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Serum and Urine Levels of Vascular Endothelial Growth Factor as Prognostic Markers in Patients with Bladder Cancer

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Abstract

Background: Bladder cancer is the second most common urinary cancer after prostate cancer. Recent studies have shown higher serum and urinary vascular endothelial growth factor (VEGF) in increased angiogenesis. In this study, the mean serum and urine level of VEGF was assessed in patients with bladder cancer.

Methods: In this case-control study, 46 patients with bladder cancer referred to Imam-Khomeini Hospital in Tehran, Iran and 38 subjects as control, were enrolled and the mean serum and urine level of VEGF was assessed and compared between the groups.

Results: The mean serum level of VEGF was 478.7, 518.4, and 648.1 in control, low-grade, and high-grade groups, respectively, with no significant difference (P=0.175). The mean urine level of VEGF was 414.2, 968.3, and 848.4 in control, low-grade, and high-grade groups, respectively, with significant difference (P=0.010).

Conclusion: The mean urine level of VEGF in patients with bladder cancer is higher than healthy subjects.

Keywords: Vascular endothelial growth factor (VEGF), Bladder cancer, Tumor marker

Introduction

Bladder cancer is the second most common urinary cancer after prostate cancer and remains to be the sixth most common cause of cancer-related death.[1] Despite the current advances in screening and multimodal therapy, bladder cancer prognosis is still poor. Currently, several prognostic factors such as tumor size, grade, stage, and vascular invasion have been extensively studied.[2-4] Angiogenesis, as a source of oxygen, nutrients, and growth factors for tumor cells, plays an important role in tumor growth and metastasis.[5] Vascular endothelial growth factor (VEGF) is a 45-kilodalton homodimeric glycoprotein, which induces angiogenesis and plays a major role in predicting the poor prognosis of various cancers such as lung, liver, stomach, ovary, and osteosarcoma cancer.[6-15] VEGF exists in four different forms. The main

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ligand for angiogenesis is A-VEGF which binds to VEGFR-1 and VEGFR-2 receptors and generates major signals for angiogenesis. VEGFR-3, VEGF-D, and VEGF-C are associated with lymphangiogenesis. VEGF initially interacts with VEGFR-2 and stimulates tumor cell proliferation and migration, and vascular permeability. Subsequently, it interacts with VEGFR-1, resulting in the formation of new vascular tubules.[16] However, the prognostic value of VEGF in bladder cancer is yet to be elucidated. Yang et al.[17] and Theodoropoulos et al.[18] initially introduced the association of VEGF with poor bladder cancer prognosis. However, contradictory results have also been reported.[19-21] On the other hand, cystoscopy is a gold-standard approach to assess bladder cancer, in which the compliance rate in patients is low and there is a false negative rate of 10 to 40 %.[11] Therefore, the use of serum and urinary markers is conducive. Cytology has a high specificity (93%) and a low sensitivity, especially in low-grade, low-stage tumors.[12] Adjunctive use of urinary markers results in higher diagnostic value. VEGF, a factor initially known as a promoter of endothelial cell proliferation and migration,[22] was shown to be associated with bladder cancer.[23]

Recent studies have shown higher serum and urinary VEGF in increased angiogenesis.[24-27] In this study, the mean serum and urine level of VEGF was assessed in patients with bladder cancer. Further evaluation was the association between invasion, grade, and prognosis.

Materials and Methods

In this case-control study, 46 consecutive patients with bladder cancer (TCC type), hospitalized in the Imam-Khomeini Hospital and 38 controls with hematuria, due to benign diseases such as UTI and BPH, were enrolled. The two groups were matched for age and gender. Also, the following characteristics were assessed: age, gender, size, type of surgery, lymphovascular invasion, perivesical fat involvement, lymphatic involvement in CT scan, muscular involvement, marginal involvement, pathologic grade, smoking, and recurrence. Venous blood (10 mL) and urine sample (100 mL) were obtained from both groups. The serum and urine levels of VEGF were then assessed and compared between the groups. Urine and serum VEGF levels were assessed using the same kit. Concentration of VEGF was evaluated using a commercially available ELISA kit (eBioscience, USA), according to the manufacturer's instruction. The mean VEGF levels were reported in pg/mL.

Data analysis was performed by SPSS (version 13.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Pearson, Independent-Sample-T, and ANOVA tests were used and *P* values less than 0.05 were considered statistically significant.

This project was approved by the Ethics Committee of the Medical Research Department of Tehran University of Medical Sciences (TUMS) (Ethics code: IR.TUMS.REC.1396.2932).

Results

Table 1 shows the mean and standard deviation (SD) of the serum and urine level of VEGF in low-grade and high-grade TCC, as well as, control group. Patients were male in 81.5%, 84.2%, and 78.9% of low-grade TCC, high-grade TCC, and control group, respectively *(P*>0.05).

The mean (SD) serum level of VEGF was not significantly different between the groups (*P*=0.175). The mean (SD) urine level of VEGF was 414.2 (272.4), 968.3 (1089.1), and 848.4 (822.5) in control, low-grade, and high-grade groups, respectively, which shows a significant difference (*P*=0.010).

The age and size of tumor had no effect on serum and urine levels of VEGF (*P*>0.05). The effects of categorical variables on serum and urine levels of VEGF are shown in table 1, where no factors associated with the urine levels of VEGF are observed.

Discussion

The association of high serum and urine levels of VEGF with angiogenesis has been reported. In this study, the association of high serum and

Table 1. Effects of categorical variables on S- VEGF* and U-VEGF**

		S- VEGF			U-VEGF		
		Mean	**SD**	***P*-value**	**Mean**	**SD**	***P*-value**
Gender	Male	514.89	323.33	*P*=0.368	763.49	323.33	*P*=0.347
	Female	593.00	333.31		380.29	333.31	
Muscle Invasion	Positive	659.74	396.52	*P*=0.161	1053.65	396.52	*P*=0.186
	Negative	498.28	342.18		805.46	342.18	
Margin	Positive	856.92	486.25	*P*=0.662	579.52	486.25	*P*=0.429
	Negative	711.50	381.04		981.57	381.04	
Perivesical fat invasion	Positive	780.87	427.40	*P*=0.031	1177.64	427.40	*P*=0.322
	Negative	506.34	334.08		837.41	334.08	
Lymphovascular Invasion	Positive	760.92	416.46	*P*=0.007	1237.47	416.46	*P*=0.091
	Negative	461.24	299.68		731.94	299.68	
Surgical Lymph Node	Positive	790.43	425.97	*P*=0.918	899.33	425.97	*P*=0.652
	Negative	762.20	452.76		678.20	452.76	
Positive Lymph Node in CT	Positive	828.00	343.67	*P*=0.037	1165.68	343.67	*P*=0.471
	Negative	529.69	357.52		884.81	357.52	
Recurrence	Positive	639.91	379.10	*P*=0.061	933.02	379.10	*P*=0.883
	Negative	416.74	317.67		886.19	317.67	
Smoking	Positive	615.11	394.54	*P*=0.190	967.75	394.54	*P*=0.574
	Negative	449.83	281.75		779.97	281.75	

*Serum-Vascular Endothelial Growth Factor; **Urine-Vascular Endothelial Growth Factor

urine levels of VEGF with bladder cancer and also the grade and invasion of the tumor were assessed. The results revealed that the mean serum level of VEGF was 478.7, 518.4, and 648.1 in control, low-grade, and high-grade groups, respectively, which shows no significant difference. However the mean urine level of VEGF was 414.2, 968.3, and 848.4 in control, low-grade, and high-grade groups, respectively, indicating a significant difference.

Bernardini et al.[13] assessed 58 patients with bladder cancer and reported serum levels of VEGF 248 pg/mL and 100 pg/mL in case and control groups, respectively, which is significantly different between the two groups. The serum levels of VEGF were related to tumor stage, grade, vascular invasion, carcinoma in situ, and metastasis. However, in the present study, there was no difference regarding the serum levels of VEGF, which may be due to lower sample size. Bian et al.[24] assessed 100 patients with bladder cancer concerning urine levels of VEGF and reported a sensitivity of 69% versus 88% in those with other causes of hematuria. In the current research, the mean urine level of VEGF was 414.2, 968.3, and 848.4 in control, low-grade, and high-grade groups, respectively, hence the significant difference among the groups.

Urquidi et al.[14] compared the urine levels of VEGF in control and bladder cancer groups. They reported a sensitivity and specificity of 83 and 87 %, respectively. Goodison et al.[25] reported a high sensitivity and specificity of 90 and 97%in the combination of VEGF with APO-E and interleukin-8. In a meta-analysis, Huang et al.[26] reported that VEGF was related to disease-free survival and disease-specific survival in patients with bladder cancer. However, the urine VEGF was associated with higher grades in the present study and recurrence was not a related factor.

Li et al.[27] assessed the association of C-VEGF and CT-scan findings and lymphatic metastasis and reported higher levels in tumor versus normal epithelium and those with lymphatic metastasis.

Similarly, in our study, the serum VEGF was related to RC surgery, perivesical fat, lymphovascular invasion, and lymphatic involvement in CT-scan.

Totally, according to the obtained results, it may be concluded that the mean urine level of VEGF in patients with bladder cancer is higher than healthy subjects. Therefore, the changes in the urine level of VEGF following treatment may imply the necessity of using new drugs for the treatment of bladder cancer and propose a prognostic factor. However, further studies with larger sample sizes, multicenter sampling and comparison with other laboratory tests would result in more definitive results.

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Conflict of Interest

None declared.

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