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IMPLICATION OF HEPATITIS C VIRUS ON DEVELOPING OF RHEUMATIC DISEASES

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Abstract:

Hepatitis viruses can cause not only liver damage in the form of acute hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma, but also damage to other organs and systems, and in some cases induce independent diseases. Currently, replication of the hepatitis C virus has been proven in peripheral mononuclear cells and bone marrow cells, mainly in B-lymphocytes, in the myocardium in patients with myocarditis or cardiomyopathy, in the skin, in the epithelium of the ducts of the exocrine glands, and in the vascular endothelium in cryoglobulinemic syndrome. The detection of serological markers of autoimmunity in HCV infection, including some organ-specific autoantibodies, suggests autoimmune mechanisms underlying a number of extrahepatic symptoms. For this reason, it is often considered in differential diagnosis in many areas of clinical medicine. Because the diagnostic, therapeutic strategies and prognosis of rheumatic and HCV-induced diseases can be quite different.

Keywords: HCV, arthritis, rheumatoid arthritis, connective tissue disease, fibromyalgia, hepatitis C, systemic lupus erythematosus, vasculitis.

RELEVANCE: The World Health Organization estimates that 130-170 million people worldwide suffer from chronic HCV infection [10,33,36,44,60,62], in 2016, approximately 399 000 people died from hepatitis C. Among the causes of death, chronic viral hepatitis (CVH) ranks 9th. Hepatitis C virus (HCV) affects liver cells, which becomes chronic in 70-80% of cases. The general course of HCV infection is usually chronic, systemic, asymptomatic and can induce, usually after 20 years or more, severe complications, such as cirrhosis of the liver and hepatocellular carcinoma. Diagnosis of HCV infection is difficult because the course of the disease is asymptomatic. It is usually diagnosed by chance by serological screening or in connection with diagnosis of end-stage liver disease. Many have proven that HCV is much more than a simple liver infection. Indeed, this virus is involved in the pathogenesis of several autoimmune disorder diseases that can affect virtually any organ of the body [14,43]. And also causes damage to some blood cells - neutrophils, monocytes, B-lymphocytes, etc. The spectrum of extrahepatic manifestations of viral hepatitis C (HCV) varies from mild or moderate manifestations, such as joint syndrome (arthritis or arthralgia), mixed cryoglobulinemia, vasculitis of small and medium vessels, Sicca syndrome, peripheral neuropathy, severe, life-threatening complications, mainly tumor diseases. For this reason, it is often considered in differential diagnosis in many areas of clinical medicine. Because diagnostic, therapeutic strategies and prognosis of rheumatic and HCV-induced diseases can be quite dissimilar (Table 1).

Table 1 Resource requirements by component
Organ-specific manifestations of viral hepatitis C (HCV) in patients with extrahepatic manifestations in severity

	Mild to moderate severity	Severe manifestation	Potentially fatal manifestation
1	Purpura	Persistent multiple skin ulcers that do not heal	Rapidly progressive glomerulonephritis
2	Sporadic skin ulcerations	Finger ischemia	CNS lesions
3	Arthralgia /Arthritis	Severe neuropathy (motor or motor-sensitive)	Acute necrotizing intestinal vasculitis
4	Non-inflammatory muscle pain	Glomerulonephritis with / without renal failure / nephrotic syndrome	Alveolar hemorrhage

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5	Common disorders (malaise, fever)	Interstitial lung disease	Coronary artery disease
6	Mild to moderate neuropathy (sensitivity)	Vascular gastrointestinal lesions (non-necrotizing)	
7	Тяжелые аутоиммунные цитопении	Withimptomatic hemolyticanemia, thrombocytopenia	

HCV INFECTION WITH CRYOGLOBULINEMIA

Currently, chronic HCV infection is considered as a chronic generalized viral infection, i.e. as a systemic disease [1 0,39,37]. Persistence of HCV leads to constant antigenic stimulation of B-lymphocytes, which proliferatewith the formation of B-cell clones that produce **cryoglobulins** - immunoglobulins, reversibly precipitating at temperatures below 37 ° C, which are the basis of immunopathological disorders in CV [3]. **Cryoglobulinemia is** one of the most common disorders associated with hepatitis C. They can accumulate in small and medium-sized blood vessels, causing difficulty in blood flow. This, in turn, leads to a number of problems. Most often, patients with KG have cutaneous purpura, arthralgia, general weakness (Melzer's triad). However, more severe lesions of internal organs are also possible, determining the prognosis in patients with HCG [2]. So, according to S.Y. Milovanova et al. [4], the spectrum of extrahepatic lesions in patients with CG with CG was characterized by a high frequency of widespread purpura with the possibility of ulcerative-necrotic skin changes, joint damage with the development of arthritis, severe forms of kidney damage with high arterial hypertension and renal failure, pulmonary vasculitis, as well as a greater incidence of severe Raynaud's syndrome and "dry syndrome" compared to those in patients without KG. The most typical symptom of mixed cryoglobulinemia is polyarthralgia (up to 70% of patients), which are recurrent in nature. Characteristic localization - hands and knee joints (up to 45% of cases), elbow and ankle joints (up to 25%). Obvious arthritis is rare. They may be accompanied by minor deformations and radiographic changes in the long course of the process. Approximately 80–90% of patients with mixed cryoglobulinemia show signs of infection caused by HCV, and RNA of this virus can be found in the serum and cryoglobulins of patients [4]. The relationship between HCV infection and cryoglobulinemic mesangiocapillary glomerulonephritis has been convincingly shown. Of interest are such extrahepatic manifestations of HCV as chronic fatigue syndrome, non-insulin-dependent diabetes mellitus, malignant B-cell proliferation (especially HCV-associated lymphoma of the spleen), etc. [71]. In patients with hepatitis, various non-organic autoantibodies are detected in low titers - antinuclear factor (in a third of patients), anticardiolipin antibodies (more often in cryoglobulinemic syndrome). Antibodies to smooth muscles, to parietal cells of the stomach, antineutrophil cytoplasmic antibodies, etc. Cryoglobulinemia occurs in 28-63% of cases, a decrease in the hemolytic activity of complement - in 39-50%, antibodies to thyroglobulin - in 4-42%. The infection is characterized by a high frequency of RF production (45-70%). At the same time, there are not only polyclonal IgM-RF (the basis of type III cryoglobulins), but also a highly specific (with the same idiotyp) monoclonal IgM-RF, which is the basis of type II cryoglobulins [8]. This specificity of monoclonal RF suggests that its production is due to stimulation by the same antigen. It is believed that the role of the antigen in this case is played by the HCV complex with low-density lipoproteins of the host [4]

VIRAL HEPATITIS C AND ARTHRALGIA, ARTHRITIS

The most frequent extrahepatic manifestation of HCV infection is joint damage. Cacoub and co-authors reported that 23% of 1614 patients with chronic hepatitis C, in general, suffered from arthralgia. However, asymptomatic **joint involvement appears to be much more common.** Iagnocco et al. found that 96.5% of the 29 HCV patients without articular symptoms had minor inflammatory changes in the knee, hip, or shoulder joints on ultrasound, a highly sensitive joint research method [25]. However, no other joints were examined. Based on this observation and studies reporting arthritis in only 4-5% or less of HCV patients [58]], it can be assumed that these small percentages represent only the tip of the iceberg of general joint inflammation associated with HCV. In any case, it should be emphasized that some clinical reports regarding extrahepatic manifestations of HCV infection have been made by non-rheumatologists who could mistakenly diagnose milder forms of arthritis with arthralgia. The clinical picture of HCV-associated arthritis (HCVAA) has been outlined on the basis of several studies [58]. Studies have shown that the prevalence of joint syndrome associated with hepatitis C virus (HCVaA) is about 4% of patients with HCV. This is a small percentage, because many patients are diagnosed with a joint event only when consulting a specialist. Poanta L. et al. undertook a prospective study that presented evidence that 20% of patients infected with HCV would have arthralgia in the first year [13]. The articular manifestations present in patients

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with HCV have been observed to be a type of rheumatoid arthritis or arthritis associated with cryoglobulin deposits. These patients have a high prevalence of positive rheumatoid factor (RF) and therefore can often be misdiagnosed with RA [79]. The differential diagnosis between RA as HCV-associated arthritis and true RA can be problematic, as their clinical picture can be very similar (Table 2).

Table 2 Resource requirements by component
Comparison of clinical and laboratory manifestations of arthritis associated with HBC and rheumatoid arthritis (RA)

№	Signs	HCVaA	RA
1	Peripheral symmetrical polyarthritis	Revealed	Revealed
2	Erosion	possible (?)	identified (not at the beginning)
3	Rheumatoid nodules	not revealed	frequent
4	Prolonged morning stiffness	frequent	frequent
5	Increased ESR	~ 50%	Revealed
6	Rheumatoid factor	frequent	frequent
7	Antibodies against CPD	not revealed	frequent

American Rheumatica Association's RA classification criteria: Not useful for this purpose because HCV-related arthritis can easily meet these criteria [50,67]. However, in RA, as in HCV-related arthritis, ESR may be normal and rheumatoid nodules absent, while prolonged morning stiffness and positive rheumatoid factor are characteristic of both disorders. Some authors have described RA-like HCV-related arthritis. as non-erosive [38,80], but others have reported erosion in 20-30% of patients with HCV infection and polyarthritis [5,8]. In these cases, a random association between the presence of HCV and true RA cannot be ruled out. In this regard, it should be remembered that studies that have revealed an increased prevalence of HCV in patients with RA [9,17] , and a study that showed a higher prevalence of erosive arthritis associated with HCV infection [19] was conducted in Italy. In this country, the prevalence of HCV infection among adults is particularly high and ranges from 3.2% to 24.6% in different geographical areas
[15, 39, 53, 63, 68] . Recent work from the U.S. and France did not report a link between RA and HCV [24,40]. However, in our experience, the course of HCV-associated arthritis is usually much less aggressive than RA [50]. An important contribution unlike RA fromHCV liarthritis can come from c detection of antibodies to keratin. Kessel demonstrated that this test was positive in 60.6% of RA patients and only 8% of those with HCV-related arthritis [28]. Recently, antibodies against cyclic citrullinated peptide (anti-CCP) have also been shown to be very beneficial. They were found in 76.6% of 30 patients with rheumatoid arthritis, but not in any of the 31 patients with HCV infection alone. and none of the 8 patients with HCV infection and joint involvement [11]. In Tubi's experience, the presence of IgA rheumatoid factor in HCV patients suggests a diagnosis of HCV-related arthritis when the search for IgM rheumatoid factor is negative [73]. In some cases (especially in early arthritis), a clear distinction between the two may not be possible. In any case, All patients with symmetrical arthritis should be differentiated from the more frequent subgroup of arthritis associated with HCV.

A less common subgroup of HCV-related arthritis, consisting of non-erosive monooligoarthritis localized mainly in the lower extremities and often having an intermittent course, must be differentiated from several primitive forms of arthritis, in particular arthritis associated with crystals (urate and calcium pyrophosphate), and spondyloarthropathy. HCV-related arthritis mainly affects the ankles [19] and is apparently characterized by the presence of anti-HCV antibodies in the serum and (often) type II or III cryoglobulinemia (with or without cutaneous vasculitis). In gout-related arthritis, the local signs of inflammation are usually greater, and crystals can be found in synovial fluid. In gout, typical radiographic abnormalities have been described. such as soft tissue urate deposits, paraarticular erosions, and osteolytic areas [35,69]. However, they usually appear several years after the onset of the disease. In calcium pyrophosphate arthropathy, punctate and linear calcifications can be detected by X-rays in fibrous cartilage, articular cartilage, and joint capsules [34] . It should be remembered that these calcifications can be present completely asymptomatically, especially in elderly patients, and that they can coexist with other rheumatic disorders. Lesions of the spine, chest and sacroiliac joints, as well as extra-articular manifestations, such as peripheral enthesitis, tenosynovitis and bursitis, are often found in spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease and

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undifferentiated spondylitis). Several imaging techniques (X-ray, MRI, CT, ultrasound) have been usefully used to identify various lesions. In reactive arthritis, there are clinical and/or laboratory signs of initiating infections [54]. Taglione and colleagues from Italy reported an increased prevalence (12%) of HCV infection in 50 patients suffering from psoriatic arthritis (PSA) [72]. Our data did not confirm this observation [55].

The high incidence of PSA in Italy could contribute to a random association [56]. Treatment of HCV-related arthritis is often based on taking NSAIDs, low doses of oral corticosteroids, and hydroxychloroquine [50,57]. Israeli authors have suggested the use of alpha-inteferon and ribavirin [67] . Although little research has been done in this area, the use of more aggressive treatments for HCV-related arthritis or other arthritis in patients with HCV positive appears risky due to the possible negative effects on liver disease [47]. For this reason, in our departments, we screen all patients observed with any arthritis for HCV infection. However, recent evidence suggests the safe use of tumor necrosis factor antagonists alpha [29,32,52,61] in small groups of patients with rheumatic disorders and chronic hepatitis C.

FIBROMYALGIA

Fibromyalgia (FM) is a syndrome characterized by diffuse and chronic pain in the musculoskeletal system and soreness in certain anatomical areas [21,78]. Other often associated symptoms are fatigue, headache, irritable bowel syndrome, and sleep disturbances [21,78] . This syndrome can occur in a primitive (idiopathic) way or can be associated with several chronic diseases. In any case, patients suffering from this disorder represent one of the largest groups that are referred to rheumatology departments. The prevalence of FM in HCV-positive subjects can range from 5% to 19% [12,23,30]. According to many authors, HCV patients do not make up a significant percentage of the large number of FM patients in the general population. In contrast, Rivera and colleagues found antibodies against HCV in 15.2% of their FM group [66]. In any case, HCV infection should be borne in mind as a possible cause of secondary FM even in subjects without elevated serum transaminase levels [66].

HEPATITIS C VIRUS AND SYSTEMIC TORACIAL LUPUS

SLE is a common connective tissue disease and its prevalence is estimated to be between 15 and 200 per 100,000 people [22,26]. Damage to the joints, mucous membranes, kidneys, hematological organs, central nervous system, liver, and lungs is well documented in this disease. The pathophysiology of SLE is multifactorial and involves environmental triggers such as viral infections [64], with HCV considered one of the suspected viruses [42] . HCV infection and SLE may have common clinical and serological features. Extrahepatic manifestations of HCV may mimic SLE with accompanying symptoms such asarthralgia, myalgia, Sicca syndrome, and a positive response to antinuclear antibodies (AHA) [20,48]. One study found that the prevalence of HCV infection in patients with SLE was higher than in the general population [6] . In another study, the prevalence of HCV among patients assessed for SLE was 10% [46]. In a study conducted in Egypt, the incidence of HCV infection among patients at a rheumatology clinic was 18.5%. Only 7% had clinical symptoms of HCV infection [18] . Known serological abnormalities can occur with HCV infection. ANA positivity has been reported to be between 10% and 30% [45.59] and HCV infection is associated with cryoglobulinemia [69]. All but one study has shown that a positive response to HCV antibodies is more common in patients with SLE than in patients with HCV infection [16,27] . Therefore, low titer-rated AHAs, a double-stranded DNA (dsDNA) response, fewer skin signs, liver damage, and cryoglobulinemia should alert physicians to HCV screening in patients with SLE. It was also emphasized that HCV screening should be carried out before a diagnosis of SLE is confirmed [37,41,77]. There is evidence that the use of IFN in the treatment of HCV infection can trigger autoimmune disorders, including SLE [7]. The incidence of autoimmune diseases in patients receiving IFN is between 4.3% and 18.5% [7] . Between 1990 and 2010, twenty-six cases of IFN-induced SLE were reported [75,76]. The period between initiation of TREATMENT with IFN and the onset of SLE symptomsranged from 2 months to 7 years [75,76]. IfN-induced SLE symptoms regressed approximately 1 week after ifn treatment was discontinued [49] . Consequently, patients receiving IFN treatment should be monitored for the development of autoimmune diseases, including SLE [65]. Thus, extrahepatic manifestations of HCV infection may mimic signs resembling SLE. Further testing of anti-Smith antibodies, anti-dsDNA and antinucleosomal antibodies may help clinicians establish a diagnosis of SLE. Although the relationship between HCV and SLE is still uncertain, it has been suggested. the assumption that HCV may play a role in the occurrence of SLE.

CONCLUSION. Diagnosis of viral hepatitis is often difficult and delayed. This is due to a long latent period before the development of the clinic of chronic liver disease, the presence of jaundice and subclinical forms of the lesion, the systemic nature of the lesion in the debut. Caution about hepatitis and knowledge of the features of their extrahepatic manifestations can improve diagnosis. HCV infection can mimic many

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rheumatic diseases through its autoimmune manifestations. Itshould be emphasized once again that HCG is an infection with damage to various organs and body systems, which requires the consolidation of the efforts of specialists in various fields to further study the pathogenesis of infection and develop approaches to diagnosis and therapy of patients with HCG with extrahepatic manifestations, in particular, with rheumatic diseases. .

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