Ulcerative colitis and Crohn's disease: modern notions (part 1). Definition, terminology, prevalence, etiology and pathogenesis, clinical features, complications, classification

Y. S. Tsimmerman, I. Y. Tsimmerman, Y. I. Tret'yakova

Perm State Medical University n. a. E. A. Vagner, Perm, Russia

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Ulcerative colitis (UC) and Crohn's disease (CD) are among the most complex and mysterious diseases in gastroenterology.

Definition. UC is a chronic inflammatory disease of the mucous membrane of the colon of unknown etiology with the development of its ulcer-necrotic changes, localized mainly in the distal parts of it, originally affecting the colon, followed by the proliferation in the proximal direction, and in 10% expanding to all the colon (rarely — with reflux ileotyphlitis); proceeds with a variety of local and systemic complications, and extraintestinal manifestations.

CD is a chronic granulomatous inflammatory bowel disease of unknown etiology with involvement in the pathological process of all layers of the intestinal wall, characterized by intermittent (segmental) type of lesions of various parts of the digestive tract with the formation of fistulas and abscesses, stenosis affected areas of the intestine and diverse intestinal and extraintestinal manifestations and complications [1, 7, 25].

UC and CD are the organic pathological processes that are not (yet) given a complete cure [1, 7].

Terminological problems. The first description of UC by S. Wilks was presented in 1859 in the Medical Times and Gazette, and in 1875 S. Wilks and W. Moxon gave its morphological characteristics [39, 60]. CD was first described by a group of authors (B. B. Crohn, L. Ginzburg, G. D. Oppenheimer) in an article published in 1932, entitled "Regional ileitis" [33].

At various times as synonyms UC featured the terms "cryptogenic or idiopathic ulcerative hemorrhagic colitis", "muco-hemorrhagic ulcerative rectal colitis" and most of all — "ulcerative colitis", which we consider obsolete. This term was proposed by A. S. Kazachenko in 1913 to distinguish UC and other ulcerative colitis of well-known (infectious) aetiology (tuberculosis, luetic), which at that time were widespread [9, 27]. Now this distinction has lost relevance and we should use internationally accepted term "ulcerative colitis" [27].

Synonymous with Crohn's disease at different times were the terms "terminal ileitis", "granulomatous enterocolitis", "regional enterocolitis" and others. In the end, they stopped at the eponymous term "Crohn's disease" [39].

The International Classification of Diseases and Related Health Problems, Tenth Revision, published by WHO in 1995 (ICD-10), UC outlined the following ciphers: K51. (Ulcerative colitis), K51.0. Ulcerative (chronic) enterocolitis, K51.1. Ulcerative (chronic) ileocolitis, K51.2. Ulcerative (chronic) proctitis, K51.3. Ulcerative (chronic) rectosigmoiditis; CD — codes: K50. Crohn's disease (regional enteritis), K50.0. Crohn's disease of the small intestine, K50.1. Crohn's disease of the colon, K50.8. Other types of Crohn's disease, and K50.9. Crohn's disease, unspecified.

Prevalence. Incidence of UC in different countries varies from 27-117 cases per 100,000. Population with the "peak" of disease between the ages of 20 to 40 years old, more frequently in men than in women (1.39:1); the second "peak" of disease is marked after 55 years.

Primary morbidity of UC is 8-10 cases per 100,000 in a year [7].

Over the past 30-40 years we have seen an increased incidence of CD from 20-30 to 40-50 per 100,000 of population (approximately 2 times), most often among young people (20-30 years), with a certain predominance of women (1.12:1). At the same time isolated lesion of the colon (granulomatous colitis) is more common in older people [7]. There are cases of CD in childhood, especially in the presence of family history of CD. Thus, a positive family history was observed in 30% of patients with CD, developed in children [23]. Most are diagnosed with CD in the northern

European countries, Canada and the US, especially among persons of Jewish nationality [23]. The frequency of new cases of CD varies in the range from 2 to 4 cases per 100,000 in a year [7].

Etiology and pathogenesis. Etiology of UC and CD has not yet been established, but it is obvious that it is a multifactorial disease. Initially, given that the human intestine in normal and pathological state is colonized by huge number of different microorganisms, etiological factors of CD and UC were looking for among the bacteria — pathogens of intestinal infections *(Shigella, Salmonella, Yersinia, Campylobacter jejuni,* and others), enteroviruses (rotavirus, astroviruses), opportunistic pathogenic fungal *(Candida albicans, Saccharomyces cerevisiae),* and chlamydia *(Chlamydia trachomatis),* but attempt to prove their role in the development of CD and UC failed.

The greatest attention (as a prospective etiological factors of CD and UC) is attracted by *Mycobacterium paratuberculosis* and measles virus [35, 53, 54].

Mycobacterium causes the development of granulomatous disease in ruminants (morbus Johnes), which histologically is similar to CD. Given mycobacteria, however, it failed to detect neither in CD, nor in UC. Furthermore, specific T-cell immune responses directed against different strains of mycobacteria were similar in CD and control groups, atuberculostatic therapy was ineffective [1, 53, 54].

With regard to possible aetiological role of measles virus in UC and CD, this assumption has arisen due to the fact that it has the ability to damage the endothelium of the capillaries, causing the development of vasculitis, ischemia and inflammation. In addition, patients with CD and UC were detected to have particles resembling the measles virus. The attention of researchers also drew increased risk of CD and UC after an outbreak of measles, but after the introduction of measles vaccination number of patients with measles has dropped dramatically, and the number of patients with CD and UC, in contrast, has continued to grow [1, 35].

In the pathogenesis of CD and UC a certain role belongs to genetic factors. Emphasizing the role of "family savings", when CD and (rarely) UC are developed in several generations of blood first-degree relatives [6]. Thus, J.-F. Colombel [32]

described 72 families in which 2-3 cases of CD and more were diagnosed. At UC familial cases of the disease are much rarer.

It is indicated that the relative risk of developing CD from blood relatives of 10%, and with a positive family history — 30% [6].

In the presence of UC in both parents to 20 years the disease develops in 52% of children. In 44% of cases concordance for monozygotic twins is observed in CD, 6.3% — for UC [29, 30].

If CD is more common haplotype association with HLA-DR1, UC — with HLA-DR2 and loci of chromosomes 2 and 6 (immunogenetic risk factor). Moreover, in CD 50% of cases NOD2 mutation on chromosome 16 (independent risk factor) is observed. Overall, 7 loci identified on chromosomes responsible for predisposition to CD and UC [30]. We have recently studied genes associated with CD, in particular gene HETD2/CARDI5, located on chromosome 16 (locus 1), and gene OKTN — on chromosome S (locus 5). Investigation of mutations of these genes revealed that the defective location of muramyl dipeptide (total bacterial cell wall components) leads to the activation of nuclear factor NF-kB, and is associated with structural lesions of the small intestine [6, 59].

Of great importance in the pathogenesis of UC and CD are immune mechanisms that are responsible for the epithelium (the barrier) of the intestinal wall. The intestinal epithelium is a component of an intestinal mucosal system associated with its mucosa (MALT). Its main function — preservation of immune areactivity (tolerance) against various antigens and mitogens, but also development of cytokine suppressive activity [7]. Upon genetically deterministic (primary) increased permeability of the intestinal epithelial barrier, flowing with the damage of the cytoskeleton of epithelial cells, enterotoxins penetrate from the intestine into the bloodstream, as well as non-dissected protein substances that preserved antigenic properties, which sensitize a microorganism, stimulating the production of antibodies.

In patients with UC and CD we revealed autoantitbodies to intestinal cells. The presence of perinuclear anti-neutrophil cytoplasmic antibody (pANCA) in the absence of *Anti-Sacchoromyces cerevisiae-antibodies* (ASCA) is characteristic of

UC, and the absence of pANCA in the presence of ASCA — for CD [6]. pANCA are the specific tissue antigens to autoantibodies granulocytes, which can act as triggers of cytotoxic activity with perinuclear distribution type [1, 4, 7, 15, 24, 31, 45, 48]. In pANCA-positive UC patients often defined allele of adhesion molecules (ICAM-1) and the presence of immune vasculitis. At the same time changed neutrophil function, show their pro-inflammatory activity [7, 14].

Cytokines — a protein products produced by nearly all cells of the human body. They perform important regulatory functions. Standing out in the extracellular space, cytokines associated with cell receptors and "launch" a cascade of reactions. Causing stimulation or inhibition of various processes (proliferation, migration, secretion, expression of surface antigens and receptors), cytokines regulate differentiation and maturation of various immune cells, control the production of antibodies and cytotoxic activity, particularly causing the immune response.

Interleukins (IL) function as mediators of protein, as a subfamily of cytokines. 6 groups of cytokines are distinguished, including interferons (IFN) — immunomodulatory agents, chemokines — regulators of inflammatory reactions, tumor necrosis factor α (TNF) — inducers of inflammation, and regulators of apoptosis, etc.

There are pro-inflammatory cytokines: IL-1, IL-2, IL-6, IL-8, TNFα and IFNγ, etc.; anti-inflammatory cytokines: IL-4, IL-10, IL-11, and others. [22, 28, 36].

At UC and CD pro-inflammatory cytokines are prevalent. They increase the production of nitric oxide (NO), which is formed by immune cells and enterocytes. Changes in NO levels result in damage to the cytoskeleton enterocytes and increased permeability of the intestinal wall. Some importance in the pathogenesis of UC and CD belongs to the pathogen-associated molecular patterns, and so called assessory molecula [27].

Upon UC the concentration of IL-1 (β-promoter region of the IL-1) is increased in 15-25 times, upon CD — 6 times. At the same time IL-8 increases, carrying chemotaxis, which results in the migration of neutrophils, lymphocytes and monocytes in inflammation. In these patients the concentration of TNFα is

significantly increased — one of the most active promoters of inflammation in the intestines.

At the same time the level of IL-10 (anti-inflammatory cytokine) for UC and CD is reduced by 37-41% [22]. The cytokines IL-4 and IL-10 induce humoral mediated immune response by stimulating the formation of immunoglobulins G, A and E, and activation of eosinophils [7].

Besides cytokines, there are other mediators: leukotrienes (LT), prostaglandin, platelet activating factor, complement factor C4. Thus, LTV is a mediator of inflammation, stimulating the formation of TNFα and IFNγ with chemotactic activity [22, 36].

Some contribution to the pathogenesis of UC and CD brings the accumulation of oxygen free radicals that have a direct toxic effect, and an increase in the content of some neuropeptides (vasoactive intestinal peptide, substance P, somatostatin), which stimulates the synthesis of prostaglandin E and thromboxane B_2, reinforcing the processes of proliferation and release LTV and histamine [7, 4, 16, 20, 24]. An indication of accumulation of products of free radical oxidation of lipids may be the level of the enzyme NO-synthase [7].

We can’t completely exclude pathogenetic role in UC and CD of pathogenic microflora, which permanently (continuously) stimulates the immune system of the intestine [2, 17, 19, 31, 51]. It is believed that the formation of bacterial patosymbiosis promotes immune inflammation [31, 36, 51].

Clinical picture. The course of UC and CD is characterized as long and torpid with periodic severe exacerbations (attacks). Chronic relapsing within UC and CD was noted in 70-80% of cases [15]. Patients worried about the frequent, not strictly localized abdominal pain, especially in CD (85-90%); at UC pain usually occurs during defecation and is accompanied by tenesmus. This is most often a left-sided pain in the UC and in CD — right-sided and is located in the abdomen. The second most frequent complaint (at 65-90% of patients) is diarrhea (up to 10 times a day or more) mixed with blood, mucus, and (rarely) of pus in the stool (in UC) up to profuse bleeding with the development of posthemorrhagic iron deficiency anemia.

With the lesion of the small intestine in CD gradually develop trophological insufficiency, food intolerance, reduced activity of membrane and cytosolic enzymes, resulting in the clinical syndromes appearing in maldigestion and malabsorption, disaccharidase and then peptidase deficiency, progressive weight loss.

In this most common symptoms of intoxication are observed (fever, weakness, malaise, a sharp decline in performance), as well as dyspeptic symptoms (nausea, vomiting).

On examination, patients with CD of the colon (granulomatous colitis) can detect perianal lesions (abscess), cracks, perianal abscesses, fistulas); in UC they are rare. Some (10%) patients have clubbing of the fingers as drumsticks. On palpation of the colon is determined moderate soreness on the left (in UC) or right (in CD) upon palpating the terminal segment of the small intestine and the cecum.

The severity of clinical symptoms is defined by distribution (length) intestinal lesions, its severity, the presence of complications, the nature and the amount of extra-intestinal lesions [1, 4, 7, 9, 10, 21, 24].

Some authors distinguish the types of intestinal lesions in CD: type 1a —one segment of the small intestine; type 1b — the ileocecal region; type 1c — segment of the colon; type 2a — in the pathological process involved both small intestine segments, and colon; type 2b — associated lesions of intestine and stomach, esophagus and/or the oral cavity [18].

UC is classified by localization: distal colitis (proctitis or proctosigmoiditis) — 40-50%, left-sided colitis with lesions of the colon to the right bending — 30-40%, total colitis — 10-20%; by the course: "lightning" (fulminant) form, acute form (first attack), chronic relapsing form, continuous form (more than 6 months); by severity of the clinical course (criteria of S. Truelove and L. Witts [57]): considering stool frequency (less than 6 times, more than 6 times, 10 times a day), presence and severity of bleeding (weak, profuse, continuous), presence of fever (no, more than 37,5°C, more than 38,8°C), laboratory parameters: hemoglobin content (more than 100; less than 100; less than 80 g/l), ESR (less than 20, 20-30, more than 50 mm/h),

level of albumin (norm, more than 30, less than 30 g/l), tachycardia (no, less than 90, more than 90 per minute) [1, 24].

Classification of CD is proposed N. Bockus [39], who provides 7 forms of the disease: terminal ileitis (25-30%); common ileitis; jejunoileitis; enterocolitis (40-50%); granulomatous colitis (15-25%); anal lesions (30-40%); widespread lesions of the digestive tract, involving the stomach and esophagus (3-5%) [5, 44].

To determine the activity of CD we use activity index by W. Best [37] in points. At the same time we take into account:

1. number of bowel movements (within 7 days): X x 2 (coefficient) points;
2. intensity of abdominal pain (7 days): no pain (0 points), mild pain (1 point), moderate pain (2 points), severe pain (3 points) x 5 (coefficient) points;
3. general state of health (in the last 7 days): good (0 points), satisfactory (1 point), poor (2 points), very bad (3 points) x 5 (coefficient) points;
4. underweight (defined by the formula: actual body mass/proper body weight) x 100 (coefficient) points;
5. tension upon abdominal palpation: no (0 points), doubtful (2 points); expressed (5 points) x 10 (coefficient) points;
6. need in the treatment of diarrhea: no (score 0), yes (1 point) x 30 (coefficient) points;
7. hematocrit: the difference between the available indicators and the norm (for men — 47, women — 42) x 6 (coefficient) points;
8. presence of other CD symptoms: absent (0 points), present (1 point) x 1 (coefficient) points (arthralgia, arthritis, iridocyclitis, uveitis, nodular erythema, pyoderma, aphthous stomatitis, anal fistula, adrectal abscess, fistula and abscesses of other localization, fever (over 37,5°C during the last 7 days).

Best total index — a score of 8 points. Score: 150 points or less — no activity; more than 150 points — active course of CD. Mild form of CD — 150-300 points, moderate — 300-450 points, severe — more than 450 points [25].

Complications. There are local and systemic complications of UC and CD. Among the local complications of UC should be called massive (profuse) intestinal bleeding; perforation of the colon; toxic megacolon (acute toxic expansion of the colon); malignancy [1, 4, 7, 9, 24].

Massive intestinal bleeding in UC is relatively rare. In much of the cases timely and adequate pharmacotherapy avoids surgery.

Perforation of the colon often occurs in the form of lightning form of UC during the next exacerbation (attack) of the pathological process, often on the background of toxic megacolon, and is caused by necrotizing process in the intestinal wall, proceeding with its expansion and thinning. A role in the development of perforations belongs to the pathogenic intestinal microflora, especially enterotoxigenic E. coli *(Escherichia coli).* Perforation of the colon is one of the main causes of death in UC. However, in chronic relapsing course of UC perforation of the colon is a rare phenomenon, an abscess often develops in the intestinal wall.

Toxic megacolon is a consequence of necrotizing process in the colon and enterotoxaemia. At the same time there is widespread or segmental expansion (dilation) of the colon, usually developing during the next exacerbation (attack), which requires emergency intensive detoxification therapy, and when it is ineffective — surgery.

As for possible malignancy in UC, the risk of developing colon cancer actually increases with disease duration of more than 10 years, particularly in those patients with UC that developed at a young age (10-18 years).

Upon CD local complications occur most often in cases when the disease is accompanied by extraintestinal (systemic) manifestations. First of all, you need to name the appearance of inflammatory infiltrates and abscesses in the abdominal cavity, often localized in the right iliac fossa. Abscesses are usually combined with intraintestinal and external fistulas (perianal, intra-muscular, rectovaginal) and interintestinal adhesions, and strictures of colon lesions that are localized usually distal to infiltrate. In those cases when the abscess extends to the abdominal wall

fluctuations appear. The development of an abscess is accompanied by high fever, leukocytosis, elevated erythrocyte sedimentation rate.

Another local complications of CD is a partial intestinal obstruction that often develops in lesions of the small intestine and its stenosis due to inflammation (swelling, spasms) and subsequent scar changes, violating the passage of intestinal contents.

Massive intestinal bleeding in CD is extremely rare (1-2% of cases), mostly in granulomatous colitis.

Very rare complications of CD include perforation of intestine into the free abdominal cavity and toxic megacolon, the development of which can be triggered by taking anti-diarrheal and irrigo- and colonoscopy.

Fever in CD occurs in about 1/3 of patients and is due to the development of septic processes (abscess, fistula, inflammatory infiltrate) [1, 4, 7, 9, 24, 39].

In patients with UC and (very rarely) with CD the risk of developing colorectal cancer (CRC) is largely dependent on the length of the colon lesions, duration of disease, as well as the combined flow of UC with primary sclerosing cholangitis (PSC), which is found upon UC in 2-5% of cases. A certain importance is CRC in a history of genetic first-degree relatives and the lack of folic acid (folate). Upon left-sided UC, risk of developing CRC increases by 4 times, at the distal UC — 1.5 times; upon combined UC and PSC and duration of the disease is more than 10 years CRC develops in 9% of patients, over 20 years — 30%, more than 25 years — 50% [1, 4, 38].

In general, the relative cumulative risk of CRC in UC reaches 3,1-5,7 [4]. Risk of malignancy in UC upon disease duration of 20 years is 7.2%, 30 years — 16.5%, 35 — 25%, particularly above the age of 35-45 years. In total UC risk of CRC becomes 19-fold [42].

Deficiency of folate in UC occurs when ileocolitis and long-term treatment with sulfasalazone, which inhibits the absorption of folic acid.

Morphological risk factor for CRC in UC is a dysplasia of colonic mucosa and formation of inflammatory pseudopolyps in it. In low-grade dysplasia it is associated with carcinoma invasive of colon in 19% of cases; high grade dysplasia — 43% [3].

Among the molecular mechanisms of the development of CRC in UC we should mention the presence of proto-oncogenes, mutations in genes-suppressors of tumor growth, genes-regulators of apoptosis: k-ras (proto-oncogene), APC gene (tumor suppressor) and p53 (apoptosis regulator gene). Immunohistochemical proliferation index Ki-67 and PCNA in cells reflect their degree of dysplasia.

From laboratory methods for diagnosis of CRC in patients with UC should be called fecal calprotectin determination (calcium-binding protein found in neutrophils, activated macrophages and monocytes); sensitivity — 60%, specificity — 30% [43].

About systemic complications in UC and CD is said in those cases when there are multiple extra-intestinal manifestations of the disease [8, 11, 13, 55].

The most common skin changes in the UC and CD are erythema nodosum, and (upon exacerbation of the process) development of panniculitis — inflammation of the fibrous subcutaneous tissue.

In some cases on the skin of the lower limbs and other parts of the body appears pyodermia gangrenosa, which is transformed into the suppurative necrotic ulcers with a red rim.

Sweet-syndrome is described as neutrophilic dermatosis with the formation of painful erythematous nodes.

Panarteritis nodosa affects the skin of the lower extremities in the form of numerous subcutaneous nodules up to 2 cm in diameter, and proceeds with the obliteration of subcutaneous blood vessels and a tendency to ulceration.

Epidermolysis bullosa is characterized by the formation of bubbles in the elbows, knees, hands with subepithelial deposition of immunoglobulin G.

Cutaneous vasculitis necrotica takes place with the advent of purpura, nodules, plaques and ulcers on the skin of the extremities (especially fingers), prone to necrosis.

Exanthema vesiculo-pustularis is characterized by the presence of pustular lesions and inflammatory infiltrates in the skin and around the vessels (perivascular region).

In addition, patients with UC and CD on the face and in the mouth (in the mucosa of the cheek and gums), reveal the erythematous plaques, ulcers and aphthae; hyperplastic changes in the mucous membrane in the form of a cobblestone street, and histologically — the presence of granulomas.

At UC often defined erythema nodosum, exanthema vesiculo-pustularis, and in CD — granulomatous pyoderma, panarteritis nodosa, epidermolysis bullosa, changes in the mouth. Other skin changes occur with equal frequency in both diseases [1, 12, 26, 47, 50].

At UC and CD there are various joint damages: peripheral mono- and polyarthritis (up to 25% of cases), sacroileitis (50%), ankylosing spondylitis, and others. Most affected are the knee and ankle joints. The lesions are usually asymmetrical; effusions are usually accumulated in the affected joints, they are deformed, the skin over them is hyperemic.

Eye involvement at UC and CD is found in 2-10% of cases, more often in CD: iridocyclitis, episcleritis proceeding with the sclera and conjunctiva hyperemia, burning sensation and irritation.

In some cases the pathological process involves hepatobiliary system as cholecystolithiasis, steatohepatitis (up to 50% of the cases), sometimes primary sclerosing cholangitis (from 2-7.5%), most often in UC or autoimmune hepatitis (in 1-5%).

One of the most common lesions is a vasculitis localized in various organs, including the lungs, which course is with vasoconstriction associated with thrombosis and thromboembolism.

Bone lesions include osteoporosis (7%) and osteonecrosis, often hitting the hip and knee joints.

Occasionally developing pancreatitis occurring with exocrine pancreatic insufficiency, kidney damage; neurological disorders are observed [34, 40, 49, 56, 58].

Information about the extra-intestinal manifestations of UC and CD is important, suggesting that they are common, systemic diseases. At the same time we still not completely understood mechanisms involving other organs in the pathological process at UC and CD [12].

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Ulcerative colitis and Crohn's disease: modern notions (part 1). Definition, terminology, prevalence, etiology and pathogenesis, clinical features, complications, classification

Y. S. Tsimmerman, I. Y. Tsimmerman, Y. I. Tret'yakova

Perm State Medical University n. a. E. A. Vagner, Perm, Russia

Key words: ulcerative colitis, Crohn's disease, etiology and pathogenesis, classification, diagnostics and treatment

Definitions of ulcerative colitis (UC) and Crohn's disease (CD) are given, related terminological problems are discussed, the prevalence of UC and CD in the population is considered along with their etiology, pathogenesis, clinical symptoms, complications and extraintestinal (systemic) lesions. Classification and diagnostics of UC and CD are discussed with special reference to current international recommendations on their diagnostics and differential treatment.