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LIVER ABNORMALITIES IN RHEUMATOID ARTHRITIS

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Abstract: The essence of the pathological process in rheumatoid arthritis (RA) consists in generalized immunological (autoimmune) inflammation, leading to the development of synovitis, as well as a wide range of extra-articular organ manifestations [3], of which the pathology of the gastrointestinal tract is 11%, including hepatomegaly in 19, 5% of them. Views on the causes and nature of hepatic pathology in RA have changed over time, depending on the point of view of researchers on the pathogenesis of the disease, expanding the spectrum of medicinal, often hepatotoxic, agents used in rheumatology.

Key words: Rheumatoid arthritis, chronic liver diseases, non-steroidal anti-inflammatory drugs, cholestasis, cytolysis, hepatocytes.

Relevance. In the 60s-70s, the role of the primary focus of inflammation - the synovial tissue as an inducer of autoallergic processes - was discussed (T. Higashi, F. Hasegava, 1960); organ-specific autoantibodies (L. T. Piai, 1967), increased permeability of the vascular wall, instability of hepatocytes, leading to hyperenzymemia, dysproteinemia (P. Borset, E. Pecters, 1961); decrease in the reserve of vitamins, impaired enzymatic function (ME Kurmaeva, 1969) and blood circulation in the liver (VF Sysoev, ES Mach, 1966) [cit. by 9].

The interpretation of changes in the functional ability of the liver also differed. Most researchers already at an early stage of RA noted a violation of its detoxification, pigment, protein-forming and carbohydrate functions, others believed that the organ's function suffers only in amyloid lesions [24]. Structural changes, on which the functioning of the liver directly depends, were described by domestic pathomorphologists as granular, fatty degeneration, deposition of amyloid masses, less often annular cirrhosis and necrosis of hepatocytes [21].

Similar changes were found in the liver tissue in RA and other researchers [1,24]. Moreover, in the work of VV Vasilenkaitis [4], a correlation between structural and functional hepatic disorders and the activity of the rheumatoid process was demonstrated.

Currently, two types of functional and morphological changes in the liver in RA are generally recognized:

1. Deposition of amyloid masses along the intralobular capillaries between stellate endothelial cells, in the reticular stroma of the lobules, the walls of vessels, ducts, and the interstitial tissue of the portal tracts with atrophy of hepatocytes.
2. Inflammatory and sclerotic changes in the portal tracts and stroma as a morphological expression of immune disorders [8, 17].

It is also impossible to exclude the effect on the liver of drugs (primarily cytotoxic) used in the treatment of RA. Back in the 60s, it was suggested that with prolonged use of antirheumatic agents,

oxidative-energy processes weaken, causing a reduced consumption of oxygen by tissues, in particular by liver cells [9].According to the results of the analysis carried out at the Institute of Rheumatology of the Russian Academy of Medical Sciences during 1999, an increase in aminotransferases was noted in inpatients with rheumatic diseases in 6% of cases [5].Non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying (basic) drugs are widely used in rheumatology. NSAID-induced gastropathies are a common complication of anti-inflammatory therapy. Liver damage that occurs while taking NSAIDs also deserves attention [12]. According to some authors, no clinical signs of NSAID-induced hepatopathy are detected [44]. At the same time, the literature describes the development of "salicylic" hepatitis, accompanied by an increase in the level of aminotransferases and confirmed by the study of liver biopsy [58].

According to a number of authors [29, 66], in patients with RA while taking NSAIDs, the level of aspartate aminotransferase [AsAt] may increase, which, however, rarely serves as a reason for discontinuation of the drug. Cases of the development of intrahepatic cholestasis have been described while taking piroxicam, confirmed by computed tomography and liver biopsy [39]. Diclofenac was hepatoxic in 7 patients with RA (1 of them with a lethal outcome) [38]. In a comparative study of celecoxib (a specific inhibitor of COX-2) compared with other NSAIDs, its lower hepatoxicity was shown [47].

Slow-acting, disease-modifying agents include aminoquinoline drugs, sulfasalazine, gold salts, D-penicillamine. With the appointment of D-penicillamine, the development of cholestatic jaundice was noted [20]. Changes in liver function, including an increase in the level of aminotransferases, as a side effect of sulfasalazine (SD), was observed in 4.7% of patients with RA [61, 27, 32]. A fatal outcome was also described due to massive liver necrosis in a patient with Sjogren's syndrome who was taking SZ [48].

In Uzbekistan patients with chronic viral hepatitis, an increase in the level of aminotransferases was detected in 53% of cases with the use of Plaquenil, in 55.6% - SD and was not observed with the use of gold preparations for intramuscular administration and methotrexate (MT) [50]. In one patient, while taking azathioprine, the authors revealed the activation of chronic viral hepatitis B. The intake of basic drugs in RA patients with chronic viral hepatitis was more often accompanied by the manifestation of drug hepatotoxicity compared with the group of RA patients without hepatitis [50]. Cytotoxic immunosuppressants - MT, cyclophosphamide (CF), azathioprine, cyclosporin A and their combinations - are increasingly being introduced into the practice of rheumatologists. It is reported that the combination of Plaquenil and MT leads to a decrease in the hepatoxicity of the latter [41]. But if in the 60s drugs with a possible hepatotropic effect (D-penicillamine, cytotoxic drugs) were used relatively rarely, mainly in refractory RA, now the treatment tactics have changed and basic drugs are beginning to be included in complex treatment in the early stages of RA. First of all, this concerns the "gold standard" - MT, when taken, there is a moderate increase in the level of aminotransferases, especially aspartic [20]. A dose-dependent transient increase in the level of aminotransferases is a common side effect of MT, which manifests itself after 4-5 days from the start of treatment and persists for 1 to 2 weeks after discontinuation. A twofold or threefold increase in the level of aminotransferases is not a reason for the abolition of MT, and a more significant increase in the level of enzymes indicates the need to reduce the dose or interrupt treatment [15, 45, 63].

A retrospective study of 188 autopsy cases of RA from 1958 to 1985, that is, before the widespread use of MT, revealed pronounced fibrotic liver damage (3-4 points) in only 2 cases [62]. Other authors in liver biopsies of patients taking MT for a long time also found moderately pronounced histological changes - fatty degeneration, periportal lymphocytic infiltration and fibrosis [67, 68, 69]. Risk factors for the development of side effects from the liver when taking MT are alcoholism, old age, obesity, diabetes mellitus, impaired renal function, contact with hepatotoxic substances [20]. Opinions regarding the risk of developing liver fibrosis and cirrhosis during treatment with MT are controversial. It is believed that liver

damage is more often observed in the treatment of MT in patients with psoriasis than in RA [31]. Liver fibrosis, according to a number of researchers, is found in almost a third of patients receiving MT for more than 2 years, but cirrhosis rarely develops [25, 36, 60, 63].

The high infection of the world's population with the hepatitis B virus (about 2 billion people) and hepatitis C (about 500 million people) makes a significant risk of developing progressive chronic liver diseases, which can occur as an independent disease or combined with other competitive diseases [13]. To date, the following hepatitis viruses are known: A (HAV), B (HBV), C (HCV), D (HDV), E (HEV), F (HFV), G (HGV), as well as recently discovered TTV, SEN -V. The ability to chronicize in the form of persistence or latently existing (for a long period - up to 20 years) has been proven for hepatitis B, C, D viruses. Most of the infected consider themselves healthy, remaining potential sources of infection [2, 7, 18, 19].

Studies of the last decade using immunological, molecular biological (PCR, molecular hybridization), as well as morphological methods have significantly expanded the understanding of the pathology caused by hepatitis viruses. Until the early 1990s, most virologists believed that the hepatitis B virus was severely hepatotropic. However, the detection of antigens not only in the liver, but also in other organs (kidneys, spleen, muscles, lymph nodes), cast doubt on this. In 1989, similar data were obtained by Russian molecular biologists and confirmed by extensive clinical material [2]. This made it possible to classify viral hepatitis not as a liver disease, but as a systemic (generalized) process [2,7].

The evidence of HCV and HBV replication in monocytes and macrophages [2], which may be the reason for the "escape" of hepatitis B and C viruses from immune surveillance, has attracted special attention. The transferred HCV infection does not induce a strong immune defense; moreover, the possibility of re-infection not only with other genotypes, but also with homologous strains of the virus is allowed [10]. Due to the fact that one of the most frequent manifestations of chronic viral hepatitis C, especially in patients with cryoglobulinemia, is articular pathology of the type of mono- or oligoarthritis (more often - large and medium-sized joints), with an intermittent course, but without destruction of the articular surfaces, arises the question of the relationship between chronic viral hepatitis and RA.

For the first time the relevance of studying rheumatological aspects of chronic hepatitis was formulated by E.M. Tareev in 1979 [22]. One of the first descriptions of the development of RA with a typical X-ray picture, histological changes in synovia and the presence of RF in acute hepatitis belongs to E. L. Monis and M. V. Stevens [51].

Later, similar observations were made by domestic scientists (E. M. Tareev, Z. G. Aprosina, T. N. Lopatkina). The reason for a new wave of interest in the problem of the relationship between RA and hepatitis was the description of clinical cases of the onset of RA after vaccination against hepatitis B in individuals with a certain genetic predisposition (carriers of the HLA-DR4 antigen), which made it possible to consider the hepatitis virus as a trigger in the development of RA [26, 50].

In the etiology of RA, the role of chronic viral infection has been actively discussed in recent years. Works of this kind are aimed at isolating an exogenous agent capable of causing immune inflammation in synovial tissue with its subsequent self-maintenance. But although the hypothesis according to which the virus plays a certain role in the etiology of RA has been widely discussed in the literature since the early 70s, it was not possible to detect latent viruses in the cells of rheumatoid synovial tissue by the methods of cultivation, co-cultivation, and cell fusion for a long time. This theory was supported only by the results of electron microscopic studies of rheumatoid synovial tissue, which revealed structures resembling viral material or products of the interaction of the virus with host cells [35, 43, 53, 54]. The spectrum of viruses ka to possible triggers of RA is very wide [6, 26,28, 30,

33-35, 37, 40, 42, 43, 49, 52-57,59, 65]. One gets the impression that there is no single etiological agent for RA.

As for hepatitis viruses, they most likely damage the macrophage system of the liver, which leads to a decrease in the clearance of antigens and immunoglobulins.

Chronic antigenic stimulation is accompanied by poly and monoclonal proliferation of B-lymphocytes, increased production of immunoglobulins and the formation of immune complexes, including mixed cryoglobulins (CG), accumulating in the circulation [11]. According to some authors, CGs can exhibit RF activity and appear at the second stage of the regulatory response as a reaction to infection or an inflammatory process in the body [11]. Recently, more and more studies have confirmed the close relationship between HCV infection and "essential" cryoglobulinemia. HCV infection is characterized by a unique immunological phenomenon - no other infection has such a frequent production of RF and such a high specificity. Not only polyclonal, mainly Ig M RF, which is the basis of type 3 cryoglobulinemia, is produced, but a special clone of B-lymphocytes producing highly specific Ig M [11].

It is known that the deposition of immune complexes in the walls of blood vessels or in situ upon activation of the complement system leads to the development of vasculitis [14] and such clinical manifestations as cutaneous vasculitis, purpura, glomerulonephritis, neuropathy, and Raynaud's phenomenon. It was found that the frequency of detection of antibodies to HCV in patients with mixed cryoglobulinemia reaches 70%, HCV RNA in blood serum is detected in 71-86%, and in cryoprecitates in 93% of cases [11].

Clinical data, as well as a high percentage of changes in liver function tests in RA patients, in the absence of a history of hepatic pathology, may indicate the presence of chronic hepatotropic viral infection in some patients.

A screening analysis of 373 case histories of patients with RA observed at the Institute of Rheumatology in 1999 revealed an increase in AlAt in 29, AsAt in 23, alkaline phosphatase in 15, and GGTP in 14 patients. Moreover, these changes could be associated with the intake of antirheumatic drugs only in 8 patients.

Clarification of the nature of liver damage in RA has not only theoretical, but also practical significance, since in liver pathology (including chronic viral hepatitis), a protracted course and progression of rheumatic diseases are more often observed.

The study of the role of viral infection and cryoglobulinemia in the pathogenesis of RA dictates the need for further research in this direction using modern diagnostic methods, including immunological and morphological ones. Solving the problem will reveal the mechanism of cryoglobulinemia development, as well as clarify the tactics of therapeutic measures for RA with concomitant infection with hepatitis B and C viruses.

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