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CLINICAL RESEARCH

# Causative Role of *Ureaplasma Urealyticum* and other Sexually Transmitted Infections in the Urethral Meatus Polyp Development in Women

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## Abstract

The objective of this study was the investigation of the influence of ureaplasmal infection on the development of urethral meatus polyps in women. The article presents the results of the examination of women with chronic cystitis and urethritis over a 0.5- to 5-year duration, complicated by the presence of urethral meatus polyps and associated with concomitant *Ureaplasma urealyticum* and other sexually transmitted infections (STI). This was based on the culture analysis of the cervical and urethral content, and PCR-diagnostics of STI, as well as a complex pathomorphologic study of the resected polyps, including electron microscopy. In this study, 98 women between 45 and 60 years (52.5 ± 4.9 years) were examined, who had undergone radiowave resection of the polyps: 52 women were infected by STI, including *Ureaplasma urealyticum, Mycoplasma genitalium, Mycoplasma hominis, Chlamydia trachomatis and Trichomonas vaginalis*, while the remaining 46 women had been diagnosed as not having STI. According to the culture results in the women with STI, *U. urealyticum* was identified as a monoinfection in 69% of cases, while in the remaining 31% of cases it was evident in the form of mixed infections, mainly in association with *Mycoplasma hominis* (17.5%) and *Trichomonas vaginalis* (13.5%). Pathomorphological examination of the urethral meatus polyps of the women with *U. urealyticum* and other STI demonstrated the proliferative character of the remodeling of the surface epithelium with hyperplasia, acanthosis, and keratinization of the stratified squamous epithelium and synchronous changes in the underlying connective tissue - impaired microcirculation and the diffuse inflammatory cell infiltrates with transepithelial leukopedesis. Using electron microscopy in the fibroblasts and plasma cells of the resected polyps the markers of *U. urealyticum* were detected in patients with negative results of the bacteriological diagnostic methods.

***Keywords***: *female urethral meatus polyp; Ureaplasma urealyticum; sexually transmitted infections; pathomorphology.*

## Introduction

Urethral polyps in women can develop between 58 and 60 years and can be found to occur in any locus of the urethra, although more often in the outer diameter. The emergence of the urethral polyps is associated with menopausal dishormonal changes combined with disturbance of the blood supply in the urethral wall; the role of urogenital STI (Chlamydia, Mycoplasma, viruses and other) is also discussed [1].

*Ureaplasma urealyticum* is a prokaryotic representative with a chemiosmotic energy production mechanism, which requires quite unusual habitat conditions. This microorganism occurs most frequently in patients from urological clinics [2] and is associated with a variety of urinary tract diseases including urinary tract infection, encrusted cystitis [3], urethritis [4], chronic prostatitis [5] and urolithiasis [6]. Moreover, two species of *Ureaplasma (urealiticum and parvum*) are likely to also be responsible for several pathological processes such as chorioamnionitis, spontaneous abortion, stillbirth, endometritis, neonatal neuropathies and pneumonia [7]. *U. urealyticum* and *U. parvum* are among the most common microorganisms isolated from the human urogenital tract. Infection rates as high as 40 to 80% in women and up to 50% in men have been reported [8]. Ureaplasma may be also responsible for some cases of acute urethral syndrome in women [2]. Most lower urogenital tract infections appear to be asymptomatic [9, 10].

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It is important to emphasize that most investigations are devoted to the pathogenic potential of Ureaplasma detected in the urogenital tract as mono- or mixed infection; however, only a few studies have attempted to unravel the mechanisms of the asymptomatic course of the microbial persistence [2, 11]. The pathogenesis of the ureaplasmosis with emphasis on the structural basis of the macro- and microorganism relationships is the subject of a very limited number of studies.

The objective of this study is to conduct a complex investigation of polyps of the urethral meatus in women diagnosed with *U. urealyticum* and Ureaplasma combination along with other non-gonorrheal pathogenic and non-pathogenic agents of urogenital infections.

## Material and Methods

***Patients:*** In this study, 98 women aged 45-60 years (52.5 ± 4.9 years) suffering from urethral meatus polyps for 0.5 to 5 years' duration complicated with chronic cystitis and urethritis were examined. The patients were divided into two age-comparable groups: the 1st included 52 women (47.2 ± 5.9 years) infected by STI and *U. urealyticum* combined or not combined with different combinations of *Mycoplasma genitalium, Mycoplasma hominis, Chlamydia trachomatis* and *Trichomonas vaginalis*; the 2nd group included the remaining 46 women (57.2 ± 6.3 years) diagnosed with the absence of STI.

All the women were subjected to a thorough clinical examination, and the anamnesis, social and marital status were also assessed. Laboratory and instrumental examinations included a gynecological inspection, molecular-biological and culture analyses of the scrapings by endocervical curettage of the cervical canal for STI, and cystoscopic examination in all the patients. In all the cases, after local anesthesia with 2% novocaine solution surgical treatment was performed, i.e. the radiowave polyp excision («Fotek E300», Russia) followed by a complex pathomorphological study.

***Pathomorphological study***: For light and electron microscopy, the polyp samples were fixed in 4% paraformaldehyde solution (pH 7.2-7.4). Paraffin sections were stained with hematoxylin and eosin, by Van Gieson and PAS-reaction. For electron microscopy, the samples were post-fixed in 1% $OsO_4$ and after dehydration were placed in the Epon-Araldite mixture [12]. Semi-thin sections were stained with toluidine blue. The study of paraffin and semi-thin sections was performed using the universal microscope Axio Scope.A1 (C. Zeiss). Ultrathin sections were contrasted by uranyl acetate and lead citrate [12] and examined under the electron microscopes JEM 1010 and JEM 100 S at 80 Kw.

## Results

In the 1st group, the presence of STI contributed to the development of polyps at a younger age (60% of women 47.5 ± 2.3 years); when the disease became more durable, recurrences were observed at 1.5 times more often than in the women of the 2nd group with polyps and lacking STI. The chronic recurrent inflammatory diseases of the female reproductive organs and the urinary system were mentioned in the anamnesis, including 2.5 times more frequent data concerning the previously diagnosed and treated urogenital infections.

In the 2nd group, the urethral polyp development occurred after gynecological operations, as well as during the premenopausal and postmenopausal periods. The essential symptoms of the disease in the 1st group were characterized by inflammatory features: frequent urination, itching in the urethra, urethrorrhagia; in the 2nd group, the obstructive character predominated with difficulty in urinating and urine stream spraying (Fig.1).

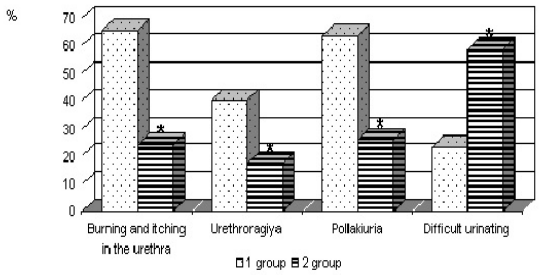


***Figure 1.***
*The frequency of the most common symptoms of urethral polyps.*P<0.05 between groups.*

According to the PCR-diagnostics of the cervical canal content, *U. urealyticum* as monoinfection was revealed in 71% women, and in association with *M. hominis* (11.5%), *M. genitalium* (9.6%) and *Ch. trachomatis+Tr.vaginalis* (7.7%) of cases of the 1st group, respectively.

According to the culture results in the women with STI, *U. urealyticum* was identified as a monoinfection in 69% of cases, while in the remaining 31% of cases it was evident in the form of mixed infections, mainly in association with *Mycoplasma hominis* (17.5%) and *Trichomonas vaginalis* (13.5%).

In the cases of *U. urealyticum* monoinfection, under the light-optical study, the urethral polyps appeared as large fibroepithelial structures, with stratified squamous non-keratotic epithelium inherent in the distal urethra (Fig. 2, 3), and sometimes in combination with the multi-layer prismatic epithelium inherent in the intermediate urethra. In one half of the cases the epithelial-stromal boarding in polyp samples was characterized by the acanthosis phenomenon, namely multiple papillary excrescences of the stroma in the epithelial thickness with a large number of blood microvessels with dilated lumen, often with erythrocyte stasis. In the perivascular foci, mild to moderate swelling was developed, usually accompanied by mast cell degranulation and pulping bundles of collagen fibers.

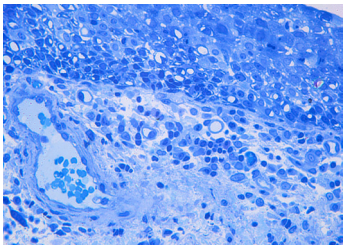

***Figure 2.***
*Urethral meatus polyp. Ur. urealyticum monoinfection. Stratified squamous non-keratotic epithelium; the epithelial cells with large cytoplasmic vacuoles; predominantly mononuclear infiltration of the stroma. Semi-thin section, toluidine blue. Magnification x 350.*

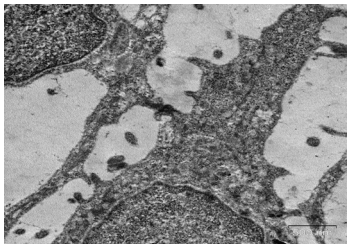

***Figure 3.***
*The part of the Figure 2. Prominent squamous epithelial peri-nuclear and intercellular swelling; destruction of the desmosomes. Electron microscopy. Magnification x 20000.*

Among the other perivascular and diffuse cellular infiltrate components, mononuclear cell elements were observed: lymphocytes, plasma cells and fibroblasts, as well as single smooth muscle cells, macrophages and neutrophils (Fig.4). In the other half of the cases, small perivascular lymphoid aggregates were seen.

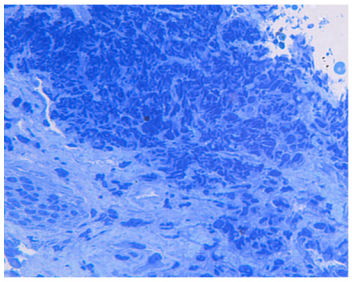

***Figure 4.***
*Urethral meatus polyp. Ur. urealyticum monoinfection. Fibrotic stroma with mild inflammatory infiltration. Semi-thin section, toluidine blue.*
*Magnification x 250.*

The squamous epithelial cells contained numerous microfilament bundles, and during the terminal differentiation and outward migration the membrane cytoplasmic organelles of epitheliocytes underwent destructive changes. It is important to note that sometimes the focal alteration of mitochondria and cytoplasmic reticulum as well as the formation of osmiophilic residual bodies occurred in the basal epithelial cells. This caused a biosynthetic function decrease, followed by reduction of microfilaments and finally a focal epithelial layer disintegration and acantholysis.

The electron-microscopic study revealed the ultrastructural polymorphism of the connective tissue cells. Some plasma cells contained the intracellular bodies of *U. urealyticum* resulting from intracytoplasmic reaction (Fig.5). The infected cells were not destroyed, and among their features were significant reduction of the protein synthesis and some mitochondrial membrane vacuolization. Such plasma cells were seen as a reservoir for the intracellular persistence of the intracellular parasites without cytodestruction. The other connective tissue cells showed moderate functional activity with secondary phagosome formation in the macrophages and numerous specific granules in the neutrophils.

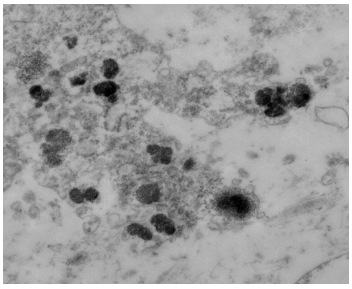

***Figure 5.***
*Urethral meatus polyp. Ur. urealyticum monoinfection. The swelling plasma cell cytoplasm with polymorphic osmiophilic residual and microbial bodies. Electron microscopy.*
*Magnification x 45000.*

In the cases with mixed infection (the 2nd group), polyp macroscopy was the same; however, the stratified squamous epithelium was characterized by hyperplasia with prominent height increase and focal keratinization in 12% of the cases. In 5% of cases, Brunn's nests were visible, which are pear-shaped proliferates of the transitional epithelium shifted deep into the stroma. In the polyp epithelium, marked destructive, metaplastic and dysplastic changes were often found. The destructive epithelial changes (erosion and ulceration) combined with the foci of leukoplakia and dysplasia.

The proliferative response of the epithelium was accompanied by synchronous changes in the underlying connective tissue, expressed as increased vascularization, perivascular edema, single hemorrhages and recruitment by numerous cell populations.

Acute and chronic disorders of the microcirculation contributed to the formation of inflammatory cell infiltrates, usually diffuse and massive, and large in number, with a large proportion of neutrophils and trans-epithelial leukopedesis, accompanied by severe degenerative changes in the epithelial cells and the basal cell proliferation.

The diffuse cellular infiltrates contained neutrophils, numerous lymphocytes, plasma cells, and to a lesser extent, macrophages, mast cells and fibroblasts and fibrocytes, besides single smooth muscle cells. In a great many cases, compared with *U. urealyticum* monoinfection, small and large lymphoid aggregates were found.

The electron-microscopic study revealed more prominent ultrastructural polymorphism of the epithelial cells compared with *U. urealyticum*-monoinfection, with the more pronounced processes of autophagy and compensatory cellular proliferation in the basal and intermediate epithelial layers. In a mixed infection in the epithelial cell cytoplasm, secondary lysosomes were formed as well as polymorphic vacuoles, which most likely illustrate the process of the destruction of the canals of the granular cytoplasmic reticulum. Signs of the declining function of protein synthesis were combined with the mitochondrial degeneration.

The ultrastructural organization of the cellular elements of the inflammatory infiltrates testified to their high functional activity. Undifferentiated single microbial cells and colonies of mycoplasmas were localized in the plasma cells, as well as fibroblasts lacking specific ultrastructural features characteristic of these mononuclear cells. Significantly more pronounced phagocytic activity of macrophages was typical.

## Comments

The urethral mucosal prolapse and polyps, often identical in clinical manifestations, are specific diseases in postmenopausal women. The polyps are benign tumors of the urethral mucosa arising from the impact of various factors: the violation of the vaginal flora in women due to dysbiosis and hormonal changes, as well as due to mechanical injury in cases with close localization of the urethral meatus to the vagina; in addition, the pathogenetic role of chronic inflammatory diseases of the bladder and urethra in mycoplasma infection are discussed. The large urethral polyp runs his wedge resection.

It is believed that the fibroepithelial urethral polyps with their numerous smooth muscle cells in the stroma are more common in pediatric patients, with outgrowths of the urethral mucous membrane in middle-aged women with chronic inflammatory processes; post-menopausal women, in most cases, reveal «polypoid» damage, in which the proportion of the smooth muscle cells is relatively small [1]. However, in a long-term persistence of mixed STI, the smooth muscle cells were found to be more numerous and heterogeneous in ultrastructure.

*U. urealyticum* is presented with 2 biovars, which consist of 14 serovars, persisting in different animals, indicating the ancient evolutionary and widespread nature of the organism in nature [8]. Ureaplasmas interact and colonize the surface of the respiratory and urogenital tracts by attaching to the host plasma membrane,

which may damage the host cells by producing superoxide radicals. Besides, the phospholipases of the Ureaplasmas, also localized at the plasma membrane, could interact with the host cell plasmalemma being a significant factor of mycoplasmal virulence [13, 14], which is important for understanding of the pathogenesis of the diseases of the genitourinary system.

During intravaginal infection with *U. parvum* of the genetically inbred Fisher rats, the animals with asymptomatic urinary tract infection were revealed to possess a remarkable feature which was the presence of a «resting» urothelium, in spite of the presence of microorganisms [2], which is very different from the results of similar experiments using *E. coli* [15]. Ureaplasma affects the urothelial function in that it counteracts the innate immune response and supports microbial colonization. It has been demonstrated that the Fisher rat bladder tissue, vigorously infected with *U. parvum,* regardless of the asymptomatic or complicated clinical profile, had significantly damaged (phosphorylated) actin-binding proteins: vinculin, alpha-actinin and filamin A. These proteins provide and regulate cytoskeletal functions during cellular adhesion, mobility and signal transduction processes, including those involved in the innate and acquired immune response [2].

Thus, ureaplasma can modulate the cellular functions of cell motility and cell death; hence, the immune and inflammatory responses constituting the pathogenesis of the ureaplasmal mono- and mixed infections.

## Conclusion

The chronic *U. ureaplasma* monoinfection and its combination with other STI agents causing the urogenital infection are characterized by a positive parenchymal-stromal correlation between the proliferative and metaplastic reactions of the surface epithelium of the urethral meatus polyps and the connective tissue remodelling. The urethral polyps in the cases of *U. ureaplasma* monoinfection reveal a lesser expression of the proliferative responses of the surface epithelium and the total absence of polymorphic inflammatory cell infiltration, even in the presence of the microorganisms in the mononuclear cells of the connective tissue, which indicates their reservoir function underlying the persistent nature of ureaplasma infection. The pathogenic activation of ureaplasma infection is likely to be induced by the addition of other factors, such as the modulation of the overall immunity of the infected women, undergoing hormonal changes or other pathological processes.

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