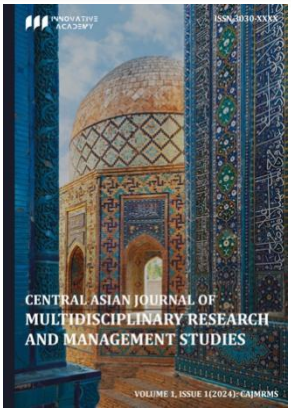

Immunological assessment of the course of the disease in synovitis of the knee joint

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ABSTRACT

The synovium is a frequent target in rheumatic diseases. The search for diagnostic criteria and determination of the dynamics of the pathological process necessitate standardization of biopsy diagnostic methods and quantitative assessment of morphological changes using digital imaging methods. The main methods for obtaining samples of the synovial membrane are considered. The main morphological and immunohistochemical differences in synovitis in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis are presented. Various immunological and autoinflammatory mechanisms for the development of these diseases have been shown. Inflammation in the synovium in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis is characterized by various stages of morphogenesis, as evidenced by the expression of various cellular markers. Rheumatoid synovitis is an autoimmune process, synovitis in ankylosing spondylitis is characterized by autoinflammatory processes, and in osteoarthritis, biomechanical factors are the leading ones, as initiators of inflammation in the joint.

Introduction. The synovium is a common target in rheumatic diseases, so we explain the interest in its morphological changes for scientific and diagnostic purposes. The search for diagnostic criteria and determination of the dynamics of the pathological process necessitate a quantitative assessment of morphological changes using digital imaging methods. The histological results obtained may be more informative than data from serological and clinical studies. Immunohistochemical and morphological changes in the synovium of affected and clinically intact joints may be identical [1]. Histological examination of the synovial membrane has become possible even in the early stages of the disease and can contribute to the study of not only pathogenetic links, but also biological markers of diseases, and, consequently, possible mechanisms of therapeutic effects.

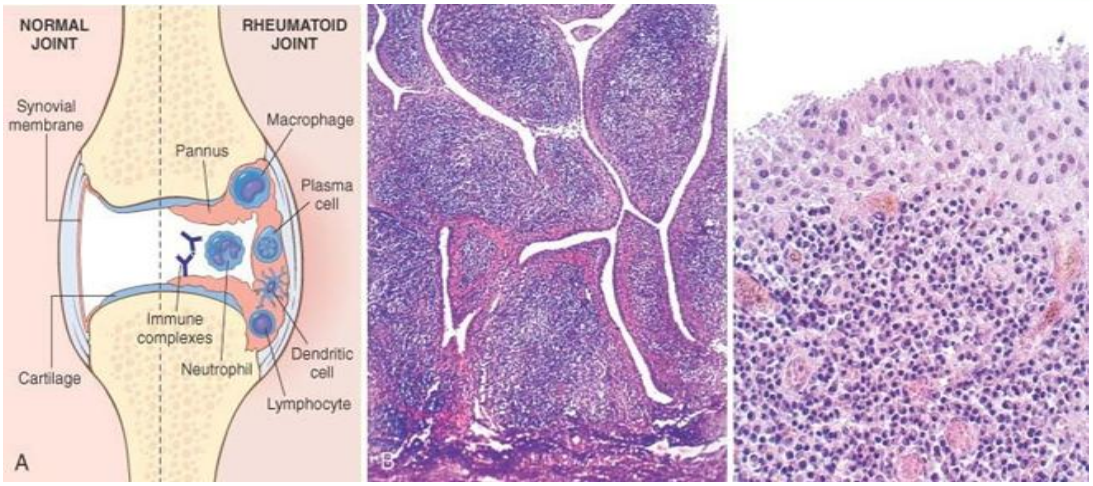
Biopsy methods. Three percutaneous minimally invasive methods are acceptable [2]. Blind needle biopsy of the synovium of the knee joint is the most accessible and safe. The method is easy to use and can be carried out in any rheumatology hospital, does not require special technical equipment and does not require significant financial costs. However, tissue fragments from fixed joints are not available for study, which is the most important disadvantage of this method. This biopsy can be performed under ultrasound guidance. This is

a relatively new method that can be used using local anesthesia of small and large joints, bursae and tendon sheaths. A sonographic image obtained multiple times during a single examination shows the arthroscopist the best areas for biopsy. This approach is undoubtedly useful in research, but has some disadvantages. For example, bony components such as the patella can create ultrasound interference, limiting access, especially in problematic joints. There are no data in the literature yet on studies of clinically unchanged joints. Ultrasound is suitable for joint selection, to identify affected joints, and is a good method for taking synovium. There are no studies yet on the suitability of the obtained samples for laboratory technologies, such as quantitative PCR, cell culture, etc. Despite the attractiveness of this method, its validation is necessary. Taking samples of the synovium during arthroscopic examination is one way to obtain tissue. Arthroscopic biopsy is safe and well tolerated by patients. Although arthroscopy is expensive and requires additional training, it is currently considered the gold standard for examination and biopsy. It allows you to obtain biopsies from various parts of the joints. The material collected in this way is suitable for morphological diagnosis even of ankylosed joints. The activity of inflammation in one joint correlates with damage to other joints. This method allows for dynamic observation of the affected joint during clinical trials.

Various cellular elements participate in the inflammatory process of the synovial membrane: T-lymphocytes, B-lymphocytes, macrophages and fibroblasts, but the balance of cells and the cytokines they synthesize are different, which distinguishes the morphological picture of synovitis in different diseases. The study of the immunological characteristics of the synovial membrane contributes to the study of the pathogenesis of each disease separately. It has been noted that the severity of infiltration by T and B cells significantly distinguishes rheumatoid synovitis from synovitis in other diseases [3]. In the subsynovial layer, immunohistochemical methods reveal large numbers of T and B cells [4]. It is assumed that, in addition to a decrease in the number of T cells and disruption of their function, under certain conditions there is a suppression of T cell subclasses or T cell factors in the periphery. There is a regulatory subclass of T cells (Tr1), which has low proliferative activity and synthesizes a large amount of IL-10 and a small amount of IL-2 and IL-4. It is IL-10 that functions as a growth factor for regulatory T cells (Tr1). These cells are functionally close to Th0 and Th1 in terms of the level of synthesis of interferon-γ and transforming growth factor-β, respectively [5].

Rheumatoid synovitis is characterized by pronounced proliferative and inflammatory changes with the formation of follicle-like structures (Fig. 1). Some authors regard this morphological picture as a variant of the pathophysiological subtype of rheumatoid arthritis (RA) [6]. Such patients have severe inflammation of the synovium, with a predominance of macrophages (CD68+) in the infiltrate, increased synthesis of tumor necrosis factor-α (TNF-α) and lymphotoxin-β, as well as a high level of C-reactive protein in the synovial tissue.

Fig. 1



It should be noted that lymphocytic neogenesis is not associated with the severity of the erosive process in the joints or the development of rheumatoid nodules [7]. It should be noted that follicle-like structures in the synovium are also found in other non-antibody associated synovitis, for example, in psoriatic arthritis and osteoarthritis. This is probably a manifestation of ectopic maturation of B lymphocytes into plasma cells (CD38+). Considering the presence of CD22L+ and CD20+ cells in the center of follicle-like structures, their appearance can be regarded as a manifestation of ectopic lymphoid neogenesis. However, these data do not answer the question of whether lymphoid neogenesis in RA is a cause or a consequence of inflammation. The manifestation of lymphocytic neogenesis is considered as the 2nd and 3rd degrees of inflammatory infiltration in RA. Analysis of clinical and laboratory parameters in patients with such a morphological picture in the synovium showed that we are not talking about the subtype of RA, but only about the severity of inflammation of the synovium and the systemic nature of the rheumatoid process [7].

Cells expressing CD68 play a significant role in the morphogenesis of rheumatoid synovitis. They are macrophage in nature and are predominantly antigen presenting cells. Along with this, they synthesize various proinflammatory cytokines and metalloproteinases in the joint cavity. These cells positively correlate with clinical signs of disease remission and do not depend on the mechanism of action of the underlying anti-inflammatory drug. Quantitative determination of macrophages in the synovea is a reliable indicator for assessing the effectiveness of local biological effects in the early stages of RA treatment and is less sensitive to placebo.

Patients with a high number of macrophage elements in the synovium at the onset of the disease are at risk for an aggressive course of the disease. Tissue macrophages are a source of synthesis of pro-inflammatory cytokines, such as IL-1 and TNF-α. TNF-α, in turn, induces the synthesis of matrix metalloproteinases, cysteine and other mediators that have a damaging effect on the cartilage matrix. These changes are detected already at an early stage of the disease.

An important role in the rheumatoid process is played by B cells, which are at various stages of differentiation. They are the ones who synthesize IgM, IgG and IgA in the synovium. However, the mechanisms of regulation of the immune response are still insufficiently studied. The potential role of B cells is controlled by macrophages in the synovium. B cells differentiate into antibody-synthesizing plasma cells. Autoantibodies stimulate Fc receptors, which are expressed in large numbers on macrophages. Autoantibodies and immune complexes activate the complement system to release C5a, which attracts macrophages. Along with this, B cells can synthesize cytokines and activate T cells that synthesize TNF and granulocyte-macrophage colony-stimulating factor. Proinflammatory cytokines stimulate stromal cells to

further increase the synthesis of granulocyte-macrophage colony-stimulating factor. TNF and granulocyte-macrophage colony-stimulating factor are important for maintaining the macrophage clone and their metabolism.

The inflammatory infiltrate in RA differs in localization and cellular composition. Firstly, these are perivascular lymphocytic accumulations, consisting predominantly of CD4+ cells, B lymphocytes, a small number of CD8+ cells and dendritic cells. Secondly, there are scant diffuse infiltrates of T cells. Lymphocytes, macrophages and dendritic cells (CD21L+) are in close functional interaction. It is possible that activated perivascular T lymphocytes directly stimulate the migration of macrophages into the tissue. This mechanism initiates the synthesis of cytokines and metalloproteinases [11]. The data obtained support the hypothesis of macrophage-associated disorders in RA, and the success of therapy may be based on the search for an effect on this part of inflammation.

In the development of synovitis in osteoarthritis, the leading cause is biomechanics (damage to the meniscus, overexertion, hypermobility, anatomical deviations) [17]. To understand inflammation in this case, one must keep in mind the mechanical factor. Trauma and other damage lead to the synthesis of damaging molecules (damage-associated molecular patterns - DAMPs), including extracellular matrix and intracellular alarmins, which, through signal recognition receptors on synovial macrophages, fibroblast-like cells or chondrocytes induce local synthesis of proinflammatory mediators. Inflammation-induced angiogenesis and increased vascular permeability lead to the infiltration of plasma proteins that act as DAMPs [18].

Acute and chronic synthesis of inflammatory mediators leads to cartilage damage either directly or through the induction of proteolytic enzymes, which enhance the vicious circle of innate immune activation in osteoarthritis [19].

The inflammatory infiltrate in osteoarthritis is represented primarily by macrophages, a small number of T and B lymphocytes, mast cells and NK cells. T cells perform an angiogenic function and are localized in perivascular spaces [20]. T cells are activated by an antigen, probably an autoantigen against cartilage tissue. The autoantigen is secreted by cartilage (chitinase-3-like protein and collagen II peptides). The infiltrate is polymorphic, and inflammation generates disease progression [21, 22].

Conclusion. Inflammation in the synovium in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis is characterized by various stages of morphogenesis, as evidenced by the expression of various cellular markers. Rheumatoid synovitis is an autoimmune process, synovitis in ankylosing spondylitis is characterized by autoinflammatory processes, and in osteoarthritis, biomechanical factors are the leading ones as initiators of inflammation in the joint.

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