



Clinical Research

# Causative Role of Sexually Transmitted Infections in the Development of Chronic Cystitis Complicated With Leukoplakia of the Bladder

Alexander I. Neymark, PhD, ScD, Yuliya S. Kondratyeva, PhD\*

*Altai State Medical University, Barnaul, Russian Federation*

---

## Abstract

The objective of this study was the investigation of the influence of chlamydial, mycoplasmal and trichomonas infection on the development of urinary bladder leukoplakia. The article presents the results of the examination of women with chronic cystitis complicated with leukoplakia of the bladder, and associated with concomitant sexually transmitted infections, including the results of culture analysis of the cervical canal content and urinary bladder biopsy samples, as well as molecular-biological analyses confirming the presence of sexually transmitted infections, pathomorphological characteristics of tissue samples from leukoplakia foci typical for different types of infectious agents. In this study, 60 women with chronic cystitis, complicated with leukoplakia of the bladder and associated with concomitant sexually transmitted infections were examined. Using PCR diagnostics, *Mycoplasma hominis* and *Chlamydia albicans* were found to be the most frequently occurring agents, followed by *Ureaplasma urealyticum*, *Chlamydia trachomatis* and *Trichomonas vaginalis*. The results of culture analyses demonstrated that *M. hominis* and *U. urealyticum* were prevalent in patients with chronic urinary tract inflammatory processes, followed by *Tr. vaginalis*. *Candida* fungi show practically the same frequency of occurrence. The pathomorphological examination of the foci of leukoplakia in the urinary bladder (in 30 subjects) demonstrated metaplasia of the transitional epithelium to the stratified pavement squamous epithelium with inflammatory cellular infiltration of the lamina propria in all types of infections. The intensity of the urothelial transformation and stromal inflammatory processes were determined by the type of predominant infection. Pathomorphological characteristics of the foci of leukoplakia correlate with the etiology of chronic inflammation and are relevant for etiological diagnosis and treatment. *IJBM* 2012; 2(3):192-196. © 2012 International Medical Research and Development Corporation. All rights reserved.

**Key words:** *sexually transmitted infections in women, chronic cystitis, leukoplakia of bladder.*

## Introduction

According to the WHO statistics, 340 million people between the ages of 15 and 49 get sexually transmitted infections (STI) annually [1]. The most frequently identified bacterial STI are *Neisseria gonorrhoeae*,

*Chlamydia trachomatis*, *Treponema pallidum*, *Mycoplasma genitalium* and *Ureaplasma urealyticum*. The treatment of STI complications involves considerable expense for the diagnostics and treatment of the inflammatory diseases of the pelvic organs and chronic pelvic pain in women, and most often the examinations are triggered by infertility. Most often, STI cause the development of inflammatory diseases of the genital and reproductive tracts and excretory tracts [2, 3]. Chlamydial infection is diagnosed as cystoureteritis in 30-40% cases [4, 5].

The epidemiologic role of cystitis caused by certain chlamydial and mycoplasmal types of infection is increasing annually [6, 7]. These infectious agents may lead to acute and chronic forms of cystitis with concomitant proliferative

---

\*Corresponding author: Assoc. Prof. Yuliya S. Kondratyeva, PhD, Department of Skin and Venereal Diseases, Altai State Medical University, 62B, Molodezhnaya str., apt. #48, Barnaul, Altai Krai, Russian Federation.

Tel: 7-903-9963341.

E-mail: [julia\\_jsk@mail.ru](mailto:julia_jsk@mail.ru)

changes in the urinary bladder mucosa [8]. The diagnosis of cystitis is confirmed for 15-20 thousand per 1 million people annually; this implies that every 4<sup>th</sup>-5<sup>th</sup> woman had cystitis in one form or another, and 10% of patients suffer from recurrent cystitis with different intensity of dysuric disorders [8, 9]. However, STI agents unlike non-specific ones cause unusual inflammatory alteration of the genitourinary tissue, namely post-inflammatory urothelial changes with concomitant squamous metaplasia of the transitional epithelium (leukoplakia) in 50-80% of women with chronic cystitis, which appears to be the histological form of chronic inflammation [9-12]. Stratified pavement epithelium formation in the urinary bladder is explained by its better stability under conditions of the long-term effect of harmful agents such as STI [13].

In spite of the high prevalence of the STI rate, in many cases of chronic cystitis and persistent dysuria in women, very little attention is paid to the diagnostics of these infectious agents. This in turn may reduce the efficacy of further treatment and cause the recurrent clinical course of the disease with the development of more severe complications such as leukoplakia of the urinary bladder.

In light of this, studying the etiology and pathogenesis of chronic recurrent cystitis complicated with urinary bladder leukoplakia and associated with STI becomes important to identify the appropriate diagnostic methods and treatment.

## Material and Methods

In this study, 60 women with chronic cystitis complicated with urinary bladder leukoplakia and associated with STI were enrolled in the study. The age of subjects varied from 16 to 63 years of age. All the women were subjected to a thorough clinical examination, with assessments of anamnesis, social and marital status. Laboratory and instrumental examination included a gynecological exam, molecular-biological and culture analyses of the scrapings by endocervical curettage of the cervical canal for STI in all patients, biopsy sampling from the urinary bladder leukoplakia foci in 30 patients followed by the culture and morphological examination of the samples, and cystoscopic examination for all the patients.

The identification of STI was done using the PCR with fluorescent hybridization endpoint detection. Culture analyses of the cervical canal scraping were performed in the culture substrates at 37°C, between two and six hours depending on the type and properties of the infectious agent.

Biopsy samples from the leukoplakia foci in the urinary bladder mucosa were homogenized, and the derived suspension was added to a 24-h monolayer of L929, McCoy, HeLa cells and others. The inoculations were incubated at 37°C for 3 to 5 days (based on the life cycle of infectious agent). Normally the growth of *U. urealyticum* culture is defined in 1 to 3 days, *M. hominis* in 3 to 5 days, *C. trachomatis* in 48-60 hours, and *Tr. vaginalis* in 2 to 4 days. The composition of the fluid substrates was specially balanced for each specific type of infectious agent.

Light optic examination of the biopsy samples of the urinary bladder mucosa from the leukoplakia

foci was performed using the automatic system of histological processing of tissues «Histokinette», controlled microprocessor paraffin embedding system «Histoembedder» for making paraffin blocks with subsequent preparation of 4 µm serial sections using a sliding microtome «Histosleid», and an automatic staining system «Autostainer XL» (BRD, Leica). Hematoxylin and eosin Van Gieson's stain [14] were used, and the reaction with Schiff's Reagent (controlled by pancreatic amylase) was performed to identify the glycomucoproteins and glycogen. Prepared samples were analyzed using microscopes «Laborlux» and «Aristoplan» with «Ortomat E» camera and a color microscopic system with videoprinter «Sony» (BRD, «Leica»).

## Results

Female patients were observed based on the following age distribution: between 16 and 25 years of age – 11 patients; between 26 and 35 years of age – 16 patients; between 36 and 45 years of age – 14 patients; between 46 and 55 years of age – 14 patients; above 56 years of age – 5 patients. Thus, according to the data obtained from the female patients with chronic cystitis, infections were found to be more prevalent in the younger women.

The following complaints were recorded: polyuria, lancinating pain at urination with periodic itch and heat, urination in small portions, pubic pains when the urinary bladder overflowed or just post urine evacuation, imperative vesical tenesmus, nycturia (1-8 times). Frequency of urination varied from 6 to 27 times per day and 5 patients complained of urine incontinence. Chronic recurrent cystitis was registered in the anamnesis of each of the subjects.

Totally 7 patients had more than 8 years' duration of history of the disease, 10 patients had 4 to 8 years, 27 patients had 2 to 4 years, and 16 patients had 0.5 to 1 year. All of them had earlier received multiple courses of treatment on an outpatient basis.

In the context of sexual anamnesis, the patients were distributed as follows: virgo – 0, only one intercourse partner – 32 women, more than one intercourse partner since the beginning of sexual life – 18 women. There were 8 patients with premenopausal syndrome and 11 menopausal women.

According to results of the PCR investigation of the cervical canal contents *U. urealyticum* and *M. hominis* were found to occur most frequently, in 64.4% and 26.9% of cases, respectively. Due to the great attraction for the genitourinary tract by these microorganisms, the percentage of positive results for them was relatively high.

The frequency of occurrence of the different types of infectious agents colonizing the cervical canal was analyzed. The most frequent was *M. hominis* detected in 39 patients (65.0%) and *C. albicans* in 33 (55.0%). They were followed by *U. urealyticum*, observed in 18 women (30.0%), *C. trachomatis* in 15 (25.0%) and *Tr. vaginalis* in 14 (23.3%).

The results of the culture analyses of the cervical canal contents and urinary bladder biopsy samples from 30 patients were compared (Table 1). The following differences were noted: *C. trachomatis* was significantly rare in the biopsy samples of urinary bladder mucosa (8.6%) than in

**Table 1**

Comparative results of cultural examination of biosamples from cervical canal and biopsy samples of urinary bladder mucosa (n=30)

Infectious agent	Cervical canal		Biopsy samples of urinary bladder mucosa	
	Number	%	Number	%
Chlamydia trachomatis	7	23%	3	8.6%
Mycoplasma hominis	21	71.4%	17	57.1%
Ureaplasma urealyticum	9	31.4%	11	37.1%
Trichomonas vaginalis	7	23%	7	23%
Candida albicans	13	43%	15	50%

the cervical canal scrapings (23.0%). At the same time the infectious agent *U. urealyticum* occurred more frequently in the urinary bladder biopsy samples (37.1% versus 31.4% in the cervical canal). *M. hominis* was more frequent in the cervical canal (71.4% versus 57.1% in the urinary bladder). *Tr. vaginalis* was recorded with modest frequency in the biopsy samples and cervical canal scrapings (23.0%), whereas *C. albicans* was determined in 43.0% and 50.0% of the cases, respectively.

Cystoscopy was performed in all the patients for diagnostic and treatment purposes. Foci irregular in shape, yellowish and white or silvery in color, with well-defined edges and rough surfaces, rising above the unaltered normal mucosa were observed in 47 patients (78.3%) by cystoscopy. In 13 patients (21.7%), the mucosa around the foci of leukoplakia was hyperemic with an intensified vascular pattern and edematous, i.e. showing signs of exacerbation of chronic cystitis.

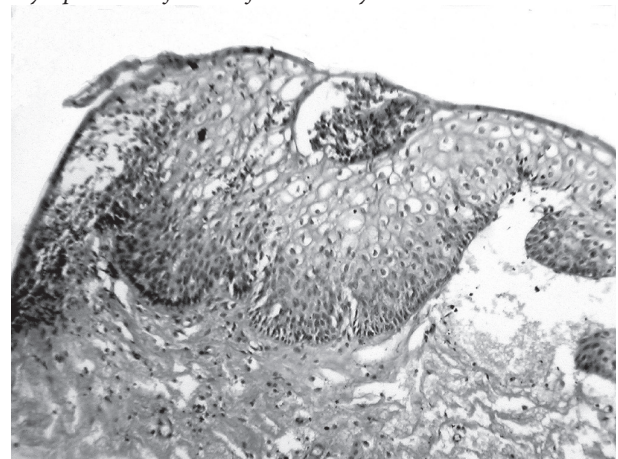
Hyperplastic and metaplastic changes of the urothelium, parakeratosis and inflammatory infiltration of the pars propria were found in all the patients (n=30) and were referred to as common pathomorphological signs. The degree of intensity of the dystrophic changes of the stratified pavement and transitional epithelium, the combination of metaplastic and dysplastic processes and the intensity of inflammatory reactions depended on the predominant type of infection.

In the case of mycoplasmal infection (9 cases – 30.0%) dystrophic and lytic changes in the urotheliocytes (formation of vast vacuoles and cell destruction) were most intensive and acantholysis with vesicle formation in the stratum spinosum was highly frequent. Edema, vascular plethora and hemorrhage were observed in the lamina propria. In some cases, the edema was accompanied by the appearance of subepithelial vesicles (Fig. 1). Inflammatory cellular infiltration was represented by small lymphoid assemblies. Such changes were revealed in 78.0% cases. Occurrence of intensive lesions and hemorrhage was caused by intracellular localization of the infectious agent and the associated destruction of the intracellular structures and vascular endothelium.

In the case of mixed mycoplasmal infection with chlamydiosis and trichomoniasis (11 cases – 36.6%), the

**Figure 1**

Mycoplasmal infection of the urinary bladder.



Squamous metaplasia, parakeratosis. High-grade dystrophy of the stratum spinosum cells. Acantholysis. Subepithelial vesicle. Low-grade inflammatory infiltration of the lamina propria. Hematoxylin and eosin stain. 250-fold magnification.

intensity of the inflammatory cellular infiltration was significantly increased. Lymphocytes and plasmacytes were prevalent and leukocytes appeared in a cellular content of the inflammatory infiltrates. Inflammatory infiltration was localized not only within the lamina propria but had also penetrated into the epithelium (Fig. 2).

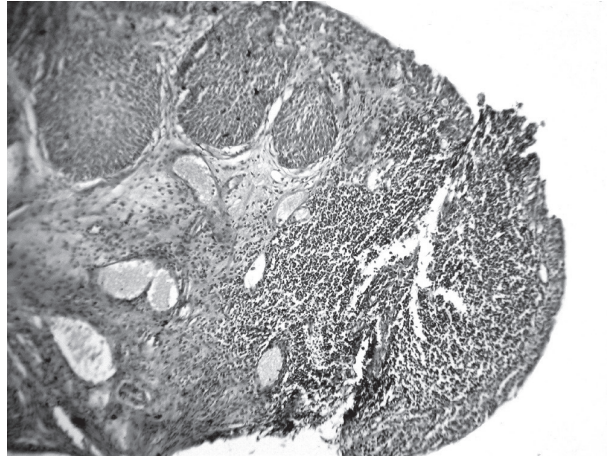
Absolute affinity of the chlamydia to the pavement epithelium was associated with intensive lesions of the epithelial cells exposed to metaplasia, with frequent formations of acute erosions (in 4 cases out of 6). The intensity of the inflammatory infiltration was high, especially in cases of the association of chlamydiosis with trichomoniasis (Fig. 3).

## Comments

The results of the culture analyses demonstrate that *M. hominis* and *U. urealyticum* play a major role in the development of the chronic inflammatory processes of the genitourinary tract and are followed by *Tr. vaginalis* in the

**Figure 2**

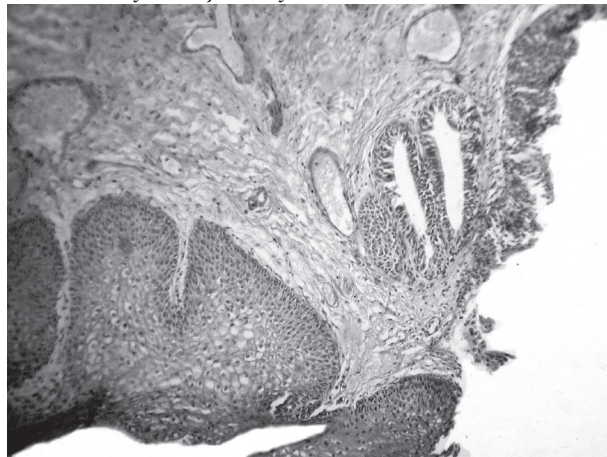
Association of mycoplasmal infection with chlamydia and trichomoniasis.



High-grade inflammatory cellular infiltration and edema of the mucosa lamina propria. Hematoxylin and eosin stains. 100-fold magnification.

**Figure 3**

Association of chlamydial infection with trichomoniasis.



Simple leukoplakia. Acute erosion of the pavement epithelium. Inflammatory cellular infiltration with the formation of nodes composed of lymphocytes, plasmacytes and histiocytes. Hematoxylin and eosin stains. 250-fold magnification.

context of prevalence. *Candida* fungi have practically the same frequency of occurrence.

Associations of pathogens such as *M. hominis* (71.4%), *U. urealyticum* (31.4%), *C. trachomatis* (23.0%) and *Tr. vaginalis* (23.0%), *C. albicans* were registered in the cervical canal in 43.0% cases.

Associations of *M. hominis* (57.1%) and *U. urealyticum* (37.1%), *Tr. vaginalis* (23%) and *C. trachomatis* (8.6%) were the most frequently occurring infections; however, *C. albicans* was found in the urinary bladder biopsy samples of 50.0% of the patients.

The analysis of these data demonstrates the identity of the microflora in the cervical canal and urinary bladder mucosa foci exposed to transformation in the case of leukoplakia. It confirms a common perception of the ascending path of infection. It also explains the recurrent

form of chronic cystitis in women infected by an intercourse partner.

The comparative analysis of the microscopic changes in the urinary bladder mucosa associated with STI revealed both common morphological features and different morphological signs and their different intensity, typical for the various types of infectious agents and their associations.

## Conclusions

In the clinical course of chronic cystitis associated with STI, the major burden is persistent dysuric disorders, almost unbearable pain and a highly resistant-to-treatment psychoneurological syndrome. Sexual functions worsen and quality of life begins to decrease.

Based on the data of the research of the different STI agents colonizing the genitourinary tract, the most frequent causes of leukoplakia were *M. hominis* and *U. urealyticum*, followed by *C. trachomatis* and *Tr. vaginalis*. It is important to note that specific STI agents were frequently observed in the genital and urinary tracts. At the same time, the spectrum for infectious agents was almost identical both in cervical canal scrapings and biopsy samples from the leukoplakia foci in the urinary bladder mucosa.

For all types of recorded infections, metaplasia of the transitional epithelium to the stratified pavement squamous epithelium with concomitant inflammatory cellular infiltration of lamina propria was revealed. The intensity of the urothelial transformation and stromal inflammatory processes were determined by the type of predominant infection and differed in the presence of mono- and mixed infections.

We suggest that in several cases, urinary bladder infection in women can be caused by STI agents due to close sexual contacts, and this concept should form the basis for treatment and preventive measures on an outpatient basis. A thorough examination of patients with leukoplakia of the bladder will facilitate not only defining the degree of inflammatory reaction in the genitourinary tract but also help in selecting a therapeutic approach in each particular clinical case.

## References

1. Global strategy for the prevention and control of sexually transmitted infections: 2006-2015. Breaking the chain of transmission. *J Vestnik Dermat and Venerol* 2008; 4:17-29. [in Russian]
2. Khrianin AA. Infections of *Mycoplasma*, Moscow, PAGRI, 2006. [in Russian]
3. Kubanova AA, Rakhmatulina MR. Urinogenital infectious diseases caused by genital mycoplasma. Clinical recommendations. *J Vestnik Dermat and Venerol* 2009; 3:78-82. [in Russian]
4. Kosova IV. Genitourinary infections role in cystitis and non-obstructive pyelonephritis etiology. Ph.D. thesis, Moscow, 2005. [in Russian]
5. Burkhard FC, Blick N, Studer UE. Urinary urgency,

- and chronic urethral and/or pelvic pain in females. Can doxycycline help? *J Urology* 2004; Jul: 172(1):232-235.
6. Adaskevich VP. Sexually transmitted infections. Physician handbook, Moscow, 1999. [in Russian]
  7. Rakovskaya IV. Human mycoplasma and mycoplasmal infections. *J Clin Lab Diagnostics* 2005; 3:25-32. [in Russian]
  8. Loran OB, Sinyakova LA, Kosova IV. Genitourinary infections role in cystitis and non-obstructive pyelonephritis ethiology in women (part 2), *J Urology* 2005; 3:63-66.
  9. Okamura K, Ito K, Suzuki Y, Shimoji T. Histological study of cases of bladder cancer and chronic cystitis with difficulty in cystoscopic diagnosis. *Hinyokika Kyo* 1984; 30(4):459-465.
  10. Vitoratos N, Gregoriou O, Papadias C, Liapis A, Zourlas PA. Sexually transmitted diseases in women with urethral syndrome. *Int J Gynaecol Obstet* 1988; 27(2):177-180.
  11. Murakami S, Igarashi T, Takahara M, Yamanishi T, Shimazaki J, Shigematsu H. Squamous metaplasia of the trigone in women with recurrent cystitis syndrome. *Hinyokika Kyo* 1985; 31(2):301-07.
  12. Vozianov AF, Romanenko AM, Klimenko IA. Precancer and early forms of urinary bladder cancer. Kiev, Health, 1994. [in Russian]
  13. Gumus E, Yilmaz B, Miroglu C. Extensive bilateral renal pelvis, ureter and bladder leukoplakia. *Int J Urol* 2003; 9:653-655.
  14. Sarkisov DS, Petrov YL. Microscopic techniques. Moscow, 1996. [in Russian]