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Extraintestinal Manifestations of Ulcerative Colitis: The Opinion of a Rheumatologist and Proctologist

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Abstract: Extraintestinal manifestations of ulcerative colitis (UC) are detected in up to 25% of patients, more often with pancolitis. Various extraintestinal manifestations may develop, which are important in the diagnosis for both a rheumatologist and a proctologist: Erythema nodosum and gangrenous pyoderma due to circulating immune complexes, bacterial antigens and cryoproteins. Approximately 10% of patients with active colitis show aphthae on the oral mucosa, which disappear as the activity of the underlying disease decreases. 10% of patients suffer from inflammatory diseases of the eye (episiscleritis, uveitis, conjunctivitis, keratitis, retrobulbar neuritis, choroiditis). Often they are combined with other extraintestinal symptoms. The arrow indicates the synechia between the iris and the lens capsule. Inflammatory diseases of the joints: arthritis (25%), sacroileitis (15%) and ankylosing spondylitis (10%) can be combined with colitis or occur before the onset of the main symptomatology. Osteoporosis, osteomalacia, ischemic and aseptic necrosis are among the complications of corticosteroid therapy. Approximately 35% of patients with UC were diagnosed with dysfunction of the respiratory system. The relationship between acute pancreatitis and antibodies to exocrine pancreatic tissue and the true extraintestinal symptoms of ulcerative colitis remains a subject of discussion. In the acute phase of UC, a slight increase in serum transaminases is observed quite often, however, against the background of a decrease in the activity of the underlying disease, the indicators return to normal. While maintaining an increase in the levels of these enzymes, one should bear in mind the possibility of developing primary sclerosing cholangitis. Vasculitis, glomerulonephritis and myositis are rare extraintestinal symptoms. Assessing the severity of UC with extraintestinal complications can be interpreted differently by a rheumatologist and proctologist. From the point of view of a proctologist: usually, the severity of the disease and its activity correspond to the extent of damage to the mucous membrane of the colon, the frequency of relapse and the development of extraintestinal complications. From the point of view of a rheumatologist: the development of extraintestinal articular complications corresponds to a severe degree of ulcerative colitis of the colon and requires complex treatment.

Keywords: Extraintestinal, Manifestations, Ulcerative Colitis, Complications

Introduction

The commonality of pathogenetic lines and immune “participants” in the development of a typical clinical picture of inflammatory bowel diseases (IBD), in particular Ulcerative colitis (UC), as well as rheumatoid arthritis (RA), has become more and more noticeable in recent years. One of the most serious problems of modern proctology is inflammatory bowel disease. IBD, namely Ulcerative colitis, are characterized by non-specific immune inflammation of the intestinal wall - superficial in UC. UC is a chronic disease in which diffuse inflammation localized within the mucous membrane affects only the colon in different ways. (Satsangi & Satherland, 2003; Sartor, 2004).

At the moment, IBD are considered polyetiological diseases with a genetic predisposition. The idea of the autoimmune nature of IBD has received new development due to the information that the commensal microflora and its metabolic products serve as autoantigens, and the development of inflammation occurs due to the loss of tolerance to substances of the normal intestinal flora, which are usually harmless. The frequency of microbiota

disturbances in IBD reaches 60–90%. Autoimmunization, as well as a high concentration of circulating immune complexes, indicate a selective loss of immunological tolerance, which ultimately leads to an intense inflammatory process. (Sieper et al., 2009; Rodriguez et al., 2008). At that time, in the mucous membrane of the colon of patients with UC, a significant amount contains long-living IgG-producing plasma cells, as well as polymorphonuclear leukocytes, which produce a large number of metalloproteinases that cause destruction of the extracellular matrix and basement membranes.

A characteristic histological sign of UC is the formation between the crypts of the mucous membrane of microabscesses, the so-called "crypt abscesses", which are a cluster of polymorphonuclear leukocytes. Macrophages are also one of the main cellular elements of inflammatory infiltrate in IBD. The former come from circulating monocytes, make up 30-40% of the macrophage guts present in the mucous membrane of the intestine, and develop and support a chronic inflammatory process in the colon.

Inflammatory intestinal wall infiltrate in UC is represented by those cells (mainly neutrophils and monocytes) that migrated here from the peripheral bloodstream. Inflammation of leads to an imbalance of cytokines, which determines the features of the course of IBD. Changes in cytokine regulation are an increase in the production of inflammatory cytokines, primarily TNF-α, as well as interleukins-1, -6, -8, -12 with a decrease in anti-inflammatory interleukins-4, -10, -11, as well as a pronounced imbalance of regulatory IL cytokines -2, -5.

In inflammation, this cytokine stimulates Th1-helpers and macrophages, induces acute phase systemic reactions with increased synthesis of IL-1, -2, -6, -8. If an increase in IL-2 provides autocrine stimulation of T-lymphocyte proliferation and stimulates the growth of B-lymphocytes, the functional activity of natural killers, leads to the activation of macrophages, which means clonal proliferation and differentiation of lymphocytes, then IL-8 stimulates chemotaxis and activates T lymphocytes with the formation of oxygen radicals and the release of lysosomal enzymes.

Rheumatoid arthritis (RA) refers to a group of diseases characterized by polarization of the immune response according to the type 1 T helper immune response, which is manifested by overproduction of pro-inflammatory cytokines such as IL-6 and TNF-α. The earliest manifestations of RA are inflammation and occlusion of the small vessels of the synovial membrane. There is evidence of a role in RA in asymptomatic urinary tract infection caused by Proteus. A number of foreign scientists, such as Rashid T., Ebringer A., McGuckin M.A. It is believed that in genetically predisposed individuals, a causative microbe can initiate a disease, followed by the development of antimicrobial and cross autoantibodies that bind to antigens and damage tissues by activating the complement system and the production of cytotoxic products by inflammatory cells.

The essence of the pathological process in RA is systemic autoimmune inflammation, which affects the synovial membrane of joints with maximum intensity. In the synovial tissue there is an increase in the number of type A synoviocytes (cells resembling macrophages) and B (cells resembling fibroblasts), infiltration by immune and inflammatory cells (macrophages, T and B lymphocytes, plasma and dendritic cells), the formation of follicles consisting of lymphoid cells that resemble the germinal centers of lymph nodes. An early sign of rheumatoid synovitis is the formation of new vessels (angiogenesis or neovascularization). (Orchard et al., 2009; Reinshagen, 2009).

Synovial fluid contains more neutrophils than lymphocytes. The immune complexes formed in it activate complement; at the same time, anaphylatoxins and chemotaxis factors are released, which cause the adhesion of leukocytes to the endothelium of postcapillary venules. Complement activate and IL-1, TNF-α and leukotriene B4, secreted by the macrophages of the synovial membrane. Along with this, TNF-α, C5a, leukotriene B4 and IL-8, histamine and prostaglandin E2 contribute to the release of neutrophils from the vascular bed into the synovial fluid. Once in the synovial fluid, neutrophils absorb immune complexes, which leads to the release of free oxygen radicals and other substances that enhance the inflammatory response. (Nguyen & Sam, 2007).

Cell interactions are considered an important factor in the development of RA. Intercellular interactions are regulated by cytokines, which in particular produce activated synovial cells. These cytokines are likely to stimulate the inflammatory response in the synovial membrane, the release of cells and inflammatory mediators into the synovial fluid, the proliferation of synoviocytes, and are involved in the destruction of cartilage and bone and the development of extra-articular manifestations of rheumatoid arthritis.

Method

Of the variety of pro-inflammatory cytokines, TNF-α deserves special attention. In addition to macrophages, different types of cells synthesize it - T-helpers of the 1st type, endothelial cells, but monocytes / macrophages, of course, are its main source. No wonder it is considered one of the key in the process of inflammation in RA, Crohn's disease and other autoimmune diseases. TNF-α, on the other hand, determines the expression of adhesive molecules on endothelial cells, as a result of which the influx of phagocytes into the focus of inflammation increases. (D'Incà, et al., 2009).

A significant percentage of patients with RA, namely 80%, have antibodies (IgM and IgG), mostly defined as rheumatoid factor (RF). Antibodies accumulate in the synovial membrane and activate complement in the synovial fluid. The absorption of RF by macrophages and neutrophils, which is cytological defined as the presence of phagocytes, stimulates the formation of cytokines and the release of proteolytic enzymes that enhance inflammation. RF is one of the prognostic markers of destructive joint damage.

Results and Discussion

From all of the above, it follows that the pathogenesis of IBD and RA shows many similar links: the common immune participants of inflammation and the forms of their interaction, the cellular composition of inflammatory infiltrate of the intestinal wall and synovial membrane of the joints, overproduction of pro-inflammatory cytokines, in particular TNF-α, as well as overproduction of antibodies, namely IgG. Often with IBD, there is also articular syndrome, as well as with RA, there may be intestinal damage. Sometimes intestinal manifestations of autoimmune processes come to the fore, or, conversely, articular syndrome masks intestinal pathology, i.e. we are already talking about the common clinical manifestations of IBD and rheumatoid arthritis. (Sulyma, & Sulima, 2018). From all of the above, it follows that further study of the functional activity of blood cells, in particular neutrophils and monocytes, which are directly involved in the development of inflammatory reactions and are the main components of inflammatory infiltrates of the intestinal wall and synovial membrane in IBD and rheumatoid arthritis, will help to more deeply uncover the issues of their pathogenesis.

Conclusion

Extraintestinal manifestations, which occur in patients with Ulcerative Colitis, often affect the articular surfaces, which complicates the course of the disease and requires the joint action of proctologists and rheumatologists. Creation of effective protocols for complex and combined treatment of extraintestinal manifestations of ulcerative colitis and their use in patients will improve their quality of life.

Recommendations

It is recommended to use the available data in the treatment program in patients with joints manifestations in inflammatory bowel diseases.

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