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Systemic Damage in Rheumatoid Arthritis

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Abstract As a systemic autoimmune disease, rheumatoid arthritis (RA) usually causes damage not only to joints, but also to other tissues and organs, including the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system. Excessive complications are closely related to the prognosis of patients with RA and even lead to increased mortality. This article briefly describes the serious complications of RA, focusing on its frequency, pathogenesis, clinical features, and treatment methods so that clinicians can better manage the complications of RA.

Keywords Rheumatoid arthritis, Complications, Frequency of occurrence, Treatment, Prospects

1. Introduction

Rheumatoid arthritis (RA) is defined as a systemic autoimmune disease associated with a chronic inflammatory process that gradually leads to joint destruction, deformity, disability, and even death [11]. It is a widespread disease worldwide, with a prevalence of approximately 0.5-2%, and it is more common in women, smokers, and people with a family history [2-10]. Currently, the etiology of RA is not fully understood, but what attracts attention is the immune processes occurring in the synovial membrane of the joint and synovial fluid [23,34], during which synovial macrophages secrete cytokines such as tumor necrosis factor (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), which together stimulate the activity of osteoclasts in inflammation and fibroblast-like synoviocytes (FLS), which leads to the progression of bone erosion [5]. In addition, activated FLS can produce matrix metalloproteinase (MMP), which leads to cartilage degeneration [6]. Nuclear factor kappa, an amplifier of the light chain of activated B cells (NF-kB), is involved in the pathogenesis of chronic inflammatory diseases, and FLS stimulates the NF-kB signaling pathway, allowing T cells to bind to proteins on the surface of osteoclasts, which also leads to the further development of bone tissue. erosion, as it increases the activity of osteoclasts [7]. FLS can migrate from one joint to another, leading to symmetrical joint destruction typical of RA [8]. In addition, the presence of autoantibodies in the blood serum of patients with RA is a sign of the disease, the most prominent of which are rheumatoid factor (RF) and antibodies to citrullinated protein (ACPP). These autoantibodies are found in 50-80% of patients with RA (9), and they have also been found to have recently identified antibodies such as carbamylated protein antibodies and anti-acetylated protein antibodies [1].

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The production of antibodies leads to inflammation; Citrullination leads to an immune response that indicates the formation of ACPP; ACPP may play an important role in the long-term inflammatory process, and its presence directly links bone erosion and pain in patients with RA.

As a systemic disease, RA usually causes damage to other tissues and organs besides joints, including the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system. The results of the study show that about 40% of patients with RA suffer from complications, and the incidence of serious complications is 8.3%, among which cardiovascular diseases, interstitial lung diseases, osteoporosis and metabolic syndrome are more common. The presence of complications seriously reduces the quality of life of patients with RA and even leads to an increase in mortality from RA. Complications of RA are usually closely related to the prognosis and require early diagnosis and active intervention, and the main goals of treatment include reducing disease activity and controlling extra-articular lesions in RA. Currently, treatment methods for complications of RA are relatively limited. In this article, we mainly summarize the manifestations of severe extraarticular injury in RA and discuss its pathogenesis, frequency of occurrence, clinical features and treatment methods, hoping to provide some recommendations for clinical practice [11-22].

Cardiovascular diseases in RA

Pathogenesis of RA-cardiovascular diseases

It is well known that patients with RA can become disabled, but the main cause of their death is cardiovascular diseases (CVD). Many studies have shown that the incidence of cardiovascular diseases in patients with RA is 30-60%, mainly pericarditis, myocarditis and heart failure, as well as coronary heart disease. Epidemiological studies show that synovial tissue and circulating immune cells in RA secrete pro-inflammatory cytokines such as TNF-α and IL-6, which directly lead to systemic inflammation and the occurrence of cardiovascular diseases. Hyperactive immune cells, such as lymphocytes and B lymphocytes, can affect the

cardiovascular system through a variety of mechanisms [23-27]. Autoantibodies in RA affect the cascade of all structures of the cardiovascular system, from the myocardium to the heart valves, the conduction system and the vascular network. Patients infected with ACPA have more severe disease activity, which further leads to the development of atherosclerosis and increases mortality from CVD. In addition, ACPA is also observed in patients with cardiovascular diseases who do not suffer from RA, and has unfavorable outcomes. Imaging methods are necessary to identify and assess the risk of cardiovascular diseases in RA, and ultrasound examination of the carotid arteries, the rate of pulse wave propagation in the aorta or the blood pressure index and the ankle-brachial index, echocardiography and magnetic resonance imaging of the heart can be used to assess the risk of cardiovascular diseases in patients with RA in a clinical setting. practice. Early detection and diagnosis of cardiovascular diseases in patients with RA is crucial for prognosis and management [27-31].

Pericarditis

Pericarditis is one of the most common cardiac manifestations of RA. In many patients with early RA, pericarditis may become more complicated or develop before the development of RA. Pericarditis is an inflammation and accumulation of fluid in the pericardium, and approximately 15% of patients with RA have symptoms. However, electrocardiography shows that approximately 20-50% of patients have pericardial damage, clinically manifested by chest pain or shortness of breath. Therefore, a thorough physical examination and antibody screening are necessary to determine as soon as possible whether RA is complicated by pericarditis. Early diagnosis and effective treatment of pericarditis significantly improves the prognosis in patients with RA [31-33].

Myocarditis

Myocarditis is the result of persistent inflammation in the myocardium and is histologically characterized by cellular infiltration consisting of lymphocytes, histiocytes and macrophages, which can form nodular granulomatous lesions. The degree of myocardial dysfunction is related to the activity of the disease in RA, since key inflammatory cytokines in RA, such as TNFa, IL-1, and IL-6, can induce myocardial and vascular dysfunction and promote left ventricular remodeling and fibrosis [34].

Arrhythmia

Arrhythmia is another common cardiac complication in patients with RA, which may be secondary to conduction disturbances. Its causes are ischemia, rheumatoid nodules and amyloidosis. Recent studies show that symptoms and increased activity of the sympathetic nerves can lead to cardiac arrhythmias, and Holter monitoring can detect latent arrhythmias with greater accuracy [33].

Coronary heart disease

The main etiology of coronary heart disease in RA may be associated with atherosclerosis, accelerated systemic inflammatory response, impaired lipid metabolism and endothelial dysfunction. Chronic inflammation and reaction to reactive oxygen species (ROS) in RA are the basis of the pathogenesis of atherosclerosis. ROS are a group of small active substances that play a key role in the regulation of biological cellular processes. The balance between ROS and antioxidants is crucial for maintaining cellular homeostasis, so an imbalance between oxidants and antioxidant mechanisms can lead to a state of oxidative stress. Excess ROS can lead to vascular damage as a result of a complex cascade of processes, including oxidative modification of lipoproteins, activation of the endothelium and accelerated atherosclerosis due to migration and differentiation of leukocytes. Pro-inflammatory cytokines and chemokines, as well as IL-1 and intercellular and vascular adhesion molecules, are highly expressed in atherosclerotic lesions, promote leukocyte recruitment, disrupt vasodilation, cause oxidative stress, and promote blood clotting [16].

Heart failure

Heart failure is the leading cause of death in patients with RA, and the prevalence of heart failure in patients with RA is also twice as high as in the general population, and it is generally more common in women than in men. Studies have shown that patients with RA are more likely to develop heart failure due to diastolic dysfunction, which may be associated with systemic inflammation. Elevated levels of c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), RF, ACPA, and inflammatory cytokines may contribute to the progression of heart failure in RA [19].

Treatment of RA-cardiovascular diseases

An increasing amount of evidence confirms that long-term use of NSAIDs can potentially lead to cardiovascular risks, despite a decrease in disease activity and some adverse outcomes in the treatment of traditional drugs for RA. NSAID anti-inflammatory drugs have a therapeutic effect by inhibiting cyclooxygenase isoforms. These drugs inhibit prostacyclin production, which leads to vasoconstriction, increased blood pressure, rupture of atherosclerotic plaques and thrombosis, therefore they are considered to be the main cause of cardiovascular diseases in RA. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as rofecoxib were the main treatment for patients with osteoarthritis and other types of pain, but because controlled trials and other meta-analyses showed an increased risk of cardiovascular disease in patients with RA, rofecoxib was withdrawn from the market. Glucocorticoids are commonly used to treat RA, mainly for short-term control of disease activity. However, glucocorticoids can worsen arterial hypertension or cause a violation of blood lipids and glucose tolerance, insulin resistance and obesity, as well as contribute to the occurrence and development of cardiovascular diseases. Studies have shown that the use of statins in patients with RA can reduce the degree of atherosclerosis and plaque formation in the carotid arteries. In patients with RA who received at least one disease-modifying antirheumatic drug (PRPMZ) and statins simultaneously, there was a 21% decrease in mortality

from RA and cardiovascular diseases, and disease activity decreased significantly in those patients with RA who had statins added to methotrexate (MTX) and corticosteroids. and this may indicate a clear positive effect of statins in the fight against RA [37].

MTX is the "gold standard" of RA treatment because it has important immunosuppressive and anti-inflammatory effects and inhibits dihydrofolate reductase. Many studies have demonstrated the benefits of MTX. Approximately 25-40% of patients treated with MTX alone showed significant improvement, since MTX can play a role in improving microvascular endothelial function by reducing the degree of RA disease activity, reducing the risk of cardiovascular diseases in patients with RA, and reducing their mortality. In addition, methotrexate appears to have cardioprotective properties against lipids and endothelium, unlike in patients receiving adalimumab. Similarly, hydroxychloroquine (HCQ) has been found to have a protective effect on vascular endothelium in patients with RA and reduce cardiovascular risk in patients with RA. HCQ treatment can reduce the level of low-density lipoproteins and triglycerides in the blood serum and plays the role of a means of preventing platelet aggregation, therefore it is considered cardioprotective. TNF-α inhibitor therapy in RA reduces the risk of cardiovascular diseases by suppressing endothelial dysfunction and slows down the progression of atherosclerosis by reducing the expression of pro-inflammatory cytokines and endothelial adhesion molecules. In a controlled study, TNF-α inhibitors improved myocardial inflammation and perfusion in patients with RA-CVD compared with standard disease-modifying antirheumatic drugs [41-43].

Recently, metabolic modulation therapy has become a popular area of research. Sirtuin 1 (SIRT1) is a sirtuin involved in a wide range of regulation of transcription and metabolism, which can affect cell proliferation and inflammatory responses and inhibit the activation of NF-kB-dependent inflammation. Some SIRT1 activators, such as resveratrol, a polyphenol found in wine, have been extensively studied as SIRT activators, and they have powerful antioxidant, anti-inflammatory, and antitumor properties. Resveratrol can inhibit the NF-kb-dependent inflammatory response, and its effect on patients with RA is under evaluation. It is noteworthy that blood serum biochemical parameters such as CRP, ESR, MMP-3 and IL-6 were also significantly reduced in patients receiving resveratrol. In addition, metformin and its phenformin analog are hypoglycemic drugs used in patients with diabetes mellitus.; Although the exact mechanism of action remains unclear, their effect on AMPK (adenosine-5'-monophosphate-activated protein kinase) may contribute to the beneficial secondary effects of these drugs, such as reducing inflammatory markers, improving lipid metabolism, and reducing experimental autoimmune arthritis, based on the importance of AMPK for T cells in RA. In particular, metformin, as an AMPK activator, can inhibit FLS migration, suppress the expression of pro-inflammatory cytokines, and reduce inflammation in RA and related diseases.

Some pathways involve extracellular targets. Mavrilimumab is a monoclonal antibody against granulocyte–macrophage colony-stimulating factor (GM-CSF), and GM-CSF is expressed at high levels in synovial fluid and plasma, as well as in synovial tissue cells of patients with RA. Phase I and II studies of mavrilimumab in the treatment of RA have shown satisfactory safety and efficacy (66). GM-CSF highlights the influence of "inflammatory" pathways on arteriosclerosis and endothelial dysfunction. Based on this, it is expected that more potential therapeutic targets will be developed to improve the treatment of cardiovascular diseases in patients with RA.

Lung diseases in RA

Pathogenesis of lung diseases in RA

Interstitial lung diseases (ISL)

IBD is a serious pulmonary complication of RA, leading to a 10-20% mortality rate in RA. Lung damage is common in patients with RA, among whom the incidence of pulmonary complications is approximately 60-80%. Clinical manifestations include interstitial lung diseases, small respiratory tract diseases, rheumatoid nodules, pleural effusion, pulmonary vasculitis, pulmonary fibrosis, etc. Although RA can affect many parts of the respiratory system, such as the respiratory tract or pleura, damage to the lung parenchyma is associated with the highest morbidity and mortality. One diagnostic study showed that approximately 50% of RA patients had interstitial lung disease, of which only 10% had clinically significant symptoms such as cough and progressive shortness of breath during exercise, and this is due to the fact that the inflammatory process in RA, mediated by cytokines, chemotactic factor and growth factor, It can promote the proliferation of FLS, increase the risk of extracellular matrix synthesis and deposition, and lead to pulmonary fibrosis. The most common forms of RA-ILD are common interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). There are no universal recommendations for the treatment of RA-ILD, therefore, accurate screening and diagnosis of the development of ILD in patients with RA is crucial for future research and treatment of patients with RA. Histological biopsy, lung function examination, and high-resolution computed tomography (CT) are valuable tools for the diagnosis and evaluation of RA-ILD, and CT allows accurate detection of cellular and traction bronchiectasis, as well as reticular abnormalities and "frosted glass opacity" in NSIP.

Pleurisy and pleural effusion

Pleurisy and pleural effusion are the most common pleural manifestations seen in patients with RA, with only 3-5% of patients experiencing clinical symptoms such as cough, shortness of breath, chest pain, and fever, which means that in most patients with RA, pleural disease has no clinical manifestations. As for the pathogenesis, studies have shown that IgG, IgE and other antibodies contribute to the formation of immune complexes that destroy the capillary endothelium and increase the permeability of the capillaries of the pleural cavity. Ultrasound-guided thoracentesis may be an important study in patients with RA with pleural effusion.

Damage to the respiratory tract (bronchiolitis, bronchiectasis and ring-shaped arthritis) The prevalence of respiratory tract diseases in RA is high, as they affect from 39% to 60% of patients with RA and can affect any part of the respiratory tract, including the large and distal small airways. The most common manifestations are bronchitis, bronchiectasis, and maxillary arthritis. Lung function tests and CT scans can help diagnose diseases related to the respiratory tract. Chronic inflammatory infection is the main cause of bronchiectasis in patients with RA, and bronchiolitis is characterized by damage to the epithelium of the respiratory tract, which leads to air flow obstruction. Due to the fact that the midline of the vocal cords is displaced, maxillary arthritis is manifested by hoarseness of voice, sore throat, shortness of breath and stridor, which are primarily caused by thickening of the synovial membrane of the maxillary joint and persistent erosion of cartilage.

Treatment of lung diseases in RA

Treatment options for RA-interstitial lung diseases (ILD) are complicated by the possible pulmonary toxicity of many UAVs, but their ability to improve lung function and stabilize pulmonary symptoms has been demonstrated. Thus, joint and lung damage should be independently assessed for therapeutic purposes. The Spanish Society of Rheumatology recommends the use of abatacept and rituximab in patients with RA- ILD. A retrospective study showed that the use of abatacept, a costimulating T-lymphocyte antagonist, improved ILD in approximately 88% of cases and reduced the risk of infection. In addition, abatacept significantly reduced lung density and fibrotic histology, as well as improved lung function. Finally, data from a retrospective multicenter study conducted in Italy in 2020 showed that 86.1% and 91.7% of patients with RA-ILD who received abatacept for at least 6 months had stable or increased accelerated lung capacity and the ability to disperse carbon monoxide, respectively, while 81.4% of the patients had stable or improved CTB of the chest. Rituximab is considered safe for the treatment of RA-ILD, which is confirmed by observational studies. In addition, a large observational study of patients with RA-ISL showed that lung function in most patients with ILD remained stable or improved after treatment with rituximab over a long follow-up period. The British College of Rheumatology recommends that doctors prescribe TNFi with caution to patients with RA-ILD and recommends rituximab for the treatment of refractory ILD.

Interstitial lung disease is characterized by inflammation of the alveoli and interstitial fibrosis, which is why antifibrotic drugs such as nintedanib and pirfenidone have become the focus of attention, and it has been proven that nintedanib and pirfenidone slow down the progression of the disease in patients with idiopathic pulmonary fibrosis. In addition, tocilizumab as monotherapy can stabilize or even improve heart failure, and as an IL-6 receptor antagonist, tocilizumab can have an antifibrotic effect by blocking IL-6R, which means that this treatment is potentially useful in RAILS-related pulmonary fibrosis. Despite the fact that there are still many problems in practical clinical use, the efficacy and safety of antifibrotic drugs in patients with RA are still under constant research to improve work control.

In addition, elderly or debilitated patients, as well as patients with multiple concomitant diseases, can use non-drug conservative treatment methods such as pulmonary rehabilitation and additional oxygen access. The role of physical rehabilitation of the lungs in RA is unclear, but it has a beneficial effect on improving shortness of breath, functional performance, and quality of life in idiopathic RA. However, shortness of breath and poor joint mobility in patients with ILT limit their pulmonary rehabilitation, therefore, patients with ILD should undergo pulmonary rehabilitation in the early stages of the disease. Additionally, supplemental oxygen can be used as primary palliative care to improve the quality of life of patients with severe lung diseases and reduce respiratory symptoms during daily activities. At the same time, smoking is a major risk factor for the progression of RA-ILD, and quitting smoking is important for patients with RA-ILD.

Lung transplantation may be a treatment option for end-stage RA-ILD, while only a few studies have evaluated post-transplant outcomes in patients with RA-ILD. A recent study showed that patients with various connective tissue diseases (including RA) had similar rates of acute or chronic rejection after lung transplantation compared with patients with idiopathic pulmonary fibrosis, and there was no significant difference in survival. Lung transplantation may be an option for young patients with advanced refractory disease, but is not suitable for elderly patients at risk of developing multiple comorbidities, inactivity, and other serious extra-articular injuries.

Metabolic syndrome in RA

Pathogenesis of cancer metastases

The main features of metastases in patients with RA are related to the activity of the disease caused by inflammation, and mainly include insulin resistance (IR), central obesity, dyslipidemia, and hypertension; these manifestations. The prevalence of metastases in patients with RA varies widely worldwide and ranges from 14.32% to 37.83% according to various criteria. In addition, metastases are closely associated with the accelerated development of atherosclerosis and an increased risk of cardiovascular diseases and are considered a characteristic pathogenesis of cardiovascular diseases. Studies have shown that IR is a fundamental characteristic of metastases in RA and is directly related to the levels of IL-6, TNF-α, CRP and ESR. IR caused by RA leads to increased systemic inflammatory reactions and directly affects endothelial dysfunction. In addition, the constant increase in the number of macrophages in adipose tissue in obesity is considered a key link in metabolic inflammation. Recent studies have revealed the heterogeneity of macrophages of adipose tissue and their interaction with adipocytes, endothelial cells and other immune cells in the microenvironment of adipose tissue. Adipose tissue is a multifunctional organ that, in addition to its central role in storing lipids, secretes many hormones.

These various products, collectively called “adipocytokines" or “adipokinases,” are responsible for the immune response and inflammatory mediators. RA is associated with IR, dyslipidemia, and changes in the adipokine profile. In RA, adipocytes and their surrounding macrophages stimulate the production of pro-inflammatory cytokines by cells of innate and adaptive immunity, which cause cartilage destruction and dysregulation of osteoblasts, leading to arthritis and metastasis.

2. Conclusions

Complications in RA are a serious scientific problem that deserves attention. However, current international research on the pathological mechanism of complications in RA remains unclear, and safe and effective clinical drugs and methods are limited. Given that most of the extraarticular injuries in RA are related to the activity and severity of the disease, the optimal treatment for RA should be to control the activity of the disease, and earlier and aggressive treatment of RA can reduce the impact of complications on the prognosis. Although there are some recommendations for the treatment of complications related to RA, the range of recommendations, including acute and cardiovascular diseases, is still limited. In this review, we discuss the pathogenesis, incidence, and updated recommendations for the treatment of serious complications such as cardiovascular problems and lung damage in patients with RA. We hope that the recommendations discussed in this article will help clinicians better navigate treatment options for RA complications.

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