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Ultrastructural mechanisms of recurrent cystitis formation in women (a pilot study)

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Abstract. Comparative studies were conducted on the ultrastructural state of the urothelial barrier of the bladder in a patient without a urogynaecological history and in four patients with recurrent cystitis, both before and after standard treatment, which included bladder instillations of a solution containing hyaluronic acid. Clinical, laboratory, and instrumental baseline investigations were supplemented with high-tech scanning electron microscopy of urothelial biopsies at magnifications of up to 7000 times. Visual differences were identified in the integrity of the urothelial barrier between the patient without a urogynaecological history and the patients with recurrent cystitis. Following the comprehensive therapy, there was a tendency towards a reduction in the width of intercellular spaces, along with an increase in the size of urothelial cells and a decrease in clinical and laboratory manifestations. One of the key factors contributing to the recurrence of cystitis in women is the insufficiency of the urothelial barrier.

Keywords: Scanning electron microscopy, recurrent cystitis, urothelial barrier, urothelium, treatment

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Introduction. Recurrent cystitis is one of the most common bacterial infections in women, representing a pressing issue in modern urology and gynecology [1-4]. The European Association of Urology (EAU) defines recurrent cystitis as three or more episodes within 12 months or two or more episodes within six months [5]. Due to its high prevalence, this pa-

thology imposes a significant burden on healthcare systems and impairs the quality of life of affected patients [6,7]. Despite advances in modern treatment modalities, the recurrence rate remains high, highlighting the need for a deeper understanding of the pathogenetic mechanisms underlying this condition [8-10]. To date, the ultrastructural changes in the urothelial barrier have been insufficiently studied. According to some studies, these changes may play a key role in disrupting barrier function, facilitating the penetration of microorganisms and aggressive urinary components into the deeper layers of the bladder wall [11-13]. Ultrastructural alterations, such as widening of intercellular spaces, microplicae formation on cell membranes, and changes in urothelial cell morphology, may represent the initial stage of inflammation and subsequently trigger recurrences [14-16]. The use of advanced techniques, such as scanning electron microscopy, enables detailed visualization of ultrastructural changes and helps elucidate their role in the pathogenesis of recurrent cystitis. Understanding the mechanisms underlying the impairment of urothelial barrier integrity may contribute to the development of novel preventive and therapeutic strategies aimed at restoring its structure and function.

Currently, the search for more effective treatment modalities that prevent recurrences and improve prognosis in patients with recurrent cystitis remains a relevant challenge in modern urogynecology.

Therefore, the aim of this study was to evaluate the role of the ultrastructural state of the bladder urothelial barrier in the pathogenesis of recurrent cystitis in women.

Materials and methods. Referred by obstetricians-gynecologists, after exclusion of gynecological pathology, 4 female patients aged 42 (4.6) years were admitted to the urology department of the Tyumen Regional Clinical Hospital No. 2 to verify the causes of recurrent cystitis. The clinical diagnosis was established on the basis of basic laboratory and instrumental investigations at the outpatient stage but did not answer the questions regarding the causes of recurrence occurring more than 6 times per year. Under general anesthesia, cold-forceps biopsy of the bladder urothelium was performed during cystoscopy before and after standard therapy supplemented with intravesical instillations of a hyaluronic acid-containing solution, with a positive clinical and laboratory effect. The protocol of high-technology specialized examinations included scanning electron microscopy (SEM) of urothelial biopsy specimens at magnifications of up to 7000×. SEM was performed according to the standard technique using a Hitachi High-Tech SU3800/SU3900 scanning electron microscope. For comparison, as a conditional norm, we used the results of a bladder wall biopsy specimen from woman A., aged 32 years, with no urogynecological history, obtained during surgical repair of a traumatic rupture. Based on the results of scanning electron microscopy at magnifications of up to 7000×, ultrastructural changes in urothelial cells and intercellular spaces ensuring the integrity of the urothelial barrier were evaluated; under normal conditions, this barrier prevents the penetration of aggressive urinary components into the deeper layers of the bladder wall.

The study was reviewed by the Ethics Committee (Order No. 1052 dated 08.10.24) of Tyumen State Medical University, Ministry of Health of Russia, and a conclusion on compliance with the requirements of the Declaration of Helsinki was issued. Protocol No. 124 was signed on October 23, 2024. Voluntary informed consent was obtained from all patients for participation in the study.

Results and discussion. As part of the investigation of this issue, we conducted a prospective pilot study examining the ultrastructural state of the bladder urothelial barrier during the clinical course of recurrent cystitis, as well as following pathogenetically grounded combination therapy.

At the first stage of the pilot study, the results of scanning electron microscopy of a bladder urothelial biopsy specimen obtained during surgical repair of a traumatic rupture were adopted as a conditional norm for the ultrastructural state of the urothelial barrier. In patient A., aged 32 years, with no urogynecological history, SEM of the urothelial biopsy specimen revealed a structure of the superficial epithelial layer of the bladder close to normal. In this projection, the umbrella cells were polygonal in shape and relatively uniform in size, with an absence of widening of the intercellular borders. This ensures the impermeability of the bladder urothelial barrier to aggressive urinary components (enzymes, urinary toxins, peroxides, ions, and free radicals) due to the integrity of the biological mem-

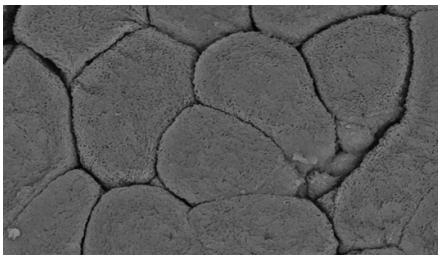

Fig. 1. SEM ultrastructural state of the urothelial barrier in patient A., 32 years old, with no urogynecological history and traumatic bladder rupture

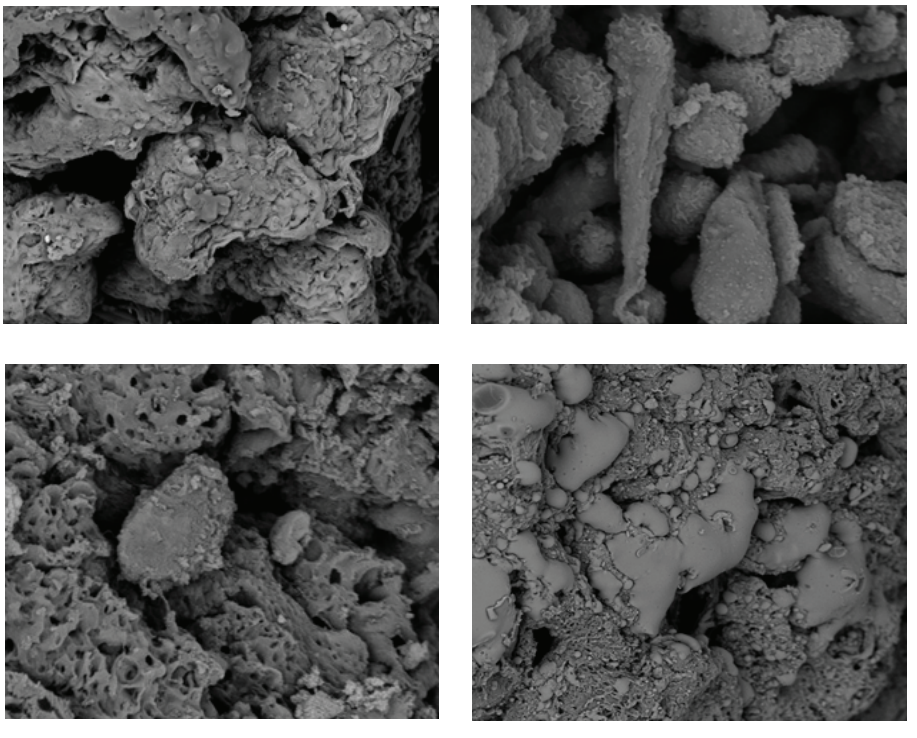

Fig. 2. SEM ultrastructural state of the urothelial barrier in patients with clinical, laboratory, and instrumental manifestations of recurrent cystitis before treatment

branes of urothelial cells and prevents the appearance of destructive changes in the deeper layers of the bladder wall (Fig. 1). The integrity of the urothelial barrier is maintained by the coverage of the majority of the urothelial area by intact umbrella cells.

In patients with recurrent cystitis (more than 6 episodes per year), various ultrastructural defects were observed, along with a general tendency towards alteration in the structure of the superficial epithelial layer of the bladder: the surface epithelial cells were irregular in shape, some cells were reduced in size with pronounced microplicae formation on their membranes. Significant widening of the borders between urothelial cells was present, with the formation of wide intercellular channels and exposure of the lamina propria of the mucosa (Fig. 2). Primary aseptic membranodestruction of urothelial cells appears to be one of the mechanisms facilitating uropathogen adhesion and the development of clinical manifestations of recurrent bladder pathology. Disruption of the urothelial barrier integrity is characterized by a reduction in the area covered by intact umbrella cells of the urothelium.

Visual changes in the size and shape of urothelial cells, with the formation of wide intercellular spaces, are accompanied by the penetration of aggressive urinary components into the deeper layers of the bladder wall, representing one of the main causes of recurrent cystitis development.

To confirm the aforementioned hypothesis, we studied the ultrastructural state of the urothelial barrier after combination therapy with a positive clinical and laboratory effect, which included standard anti-inflammatory treatment supplemented with intravesical instillations of a viscoelastic membrane protector solution containing hyaluronic acid (Fig. 3).

In patients with recurrent cystitis, 12 weeks after completion of comprehensive treatment, against the background of normalization of clinical and laboratory manifestations, a general tendency towards restoration of the structure of the superficial epithelial layer of the bladder was observed, along with a reduction in the width of intercellular spaces, which creates conditions for protecting the urothelium from the toxic effects of urine. Following the treatment, an increase in the area covered by intact umbrella cells of the urothelium was observed; however, complete restoration of cells was not achieved.

The results of this study confirm the hypothesis regarding the key role of ultrastructural changes in the urothelial barrier in the pathogenesis of recurrent cystitis in women. In particular, the detected widening of intercellular spaces indicates impairment of the integrity of the urothelial lining, which facilitates the penetration of microorganisms and aggressive urinary components into the deeper layers of the bladder wall. Of particular significance is the observed tendency towards restoration of the urothelial barrier structure following comprehensive treatment, including hyaluronic acid instillations. This supports the hypothesis regarding the potential for restoring the ultrastructural characteristics of the urothelium and, consequently, enhancing its barrier function in the course of pathogenetically grounded therapy. The main limitation of this study is the absence of a placebo-controlled group; furthermore, the positive dynamics observed in the urothelium could have resulted from spontaneous recovery. Despite the limited sample size, the obtained data warrant the conclusion that further research is needed to investigate the molecular and ultrastructural mechanisms of urothelial barrier damage.

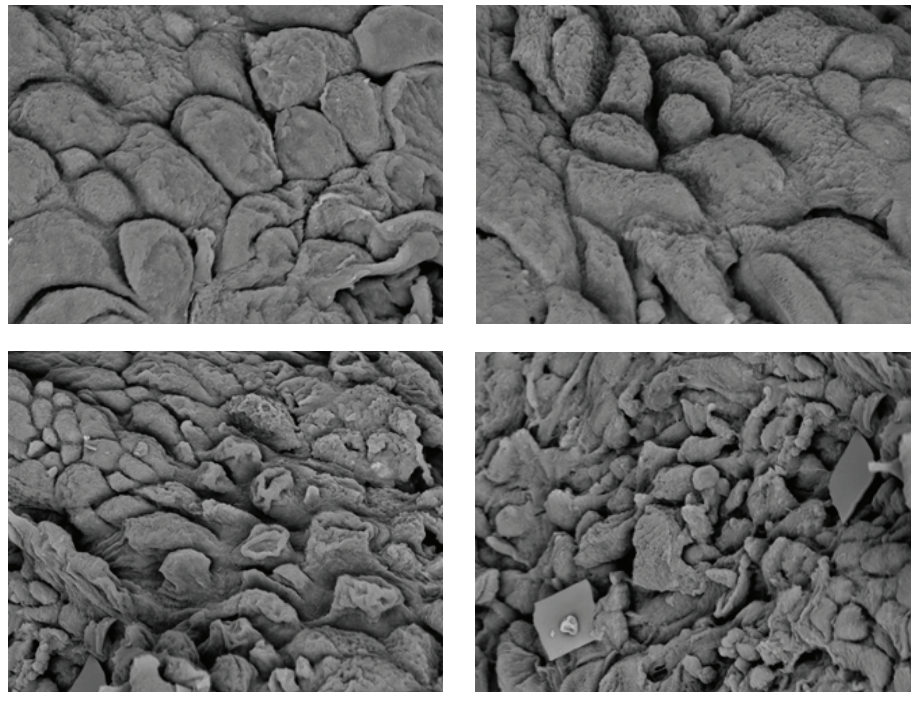

Fig. 3. SEM ultrastructural state of the urothelial barrier in patients with clinical, laboratory, and instrumental manifestations of recurrent cystitis 12 weeks after comprehensive treatment

Thus, ultrastructural changes in the urothelial barrier represent an important component in the pathogenesis of cystitis recurrences, which may contribute to improving diagnostic and therapeutic approaches for this common disease. Further research in this direction may be beneficial for a deeper understanding of the pathogenesis of urinary tract infection recurrence, which is of fundamental importance in clinical medicine.

Conclusions. One of the key factors in recurrent cystitis in women is the failure of the urothelial barrier due to a reduction in cell size with widening of intercellular spaces, which initiate the penetration of aggressive urinary components into the deeper layers of the bladder wall. Combination therapy reduces the aggressive impact of urine on the bladder wall, as confirmed by the resolution of clinical and laboratory manifestations of recurrent cystitis.

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The incidence and structure of concomitant diseases in patients with oncological pathology of the abdominal organs

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Abstract. We analyzed the incidence and structure of concomitant pathology in 216 patients hospitalized for surgical treatment for oncological diseases of the abdominal organs, and evaluated the comorbid status and its effect on the duration of inpatient treatment.

Results and discussion. It was found that 78,2% of patients with abdominal oncopathology had concomitant diseases, among which diseases of the cardiovascular system (76,8% of patients), type 2 diabetes mellitus (17,1%), chronic lung diseases (15,3%) and kidney diseases (11,6%) prevailed. 57,9% of patients had the Charslon comorbidity index of 5 or more. The duration of treatment of those patients in the intensive care unit was significantly higher and amounted to: total – 16 [14-17] bed days (p=0.046), of which 7 [6-8] (p=0,034) were preoperative and 9 [8-10] were postoperative bed days (p=0,042).

Conclusion. The conducted study confirms the need for a targeted study of concomitant pathology in patients with abdominal oncological pathology, as a factor that significantly affects the tactics of surgical treatment and the timing of inpatient treatment.

Keywords: abdominal oncological pathology, concomitant diseases, comorbidity, period of treatment.