 0.4430) of staining. Due to large number of positivity of CD44s expression our cases, statistical comparison with only 3 CD44s negative patients is not clinically meaningful. So we can not comment on prognostic significance of CD44s expression. CD44s expression positivity, in most of our

cases, and in reported two series, lead us to think that CD44s may be an important marker for prognosis and may explain general poor prognosis of esophageal cancers.

Relationship between increase in CD44 expression and more advanced tumor is another indirect evidence of CD44s participation in malign process. This idea is best described in a study with colorectal cancer patients. Polyps of patients with early adenomas showed limited CD44v6 expression, while in late adenomas this number increased up to 50%. While the disease progressed from non-metastatic to metastatic, CD44v6 positive patient rates raised to 80% from 50%.¹² Some other studies also revealed that CD44s and v6 has increased expression in metastatic phases of colorectal and gastric cancers.^{31,32}

Direct relationship between increased expression of CD44 and its isoforms, and progression to metastatic phase is also shown in tumors including papillary thyroid carcinoma (CD44v6), renal cell carcinoma (CD44s, v6 and v10), and breast cancer (CD44v3, v4, v5, v6, v7, v10).³³⁻³⁵ On the other hand, loss of CD44 expression in some cancers including head and neck squamous cell carcinoma (CD44v6 and v9), non-small cell lung cancer (CD44s and v6), prostate cancer (CD44s and v6) and ovary carcinoma (CD44v3, v4, v5, v6, v7, v9, v10) has been reported. Thus, on contrary to common belief, loss of CD44 expression can also be related to progression of disease.^{36,37}

In our study univariate analysis, the parameters that significantly effected overall survival included treatment modality (p= 0.0065), clinical stage (p= 0.0191) and tumor size (p= 0.0210). In multivariate analysis, only the treatment modality (p= 0.018) was found to be statistically significant.

In conclusion, very high (91.4%) CD44s expression was observed in squamous cell cancer of esophagus patients. Our study did not show any prognostic significance of CD44s, this might be low patient number in our cohort. Only treatment modality was found to be significant prognostic factor on esophageal cancer in our study. However, further studies with large patient populations are needed to elucidate the role of CD44s expression in prognosis of esophageal cancer.

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