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SIGNIFICANCE OF IMMUNE-INFLAMMATORY PROCESSES IN ASEPTIC NECROSIS OF THE FEMORAL HEAD IN PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

This article presents data on clinical manifestations and immunological parameters of patients with rheumatoid arthritis accompanied by aseptic necrosis of the femoral head. The results of studies have shown that clinical manifestations of the joint syndrome and immuno-inflammatory processes in RA with ANGBC have their own peculiarities. This is reflected in the aggressiveness of the joint syndrome, rapid progression of radiological changes against the background of persistent activity. RA with ANGBC is accompanied by suppression of T- and B-cell immunity on the background of which there is hyperexpression of proinflammatory cytokines.

Despite the development of modern medicine, aseptic necrosis of the femoral head (ANFH) is one of the most urgent problems in both orthopaedics and rheumatology. ANFH is a severe disease associated with impaired blood supply to the bone, leading to its destruction [1,15]. It usually affects patients in their 30s and 50s, followed by progressive destruction of the femoral head and general degenerative changes of the hip joint. Consequently, it can lead to disability in the absence of timely treatment. It is known that the main causes of ANFH development are trauma in 16.4% of cases, 24.1% long-term corticosteroid use, 30.7% related to alcohol abuse, and in 28.8% of cases the cause remains unknown. However, nowadays, vascular disorders and autoimmune diseases have begun to be emphasised as causes in the development of ANFH [4]. This is due to the fact that theories of pathogenesis more often consider three main problems: vascular disorders; metabolic disorders; congenital anatomy-functional insufficiency of the hip joint.

According to the vascular theory, ANFH is the result of local blood circulation disorders, and two variants of disorders are possible: arterial trunks patency or venous outflow [2,7]. Opinions of the authors [9,13] differ in the emphasis given to arterial, venous or combined disturbance of blood flow. However, it is believed that this process is based on hypertrophy of fat cells, fat embolism, intravascular hypercoagulation, and osteocyte apoptosis, which eventually leads to impaired blood circulation in bone and bone marrow vessels and leads to ischaemic necrosis of bone tissues with subsequent mechanical failure and bone collapse [10]. In turn, autoimmune mechanisms also play an important role in impaired microcirculation, as immunological shifts often contribute to arterial endothelial damage [3,8]. However, it is clear from the literature that the study of the pathogenesis of ANFH over the years has not yielded specific uniform results, making this problem difficult to solve from the point of view of many specialists. This is due to the fact that ANFH is one of the multifactorial, polyetiological diseases.

Inflammatory changes accompanying the rapid destructive process can be interrelated with the cause of the process development, as well as be its consequence. Autoimmune disorders correspond to the manifestation of autoaggression towards the tissues of the own organism of organ-nonspecific nature [5,6]. The immunological shift indicates the systemic nature of the pathology, which requires further study and expansion of the scope of research. Therefore, in this article we have considered immuno-inflammatory aspects of ANFH, as it is one of the urgent problems of modern medicine, it needs more attention from specialists not only in traumatology and orthopaedics and rheumatology, but also from doctors of other specialities, in order to study the etiology and pathogenesis of this problem in more detail.

The aim of the present study was to analyse the peculiarities of clinical and immune-inflammatory manifestations of ANFH using RA as an example.

Materials and methods.

The study included 56 patients with rheumatoid arthritis (RA), (58.2±4.6 years; disease duration 10.3±5.8 years) without ANFH

and 31 patients with RA (59.5±3.5 years; disease duration 11.1±3.3 years) with ANFH.

The comparison group consisted of 10 virtually healthy volunteers, of similar mean age (59.7±6.1 years), without an aggravated rheumatological history.

Disease activity and severity of joint syndrome were determined by the number of painful and swollen joints, DAS 28 and SDAI indices, and pain was assessed by 100-mm visual analogue scale (VAS). All patients underwent standard radiography and magnetic resonance imaging (MRI) of the hip joints. The radiological stage of RA was determined according to the modified Steinbrocker method [11,19].

T- and B-lymphocytes were studied in immunofluorescence test using monoclonal antibodies. The concentration of TNF-α and IL-6 was determined by enzyme immunoassay. Statistical processing of the study results was carried out by methods of parametric statistics with calculation of arithmetic mean (M) and mean square error (m). The reliability of differences was assessed by Student's criterion with Bonferonni correction.

Results and discussion.

The results of the study showed that RA patients with ANGBC had bilateral lesions in 19.4% of cases. The extent of aseptic changes was < 15% of the femoral head in 48.3% of patients; the extent of 15%-30% of changes in 32.3% of patients and the extent of changes > 30% of the femoral head in 19.4% of patients. Analysis of factors that could be probable causes of ANGBC showed that 32.3% of RA patients received glucocorticoids (prednisolone, methylprednisolone), 6.5% used alcohol and 19.4% had bad habits. The patients who were included in the study did not suffer from diabetes mellitus and did not suffer from any trauma.

As the results of the studies showed, the clinical manifestations, in particular the joint syndrome in RA was different in the two groups. As can be seen from Table 1, in RA patients with ANFH it was characterised by aggressiveness. Thus, the average number of swollen and painful joints was significantly higher in RA patients with ANFH compared to RA patients without ANFH (p<0.05). In turn, the duration of morning stiffness in RA patients without ANFH was significantly shorter than in the group of RA patients with ANFH (p0.05). When analysing the indices, a significant difference between the groups was also revealed (p<0.05) in the index reflecting the functional capabilities of the joints (HAQ). Characterising the joint syndrome, it should be noted that sacroileitis was more frequent in RA patients with ANFH (p<0.01).

Table 1.

Comparative analysis of joint syndrome in two groups

Features	RA without ANGH (n=56)	RA with ANFH (n=31)	p
Arthritis of more than 3 joints %	100	100	p>0,05
Morning stiffness, min	92,8±15,6	189,8±20,4	p<0,05
Pain, VAS, mm	62,1±0,74	91,3±1,12	p<0,05
Number of painful joints	9,52±2,13	14,28±2,24	p<0,05
Number of swollen joints	4,64±1,16	8,38 ±2,58	p<0,05
Presence of sacroileitis %	3,6	25,8	p<0,01
Ritchie Index	8,77±4,35	9,53±4,32	p>0,05
HAQ in points	9,18±1,01	15,81±2,14	p<0,05

Note. p - indicator of significance of differences in indicators between groups. VASH is a visual analog scale.

It should be noted that one of the characteristic features of the clinical course of RA is the progression of destructive changes in the joints. Radiological studies are the main method for detecting this process [14,21]. The importance of the data on radiological changes in the joints of the upper and lower extremities lies in the fact that they are one of the criteria for accurate diagnosis of RA. Thus, the analysis of the dynamics of radiological changes in the joints of the hands from the beginning of the process (Table 2) showed that in RA patients with ANFH, the erosion process progressed in a short period of time. It should be noted that against this background, early joint destruction, i.e., ankylosis, developed over a short period of time, unlike in RA patients without ANFH (p<0.01).

Table 2.

Dynamics of X-ray changes

Radiological stages	RA without ANFH (n=56)	RA with ANFH (n=31)	p
	Period from onset of disease to onset of symptoms (in years)		
I stage	0,64±0,48	0,31±0,17	p<0,05
II stage	2,61±0,56	1,14±0,42	p<0,05
III stage	4,55±0,49	2,29±0,67	p<0,02
IV stage	8,23±1,42	3,12±0,09	p<0,01

Note. p - indicator of significance of differences in indicators between groups.

Comparative analysis, reflecting the activity of the disease and radiological changes, established significant differences between the groups. As can be seen from the 3rd table, in RA patients with ANFH, radiological changes in the joints were accompanied by rapidly progressive recurrent activity (p<0.02). In turn, in RA patients without ANFH, activity prone to slow radiological progression was revealed (p<0.01). This indicates that against a background of high disease activity, radiological progression occurs and there is a risk of ANFH development.

Table 3.

Activity of RA and dynamics of radiological features

Disease activity	Groups	Progression of radiological signs	
		Slow	Fast
Low or moderate downward trend (%)	RA without ANFH	55,4	16,1
	RA with ANFH	12,9	25,8
	p	p<0,01	p<0,05
High or recurrent (%)	RA without ANFH	16,1	12,5

	RA with ANFH	35,5	41,9
	p	p<0,05	p<0,02

Note. p - indicator of significance of differences in indicators between groups.

The results of immunological studies show that they have certain characteristics in RA patients with ANFH. As can be seen from Table 4, a significant decrease in both the total pool of T-lymphocytes ($p<0.05$) and their subpopulation of T-suppressors ($p<0.02$) is observed in them. However, the obtained results indicated that in RA patients with ANFH, no changes in T-helpers were observed ($p>0.05$). However, at the same time, a tendency towards an increase in B-lymphocytes was observed in RA patients without ANFH. On the contrary, compared to the indicators of healthy individuals, a significant decrease in the total pool of B-lymphocytes is observed in RA patients with ANFH. It is known, natural killer cells (NK) are capable of enhancing the proliferation of T-cell colonies, inhibiting the differentiation of B-lymphocytes, and inhibiting the synthesis of antibodies. The study of the content of natural killers in the peripheral blood of RA patients showed a significant decrease ($p<0.01$) in RA patients without ANFH.

It is known that pro-inflammatory cytokines participate in the activation and regulation of the inflammatory response in the body [17,22]. They play a key role in the immune system, helping the body fight infections, injuries, and other pathogenic effects [12,20]. However, they also participate in the development of autoimmune and inflammatory diseases.

Table 4.

Immune system indicators

Indicators	Healthy n=10	RA without ANFH n=56	RA with ANFH n=31
T-lymphocytes, %	68,3±5,4	57,2±2,1	36,1±3,2*#
B-lymphocytes, %	17,7±1,7	19,8±1,9	11,3±1,4*#
T-helpers, %	36,6±2,8	35,4±5,5	20,9±1,5*
T-suppressors, %	17,4±2,1	19,2±2,6	9,7±1,7*#
NK, %	7,9±1,3	5,9±1,2	3,1±0,8*#
TNF-α	1,1±1,3	6,4±1,3*	15,2±1,3*#
IL-6	1,7±0,3	5,2±1,2*	17,1±3,1*#

Note. Significance indicator of differences between groups $p<0.05$: * - relative to the healthy group; # - between groups of RA patients.

The study of some key cytokines has established that their hyperexpression is observed in RA patients of both groups. As can be seen from Tab. 4, the blood concentration of TNF-α is significantly increased in both groups in relation to the healthy controls. However, there is also a significant difference between the groups of RA patients, as the concentration of TNF-α in RA patients with ANGBC is almost 2.5 times higher than in RA patients without ANGBC. This may be due to the ability of TNF-α to destroy cartilage and bone or its overexpression is manifested as a response to tissue necrosis [16,25]. In turn, IL-6 concentration was also increased in both groups relative to that of healthy controls. But, in RA patients with ANGBC the index differed by 3 times. It is known that IL-6 stimulates B-cell differentiation and antibody production and supports inflammation by activating T-cells and macrophages [23,24].

Thus, clinical manifestations of the joint syndrome and immuno-inflammatory processes in RA with ANGBC have their own peculiarities. This is reflected in the aggressiveness of the joint syndrome, rapid progression of radiological changes against the background of persistent activity. RA with ANGBC is accompanied by suppression of T- and B-cell immunity on the background of which there is hyperexpression of proinflammatory cytokines.

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