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SYNDROME OF INCREASED EPITHELIAL PERMEABILITY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Currently, the role of the syndrome of increased epithelial permeability of the mucous membrane of the gastrointestinal tract, primarily the intestine, as the main pathogenetic mechanism for the development of inflammatory diseases not only of the intestine, but also of other organs and systems, including rheumatological diseases, is being discussed. The integrity of the intestinal barrier was assessed using morphological examination of mucosal biopsies (CO) of various gastrointestinal tract sections, followed by staining with hematoxylin and eosin. Electron microscopy can be used to visualize the distances between epithelial cells and the width of intercellular spaces. he analysis of the conducted studies revealed significant morphological shifts in all the studied departments of the digestive tract in rheumatological diseases, which are expressed in an increase in infiltration of the stroma of intestinal villi by lymphocytes and plasma cells, expansion of microvessels, an increase in the number of interepithelial lymphocytes, an increase in intercellular gaps, loss of enterocytes connection with the basal with the basal membrane, which indicates the development of SPEP in this category of patients.

Currently, it is promising to study the role of the syndrome of increased epithelial permeability (SPEP) of the mucous membrane of the gastrointestinal tract (GIT), primarily the intestine in the pathogenesis of inflammatory diseases not only of the intestine, but also of rheumatoid arthritis, immunodeficiency states, multiple sclerosis [1,2,3]. Sincethe lysisto-epithelial barrier of the gastrointestinal tract is a multi-component structure that acts as a barrier that regulates the passage of pro-inflammatory molecules, microorganisms, toxins, antigens and pathogens into the internal environment of the body and ensures the development of immune reactions.

Withthe lysisto-epithelial barrier, it can be conditionally divided into three levels - preepithelial, epithelial and subepithelial [1]. The main component of preepithelial protection are mucins - highly glycosylated glycoproteins, which, due to their specific properties, protect the internal environment of the body from bacteria and damaging agents [4].

Secreted mucins MUC2, MUC5AC, MUC5B and MUC6 are the main components of the mucous layer and provide its viscoelastic properties. It has been established that the main universal mucin, which is secreted in all parts of the gastrointestinal tube and plays a key role in maintaining intestinal homeostasis, is MUC2 [5].

Epithelial defense is represented by various types of cells: enterocytes, goblet cells, enteroendocrine cells, Panet cells and undifferentiated epitheliocytes. Epithelial cells are connected to each other by multicomponent complexes consisting of tight junctions (TJs) of adhesive compounds and desmosomes. Dense contacts regulate the flow of water ions and small molecules, forming a dynamic intestinal barrier [6]. The tight contacts consist of a series of transmembrane proteins comprising occludine, claudins, connective adhesion molecules,

tricellulin, which are bound to actin and myosin filaments by cytoplasmic proteins ZO 1, 2 and 3 (zonula occludens) [9,10]. Proteins of dense contacts can be damaged by various pathogens with a subsequent increase in epithelial permeability and bacterial translocation.

The subepithelial level is represented by its own plate (lamina propria) of the mucous membrane, which contains immunocompetent cells that secrete IgA, cytokines, chemokines and proteases involved in the immunological defense mechanisms of the body. The tissue subepithelial complex provides regulation, trophism and kinetics of the integumentary epithelium, implements the reactions of nonspecific and specific immune defense.

The mucous membrane of the gastrointestinal tract has a global surface area of more than 200m^2 becomes the first barrier to protect the internal organs from the effects of external factors. Factors that determine the state of the intestinal barrier are: the epithelial layer of the mucous membrane with interepithelial contacts and cells of the immune system, the layer of parietal mucus, the microbiota, as well as the vascular barrier [1,7, 8].

The gut microbiota is involved in almost all processes of food metabolism, participates in the synthesis of vitamins, in cholesterol catabolism, forms numerous immune reactions associated with innate and adaptive immunity, and modulates human relationships with pathogenic microorganisms [11, 12]. During the formation of the syndrome of increased permeability, a large number of antigens enter the systemic circulation, which leads to the launch of the protective mechanisms of the immune system.

The development of SPEP is closely interrelated with inflammation, which is part of the pathogenesis of most rheumatological diseases. One of the mechanisms of SPEP is associated with the activation of intracellular kinases and the reduction of actin-myosin intracellular structures under the action of pro-inflammatory cytokines: tumor necrosis factor (TNF-α), interleukin-1 (IL-1ß), which leads to the rapid discovery of tight joints *(TJ)* between enterocytes by moving ZO-1 and occludin inside the cell [13, 14].

Many pro-inflammatory cytokines (TNF-α, IL-1ß, IL-6, IL-12, etc.) are able to cause oxidative stress in the cell, reduce the expression of ZO-1, occludin and other components of TJ, which leads to permeability of dense compounds [15]. The third mechanism of SPEP is the action of matrix metalloproteinases (MMP) on the components of TJ - occludine, claudins, ZO proteins, which also causes disorganization of TJ [16]]. It is known that MMP and oxidative stress enhance the formation of each other and their levels correlate with each other. For a long course of the inflammatory process, it is possible to rebuild dense compounds by increasing the expression and appearance of claudine 2 in their composition. The role of zonulin is a protein that can reversibly increase the permeability of the intestinal wall, changing the structure of tight junction TJ (tight junction TJ) of the lateral surfaces of the cells of the intestinal epithelium, andnot enough with inflammation.

The balanced gut microbiota stimulates resident macrophages to release large amounts of interleukin (IL) 10 and transforming growth factor beta, thereby preventing an increase in the number of pro-inflammatory T helper 17 (Th17) cells, and as a result inhibiting the development of SPEP.

In this regard, maintaining the integrity of the intestinal barrier can be of great importance in the development of rheumatoid arthritis.

MATERIALS AND METHODS OF RESEARCH

Under observation were 35 patients with RA (women 24, or 68.6%, men 11, or 31.4%).The average age of patients was 39.4 ± 1.1 years. The average duration of the disease is 9.8 ± 2.1 years.

Onthe integrity of the intestinal barrier with the help of morphologicalstudies of biopsy specimens of the mucous membrane (CO) of various parts of the gastrointestinal tract with subsequent staining with hematoxylin and eosin, which makes it possible to identify ulcerative defects, erosion of CO, to assess the density of cellular infiltrate and its composition, as well as the degree of atrophy that can serve as indirect signs of altered permeability [17]. Electron microscopy can be used to visualize the distances between epitheliocytes and the width of the intercellular spaces.

For light microscopy, biopsy specimens of the mucous membrane of the stomach, duodenum and colon were recorded in a 10 - to 12% solution of formalin on a Lilly phosphate buffer. Paraffin sections were stained with hematoxylin - eosin.

For transmission electron microscopy (TEM), tissue samples were recorded with a 2.5% solution of glutaraldehyde on a phosphate or cacodylate buffer, after dehydration in alcohol - acetone was poured with epono - araldite mixture. Ultrafine slices obtained on the ultratom "Ultracut" contrasted in the apparatus "Ultrostainer" and viewed in an electron microscope Hitachi H-600.

For scanning electron microscopy (SEM), the preparations after the above fixation were dehydrated in acetone alcohol, then dried by the critical point method in the HCP-2 apparatus and sprayed with gold in the IB-2 apparatus. Examined in an electron microscope Hitachi S405A.

Computer processing of microphotographs was carried out on a Pentium computer - W) using the application programs "Exel -Office" Microsoft - "Windows-Professional".

RESEARCH RESULTS AND THEIR DISCUSSION

Ananalysisof the studies revealed a significant morphological shiftin all the studied parts of the digestive tract in rheumatoidarthritis (RA).

During the study, in patients with rheumatoid arthritis , significant changes in the mucous membrane of the duodenum were revealed, which are expressed in an increase in the infiltration of the stroma of the intestinal villi by lymphocytes and plasma cells, the expansion of microvessels, an increase in the number of interepithelial lymphocytes, the location of epithelial nuclei at different levels, which creates the impression of false multi-row. The brush edge is preserved, as well as the integrity of the epithelial lining of the villi. Most of the goblet cells are empty. In the intervillous spaces, contents of a different nature are determined, among which microorganisms can be distinguished.

In the mucous membrane of the colon, the infiltration of the stroma also increases, the number of interepithelial lymphocytes increases.

Scanning electron microscopy (SEM) shows that the microrelief of the surface of the mucous membrane of the pyloric section of the stomach largely loses its regularity. The apical parts of the superficial dimple cells are located at different heights. There are intercellular gaps and

depressions. On the surface of the cells there is a small number of various inclusions and overlays. There are also microerosions of the apical parts of epitheliocytes.

The villi of the duodenum have a fairly regular leaf-like shape with a small number of different inclusions on the surface. Among which you can distinguish erythrocytes, lymphocytes and other formations.

The lumens of the crypts of the colon are filled with mucus, various inclusions, including microorganisms, are located in it. On the surface of epitheliocytes, small erosions are determined.

Changes in the morphology of gastrointestinal CO exacerbatethe occurrence of nonsteroidal anti-inflammatory drugs (NSAIDs).

In the stroma of the mucous membrane of the pyloric section of the stomach, the number of plasma and other infiltrate cells increases. Superficially, dimple epitheliocytes are characterized by pronounced polymorphism. This polymorphism is expressed in the different height and shape of the cells and the content of the mucoid. The number of interepithelial lymphocytes increases. The intercellular spaces in the basal parts of the epitheliocytes expand significantly, which leads to their extrusion. There are significant areas of eroded surfaces of epitheliocytes.

Significant changes are also noted in the mucous membrane of the duodenum.

The number of infiltrate cells increases significantly. In this case, plasma cells dominate in the stroma of the villi. The basal parts of the enterocytes are enlightened, the intercellular gaps increase. Some enterocytes lose their connection with the basement membrane. However, in the duodenum at the debut of the use of NSAIDs, there are no violations of the integrity of the epithelial lining and the formation of microerosions.

SEM studies have shown that in the pyloric part of the gastric mucosa, the "debut" of the use of NSAIDs causes significant changes in the microrelief of the surface. The apical parts of the cells become different in shape, size and height, which leads to a violation of the rhythmicity and relative symmetry of the microrelief.

On the surface of the cells, numerous microerosions are determined. The number of overlaps on the surface of cells increases, the intercellular spaces expand.

Morphological studies have shown that the very presence of PA causes significant changes in the pyloric part of the stomach of the duodenum and colon.

Before starting to take NSAIDs, these changes are in the nature of chronic inflammation, expressed to one degree or another. For the stomach, this picture fits into the framework of chronic gastritis without atrophy. For the duodenum - moderately pronounced duodenitis. In the colon, changes occur in the form of moderate colitis.

The initial use of NSAIDs calls for more pronounced changes in the mucous membrane.

In the mucous membrane of the pyloric section of the stomach, there are violations of the connections of the integumentary - dimple cells with the basement membrane, the expansion of intercellular spaces in the basal part of the epithelium, the appearance of microerosions on the apical surfaces of epitheliocytes and their pronounced polymorphism. At the same time, there is an increase in inflammatory changes.

Changes in the mucous membrane of the duodenum also indicate an increase in the manifestations of inflammation and a weakening of the strength of the epithelial lining.

In the colon, changes under the influence of NSAIDs are expressed to the least extent.
According to modern concepts, SPEP and disruptionof the microbiota is consideredas a trigger factor in the etiopathogenesis of PA [18]. Hepublished works in which he studiedtheeffect of correction of increased permeability of gastrointestinal co and microbiological disorders on the development and course of RH. Thus, there is evidence indicating a decrease in the activity of the disease, the level of pro-inflammatory cytokines and CRP in patients with RA with gingivitis after effective sanitation of the oral cavity [19, 20]. A number of works are devoted to the effectiveness of probiotics in RA, AS and SLE [21, 22, 23]. A significant increase in the permeability of intestinal CO has been established, not only in patients with AS, but also in their closest relatives, which indicates the genetic nature of intestinal permeability disorders leading to the development of SPEP [24], which requires an integrated approach to the treatment of patients with this group of diseases, aimed both at reducing the severity of autoimmune damage to the elements of the musculoskeletal system and at reducing the severity of SPEP.

FINDINGS

Thus, a key role in maintaining the integrity of the intestinal barrier is played by dense contacts between epithelial cells and the microbiota. The pathological permeability of the intestinal barrier leads to the translocation of bacteria and their metabolites into the internal environment of the body, which can cause inflammatory changes in the target organs and create a pathophysiological basis for the development of a number of autoimmune diseases. Understanding the role of the syndrome of increased epithelial permeability of the intestinal barrier will expand the understanding of the pathogenesis of RA, which will allow the development of effective approaches to the treatment of patients in this group

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