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THE PATHOPHYSIOLOGY OF ULCERATIVE COLITIS. THE CURRENT STATE OF THE PROBLEM OF ETIOLOGY, EARLY DIAGNOSIS AND TREATMENT

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Abstract: General Background: Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases that significantly impact patients' quality of life and present substantial healthcare challenges globally. **Specific Background:** This review provides a comprehensive analysis of contemporary literature regarding the etiology, pathophysiology, diagnosis, and treatment of UC and CD. It highlights the prevalence of these conditions both worldwide and specifically in Uzbekistan, emphasizing their clinical significance. **Knowledge Gap:** Despite advancements in understanding these diseases, challenges persist in the early diagnosis and management of UC and CD, particularly due to the absence of standardized diagnostic tests for assessing intestinal inflammation. **Aims:** The objective of this review is to synthesize current knowledge on the interplay between UC and primary sclerosing cholangitis, explore therapeutic options available internationally, and identify effective pharmacological agents used to achieve and maintain remission. **Results:** The findings reveal critical insights into the epidemiological trends of UC and CD, the complex relationship between these diseases and primary sclerosing cholangitis, and the varied therapeutic strategies employed in different countries. **Novelty:** This review uniquely addresses the underexplored relationship between UC and primary sclerosing cholangitis while providing a focused discussion on therapeutic modalities that may enhance patient outcomes. **Implications:** The insights gained from this analysis underscore the need for improved diagnostic methods and tailored treatment approaches to better manage UC and CD, ultimately informing clinical practice and guiding future research in this area.

Keywords: Ulcerative Colitis, Crohn's Disease, Etiology, Diagnosis, Treatment.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum with damage to the mucous membrane and submucosal layer of the intestine and the formation of ulcers. Over the past few years, the prevalence of UC has increased worldwide [6]. There are significant differences in the incidence and prevalence of UC in different regions of the world [1, 6]. Thus, the incidence rate of UC can range from 0.5 to 31.5 per 100 thousand people annually, depending on the studied population. In Asian countries, the prevalence of UC ranges from 5.3 to 63.6 cases per 100,000, and in North America — from 37.5 to 238 cases per 100,000 population [7]. Over the past 50 years in Western Europe, the incidence of UC has increased from 8 to 14 new cases per year per 100,000 population, and the prevalence has increased from 120 to 200 per 100,000 people[8, 9]. In recent decades, there has been an increase in the incidence of UC in developing countries in Africa, Asia and South America, including Brazil and Taiwan [10, 11].

Stress conditions, perverted immune reactions of the body, and increased pathogenic properties of the intestinal flora play a role in its occurrence and development. Inflammation can spread throughout the mucous membrane of the colon or be limited to the lesion of its individual

segments, on which the course of the disease depends. [15]In the acute stage of the disease, frequent stools (bowel movements contain blood, mucus, pus), abdominal pain, high fever, severe intoxication are characteristic. Complications are possible: bleeding, perforation of the intestine with the development of peritonitis, etc. With a chronic course, periods of exacerbations are replaced by remissions; with a more severe lesion of the intestine, a continuous course of the disease is observed with moderately pronounced disorders of intestinal function, changes in protein, vitamin and water-salt metabolism [2]. Crohn's disease is a chronic inflammatory disease that affects the entire gastrointestinal tract — from the mouth to the anus. Unlike ulcerative colitis in Crohn's disease, all layers of the intestinal wall are involved in the inflammatory process.[19] In most cases, inflammation first occurs in the ileum, and then passes to other parts of the intestine. At the same time, the symptoms of acute ileitis (inflammation of the ileum) are indistinguishable from the symptoms of acute appendicitis, so patients are often diagnosed with the true diagnosis during surgery [16-17].

The pathogenesis of the disease assumes the importance of changes in immunological reactivity, dysbiotic shifts, allergic reactions, genetic factors, and neuropsychiatric disorders [20]. There is a genetic predisposition to UC (familial cases of ulcerative colitis) and the association of UC with antigens 53 of the histocompatibility complex HLA. Among the closest relatives, YAK occurs 15 times more often than in the general population [4]. Genetic predisposition — this theory is supported, for example, by the fact that ulcerative colitis is more characteristic of the white population than of African Americans. Jews are particularly at risk.[21] The role of bacteria and viruses. Ulcerative colitis is provoked by external causes — improper nutrition, bad habits, taking certain medications (for example, oral contraceptives, NSAIDs), stress.[25] Recently, ulcerative colitis has been increasingly considered as an autoimmune pathology.[24]

Methods

The data available to date demonstrate the central role of dysregulation of the immune response against the intestinal microflora in combination with disruption of the anti-inflammatory or pro-inflammatory pathways in the pathogenesis of UC[26-27]. Aberrant immunological reactions that occur in the intestine can affect the epithelial barrier, increasing its permeability to new antigens, which leads to persistent chronic inflammation [30]. It is assumed that both innate and adaptive immunity are involved in maintaining intestinal homeostasis, and various inflammatory immune cells such as neutrophils, CD4+ T cells and macrophages are involved in this process[4]. at the level of the local endocrine system of the colon mucosa, there is an increase in the production of proinflammatory hormones – vasointestinal peptide (VIP) and a decrease in the production of counterinflammatory neuropeptides (bombesin, somatostatin), which leads to impaired motility, microcirculation disorder and impaired trophism of colonocytes [5,6,14]. Of considerable importance in the development of this pathology is a violation of the lymphoid tissue of the intestine, which depends, among other things, on 12 experimental and clinical gastroenterology 2019 clinical gastroenterology

Results and Discussion

Clinical gastroenterology of the state of the microflora of the gastrointestinal tract (gastrointestinal tract). Microbial antigens are presented in lymphoid tissue to lymphocytes, thereby ensuring the transition of Th 0 to Th 1 (proinflammatory) or Th 2 (anti-inflammatory) immune response. It is clear that normally, the known antigen of the harmless autochthonous intestinal microflora will never cause a Th 1–immune response. In IBD, on the contrary, the Th 1 response causes inhibition of cytokines of Th 2 lymphocytes and an uncontrolled inflammatory response.[31]

Of course, the dysfunction of the gastrointestinal microbiocenosis also plays an important role. The intestinal microflora from birth is an obligatory participant in the processes of development and formation of the local immune system, promotes the formation of the physiological cellular composition of the intestinal wall, in addition, provides colonization resistance and inhibits pathogenic microflora with the help of various metabolites (mainly short-chain fatty acids).[32] However, its own microflora can exacerbate autoimmune inflammation in NJAC by colonizing the affected areas of the intestinal mucosa. The commensal microflora also supports inflammation, which, under certain conditions, can become pathogenic and act as a trigger for relapses and septic complications of NAC [33-34].

Morphological and endoscopic studies in the diagnosis of IBD currently play a major role in the diagnosis of IBD, as they allow us to identify the nature, prevalence and degree of activity of the process, differentiate between IBD and Crohn's disease (CD), exclude intestinal ZNO, and monitor the effectiveness of therapy.[39] Despite this, these methods still have a fairly high cost and relative reliability: after all, the diagnosis is not always verified after instrumental studies, there is a problem of insufficient preparation of patients for the study, the impossibility of carrying it out, due to the severe condition of the patient or the acute course of this disease (high risk of intestinal perforation), difficulty in taking biopsy material due to poor visualization or an uncharacteristic endoscopic picture of the mucosa. The subjective factor also plays an important role in these studies: the diagnosis depends on the morphologist - during histological examination and on the endoscopist – with complete fibrocolonoscopy, rectoromanoscopy, esophagogastro duodenoscopy.[29] Radiological research methods in IBD do not lose their importance due to their significant informative value, low cost, and relative simplicity of the method.[27] Analysis of the position, shape (severity of gaustation), size, intensity of shadow, specific mucosal pattern, contrast, presumed intestinal function (to promote contrast) makes it possible to detect radiological symptoms specific to NYC: wall rigidity, fringe structure, abscesses, strictures, ulcers in the form of cufflinks, narrowing of the lumen in some areas of the intestine (a symptom of a "shoelace") [31-32]. Additionally, MRI, CT methods can be used for the diagnosis of NAC (if endoscopic methods are not possible), ultrasound examination is of great importance in the management of pregnant patients complicated by concretions of the kidneys and biliary tract forms of NAC, which is also characterized by specific signs of NAC – a symptom of the target, extended anechoic thickening of the mucous membrane, possibly a decrease in the intestinal lumen, a violation peristalsis. However, the laboratory criteria of the NAC are considered to be newer and more promising. In some cases, if it is impossible to perform a colonoscopy on a patient, an irrigography is performed – an X–ray examination of the colon using a contrast agent, which allows detecting defects of the mucous membrane - erosions and ulcers, pseudopolypes and altered, deformed areas of the intestine as a result of the inflammatory process [19-20].

In the initial diagnosis of ulcerative colitis, it is necessary to exclude the infectious nature of the disease (feces are analyzed for pathogens of bacterial and parasitic intestinal infections), as well as to determine the level of fecal calprotectin — this indicator characterizes the intensity of inflammation in the intestine [8-9]. Treatment. The diet prescribes various variants of a diet that slows down intestinal transit (4, 4a, 4b), rich in protein, with a restriction of fats. The goals of treatment of NAC are induction and maintenance of clinical and endoscopic remission, improvement of the patient's quality of life, prevention of recurrence and prevention of complications. The introduction of the achievements of molecular biology and genetics into the diagnosis and treatment of UC has been 0 years old.[25] A huge amount of data testified to the complexity of the pathogenesis of UC. Molecular research methods have shown that such a cytokine as tumor necrosis factor α (TNF-α)

plays an important role in the inflammatory process in IBD, which served as the main reason for the development of monoclonal antibodies against the inhibition of the action of TNF-α. In the 1990s, studies were conducted in which high concentrations of TNF-α were found in blood, feces and biopsies of the colon mucosa, which led to the use of anti-TNF drugs in the treatment of UC patients [31-32]. In 2016 vedolizumab, a humanized monoclonal antibody blocking integrin α4β7, was approved for the treatment of UC [32]. In 2019, in Europe, and in 2020 in Russia, another anti–cytokine drug, ustekinumab, a human monoclonal antibody with high specificity to the p40 subunit of interleukins 12 and 23, was registered for the treatment of UC patients [23]. Despite the many genetically engineered biological drugs used to treat UC, up to 15-20% of patients need other therapies. In light of this, it is necessary to search for new methods for the treatment of UC. The complex of pathological processes that occur in IBD requires the restoration of a disturbed imbalance of the immune system, normalization of the balance of the intestinal microbiota and regeneration of the damaged intestinal mucosa. At the same time, only cell therapy can carry out the process of restoring damaged intestinal tissues and correcting immunological disorders at this stage of medical science. Controlled differentiation of somatic stem cells has great therapeutic potential for tissue regeneration and the treatment of many degenerative and autoimmune diseases. Advances in the study of the immunosuppressive and regenerative effect of mesenchymal stromal cells eventually led to the development of new treatments for UC patients [30]. The introduction of the achievements of molecular biology and genetics into the diagnosis and treatment of UC has been 0 years old. A huge amount of data testified to the complexity of the pathogenesis of UC. Molecular research methods have shown that such a cytokine as tumor necrosis factor α (TNF-α) plays an important role in the inflammatory process in IBD, which served as the main reason for the development of monoclonal antibodies against the inhibition of the action of TNF-α. In the 1990s, studies were conducted in which high concentrations of TNF-α were found in blood, feces and biopsies of the colon mucosa, which led to the use of anti-TNF drugs in the treatment of UC patients [35]. In 2016 vedolizumab, a humanized monoclonal antibody blocking integrin α4β7, was approved for the treatment of UC [32].

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Conclusion

In conclusion, this review underscores the intricate relationship between ulcerative colitis (UC) and Crohn's disease (CD), revealing how microbial dysbiosis contributes to the pathogenesis and exacerbation of these inflammatory bowel diseases. Our findings indicate that while significant advancements in diagnostic and therapeutic strategies have been made, including the use of biologics targeting tumor necrosis factor α and integrin α4β7, challenges remain in achieving consistent patient remission and addressing the complexities of disease management. The implications of this research highlight the necessity for innovative diagnostic methods and personalized treatment plans that

account for the unique immune responses and microbiota profiles of patients. Future research should focus on exploring novel therapeutic approaches, such as cell therapy and further elucidation of the microbiome's role in disease modulation, to enhance treatment efficacy and improve the quality of life for individuals affected by UC and CD.

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