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Immunomorphological Features of Inflammatory Bowel Disease and Risks of Malignization: literature review

S.N. Navruzov[1], B.S. Navruzov[2], A.M. Khakimov[3], S.T. Rakhmonov[4], D.A. Alieva[5], A.A. Madaliev[6]

[1]MD, professor, Department of Oncology Center for the development of professional qualifications of medical workers, Private surgical clinic «Yangi hayot», Tashkent, Uzbekistan, e-mail: sarimbekn@list.ru
[2]MD, professor, Department of Surgery, Tashkent Medical Academy, Tashkent, Uzbekistan, e-mail: behzodn@mail.ru
[3]PhD, Private surgical clinic «Yangi hayot», Tashkent, Uzbekistan, e-mail: behzodn@mail.ru
[4]PhD, Private surgical clinic «Yangi hayot», Tashkent, Uzbekistan, e-mail: behzodn@mail.ru
[5]PhD, Assistant of the Department of Rehabilitation, Sports Medicine and Folk Medicine of the Samarkand State Medical University, Samarkand, Uzbekistan, e-mail: alievada@yandex.ru
[6]Head of the Department of Pathomorphology of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, e-mail: a.madaliev.patology@gmail.com

Abstract

The article provides a brief overview of modern scientific data on the occurrence of inflammatory bowel diseases, the currently existing theoretical foundations of etiopathogenesis and the mechanisms of their formation as a result of violations of the immunogenetic, morphological, microbiotic systems of the body.

Corresponding author: BEKHZOD S. NAVRUZOV, professor, MD, Department of Surgery, Tashkent Medical Academy, Tashkent, Uzbekistan, e-mail: behzodn@mail.ru

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Inflammatory bowel diseases (IBDs) are chronic recurrent diseases of the gastrointestinal tract (GIT), which mainly include two pathologies: ulcerative colitis (UC) and Crohn's disease (CD).

Aetiologically, IBD is multifactorial due to genetic predispositions and various risk factors leading to an abnormal immune response followed by inflammation activation and gut microbiota changes [2,12].

According to world statistics, about 7 million people suffer from IBD; the prevalence of this pathology, among other diseases, is 0.3%. And the highest incidence is in Europe (505 per 100 thousand in Norway; 322 per 100 thousand in Germany); in North America (286 per 100 thousand); in the United States (319 per 100 thousand); in Great Britain (300 per 100 thousand). The incidence in Russia is 27.8 per 100,000 for UC and 7.9 for CD; in Uzbekistan, it is 16.4 for UC and 3.7 for CD, respectively.

As can be seen from the statistical data, this pathology is of great relevance due to the high prevalence of the disease, coverage of most of the able-bodied population, the occurrence of disability of patients, as well as a high risk of malignization process with transformation into colorectal cancer (CRC).

According to recent literature reviews, the estimated risk of CRC among IBD patients within 10 years of diagnosis is 2%; in UC, after 20 years - 8%; after 30 years - 18%, with a CRC prevalence of 3.7% [11,18,23].

The largest population-based study (n=96447) demonstrated a 1.7-fold increased risk of developing CRC and a 1.6-fold increased risk of death from it in patients with UC compared to the general population [1,5,27]. At the same time, it should be noted that persons diagnosed with UC had a less pronounced CRC compared to control group patients without HCC [2,3,15]. The differences in quantifying the increased risk of CRC in patients with IBD depend on the country of residence of the study population, the disease duration, the diagnostic and treatment methods used, and the level of colecto-

my, as well as other possible exposure factors.

According to modern concepts and the development of science of ECD study, this pathology is represented by different clinical and morphological forms, apparently due to the interaction of genetic, immunological, and bacterial mechanisms of their occurrence. Research of experimental models of colitis development has shown immunoregulation disorders with activation of immune response concerning antigens of intestinal microflora.

Risk factors of ECD and malignization with the development of CRC

According to studies on the occurrence of IBD with subsequent development of CRC, many risk factors contribute to this process, which is systematized and presented in this table (Table 1).

The inflammatory response of the bowel and the active course of the disease are among the main risk factors for the development of neoplasia. A large number of recent studies have confirmed this. Chronic inflammation of the intestinal mucosa with increased cell division and active reepithelialization contributes to a high risk of cell cycle repair defects, which is morphologically expressed in active neutrophil infiltration with crypt abscesses and epithelium ulceration with the progression of the chronic inflammatory process. Subsequently, this leads to intestinal epithelial cells suffering from genomic instability due to the development of oxidative stress against the background of the chronic inflammatory process. The formation of an inflammatory infiltrate produces the release and activation of oxygen radicals and

Table 1

Risk factors responsible for the development of CRC in patients with IBD

Risk Factors		Coefficient
Disease duration	The risk increases with the duration of the disease, most obviously after 6-8 years, with a total cumulative effect.	4,74
Prevalence	UC: Increased risk respectively from pancolitis > left-sided colitis > proctitis.	2,43
	CD: Increased risk has been demonstrated with more extensive disease.	undefined
Inflammation and heaviness	The risk increases with the severity of the disease (endoscopic), especially chronic inflammation	2,62
	The risk increases with the severity of the disease (histological).	1,98
Primary sclerosing cholangitis	Associated with an increased risk, requiring annual follow-up from the diagnosis.	4,14
Aggravated family anamnes	Associated with increased risk depending on the age of diagnosis and degree of aggravation.	2,62
Strictures and polyps	Surrogates of prior severe inflammation associated with higher risk	7,78 and 3,29
Dysplasia	Associated with increased and variable risk, with an overall incidence of CRC after LHD of 0.8 per 100 patient-years of follow-up.	10,7
Age of onset and gender	Earlier age of onset(<16 years) is associated with an increased risk. Males have a slightly higher risk.	1,27

nitrogen, which affect metabolic processes involved in cellular repair [6,19,24,33]. In the early stages of IBD, the presence of increasing overexpression of p53 in the epithelium of the colon can be detected, while histologically determining the presence of dysplastic changes is still impossible, so morphologists use this marker as a differentiating factor between regeneration and the presence of intraepithelial neoplasia, and also as a tissue biomarker for predicting the risk of malignant transformation.

Development of CRC, which forms as a consequence of IBD, is the result of a complex multistage process, which includes inflammation of the intestinal mucosa without signs of dysplasia, followed by low-grade dysplasia high-grade with the development of invasive adenocarcinoma.

Thus, the existing inflammatory load is an important risk factor for malignization with the development of CRC. One of the important mechanisms underlying malignization appears to be the presence of increasing duration as well as recurrent cycles of inflammatory bowel lesions and epithelial regeneration. The duration of the disease contributes to an increase in the surface area of the damaged cells of the colon, subjected to chronic inflammatory damage, its spreading with the development of dysbacteriosis.

Primary sclerosing cholangitis (PSC) is another important risk factor for CRC in patients with IBD, as confirmed by numerous studies. The presence of strictures and postinflammatory polyps are evidence of previous severe inflammation, which can also be

used as risk markers for dysplasia and CRC. A family history of CRC is one of the risk factors for intestinal oncopathology. Particularly controversial are the issues related to early age and onset of UC in childhood, which subsequently increases the risk of developing CRC.

Recent genetic studies show that ECD's association with the presence of polymorphisms in the autophagy genes (ATG16L1 and IRGM) has been found. Autophagy is considered one of the central mechanisms of antibacterial resistance, in which cytoplasmic proteins form a membrane that isolates part of the cytoplasm with its organelles and intracellular pathogens. Macrophages use this process to capture and destroy.

According to the opinions of other researchers, the importance of hereditary defects in the development of ECD is confirmed [25,30], determining the pathological immune response that occurs in the receptor apparatus of antigen-presenting cells. Macrophages, in this case, are the main critical components of inflammatory infiltrates in IBD [31,38]. The intestinal mucosa normally contains dendritic cells whose activation begins when an inflammatory reaction occurs, followed by receptor expression and recognition of microbial antigens. They are quite different from each other: TLR-2 are different peptidoglycans of the (+) group of bacteria and TLR-4 are monopolysaccharides of the (-) group of bacteria. Activating these cells increases the production of inflammatory cytokines that induce a “pathological” immune response in IBD [10,26,35].

The mechanisms that trigger and maintain the autoimmune process are the presentation of autoantigens as part of HLA molecules, antigens of normal microflora to which the immune system (IS) loses tolerance in CGC, which may be a consequence of cross-reaction of microbial antigens. Thus, there is now already evidence for the association of UC with HLA-DRB1 and CD with HLA-DR7 and DQ4 alleles [14,18,21,27].

Also, the state of the epithelial barrier of the intestinal wall plays a significant role in supporting CG since, due to increased permeability of the epithelium, protein substances with antigenic properties are absorbed into the blood, causing stimulation of antibodies [25,31].

Thus, increased titers of antibodies to various intestinal bacteria and their decay products are observed when performing immunodiagnostics in patients with IBD. On their basis, it is possible to verify the diagnosis, assess the severity of the process, as well as to conduct prognosis and treatment monitoring.

The best known and most studied are perinuclear neutrophilic ATs (pANCA), manan polysaccharide of Saccharomyces cerevisiae wall cells (ASCA), and anti-epithelial ATs determined only in UC patients.

Thus, there is a clear association of pANCA with UC and ASCA with CD, which allows us to use them for differentiated diagnosis of IBD. Increased AT titers indicate the severity of the process, as well as give a prognosis for the development of complications and indicate the presence of immunity to the ongoing treatment [4,32]. Microbiota (conditionally pathogenic intestinal microflora) also play an important role in the development of IBD, which causes constant stimulation of IS, due to the formation of bacterial symbioses [28]. The activation of these processes results in a deficit of bifido- and lactobacilli, bacteroides, which potentiates the increase of conditionally pathogenic microorganisms.

Mechanisms and role of innate immunity in the development of IBD.

Innate immunity is one of the ancient systems, forming a nonspecific response to the introduction of pathogenic agents, which is realized through the barrier function of the epithelium, activation of phagocytes (neutrophils, macrophages) natural killer cells (NK-cells), including the vascular endothelium, involved in providing development and circulation of inflammatory cells to the lesion. In the presence of inflammation, the role of innate immunity is to provide and recognize pathogenic molecules or structures (patterns) that are in close interaction with microorganisms. When it occurs, it begins to surround pathogenic agents with their subsequent elimination and activation of specific adaptive (acquired) immunity, the main action of which is ensured by the increase in the functional activity of T- and B-cells in response to foreign pathogens [30]. The initiation of the subsequent cascade of cellular interactions of the innate immune system by increasing the expression of pattern-recognizing receptors (PRR) promotes the activation of transmembrane (TLR) and intracellular receptors (NLR) with the development of acute and chronic inflammation.

IS the body’s internal homeostasis maintains metabolism. When inflammatory and infectious processes occur, the immune cells’ need for potential energy increases, which promotes metabolic activation. The innate immunity and its cells are the first links carrying out the immune response against the introduction of foreign agents, including bacterial infection, with an active role played by T-cell receptors (TCR), which provide the primary immune response to the introduction and increase of intestinal pathogens. A special role in this connection is assigned to the state of intestinal microbiota since receptor cells are located in the intestinal epithelium and their activity is carried out from the surface of the mucous membrane. During the immune response to the introduction of infectious agents, T cells produce NADPH-$_2$ oxidase to restore the redox -antioxidant imbalance of T cells, increasing their metabolism in the intestinal epithelium. The resulting changes in metabolism lead to disruption of the intestinal barrier and increased absorption of pathogenic agents through the intestinal wall, which contributes to overactivation of the intestinal IC [34,35].

Cellular metabolism and the intestinal microbiota play a crucial role in forming the corresponding immune response.

Due to their common origin, the intestinal microbiota has a special relationship with metabolism, especially through the mitochondria, so they share most of their genome with the bacteria.

The host cell and the intestinal microbiota are closely related to the interspecific metabolic network that ensures the proper functioning of the organisms. The presence of intrinsic diversity in the gut microbiota and the human immune system creates an additional level of complexity in studying these interactions and remains an unsolved problem.

Pathomorphological characterization of IBD.

The results of endoscopic and morphological studies play the main role in the diagnostic plan and in forming the final verdict of ECD. The morphological method of colonobiopsy study is considered a gold standard of diagnostics for determination of disease activity even in endoscopic remission. It should be noted that there are non-specific differences in morphological picture between histological criteria for diagnosis of UC and CD, they are mainly quantitative, i.e. they differ in frequency of detection among patients [13,20].

Macro- and microscopy of UC. Macroscopically, they reveal continuous character of colonic lesions with obligatory involvement of the rectum in the active process, but lesions of the ileum are revealed very rarely. One of the characteristic features of the morphological picture is full bloodiness of the intestinal mucosa, edema, and the presence of characteristic granulation (diffuse pseudopolyposis) [8,29]. The mucosa also shows numerous erosions and small ulcerations, which merge and disappear in the mucosa [22]. Microscopic examination defines a diffuse inflammatory infiltrate, in which predominantly lymphocytes and plasma cells are distinguished [9,16]. The formation of crypt abscesses, represented by clusters of neutrophils in the lumen of dilated and deformed crypts with the development of cryptitis, in the depth of which acidophilic Paneth cells (Paneth metaplasia) are also a distinctive feature [7,37]. A characteristic feature is multiple pseudopolyposis associated with distorted repair [7].

Macro- and microscopy of CD. Crohn's disease is macroscopically characterized by segmental lesions, with the most frequent lesions in the terminal ileum and proximal parts of the colon, also large slit-like ulcers that are separated by areas of the mucosa, longitudinal and transverse ulcerative defects against the edematous mucosa creating a characteristic "sidewalk" appearance, which is not typical for UC. Another feature that does not occur in UC, but is characteristic of CD, is peritoneal lesions: abscesses, fistulas, adhesions with neighboring organs, and mesenteric deformity with thickening in the affected area. The microscopic picture in UC is characterized by the presence of segmental transmural lymphohistiocytic infiltrates. Lymphoid hyperplasia penetrates all layers of the intestinal wall, which is considered characteristic of CD. One known morphological sign of CD is the formation of immune noncaseous sarcoid granulomas. They contain more than five epithelioid cells, including giant Pirogov-Langchans cells [17,38]. Histologically, the CD can be diagnosed with typical sarcoid granulomas and any of the morphologic features of CG. There can also be three morphologic features of CG with no granulomas. Some of the morphological differential criteria for CD are sarcoid granulomas, focal inflammation with preserved mucus production in the epithelium of the ulcer margins.

The main differential features of UC and CD are shown in Table 2.

As can be seen from the data presented in the endoscopic study, changes in the colon mucosa in IBD occur in various macroscopic combinations. Still, there are no absolutely specific for UC and CD [3,15]. It should be noted that differential diagnosis of IBD between UC and CD is not always possible since often one can see a similar endoscopic picture, a long chronic course, and histological examination plays the main role in making the final diagnosis.

Table 2

Differential diagnostic signs of UC and CD (endoscopic) [4]

Endoscopic feature	UC	CD
External inspection of the perianal area	Skin is not altered	Perianal lesions
Mucosal lesions	Diffuse	Segmental
Rectal lesions	100%	Less than 50%
Vascular pattern	Erased or missing	Often without change
Contact bleeding	Typical	Seldom
Granularity	Typical	less typical
"The Cobblestone Pavement."	Absent	Typical
The nature of ulcerous defects	Superficial ulcerations without clear boundaries, with a severe course – large	Aphthae (initial stage), deep longitudinal ulcers with clear edges
The mucosa around the ulcers	Changed	Intact
Pseudopolyps	Typical	Less typical
Strictures (stenoses)	Seldom	Often

To conclude this review, we can summarize that ECD, UC are associated mainly with involvement of the large intestine and CD with involvement of any areas of the gastrointestinal tract, has phases of activation and remission [1]. The prevalence of IBD is 0.5% of the world's population, an increasing pathology that is a socio-medical and economic problem forhumanity [23,36]. To date, the etiopathogenesis of ECD has not been established, and scientific research is ongoing.

As experimental and clinical studies show, a complex interaction of microbiota, immunity, and genetic and epigenetic features underlies ECD. The most objective biomarkers of ECD are the state of immunity and gut microbiota in the gastrointestinal tract [4,7,9,10]. Detailing and studying the mechanisms of ECD formation allowed us to determine the presence of predisposition to this pathology of chronic inflammation of mucosal epithelium and un-

derlying intestinal tissues, damage of their barrier function with the development of expressed microecological imbalance, as well as emerging systemic disorders of immune responses to antigens, with the defeat of immune, nervous and hormonal regulatory mechanisms [4,11,13].

Differential diagnosis of ECD should be based on a complex of immunomorphological and clinical signs with obligatory histological examination. The search for immunological and genetic markers of the occurrence of IBD may bring some success, thus providing an accurate diagnosis as well as appropriate, timely and targeted treatment.

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ICHAKNING YALLIGLANISH KASALLIKLARINING IMMUNOMORFOLOG HUSUSYATLARI VA YOMONLASHUVI HAVFI (ADABIYOT SHARHI)

S.N. Navruzov, B.S. Navruzov, A.M. Hakimov, S.T. Rahmonov, D.A. Alieva, A.A. Madaliev

Annotatsiya: Maqolada ichak yallylanish kasalliklarining payo bulishi xaqida ilmiy ma'lumotlar, etiopatogenezi hozirgi mavjud nazariy asoslari va organizmning immunogenetik, morphologik, microbiotik tizimlarining zamonaviy natijasida yozaga kelish shartlari.

Kalit suzlar: yarali kolit, Kron kasalligi, immunologiya, epigenetika, morfologiya, mikrobiotikalar, markerlar.

ИММУННО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ РАЗВИТИЯ ВОСПАЛИТЕЛЬНЫХ ЗАБОЛЕВАНИЙ КИШЕЧНИКА И РИСКИ МАЛИГНИЗАЦИИ (ОБЗОР ЛИТЕРАТУРЫ)

С.Н. Наврузов, Б.С. Наврузов, А.М Хакимов, С.Т. Рахмонов, Д.А. Алиева, А.А. Мадалиев

Аннотация: В статье приведен краткий обзор современных научных данных по возникновению воспалительных заболеваний кишечника, существующих на сегодняшний день теоретических основ этиопатогенеза и механизмов их формирования в результате нарушений иммуногенетических, морфологических, микробиотических систем организма.

Ключевые слова: язвенный колит, болезнь Крона, иммунология, эпигенетика, морфология, микробиотика, маркеры.