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PATHOMORPHOLOGICAL CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF LEUKOPLAKIA AND CHRONIC RECURRENT PAPILLOMAVIRUS CYSTITIS

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Introduction: According to the literature of recent years, there has been an increased interest in non-oncological diseases of the bladder, between which differential diagnostics have to be carried out in order to determine a plan for the diagnosis and treatment of patients with these nosologies. There are often certain difficulties in the differential diagnosis of some forms of viral cystitis and leukoplakia
Objective: to determine pathomorphological criteria for the differential diagnosis of leukoplakia and chronic recurrent papillomavirus cystitis.
Materials and methods: The prospective study included 85 sexually active patients aged 20–45 years, who were divided into two groups depending on the etiological factor. Patients of group I (n=70) – with chronic recurrent cystitis (CRC) of papillomavirus (PV) etiology, group II (n=15) – with leukoplakia. All patients were examined in accordance with the recommendations of the European Association of Urology (EAU) and the Russian Society of Urology (ROU); an additional endoscopic examination of the bladder (cystoscopy) was performed, followed by a morphological examination of the bladder biopsy.
Results: A morphological examination of biopsy tissue in all patients of group I revealed koilocytic transformation of the urothelium combined with non-keratinizing metaplasia of the urothelium, and in patients of group II, in all cases, keratinizing metaplasia of the urothelium with hyperkeratosis was detected.
Conclusion: Morphological examination is the gold standard in differential leukoplakia and chronic recurrent papillomavirus cystitis

K e y w o r d s: leukoplakia; chronic recurrent cystitis; papillomavirus infection

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Introduction. According to the recent publications, there is an increased interest in non-oncological diseases of the bladder, where it is necessary to carry out differential diagnostics in order to determine the diagnostic and treatment strategy [1, 2]. Some difficulties are often encountered in the differential diagnosis of some forms of viral cystitis and leukoplakia [1, 3, 4].

In viral cystitis, the most characteristic proliferative features in the bladder wall, identical to leukoplakia, are recorded in chronic recurrent cystitis of papillomavirus etiology [4, 5].

Human papillomavirus (HPV) in the bladder causes cytological changes in the multilayered layer of the urothelium, which are manifested by metaplasia with koilocytic atypia. In this case, a number of important functions of the bladder are disrupted, including barrier, immune, hormonal and others [6, 7]. As a rule, koilocytic changes of the urothelium is characterized by the absence of the keratinization. In addition, a long-term persistent infectious and inflammatory process of papillomavirus etiology can be a basis for the development of proliferative forms of HPV, including genital warts, inverted papilloma and bladder neoplasia, which in some cases, namely leukoplakia, can be precancerous lesions [5, 8, 9].

Bladder leukoplakia is characterized by proliferation and squamous cell metaplasia of the urothelium with keratinization. Its pathogenesis is associated with the involvement of infectious and inflammatory factors [4, 10].

In most cases, both diseases have a similar clinical and laboratory manifestations, including pain, increased frequency, urgency and hematuria [4, 11]. It is possible to differentiate papillomavirus cystitis only by characteristic endoscopic and morphological features [12].

Aim. To determine pathomorphological criteria for the differential diagnosis of leukoplakia and chronic recurrent cystitis associated with HPV.

Materials and methods. Ethical statement. The study was designed and carried out in accordance with the provisions of the Helsinki Declaration (revised in Fortaleza, Brazil, October 2013) and approved by the Local Independent Ethics Committee of the Rostov State Medical University of the Ministry of Health of the Russian Federation based on the review of the design and the implementation plan (protocol No. 16/17 dated October 5, 2017).

The study was carried out as part of the dissertation work «Optimization of differential diagnostics and choice of first-line therapy for chronic recurrent cystitis in women» and did not have sponsorship support.

Patients. The prospective study included 85 sexually active patients aged 20–45 years who had previously had

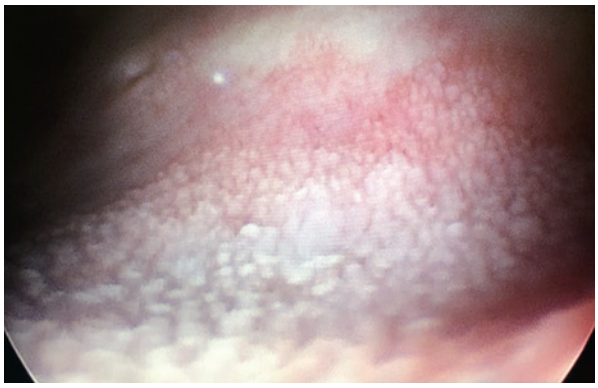


Fig. 1. Cystoscopy. Exophytic lesions of the urinary bladder

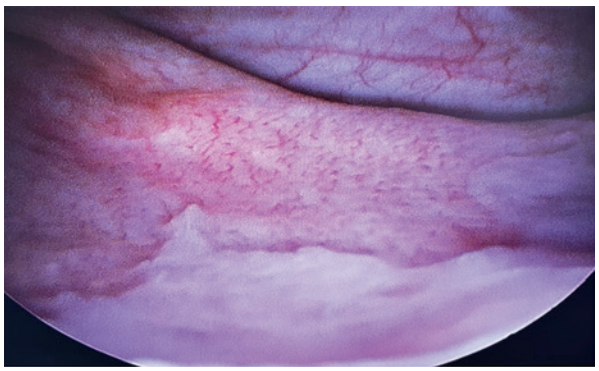


Fig. 2. Cystoscopy. Leukoplakia of the urinary bladder

recurrent lower urinary tract infection, particularly of HPV etiology during a phase of exacerbation. Inclusion criteria: age over 18 years, clinically and laboratory confirmed diagnosis of chronic recurrent cystitis of HPV etiology, and signed consent to participate in the study. Exclusion criteria: age over 45 years, cystitis caused by other non-infectious causes (interstitial, radiation, chemical, foreign-bodies, drug-induced); proven neurogenic dysfunction of the lower urinary tract; sexually transmitted diseases; infectious and inflammatory diseases of the upper urinary tract; infectious and inflammatory diseases of the female reproductive system; bladder stones; bladder outlet obstruction; concomitant cardiovascular, neurological, endocrine, systemic diseases; hormonal disorders of female reproductive system; prior or current history of oncological diseases; congenital anomalies of the urinary tract and female reproductive system; immunodeficiency states of various origins; pregnancy/lactation, menopause and the postmenopause; contraindications to general anesthesia.

Initial examination of patients included history taking and bacteriological examination of the morning midstream urine to exclude the bacterial cystitis. Bladder damage by HPV was confirmed by polymerase chain reaction (PCR) test of the morning midstream urine, urethral and vaginal swabs, and cytological examination of 24-hours urine. The final distribution of groups was performed after cystoscopy. In group I (n=70), a chronic recurrent cystitis of HPV etiology was diagnosed, while in group II, 15 patients with leukoplakia were included.

Bladder biopsy. During the remission phase of the cystitis, all patients underwent standard cystoscopy after premedication under general anesthesia. "Cold" biopsies were taken from the altered areas. The obtained morphological material was fixed in a solution of neutral 10% buffered formalin «HistoSafe®» (OOO «ErgoProduction», St. Petersburg, Russia) with a 24-hour exposure. Histological processing (dehydration-degreasing, enlightenment, paraffinization) was performed using standard technology in a tissue processor. Sections from paraffin blocks of 3-5 μm thick were obtained using a Leica RM 2265 rotary microtome (Leica Microsystems GmbH, Wetzlar, Germany), stained with Hematoxylin-eosin [H&E] (BlikMedicalProduction, Russian Federation). Microscopy of the slides was done using a direct light microscope Leica DM2000 (Leica Microsystems GmbH, Wetzlar, Germany) in resolutions x100, x200, x400. Photofixation of pathomorphological changes was performed with a digital camera Leica DFC295 3 Mpx (Leica Microsystems GmbH, Wetzlar, Germany). During microscopic study, the urothelium, signs of tissue inflammation, features of the cellular infiltrates and pathological transformation of tissues were evaluated.

Results. During cystoscopy in patients of group I, a presence of exophytic, polypoid whitish, whitish-gray lesions localized in most cases in the bladder trigone was found during cystoscopy (*Fig. 1*).

Unlike leukoplakia, whitish lesions in chronic recurrent cystitis, associated with HPV, are characterized by multiple separately located, merging pathological structures like snow. This is called «a positive symptom of snow or snowstorm», which was seen in the group I in 96 (100%) patients. At the same time, abnormalities in the bladder trigone were noted in 76 (79.2%) cases, in the bladder trigone in combination with the lateral wall of the bladder in 25 (26.0%), and abnormalities in whole bladder in 1 (1.0%) patient. After contact with a cystoscope, polypoid formations are easily separated from the bladder wall and do not cause bleeding.

In patients of group II, a single lesion (patch) with a «positive carpet symptom» rising above the urothelium was found. Localization of leukoplakia in most cases [n=10; 66.7%] was noted in the bladder trigone, while in 5 (33.3%) patients there was an additional lesion at the lateral wall (*Fig. 2*).

In morphological analysis, there was chronic inflammation in all patients in group I with signs of HPV lesions in the mucous membrane with hyperplasia, squamous cell subtotal or total metaplasia. In most cases it manifested as lymphocytic infiltration with an admixture of plasma cells, in addition to impairment of the vascular architectonics and mucosal edema. All patients had total koilocytic transformation of the urothelium. In most cases, koilocytes were randomly located in the epithelium and were characterized by abnormal, sharply enlarged, dark, irregularly shaped nuclei with a folded borders and a perinuclear zone or a halo of enlightenment. In addition, most altered urothelial cells in HPV showed pronounced dystrophic changes in the nuclei, including hyperchromatism, hypertrophy, karyorrhexis, and karyopyknosis (*Fig. 3*).

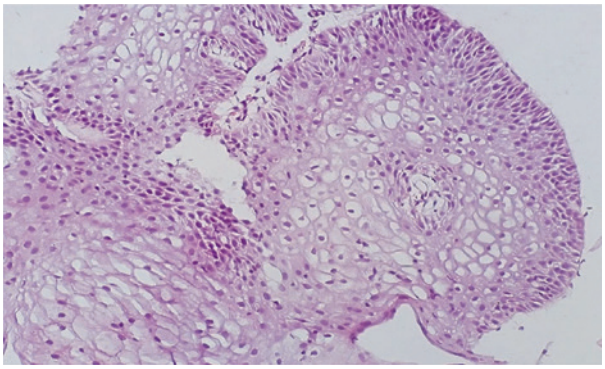


Fig. 3. Morphological study. Pathological reorganization of urothelial cells: papillomatous hyperplasia with signs of HPV infection (koilocytosis, dyskaryosis). [H&E, magnification x200]

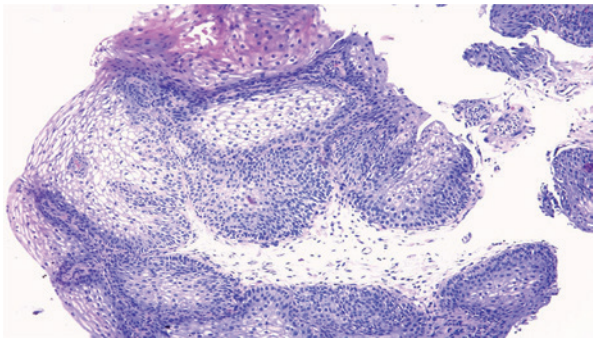


Fig. 4. Morphological study. Pathological reorganization of urothelial cells: squamous cell metaplasia with keratinization, hyperkeratosis [H&E, magnification x100]

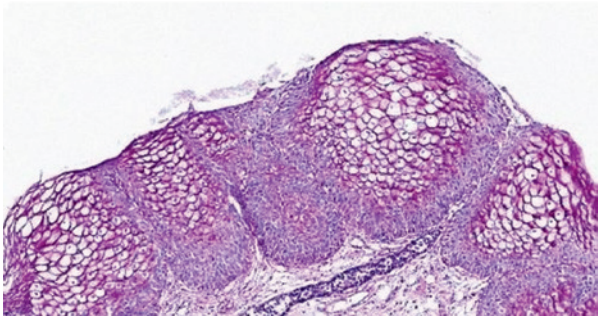


Fig. 5. Morphological study. Pathological reorganization of urothelial cells: squamous cell metaplasia with eosinophilic staining of flat hyperkeratotic (glycogenized) flat epithelium [H&E, magnification x100]

In all patients in group II, the pathomorphological picture was characterized by the presence of squamous cell metaplasia with a pronounced keratinization of the urothelium, combined with hyperkeratosis (*Fig. 4*).

In addition, 13 (86.7%) patients had metaplasia with diffuse hyperkeratosis (*Fig. 5*).

Discussion. According to the literature, leukoplakia is a cause of 7-8% of hospitalizations of women with non-oncologic bladder lesions, which suggests that it may not be as rare as other studies have shown [3]. Most urologists consider non-oncologic bladder diseases with a typical lesion of the bladder trigone as leukoplakia. In addition, leukoplakia is a «waste basket» for all underdiagnosed bladder conditions [4]. The leading method of differential diagnosis of bladder proliferative diseases is cystoscopy with a biopsy and morphological examination [13, 14]. The main morphological sign of leukoplakia is the presence of squamous cell keratinizing metaplasia of the urothelium. Non-keratinizing squamous cell metaplasia is often observed without clinical manifestations. It is localized in the bladder trigone (especially in women) and is rich in glycogen. This is considered a variant of normal histology without an increased risk of neoplastic progression and predisposing factors. However, in the presence of a long-term infectious and inflammatory process, neurogenic dysfunction of the lower urinary tract associated with chronic urinary retention, dysfunction of local immunity, dysbiosis of the urinary tract, squamous cell metaplasia can transform into keratinizing [4]. Cystoscopically keratinizing metaplasia (leukoplakia) is designated by many authors as any whitish exophytic lesions in the bladder trigone. In our study, we proposed diagnostic approaches to the differential diagnosis of leukoplakia and chronic recurrent cystitis, associated with HPV. The main diagnostic methods that allow identifying and describing squamous cell metaplasia are cystoscopy, biopsy and morphological examination [12].

Conclusion. The morphological method is the gold standard in the differential diagnosis of leukoplakia and papillomavirus cystitis. In leukoplakia, there is keratinizing squamous cell metaplasia, which is combined with hyperkeratosis. Conversely, in chronic recurrent cystitis, associated with HPV, non-keratinizing metaplasia is found in combination with koilocytic changes.

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