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Local levels of lymphocytes and cytokines in colon cancer patients with bowel obstruction

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ABSTRACT

Purpose of the study. To study local immunity and cytokine levels in colon cancer patients with subcompensated intestinal obstruction.

Patients and methods. In 60 patients with locally advanced left-side colon carcinoma (30 with and 30 without bowel obstruction) during the surgery samples of tumor, peritumoral area and resection line tissue were obtained. After disintegration of tissue samples T-, B-, NK-lymphocytes` subsets (CD3+, CD4+, CD8+, CD4+CD25+CD127dim, CD19+, CD16+CD56+) were studied by flow cytometry and inflammatory cytokines` content (TNF-α, IL-1α, IL-6, IL-8) via ELISA test.

Results. Higher levels of interleukins were shown in the tumors of patients in both groups compared to the tumor-free tissue samples. In the presence of subcompensated intestinal obstruction, local levels of proinflammatory cytokines were higher than in patients who did not have it: IL-6 and IL-1a in all tissues studied, IL-8 in tumor and peritumoral zone samples; TNF-α – in the tumor and the resection line. In the absence of intestinal obstruction in the tumor tissue, compared with non-tumor samples, the content of T-lymphocytes was increased due to CD4+ and CD8+, and Tregs levels were lower. These differences were leveled in the presence of intestinal obstruction, i. e. accumulation of T-lymphocytes in the tumor, providing adaptive immunity, was not observed in such patients. Their lower levels of CD8+ T cells and higher levels of Tregs in the tissue of the resection line form a low cytotoxic potential of the tissue remaining after surgery.

Conclusions. The presence of subcompensated intestinal obstruction in patients with colon cancer leads to a number of quantitative changes in local immunity factors compared with patients in whom it was not detected or was compensated. Among these changes, a particularly unfavorable content of pro-inflammatory cytokines, in particular IL-6, in the tissue of the resection line, along with a lower number of CD8+ T lymphocytes and a higher number of Tregs, which suggests a decrease in antiproliferative potential not only in the tumor, but also in non-tumor tissues.

Keywords: colon cancer, bowel obstruction, cytokines, lymphocytes, local immunity

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013, were observed in the work. The study was approved by the Committee on Medical Ethics of the National Research Medical Center of Oncology (extract from the minutes of meeting No. 2 dated 01/22/2021). Informed consent was obtained from all participants in the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Локальные уровни лимфоцитов и цитокинов у больных раком ободочной кишки при субкомпенсированной кишечной непроходимости

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РЕЗЮМЕ

Цель исследования. Изучение факторов локального иммунитета и состава ряда интерлейкинов у больных раком ободочной кишки при субкомпенсированной кишечной непроходимости.
Пациенты и методы. У 60 больных местнораспространенным раком левого фланга ободочной кишки (30 с субкомпенсированной кишечной непроходимостью и 30 без нее) при проведении операции, выполненной первым этапом лечения, брали образцы тканей опухоли, перитуморальной зоны и линии резекции, в которых методом проточной цитометрии изучали состав субпопуляций Т-, В-, NK-лимфоцитов (CD3+, CD4+, CD8+, CD4+CD25+CD127dim, CD19+, CD16+CD56+), иммуноферментным методом – уровни цитокинов (IL-6, TNF-α, IL-1α, IL-8).
Результаты. Исследования показали более высокие уровни интерлейкинов в опухолях больных обеих групп, чем в неопухолевых тканевых образцах. При наличии субкомпенсированной кишечной непроходимости локальные уровни провоспалительных цитокинов были выше по сравнению с больными, у которых она не выявлена: IL-6 и IL-1α во всех исследованных тканях, IL-8 – в образцах опухоли и перитуморальной зоны; TNF-α – в опухоли и линии резекции. При отсутствии кишечной непроходимости в опухолевой ткани по сравнению с неопухолевыми образцами было повышено содержание Т-лимфоцитов за счет CD4+ и CD8+, а уровни Tregs были ниже. Эти различия нивелировались при наличии кишечной непроходимости, т. е. накопления в опухоли Т-лимфоцитов, обеспечивающих адаптивный иммунитет, у таких больных не наблюдалось. Более низкий уровень у них CD8+ Т-клеток и более высокий – Tregs в ткани линии резекции формирует низкий цитотоксический потенциал ткани, остающейся после операции.
Заключение. Наличие у больных раком ободочной кишки субкомпенсированной кишечной непроходимости приводит к ряду количественных изменений факторов локального иммунитета по сравнению с больными, у которых она не выявлена или была компенсированной. Среди этих изменений представляются особенно неблагоприятными более высокое содержание провоспалительных цитокинов, в частности, IL-6, в ткани линии резекции, наряду с более низким количеством CD8+ Т-лимфоцитов и более высоким – Tregs, что предполагает снижение антипролиферативного потенциала не только в опухоли, но и в неопухолевых тканях.

Ключевые слова: рак ободочной кишки, кишечная непроходимость, цитокины, лимфоциты, локальный иммунитет

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по медицинской этике ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 22.01.2021 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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Bowel obstruction (BO) is one of the most common complications. It is described in 20 % of cases of colon cancer, with the predominant frequency in its left flank [1]. Mechanical BO is a consequence of the cessation of the passage of chyme through the intestine due to complete or partial obstruction of its lumen, accompanied by intoxication and several metabolic, microbiological, immunological, and other disorders. As indicated in the Clinical Recommendations of 2023, the modern classification of BO that occurs in patients with colon cancer divides it according to the degree of compensation into compensated (intermittent constipation accompanied by delayed stools and difficulty in gas discharge; abdominal X-ray may show pneumatization of the colon with single fluid levels in it); subcompensated (delayed bowel movements, stool and gases for less than 3 days, small intestinal arches, pneumatosis and Cloiber's bowls in the right half of the abdomen are determined on the X-ray; there are no signs of polycranial dysfunctions; conservative therapy is effective); decompensated (retention of stool and gases for more than 3 days; radiological signs of both large and small intestinal obstruction with localization of small intestinal levels and arches in all parts of the abdominal cavity; vomiting with stagnant contents; the presence of organ dysfunctions [2]. Disorders caused by BO affect various processes. Stretching of the proximal intestine leads to stagnation of intestinal contents, buildup of toxic products, and increased inflammatory processes [3]. At the same time, the barrier function of the intestinal mucosa suffers, dysbiotic changes and bacteremia develop with the risk of peritonitis and endotoxemia [4], which are accompanied by a massive release of cytokines [5]. Many of them are tropic to vascular endothelium and cause microcirculation disorders with microthrombosis, which can also lead to necrosis of the intestinal wall with the possibility of perforation.

Immunological changes, especially local ones, in BO have been studied poorly and mainly experimentally. Therefore, an experimental model of partial obstruction of the distal colon has shown that it causes depletion of both B-lymphocytes and both major T-cell subpopulations in lymphoid organs [6]; the authors attribute this to a violation of the composition of the microbiota, hyperproduction of IL-6, corticosterone and osteopontin. The BO model shows an increase in the permeability of the colon mucosal barrier and translocation of the microbiota, which, according to the authors, also causes adverse immunological changes [7].

However, when analyzing the clinical material, attention is paid to many factors of the development of BO in patients with colon cancer (late diagnosis, macroscopic tumor morphology, vascularization and thickness of the intestinal wall, peristalsis activity), but the state of immunity is not mentioned, which indicates the unexplored nature of this problem, as shown in a recent review [1]. Only a few studies can be indirectly related to this topic: for example, the difference in the metabolome in patients with non-cancerous and tumor BO was considered, and in the latter case, the predominance of tryptophan metabolism disorders was noted [8], and, as is known, the products of altered metabolism of this amino acid have significant immunosuppressive and pro-oncogenic effects [9].

The purpose of the study was to study the factors of local immunity and the composition of several interleukins in the tissues of patients with colon cancer with subcompensated intestinal obstruction.

PATIENTS AND METHODS

The study included 2 groups of patients with locally advanced colon cancer (left side): 30 patients with subcompensated BO and 30 patients without obstruction (total n = 60). The study was approved by the Committee on Medical Ethics of the National Research Medical Center for Oncology (extract from the minutes of meeting No. 2 dated 01/22/2021. Informed consent was received from all participants in the study. Female patients prevailed in each group (54 and 56 %, respectively), the average age was 64 ± 5.5 and 65 ± 6.3 years, respectively. There were no significant differences between the groups in terms of gender, age, and the presence of concomitant diseases. Radical surgical interventions were performed in all patients during the first stage of treatment.

The exclusion criteria were the presence of preoperative drug treatment, the presence of infectious complications and peritonitis, tumor localization in the right side of the colon, decompensated intestinal obstruction.

The diagnosis of BO caused by a tumor was established preoperatively clinically and radiographically.

To assess local cellular immunity and cytokine composition, tumor tissue samples (TTS) were taken during surgery, as well as visually unchanged tissue sections, moving away proximally 1–3 cm (peritumoral zone, PZ) and 10 cm (resection line, RL) from the edge of the tumor. The concentration of interleukins (IL-1α, IL-6, IL-8) and tumor necrosis factor (TNF-α) was determined in the homogenates of the obtained tissue samples by ELISA using Vector-Best test systems (Novosibirsk) with the calculation of the specific content (per 1 g of protein determined by the biuretic method). The levels of lymphocytic subpopulations were determined in the homogenates of tissue samples using flow cytometry (FACS Canto II, BD) using the T-B-NK panel, the results were expressed as a percentage.

Statistical analysis

Statistical analysis of the results of the study was carried out using the Statistica 13.3 program (StatSoft, USA). The normality of the distribution was checked using the Shapiro-Wilk criterion. Since the distribution of the data was not normal, the Mann-Whitney criterion was used for their statistical processing; quantitative indicators were presented as the median of both the lower and upper quartiles (Me; LQ; UQ). Intergroup differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

The amount of total protein in the studied tissues did not differ significantly, the variability of data on this indicator is insignificant. The specific content of pro-inflammatory cytokines in the homogenates of the studied tissue samples of patients in the main and control groups is shown in Table 1.

As can be seen from the data presented in Table 1, the content of the studied cytokines in the tumor was statistically significantly higher than their levels in samples of both non-tumor tissues, and this was observed in both compared groups regardless of the presence of BO. Thus, in patients of both groups, the content of all cytokines studied did not differ between the peritumoral region and the resection line, and in the tumor tissue it was higher than in both non-tumor tissues.

An intergroup comparison of tissue cytokine levels revealed that the presence of BO is accompanied by a higher content of TNF-α, IL-6, IL-8, and IL-1a in tumor tissue (by 1.7, 2.2, 1.7, and 2.6 times, respectively) than in the absence of BO (for all cytokines, $p < 0.05$). The levels of IL-6, IL-8, and IL-1a in the PZ tissue of patients with BO were also statistically significantly higher than in patients without BO: 6.3, 2.3, and 2 times, respectively. In the tissue of the resection line with BO, the levels of IL-1a were 2.7 times

Table 1. Specific cytokine content in colon tumor tissues, peritumoral zone, and resection line of colon cancer patients with absence and presence of BO

Tissue samples	Specific content of cytokines (pg/g protein)							
	TNF-α		IL-6		IL-8		IL-1α	
	No BO	BO	No BO	BO	No BO	BO	No BO	BO
Tumor, Me	1.5* **	2.6* ** Δ	7.0* **	15.5* ** Δ	23.2* **	41.3* ** Δ	20.3* **	52.3* **Δ
LQ	1.0	2.3	4.5	12.8	19.5	33.4	13.5	38.9
UQ	2.1	3.1	10.0	18.7	28.7	45.8	23.6	60.7
Peritumoral zone, Me	0.5	0.9	0.8	5.1 Δ	8.2	19.2 Δ	9.2	18.1Δ
LQ	0.2	0.5	0.3	3.2	5.5	15.5	5.7	14.0
UQ	1.0	1.5	1.0	11.4	11.2	22.7	13.1	26.2
Resection line, Me	0.5	1.3 Δ	1.2	5.5 Δ	10.1	13.0	7.0	19.0 Δ
LQ	0.3	1.0	0.6	3.5	6.7	9.7	4.8	15.7
UQ	1.0	1.8	1.4	8.9	12.5	15.5	10.2	22.6

Note: * – differences from the PZ indicator; ** – differences from the RL indicator; Δ – differences between groups ($p < 0.05$)

higher, and IL-6 was 4.6 times higher than in patients without BO ($p < 0.05$). As can be seen from Table 1, the IL-6 content had the maximum differences between the compared groups in the samples of non-tumor tissues (PZ and RL) (in all cases, $p < 0.05$), and the differences in TNF-α were minimal.

The content of T-lymphocytes of the main subpopulations in the studied tissue samples of patients of the compared groups is shown in Table 2, which shows that the total number of T-cells (CD3+) in the tumor tissue of patients without BO was statistically significantly higher than in patients with subcompensated BO. These differences were observed due to higher levels of both major T-lymphocyte subpopulations (CD4+ and CD8+), while the Tregs content in these patients was 2 times lower; for all T cells, $p < 0.05$. There were no statistically significant differences between the groups in PZ, however, higher Tregs levels with lower CD8+ levels were detected in the RL tissue of patients with BO. It should be noted that in the presence of BO, the T-cell composition of PZ and RL had no statistically significant differences from the tumor tissue, whereas in the absence of BO, it was expressed in CD3+, CD4+ and CD8+ levels, which in the tumor tissue exceeded their content in non-tumor samples by 1.5–2 times.

The assessment of the content of natural killers in tumor tissue samples of patients without BO showed its higher value in PZ tissue compared with the tumor (Me 10.1 [6.4;12.5] and 4.1 [2.9;5.0] %), respectively ($p < 0.05$), which was not observed in patients with BO, in whom the level of these cells in the tumor, although it was slightly higher than in the non-tumor samples, however, without statistical significance. There were also no intergroup differences in this indicator.

The content of B-lymphocytes in the PZ and RL of both patients with and without BO was statistically significantly higher than in the tumor. Their level was minimal in the tumor samples of patients with BO (Me 4.7 [3.3;6.0] versus 19.2 [11.0;23.5] % with BO), and there were no intergroup differences in the tissues of PP and LP (in PZ of patients with BO 37.0 [24.4;41.2] versus 29.3 [15.5;34.2] without BO; in RL 37.2 [28.5;41.4] versus 29.2 [20.2;33.5] %, respectively, $p > 0.05$).

DISCUSSION

We noted a number of differences between cellular and cytokine factors in patients with colon cancer of the left flank with the presence of subcompensated BO and the absence or compensated BO. Subcompensated BO is accompanied by a number of unfavorable differences. First of all, it is a high level of tissue pro-inflammatory cytokines, including IL-6, which is

Table 2. The content of T-lymphocyte subpopulations in colon cancer tissues, peritumoral zone, and resection line of colon cancer patients with absence and presence of BO

Tissue samples	T-lymphocyte subsets (%)							
	CD3+		CD4+		CD8+		Tregs	
	No BO	BO	No BO	BO	No BO	BO	No BO	BO
Tumor, Me	88.0* **	62.2 Δ	51.4* **	39.2 Δ	38.2*	21.5 Δ	7.1	15.2 Δ
LQ	69.2	50.4	46.3	29.3	31.3	15.2	3.3	11.4
UQ	91.1	67.6	59.8	45.0	44.6	28.3	9.1	21.0
Peritumoral zone, Me	63.0	55.2	33.5*	34.3	26.2	19.9	4.4	12.0
LQ	55.4	48.4	27.4	24.2	18.0	13.3	3.1	5.8
UQ	67.2	66.1	40.1	38.1	30.4	31.4	4.9	14.9
Resection line, Me	65.6	60.2	25.1*	27.4	44.5**	25.8 Δ	3.9	9.8 Δ
LQ	61.5	52.9	14.9	21.1	35.2	18.9	1.9	4.7
UQ	68.0	69.9	30.7	30.2	47.9	30.3	4.6	12.5

Note: * – differences from the PZ indicator; ** – differences from the RL indicator; Δ – differences between groups ($p < 0.05$)

well known to have pro-oncogenic and pro-angiogenic effects, contributing to invasion, metastasis, and epithelial-mesenchymal transition [10– 11]. Its high content not only in the tumor, but also in non-cancerous tissues, primarily in the resection line, may characterize the condition of the latter as less favorable than in patients without BO. Other cytokines we studied also create a microenvironment that promotes tumor growth and spread. The pro-oncogenic effect of IL-6 is mediated through the transcription factor STAT3, and TNF-α through NF-kB, the synergistic activation of which causes the growth of colorectal cancer cells [24]. Similar properties have been described for IL-1 [25] and IL-8 [26].

As for the local content of lymphocytes, the differences we found between patients with and without BO relate primarily to the T cell population: in the presence of subcompensated BO, their levels turned out to be lower than in the absence of it, due to the lower content of both T helper cells and cytotoxic lymphocytes (CTL). The higher Tregs level found in patients with BO, along with a low CD8+ cell count, suggests a low cytotoxic potential of the tissue, which is especially important for the resection line. The importance of the immunological microenvironment of the tumor has been repeatedly described in the literature both in terms of prognosis and for effective immunotherapy, in particular, with immune checkpoint inhibitors, as well as chemotherapy [12, 13–16]. The literature attaches great prognostic importance to locally present T lymphocytes – their number and subpopulation composition, primarily the content of CD8+ T cells, as well as their functional activity [17–22]. In the occurrence and progression of a malignant tumor, in the colon, "immunoredaction" plays an important role, i. e. The accumulation of immune system factors in it that can exhibit pro-oncogenic rather than antitumor effects [23]. Apparently, BO, which causes a violation of the composition of the microbiota and passage of intestinal contents, contributes to the development of this process.

CONCLUSION

Thus, we have established that the presence of subcompensated intestinal obstruction in patients with colon cancer leads to a number of quantitative changes in local immunity factors and tissue cytokine content compared with patients in whom it was not detected or was compensated. Among these changes, the higher content of pro-inflammatory cytokines (IL-6, IL-1a, TNF-α) in the tissue of the resection line is particularly unfavorable, along with a lower number of CD8+ T lymphocytes and a higher number of Tregs, which suggests a decrease in the antiproliferative potential of the tissue remaining in the patient's body after surgery. interventions in patients with colon cancer complicated by intestinal obstruction.

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