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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Correlation of urinary histamine concentration with mast cell density in patients with non-muscle invasive urothelial bladder carcinoma

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SUMMARY

Introduction/Objective There are no reliable tumor markers for non-invasive detection of bladder cancer and monitoring patients after treatment. The role of mast cells in oncogenesis is still unknown.

Methods Our study is an open, longitudinal, prospective follow-up study conducted over six months after surgical treatment of bladder cancer, with preoperative sampling of the first morning urine sample to determine the histamine concentration level. The research included 60 patients of both sexes, aged ≥ 18 years, with the first presentation of a non-muscle invasive bladder cancer. Patients in the study underwent follow-up control urethrocystoscopy postoperatively. The concentration of mast cells in tumor tissue was specified.

Results The study included 35 (58.3%) men and 25 (41.7%) women with an average age of 70.15 ± 9.38 years. The mean urinary histamine levels before surgery in patients with non-muscle-invasive bladder cancer were 11.06 ± 5.79 ng/mL. The mean urinary histamine levels before surgery ($t = 2.46$; $p = 0.02$) and six months after surgery ($t = 2.34$; $p = 0.02$) in patients with T1 stage were statistically significantly higher than the urinary histamine levels in patients with Ta stage of urothelial bladder cancer. Patients with higher histamine concentration in urine before surgery had a higher number of mast cells.

Conclusion The mean urinary histamine value before surgery, three, and six months after surgery is statistically significantly lower than the reference urinary histamine values. The urinary histamine values in patients with T1 stage are higher than in patients with Ta stage. Statistically significant correlation between mast cell concentration and histamine was determined before surgery.

Keywords: bladder cancer; mast cells; histamine; urine

INTRODUCTION

Urothelial bladder cancer is a complex disease characterized by high morbidity and mortality rates despite complex multimodal treatment. The survival of patients with bladder cancer has not significantly increased, and there is still a high rate of tumor recurrence and significant impairment of quality of life [1, 2, 3].

Epidemiologically, bladder cancer is the most common malignant disease of the urinary tract in both sexes [1, 2]. The incidence of bladder cancer is estimated to double by 2040 [1, 2]. In the male population only, bladder cancer is the seventh among the total number of malignant tumors diagnosed worldwide, while in the female population, it ranks 17th globally [2–5]. Among newly detected bladder tumors, 70–75% are non-muscle-invasive, while the remaining 20–25% are muscle-invasive urothelial carcinoma [1, 4]. When considering only the non-muscle-invasive form, about 70% are stage Ta tumors, 20% are stage T1 carcinomas, and 10% are intraepithelial neoplasia or *carcinoma in situ* (CIS) [1, 3, 4].

Although bladder cancer is one of the most common malignant diseases in the human population, there is no reliable tumor marker that would enable early and non-invasive detection and would be applied in monitoring patients after treatment [6, 7].

The results of published research about the role of mast cells in oncogenesis and the biology of malignant tumors are contradictory, especially in urogenital cancers [8–18]. Data indicate that increased mast cell concentrations in tumor tissue are associated with poor prognosis in rectal cancer, melanoma, non-small cell lung cancer, endometrial cancer, multiple myeloma, and Hodgkin lymphoma [6, 7, 9, 10, 15]. At the same time, increased mast cell concentrations in tumors are associated with improved survival in breast cancer, advanced non-small cell lung cancer, and ovarian cancer [8, 9, 15]. In certain malignant tumors, mast cells occur in higher concentrations within the tumor tissue [14], while in other tumors they occur in

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higher concentrations in the peritumoral tissue [15]. Mast cells are instrumental in immune response and are one of the main sources of histamine [19, 20]. By secreting pro-angiogenic molecules, mast cells also play an important role in angiogenesis [5, 6, 7].

METHODS

This study is an open, longitudinal, prospective follow-up conducted over six months following transurethral resection of the bladder tumor by monopolar resectoscope at the Urology Department of the University Clinical Center of Vojvodina in Novi Sad. The study was conducted from December 1, 2023 to November 1, 2024.

Our research included 60 patients of both sexes, aged ≥ 18 years, with the first presentation of a non-muscle invasive form of urothelial bladder cancer. Preoperative collection of first-morning urine samples was done in order to determine histamine concentration. Patients included in the study were followed up with control urethrocystoscopy three months and six months postoperatively. Before the control urethrocystoscopy, urine samples were collected by spontaneous voiding of the first-morning urine.

The study did not include patients with recurrent bladder tumors, patients with other previously diagnosed malignancy, patients with other concomitant malignancies, as well as patients with allergic or autoimmune diseases and idiopathic mast cell activation syndrome. Individuals receiving antihistamine and/or mast cell stabilizer therapy at the time of enrollment, or within the preceding six months, were excluded from the study.

Patients with pathologically confirmed T2–T4 stage of the disease were excluded from the study, as well those in whom the final pathological examination established the absence of urothelial carcinoma. Patients who did not provide all three planned urine samples were also excluded from the study.

The histological examination of surgically removed tumor tissue included tissue fragments fixed in formalin, molded into paraffin molds and stained with the standard hematoxylin and eosin method. Two additional slides were made, of which, special May-Grünwald Giemsa (MGG) straining was applied to one slide, while immunohistochemical staining (IHC) with the primary monoclonal antibody monocarboxylate transporters (MCT) was performed on the other with the aim of visualizing mast cells in the tumor tissue. Before applying additional stains, a representative paraffin block was selected, and in the case of immunohistochemical analysis, tissue preparation for IHC was performed. After automatic deparaffinization of the bladder tumor sample, the following was done: automated special MGG staining on plate 1 and automated IHC with the monoclonal antibody mast cell tryptase- MCT (monoclonal mouse anti-human clone 10D11, dilution: 1/80, Novocastra Laboratories, Newcastle upon Tyne, United Kingdom) on plate 2. Positive MCT expression represented cytoplasmic staining of tumor cells of any staining intensity. On photographs of 10 fields of view, at 400 × magnification, the surface numerical density of mast cells was analyzed using the Fiji software (ImageJ, LOCI, University of Wisconsin, Madison, WI, USA) program and the Cell Counter function. The mean value was calculated from the number of mast cells per high power field.

To determine urinary histamine concentration, an immunodiagnostic antigens assay (Histamine ELISA, Abcam, Cambridge, United Kingdom) was used. An amount of 10–15 ml of the first-morning urine sample was diluted with reaction buffer in a 1:15 ratio. Then 75 μL of derivatization agent were added to the tube and mixed by repeated inversions. This was followed by a one-hour incubation at room temperature (15–30°C) in a horizontal shaker. After that, 50 μL of histamine antibodies were added and incubated for one hour at room temperature (15–30°C) in a horizontal shaker. The microtiter plate was washed with wash buffer, substrate was added, and incubated for 12–19 minutes at room temperature in the dark. A stop solution was added and the absorbance was immediately determined with an ELISA reader at 450 nm. The obtained histamine concentration values were multiplied by a dilution factor of 15 and expressed in ng/ml. The reference value of histamine in urine is 0.67 ng/ml with a standard derivative of 0.18 ng/ml. The histamine value from the stated unit can be converted to nmol/l using the following formula: histamine (ng/ml) × 8.997 = histamine (nmol/l).

Statistical analysis

Continuous variables were presented as mean ± SD, and differences between groups were analyzed using the student t-test (t) / Mann–Whitney (U). A value of $p < 0.05$ was considered statistically significant. Categorical variables were presented as counts and percentages. Non-parametrically distributed continuous variables were presented using the median, minimum, and maximum values. The relationship between urinary histamine concentration and cancer recurrence was examined using Fisher's exact test. All statistical analyses were performed using SPSS Statistics for Windows, Version 17.0. (SPSS Inc., Chicago, IL, USA).

Ethics: All patients provided written consent prior to their enrollment in the study. The treatment protocol was approved by the Ethics Committee of the University Clinical Centre of Vojvodina (November 16, 2023; No. 600-235). The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association.

RESULTS

The study included 35 (58.3%) men and 25 (41.7%) women with an average age of 70.15 ± 9.38 years. The average age of the male population was 70.94 years and 69.04 years in female population. An average age of the subjects with Ta stage tumors was 68.87 years, while the average age of the subjects with T1 stage was 72.28 years. Intravesical

Table 1. Demographic and pathohistological characteristics, therapy and recurrence of urothelial bladder carcinoma

Parameters	Frequency	Percentage (%)
Sex		
Male	35	58.3
Female	25	41.7
Type of bladder cancer		
Infiltrative urothelial carcinoma	14	23.3
Papillary urothelial carcinoma	46	76.7
Grade		
High grade	36	60
Low grade	24	40
Stage		
pT1	21	35
pTa	39	65
Macroscopic appearance of the tumor		
Polypoid	23	38.3
Papillary	37	61.7
Tumor base		
Wide	25	41.7
Narrow	35	58.3
Intravesical BCG therapy		
Yes	29	48.3
No	31	51.7
Mitomycin C therapy		
Yes	3	5
No	57	95
Relapse		
Yes	3	5
No	57	95

BCG – Bacillus Calmette–Guérin therapy

Bacillus Calmette–Guérin (BCG) therapy was received by 29 (48.3%) patients, while therapy with Mitomycin C was received by only three (5%) patients. Only three (5%) patients had a recurrence of bladder cancer (Table 1).

The mean urinary histamine levels in patients with Ta and T1 stage are shown in Table 2. The reference urinary histamine levels are 13 ± 4 ng/ml (range 5–21 ng/ml). The mean urinary histamine levels before surgery ($t = -2.59$; $p = 0.01$), three months ($t = -9.26$; $p < 0.001$) and six months ($t = -5.65$; $p < 0.001$) after surgery were statistically significantly lower than the reference values. The mean urinary histamine levels before surgery ($t = 2.46$; $p = 0.02$) and six months after surgery ($t = 2.34$; $p = 0.02$) in patients with T1 stage were statistically significantly higher than the urinary histamine levels in patients with Ta stage of urothelial bladder cancer. The mean age and mast cell count were not statistically significantly different between T1 and Ta stages (Table 2).

A statistically significant weak correlation between mast cell concentration and histamine was found only in the preoperative period ($r = 0.35$; $p = 0.01$). With each increased in histamine concentration (not exceeding the reference values), the concentration of mast cells in bladder

Table 3. Prevalence of pT stage of urothelial bladder carcinoma depending on different variables

Variables		pT Stage		p
		T1	Ta	
Sex	Male	15	20	0.17
		71.4%	51.3%	
	Female	6	19	
		28.6%	48.7%	
Bacillus Calmette–Guérin therapy	Yes	15	14	0.01*
		71.4%	35.9%	
	No	6	25	
		28.6%	64.1%	
		66.7%	28.2%	
Mitomycin C	Yes	1	2	0.99
		4.8%	5.1%	
	No	20	37	
		95.2%	94.9%	
Relapse	Yes	1	2	0.99
		4.8%	5.1%	
	No	20	37	
		95.2%	94.9%	

*$p < 0.05$

Table 4. Incidence of bladder cancer recurrence depending on the urinary histamine concentration

Histamine concentration		Relapse		p
		Yes	No	
Before operation	Lower	3	34	0.28
		100%	59.6%	
	Higher	0	23	
		0%	40.4%	
Three months after operation	Lower	3	52	0.98
		100%	91.2%	
	Higher	0	5	
		0%	8.8%	
Six months after operation	Lower	3	46	0.98
		100%	80.7%	
	Higher	0	11	
		0%	19.3%	

Table 2. Age, urinary histamine concentration, and intratumoral mast cell density in patients with different stages of urothelial bladder cancer

Variables	pT stage				Student t-test (t) / Mann–Whitney test (U)	p
	T1		Ta			
	$\bar{x}$	SD	$\bar{x}$	SD		
Age (years)	72.29	7.29	69.00	10.23	1.30	0.19
Histamine before surgery (ng/ml)	13.47	4.63	9.77	5.99	2.46	0.02*
Histamine – three months after (ng/ml)	7.79	4.66	7.44	4.54	0.29	0.77
Histamine – six months after (ng/ml)	11.38	5.85	8.41	3.95	2.34	0.02*
Mast cell density (number/μm^2)	0.07255	0.02344	0.06256	0.02586	359.50	0.29

*$p < 0.05$

Table 5. Urinary histamine concentration and intratumoral mast cell density depending on implemented intravesical Bacillus Calmette–Guérin (BCR) therapy

Variables	BCG therapy				Student t-test (t) / Mann–Whitney test (U)	p
	Yes		No			
	$\bar{x}$	SD	$\bar{x}$	SD		
Histamine before operation (ng/ml)	12.07	5.27	10.11	6.18	1.32	0.19
Histamine – three months (ng/ml)	6.89	4.29	8.19	4.75	-1.12	0.27
Histamine – six months (ng/ml)	10.15	5.09	8.79	4.64	-1.07	0.28
Mast cell density (number/μm^2)	0.06537	0.02445	0.06669	0.02645	260.50	0.58

cancer tissue also increases. There was no statistically significant correlation between mast cell concentration and histamine concentration three and six months after surgery (Table 4).

The use of BSG therapy was statistically significantly associated with the stage of the disease (Fisher's exact test = 6.90; p = 0.01) with a weak correlation coefficient (φ = 0.34; p = 0.01). Patients who received BCG therapy were more often in the pT1 stage. No statistically significant association was found between sex, use of Mitomycin C, and the recurrence with the pT stage of bladder cancer (Table 3).

Histamine concentrations in urine during the examination were divided according to the mean values: lower histamine values (< 13 ± 4 ng/ml) and higher histamine values (≥ 13 ± 4 ng/ml). Histamine concentrations before surgery (Fisher's exact test = 1.96; p = 0.28), three months after surgery (Fisher's exact test = 0.28; p = 0.98) and six months after surgery (Fisher's exact test = 0.71 p = 0.98) were not statistically associated with bladder cancer recurrence (Table 4).

Comparing the concentration of histamine in urine before surgery, three and six months after surgery, as well as the number of mast cells in patients with and without BCG therapy, no statistically significant differences were found (Table 5).

DISCUSSION

Considering the prevalence and incidence of urothelial bladder cancer worldwide [1, 2], our research is dedicated to improving the existing knowledge about non-muscle invasive bladder cancer.

Previous studies have shown a higher incidence of bladder cancer in males than in females [1, 2]. The sex and the age distribution of the subjects in our study is consistent with previous studies [1, 2, 21, 22]. No sex differences were found in overall survival after treatment of non-muscle invasive bladder cancer [21, 22]. According to current data, the average age of patients with non-muscle invasive bladder cancer is 73 years [1, 2, 21, 22]. The average age of the subjects in our study was 70.15 years. The average age of the male population of subjects is 70.94 years, and the average age of female subjects was 69.04 years. The results of our study are in agreement with the results published by other researchers [1, 2, 21, 22]. Our study found no statistically significant difference in the average age of Ta and T1 stage groups. Literature data indicate that older patients are more likely to develop high-grade tumors and multifocal disease with a higher rate of recurrence and disease progression compared to those younger than 65 years of age [22, 23, 24].

The available results on the role of mast cells in carcinogenesis are contradictory, especially in the case of bladder tumors [12, 15–19]. Authors have found a positive correlation between the concentration of mast cells in the *lamina propria* of the mucosa, the degree of tumor differentiation, and the pathological grade in bladder cancer [13, 25]. A review of the existing literature found a small number of published scientific research results that examined the role of mast cells in urothelial bladder cancer [13, 16, 17, 18].

Dowell et al. [25] found that the most abundant Interleukin-17-positive cells in bladder tumors are mast cells. In patients with primary and concomitant CIS who received intravesical BCG immunotherapy, higher Interleukin-17+ cell counts were associated with improved event-free survival [25].

The results of the study by Popov et al. [26] indicated a positive relationship between mast cell concentration in tumor tissue and the cancer recurrence, but did not detect a relationship between mast cell concentration and the time of recurrence, or a relationship with tumor stage and grade, sex, and age of patients. Our results are consistent with the data from the study of Popov et al. [26].

Simsekoglu et al. [27] were the first who examined the predictive value of mast cells in patients who underwent surgery for non-muscle invasive bladder cancer and then received intravesical immunotherapy with BCG. This study found that histamine concentration significantly increased after the start of intravesical BCG instillation, but no correlation was found between tumor stage, urinary histamine concentration, and the presence of a local response to BCG instillation [27]. In our research the concentration of histamine before surgery and during follow-up was not statistically associated with bladder cancer recurrence nor was it related to BCG therapy. The obtained results are in agreement with the results of Simsekoglu et al. [27].

Our results show that the mean urinary histamine levels before surgery and six months after surgery in patients with T1 stage were statistically significantly higher than the urinary histamine levels in patients with Ta stage of urothelial bladder cancer. The results indicate that a correlation can still be established between the stage of the bladder tumor and urinary histamine levels, although histamine levels in patients with bladder cancer are still lower than the reference values. Researchers have found that the T1 tumor population is very heterogeneous [28, 29]. It is assumed that the same density of tumor infiltration by mast cells, depending on the number and type of existing genetic mutations of urothelial cells, causes different degrees of malignant transformation in different individuals [28,

29]. In our case mast cell density did not differ statistically significantly between T1 and Ta stages.

A study conducted by Sari et al. [28], with 78 subjects, found a statistically significant correlation between the concentration of mast cells in tumor tissue, tumor grade, and stage of the disease ($p < 0.05$; $r = 0.69$ and 0.63). It was found that a higher concentration of mast cells in bladder cancer tissue was statistically significantly associated with a higher density of capillary blood vessels per unit volume of malignant tumor ($p < .05$, $r = 0.56$). Interestingly, the tumor concentration of mast cells in the bladder mucosa in the immediate vicinity of the tumor was higher compared to the concentration of mast cells in the tumor tissue itself ($p < 0.001$) [28]. There are assumptions that the surrounding tissue, which is not microscopically malignantly transformed, plays a key role in the survival of neoplastic tissue [13–17, 28, 29].

While the predictive role of the initial concentration of tumor mast cell infiltration and patient survival after radical cystectomy has been established in muscle-invasive urothelial bladder carcinoma [29], this correlation has not been clarified in the non-muscle-invasive form. Patients with a higher concentration of mast cells in the tumor stroma before radical cystectomy have been found to have a statistically significantly worse overall survival and recurrence-free survival compared to patients with a lower concentration [29].

Findings reported by Sari et al. [28] were in agreement with our results, as no statistically significant correlation between the concentration of mast cells in the bladder tumor tissue, tumor stage and grade was established, observing and comparing the concentration of mast cells in Ta, T1, and T2 stage tumors, although T2 tumors showed the highest concentration of mast cells in tumor tissue [28]. In our study, observing the mean value of mast cell density, it was found that the mast cells density in pTa tumor tissue was lower compared to the number of mast cells in tumor tissue at the T1 stage of the disease (0.06 *vs.* 0.07).

Histamine concentration in blood and urine can be affected by numerous factors [30]. Researchers have found that the bladder mucosa of patients with interstitial cystitis contains an increased concentration of mast cells, while the urine of these patients contains an increased concentration of methylhistamine, which is the main metabolite of histamine [30].

The primary limitation of our study was the relatively short duration of patient follow-up. An additional limitation was the number of subjects in the study. The sample of subjects was relatively small, but it was in correlation or even larger than the number of subjects in previously conducted studies. In most studies, subjects with muscle-invasive cancer were also included.

CONCLUSIONS

The mean urinary histamine value before surgery, three and six months after surgery is statistically significantly lower than the reference urinary histamine values. The mean urinary histamine values before surgery and six months after surgery in patients with T1 stage are statistically significantly higher than the urinary histamine concentration in patients with Ta stage. Histamine concentration before surgery and during follow-up was not statistically associated with bladder cancer recurrence.

There is no statistically significant difference in terms of the number of mast cells in the tumor tissue between Ta and T1 stages. A statistically significant correlation between mast cell concentration and histamine was determined before surgery but not in follow-up. With each increase in histamine concentration, the concentration of mast cells in bladder cancer tissue also increased.

Comparing the concentration of histamine in urine before surgery and during follow-up, as well as the number of mast cells in patients with and without BCG therapy, no statistically significant differences were found.

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Повезаност концентрације хистамина у урину са густином мастоцита код болесника са немишићно-инвазивним уротелним карциномом мокраћне бешике

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САЖЕТАК

Увод/Циљ Не постоје поуздани туморски маркери који би омогућили неинвазивно откривање карцинома мокраћне бешике и који би се примењивали у праћењу болесника после лечења. Улога мастоцита у процесу онкогенезе и даље је неразјашњена.

Методе Спроведена је отворена, лонгитудинална, проспективна студија са шестомесечним праћењем болесника после хируршког лечења карцинома мокраћне бешике, уз преоперативно узорковање првог јутарњег урина ради одређивања концентрације хистамина. Истраживање је обухватило 60 болесника оба пола, старости ≥ 18 година, са првом презентацијом немишићно-инвазивног карцинома мокраћне бешике. Болесници у истраживању су праћени контролним уретроцистоскопским прегледима. Утврђена је густина мастоцита у туморском ткиву.

Резултати Студија је обухватила 35 (58,3%) мушкараца и 25 (41,7%) жена са просечном старошћу од 70,15 ± 9,38 година. Просечни нивои хистамина у урину пре операције код болесника са немишићно-инвазивним карциномом мокраћне бешике били су 11,06 ± 5,79 *ng/ml*. Просечни нивои хистамина у урину пре операције ($t = 2,46$; $p = 0,02$) и шест месеци после операције ($t = 2,34$; $p = 0,02$) код болесника са стадијумом *T1* били су статистички значајно виши од нивоа хистамина у урину код болесника са стадијумом *Ta* уротелног карцинома мокраћне бешике. Болесници са вишом концентрацијом хистамина у урину пре операције имали су већи број мастоцита.

Закључак Просечна вредност хистамина у урину пре операције, три и шест месеци после операције статистички је значајно нижа од референтних вредности хистамина у урину. Просечне вредности хистамина у урину код болесника са стадијумом *T1* статистички су значајно веће од концентрације хистамина у урину код болесника са стадијумом *Ta*. Статистички значајна корелација између концентрације мастоцита и хистамина утврђена је пре операције.

Кључне речи: карцином мокраћне бешике; мастоцити; хистамин; урин