



Review Article

Rheumatoid Arthritis and Pannus

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Abstract

Rheumatoid arthritis is a chronic inflammatory systemic autoimmune disorder that affects the joints, but often also other organs. It is the most common inflammatory rheumatic disease. Patients with rheumatoid arthritis suffer from chronic joint pain, disability, and increased mortality. The joints affected are usually those of the limbs, hands, and feet. If rheumatoid arthritis is not controlled with appropriate medication, it gradually leads over the years to destruction and permanent deformation of the joints, due to erosion of the cartilage and bone. The result of the condition is the disruption of joint mobility, the irreversible functional disability, the impairment of the patient's productivity and quality of life. The disease requires long-term medical monitoring and appropriate medication to suppress the inflammatory process, prevent deformities and maintain patients' functionality. One of the effects of the disease is the appearance of pannus, which is an aggressive structure in the inflamed rheumatoid joint that invades the cartilage and bone, thus causing irreversible joint damage. This article focuses bibliographically on rheumatoid arthritis and pannus to reveal the relationship between them.

Keywords: Joints, Pannus, Rheumatoid arthritis

Introduction

Rheumatoid arthritis is an autoimmune inflammatory disease, accompanied by multi-organ disorders, characterized by pain, swelling and stiffness of multiple joints. Joint destruction progresses rapidly after disease onset, resulting in irreversible physical dysfunction and deformity of affected joints in patients. The progression of rheumatoid arthritis is fluctuating, with episodic exacerbations and no optimal treatment. The symptoms of the disease gradually worsen, until the joints suffer irreversible damage, with the person being affected both in terms of physical and psychological function. In addition, the complications of the disease and comorbidities reduce the life expectancy of patients by a few years. The effective therapeutic approach requires early diagnosis and optimal pharmacological treatment, related to periodic evaluation of its therapeutic effectiveness.

Rheumatoid arthritis can affect many tissues and organs, but usually affects the joints peripherally and leads to cartilage and bone destruction. To date, there is no complete cure for rheumatoid arthritis, due to the

heterogeneity and multiple forms of this disease. One of the many important clinical features of this disease is that patients with rheumatoid arthritis usually have an abnormal hyperplastic synovium, known as a “pannus” within the joint. Pannus usually develops in a tumor-like manner and can erode the cartilage and bone in the joints. The purpose of this article is to demonstrate the relationship between rheumatoid arthritis and pannus.

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Identifying rheumatoid arthritis

Rheumatoid arthritis has been defined as a systemic autoimmune disease, associated with a chronic inflammatory process, which can damage both joints and extra-articular organs, including the heart, kidneys, lungs, digestive system, eyes, of the skin and the nervous system^{1,2}.

Rheumatoid arthritis was first described in the thesis of Augustin Jacob Landre-Beauvais, who in 1800 was working at one of the most famous hospitals in France, the Salpetriere in Paris. He was the first doctor to notice the symptoms presented by the disease, as they are known today. Examining many patients who presented with joint pain, he concluded that these patients were suffering from a previously unstudied disease, which he named "Primary Asthénique Goutte"³. The next scientist to report on rheumatoid arthritis was Alfred Garrod, an English physician in the mid-19th century. Garrod was the first to distinguish gout from other joint conditions, as he found a high percentage of uric acid in the blood of patients suffering from gout, which was not present in patients suffering from other forms of the disease. Then Archibald Garrod, in 1890, wrote a treatise on rheumatism and rheumatoid arthritis. In this text, the term "Rheumatoid Arthritis" is mentioned for the first time, which he invented himself and which was finally established, as it described in the best possible way the effect the disease had on the patients³.

Rheumatoid arthritis is the most diagnosed form of inflammatory arthritis, with a prevalence of up to 1% of the world's population, mainly in industrialized countries⁴. Its appearance is more common in women than men in a ratio of 3 to 1, in people who smoke and in those who have a family history of the disease⁵. It can appear at any age, however the usual age group of onsets is between 30 and 50 years⁶.

The disease can cause severe disability or significant limitation of the person's functionality, even during the early stages of its manifestation, in a percentage of up to 10% of sick people⁷. Patients suffering from rheumatoid arthritis often experience very serious pathological conditions, such as secondary osteoporosis, with subsequent vertebral or non-vertebral fractures. Viral or bacterial infections, mainly skin, pulmonary and joint infections, are common, which are a consequence of the immunosuppression caused by the disease itself or the medication⁸.

The most common symptoms of the disease are pain and swelling observed in the joint area⁹, as well as morning stiffness^{5,10}. The patient may experience redness in the joint area, swelling, pain and an increase in temperature. Consequence of the above situation, is the deformation and stiffness. In many cases, sufferers also experience loss of energy, fatigue, and anorexia. The stiffness that the person presents in the muscles and joints is more intense in the morning hours and during periods of inactivity, such as for example if the person is in a sitting position for a long time¹¹.

Due to the autoimmune nature of the disease, the patient has periods of remission and periods of exacerbation. When

the tissues are inflamed, then the disease is in an active state, while when the inflammation subsides, then the disease is inactive. The onset of symptoms can be spontaneous, and their duration can be weeks, months or even years. When the disease is in remission, then the patient feels well, but when the patient relapses, then the symptoms of the disease reappear. The course of the disease varies from patient to patient¹².

The diagnosis of rheumatoid arthritis is based on medical clinical examination, with the physician looking at the history of symptoms, the joints that are inflamed, the patient's degree of tenderness, swelling, and the level of deformity. Carrying out blood tests as well as X-rays is a common procedure followed during the diagnosis of the disease¹³. Rheumatoid arthritis is a multifactorial disease caused by genetic and environmental factors. The genetic risk for rheumatoid arthritis estimated by scientific studies is approximately 50%¹³. Smoking is also associated with the development or exacerbation of the disease, according to existing research data¹⁴. Dietary factors and consumption habits have also been evaluated for disease occurrence^{15,16}.

Rheumatoid arthritis significantly affects the quality of life of patients, since it causes pain and destruction of the joints, which in fact takes place with progressive deformation. The mobility of the joints is limited, resulting in the functional incapacity of the individual. In the long term, the disease can lead to complete destruction of the joints, thus requiring the patient to undergo surgery^{17,18}. The disease has been associated with an increased risk of mortality, due to the complications it presents, which come from the disease itself, but also from the treatment¹⁹. The disease essentially brings about significant consequences on a personal, social, and economic level, both for the patient himself and for the community⁶.

Identifying "pannus"

The synovial membrane is found between the joints of the body, connecting to cartilage, the soft, spongy material that is present at the ends of bones and helps protect them. In a healthy joint, the synovial membrane acts as a lubricant, providing nutrients and even helping to make lubricating materials such as collagen. Its main function is to nourish joint cartilage, producing synovial fluid, which is rich in hyaluronic acid^{20,21}.

When the person suffers from rheumatoid arthritis, there is a possibility that the synovial membrane starts to grow disproportionately²². The extra synovial tissue that is present will thicken and grow in areas where it shouldn't, consisting mostly of immune system cells. Continued inflammation in the synovium leads to the distension of the membrane, which forms the pannus, which contains fibroblasts, macrophage cells, vessels, and granulation tissue, reaching the hyaline articular cartilage and subchondral bone. This leads to the formation of typical erosions^{23,24}. This extension in

rheumatoid arthritis is also referred to as “malignant mesenchymal transformation”²⁵.

Although pannus functions as a tumor in terms of its growth, it is not a type of cancer as it does not spread to other parts of the body. Pannus develops significantly in the joints if the patient suffering from rheumatoid arthritis does not receive treatment, or if the following treatment is not effective. In rheumatology, pannus refers to an aggressive structure in the inflamed rheumatoid joint, invading cartilage and bone, thus causing irreversible joint damage²⁶. It is well documented that pannus can lead to spinal cord instability and injury due to compression of the cervical-medullary junction²⁷⁻²⁹.

Since the initial clinical description of rheumatoid arthritis, pannus has played a pivotal role in the development of the disease as its role has been understood alongside the improvement in the development of histological molecular biology and imaging techniques. The original clinical and histological description of pannus was described in 1859 by Garrod. The symptoms of pannus are very similar to those of rheumatoid arthritis, as the person experiences pain, swelling, stiffness and tenderness in the joints, often on both sides of the body, for example both knees, and both wrists. After the formation of pannus, pain in formation may worsen, swelling may increase, and the joint may become deformed.

Joint involvement tends to be symmetrical and involves the small joints. Stiffness, typically, is worse in the morning, after getting up, usually lasts more than 30 minutes, and can be prolonged throughout the day. During the clinical examination, the swelling of the joint is visible or palpable, while the tissue is recognized as spongy and soft, edematous, warm, especially, in the early stages of arthritis. The hypertrophic synovial membrane acquires the ability to locally invade the adjacent bone or cartilage. The pannus is an aggressive structure, which has the characteristics of a tumor, as mentioned, causing erosion of the joint. Because of the above fact, the loss of bone mass occurs in bones located near joints, i.e., peri-articular osteoporosis. As time passes and there is no therapeutic inhibition of disease progression, more serious damage takes place, such as wear of the articular cartilage and erosions in various parts of the bones, which are included in the joint. Frequent monitoring of rheumatoid arthritis prevents the formation of pannus, while recent advances in the field of rheumatoid arthritis, especially at the level of diagnosis and treatment, prevent its occurrence.

Three types of pannus with cartilage junction have been observed in rheumatoid arthritis: 1) cellular pannus, without vascular proliferation, which is rich in phagocytic and fibroblastic cells, which invade hard tissues, 2) cellular pannus with proliferating small blood vessels, that penetrate the hard tissues and 3) the inactive fibrous pannus that covers the hard tissues³⁰. Two different histological features of the cartilage-pannus junction have been observed. One involves the pannus cartilage junction, which is a distinct

infiltrative junction adjacent to the surface of the cartilage, and the second involves a diffuse fibroblastic cartilage pannus junction, known as the transitional fibroblastic zone, where the junction of soft and hard tissue forms a distinct cartilage – pannus^{31,32}. Ultimately, rheumatoid arthritis leads to erosion of the joint surface, contributing to joint deformation, loosening and loss of function.

It is possible to suppress the inflammatory reaction of pannus if the patient is given timely treatment. Otherwise, the disease can take a chronic, aggressive form, with destruction of the joints. The critical point, at which the inflammation turns into a chronic phase, is the activation of endothelial cells, with simultaneous increased expression of adhesion molecules and release of chemical factors from synovial cells³³. As a result of inflammation, hyaluronan increases more and more, is synthesized locally and partly by polymerization resulting in morning stiffness mainly³⁴, while at the same time molecules that sensitize the primary afferent pathogenic nerves lead to sensitivity to movement and pressure, or and in pain, even if the patient is at rest³⁵.

In recent years, the biopsy of damage to the synovial tissues has been considered one of the most powerful tools that treating physicians have in their hands to elucidate the initial events of rheumatoid arthritis. The immunological, histological, and chemical analyzes of the disease, using targeted biopsy samples, in studies that have been carried out have shown that the histopathological characteristics of the synovial membrane during the early phase of rheumatoid arthritis are representative of the characteristics during the long-term phase, when it occurs and pannus^{36,37}, which in turn indicates quantitative and not qualitative differences between the various stages of the disease^{38,39}.

Therapeutic approaches to rheumatoid arthritis and pannus

There is no treatment that leads to a complete cure of rheumatoid arthritis, however if a valid diagnosis is made and through appropriate treatment, the course of the disease can be significantly modified. The main goals of the therapeutic approach to the disease include complete remission, relief mainly from pain and control of symptoms in general, prevention of damage and joints and therefore prevention of deformities, problems arising due to functional motor skills disorders and by extension the possibility of disability, as well as to seek to improve the quality of life of the patients.

However, for the therapeutic approach to be successful, it is required that the disease be diagnosed in time, that there be immediate and correct therapeutic intervention, that the patient be monitored by specialized medical personnel, that the treatment that follows be individualized, depending on the particularities it presents, that he be trained, and that the patient complies with the doctor's instructions. The drugs that are basically used to treat rheumatoid arthritis are divided into analgesics, glucocorticoids (cortisone), non-steroidal anti-inflammatory drugs, disease-modifying drugs,

and biological modifiers. The goal of the antirheumatic drugs used is to modify the disease, to reduce pain and inflammation, to limit or prevent joint damage^{40,41}.

The combination of non-steroidal drugs and steroidal anti-inflammatory drugs is used so that the patient gets immediate relief from pain, stiffness and swelling. Glucocorticoids have traditionally been classified as steroidal anti-inflammatory agents, but according to research data they have a slow disease-modifying effect^{42,43}. Biologic drugs are combined with non-biologics⁴⁴, and if treatment with non-biologic drugs is started early, there is a significant possibility of achieving disease remission.

The treatment without the use of drugs concerns the education of the patient mainly through psychological support, his rest when he faces acute phases of the disease, the performance of appropriate exercises, physical therapy, occupational therapy, his participation in dietary counseling, as well as interventions that reduce cardiovascular risk, prevent osteoporosis, vaccinate the patient to limit infectious complications due to immunosuppressive therapy, use corrective means, such as for example splints and special shoes to prevent deformities, as well as the greatest possible preservation of the kinesiological range of the joints. The training of the patient aims to increase his performance, to facilitate the successful organization of his life and prevention at the level of loss of his functionality. The aim is also to improve the psychological state of the patient, so that he can control the symptoms, developing self-management methods and developing self-efficacy methods⁴⁵.

The disease is treated surgically only when there are joints with severe functional limitations and very intense pain, as for example happens with knee or hip arthroplasty. It is recommended to increase the consumption of foods that are anti-inflammatory, such as fruits and vegetables that are rich in plant fibers⁴⁶. Also improving the patient's sleep habits can improve the immune system⁴⁷ and keep inflammation under control⁴⁸. By having the patient use stress reduction strategies such as meditation, nature walks or listening to music, which can limit the release of stress hormones from the body, all the above help to improve inflammation. Cultivating positive social relationships and limiting negative ones that can increase levels of stress and inflammation is also considered a helpful practice⁴⁹.

The treatment approach for pannus is the same as for rheumatoid arthritis, as the goal is to treat inflammation throughout the body, not just specific joints. Considering that the appearance of pannus is an indication that the person suffers from a severe and long-term rheumatoid arthritis, usually during treatment, first-line treatments with non-steroidal anti-inflammatory drugs, without a doctor's prescription, are not carried out. The therapeutic approach is directly dependent on the symptoms the person will present, the previous treatments they have received and the length of time they have had rheumatoid arthritis. Reducing inflammation throughout the body also helps to eliminate

pannus, as well as other symptoms, such as fatigue. Surgery to remove it from a joint is rarely recommended. The operation is performed when the rheumatoid pannus does not go away with drugs or injections, with the aim of removing the inflamed tissue. The form of surgery is called atherectomy. Although rarely recommended, atherectomy can help relieve symptoms such as pain and stiffness in joints such as the knee, elbow and wrist⁵⁰. The benefits of an atherectomy can last for years. Also, in some cases, total arthroplasty takes place, which is considered the final option for the treating doctors, but also the most appropriate solution, to treat the pain and the loss of functionality of the joint⁵¹.

Discussion

From the aforementioned, it follows that rheumatoid arthritis is a disease with significant heterogeneity, which demonstrates the necessity for future research to consider the need to stratify patients, as well as those at risk of becoming ill, through the assessment of the determinants of the disease (genes and environment), as well as the available immunological data. The proper study of rheumatoid arthritis can only take place when longitudinal studies of the disease are carried out, focusing initially on those people who are at risk of developing the disease and in whom joint inflammation has not yet developed. Rheumatoid arthritis in the various phases of disease progression, especially before and during pannus formation. Especially, if it includes pannus, is a particularly painful and disfiguring condition, which significantly prevents the patient from having a good daily life, limiting his self-care possibilities, his social life, his mental health, with the treatment to be particularly expensive, as well as his care in general, as he needs constant medical monitoring. Joint destruction, which is associated with prolonged arthritis, develops immediately after the onset of the disease. The deformity of the affected joints is irreversible and causes physical dysfunction.

The most frequent form of the disease is the gradual mild onset, which usually affects small joints, with the symptoms developing in the body progressively. It is a disease in which the body's immune system mistakenly attacks healthy cells and the surrounding elements. Although the causes of the disease are not fully understood, scientists have concluded the interaction of genetic, hormonal and environmental factors. Inflammation is the central mechanism in the progression and manifestation of the disease, culminating in the appearance of pannus. Pain, stiffness and swelling of the joints are characteristic manifestations of the disease.

Correct diagnosis and treatment are considered key components of treating the disease from its initial stages. Both new therapeutic approaches, as well as preventive measures before the onset of the disease, are considered key motivations especially for clinicians and researchers, to treat the disease effectively. Early diagnosis is very important, as the disease progresses rapidly. The early diagnosis of the disease results in the early initiation of

active treatment, resulting in a slower progression of the disease. The diagnosis of rheumatoid arthritis is usually clinical, however, especially during the early stages of the disease, it is often difficult to diagnose. Both the etiology, as well as the type and severity of the symptoms, show great diversity, from patient to patient. An accurate diagnosis of the disease can take a long time, as a multitude of laboratory tests are required to confirm the findings of the clinical tests.

Rheumatoid arthritis can affect any joint, although the small joints of the hands seem to be the ones with the greatest frequency. The inflammation and its progression to pannus, can devastatingly affect the patient's vital functions, such as vision, respiratory function, and even cardiac function. The treatment aims to limit inflammation and prevent joint damage. Also, the therapeutic treatment aims to improve the functionality of the joints and, in general, the overall quality of life of the patients. Medication must be early, active, but also individualized, as each patient is a unique case. The goal of medication is to limit inflammation in the body, pain, and the destructive effects of inflammation.

It is recommended that wider investigations be carried out on both rheumatoid arthritis and pannus, for which as found by the present literature review, the existing research literature is quite limited. It is recommended that scientists focus on the issue of pannus, to establish the necessary interventions and preventive measures, so that it does not manifest itself in patients with rheumatoid arthritis, as its appearance shows the deterioration of the patient's condition.

Authors' contributions

PP: Drafted the manuscript, reviewed literature. **GIL:** Proof-edited the manuscript and gave final permission for publication. All authors read and approved the manuscript.

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