

FREQUENCY OF LEUKOPLAKIA OF THE BLADDER AND THE ROLE OF SURGICAL TREATMENT : AN ANALYSIS OF A SIX-YEAR PERIOD

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Abstract

Introduction: Bladder leukoplakia, or squamous keratinizing metaplasia (SKM), is a rare disease in which the normal transitional epithelium is transformed into a squamous epithelium over which there is a layer of keratin. In most patients, typical non-specific symptoms of the lower urinary tract are expressed. Worldwide the representation of leukoplakia of the bladder is 1:10 000 cases. Surgical treatment is currently the gold standard in leukoplakia therapy.

Goals: The goals of the study are to determine the prevalence of bladder leukoplakia, as well as the impact of surgical treatment of leukoplakia on the improvement of lower urinary tract symptoms.

Materials and methods: We analyze a series of 2,665 patients diagnosed with cystitis, out of a total of 70,620 patients from the entire territory of the Republic of N. Macedonia, who were examined and treated in the urology department at the GOB "8th of September" - Skopje, for the period from 01.01.2018 to 01.06.2024.

Results: Out of 70 620 patients, 2665 patients (3.77%) were diagnosed with cystitis, of which 1768 (66.4%) were female. The IPSS (international prostate symptom score) questionnaire showed a postoperative improvement of 65.4%.

Conclusion: Leukoplakia of the bladder is a rare urological disease, which is exclusive to the female sex. The postoperative result of the IPSS score questionnaire showed a significant improvement in symptoms.

Keywords: bladder leukoplakia, lower urinary tract symptoms, IPSS score.

Introduction

Squamous keratinizing metaplasia (SCM) of the bladder, also known as leukoplakia of the bladder, is defined as the transformation of the normal multilayered transitional epithelium of the bladder into a multilayered squamous epithelium, which may be covered with a layer of keratin in squamous keratinizing metaplasia, or to be without a keratinized layer in squamous metaplasia.

Rare bladder diseases include leukoplakia (white plaques on the bladder), malakoplakia (brown plaques on the bladder), bladder amyloidosis, bladder sarcoidosis, and megacystic bladder syndrome.

Leukoplakia pathohistologically is a metaplastic lesion, which occurs as a reaction of the normal multilayered transitional epithelium to chronic irritation such as frequent and long-term urinary infections, calculus of the bladder or a foreign body.

In the literature, chronic infection is often associated with leukoplakia. [1,3] It is often found in chronic cystitis, calculus of the bladder, schistosomiasis and long-term wearing of a urinary catheter. However, in some patients neither functional nor anatomical obstruction can be proven, and urine cultures are sterile.

Epidemiology

In the literature, the global prevalence of bladder leukoplakia among urological diseases is 1:10,000 cases [2], which makes it a rare disease, although recent research shows a much higher frequency. [5,7]. The symptoms of leukoplakia are long-lasting and refractory to conservative therapy. Lower urinary tract symptoms (LUTS), pollakisuria, dysuria, urgent urination, as well as signs of urinary infection are common. The infection is present in 50% of patients [3,5]. Some patients have difficult and painful urination as well as hematuria. Several studies have investigated the relationship between leukoplakia and its transformation into bladder cancer, which cannot be confirmed due to the small percentage of simultaneous occurrence of leukoplakia and bladder cancer [3,13]. For now, endoscopic surgical treatment is the gold standard in the therapy of leukoplakia, which is proven by the improvement of the initial IPSS score, in relation to the control postoperative IPSS score.

Etiology

The bladder has endodermal and mesodermal origins. The presence of ectodermal cells in the bladder mucosa is explained by the process of squamous metaplasia. Metaplasia represents the transformation of one type of tissue into another type of tissue, which is morphologically and functionally different. Mostofi believes that the transitional epithelium has a great capacity for metaplasia and neoplasia under the influence of various stimuli (chronic irritation, infection, hormone imbalance or vitamin deficiency) [1].

Embryological theory considers that leukoplakia develops from ectodermal cells, which during embryogenesis accidentally or by genetic mechanism came to the urinary tract. It is possible that during the caudal dislocation of the Wolff duct, dislocation of some ectodermal cells may occur.

Pathology

Leukoplakia can appear in different places in the bladder and urinary tract, but the most common localization is in the trigonum of the bladder. Microscopically, there is a picture of multilayered squamous epithelium with keratinization. Apart from squamous metaplasia, pathohistological criteria for leukoplakia include acanthosis, cellular atypia and dysplasia.

Keratinization is a basic pathological criteria that distinguishes leukoplakia from multi-layered squamous epithelium of the vaginal type. "Vaginal-like" epithelium is often found on the trigone in women. Multilayered squamous epithelium without keratinization is found on the trigone and the posterior part of the urethra in 50-70% of women in the reproductive period of life [1]. Under the influence of sex hormones, this epithelium changes during the menstrual cycle and over the years.

In addition to squamous metaplasia with keratinization, inflammatory changes can also be found in the vaginal wall beneath these lesions. Electron microscopy showed a distinct type of basal cells with small, dense granulations. These cells resemble Merkel cells found in the skin and have hormonal and sensory functions. This type of cells is found not only in the zone of leukoplakia but also in the zones of "Vaginal-like" epithelium of the trigonum of the bladder in women. The presence of these cells supports the theory of dislocation of ectodermal cells during embryogenesis. [1]

Symptoms and signs

The symptoms of leukoplakia are long-lasting and refractory to conservative therapy. Lower urinary tract symptoms (LUTS), pollakisuria, dysuria, urgent urination, as well as signs of urinary infection are common and most common. In our study, infection was present in 48% of patients. Some patients have difficult and painful urination as well as hematuria. Whitish scrums can be seen in the urine. In certain cases, calculi have also been found in the bladder. [1,2]

Diagnosis

Cytological examination of the urine shows numerous mature squamous cells and keratin material, in addition to transitional epithelial cells.

For diagnosis, the gold standard is cystoscopy, which shows a "snowstorm" phenomenon (floating scrums) and characteristic shiny, whitish "velvet" plates on the trigone of the bladder. In rare cases, almost the entire wall of the bladder is covered with irregular whitish membranes. Inflammatory bullous tumor-

like changes may also be seen. Therefore, a transurethral biopsy that shows the pathohistological character of the change is required for definitive diagnosis. [1]



Figure 1. Bladder leukoplakia

Leukoplakia and carcinoma

According to some authors, the simultaneous occurrence of leukoplakia and squamous cell carcinoma of the bladder ranges up to 37%. [1] This occurrence is more common in the bladder than in other parts of the urinary tract. According to other authors, the simultaneous occurrence during the initial diagnosis is lower and ranges from 10-20% [3]. The occurrence of cancer in the later period of multi-year follow-up of the patient is even rarer. In our study, that percentage is 0.002%.

Treatment

The etiology of squamous keratinizing metaplasia is still unclear, and there is currently no effective medical therapy. Antibiotics, alpha blockers and anticholinergics are effective in lower urinary tract symptoms associated with benign prostatic hyperplasia and not in leukoplakia.

More recently, intravesical instillation of hyaluronic acid has also been used, but with limited success.

Combined therapy is recommended as the best treatment, i.e. resection and electrocoagulation of the lesion with subsequent instillation of hyaluronic acid.

Goals

To determine the prevalence of bladder leukoplakia in female patients,

To determine the impact of surgical treatment of leukoplakia on the improvement of lower urinary tract symptoms

Materials and methods

The subject of evaluation was the total number of patients with a urological diagnosis according to the International Classification of Diseases ICD-10, who were examined in the GOB “8th of September” - Skopje, in the urological department, for a period of the last 6 years, from 01.01.2018 to 01.09.2024 year. Data from the hospital's electronic record system – HIS were used. Then the patients were selected according to the international designation for cystitis according to ICD-10, N30. Inclusion criteria were implemented which included female patients, age 18 to 70 years, with bladder leukoplakia proven by cystoscopy.

Bipolar transurethral resection of leukoplakia was performed in a series of 50 patients, and control examinations were performed three months after the intervention, after which the data were evaluated and compared with the baseline results. The patients were recruited through the urology department at the GOB "8th of September". Then followed the rest of the examinations, which were also carried out in the GOB "8th of September". The tests included:

1. **IPSS score (international prostate symptom score) questionnaire** - patients filled it in the urology department

International Prostate Symptom Score (I-PSS)							
In the past month:	Not at All	Less than 1 in 5 times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your Score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							
Score: 1-7 Mild		8-19 Moderate			20-35 Severe		
The first seven questions of the I-PSS are from the American Urological Association (AUA) Symptom Index							
Quality of Life Due to Urinary Symptoms							
	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 2. IPSS score – questionnaire

2. **Questionnaire** - contains demographic and anamnestic data
3. **Laboratory analyzes** - were performed in the central laboratory at the GOB "8th of September" and included: complete blood count (CBC), basic biochemical analyses, urine, hemostasis, viral markers for hepatitis B, hepatitis C and HIV, blood group and Rh factor
4. **Urine culture** - done in a microbiological laboratory
5. **Ultrasonography of the urinary tract** - performed in the urology department
6. **Cytological analysis of urine** - performed at the pathology department

7. **BTA (bladder tumor antigen) immunohistochemical test** - performed in a certified laboratory
8. **Cystoscopy** - performed at the urology department
9. **Pathohistological analysis** - performed at the Department of Pathology at the GOB "8th of September"

A control examination with a completed new IPSS score questionnaire, and a control cystoscopy was performed in all patients three months after the intervention.

The patient monitoring protocol has been modified according to the latest recommendations of the EAU (European Association of Urology) for preoperative preparation of patients.

Exclusion criteria were: male gender, age below 18 and above 70 years, negative cystoscopy findings, acute cystitis and neurogenic bladder.

Results:

Table 1. Data on the total number of patients

Total number of patients	70 620 (100%)
Patients diagnosed with cystitis	2665 (3.77%)
Sex	Women 1768 (66.4%)
Patients with proven leukoplakia	96 (5.4%)
Patients with proven bladder cancer	2 (2.08%)

This table shows us an increased frequency of cystitis in women with 66.4%, leukoplakia was proven in 5.4% of the total percentage of patients diagnosed with cystitis, and cancer in 2.08%.

Table 2. Demographic characteristics and anthropometric measurements of the studied group of 50 patients

Age (yrs) - median (rank)	44 (18-70)
Sex	Female (100%)
Height (cm) - median	164
Weight (kg) - median	67

All patients were female, and the median age was 44 years, with a range from 18 to 70 years.

Table 3. Medical history surrounding the underlying disease

Operative treatment and finding	initial score n(%)	control result n(%)
Positive cystoscopy finding	50 (100%)	0 (0%)
Positive urine culture	24 (48%)	5 (10%)
Positive BTA test	2 (4%)	1 (2%)
Cytological analysis of urine	Cl. group I 36 (72%)* Cl. group II 12 (24%) Cl. group III 2 (4%)	Cl. group I 44 (88%)* Cl. group II 6 (12%) Cl. group III 0 (0%)

*cytological classification group

All patients had a positive cystoscopic finding at the initial examination, no patient had a recurrence at the follow-up cystoscopic examination three months after the intervention. 48% of the patients had a positive urine culture at the first examination, and only 10% at the control examination. 4% had a positive BTA – bladder tumor antigen (BTA) test at the first examination compared to 2% at the control examination. The cytological analysis of the urine at the control examination noted an increase in the percentage in the first classification group, and a decrease in the second and third group.

Table 4. Urine analysis

Laboratory analyzes of urine	initial score n(%)	control result n(%)
Glucose	5 (10%)	3 (6%)
Erythrocytes	39 (78%)	11 (22%)
Leukocytes	40 (80%)	9 (18%)
Nitrites	16(32%)	4 (8%)
Ph value of urine	5.5	5.7

The laboratory analysis of urine showed a drastic decrease in the percentage of erythrocytes, leukocytes and nitrites at the control examination.

Table 5. Pathohistological results

Pathohistological analysis	result n(%)
Squamous metaplasia	28 (56%)
Squamous keratinizing metaplasia	17 (34%)
Chronic cystitis	5 (10%)

Pathohistologically, the highest percentage, 56%, was squamous metaplasia, 34% had squamous keratinizing metaplasia, and 10% was diagnosed with chronic cystitis.

Table 6. * IPSS score international questionnaire first part

IPSS score parameters	Preoperative	Postoperative
How often in the past month did you have a feeling of incomplete emptying of the bladder after urinating? (0-5)	4	1
How often in the last month did you have to urinate again in less than 2 hours? (0-5)	2	2
How often in the last month did you stop and start urinating several times? (0-5)	3	1

How often in the last month have you had difficulty holding (delaying) urination? (0-5)	4	1
How often in the last month did you have a weak stream of urine? (0-5)	3	1
How often in the last month did you have to strain to urinate? (0-5)	3	1
How often in the last month have you woken up to urinate? (points according to the number of urinations) (0-5)	3	2
*Total IPSS score	22	9

*a score of 0-7 indicates mild symptoms, 8-19 indicates moderate-severe symptoms, 20-35 indicates severe symptoms

* never 0, less than once 1, less than half the time 2, about half the time 3, more than half the time 4, almost always 5

The total IPSS score showed a decrease from 22 points at baseline to 9 points at follow-up.

Table 7. *Quality of life as a result of urinary symptoms

If you had to spend the rest of your life with the urinary symptoms you have now, how would you feel?	Preoperative n50	Postoperative n50
Delighted 0	0	7
Satisfied 1	0	23
Generally satisfied 2	3	10
Equally satisfied and dissatisfied 3	12	6
Mainly dissatisfied 4	23	4
Unlucky 5	8	0
Terrible 6	4	0

*second part of the IPSS score questionnaire

This table shows us a significant improvement in the quality of life at the follow-up examination, compared to the initial examination.

Discussion

This study covered the frequency of leukoplakia, as well as the impact of its surgical treatment on symptoms of the lower urinary tract in women. The data for all the patients in our study were from the electronic data system in the GOB "8mi Septemvri" for a period of the last 6 years, starting from 01.01.2018 to 01.06.2024. Then, based on the total number of patients, several inclusion and exclusion criteria were implemented, after which an appropriate selection, epidemiological analysis, and data analysis on the

impact of the surgical treatment of leukoplakia in a group of 50 patients, treated in the GOB "8th of September" was made.

In the world literature, the incidence of leukoplakia is 1:10,000 urological cases [2]. Recently, thanks to the development of urology and diagnostic procedures such as cystoscopy, cytology, BTA test and others, the frequency of leukoplakia is increasing, [5,7] as well as the impact it has on the symptoms and quality of life of the affected patients. Regarding the total examinations, leukoplakia is represented by 0.13%, that is, 1:735 cases, and the simultaneous finding of leukoplakia and bladder cancer was in 0.002% of patients, that is, 1:35,310 cases. The study group of 50 patients was exclusively female, aged 18 to 70 years, with a median age of 44 years. All patients reported lower urinary tract symptoms lasting up to one year. All had been treated with antibiotic therapy for lower urinary tract symptoms at least once in the past 6 months.

From the results we can conclude that there is a significant postoperative improvement in the cystoscopic finding of 100%, the percentage of positive urine cultures also decreased from 48% to 10%, and the BTA test recorded a decrease from 4% to 2%. There is also an improvement in the classification groups of the cytological analyses, i.e. an increase in the postoperative percentage in the first classification group from 72% to 88%, with a consequent decrease in the percentage in the second from 24% to 12% and in the third classification group from 4% to 0%. We also note an improvement in the laboratory analysis of urine. The presence of erythrocytes in urine decreased from 78% to 22%, leukocytes from 80% to 18% and nitrites from 32% to 8%.

Pathohistological analysis showed a predominance of squamous metaplasia with 56% of cases, followed by squamous keratinizing metaplasia with 34% and chronic cystitis with 10% of cases. The analysis of the epidemiological characteristics of this study show us that the prevalence of bladder leukoplakia in the female population is more frequent than previously thought 1:10,000 [2], and our study showed a frequency of 1:735, which is in trend with the new world researches [5,7].

Regarding the improvement of lower urinary tract symptoms according to the IPSS score, our study showed an improvement from baseline 62.8% to postoperative 25.7%, and regarding the improvement of the quality of life, it showed an improvement of 66.4%, compared to studies of Constantini et al, Hussain et al. and Benelli's study [10,2,5] postoperatively observed improvement of lower urinary tract symptoms in 68%, 72% and 75% of patients.

The results of this study indicate the increasing frequency of squamous keratinizing metaplasia of the bladder in women and its close connection with the symptoms of the lower urinary tract. Transurethral resection proved to be a superior therapeutic method in relation to conservative treatment

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