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THE ROLE OF BIOLOGICAL MARKERS IN THE DIAGNOSIS OF POSTOPERATIVE INFECTIONS IN COLORECTAL CANCER SURGERY (review)

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Infectious complications in colorectal cancer surgery is one of the major problems in postoperative complications structure. The frequency of the latter is 5-22%, and in 5-20% of cases such complications lead to death. It should be noted that the development of postoperative complications leads to a decrease in the quality of life of patients, general and relapse-free survival of patients operated on for colorectal cancer. One of the promising ways to diagnose postoperative infectious complications after surgery is to assess the level of biological markers of plasma inflammation. It can be used to identify patients with a high probability of infection and be an indication for earlier additional methods of diagnosing complications.

Currently, biomarkers that are used for early postoperative infection detection include increase in the leukocytes level in peripheral blood, CRP, PCT, CD64 neutrophils and others. Despite the large number of studies, the question of the role of these biomarkers in postoperative infections diagnosis in the patients who under went colorectal cancer surgery remains unclear.

[Key words: colorectal surgery, rectal cancer, colon cancer, inflammatory biomarkers, surgical site infection, CRP, PCT, CD64 neutrophils, HLA-DR monocytes]

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Early detection of purulent-septic complications, including the failure of intestinal anastomoses, occupies a leading place in the list of urgent problems of Coloproctology [1]. Despite the sufficiently studied aspects of preoperative preparation of patients in order to reduce the risk of postoperative infection (PI) [2], the latter remains the main cause of mortality, decrease of quality of life, reduction of overall and disease-free survival of patients operated on for colorectal cancer [3].

In the structure of PI there are 2 following groups: surgical site infection (SSI) and postoperative distant infection. The term SSI was introduced in 1992 by the USA Center for disease control and prevention and serves as a definition of infection occurring within 30 days after surgery, and in the case of an implant for one year. Among the SSIs there are deep, superficial and intra-abdominal infections. The reason for the last in most cases is the failure of the intestinal anastomosis, which can occur in the form of an abscess of the abdominal cavity or pelvis, local or diffuse peritonitis [4]. Postoperative distant infection should include pneumonia, urinary tract infection, septicemia, and infection in the area of parenteral manipulation [5].

The incidence of SSI after scheduled colon surgeries accounted for 16.4% [6], and in patients undergoing rectal surgery, this figure may reach 22% [6,7], and in 5-20% of cases such complications lead to a fatal outcome [2,6].

PI is not only one of the causes of patient mortality, but it also worsens the results of overall and disease-free survival. In 2015 Artinyan A. et al. [3] made a retrospective analysis of 12,075 patients who underwent surgery for colorectal cancer, for the period from 1999 to 2009, who were divided into groups depending on the presence or absence of postoperative complications (PC), as well as its nature: infectious or non-infectious [3].

The presence of any PC was found to be independently associated with reduced long-term survival (HR=1.24; 95% CI 1.15-1.34; p<0.001). Patients with PI were at higher risk (HR=1.31; 95% CI 1.21-1.42; p<0.001). At the same time, the severity of PI correlated with a decrease in overall survival (HR=1.41; 95% CI 1.15-1.73; p<0.001).

Similar data are given in the work of Povšič M. (2016) [8].

Postoperative infectious complications significantly increase the average hospital stay and the treatment

cost of this category patients, as stated in the work of Kashimura N. et al. [9]. In their retrospective comparative study, they analyzed the effect of infection in the surgical site on the duration of postoperative hospital stay and treatment cost among 167 pairs of patients.
According to the results of the study the appearance of PI increased the average hospital stay by 17.8 days (p=0.001) and the average cost of treatment – by US$5,938 (p<0.001) compared with the patients without PI.
Clinical manifestations of PI in the early postoperative period are non-specific and difficult to distinguish from the syndrome of systemic inflammatory response (SSIR) as the result of surgical procedure. Unlike PI, SSIR is usually resolved independently, but in some cases can occur as sepsis and septic shock [10].
A reliable symptom of PI is the confirmation of the presence of an infectious focus. With this objective, in clinical practice, a microbiological study is carried out to verify the pathogen. Determination of the etiological agent of PI can reveal its sensitivity to antibacterial drugs [10]. The period of bacteriological examination is at least 6 hours. Further study of antimicrobial sensitivity requires additional time of between 24 and 48 hours [11].
The development and introduction into clinical practice of molecular genetics research methods, such as polymerase chain reaction (PCR), has reduced the time of detection of the PI pathogen to several hours. Despite the speed of obtaining the result during the PCR study, it is very difficult to determine the viability of the microorganism and assess its role in the development of infection, as well as to monitor antibiotic resistance [12]. In addition, the increase in the cost of PCR varies from 3 to 10 times compared to the cost of microbiological examination by bacterial cultivation [13].
These problems as well as the need to predict the development of complications at the preclinical stage, led to the search for new biomarkers associated with inflammation. The term «biomarker» means a laboratory indicator that has a certain unit of measurement and numerically characterizes the biological processes occurring in humans in normal and pathological conditions [14]. Currently, the most studied biomarkers of inflammation include C-reactive protein, procalcitonin, presepsin and CD64 neutrophils.
Assessment of C-reactive protein (CRP) levels is one of the most common tests used in clinical practice to diagnose and control PI therapy. It was discovered in 1930 and refers to acute phase inflammation proteins [15], demonstrating a 1000 – fold increase in concentration during injury, inflammation, or tissue necrosis [16,17].
The level of CRP correlates with the severity of an inflammatory reaction or injury [16]. In 2014 Singh P. et al. [18] conducted a meta-analysis to assess the level of CRP as a predictor of insolvency of anastomosis. Seven publications were selected, including 2,483 patients after colorectal surgery. The highest values of sensitivity and specificity of the biomarker were detected, on average, on the 5th postoperative days and amounted to 86% for both indicators at the threshold level of CRP 144 mg/l (p<0.001).
Similar data were obtained in the meta-analysis by Gans S. et al. (2015) [19]. The ease and cheapness of the method and direct correlation with the severity of inflammation made CRP a widely used test in the PI diagnosis, but nonspecific increase in its concentration and low prognostic significance in the early postoperative period dictate the need to search for new biomarkers of inflammation.
Procalcitonin (PCT) is a precursor protein to the calcitonin hormone. Normally, its concentration in blood plasma is very low and is less than 0.01 ng/ml [20]. Its increase occurs in severe generalized bacterial, parasitic or fungal infections without changing in viral infection [21]. For more than 30 years of its application in clinical practice, many studies have been published, the data of which often contradict each other [22,23]. Some studies indicate that PCT levels are elevated in SSIRs, extensive injury, and burn injuries [24].
In 2018, Tan, W. et al. [25] conducted a meta-analysis that assessed the diagnostic significance of the PCT test on the 3-5th days after surgery as a predictor of intraabdominal infection after colon surgery. The study analyzed 8 studies, including 1,629 cases. The PI frequency was 5.7% on the 3rd day, 9.7% – on the 4th and 6.3% – on the 5th day.
The area under the curve and the thresholds on the 3rd, the 4th and the 5th days after surgery were 0.83 (95% CI 0.78-0.88) and 1.45 ng/ml, 0.79 (95% CI 0.64-0.93) and 1.28 ng/ml and 0.94 (95% CI 0.91-0.97) and 1.26 ng/ml, respectively.
The highest diagnostic value of PCT level determination was established on the 5th day with sensitivity of 78% (95% CI 0.65-0.89) and specificity of 88% (95% CI 0.85-0.90). Similar results were presented in a meta-analysis by Cousin, F. et al. in 2016, there were no significant differences in comparison with the use of CRP [26].
Just over 10 years ago, Japanese scientists discovered another biomarker of inflammation – sCD14-ST and named it presepsin (PSP) [27]. It is a protein with a molecular weight of 13 kDa containing an N-terminal fragment of CD14 and does not include a C-terminal site responsible for binding to lipopolysaccharide. The level of PSP increases in 2 hours after the appearance of the infectious agent in the blood, and reaches the maximum concentration in 3 hours [28].

A large number of scientific publications characterize the determination of the PSP level as an effective marker in the diagnosis of sepsis and differential diagnosis of SSIR [29,30]. In 2015, Tong X. et al. [31] conducted a meta-analysis of the PSP value as a sepsis marker.

The study included 11 studies and combined the results of treatment of 3,106 patients. According to Tong X., the sensitivity of PSP was 83% (95% CI 0.77-0.88), specificity – 81% (95% CI0.74-0.87). Similar data were given in meta-analyses by Zhang X. et al. [32] and Zhang J., et al [33]. At the same time, there are many contradictions in the results of comparative studies into assessment of sensitivity and specificity between PSP and other biological markers. In some publications, the authors conclude that PSP is the most effective marker of septic complications in comparison with PCT and CRP [29,30].

However, along with them there are a number of studies that characterize PSP as an equal or less effective predictor of infectious complications in comparison with other biomarkers of inflammation [34-36], which does not allow to make an unambiguous conclusion about the use of PSP as a universal PI marker.

In addition to the virulence and pathogenicity of the microorganism, a violation of the patient's immune status after surgery or burn lesions plays an important role in the occurrence of postoperative infection [37,38]. Early immune response to surgical trauma is associated with the activation of congenital immunity. As the first link here are phagocytes and antigen-representing cells migrating to the injury zone.

These include neutrophils, macrophages and dendritic cells [39]. Defects of this link can lead to the development of infectious complications, and therefore the assessment of changes in cellular immunity is an important marker of immunosuppression, as one of the components of the development of the infectious process [40].

Taking into account the above information, promising in the framework of laboratory diagnosis of infectious complications is the study of changes in the level of a number of indicators of cellular immunity, each of which has its place in the implementation of the response to the infectious agent: the content of cytotoxic T-lymphocytes, immunoregulatory index, T-regulatory cells, the content of $\alpha\beta$- and $\gamma\delta$ T-cells, native T-cells, memory T-cells, effect or T-cells, MAIT-cells, T-helpers 1, 2 and 17 type. Relatively recently discovered CD64 neutrophils, HLA-DR monocytes are rarely or not used in the PI diagnosis and therapy assessment due to lack of knowledge.

Recently the main method of laboratory assessment of the functional state of the human immune system is a chemiluminescent analysis of the blood by the method of two-stage stimulation [37,41], the results of which can be assessed within the first two hours from the time of the test.

Cluster of differentiation 64 (CD64) refers to a membrane glycoprotein known as an Fc receptor with high affinity for monomeric immunoglobulinamizo type IgG (FcgRI) [42]. Normally CD64 is expressed on macrophages, monocytes and eosinophils. Its appearance on neutrophils is regarded as part of the systemic immune response to infection and physiological response to microbial wall components, inflammatory cytokines, including interferon G, granulocyte colony stimulating factor, tumor necrosis factor-α, interleukin-1 and interleukin-6 [43].

Biomarker is detected in blood in 2-4 hours from the moment of infection in preclinical stage of complication [44]. CD64 neutrophil receptor (CD64n) is more sensitive and specific in the diagnosis of postoperative infection in comparison with CRP and PCT.

Jukic T., et al. in 2015 studied the dynamics of biological markers of CD64n, CRP inflammation, as well as leukocyte and neutrophil levels in 229 patients who underwent colorectal (189), maxillofacial (23) and cardiac (17) surgeries to predict PI. CD64n was the only biomarker that could predict PI ($p \leqslant 0.001$) on the 1st and the 2nd days after surgery, while the rest could not reveal statistically significant differences [45].

Similar results are described in the study by Gerrits J.H., et al. [46]. In a meta-analysis by Cid J., et al. (2010), which included 13 studies on the clinical use of this marker, the sensitivity and specificity of the latter amounted to 79% and 91%, respectively [47].

In 1991, Volk, H. et al. first described immunodeficiency diagnosed at a low level by monocytes expression of antigens of the main histocompatibility complex class II (mHLA-DR) [48]. Since that time, the reduction of HLA-DR expression has established itself as a biomarker of immunosuppression and has been used to assess the patient's immune status [49,50].

HLA-DR is a transmembrane protein that is expressed on antigen-presenting cells – monocytes, macrophages, dendritic cells, and B cells. Expression of HLA-DR on monocytes is important in representation of microbial antigens on T-lymphocytes, thus being an inducer of a specific immune response [50,51].

Maintaining a low level of its expression correlates with the severity of infection and a high risk of death [52]. Assessment of mHLA-DR expression was also successfully used as a control of immunomodulatory therapy efficacy [53-55].

For the first time the relationship between low mHLA-DR expression and the risk of sepsis after injury was presented in the work of Polk H., et al. in 1986. The authors concluded that the number and density of monocytes representing mHLA-DR on the second day

after injury have prognostic value as a marker of sepsis with sensitivity of 53% and specificity of 76% [56]. Cheron A., et al. (2010) in their work showed that mHLA-DR expression decreased from the first to the second day after injury in all patients, regardless of the occurrence of infectious complications. However, on the third and fourth day, there was a significant difference between «septic» and «non-septic» patients.
At the same time, «non-septic» patients registered an increase in the level of mHLA-DR expression, while «septic» patients had a low biomarker level (p=0.004). Multivariate logistic regression analysis showed that the mHLA-DR expression index between 1-2 and 3-4 days less than or equal to 1.2 was associated with sepsis development (HR=5.41; 95% CI 1.42-20.52).
The authors concluded that the monitoring of immune function by measuring the expression of mHLA-DR should make it possible to identify patients with predicted development of infectious complications after injury [57].
However, not in all publications the reduction of mHLA-DR expression is considered to be a factor in the prognosis of infectious complications. Oczenski W. et al. [58] (2003) in a prospective study assessed the prognostic value of decreased HLA-DR monocytes expression as an early marker of postoperative SSIR and infectious complications in 85 patients after cardiac surgery.
MHLA-DR expression was measured before the induction of anesthesia (the first control point), immediately after the surgery (the second control point), and on the first day after the surgery (the third control point). Postoperative decrease in the expression of HLA-DR monocytes was registered in all patients between the first and second ($p<0.0001$) and between the second and third ($p<0.0001$) control points (36,731±11,245 versus 17,358±5,168 versus 13,779±4,121 mAb/cell (mean number of HLA-DR antibodies per monocyte, respectively).
None of the patients showed preoperative level of mHLA-DR expression below 19,000 mAb/cell. MHLA-DR expression rates after surgery below 10,000 mAb/cell were recorded in 18 patients, but only 4 had postoperative complications in the form of SSIR or sepsis.
The lowest level of mHLA-DR expression was 5,716 mAb per cell, but the postoperative period was uneventful in this patient. The authors concluded that the absence of a statistically significant difference in the level of mHLA-DR expression between the groups on the first day after surgery, monitoring of preoperative and postoperative mHLA-DR levels for the first 24 hours is not a high-risk marker of postoperative SSIR or sepsis in the patients undergoing cardiac surgery.
In another work Skirecki T. et al. [59] (2016) compared the prognostic value of mHLA-DR and nCD64 markers expression in peripheral blood, as well as in respiratory tract secret in patients with sepsis. The study included 27 patients with septic shock. The fluorescence intensity of HLA-DR on circulating monocytes was 3.5 times lower than that of bronchial monocytes (p=0.01). CD64 expression on circulating neutrophils and bronchial neutrophils was similar (p=0.47).
Only CD64 expression on circulating blood neutrophils was statistically significant. It was 2.8 times higher in fatal cases than in survivors (p=0.031).
In connection with the results obtained, the authors concluded that the expression of CD64 peripheral blood neutrophils is a more effective predictor of high mortality risk in comparison with the mHLA-DR expression.

CONCLUSION

Colon surgery is associated with a high risk of infectious complications, which are the cause of perioperative mortality and reduced overall relapse-free survival in colorectal cancer. In addition, the development of PI requires high costs for treatment, increasing the duration of postoperative stay of the patient in the hospital. Biological markers are an effective tool in the early diagnosis of PI, but the presence of conflicting data in the world literature on the prognostic significance of each of them requires further comparative studies to determine the most sensitive, specific, and cost-effective predictor of PI.

The authors declare no conflicts of interest.

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