Clinical Case Reports International

Short Communication
Published: 14 Apr, 2022

# Changes of Microbiota and Inflammation Index in the Genital Tract Mucosa of Women with Respiratory Tuberculosis during Chemotherapy

*Kayukova SI, Lulueva ZS, Karpina NL, Ulumdzhieva VA, Sterzhanova NV and Nikonenko BV**

*Department of Immunology, Central Research TB Institute, Russia*

## Short Communication

Microbiome can affect the efficacy of drugs, as well as the use of antibiotics affects the microbiota composition [1]. Vaginal microbiome plays key role in woman reproductive health and its composition can be damaged during lengthy chemotherapy of respiratory tuberculosis [2,3].

We studied an influence of TB chemotherapy on woman vaginal microbiome composition and development of local inflammation process. The study involved women of childbearing age.

The study of the vaginal biocenosis was carried out by real-time PCR using the Femoflor reagent (manufacturer: LLC NPO DNA-Technology, patent No. 2362808 dated February 13th, 2008).

Statistical analysis was performed using scripts in the programming language R version 3.5 in the R Studio. Differences between means were assessed by use of the Mann-Whitney test. The critical level of significance was p<=0.05.

In patients with respiratory tuberculosis before the start of Chemotherapy (CT), vaginal microbiocenosis was characterized by the prevalence of *Lactobacillus* spp. – 6.1 [5.5; 6.8] genome/equivalent (g/e). Among the microorganisms forming Conditionally Pathogenic Flora (CPF), low values of Enterobacteriaceae were noted - 2.0 [1.9; 2.8] g/e, *Staphylococcus* spp. - 2.0 [1.6; 2.7] g/e, *Sneathia* spp. + *Leptotrichia* spp. + *Fusobacterium* spp. - 1.4 [0; 2.6] g/e, *Megasphaera* spp. + Veillonella spp. + *Dialister* spp. – 1.8 [0.0; 2.8] g/e, *Lachnobacterium* spp. + *Clostridium* spp. – 2.2 [1.7; 2.6] g/e, *Mobiluncus* spp. + *Corynebacterium* spp. - 2.8 [2.0; 3.1] g/e, *Peptostreptococcus* spp. – 2.2 [0; 3.0] g/e, as well as the absence of *Gardnerella vaginalis* - 0 [0; 2] g/e, *Atopobium vaginae* - 0 [0; 1.5] g/e, *Mycorlasmahominis* - 0 [0; 0] g/e; *Mycorlasmagenitalium* - 0 [0; 0] g/e; *Ureaplasma* (*urealyticum+parvum*) - 0 [0; 1.5] g/e and *Candida* spp. - 0 [0; 2.6] g/e.

After 60 and 150 days of CT *Lactobacillus* spp were not registered. The content of Enterobacteriaceae, *Staphylococcus* spp., *Sneathia* spp. + *Leptotrichia* spp. + *Fusobacterium* spp., *Atopobium vaginae*, *Candida* spp. gradually from day 0, through 60 and to the 150 increased. *Gardnerella vaginalis* has appeared.

Also, after 60 and 150 days of chemotherapy, a quantitative increase in *Eubacterium* spp.; *Lachnobacterium* spp. + *Clostridium* spp. but without statistical significance. In the course of chemotherapy, the state of the vaginal microbiota was transformed from a predominantly normocenosis (before CT initiation), through an intermediate type (day 60), to an inflammatory type (day 150).

In addition, we assed local inflammation of the lower sections of woman reproductive tract by determining the expression profile of innate immunity mRNA genes by real-time PCR (test system "ImmunoQuantex C/V", manufacturer - NPO DNA-Technology LLC, patent No. 640119 dated 01.04. 2016). Scrapings of epithelial cells from the posterolateral fornix of the vagina and cervical canal were used as biological material.

The conclusion about the presence of a local inflammatory reaction was made on the basis of the calculation of the value of the Inflammation Index, carried out by the software of the detecting cycler in automatic mode. To assess the validity of the obtained results, the cDNA amplification index of the reference β2m gene was taken into account. Primers and DNA probes were selected taking into account the structure of the genes encoding the mRNA of cytokines and did not give a positive result on the genomic DNA template.

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***Correspondence:***
*Boris V Nikonenko, Department of Immunology, Central Research TB Institute, Russia,*
*E-mail: boris.nikonenko52@gmail.com*

**Received Date**: *23 Mar 2022*
**Accepted Date:** *08 Apr 2022*
**Published Date:** *14 Apr 2022*

***Citation:***
*Kayukova SI, Lulueva ZS, Karpina NL, Ulumdzhieva VA, Sterzhanova NV, Nikonenko BV. Changes of Microbiota and Inflammation Index in the Genital Tract Mucosa of Women with Respiratory Tuberculosis during Chemotherapy. Clin Case Rep Int. 2022; 6: 1313.*

**Table 1:** List of mRNAs of genes detected using the ImmunoQuantex C/V reagent kit.

| Tube number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Name of the mRNA gene | IL1β | IL10 | IL18 | TNFα | TLR4 | GATA3 | CD68 | β2m |

**Table 2:** Interpretation of the study results.

| Inflammation Index, % | Interpretation | Conclusion about the presence of a local inflammatory reaction |
|---|---|---|
| <50 | Low | Absent |
| 50-60 | Intermediate | Cannot be ruled out |
| >60 | High | Revealed |

**Table 3:** Dynamics of pro-inflammatory cytokines in the vaginal discharge in patients during chemotherapy monitoring (g/e) Me [quartiles].

| Proinflammatory molecule | Days of chemotherapy | | | | | p 1-60-150 |
|---|---|---|---|---|---|---|
| | Before CT | 60 | p 1-60 | 150 | p 1-150 | |
| IL1B | 5.1 [4.9; 5.6] | 6.3 [6; 7] | 0.000 | 7 [6.2; 7.5] | 0.000 | 0.000 |
| IL10 | 2 [1.1; 2.4] | 3.4 [1.9; 3.6] | 0.000 | 4 [2.5; 4.2] | 0.000 | 0.000 |
| IL 18 | 4 [3.1; 4.4] | 4 [3.4; 4.4] | - | 5.5 [4; 5.8] | 0.000 | 0.000 |
| TNFα | 2.9 [2.6; 3.2] | 4.3 [3; 4.7] | 0.004 | 5.7 [3.2; 6] | 0.000 | 0.000 |
| TLR4 | 2.3 [2; 2.6] | 2.8 [2; 3.2] | - | 4.2 [2.5; 4.1] | 0.000 | 0.000 |
| GATA3 | 3.9 [3; 4.2] | 5 [4; 5.6] | 0.000 | 5.7 [4.1; 6.3] | 0.000 | 0.000 |
| CD68 | 3.9 [3.6; 4.4] | 5.5 [4; 6] | 0.000 | 6.2 [4.8; 7] | 0.000 | 0.000 |
| B2M | 4.6 [4.1; 4.9] | 6 [4.6; 6.4] | 0.000 | 6.6 [5.3; 7] | 0.000 | 0.000 |
| TLR4/GATA3 | 0 [0; 0.1] | 0.1 [0; 0.5] | - | 0.2 [0.1; 0.8] | - | 0.000 |
| TNFA/IL18 | 0.1 [0; 0.8] | 0.5 [0.1; 0.9] | - | 0.9 [0.4; 1.6] | - | 0.000 |
| IL10/IL18 | 9.5 [1.3; 10] | 9.4 [4; 16.5] | - | 12 [4.5; 16] | - | 0.001 |
| IL1B/CD68 | 10.9 [5.8; 14] | 11.6 [2.3; 28.5] | - | 11 [3.5; 14.3] | - | 0.000 |
| Inflammatory index (%) | 33.1[3.4; 44.8] | 76.9[61.5; 100] | 0.000 | 89 [45.5; 100] | 0.000 | 0.000 |

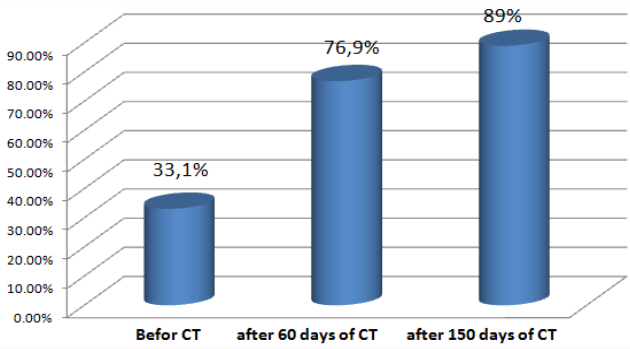


**Figure 1:** Dynamics of the inflammation index in the genital tract mucosa in patients with tuberculosis before, after 60 and 150 days of chemotherapy.

The list of mRNAs of genes detected using the ImmunoQuantex C/V reagent kit is presented in Table 1.

The diagnostic (clinical) specificity of detecting a local inflammatory reaction is 96.8 (88.8% to 99.6%). The diagnostic (clinical) sensitivity of detecting a local inflammatory reaction is 100.0 (90.7% to 100%).

Using the software, the expression ratio indices of key genes were calculated, on the basis of which the Inflammation Index was calculated. The interpretation of the inflammation index value is presented in Table 2.

Changes in RNA expression of key cytokines and markers during chemotherapy are presented in Table 3. As a rule, we see an increase in almost all markers.

Figure 1 shows the rise dynamics of the Inflammation Index during chemotherapy. The index rises from 37% on day 0 to 76.1% on day 60 and to 89% on day 150.

In fertile tuberculosis patients a correlation analysis was performed to establish the relationship between the content of *Lactobacillus* spp., conditionally pathogenic microflora, and the inflammation index. A direct correlation was found between the conditionally pathogenic flora and the inflammation index after 60 days of chemotherapy ($r=0.2$; $p \leq 0.01$) and after 150 days of chemotherapy ($r=0.3$; $p \leq 0.02$), as well as an inverse correlation between *Lactobacillus* spp. and inflammation index after 60 days of chemotherapy ($r= -0.2$, $p \leq 0.01$) and after 150 days of chemotherapy ($r= -0.3$, $p \leq 0.03$).

Thus, during chemotherapy, pathological changes in the vaginal microbiota increase, the inflammation index increases, and an inverse correlation with *Lactobacteria* sp. is observed.

In conclusion, we can assert that chemotherapy of tuberculosis causes more damage to the microbiome and health of the female genital organs than tuberculosis itself.

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