AN OVERVIEW OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic inflammation that damages synovial joints, especially the joints of the hands and feet. Most patients also experience extra-articular manifestations that can affect a variety of different organs. The disease is particularly common in women and usually has its onset in middle age, during the years when patients have significant responsibilities to their families and employers. More than 2 million Americans are affected by rheumatoid arthritis, with a high risk of disability and premature mortality. Joint damage typically begins during the first 2 years of the disease, but early treatment can help patients preserve function. It is important for primary healthcare professionals to be able to recognize rheumatoid arthritis so that patients can be referred to a rheumatologist within the first 3 months after symptom onset. The presentation and course are highly variable. The onset can be sudden, gradual, or insidious. Common features are symmetrical joint swelling and tenderness on passive motion. Other common signs and symptoms are prolonged morning stiffness, rheumatoid nodules, decreased range of motion, difficulty making a fist, decreased grip strength, deformities in the hands or feet, prolonged morning stiffness, and constitutional symptoms such as fatigue, weakness, fever, loss of appetite, and general malaise. These signs and symptoms are believed to occur because, in response to an unknown antigen, the body activates an inappropriate immune response. An inflammatory cascade is activated that causes thickening of the lining of synovial joints. Eventually, cells activated by the inflammatory cascade begin to destroy bone and connective tissue. Several biologic disease-modifying antirheumatic drugs—the newer targeted therapies for rheumatoid arthritis—are designed to interfere with specific components of the destructive inflammatory cascade. Nurses who make an effort to understand the pathogenesis of rheumatoid arthritis will be best able to teach patients how the new therapies exert their effects.


INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation in synovial joints, especially the small joints in the hands and feet. In the United States, RA is not as common as osteoarthritis, the type of arthritis associated with the “wear and tear” of aging, but it is far from rare. The Arthritis Foundation estimates that RA affects 2.1 million Americans.1 RA can occur at any age, including during childhood. Women are diagnosed with RA 2.5 times more often than men, and in women, the onset most commonly occurs between the ages of 40 and 50.2 A 30-year study at the Mayo Clinic showed that the incidence of RA rose steadily from age 35 until approximately age 85, when it declined sharply among women and slightly among men.3

RA causes joint damage in 80% to 85% of patients, typically during the first 2 years of the disease, so there is a high risk of disability.4 RA also increases the risk of mortality. According to research conducted before targeted drug therapy was introduced, people with RA are twice as likely to die compared with unaffected people the same age.5 The leading contributors to the increased risk of death are cardiovascular disease, which accounts for approxi-

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mately one third to one half of RA-related deaths, and infection, which is associated with approximately one quarter of such deaths. RA is also known to increase the risk of lymphoma, by a factor of at least 2-fold, and to increase the risk of decreased bone mineral density, even in the absence of corticosteroid therapy.

A subset of RA, called older-onset RA, begins after age 60 and is characterized by especially rapid progression of joint damage. Like RA in other adults, older-onset RA is associated with an increased risk of death, especially among patients who are seropositive for rheumatoid factor.

This article reviews the causes and consequences of joint damage in RA, the clinical manifestations in adults, and how the disease is diagnosed. Special care is taken to explain the autoimmune response involved in RA, so nurses will have a better understanding of the newer drugs that target this response.

**JOINT DAMAGE**

RA is the most common type of a group of diseases called inflammatory arthropathies. (Other examples are psoriatic arthritis and systemic lupus erythematosus.) In the case of RA, the chronic inflammation principally affects synovial joints—joints where there is space between 2 articulating bones. In a synovial joint, the bones are covered with cartilage, enclosed in a fibrous capsule, and lubricated by synovial fluid. A thin membrane called the synovium lines the joint (Figure 1).

The joint symptoms of RA are caused by synovitis—inflammation of the synovium. The synovium is invaded by immune system cells and thickens, causing the joint to swell and feel puffy to the touch (Figure 2). As the synovium overgrows, a tissue called pannus forms, which acts like a low-grade malignancy, eventually destroying bone, cartilage, and connective tissues. In addition, the inflammatory response increases blood flow to affected joints, sometimes causing them to look reddened and to feel warm to the touch.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Patients with RA vary widely with regard to the age of onset, number of joints involved, and degree of disease severity and course. Some patients have only mild symptoms and require only anti-inflammatory medication or minor lifestyle changes. Others have joint destruction even at the time of presentation. Some
patients experience flares and remissions, whereas others have a progressive course. However, most patients with RA have prolonged morning stiffness (≥1 hour) and symmetrical joint involvement (joints on both sides of the body are affected, such as the left and right wrists).11

Because the clinical presentation of RA is so variable, diagnosis in the early stages can be difficult. No single diagnostic test or finding conclusively confirms the presence of RA, and symptoms may wax and wane.11 In 1957, the American Rheumatism Association, now known as the American College of Rheumatology, published classification criteria for RA for use in clinical trials. The Table lists the criteria as revised in 1987.12 The criteria are a useful reminder of common manifestations of RA, although there are limitations in their application in clinical practice as a diagnostic tool.13 As shown in a large, longitudinal study, RA can present first as undifferentiated arthritis that does not meet the classification criteria of RA or any other specific clinical disease category.14 In some cases, a person will meet the criteria on one visit but not another, or can eventually be diagnosed as having another disease.15

Early recognition is vital, however. Disease-modifying treatment has the best chance of reducing joint damage if it is started early, within 3 months after diagnosis. Therefore, a useful goal is to have patients consult a rheumatologist within 3 months after symptom onset.16

The diagnosis of RA is generally based on 4 categories of identifying characteristics: symptoms, physical signs, laboratory test results, and radiographic (X-ray) findings. Assessment often needs to be repeated at least once before the diagnosis can be established.

**Identifying Characteristics**

**Symptoms**

RA can affect any joint, but the most characteristic early symptoms are pain or tenderness on passive motion and stiffness in the metacarpophalangeal (MCP) joints and proximal interphalangeal (PIP) joints of both hands (Figure 3). Other joints commonly affected are the wrists, elbows, ankles, metatarsophalangeal (MTP) joints in the feet, the temporomandibular joint, knees, hips, and cervical spine. Constitutional symptoms are also common because RA is a systemic disease. These can include fatigue, weakness, fever, a general feeling of ill health, and loss of appetite with weight loss.17

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tr>
<td>1. Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
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<tr>
<td>2. Arthritis of 3 or more joints</td>
<td>At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or leftPIP, MCP, wrist, elbow, knee, ankle, and MTP joints.</td>
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<tr>
<td>3. Arthritis of hand joints</td>
<td>At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint</td>
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<td>4. Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)</td>
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<tr>
<td>5. Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in &lt;5% of normal control subjects</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
</tr>
</tbody>
</table>

*For classification purposes, a patient shall be said to have rheumatoid arthritis if he has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.

MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

**Physical signs**

Inflamed joints can be swollen and, on careful examination, may feel warm to the touch. Decreased range of motion in the joints, difficulty making a fist, and decreased grip strength are other important clues. Over time, some patients with RA develop deformities in the hands or feet.\(^{15,18}\)

**Laboratory test results**

Patients with RA frequently have normal laboratory test results, especially in early disease. Therefore, although laboratory abnormalities can support a diagnosis of RA, by themselves, they are not diagnostic. For example, rheumatoid factor (RF), an abnormal immunoglobulin antibody, is present in 70% to 80% of patients with RA, but it is also present in some healthy people and in people with certain other diseases. A negative test for RF does not mean that RA is not present, and an abnormal test does not mean that RA is present.\(^{15}\)

Antibodies to cyclic citrullinated peptide (anti-CCP antibodies) are a more specific marker for RA. The sensitivity of testing for these antibodies (ability to rule out RA that is not present) appears to be 90% to 98%, and the specificity (ability to find RA that is present) is no worse than that of RF, 50% to 80%.\(^{19,20}\)

Some other laboratory abnormalities often found in patients with RA include mild anemia, thrombocytosis, and an elevated erythrocyte sedimentation rate or elevated level of C-reactive protein (markers of inflammation).\(^{15}\)

**Radiographic findings**

In many patients, RA develops first in the MCP, PIP, or MTP joints, so usually the first radiographs taken are of the hands and feet. The earliest radiographic signs of RA are symmetrical loss of cartilage, which results in joint space narrowing. Loss of cartilage and erosions (holes in the bone) first appear at the corners of the joints, where the cartilage is thinnest. As with laboratory tests, a normal radiograph does not necessarily mean that RA is not present.\(^{11}\)

**Extra-articular manifestations**

Because RA is a systemic disease, it can cause several extra-articular (outside the joint) manifestations. Men, patients with relatively more severe disease, and patients who test positive for RF are more likely than others to have extra-articular involvement.\(^{15}\)

Rheumatoid nodules (firm, nontender subcutaneous nodules that are not attached to underlying bone or overlying skin) occur in approximately 30% of patients with RA. Such nodules are most commonly found at pressure points such as the elbow, the back of the forearm, and MCP joints. Usually, they are asymptomatic, but they can be painful. They may resolve spontaneously.\(^{17}\)

Some other common extra-articular manifestations of RA are: cardiovascular involvement, including atherosclerotic heart disease, myocarditis, pericarditis, and vasculitis; pleurisy (inflammation of the membrane lining the lungs); Sjögren’s syndrome (impaired secretion of saliva and tears, leading to dry mouth and dry eyes); tenosynovitis; and eye disease (scleritis).\(^{15}\)

**Differential diagnosis**

Osteoarthritis most frequently affects the weight-bearing joints, such as the hip, but it can be confused with RA when it involves the hands. Osteoarthritis is more likely to affect the distal interphalangeal (DIP) joints and PIP joints than the MCP joints (Figure 3). Whereas RA-affected joints usually feel soft and spongy, joints affected by osteoarthritis are typically hard and bony. Patients with osteoarthritis often have localized, asymmetric joint involvement and generally experience morning stiffness and constitutional symp-
symptoms to a much lesser degree than patients with RA do. There are no characteristic laboratory abnormalities.\textsuperscript{11}

Psoriatic arthritis, like RA, is an inflammatory arthropathy. Many patients present with a symmetric arthritis involving the MCP and PIP joints, in some cases many years before the onset of skin disease. Some of the signs that can point toward the correct diagnosis are involvement of DIP joints, psoriatic skin lesions or a family history of psoriasis, and pitting of the nails or changes in their color, texture, and structure.\textsuperscript{15}

Some of the other conditions that may be considered in the differential diagnosis of RA are fibromyalgia, gout, inflammatory bowel disease, polynyalgia rheumatica, reactive arthritis, Reiter’s syndrome, systemic sclerosis, systemic lupus erythematosus, and viral infections that present with joint involvement.\textsuperscript{21}

ETIOLOGY

The etiology of RA is unknown, but it likely involves multiple factors, including a genetic susceptibility and environmental triggers. The major genetic risk factors for RA are certain forms of the HLA-DR gene (human leukocyte antigen gene, subtype DR).\textsuperscript{22} More recently, it was determined that at least 1 other gene, PTPN22, increases susceptibility to RA.\textsuperscript{23} This gene influences the age of onset of RA; people who have it develop the disease 2 years earlier, on average, than those without it. Two other genes, CTLA4 and PADI4, have weaker, more tentative connections with RA.\textsuperscript{24} These findings are important to scientists, but they do not yet affect clinical practice. Genetic factors do help explain the disease variability and why the incidence and prevalence of RA vary considerably among countries, with Finland and the United States having the highest rates.\textsuperscript{25}

For years it has been considered likely that RA has 1 or more environmental causes, in addition to genetic causes. The most well-known environmental risk factor for RA is smoking.\textsuperscript{25} An important advance occurred in January 2006, when Swedish researchers reported a new model for the etiology of RA.\textsuperscript{26} The scientists found that the risk of RA skyrocketed in people who were cigarette smokers and also had at least 1 copy of the risky HLA-DR genes. However, the smoking-genetics interaction held true only in people with RA who had anti-CCP antibodies, not in those without such antibodies. The Swedish team speculates that an immune response to citrullinated proteins is the first step in the development of RA. It appears that this immune response can be induced by long-term exposure to cigarette smoke, and that it is most likely to occur in people with HLA-DR genes.\textsuperscript{26}

More research is required to determine exactly how and when the immune system is activated in RA. In the meantime, it is important for nurses to understand how the immune response proceeds because the newer drug therapies for RA target various immune system components.

PATHOGENESIS: THE INFLAMMATORY CASCADE

RA is an autoimmune disease, meaning that the immune system mounts an attack against healthy tissues. The original antigen—the substance that triggers the immune response—is unknown; it might be an infectious agent or even a self-protein that the body mistakes as a foreign body. However, much is known about how the disease progresses. The antigen activates, or “turns on,” immune system cells called T cells, causing them to proliferate and invade 1 or more joints (Figure 4). In turn, T cells activate other immune system cells, such as macrophages, neutrophils, and fibroblasts. These cells secrete cytokines—proteins that can have direct inflammatory effects or stimulate the production of inflammatory substances. Important proinflammatory cytokines in RA are tumor necrosis factor-α (TNF-α), interleukin-

![Figure 4. Depiction of the Inflammatory Cascade that Produces Joint Damage in Rheumatoid Arthritis](image-url)

**Figure 4. Depiction of the Inflammatory Cascade that Produces Joint Damage in Rheumatoid Arthritis**

- **B cell**
- **T cell**
- **HLA-DR**
- **Antigens-presenting cells**
- **Antibodies**
- **Tumor necrosis factor (TNF-α)**
- **Interleukin (IL)**
- **Antecipital cartilage**
- **Production of collagenases and other neutral proteases**
- **Dendritic cells**
- **Macrophages**
- **Synoviocytes**
- **Chondrocytes**
- **Immune complexes**

HLA-DR = human leukocyte antigen gene, subtype DR; IFN = interferon; IL = interleukin; RFs = rheumatoid factors; TNF = tumor necrosis factor. Adapted with permission from Arend et al. Arthritis Rheum. 1990;33:305-315.\textsuperscript{11}
1 (IL-1), and IL-6. In addition to activating immune system cells, T cells promote the proliferation of osteoclasts—cells that break down bone. Other important players are B cells, which produce rheumatoid factor antibodies and anti-CCP antibodies (Figure 4). Anti-CCP antibodies are directly involved in tissue injury. Rheumatoid factors react with immunoglobulin to form immune complexes that activate inflammatory reactions, which eventually can result in joint damage and the extra-articular manifestations.

Among their other effects, B cells can directly infiltrate the joints, produce TNF-α and IL-6, and stimulate fibroblasts to release destructive enzymes. B cells even help activate T cells—in fact, there is evidence that in synovial joints, T-cell activation is dependent on B cells. Cells in the synovium (called synoviocytes) also are important in the RA disease process. The proliferation of synoviocytes is what leads to thickening of the synovium and pannus formation. Furthermore, synoviocytes, along with cells in cartilage called chondrocytes, release collagenase and other proteases (enzymes) that directly destroy the joint tissues.

It is important to understand that the inflammatory cascade is not a chain of events, but rather a web of interrelated reactions that overlap in time. This probably explains why combination therapy, in which multiple drugs are used to suppress different aspects of the immune response, is generally more successful than a single drug.

Biologic disease-modifying antirheumatic drugs—the newer targeted therapies for RA—are designed to interfere with specific aspects of the inflammatory cascade. Five of them are designed to interfere with production of cytokines: etanercept, infliximab, and adalimumab target TNF-α; anakinra targets IL-1; and tocilizumab (not yet commercially available) targets IL-6. The other 2 biologics approved for RA have different mechanisms: rituximab depletes B cells, and abatacept works early in the inflammatory response, targeting T-cell activation. These drugs are discussed in detail elsewhere in this issue.

**CONCLUSIONS**

RA is a chronic, inflammatory autoimmune disease that affects synovial joints and other parts of the body. It is more common in women than in men, and in adults it is more common after age 35. RA is a painful, debilitating disease with unknown etiology and no known cure. However, early diagnosis and treatment can decrease or eliminate joint damage, helping patients maintain function. With an estimated 2 million Americans affected by RA, it is likely that any nurse in a general practice will encounter patients with this disease. Nurses need to know the signs and symptoms of rheumatoid arthritis and be aware of the importance of referral to a rheumatologist within the first 3 months after symptom onset.

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