



Clinical – Immunological Characteristics Urogenital Candidiosis in Pations with Pulmonary Tuberculosis

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ABSTRACT

Candidal lesions of the mucous membrane of the genital organs - Urogenital candidiosis (UGK) — wide widespread disease in women of reproductive age. Its share in the structure of infectious pathology of the lower parts urogenital systems is from 24 to 45%. Approximately 75% of women experience at least one episode of vulvovaginal candidiasis during their lifetime, 40-45% have two or more episodes, 10-20% develop a complicated process, requiring long treatment [1-4]. In recent decades, candida infection has been considered How disease contemporary civilization, "disease from treatment", being reflection of dynamic changes etiological structures infectious pathology on background urbanization of society, widespread uncontrolled use of drugs funds, environmental stress and social problems that have a negative impact on human health. The very fact of the disease, itch, discomfort, pain cause at patient current psychological stress, feeling self-doubt, significantly reducing the quality of life.

Keywords:

Urogenital candidiasis, pulmonary tuberculosis, immunogram, complex treatment

Introduction. Among the factors contributing to the development of UGC, a significant role is played by hormonal imbalance, metabolic disorders, the state of the immune system, urogenital contacts, mechanical and chemical injuries, etc. [5]. One of the common causes is considered to be a change in the normal microbiocenosis of the mucous membranes and skin due to irrational or forced use. antibacterial drugs [6]. In the case of using antibiotics of various classes and as the duration of their administration increases, the risk of developing the disease increases [7]. Particularly severe forms of UGC develop in individuals with chronic infectious diseases, such as tuberculosis lung, When cessation of long-term systemic antibiotic therapy is impossible and adverse factors (changes in the state of the immune system due to the underlying disease and long-term medication)

are added up. Important place V pathogenesis UGC assigned impaired immunological reactivity. x characteristic counts switching immune response with Th1 on Th2 profile With products histamine, prostaglandin E₂, interleukins (IL)-4, 5, 6, 10 And immunoglobulin G (IgG). In recent publications, the greatest attention is paid to mucosal immunity in both men and women [8, 9]. From the modern point of view, local immune responses Although And are inseparable And subordinate part of the functioning of a single immune system, nevertheless, they have some autonomy And before last time remain the least studied link in the antimicrobial protection of the urogenital tract [10]. Among the factors of secretory immunity that are of fundamental importance in ensuring the optimal level of antimicrobial protection of the genital mucosa bodies, special

interest is participation in the pathological process of IL-8 and tumor necrosis factor- α (TNF- α), as well as terminal stable metabolites NO, inducing systemic and local inflammatory immunopathological reactions. The pathogenetic role of these mediators in urogenital candidiasis has not been studied before the end. Although their detection V vaginal discharge can be a prognostic sign of the course diseases.

Absence information By this issues Not allows you to develop methods for effective, pathogenetically justified therapy UGK at patients suffering from chronic infectious diseases, whose quality of life is significantly reduced due to the underlying process. In this context, the study of the problem of urogenital candidiasis at women, for a long time receiving ant i- bacterial therapy By about chronic infectious diseases is quite relevant [eleven].

Aim of the study research appeared analysis clinical and immune changes developing at patients with urogenital candidiasis for a long time taking antibiotic therapy for tuberculosis lung, For clarifications features currents and some immunological aspects pathogenesis diseases.

Material and Methods The study was approved by the local ethics committee Tashkent medical academy. To achieve this goal, 346 women V age 18-55 years (average age 35 years), who were on stationary treatment about various forms tuberculosis lungs. From of them 198 (57.2%) women had infiltrative tuberculosis lung, 103 (29.8%) — focal pulmonary tuberculosis, 32 (9.2%) — disseminated pulmonary tuberculosis, 13 (3.7%) - caseous pneumonia. The number and doses of antibiotics taken at all sick were the same And did not depend on the form of pulmonary tuberculosis. At the second stage of work, taking into account the inclusion and exclusion criteria were formed two groups sick. The main group consisted of 133 patients with UGC and pulmonary tuberculosis, the control group - 87 patients with pulmonary tuberculosis without UGC. Criteria inclusion sick V study served: the presence of pulmonary

tuberculosis; duration of antibiotic therapy for more than 1 month; voluntary consent to participate in the study. The criteria for exclusion of patients were: the presence of non-pulmonary forms of the tuberculosis process or severe forms tuberculosis lung, requiring surgical intervention; duration of antibacterial therapy less 1 months; age younger 18 years and older 55 years; social maladaptation patient, alcoholism, drug addiction.

All women underwent a clinical examination of the genitourinary organs, including transvaginal palpation urethra, inspection V mirrors and bimanual examination of the uterus and appendages, ureteroscopy, vaginoscopy and ultrasound examination of the pelvic organs. To quantify and describe the changes that have developed were used "Index scales symptoms" (ISHS) And "Index quality life" (KJ) . At development _ "Index quality life" behind basis did the "Indices of the quality of life of patients in dermatovenereology " [12] and the questionnaire "Change in the quality of life due to the disease" developed by V.P. Zaitsev and T.A. Ayyvazyan (2003), modified taking into account the stay of the interviewed patients in a hospital, the presence of a severe somatic process, the need to correct behavior due to the underlying disease [13]. Eight parameters were evaluated with amplitude from 0 to 3 points. How higher was total score, topics below QOL. The maximum value (24 points) corresponded himself low level QOL. By similar scheme appreciated clinical manifestations diseases: ISHS had 7 components, the maximum value was 21. The modified QoL index questionnaire is given in Appendix 1.

Verification of the diagnosis of UGC (B37.3 and B37.4) was based on microscopic examination of gram- stained preparations (the predominance of vegetative forms of fungi) and culture . (height colonies mushrooms V quantity over 10^3 cfu/ml) With subsequent identification strain pathogen.

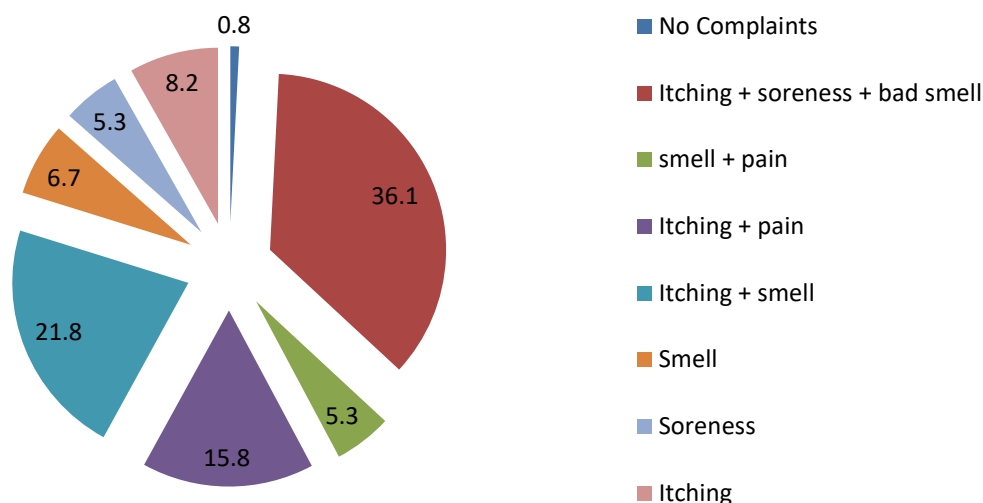
On third stage work For definitions nature of changes in mucosal immunity in women With tuberculosis lungs V case

accession UGK method of random numbers were selected patients, which was carried out immunological study vaginal secret. So, from main group were selected 40 sick, from control group — 16 women. IN vaginal secret the content of lysozyme, lactoferrin, secretory immunoglobulin A (sIgA), total IgG, IgG1 - IgG4, CH-50, C1 - C5 components of the classical complement activation pathway, TNF-a and IL-8, lipid peroxidation activity were studied. The materials were processed by the method of variation statistics using the Microsoft computer program Excel (version 5.0)

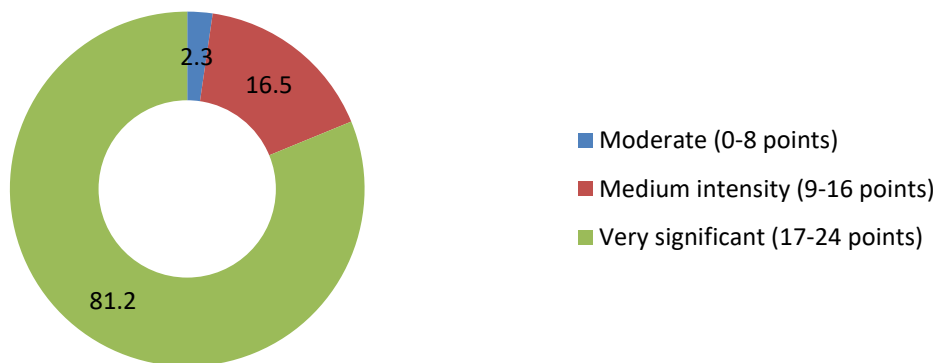
Results and discussion. UGC was diagnosed in 158 (45.7%) women with pulmonary tuberculosis who received antibiotic therapy for more than 1 year. When identifying the pathogen, *Candida* was the predominant species. *albicans* — in 122 (77.2%) patients. *C. tropicalis* was next in frequency. — in 20 (12.5%) patients, *C. parapsilosis* — in 8 (5.0%), *C. krusei* and *C. pseudotropicalis* - 5.3%. The frequency of development of the candidal process did not depend on the clinical form of pulmonary tuberculosis, since the doses of antibacterial drugs taken did not differ. UGC in women, as a rule, is accompanied by pronounced subjective sensations, among which intense itching predominates, which significantly reduces the quality of life of patients. In patients with pulmonary tuberculosis who received antibiotic therapy for a long time, not only itching and sour smell, but also soreness were noted (Fig. 1). These sensations (itching, unpleasant odor and soreness) occurred in 48

(36.1%) women. Itching alone or in combination with other symptoms occurred in 109 (82.0%) patients, most often it bothered women at night, and also after a hot bath. The intensity of the patient's itching was assessed mainly at 3 points, i.e., as very strong. In 62 patients, due to intense itching of the vulva, sleep disorders were observed (more than 7 days). In 4 women, itching had a " biopsing " character, as evidenced by the presence of excoriations and superficial scars on the vulvar mucosa. 35 (26.3%) patients complained of pain in the vulva and vagina. Only 1 patient with UGC had no complaints. The observed women rated their subjective sensations at an average of 21.3 points, with a maximum index of 24 points (the higher the index, the more pronounced the subjective sensations). Subjective sensations, depending on the severity, were divided by us into 3 groups: very significant (with indicators of 17–24 points), medium intensity (with indicators of 9–16 points) and moderate (0–8 points) (Fig. 2). Only 3 (2.3%) women considered the sensations moderate (average 10.5 points), 22 (16.5%) patients regarded them as medium in intensity, and the majority - 108 (81.2%) - very significant. When comparing the QoL index in patients with pulmonary tuberculosis with and without MHC, it turned out that even in the absence of MHC, it was significantly reduced (average 18 points). In cases of joining the UGC, the QOL index decreased more significantly and averaged 22 points (with a maximum value of 24 points).

Frequency of occurrence (in%) Subjective sensations in patients with UGC



The frequency of occurrence (in%) of subjective sensations in patients with candidiasis, depending on their severity



As a result of a clinical examination, it was found that out of 133 patients of the main group, in 59 (44.3%) the pathological process occupied only the vulva region, in 7 (5.3%) - the vagina, in 60 (45.1%) there was candida vulvovaginitis, in 7 (5.3%) the process covered the area of the vulva, vagina and cervical canal. Clinical manifestations of UGC in patients (according to the classification of A.A. Antoniev et al. (1985) [14]) are presented in Table. 1. In accordance with the

specified classification, acute and subacute catarrhal-membranous vulvitis was considered inflammation of the vulva, accompanied by intense or moderate hyperemia with a purple-bluish tint, swelling and dryness of the mucous membrane, the presence of white, crumbly, easily removable curdled films between the labia minora. chronic catarrhal vulvitis was diagnosed in cases where congestive hyperemia and infiltration, sometimes lichenification and

dryness, were observed in the mucous membrane of the external genital organs. In the area of closure of the labia minora, erosions and/or cracks were determined. Acute and subacute catarrhal-exudative membranous colpitis was manifested by diffuse congestive hyperemia, swelling, dryness of the mucous membrane and thickening of the vaginal folds, in the depths of which were found tiny curdled films that were easily removed with a swab, and bright red erosions. Chronic catarrhal colpitis was accompanied by slight congestive hyperemia and dryness mucous membrane, which was covered with a small amount of whitish-transparent films. Acute, subacute and chronic vulvovaginitis was considered a combination of lesions of the vulva and vagina with their characteristic manifestations. Of the 133 observed patients, despite the presence of pronounced subjective sensations, acute forms of the disease were detected only in 21 (15.8%) women, subacute - in 83 (62.4%), chronic — in 29 (26.3%). The most frequent clinical manifestation was subacute catarrhal-exudative membranous vulvovaginitis observed in 40 (30.1%) patients. Subacute vulvitis was the next in frequency - in 32 (20.1%) women, chronic vaginitis was less common - in 2 (1.5%). In the contingent examined by us, there were no acute and atypical forms of vaginitis, lesions of the surrounding skin. In addition to the described clinical manifestations in patients with UGC and pulmonary tuberculosis, who received antibiotic therapy for a long time, there were infiltrative forms of damage to the mucous membrane of the vulva and vagina. So, in 22 women with subacute and 10 with chronic candidal vulvovaginitis, in addition to the described changes, there were areas of infiltration of the mucous membrane of the vestibule of the vagina and the lower $\frac{1}{4}$ of the vagina without clear boundaries, dense consistency, the color did not differ from the surrounding mucous membrane, narrowing the entrance to the vagina. When viewed with a vaginal mirror, the infiltrates were easily injured and bled. As indicated in the methodological part of the work, during a

clinical examination, patients were diagnosed with ICS, the maximum value of which was 21 points. Depending on the severity of the inflammatory process and the magnitude of the ischemic heart disease, all forms of UGC were divided into 4 groups: severe form with infiltration (17–21 points), severe form (11–16 points), moderate form (6–10 points) and mild form (0–5 points). On fig. 3 shows that in 32 (24%) patients who had an infiltrative form of vulvovaginitis, the condition could be assessed as the most severe. In 75 (56.4%) women, the form of the lesion was severe (SSI ranged from 11 to 17 points). Only 8 (6.1%) patients had a mild form of the inflammatory process. The activity of the inflammatory process, identified clinically, was confirmed by the composition of the vaginal secretion and the number of leukocytes in the discharge. In 74 (55.6%) women, the number of neutrophils in the vaginal secretion exceeded 30 per field of view, although a clinically acute process occurred only in 15.7% of patients. In 56 (42.1%) women, the number of neutrophils was 11–30 in the field of view, in 3 (2.3%) - 0–10 in the field of view. Analysis of indicators of congenital mucosal immunity in the vaginal secretion of women with pulmonary tuberculosis testified to a decrease in the phlogogenic, antimicrobial potential (complement and lactoferrin) against the background of an increase in the anti-colonization barrier (mucin) of the mucous membranes of the genitourinary organs. The maximum level of mucin found in patients with UGC may reflect an increase in the function of goblet cells of the mucous membranes of the genital tract during the development of candidal lesions in this localization. In turn, lactoferrin, being an iron transporter, has a pronounced microbicidal property, and its deficiency can significantly reduce the antimicrobial potential of the secret [15]. In addition, lactoferrin belongs to the mediators of the acute phase of inflammation, so its deficiency affects the anti-inflammatory potential of the secretion and the severity of the inflammatory process. The revealed decrease in the total complement activity may be due to increased consumption

of its individual components during the formation of immune complexes, destruction of components by mycobacteria, changes in the production of these proteins by macrophages and other cells of the urogenital region.

All patients with pulmonary tuberculosis, both without the addition of UGC and with the development of concomitant candidal lesions, showed a significant decrease in the concentration of all studied

classes and subclasses of immunoglobulins compared with the control group of healthy women. It should be emphasized that the level of sIgA in women with tuberculosis and UGC was 2 times higher than that in patients without candida infection. With a high degree of reliability, in UGC, in comparison with the control group of healthy people, the content of all final stable NO metabolites, as well as the level of pro-inflammatory cytokines IL-8, TNF- α , decreased (Table 1).

Table 1

The main indicators of secretory immunity of the mucous membranes of the genitourinary organs in women with pulmonary tuberculosis and UGC

Index	Patients with pulmonary tuberculosis and UGC (n = 40)	Patients with pulmonary tuberculosis without UGC (n = 16)	Healthy (n =20)	Reliability		
				P 1-3	P 1-2	P 2-3
Protein, g / l	4.51	6.71	1.94	0.001	0.001	0.001
Mucin, g / l	3.20	2.22	1.29	0.001	0.023	0.001
Lactoferrin , ng per 1 mg of protein	282.85	288.38	503.29	0.002	0.624	0.001
CH-50, mg protein 108 units eff. say . per 1 mg of protein	2.86	1.27	4.27	0.010	0.001	0.001
C 1	0.50	0.32	1.17	0.006	0.142	0.003
C 2	0.50	0.32	1.17	0.006	0.142	0.003
C 3	0.34	0.46	0.60	0.101	0.128	0.726
C 4	0.42	0.40	1.34	0.001	0.957	0.001
C 5	0.42	0.47	0,	0.008	0.870	0.039
Immunoglobulins, mg per 1 mg of protein						
sIgA	23.77	14.68	44.26	0.001	0.026	0.001
IgG	0.163	0.267	0.409	0.001	0.057	0.05
IgG 1	0.047	0.058	0.134	0.001	0.261	0.06
IgG 2	0.052	0.057	0.165	0.003	0.537	0.001
IgG 3	0.015	0.011	0.025	0.001	0.101	0.001
IgG 4	0.003	0.003	0.008	0.010	0.814	0.001
NO ₂ , μ mol	0.45	0.22	0.90	0.001	0.025	0.001

per 1 g of protein						
NOX, μmol per 1 g of protein	2.46	1.68	4.28	0.002	0.001	0.001
NO ₃ , μmol per 1 g of protein	1.99	1.39	3.29	0.001	0.006	0.001
TNF- α , pg per 1 mg protein	0.73	0.52	1.57	0.001	0.007	0.001
IL-8, pg per 1 mg of protein	1.08	0.38	1.98	0.002	0.001	0.001

Based on the data presented, it can be assumed that it is the minimum level of sIgA, which determines the antimicrobial and anticolonization properties of the mucosal barrier, is lower than in healthy individuals, the content of IgG and its subclasses, lactoferrin, which determines the antimicrobial activity of biological fluids, the minimum level of NO, which is of great importance for intracellular killing in macrophages and initiation of inflammation, as well as the minimum level of pro-inflammatory cytokines (TNF- α , IL-8) in the vaginal secretion are the leading immune mechanisms for reducing the antifungal resistance of the mucous membranes of the urogenital tract of women in the conditions of specific treatment of the tuberculosis process in the lungs, leading, despite the high level of mucin, to fungal colonization.

Conclusions.

1. When examining 346 patients who received long-term antibiotic therapy for pulmonary tuberculosis, the diagnosis of UGC was established in 158 (45.7%) women.

2. The prevailing type of the causative agent of candidiasis in these patients was *C. albicans* isolated from 103 (77.4%) people. *C. tropicalis* found in 17 (12.7%) patients, *C. parapsilosis* — in 7 (5.3%), *C. krusei* — in 3 (2.3%), *C. pseudotropicalis* — in 3 (2.3%) women.

3. The most common were severe (in 56.4% of patients) forms of the disease, which significantly reduced the quality of life of patients. In 32 women, a rare candidal

infiltration of the vulvar mucosa occurred.

4. Colonization of the mucous membranes of the urogenital area with fungi of the genus *Candida* and the development of inflammation in response to candida infection in women who received specific treatment for pulmonary tuberculosis were accompanied by an increased content in the vaginal discharge of leukocytes (up to 30 per field of view), mucin, sIgA levels, pro-inflammatory laboratory markers: terminal stable metabolites NO, TNF- α and IL-8, as well as an increase in total complement activity.

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