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THE COURSE OF BIGHIM DISEASES IN PATIENTS WITH HIV

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Abstract:

Currently, HIV infection remains one of the leading problems of global public health. Clinical signs of HIV infection are extremely diverse and are associated with many, including rheumatic, diseases. This review examines the problem of damage to the bone and joint system in HIV infection. The detailed clinical characteristics of individual nosological forms (HIV-associated arthritis, reactive arthritis, psoriatic arthritis, etc.) are presented, the issues of their differential diagnosis are considered. Modern approaches to the treatment of inflammatory joint diseases in HIV infection, including genetically engineered biological drugs, are analyzed.

Keywords: HIV infection, rheumatic diseases, reactive arthritis, psoriatic arthritis, rheumatoid arthritis, genetically engineered biological drugs.

The human immunodeficiency virus (HIV) was first described in 1981. A few years later, the HIV pandemic took over the whole world and became one of the leading problems of global public health. In recent years, there has been a tendency to decrease the dynamics of HIV infection in some regions of the world due to the advent of highly active antiretroviral therapy (HAART), compliance with specific precautions, and the dissemination of available information among the population. Nevertheless, according to WHO statistics for 2016, the number of people living with HIV was 36.7 million, while 1.8 million new cases of infection were registered. 1.0 million people died from HIV-related causes [1]. In the Russian Federation, an increase in the number of new cases of HIV infection has been registered since 2005, while the epidemiological situation, unfortunately, continues to deteriorate. As of December 31 , 2017 The cumulative number of registered cases of HIV infection among citizens of the Russian Federation amounted to 1,220,659 people (according to preliminary data), of which 276,660 patients died [2].

The clinical picture of HIV infection is extremely diverse and may include symptoms inherent in other nosological forms. The study of rheumatological aspects within the framework of this infection began in 1987 with the description of 4 cases of reactive arthritis (ReA) in HIV-infected patients [3]. The problem of opportunistic infections that occur mainly at late stages does not lose its relevance stages of the disease, which can also be the cause of damage to the musculoskeletal system. Since the beginning of the era of VAART, new issues have emerged related to rheumatic complications of this method of treatment, as well as conditions arising within the framework of the immune reconstruction syndrome. In addition, doctors face a serious problem of choosing immunosuppressive drugs for the treatment of rheumatic diseases (RH) in conditions of HIV-induced immune disorders.

This review is devoted to the problem of damage to the bone and joint system in HIV infection. Arthralgia is most often observed in HIV seroconversion. Previously, arthralgia was observed in 34% of HIV-infected people [4], currently its frequency is 5%, which may be due to the active use of antiretroviral drugs [5]. It is assumed that arthralgia may be due to the presence of circulating immune complexes that have important pathogenetic significance in HIV infection in the human body. Transient bone ischemia is considered as an alternative cause. Arthralgias are most often intermittent in nature, mainly-they are mainly localized in the knee, elbow and shoulder joints, arthritis rarely develops. As a rule, non-narcotic analgesics are effective. Acute HIV-associated arthralgia (Painful articular syndrome) develops in 3.3–10% of cases mainly in the late stages of HIV infection [6].

It is characterized by intense, "debilitating" joint pain, lasting up to 24 hours and relieving itself. A characteristic feature of this condition is the absence of clinical signs of inflammation with a very pronounced pain syndrome. Knee joints are more often affected, shoulder and elbow joints are less common. Radiological changes are nonspecific, according to some data, osteopenia is sometimes observed. The role of VAART in the development of this syndrome remains unclear due to the small number of studies. Treatment is symptomatic. Thai scientists have shown the effectiveness of indomethacin in these patients [7]. Arthritis associated with HIV infection is non-erosive oligoarthritis, which usually occurs without damage to the mucous membranes and skin, as well as enteritis, tends to self-restriction, lasts up to 6 weeks, is not

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associated with HLA B27 or other known genetic marker. Knee (84%), ankle (59%), wrist (41%), elbow (29%), metacarpal and interphalangeal (25%), metatarsal (23%) joints are affected. Usually, radiological changes are nonspecific and range from minor periarticular osteoporosis to joint destruction [8]. In most patients, synovial biopsy reveals nonspecific chronic synovitis with infiltration of mononuclear cells, plasmocytes, thickening of the vascular endothelium, fibrosis, deposits of immunoglobulins and degenerative changes. In the synovial fluid, the number of leukocytes is no more than 2 thousand, with crops, the growth of flora is not detected. According to some studies, HIV DNA and p24 antigen were detected in the synovial fluid and synovial membrane, which may indicate the viral origin of arthritis [9]. HIV-associated arthritis is an exception diagnosis, and therefore it is necessary to carefully distinguish it from arthritis of a different genesis, especially in the presence of psoriasis–like rash and various serological markers characteristic of a particular rheumatic disease.

According to various studies, RHEA in HIV-infected patients occurs with a frequency of 0.2 to 11% [10, 11]. It should be noted that in South Africa, the incidence of RHEA, undifferentiated spondyloarthritis and psoriatic arthritis (PsA) has sharply increased with the spread of HIV, despite the lack of correlation with HLA B27, rare in the black race. However, in studies conducted in Spain, the incidence of RHEA in HIV infection is almost indistinguishable from the average in the population, while the frequency of septic arthritis and pyomyositis increases [12, 13]. To explain this spread of data, some researchers rely on the social characteristics of the virus circulation in the population and in each individual country. With mainly intravenous entry of the virus into the body of injecting drug addicts, the role of septic complications increases, whereas with sexual transmission, the risk of both HIV and some infections causing RHEA increases.

Considering the above, it is believed that when RHEA occurs against the background of HIV, the main role is played not by the virus, but rather by the patient's lifestyle [14]. On the other hand, this theory does not explain the results of African studies, where there were only isolated cases of seronegative spondyloarthritis before the HIV epidemic. At the same time, in the 1990s, with a similar lifestyle of people, the frequency of RHEA, undifferentiated spondyloarthritis sharply increased, to a somewhat lesser extent - PsA in the absence of correlation with HLAB27 [9, 15]. Thus, at present, an objective assessment of the frequency of ReA against the background of HIV infection seems difficult.

Some authors note that HIV infection is often accompanied by the presence of concomitant infectogens (Shigella spp, Chlamydia trachomatis, Entamoeba histolytica, Giardia, Lamblia, etc.), which themselves can cause RHEA [14]. The immunosuppression that occurs in HIV infection explains the more aggressive, resistant to standard therapy course of ReA. Other authors consider the cause of ReA to be the immunodeficiency virus itself [17]. Information about the association of ReA and VAART is few and often contradictory [18, 19]. RHEA in HIV infection proceeds as peripheral oligoarthritis with a predominant lesion joints of the lower extremities (knee, ankle joints), wrist joints, often with enteritis, plantar fasciitis and achillotendinitis, involvement of the skin and mucous membranes (keratoderma, circinal balanitis), dactylitis. There may be a psoriasiform rash, which makes differential diagnosis with PsA difficult. Urethritis occurs with the same frequency as in the population, and uveitis and axial spinal injury are less common. In 80-90% of cases with HIV-associated RHEA, an association with HLA B27 is detected. The possible influence of HLA B27 on slowing the progression of the disease to the AIDS stage is not excluded.

According to African researchers, the severity of skin lesions in PsA on the background of HIV infection had an inverse correlation with the severity of joint damage, and in the terminal stage of arthritis was practically not observed [26]. PsA is also considered as a predictor of severe infectious complications (in particular, pneumocystis pneumonia) and a marker of low CD4+ cell content. When PsA occurred, the average content of CD4+ cells was 160/mm3 [9].Clinically, PsA on the background of HIV infection is characterized by an erosive deforming process in the joints, symmetrical polyarticular type of lesion, severe course, refractory to therapy [7]. The knee, hip, ankle joints, small joints of the hands are most often affected. Sacroiliitis and spinal column involvement are relatively rare, whereas enthesopathies, dactylitis, tendinitis are common. Of the extra-articular manifestations, skin lesions are predominantly found, which in HIV-

positive patients can be very extensive, especially in the absence of VAART. Moreover, many dermatological diseases may have atypical symptoms against the background of HIV infection, such as skin psoriasis. Rashes can be located on the flexor surfaces of the extremities (flexor psoriasis) in contrast to the extensor in the classical form. Thick dry scales (rupioid psoriasis) may appear instead of the typical silvery-white ones. Often there are teardrop-shaped and erythrodermic subtypes. At the same time, patients with

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HIV may have several forms of psoriasis at the same time [23, 28, 29].

Vulgar psoriasis in combination with HIV infection tends to be more severe, atypical, rapidly progressing, refractory to therapy and chronic recurrent course. It should be noted that cutaneous T-cell lymphoma can be very similar to psoriasis and, therefore, it should be included in the circle of differential diagnostic search in HIV-positive patients.

A number of HIV-infected patients have a clinical picture of undifferentiated spondyloarthropathy, which is characterized by pain in the lower back, ankle and shoulder joints, achillotendinitis, dactylitis and plantar fasciitis. There is blennorrheic keratodermia, circinal balanitis and widespread psoriasis-like rashes. Uveitis and lesions of the axial skeleton are rare. During MRI examination, synovitis of the knee joints and widespread polyenthesitis with concomitant osteitis are frequent findings [1].

Rheumatoid arthritis (RA) and HIV infection have long been considered as diseases that are poorly compatible with each other before the active introduction of VAART into clinical practice. The reason for this was clinical observations that recorded a clear positive dynamics (and even remission) of the articular syndrome in RA patients after their HIV infection. It was believed that viral depletion of CD4+ cells reduces autoimmune activity, which is necessary to maintain an active inflammatory process in the joints. For this reason, the presence of symmetrical and in some cases destructive polyarthritis in HIV patients-infection was often classified as "rheumatoid-like" arthritis [32]. In the era of VAART, the possibility of having "true" RA in patients with HIV infection with a frequency of 0,1–5% [13, 33-36]. In the course of a multicenter cohort study carried out by French authors, 46 patients with RA in combination with HIV infection were identified. At the same time, 23 (64%) patients were diagnosed with RA already against the background of existing HIV infection [37]. It is believed that most cases

RA develops in the early stages of HIV infection with CD4+ > 200 cells/ml and undetectable viral load. In this group, the predominance of men is noted, which is associated with the gender characteristics of the spread of HIV infection. The average age of patients ranges from 27 to 58 years with the duration of VAART from 8 months to 9 years [38, 39, 40]. The development of RA within the framework of the immune reconstruction syndrome is described. In general, the clinical picture of RA in HIV infection and without it does not differ significantly. It is worth noting that the assessment of RA activity on the DAS-28 ESR scale is difficult due to an increase in the level of this parameter in HIV-infected patients due to nonspecific hypergammaglobulinemia associated with this infection [15].

Osteonecrosis, as well as other types of bone tissue damage (osteopenia, steoporosis), is widespread among HIV-infected patients, which is due to both the disease itself and the ongoing antiretroviral therapy. The most frequent localization of aseptic necrosis is the femoral head, the lesion of which (in the absence of complaints) was detected by magnetic resonance imaging in 4% of HIV–infected patients. Aseptic necrosis of the femoral head in 40-60% of cases is bilateral and can be combined with osteonecrotic lesion of a different localization (the head of the humerus, femoral condyles, navicular and semilunar bones, etc.). As the disease progresses, in more than 50% of cases, there is a need for surgical treatment – hip replacement [47-49]. The lesion of the osteoarticular apparatus in HIV-infected patients may also be due to septic complications.

Septic arthritis within the framework of HIV infection develops, as a rule, in drug addicts who inject drugs intravenously, or with concomitant hemophilia. The main pathogens are gram–positive cocci, hemophilic

stick, salmonella. The disease is manifested by acute monoarthritis, mainly of the hip or knee joint. In "intravenous" drug addicts, sacroiliac, sternocostal and sternoclavicular joints may be affected. The leading etiological agent of osteomyelitis and pyomyositis is Staphylococcus aureus. In general, HIV infection does not significantly affect the course of septic lesions of the musculoskeletal system. The latter, as a rule, are successfully cured with adequate antibacterial therapy and timely surgical intervention. Tuberculosis is one of the most frequent, life-threatening HIV-associated opportunistic infections. At the same time, the share of damage to the musculoskeletal system accounts for 2% of cases. The most frequent localization of the tuberculosis process in these patients is the spine, however, signs of osteomyelitis, mono– or polyarthritis may occur. Unlike classical Pott's disease, tuberculous spondylitis within the framework of HIV infection can occur with atypical clinical and radiological symptoms (mild pain, lack of involvement of intervertebral discs in the process, the formation of foci of reactive bone sclerosis), which leads to delays in diagnosis and timely treatment. In this regard, many authors strongly recommend including computer and magnetic resonance imaging in the examination plan of these patients.

The lesion of the osteoarticular system with atypical mycobacteria develops, as a rule, in the late

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stages of HIV infection, when the level of CD-4 lymphocytes does not exceed 100/mm3. Among the pathogens of this group, M. haemophilum and M. kansasii predominate (50% and 25% of cases, respectively). At the same time, there are several foci of infection, and manifestations such as nodules, ulcers and fistulas are observed in 50% of patients. Candida albicans and sporotrichosis of puppies are the main stimuli of the mycotic effects of drugs in the infected. In southern China and the countries of Southeast Asia, a dimorphic fungus of the genera Penicillium marneffei is considered the leading etiological agent. The defeat of this fungus occurs, as a rule, in the late stages of HIV infection and proceeds with fever, anemia, lymphadenopathy, hepatosplenomegaly, acute mono-, oligo- or polyarthritis, multiple subcutaneous abscesses, the formation of skin ulcers and fistulas, multifocus osteomyelitis.

Diagnosis of musculoskeletal system infection in HIV-infected patients may be difficult for the following reasons: 1) absence of leukocytosis in peripheral blood and synovial fluid, especially in the late stages of HIV infection; 2) atypical localization of the lesion; 3) pathogens isolated from the joint and from the blood may be different with polymicrobial etiology of the lesion; 4) problems with identification of the pathogen in the presence of previous antibiotic treatment; 5) the erasure of symptoms in the late stages of HIV infection, when signs of damage to other organs and systems come to the fore in the clinical picture [15]. Currently, there are no detailed clinical recommendations for the treatment of rheumatic syndromes against the background of HIV infection. In 2014, British scientists published a paper in which an attempt was made to systematize the still disparate and often contradictory data on the safety and effectiveness of the use of certain drugs in HIV-infected patients with rheumatic diseases [14]. According to the data presented in the mentioned publication, the treatment of ReA is similar to that in HIV-negative patients.

PsA therapy against HIV infection is based on the patient's immune status and the severity of the underlying disease. Of the nonsteroidal anti-inflammatory drugs, indomethacin was mainly used, which in some studies blocked replication

HIV-1 virus by 50% in vivo [53]. Sulfasalazine can also be included in the treatment regimen, taking into account its positive effect not only on the course of the disease itself, but also on HIV infection [54]. According to some data, hydroxychloroquine helps to reduce the viral load, inhibits virus replication in vivo, and is well tolerated by HIV-infected patients [14].

The world experience of successful use of tumor necrosis factor inhibitors-α (iFNO-α) – infliximab, etanercept, adalimumab in HIV-infected patients with PsA, RA and other diseases is accumulating. In a subsequent study by E.J. Cepeda et al. the effectiveness and safety of measuring INO-α in 8-protein cells and seronegative spondyloarthropathy when combining the following components: a) the number of CD4+ cells is more than 200/ml, b) the vertical load is less than 60,000 copies/m3 [7].

According to S. Wangsiricharoen et al., as a result of the use of the above-mentioned iFNO-α in HIV-infected patients with various inflammatory diseases of the joints, a significant increase in the number of serious infections, compared with those in RA without HIV, was not observed. The risks of developing serious infections also did not significantly differ depending on the initial viral load [58]. According to M. Carroll et al., the use of iFNO-α in RA patients with HIV can be considered as effective and safe as long as the infection is under control with the help of VAART [59].

Was previously used with good effect in HIV-infected patients with the development of Castleman's disease and lymphoma, but with the risk of reactivation of Kaposi's sarcoma [60]. Nevertheless, infections such as pneumocystis pneumonia and cryptococcosis have been described in RA patients who received rituximab and did not have HIV. In one observation, the efficacy and safety of ustekinumab was demonstrated [61]. In most cases, immunosuppressive therapy should be initiated only if HIV infection is controlled, namely, if the number of CD4+ cells exceeds 350 / ml without viral load on the background of HAART. A decrease in the level of CD4+ cells or an increase in viral load for a long time serves as a signal for monitoring therapy. In the course of treatment, monitoring of possible opportunistic infections is necessary [62]. There is evidence of the effectiveness of antiretroviral therapy in the treatment of PsA against HIV infection [63, 64]. Phototherapy can both reduce the number of psoriatic rashes, and enhance the replication of the virus, contribute to the progression of the disease, increase the risk of skin cancer.

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