Review Article

An overall review on rheumatoid arthritis

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Abstract
Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. According to the U.S. Arthritis Foundation, rheumatoid arthritis (RA) affects about 1.3 million Americans. The disease is three times more common in women as in men. It affects people of all races equally. Genetic factors may play some role in RA either in terms of increasing susceptibility to developing the condition or by worsening the disease process. The main genetic marker identified with rheumatoid arthritis is HLA. Candidate genes responsible for rheumatoid arthritis are HLA-DRB1, HLA-DRB4, PTPN22, and PAD I4. Alteration of these genes results in production of inflammatory cells. The symptoms include fatigue, lack of appetite, low-grade fever, muscle and joint aches, and stiffness. Tissue inflammation may lead to pericarditis, shortness of breath followed by chest pain. In this review main cause, symptoms, complications and treatment of rheumatoid arthritis was discussed in detail.

Keywords: Auto immune disease, HLA B-27, ESR Test, Rheumatoid factor, T-Cells.

1. Introduction
Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. Autoimmune diseases occur when the body's tissues are mistakenly attacked by their own immune system. The immune system contains a complex organization of cells and antibodies designed normally to "seek and destroy" invaders of the body, particularly infections. Patients with autoimmune diseases have antibodies in their blood that target their own body tissues and leads to inflammation.

1. 1. Pathogenesis
The disease process leading to rheumatoid arthritis begins in the synovium, the membrane that surrounds a joint and creates a protective sac. This sac is filled with lubricating liquid called the synovial fluid. In addition to cushioning joints, this fluid supplies nutrients and oxygen to cartilage. Cartilage is composed primarily of collagen, the structural protein in the body, which forms a mesh to give support and flexibility to joints.

In rheumatoid arthritis, an abnormal immune system response produces destructive molecules that cause continuous inflammation of the synovium. Collagen is gradually destroyed, narrowing the joint space and eventually damaging bone. If the disease develops into a form called progressive rheumatoid arthritis, destruction to the cartilage accelerates. Fluid and immune system cells accumulate in the synovium to produce a pannus, a growth composed of thickened synovial tissue. The pannus produces more enzymes that destroy nearby cartilage, aggravating the area and attracting more inflammatory white cells, thereby perpetuating the process. This inflammatory process not only affects cartilage and bones but can also harm organs in other parts of the body. The synovial lining layer of affected joints is transformed into a highly proliferative so called pannus-like tissue consisting of synovial fibroblasts (SFs), synovial macrophages, and various infiltrating inflammatory cells. This hypertrophic and edematous tissue progressively invades adjacent cartilage and bone. Subsequently, joint destruction is mediated by matrix-
Fig. 1: Normal and Arthritic Joints.

1.2. Causes
The exact reasons are unknown. The condition is most likely triggered by a combination of factors including an abnormal autoimmune response, genetic susceptibility, biologic trigger such as a viral infection or hormonal changes. T cells and B-cells are two important components of the immune system that play a role in the inflammation associated with rheumatoid arthritis. If the T cell recognizes an antigen as "non-self," it will produce chemicals (cytokines) that cause B cells to multiply and release many immune proteins (antibodies). These antibodies circulate widely in the bloodstream, recognizing the foreign particles and triggering inflammation in order to rid the body of the invasion. Due to unknown reasons both the T cells and the B cells become overactive in patients with RA. Genetic factors may play some role in RA. The main genetic marker identified with rheumatoid arthritis is HLA (human leukocyte antigen). These genetic factors do not cause RA, but they may make the disease more severe once it has developed. Infections may stimulate the immune system to prolong RA once the disease has been triggered by some other initial infection. Other potential triggers include Mycoplasma, parvovirus B19, retroviruses, mycobacteria, and Epstein-Barr virus.

1.3. Symptoms
Symptoms can include fatigue, loss of energy, lack of appetite, low-grade fever, muscle and joint aches, and stiffness. Muscle and joint stiffness are usually most notable in the morning and after periods of inactivity. Arthritis is common during disease flares. Also during flares, joints frequently become red, swollen, painful, and tender. Early symptoms of rheumatoid arthritis can be pain and prolonged stiffness of joints, particularly in the morning. Symptoms in the hands include difficulty with simple tasks of daily living, such as turning door knobs and opening jars. The small joints of the feet are also commonly involved, which can lead to painful walking, especially in the morning after arising from bed. Chronic inflammation can cause damage to body tissues, including cartilage and bone. This leads to a loss of cartilage and erosion and weakness of the bones as well as the muscles, resulting in joint deformity, destruction, and loss of function.

Complications of rheumatoid disease
Since rheumatoid arthritis is a systemic disease, its inflammation can affect organs and areas of the body other than the joints. Inflammation of the glands of the eyes and mouth can cause dryness of these areas and is referred to as Sjögren's syndrome. Dryness of the eyes can lead to corneal abrasion. Inflammation of the white parts of the eyes is referred to as scleritis and can be very dangerous to the eye. Rheumatoid inflammation of the lung lining (pleuritis) causes chest pain with deep breathing, shortness of breath, or coughing. The lung tissue itself can also become inflamed, scarred, and sometimes nodules of inflammation develop within the lungs. Inflammation of the tissue (pericardium) surrounding the heart, called pericarditis, can cause a chest pain that typically changes in intensity when lying down or leaning forward. Rheumatoid arthritis is associated with an increase risk for heart attack. Rheumatoid disease can reduce the number of red blood cells and white blood cells. Decreased white cells can be associated with an enlarged spleen (referred to as Felty's syndrome) and can increase the risk of infections. The risk of lymph gland cancer (lymphoma) is higher in
patients with rheumatoid arthritis, especially in those with sustained active joint inflammation. Firm lumps under the skin (rheumatoid nodules) can occur around the elbows and fingers where there is frequent pressure. Even though these nodules usually do not cause symptoms, occasionally they can become infected. Nerves can become pinched in the wrists to cause carpal tunnel syndrome. A rare, serious complication, usually with longstanding rheumatoid disease, is blood vessel inflammation (vasculitis). Vasculitis can impair blood supply to tissues and lead to tissue death (necrosis). This is most often initially visible as tiny black areas around the nail beds or as leg ulcers.  

1.4. Diagnosis
Rheumatoid arthritis can be difficult to diagnose. Many other conditions resemble RA. Its symptoms can develop insidiously. Blood tests and x-rays may show normal results for months after the onset of joint pain. Specific findings or presentation more likely to suggest the diagnosis of rheumatoid arthritis include morning stiffness, involvement of three joints at the same time, involvement of both sides of the body, subcutaneous nodules, positive rheumatoid factor, and changes in x-rays.

Blood Tests
Various blood tests may be used to help diagnose RA, determine its severity, and detect complications of the disease. Rheumatoid Factor
In RA, antibodies in the blood that collect in the synovium of the joint are known as rheumatoid factor. In about 80% of cases of RA, blood tests reveal rheumatoid factor. It can also show up in blood tests of people with other diseases. However, when it appears in patients with arthritic pain on both sides of the body, it is a strong indicator of RA. The presence of rheumatoid factor plus evidence of bone damage on x-rays also suggests a significant chance for progressive joint damage.

Erythrocyte Sedimentation Rate
An erythrocyte sedimentation rate (ESR or sed rate) measures how fast red blood cells (erythrocytes) fall to the bottom of a fine glass tube that is filled with the patient’s blood. The higher the sedimentation rate the greater the inflammation. Because the sedimentation rate can be high in many conditions ranging from infection to inflammation to tumors, the ESR test is used not for diagnosis but to help determine how active the condition is.

C-Reactive Protein
High levels of C-reactive protein (CRP) are also indicators of active inflammation. Like the ESR, a high result does not indicate what part of the body is inflamed, or what is causing the inflammation.

Anti-CCP Antibody
The presence of antibodies to cyclic citrullinated peptides (CCP) can identify RA years before symptoms develop. In combination with the test for rheumatoid factor, the CCP antibody test is the best predictor of which patients will go on to develop severe RA.

Tests for Anemia
Anemia is a common complication. Blood tests determine the amount of red blood cells (hemoglobin and hematocrit) and iron (soluble transferrin receptor and serum ferritin) in the blood.

Imaging Tests
X-rays generally have not been helpful to detect the presence of early rheumatoid arthritis because they cannot show images of soft tissue. However, x-rays can help track the progression of joint damage over time. The doctor may also order other imaging tests, such as ultrasound, or magnetic resonance imaging (MRI). Dual energy x-ray absorptiometry (dxa scans), also called bone densitometry, may be used to check for signs of bone density loss associated with osteoporosis.

The American College of Rheumatology has developed a system for classifying rheumatoid arthritis that is primarily based upon the X-ray appearance of the joints. This system helps medical professionals classify the severity of your rheumatoid arthritis with respect to cartilage, ligaments, and bone. Stage I
No damage seen on X-rays, although there may be signs of bone thinning.
Stage II
- on X-ray, evidence of bone thinning around a joint with or without slight bone damage
- slight cartilage damage possible
- joint mobility may be limited; no joint deformities observed
- atrophy of adjacent muscle
- abnormalities of soft tissue around joint possible

Stage III
- on X-ray, evidence of cartilage and bone damage and bone thinning around the joint
- joint deformity without permanent stiffening or fixation of the joint
- extensive muscle atrophy
- abnormalities of soft tissue around joint possible

Stage IV
- on X-ray, evidence of cartilage and bone damage and osteoporosis around joint
- joint deformity with permanent fixation of the joint (referred to as ankylosis)
- extensive muscle atrophy
- abnormalities of soft tissue around joint possible

Rheumatologists also classify the functional status of people with rheumatoid arthritis as follows:
- Class I: completely able to perform usual activities of daily living
- Class II: able to perform usual self-care and work activities but limited in activities outside of work (such as playing sports, household chores)
- Class III: able to perform usual self-care activities but limited in work and other activities
- Class IV: limited in ability to perform usual self-care, work, and other activities

1.5. Treatment of Rheumatoid Arthritis

"First-line" rheumatoid arthritis medications

Acetylsalicylate, naproxen, ibuprofen and etodolac are examples of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are medications that can reduce tissue inflammation, pain, and swelling. Aspirin in doses higher than those used in treating headaches and fever is an effective anti-inflammatory medication for rheumatoid arthritis. The newer NSAIDs are just as effective as aspirin in reducing inflammation and pain and require fewer dosages per day. The most common side effects of aspirin and other NSAIDs include stomach upset, abdominal pain, ulcers, and even gastrointestinal bleeding. In order to reduce gastrointestinal side effects, NSAIDs are usually taken with food. Additional medications are frequently recommended to protect the stomach from the ulcer effects of NSAIDs. These medications include antacids, sucralfate (Carafate), proton-pump inhibitors (Prevacid and others), and misoprostol (Cytotec). Newer NSAIDs include selective Cox-2 inhibitors, such as celecoxib (Celebrex), which offer anti-inflammatory effects with less risk of stomach irritation and bleeding risk. Corticosteroid medications can be given orally or injected directly into tissues and joints. They are more potent than NSAIDs in reducing inflammation and in restoring joint mobility and function. However, corticosteroids can have serious side effects, especially when given in high doses for long periods of time. These side effects include weight gain, facial puffiness, thinning of the skin and bone, easy bruising, cataracts, risk of infection, muscle wasting, and destruction of large joints, such as the hips.

"Second-line" or "slow-acting" rheumatoid arthritis drugs (disease-modifying anti-rheumatic drugs or DMARDs)

While "first-line" medications can relieve joint inflammation and pain, they do not necessarily prevent joint destruction or deformity. Rheumatoid arthritis requires medications other than NSAIDs and corticosteroids to stop progressive damage to cartilage, bone, and adjacent soft tissues. DMARDs can promote remission, thereby retarding the progression of joint destruction and deformity. Sometimes a number of DMARD second-line medications are used together as combination therapy. Sulfasalazine (Azulfidine) is an oral medication traditionally used in the treatment of mild to moderately severe inflammatory bowel diseases, such as ulcerative colitis and Crohn's colitis. Azulfidine is used to treat rheumatoid arthritis in combination with anti-
inflammatory medications. Azulfidine is generally well tolerated. Common side effects include rash and upset stomach. Because Azulfidine is made up of sulfa and salicylate compounds, it should be avoided by people with known sulfa allergies. Methotrexate has gained popularity among doctors as an initial second-line drug because of both its effectiveness and relatively infrequent side effects. It also has an advantage in dose flexibility. Methotrexate is an immunosuppressive drug. It can affect the bone marrow and the liver, even rarely causing cirrhosis. All people taking methotrexate require regular blood tests to monitor blood counts and liver function.

Gold salts have been used to treat rheumatoid arthritis throughout most of the past century. Gold thioglucose (Solganal) and gold thiomalate (Myochrysine) are given by injection, initially on a weekly basis, for months to years. Oral gold, auranofin was introduced in the 1980s. Side effects of gold include skin rash, mouth sores, kidney damage with leakage of protein in the urine, and bone marrow damage with anemia and low white cell count. Those receiving gold treatment are regularly monitored with blood and urine tests. Oral gold can cause diarrhea. These gold drugs have lost favor because of the availability of more effective treatments, particularly methotrexate.

D-penicillamine (Depen, Cuprimine) can be helpful in selected cases of progressive forms of rheumatoid arthritis. Side effects are similar to those of gold. They include fever, chills, mouth sores, a metallic taste in the mouth, skin rash, kidney and bone marrow damage, stomach upset, and easy bruising. People taking this medication require routine blood and urine tests. D-penicillamine can rarely cause symptoms of other autoimmune diseases and is no longer commonly used for the treatment of rheumatoid arthritis.

Immunosuppressive medicines are powerful medications that suppress the body's immune system. A number of immunosuppressive drugs are used to treat rheumatoid arthritis. They include methotrexate as described above, azathioprine (Imuran), cyclophosphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune). Because of potentially serious side effects, immunosuppressive medicines are generally reserved for those who have very aggressive disease or those with serious complications of rheumatoid inflammation, such as blood vessel inflammation. The exception is methotrexate, which is not frequently associated with serious side effects and can be carefully monitored with blood testing. Methotrexate has become a preferred second-line medication as a result. Immunosuppressive medications can depress bone-marrow function and cause anemia, a low white cell count, and low platelet counts. A low white count can increase the risk of infections, while a low platelet count can increase the risk of bleeding. Methotrexate rarely can lead to liver cirrhosis and allergic reactions in the lung. Cyclosporine can cause kidney damage and high blood pressure. Because of potentially serious side effects, immunosuppressive medications are used in low doses, usually in combination with anti-inflammatory agents.

**Conclusion**

As there is no permanent treatment further research should be carried out on life style and dietary modifications in controlling the expression of genes involved in progression of rheumatoid arthritis. Research should be continued to control the progression of disease. Scientists should concentrate on the alternative systems of medicines to improve the condition.

**References**


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