

# The Comparison between Human Leukocyte Antigen System Incidence in Patients with Bladder Cancer and Normal Controls

Siavash Falahatkar, Hadiseh Donyamali, Mohammad Ali Joafshani, Reza Shahrokhi Damavand, Saba Hoda, Samaneh Esmaeili, Keivan Gholamjani Moghaddam, Sara Nikpour

**Purpose:** To determine the frequency of human leukocyte antigen (HLA)-B5 in patients with bladder cancer compared with normal population.

**Materials and Methods:** In this cross sectional study, from November 2009 until November 2010, 35 patients with pathologic diagnosis of bladder cancer who referred to urology clinic of Razi Hospital were studied. Also, 130 healthy transplant donation volunteers who referred for HLA-typing to Guilan Blood Transfusion Organization, were selected. Inclusion criterion was pathologic diagnosis of bladder cancer regardless of stage and grade of tumor. Exclusion criteria were presence of other urologic diseases. The information of these cases was extracted from medical records, collected and analyzed.

**Results:** HLA-B5 was positive in 34.3% of the patient group and in 39.2% of the controls. Statistical analysis showed no significant association between HLA-B5 and bladder cancer ( $P = .15$ ). There were no significant differences between grade ( $P = .107$ ) and relapse ( $P = .327$ ) of bladder tumor with presence of HLA-B5.

**Conclusion:** There was no significant association between HLA-B5 and bladder cancer. The grade and the relapse of tumor had no association with presence or absence of HLA-B5.

**Keywords:** antigen presentation; histocompatibility antigens class I; urinary bladder neoplasms; humans; HLA-B5 antigen.

*Corresponding author:*

Hadiseh Donyamali, MD  
Urology Research Center,  
Guilan University of Medical  
Sciences, Rasht, Iran.

Tell: 0098 912 201 4721  
Fax: 0098 131 552 5259

E-mail: hadiseh\_donyamali@  
yahoo.com

Received April 2012  
Accepted December 2012

## INTRODUCTION

Cancer is a public health problem worldwide, predominantly in developing countries. In all types of malignancies, urogenital cancers have an important role in increasing mortality. Every year 132,000 people die from bladder cancer and its mortality rate is 10 per 100,000 in men and 2.4 per 100,000 in women.<sup>(1)</sup> The incidence of urogenital cancers varies in different regions of the world.<sup>(2)</sup> Bladder cancer is the ninth most common cancer in the world<sup>(3)</sup> and it is the fourth most common cancer in males in Iran.<sup>(4)</sup> In middle-aged and elderly men, bladder cancer is the second most common cause of malignancy after prostate cancer.<sup>(5)</sup> According to Iranian Center for Disease Control and Prevention, bladder cancer encompasses 7.04% of all cancers in Iran. The incidence rate of bladder cancer has been reported 11.30 in males and 2.86 females per 100,000. Amazingly, in some areas of Iran the incidence of this cancer reaches to as high as 15.9 per 100,000.<sup>(6)</sup>

Despite significant advances in the prevention of disease progression and improvement of survival, treatment of bladder cancer still remains a challenge. The main problem is that, patients who will have a benign clinical course of the disease are not distinguishable from those who will experience an invasive course and conventional histopathologic examination is not able to predict the biological behavior of bladder tumors correctly. Prognostic markers could help the physician to differentiate the superficial bladder cancer from invasive.<sup>(7,8)</sup>

Recently some studies demonstrated that some specific cell surface antigens are associated with poorer prognosis.<sup>(9)</sup> Human leukocyte antigen (HLA) class I molecules has an important role in the cell-mediated immune system, particularly as antigen-presenting molecules for cytotoxic T lymphocytes (CTLs). CTL can identify antigenic peptides presented on the cell surface with HLA class I molecules, and kill the target cell. Down-regulation of HLA class I was found to be involved in the immune escape of malignant tumors. It is reported that this event is noted in malignant tumors such as malignant melanoma, colorectal, lung, and ovarian cancers, and would affect survival of some patients with these diseases.<sup>(10)</sup> Distribution of HLA antigens varies in different populations. For instance there is complete absence of an antigen in a population (e.g., HLA-A1 in the Japanese race)

and the exclusive presence of an antigen in a specific ethnic population (e.g., HLA-BW24 in black).<sup>(11)</sup> Levin and colleagues investigated HLA class I expression in 33 patients with bladder transitional cell carcinoma (TCC) and its correlation with tumor differentiation and patients. They reported that the 5-year survival in patients who were positive for HLA class I, was significantly better (74% vs. 36%). These results suggest a possible role for expression of HLA class I, as a prognostic factor in patients with bladder tumor.<sup>(14)</sup> HLA class I expression has shown as a prognostic marker for muscle-invasive bladder cancer.<sup>(10)</sup>

Since HLA-B5 has the highest prevalence in the HLA-B alleles in Iran,<sup>(11)</sup> and some studies suggest a positive relationship between bladder cancer and HLA-B5, we study the prevalence of HLA-B5 in patients with bladder cancer and compare the results with HLA-B5 prevalence in healthy kidney donors.

## MATERIALS AND METHODS

### *Study Population*

From November 2009 until November 2010, 35 patients with pathologically confirmed bladder cancer were enrolled in this study. Also 130 healthy kidney donors, who referred for HLA-typing were served as controls. Inclusion criterion was pathologically confirmed bladder cancer, regardless of tumor stage and grade. Exclusion criterion was presence of other urologic diseases.

The following data were collected: age, sex, social and family history, occupational exposure related to bladder cancer; and type of drinking water. All patients followed up by cystoscopy every 3-month, and the presence of tumor were defined as a recurrence. Comparison was performed using chi-square test. The statistical package for the social science (SPSS Inc, Chicago, Illinois, USA) version 19.0 was used for statistical analysis. *P* value <0.05 was considered significant.

## RESULTS

The mean age of patients was  $45.13 \pm 51.65$  years (age range, 36 to 85 years). Of study subjects 34 (97%) were male and one was female. Transitional cell carcinoma (TCC) was the most common type of bladder cancer (94.3%). Two patients (5.7%) had a family history of bladder cancer. In 8 cases (22.9%), history of occupational exposure to industries of

**Table 1.** Grade and tumor recurrence distributions of 35 patients with bladder cancer.

Tumor characteristics n (%)	HLA-B5		Total	P
	Positive (n = 12)	Negative (n = 23)		
Grade 1	2 (16.7)	6 (26.1)	8 (22.9)	.107
Grade 2	8 (66.6)	7 (30.4)	15 (42.9)	
Grade 3	2 (16.7)	10 (43.5)	12 (34.3)	
Recurrence (+)	4 (33.4)	3 (13)	7 (20)	.327
Recurrence (-)	8 (66.6)	20 (87)		

Key: HLA, human leukocyte antigen system.

rubber, paint, textiles, resins and aluminum was positive. The relationship between tumor grade and recurrence rate with HLA-B5 are shown in Table 1.

Of cases 11 (31.4%) had stage Ta, 16 (45.7%) had stage T1 and 8 (22.9%) had stage T2 tumors.

HLA-B5 was positive in 34.3% (12) of patients group and in 39.2% (51) of controls (Table 2). Statistical analysis demonstrated that there were no significant differences in the frequency of HLA-B5 in patients with bladder cancers as compared with the healthy population ( $P = .15$ ). As well there was no statistical association between tumor grade and HLA-B5 ( $P = .107$ ) and also there was no significant correlation between recurrence of tumor and HLA-B5 ( $P = .327$ ) (Table 1).

## DISCUSSION

After confirming the diagnosis of bladder cancer, it is advantageous to determine the likely clinical course and survival outcome. The HLA genes are one of the most polymorphic loci in the human genome. The HLA complex on chromosome 6 contains more than 200 genes, over 40 of which encode leukocyte antigens. The HLA genes express on the surface of the T lymphocytes and, hence, play a major role in the regulation of the immune system. HLA molecules have a defending role by detecting self from non-self antigens. The HLA genes class I and II are different in structure and function. The involvement of the HLA system in the development of cancer is still scantily understood. Cancer cells express a number of genes that normal cells do not, and peptides from some of the protein products of these genes bind to HLA molecules. There are different reasons that the T-cell responses which motivated by these HLA-peptide complexes are not

**Table 2.** HLA-B5 frequency in patients with bladder cancer and healthy group.

	Negative	Positive
HLA-B5 in healthy group, n (%)	79 (60.8)	51 (35.2)
HLA-B5 in patient group, n (%)	23 (65.7)	12 (34.3)
	$P = .15$	

Key: HLA, human leukocyte antigen system.

effective enough to eradicate the cancer cells. One reason for the incompetence of the immune response against tumor-associated antigens is that cancer cells tend to down-regulate the expression of some HLA molecules or stop expressing them totally, therefore making them poor targets for cytotoxic T cells. On the other part, the loss of HLA molecules from the surface of cancer cells can initiate the activation of natural killer cells, which make a backup system when the cytotoxic T cells fail.<sup>(15)</sup>

Associations between HLA antigens and susceptibility to different diseases have provided new insight into pathogenetic mechanisms which put someone at higher risk of acquiring some diseases.<sup>(16)</sup> Because of different distribution of antigens in different countries, it is requisite to accommodate the antigens on the base of population. One of the strongest associations is between HLA-B27 and ankylosing spondylitis.<sup>(15)</sup> Also Falahatkar and colleagues in a study on patients with vesicoureteral reflux (VUR) found significant correlation between this disease and HLA-B9 and HLA-B44.<sup>(17)</sup> Studies of the association between HLA antigens and bladder cancer have provided inconsistent results, but do recommend that several HLA antigens may be associated with a risk of developing bladder cancer. Some studies such as Herring and colleagues and colleagues demonstrated positive association between HLA-B5 and bladder carcinoma.<sup>(12,13)</sup> Herring and colleagues in a study on 101 patients with bladder TCC found that the antigenic frequency of HLAB5 and HLACW4 is higher in patients than in healthy individuals.<sup>(12)</sup>

Tokuc and colleagues in a review of HLA antigens in 55 patients with bladder TCC found that HLAB5 incidence is increased and HLABW35 incidence is decreased and this difference is more noticeable in recurrent tumors.<sup>(13)</sup> The result of our study is in disagreement with the findings of Herring and colleagues investigation, who found a two-fold increase in the frequency of HLA-B5 in patients with bladder carci-

noma.<sup>(12)</sup> However, our study finding is in accord with the observations of Braf and colleagues, Lytton et and colleagues and Saunders and colleagues, who found no change in frequency of the HLA-B5 in patients with bladder carcinoma.<sup>(18,19,20)</sup> Some of the contrary results described in different studies may be due to the use of different populations with different risk factors. HLA antigen frequencies vary in different ethnic groups and in different geographical regions.<sup>(16)</sup> Our study limitations are very small sample sizes and lack of organized follow up program after treatment to determine prognosis and survival of patients considering their HLA-B5 situation. Further large scale studies in different ethnic group are needed to draw final conclusion.

## CONCLUSION

This study shows no significant association between HLA-B5 and bladder cancer. There is no association between the grade and recurrence rate of tumor with the presence or absence of HLA-B5, too.

## ACKNOWLEDGEMENT

We thank all participants and Guilan Blood Transfusion Organization that provided the healthy group (kidney donors) data. This study was supported by Urology Research Center of Guilan Medical University.

## CONFLICT OF INTEREST

Non declared.

## REFERENCES

1. Yavari P, Sadrolhefazi B, Mohagheghi MA, Mehrazin R. A Descriptive Retrospective Study of Bladder Cancer at a Hospital in Iran (1973-2003). *Asian Pac J Cancer Prev.* 2009;10:681-4.
2. Akbari ME, Hosseini SJ, Rezaee A, Hosseini MM, Rezaee I, Sheikhvatan M. Incidence of genitourinary cancers in the Islamic Republic of Iran: a survey in 2005. *Asian Pac J Cancer Prev.* 2008;9:549-52.
3. Badar F, Sattar A, Meerza F, Irfan N, Siddiqui N. Carcinoma of the urinary bladder in a tertiary care setting in a developing country. *Asian Pac J Cancer Prev.* 2009;10:449-52.
4. Kolahdoozan S, Sadjadi A, Radmard AR, Khademi H. Five Common Cancers in Iran. *Arch Iran Med.* 2010;13:143-6.
5. Vercelli M, Quaglia A, Parodi S, Crosignani P. Cancer prevalence in the elderly. ITAPREVAL Working Group. *Tumori.* 1999;85:391-9.
6. Sakhssalim N, Hosseini SY, Basiri A, Eshrati B, Mazaheri M, Soleimanirahbar A. Prominent bladder cancer risk factors in Iran. *Asian Pac J Cancer Prev.* 2010;11:601-6.
7. Schenkman E, Lamm DL. Superficial Bladder Cancer Therapy. *ScientificWorldJournal.* 2004;4 Suppl 1:387-99.
8. Stein J, Grossfeld G, Ginsberg D, et al. Prognostic markers in bladder cancer: A contemporary review of the literature. *J Urol.* 1998;160:645-59.
9. Amirghofran Z, Khezri AA, Mohammadi S. Expression of HLA-class I and II, ICAM-1 and CD44 Antigens in Transitional cell carcinoma of Bladder. *Iran J Med Sci.* 1997;22:145-51.
10. Homma I, Kitamura H, Torigoe T et al. Human leukocyte antigen class I down-regulation in muscle-invasive bladder cancer: Its association with clinical characteristics and survival after cystectomy. *Cancer Sci.* 2009;100:2331-34.
11. Nikbin B. Immunogenetic. In: *Immunology.* Mashhad: Astan Ghods Razavi; 1994. p. 321-68
12. Herring DW, Cartwright RA, Williams DD. Genetic associations of transitional cell carcinoma. *Br J Urol.* 1979;51:73-7.
13. Tokuc R, Akdas A, Ozerkan K, Remzi D. Association between HLA antigens and bladder tumors. *Eur Urol.* 1987;13:207-9.
14. Homma I, Kitamura H, Torigoe T, et al. Human leukocyte antigen class I down-regulation in muscle-invasive bladder cancer: its association with clinical characteristics and survival after cystectomy. *Cancer Sci.* 2009;100:2331-4.
15. Klein J, Sato A. The HLA System. *Adv Immunol.* 2000;343:782-86.
16. Romano PJ, Bartholomew M, Smith PJ, et al. HLA antigens influence resistance to lung carcinoma. *Hum Immunol.* 1991;31:236-40.
17. Falahatkar S, Mokhtari GH, AsKari SA. Correlation between HLA system and primary Vesicoureteral Reflux. *MJIRC.* 2005;8:13-5.
18. Braf ZF, Gazit E, Many M. HLA-A and HLA-B antigens in transitional cell carcinoma of the bladder. *J Urol.* 1979;122:465-6.
19. Lytton B, O'Toole C, Tiptaft R, Festenstein H, Batchelor JR. Histocompatibility Testing in Patients with Carcinoma of the Bladder. *Cancer.* 1993;52:645-47.
20. Saunders P, Anderson S, Stogdill V, Lamm D. HLA-A, B and DR in Caucasians with transitional cell carcinoma of the bladder. *Tissue Antigens.* 1983;22:389-92.