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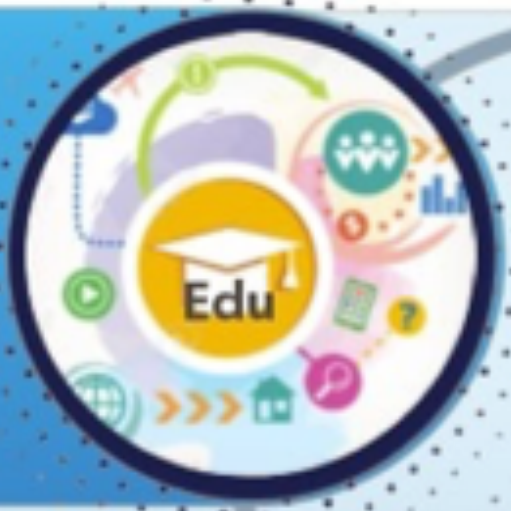

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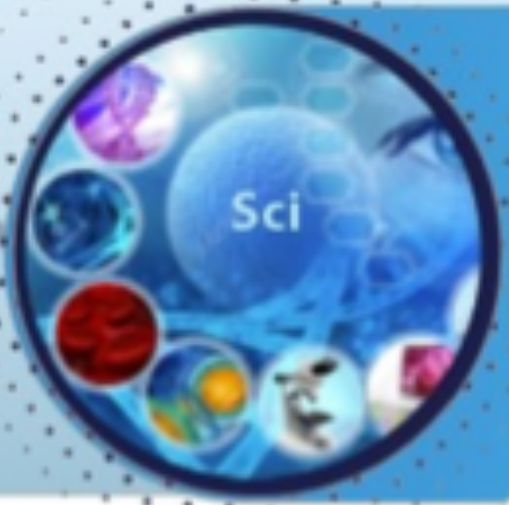

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Clinical and immunological criteria and prevention of relapse of Crohn's disease

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ABSTRACT

Background. *Recurrence of Crohn's disease (CD) in the postoperative period develops in more than 80% of operated patients.*

Material and methods. *The object of the study was the analysis of the results of examination and treatment of 82 patients with CD. General clinical, immunological, biochemical, endoscopic, visual, and statistical research methods were used.*

Results. *It has been established that relapse of the disease develops in the remote postoperative period in 59.5% of cases; it was revealed that immunological changes in CD are characterized by an imbalance of cellular and humoral immunity in the form of an increase in the expression of antigen-dependent T-naïve lymphocytes and suppression of T-regulating lymphocytes, creating conditions for an increase in immunoreactivity under the influence of active production of pro-inflammatory cytokines; it has been revealed that the low inducing properties of TGF-β and IL-4 in CD reduce the intensity of the production of anti-inflammatory cytokines, supporting the chronic inflammatory process and the intensity of granuloma formation.*

Conclusion. *The therapeutic and diagnostic algorithm developed by us for predicting and preventing the recurrence of CD has the frequency of true-positive and true-negative results, which significantly increased the frequency of the prognostic value of the method compared to the traditional one, as well as to reduce the frequency of mild and moderate forms of CD recurrence and completely avoid the development of its severe forms in the remote postoperative period.*

Keywords: *Crohn's disease, relapse of Crohn's disease, clinical and immunological prognosis criteria, prevention of Crohn's disease relapse.*

INTRODUCTION

Less than 100 years have passed since the first report of Crohn's disease (CD), which was presented in 1932 by the American gastroenterologist B.B. Crohn et al. [1] under the term "terminal ileitis". A more in-depth study in this area has led to the recognition of CD as an independent nosological unit, in which the entire intestine is af-

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fected. However, the iliac part of the small intestine still remains the predominant site of lesions in CD.

The prevalence of CD in Europe ranges from less than 10 to about 150 cases per 100,000 inhabitants [2]. An adjusted prevalence of 133 cases per 100,000 population was found in California, USA, at the beginning of this century [3]. One study conducted in South Korea showed a prevalence of 112 cases per 100,000 population [4]. The latest data on the prevalence of CD in Uzbekistan, conducted by the Republican Center for Coloproctology, equated to 80 cases per 100,000 population [5]. From the available data, it can be concluded that CD is a very common disease today.

The treatment of CD is interdisciplinary. At the same time, while drug treatment of CD is aimed at healing the mucous membrane and reducing the symptoms of the disease, surgery plays a key role in the treatment of complications of the disease such as stenosis, perforation, intestinal fistulas, and abscesses of the abdominal cavity and cellular spaces [6].

Numerous studies in this area have made it possible to develop various surgical strategies aimed at improving treatment outcomes and reducing the rate of recurrence of CD in the postoperative period. Some improvement in the results of surgical operations for CD was achieved after the introduction of laparoscopic technology. However, they could not affect the regression of the recurrence rate of CD in the postoperative period [7].

All this influenced the formation of a certain concept of the purpose of performing surgical operations in CD as the creation of conditions for slowing down the onset of recurrence, which is considered inevitable in the future. Developments in this direction are ongoing and surgical treatment of CD has yet to be discovered.

The aim of the study was to improve the results of treatment of patients with CD by developing pathogenetically substantiated clinical and immunological criteria for predicting and preventing the recurrence of this disease.

MATERIAL AND METHODS

The results of a comprehensive examination and treatment of 82 patients with CD are analyzed. The patients were divided into 2 study groups: control (42 patients) and main (40 patients). A distinctive feature of the groups of patients was the use of different approaches in predicting and preventing the recurrence of CD. As reference values, 20 healthy individuals recognized by the medical commission as practically healthy were examined.

In the control and in the main group of patients, male patients prevailed (59% and 55%, respectively), and the average age varied between young and middle (according to the WHO classification).

The criteria for inclusion in the study were: the presence of a confirmed diagnosis of CD; mandatory written consent of the patient to conduct the study; the age of patients over 18 years; absence of pregnancy and lactation period at the time of treatment and examination; the absence of a complication of CD in the form of a malignant neoplasm of the intestine, in the detection of which patients were excluded from the cohort; absence of severe extraintestinal somatic and mental pathology; absence of alcohol dependence, as well as confirmed pathologies of the immune system, including HIV infection; consent to additional laboratory and instrumental research methods. Any discrepancy with the above determined the criteria for excluding patients from the study.

CD mainly affected the terminal ileum (61%). In 24.4% of patients, combined lesions of the terminal ileum and large intestine were diagnosed. Isolated lesions of the large intestine were diagnosed in 14.6% of patients. In each study group, patients with lesions of the terminal ileum prevailed.

Perianal lesions were more characterized by the presence of rectal fistulas (75%), anal fissures (37.5%), narrowing of the lower ampullary rectum (8.3%), anal tractures (4.2%) and long-term non-healing wounds (4.2%).

The chronology of the course of the disease depended on the affected part of the intestine in CD. Thus, the least amount of time was required to affect the terminal ileum (89.7±13.4 months). For the development of CD with lesions of the large intestine, the course of the disease was on average 121.3±33 months. In patients with a chronology of CD of 179.8±43.8 months, combined lesions of the terminal ileum and large intestine were diagnosed.

Among the surgical operations undergone in anamnesis, appendectomy should be singled out, which was performed in 9 (21.4%) patients in the control group and in 15 (37.6%) patients in the study group. Operations aimed at opening acute paraproctitis were performed much more often (in the control group 35.7% of cases and in the main group of patients in 40% of cases, respectively). The list of surgeries also included excision of pararectal fistulas (16.7% of cases in the control group and 22.5% of patients in the study group, respectively), rectal fissure excision (11.9% of cases in the control group and 15% of patients in the study group, respectively), diagnostic laparotomy (7.1% of cases in the control group and 15% of

patients in the study group, respectively) and laparoscopy (14.3% of cases in the control group and 15% in the study group, respectively) patients in 20% of cases, respectively).

In 54.9% of cases, the patients had previously undergone hormonal therapy, while steroid resistance was diagnosed in 53.7% of cases.

In 84.1% of cases, patients were diagnosed with the presence of a chronic continuous course of CD. Chronic relapsing course of the disease was detected in 12.2%. The acute course of CD was diagnosed in 3 (3.7%) patients;

The study design was based on an open-label, cross-sectional, retrospective, and prospective cohort study.

All patients included in the study were operated on by us for complications of CD. In this regard, the complex of examination of patients was not only preparatory, but also dynamic, aimed at assessing the general condition of the patient, the course of the postoperative period and the features of changes in the indicators of cellular and humoral immunity in CD.

For immunological studies, blood was taken from the ulnar vein into a centrifuge tube treated with heparin in the amount of 5.0 ml.

The state of the immune system of the patients' body was assessed by the expression of CD-differentiation and activation antigens. The following markers of immunocompetent cells were determined: CD3+-, CD4+, CD8+-, CD16+-- CD25+-CD83+ lymphocytes.

Interleukins (cytokines) were determined in the blood serum of patients examined by enzyme-linked immunosorbent assay. To implement this option, two monoclonal antibodies with different etiotropic specificity to interleukins TGF-β, IL-4, IL-17, IL-21, INF-γ and TNF-α were used using special kits for enzyme-linked immunosorbent assay according to the standard procedure.

Blood sampling for immunological studies was carried out in the preoperative period and on the 7th, 14th, 30th, 90th, and 180th days of the postoperative period. At the same time, the results obtained on days 7-14 were interpreted as the results of the early postoperative period, and on days 30-180 – the results of the remote postoperative period.

Recurrence of CD was determined by the appearance of typical symptoms of the disease in the stage of clinical remission - spontaneous or medically supported.

The severity of CD recurrence was determined according to the criteria of the Society for the Study of Inflammatory Bowel Diseases at the Association of Coloproctologists of Russia (2009).

The results obtained, as they were received, were systematized in a summary unified table in Microsoft Excel, processed using Statistica for Windows (version 5.12). In accordance with the goals and objectives of the study, the calculation of elementary statistical indicators (mean values, errors of means, standard deviations, range of data dispersion), construction and visual analysis of data dispersion diagrams were carried out. The indicators were compared using signs of nonparametric criteria.

The significance of the differences between the samples, which were close to the norm in terms of the nature of the distribution, was established according to the parametric Student's test with a 95% reliable probability interval. The criterion for the statistical reliability of the conclusions obtained was considered to be the generally accepted in medicine value $p<0.05$.

The prognostic value of clinical and immunological criteria was determined by the method of evidence-based medicine based on the calculation of the frequency of occurrence of false negative and positive, true positive and negative results; the specificity and sensitivity of the test, and the validity positivity or expected value.

RESULTS

As a result of the analysis, it was found that traditional approaches to the treatment of CD in 57.1% of cases are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results. Recurrence of CD with traditional approaches to the treatment of the disease is noted in 59.5% of cases, mainly proceeding according to the mild and moderate type (88%). The chronology of the increase in the incidence of CD recurrence has the character of direct proportionality with the increase in the duration of the postoperative period.

The comparative dynamics of changes in the relative level of T-helper cells in the blood in CD was characterized by a decrease in CD4+ cell expression in the cohort of patients with relapsed disease from 26.13±1.65% in the preoperative period to 23.39±1.08% ($p<0.05$) on the 90th day of the postoperative period. In patients with long-term remission of CD, the level of CD4+ cells in the blood decreased to 25.69±2.53% only on the 30th day of the postoperative period, followed by the achievement of baseline values on the 180th day of the postoperative period to 29.13±3.11% ($p<0.05$).

Cytotoxic killer T cells in CD were characterized by increased expression in the blood. At the same time, the

mean level of expression among patients with relapsed disease was relatively lower (24.37±0.35%) than among patients with remission (24.91±2.52%), although they did not have a significant difference ($p>0.05$). Relative to the baseline (preoperative) level of CD8+ cell expression, CD8+ cell expression can be noted to be greater among patients with remission of CD than among patients with relapsed disease.

The relative value of T-regulating lymphocytes in patients with relapsed CD decreased significantly (to 11.03±0.37% on the 180th day after surgery) both in comparison with the reference values ($p<0.05$) and in comparison with the indicators of patients with remission of the disease ($p<0.05$).

In contrast to this, the development of relapse of CD revealed an increase in CD16+ cell expression from 11.49±0.13% in the preoperative period to 14.36±0.12% on the 180th day of the postoperative period ($p<0.001$).

The dynamics of increased expression was observed in the ratio of dendritic cells in the blood in patients with relapsed CD from 17.55±2.42% in healthy individuals to 26.2±0.15% on the 90th day of the postoperative period ($p<0.05$). In patients with remission of the disease, a similar dynamics was also noted, but the level of CD83+ cell expression was lower (15.67±0.13%; $p<0.05$) than the reference values.

In general, in CD, there is an imbalance in cellular immunity, which, in the event of a relapse of the disease, is manifested by an increase in the expression of dendritic cells (CD83+ cells) and natural killer T cells (CD8+ cells) against the background of a decrease in the expression of T helper cells (CD4+ cells) and T-regulating lymphocytes (CD25+ cells). Against this background, there is a progressive decrease in the immunoregulatory index (CD4+/CD8+), which indicates increased immunoreactivity of the type of autoimmune diseases. In patients with postoperative remission of CD, the opposite picture of changes in the expression of cellular immunity is noted, characterized by a stable immunosuppressive state.

A comparative analysis of changes in the level of the blood cytokine profile revealed a predominance of anti-inflammatory forms and a relative decrease in their level in CD with an increase in pro-inflammatory cytokines, mainly TNF-α (4.6-fold), IL-17 (3.2-fold) and IL-21 (2.4-fold).

In the early postoperative period of CD, there is a decrease in the proportion value of anti-inflammatory cytokines from 91.02% (reference) to 59.57%, that is, by 1.5 times ($p<0.05$) and an increase in the proportion value of pro-inflammatory cytokines from 8.98% (reference) to 40.43%, that is, by 4.5 times ($p<0.001$). In general, the intensity of changes in the cytokine profile in CD occurred due to pro-inflammatory components, which indicates the intensity of the changes occurring in the postoperative period. The long-term postoperative period in CD was characterized by a continued increase in the total value of the studied cytokines, mainly due to pro-inflammatory cytokines. The intensity of these changes depended on the outcome of the operation and, accordingly, was revealed during the randomization of patients depending on the phase of the course of CD.

In case of relapse of CD, there is a progressive decrease in TGF-β which is apparently associated with the regulatory nature of cellular immunity, which is characterized by a decrease in the intensity of expression of T-regulating lymphocytes. Low TGF-β values under the influence of macrophages and dendritic cells lead to the transformation of natural killer cells and stimulate cell apoptosis, increasing the level of hyperimmune reactions in the body.

In CD, there is an increase in the level of IL-17 in the blood, and the intensity of this process is based on the likelihood of recurrence of the disease, which may also be associated with an increase in the expression of Th17-cell T-helper cells, which are the main producers of this cytokine. This process stimulates the expression of natural killer cells and increases the susceptibility to autoimmune diseases.

Relapse of CD is accompanied by an increase in the concentration of pro-inflammatory cytokine IL-21 in the blood, which is a product of the formation of IL-17 when Th17-cell T-helper cells are activated, which was also associated with a low level of TGF-β and a decrease in the expression of T-regulating lymphocytes. At the same time, if the intensity of TNF-α formation in the blood in the early postoperative period was associated with the presence of CD itself and the severity of the surgical intervention, then in the late postoperative period, the cause of the intensive formation of TNF-α in the blood of patients was the direct development of a relapse of the disease.

The source of TNF-α formation in the blood of patients under such conditions should be considered both Th1-cell T-helpers, which activate macrophages and the intensity of the inflammatory process, and increased cell apoptosis under the influence of cytotoxic lymphocytes and natural killer cells of the lymphocyte series.

The intensity of the course of CD and the role of the intensity of INF-γ formation in the blood also appear to

be associated with the activation of Th1-cell T-helper macrophages and the production of pro-inflammatory cytokines. When antigens are identified, TNF-α is produced, which in small doses contributes to the formation of fibrous or similar cells, which is the basis for the formation of granulomas. However, in conditions of high intensification of this immune reaction, the formation of granulomas occurs against the background of a relapse of the disease.

In general, the dynamics of changes in the level of INF-γ in the blood in CD in the remission phase tended to approach the reference values, which indicated the restoration of the cellular-humoral relationship in the immune response system. The intensity of INF-γ formation in the blood under normal conditions depends on the onset of the T-cell response of innate immunity, mainly during the transition from the original cells and the presented antigens from macrophages to the Th1-cell link, and in the possibility of transition to Th2-cell lymphocytes. Thus, there is a step-by-step synthesis of both pro-inflammatory (Th1-cell) and anti-inflammatory (Th2-cell) cytokines. As a result of the correlation of such a balance of humoral immunity, the mechanism of immunoglobulin formation and an adequate response of the body to the acting antigen is launched. There is also an intensification of the formation of antibodies and the formation of an adequate immunological response.

Meanwhile, as our studies have shown, a decrease in the intensity of INF-γ formation in the blood leads to a decrease in the expression of Th1-cell T-helper cells, which reduces the intensity of the formation of anti-inflammatory cytokines. On the other hand, the low activity of Th1-cell T-helper cells leads to the stimulation of the activity of Th2-cell T-helper cells, which causes the development of not only cytokine imbalance, but also the creation of conditions for autoimmune conditions, which is the cause of CD recurrence. At the same time, the study of the level of IL-4 showed the opposite picture of changes.

The assessment of the dynamics of the correlation between the level of expression of CD3+ and CD4+ cells in the blood in CD in the postoperative period, both in the remission phase and in the relapse phase, did not have any special differences, except for a decrease or increase in relativity. Such a nature of changes was apparently associated with the early reaction of the body's immune system in differentiating between naïve T-lymphocytes and T-helper cells when macrophages present primary antigens. Along with this, the share of T-suppressors in the development of CD relapse was relatively minimal, which cannot be noted in relation to the dynamics of changes in natural killer cells, which were marked by high expression in the remote period after surgery. The correlational nature of changes in T-regulating lymphocytes and dendritic cells was multidirectional and was determined by the timing of the postoperative period in CD.

Analysis of the dynamics of changes in blood cytokines in the context of the correlation coefficient of 15 indicators revealed the presence of a high direct relationship in the general dynamics of the postoperative period in 10 (66.7%) cases. In the remaining 5 cases, the correlation was inverse and was associated with the dynamics of TGF-β. At the same time, the maximum difference was noted by the dynamics of TGF-β to IL-4 (R=-0.562) and then in descending order to TNF-α (R=-0.415). to IL-21 (R=-0.402), to INF-γ (R=-0.396), and to IL-17 (=-0.304).

It is noteworthy that the severity of the correlation value of TGF-β was noted by us in the early postoperative period than in the late postoperative period, which indicates the possibility of using this marker in predicting the recurrence of CD.

Based on the correlation and multivariate analysis, we were able to determine the main interrelated positions of the parameters of cellular and humoral immunity, which can serve as the main scheme developed by us for the pathogenesis of CD recurrence in the postoperative period.

Thus, in CD, there is an imbalance between Th1/Th2 cells and Th17/T-regulating cells, the intensity of which determines the outcome of the disease in the form of remission or relapse. Immunological disorders in relapse of CD are based on the mechanisms of autoimmune reaction formation due to increased apoptosis of cells against the background of expression of pro-inflammatory cytokines TNF-α, IL-17 and IL-21 through the induction of natural killer cells against the background of a low concentration of TGF-β. The relatively high stimulation of TGF-β production by naïve T-helper cells stimulates T-regulating lymphocytes, increasing their role in the development of tissue regeneration, and, accordingly, creating favorable conditions for the onset of the phase of remission of CD.

Substantiation of the pathogenetic relationship between changes in the indicators of cellular-humoral immunity in the mechanisms of CD recurrence allowed us to identify a number of key indicators as criteria for CD recurrence in the postoperative period.

The prognostic probability of recurrence of CD will be low if the stool rate is up to 2 times a day; normal body temperature and heart rate; there are no postopera-

tive complications or if they are only present at the Clavien-Dindo grade I level; blood abnormalities in the level of no more than one of the following indicators TGF-β, TNF-α, IL-71 and IL-21 greater than 10% of the reference value.

The prognostic probability of recurrence of CD will be high with a stool frequency of 3 or more times a day; the presence of a persistent low-grade body temperature; the presence of tachycardia; the presence of postoperative complications at the level of grade II and higher according to the Clavien-Dindo classification; abnormalities in the blood of two or more of the following indicators : TGF-β, TNF-α, IL-71 and IL-21 more than 10% of the reference value.

The effectiveness of the method developed by us for predicting the recurrence of CD in the postoperative period, due to the importance of including immunological criteria, allows us to increase the level of sensitivity of the test by 3.5 times, specificity by 1.9 times, and the prognostic value of the method by 3.3 times.

Preventive measures were based on methods of intraoperative and postoperative use of drug therapy aimed at creating an immunosuppressive state of the body.

At the first stage, during the surgical operation, after restoring the integrity of the intestinal patency in the affected area and along the root, Infliximab (Adalimumab) was administered intramesenterically at a dose of 5 mg per 1 kg of the patient's body weight in saline. Subsequently, in the postoperative period, this drug was administered intravenously at a rate of no more than 2 ml per 1 minute.

In case of a high probability of recurrence of CD, Infliximab (Adalimumab) was administered every 5 days at a dose of 10 mg per 1 kg of the patient's body weight until the level of prognostic parameters decreased. Against this background, Entivio® (Vedolizumab) was administered intravenously at a dose of 300 mg once every 7 days.

With a low probability of recurrence of CD, Infliximab (Adalimumab) was administered every 10 days at a dose of 5 mg per 1 kg of the patient's body weight until the level of normal values of prognostic parameters was reached. Against this background, Entivio® (Vedolizumab) was administered intravenously at a dose of 300 mg once every 14 days.

In the absence of a probability of recurrence of CD, conservative therapy was continued by prescribing Prednisolone at a dose of 1 mg per 1 kg per day (according to the regimen of reduction to withdrawal) and Azathioprine at a dose of 3 mg per day in tablet forms. Patients remained under dynamic control.

In general, the effectiveness of the therapeutic and diagnostic algorithm developed by us for the prevention of CD recurrence made it possible to reduce the frequency of its development in mild and moderate forms, as well as to completely avoid its severe forms.

DISCUSSION

To date, it has already been proven that the pathogenesis of CD is based on the body's immune response to tissue inflammation due to the effects of luminal bacterial antigens. The main participants in the immune response are subpopulations of T- and B-lymphocytes that penetrate the intestine during the development of Crohn's disease [8].

The pathogenesis is also supported by the interaction of these cells with integrins, adhesion molecules, and multiple chemokines responsible for the production of elevated levels of pro-inflammatory and anti-inflammatory cytokines, which are targeted by immune and non-immune cells and promote mucosal inflammation.

In the mucous membrane of patients with CD, dysregulation of various components of the immune system is invariably found. The most pronounced change is hyperactivity of T cells with excessive production of cytokines, between which IL-12 and INF-γ contribute to the lymphocyte-type Th1 phenotype, in contrast to Th2, which correlates with ulcerative colitis. In addition, the production of TNF-α has been demonstrated to increase the number of CD4+ FoxP3+ T-regulating cells, especially in the mucous membrane of children with CD [9]. Inhibition of effector cytokines such as TNF-α attenuates detrimental effects in subgroups of patients with CD [10].

Further analysis of the T cell subpopulations revealed the presence of Th1 and Th17 cells in CD, while the cytokines thought to be more involved are TNF, IL-12, and IL-23. In addition to cytokines, IL-34 is also associated with inflammatory bowel disease and, in particular, CD [11].

Although T cells are the main effector of lymphocytes in inflammation of intestinal tissues, the humoral immune system also plays an important role [12].

Medication management should be adapted to take into account various factors such as disease severity, subtype, behaviour and location. In addition, it is important to consider other factors, such as age at diagnosis, prevalence of the lesion, and extraintestinal manifestations [13]. In fact, none of the drugs used in the treatment of CD have been demonstrated to be curative or completely safe.

More recently, superselective monoclonal target antibodies have been developed that target a specific pattern of inflammation. This class includes vedolizumab, which targets molecular adhesion inhibition by inhibiting leukocyte migration, and interleukin inhibitors such as ustekinumab, a fully humanized monoclonal antibody that targets the p-40 subunit of IL-12 and IL-23 [14].

From the very beginning of the surgical treatment of CD, there was no consensus on the optimal procedure. Surgical resection of the diseased colon has become the procedure of choice for most patients with CD of the terminal ileum or with ileocolitis, including in complicated cases [15].

The term "recurrence" is used to define the appearance of new lesions after bowel resection. Active surveillance for early diagnosis of relapses is considered mandatory. For this, a wide range of diagnostic measures is used. However, most of them, such as endoscopy [16], ultrasound examination of the intestine [17], including the use of contrast [18], etc., are routine clinical research methods. Treatment methods that take into account other pathogenetic links in the development of CD are currently vague and are devoted to various comparative studies in the general system of inflammatory bowel diseases.

CONCLUSION

Traditional approaches to the treatment of CD in 57.1% of cases are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results. Recurrence of CD with traditional approaches to the treatment of the disease is noted in 59.5% of cases, mainly proceeding according to the mild and moderate type (88%). The chronology of the increase in the incidence of CD recurrence has the character of direct proportionality with the increase in the duration of the postoperative period.

In CD, there is an imbalance in cellular immunity, which, in the event of a relapse of the disease, is manifested by an increase in the expression of dendritic cells (CD83+ cells) and natural killer T cells (CD8+ cells) against the background of a decrease in the expression of T helper cells (CD4+ cells) and T-regulatory lymphocytes (CD25+ cells). Against this background, there is a progressive decrease in the immunoregulatory index (CD4+/CD8+), which may indicate increased immunoreactivity of the type of autoimmune diseases. In patients with postoperative remission of CD, there is a reverse pattern of changes in the expression of cellular immunity, characterized by a stable immunosuppressive state.

In CD, there is a multidirectional intensity of the formation of pro-inflammatory and anti-inflammatory cytokines in the blood. The inducing role of cytokines in the recurrence of CD in the postoperative period is due to the imbalance of TGF-β, IL-4 and INF-γ which are the main regulators in the differentiation of T-helper cells and T-cytotoxic lymphocytes of various links. Low TGF-β values are accompanied by the production of Th17-cell cytokines, which activate cell apoptosis, the intensity of the release of pro-inflammatory cytokines with an increase in the body's sensitization by the type of autoimmune diseases. The low inducing properties of IL-4 in CD reduce the intensity of the production of anti-inflammatory cytokines, supporting the chronic inflammatory process and the intensity of granuloma formation, in this case in the intestinal wall.

In CD, there is an imbalance between Th1/Th2 cells and Th17/T-regulating cells, the intensity of which determines the outcome of the disease in the form of remission or relapse. Immunological disorders in relapse of CD are based on the mechanisms of autoimmune reaction formation due to increased apoptosis of cells against the background of expression of pro-inflammatory cytokines TNF-α, IL-17 and IL-21 through the induction of natural killer cells against the background of a low concentration of TGF-β. Relatively high stimulation of TGF-β production by naïve T-helper cells stimulates T-regulating lymphocytes, increasing their role in the development of tissue regeneration, and, accordingly, create favorable conditions for the onset of the phase of remission of CD.

The basis of the therapeutic and diagnostic algorithm for predicting and preventing the recurrence of CD is the dynamic control of the level of cytokines (TNF-α, IL-17, IL-21 and TGF-β) in the blood, as well as the clinical signs of the postoperative course (stool frequency per day, body temperature, heart rate, the presence of postoperative complications and their degree according to the Clavien-Dindo classification), which make it possible to determine the level (low or high) of the probability of an attack, on the one hand. On the other hand, it is necessary to apply differentiated approaches to the regimen of anticytokine (Infliximab and Vedolizumab), hormonal (Prednisolone) and immunosuppressive (Azathioprine) therapy.

The effectiveness of the developed method for predicting the recurrence of CD in the postoperative period, due to the importance of including immunological criteria, makes it possible to increase the level of sensitivity

of the test by 3.5 times, specificity by 1.9 times, and the prognostic value of the method by 3.3 times. The use of the developed therapeutic and diagnostic algorithm for the prevention of CD relapse made it possible to reduce the incidence of its development in the mild form from 31% to 27.5%, in the moderate form from 21.4% to 12.5%, and to completely avoid its severe forms under the influence of pathogenetically substantiated differentiated and targeted anticytokine, hormonal and immunosuppressive therapy.

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open publication

Availability of data and material - Available

Competing interests - No

Financing – No financial support has been provided for this work

Conflict of interests-The authors declare that there is no conflict of interest.

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KRON KASALLIGI TAKRORLANISHINI KLINIK-IMMUNOLOGIK JIXATLARI VA PROFILAKTIKASI

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XULOSA

Dolzarblik. Operatsiyadan keyingi davrda Kron kasalligining takrorlanishi operatsiya qilingan bemorlarning 80% dan ko'prog'ida rivojlanadi.

Materiallar va usullar. Tadqiqot ob'ekti Kron kasalligi bo'lgan 82 bemorni tekshirish va davolash natijalarini tahlil qilish edi. Umumiy klinik, immunologik, biokimyoviy, endoskopik, vizual va statistik tadqiqot usullari qo'llanildi.

Natijalar. Kasallikning takrorlanishi operatsiyadan keyingi uzoq davrda 59,5% hollarda rivojlanadi; Kron kasalligida immunologik o'zgarishlar antigenga bog'liq T-limfotsitlar ifodasining ko'payishi va T-tartibga soluvchi limfotsitlarning susayishi ko'rinishida hujayrali va humoral immunitetning muvozanati bilan tavsiflanadi, bu yallig'lanishga qarshi sitokinlarning faol ishlab chiqarilishi ta'sirida immunoreaktivlikning oshishi uchun sharoit yaratadi; Kron kasalligida TGF-β va IL-4 ning past induksion xususiyatlari surunkali yallig'lanish jarayonini va granuloma shakllanishining intensivligini qo'llab-quvvatlovchi yallig'lanishga qarshi sitokinlar ishlab chiqarish intensivligini kamaytiradi.

Xulosa. Kron kasalligining takrorlanishini bashorat qilish va oldini olish uchun biz tomonidan ishlab chiqilgan terapevtik va diagnostika algoritmi an'anaviy holatga nisbatan usulning prognostik qiymati chastotasini sezilarli darajada oshirgan, shuningdek, Kron kasalligining engil va o'rtacha shakllarining takrorlanish chastotasini kamaytirish va operatsiyadan keyingi uzoq davrda uning og'ir shakllarining rivojlanishini butunlay oldini olish uchun haqiqiy ijobiy va haqiqiy-salbiy natijalar chastotasiga ega.

Kalit so'zlar: Kron kasalligi, Kron kasalligining takrorlanishi, klinik va immunologik prognoz mezonlari, Kron kasalligining takrorlanishini oldini olish.

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ КРИТЕРИИ И ПРОФИЛАКТИКА РЕЦИДИВА БОЛЕЗНИ КРОНА

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АБСТРАКТ

Актуальность. Рецидив болезни Крона в послеоперационном периоде развивается более чем у 80% оперированных больных.

Материал и методы. Объектом исследования явился анализ результатов обследования и лечения 82 больных с болезнью Крона. Были использованы общеклинические, иммунологические, биохимические, эндоскопические, визуальные и статистические методы исследования.

Результаты. Установлено, что рецидива заболевания развивается в отдаленном послеоперационном периоде в 59,5% случаев; выявлено, что иммунологические изменения при болезни Крона характеризуются дисбалансом клеточного и гуморального иммунитета в виде нарастания экспрессии антиген зависимых Т-наивных лимфоцитов и супрессией Т-регулирующих лимфоцитов создавая условия для нарастания иммунореактивности под влиянием активной продукции провоспалительных цитокинов; выявлено, что низкие индуцирующие свойства TGF-β и IL-4 при болезни Крона снижают интенсивность выработки противовоспалительных цитокинов поддерживая хронический воспалительный процесс и интенсивность образования гранулем.

Заключение. Разработанный нами лечебно-диагностический алгоритм прогнозирования и профилактики рецидива болезни Крона частоту истинноположительных и истинноотрицательные результатов, что существенно повлияло на повышение частоты прогностической ценности метода по сравнению с традиционным, а также снизить частоту легкой и среднетяжелой форм рецидива болезни Крона и полностью избежать развитие тяжелых ее форм в отдаленном послеоперационном периоде.

Ключевые слова: болезнь Крона, рецидив болезни Крона, клинические и иммунологические критерии прогнозирования, профилактика рецидива болезни Крона.