Rheumatoid Arthritis Case Study

JG is a 48-year old married mother. Seven months ago, JG began noticing stiffness in both hands in the morning that lasted longer and longer. Stiffness now lasted more than 1 hour every morning and included hands, wrists and ankles. She also had increasing difficulty standing for long periods at work or at home due to foot and ankle pain. She began taking ibuprofen 800mg 3 times daily and found it helped her get through her day with less pain and stiffness. Three months ago, JG noticed pain in her right and left shoulders during her work. She also began feeling extremely tired and short tempered. She had no energy to do her usual activities. Ibuprofen was no longer very effective for her pain or stiffness. One morning, Joy could not lift her arms at all without extreme shoulder pain and because of the swelling in her fingers, she had been unable to wear her wedding ring for approximately one year.

She saw her Primary Care Physician (PCP), who examined her and ran a few preliminary blood tests. The blood tests revealed positive rheumatoid factor, cyclic citrullinated peptide (CCP) antibody, elevated ESR and C-reactive protein. JG Primary Care Physician referred her to a Rheumatologist. Rheumatologist physical examination including all of JG joints, many of which were tender and swollen. At her follow-up visit with the Rheumatologist 2 weeks later, laboratories had confirmed what her history and examination indicated, that Joy had established Rheumatoid Arthritis (symptoms present for more than 6 months). Joy’s shoulders felt a little better, though she was still having pain and difficulty raising her arms. The Rheumatologist recommended she see a Physical Therapist (PT) for further assessment and treatment of her shoulders and advice on activity modification related to her work.

Objectives:

1. Explain the possible role of immune system in the pathophysiology of rheumatoid arthritis
2. List the most important cells and cytokines associated with rheumatoid arthritis
3. List the symptoms associated with rheumatoid arthritis
4. List the extra-articular manifestations of rheumatoid arthritis.
5. List the laboratory tests used in diagnosing rheumatoid arthritis.

Questions

1. Discuss the possible risk factors
2. Explain the role of T and B lymphocyte in the development of rheumatoid arthritis?
3. What would be the most important cells in the development of rheumatoid arthritis?
4. What are the most important cytokines in the development of rheumatoid arthritis?
5. Discuss the most important small joint criteria of rheumatoid arthritis
6. Discuss the most important large joint criteria of rheumatoid arthritis
7. What are the most important laboratory changes associated with rheumatoid arthritis
**Risk factors:**
1. Female gender: 3:1 females to males.
2. Increasing age: Peak onset 35 to 50 years of age.
3. Current tobacco smoking.
4. Family history of rheumatoid arthritis: The presence of major histo-compatibility complex class II human leukocyte antigens (HLA), specifically HLA-DR1 and HLA-DR4.
5. Oral contraceptive use and high ingestion of vitamin D and tea are associated with a decreased risk of RA.

**Pathophysiology**

There is NO specific trigger cause except association described between periodontal diseases with Rheumatoid arthritis through species of bacteria, Porphyromonas gingivalis.

**T lymphocytes cell activation**

T lymphocytes cell activated through second signals is delivered through the CD28 molecule on the surface of the T cell to proliferate and begin to secrete IL-17 to stimulate.

**Macrophages**

Macrophages hat has been seen as one of the master orchestrators of the effector damage in RA. Macrophages are rich sources and major producers:

a. pro-inflammatory cytokines including TNF, IL-1, IL-6, IL-8, and GMCSF. These cytokines further stimulate the macrophage, as well as other cells in the microenvironment in a including fibroblasts (fibroblast synoviocytes) and osteoclasts (through the production of RANK (Receptor activator of nuclear factor kappa-B) that they end in bone erosion), and finally at distant sites in the body through cell surface receptors including the hepatocyte which is responsible for the generation of acute phase response proteins (such as C-reactive protein).

b. prostaglandins and leukotrienes, nitric oxide, and other pro-inflammatory mediators with local and systemic effects.

c. Proteases which begin to degraded cartilage and Chondrocytes, like synovial fibroblasts, are activated by IL1 and TNF to secrete proteolytic enzymes. They may, therefore, contribute to the dissolution of their own cartilage matrix, thus explaining the progressive narrowing of joint spaces seen radiographically in this disease.

**Synovial fibroblast**

Synovial fibroblast, secretes cytokines including IL-6, IL-8 and GM-CSF, and other mediators including destructive proteases and collagenases.

**Neutrophils**

Neutrophils are recruited in very large numbers to the rheumatoid cavity where they can be aspirated in the synovial fluid. The recruitment of neutrophils to the joint is likely driven by IL-8, leukotriene B4, and possibly localized complement activation through C5a. Neutrophils in the synovial fluid are in an activated state, releasing oxygen-derived free radicals that depolymerize hyaluronic acid and inactivate endogenous inhibitors of proteases, thus promoting damage to the joint.

**B cells activation**

1. Activated B cells produce plasma cells, which form antibodies. These antibodies in combination with complement result in the accumulation of poly-morpho-nuclear leukocytes, which release cytotoxins, oxygen free radicals, and hydroxyl radicals that promote cellular damage to synovium and bone.

2. Activated B cells produce cytokines that may alter the function of other immune cells.

3. Activated B cells have the ability to process antigens and act as antigen-presenting cells, which interact with T cells to activate the immune process.
Inflammatory Mediators in Rheumatoid arthritis

A. Cytokines
The most prominent cytokines are TNF, IL-1, and IL-6. Among the important effects of these cytokines are:

1. Induction of cytokine synthesis
2. Upregulation of adhesion molecules
3. Activation of osteoclasts
4. Induction of other inflammatory mediators including prostaglandins, nitric oxide, matrix metalloproteinases
5. Induction of the acute phase response (e.g., C-reactive protein, increased ESR)
6. Systemic features (e.g., fatigue, fever, cachexia)
7. Activation of B cells (IL-6)

Other cytokines are increasingly described in Rheumatoid arthritis:

1. IL-8 which is involved in cellular recruitment
2. GM-CSF involved in macrophage development
3. IL-15 involved in T cell proliferation
4. IL-17 which has pleiotropic effects on multiple cell types including osteoblast expression of RANK (Receptor activator of nuclear factor kappa-B) leading to osteoclast activation, and IL-23 involved in increasing T Helper-1 cell differentiation.

Soluble mediators of inflammation that may diffuse in from blood and/or be formed locally within the joint cavity include:

i. Prostaglandins are involved in pain sensitization localized inflammation, and some effects on bone, and leukotrienes play roles in vascular permeability and chemotaxis.
ii. Matrix metalloproteinases (MMPs) are potent in their ability to enzymatically degrade the collagen matrix of cartilage.
iii. Kinins cause release of prostaglandins from synovial fibroblasts, and are also potent algesic (pain-producing) agents.
iv. Complement may be available for interaction with immune complexes to generate additional chemotactic stimuli.
v. The neuropeptide substance P is a potent vasoactive, pro-inflammatory peptide that has also been implicated in RA.

Rheumatoid arthritis causes an inflammatory response in synovial tissue lining the joint capsule results in synovium proliferates in an uncontrolled fashion of joints tissue. As the rheumatoid arthritis progresses, the synovium may grow larger and form an inflamed, granulated sheet of tissue called rheumatoid pannus (the hypertrophied synovium is called pannus). This pannus invades space between the bones of the joint (subchondral bone), cartilage and eventually the bone.
surface, producing erosions of bone and cartilage and leading to destruction of the joint in addition to bone and cartilage damage caused by cell and cytokines.

**Joint involvement in Rheumatoid arthritis:**
Most cases of RA display a typical symmetrical pattern of joint involvement: the proximal interphalangeal joints (PIPs) and metacarpophalangeal joints (MCPs) are often the first to be affected, then wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal (MTP) joints.

Characteristic early finding: inability to “wring out a washcloth” or produce a strong grip

The joints affected most frequently by rheumatoid arthritis are

I. Involvement of the small joints of the hands, wrists is common
   a. during the acute phase: manifested by pain, swelling, tenderness, and grip weakness
   b. during the chronic phase with lack of an adequate exercise program results: manifested by Loss of range of motion, subluxation, instability, deformity, muscle atrophy, Weakness, and deformity of the hand

Signs of late disease with irreversible damage in the hands and wrist: ① “swan-neck”, ② “boutonnière”, ③ Subluxation at the MCPs with ulnar deviation, ④ Radial deviation of the wrist

Functional difficulties with clasp, grasp, and pinch alter both strength and fine motor movement. Patients usually experience joint stiffness

① Joint stiffness typically is worse in the morning. Stiffness after rest is often called “gelling”
② Joint stiffness duration tends to be correlated directly with disease activity,
③ Joint stiffness usually exceeds 30 minutes, and may persist all day.

On examination,
① The swelling of the joints may be visible or may be apparent only by palpation.
② The swelling of the joints feels soft and spongy because it is caused by proliferation of soft tissues or fluid accumulation within the joint capsule.
③ The swelling of the joint may appear erythematous and feel warmer than nearby skin surfaces, especially early in the course of the disease.
II. Involvement of the large joints

a. The elbow and shoulder pain is may be the result of true joint involving or inflammation of soft-tissue structures such as tendons (tendonitis) or the bursa (bursitis).

b. The knee also can be involved, with loss of cartilage, instability, and joint pain. Synovitis of the knee may cause the formation of a cyst behind the knee called a popliteal or Baker cyst. These cysts may become painful as they get tense, or they may rupture, producing a clinical picture similar to thrombophlebitis secondary to the release of inflammatory components into the area of the calf muscle.

Chronic joint pain leads to muscle atrophy, which can result in a laxity of the ligamentous structures that support the knee, causing instability. Maintenance of an adequate range of motion of the knee is essential to normal gait.

c. Foot and ankle

The metatarsophalangeal joints are involved frequently in rheumatoid arthritis, making walking difficult. Subluxation of the metatarsal heads leads to “cock-up” or hammer toe deformities.

Subluxation also may cause a flexion deformity at the proximal interphalangeal joint of the toe, leading to pressure necrosis of the skin over the joint secondary to irritation caused by shoes. Hallux valgus (lateral deviation of the digit) and bunion or callus formation may occur at the great toe. A widening of the foot occurs.

d. Involvement of the spine usually occurs in the cervical vertebrae; lumbar vertebral involvement is rare.

e. The temporomandibular joint (jaw) can be affected, resulting in malocclusion and difficulty in chewing food.

f. Hip pain may occur as a result of destructive changes in the hip joint, soft-tissue inflammation (e.g., bursitis), or referred pain from nerve entrapment at the lumbar vertebrae. Inflammation of cartilage in the chest can lead to chest wall pain.

Extra-articular involvement:
Rheumatoid Nodules
Rheumatoid nodules occur in 20% of patients with rheumatoid arthritis. Rheumatoid nodules are seen most commonly on the extensor surfaces of the elbows, forearms, and hands but also may be seen on the feet and at other pressure points.

Vasculitis
Most commonly, small vessel vasculitis produces infarcts near the ends of the fingers or toes, especially around the nail beds.

Pulmonary Complications
Rheumatoid arthritis may involve the pleura of the lung, which is often asymptomatic, although pleural effusions, pulmonary fibrosis may result.

Ocular Manifestations
Ocular manifestations include
a. Atrophy of the lacrimal duct may result in a decrease in tear formation, causing dry and itchy eyes, termed kerato-conjunctivitis sicca
b. inflammation of the sclera, episclera, and cornea,

Cardiac Involvement
Rheumatoid arthritis is associated with an increased risk of cardiovascular mortality.

Felty’s Syndrome
Felty’s Syndrome (splenomegaly, neutropenia, Thrombocytopenia)

Other involvements: CNS: fatigue and reduced cognitive function, Exocrine glands: secondary Sjögren’s syndrome, Muscles: sarcopenia, Bones: osteoporosis, Cancer risk: Lymphoma, Lung cancer

Laboratory finding
1. Hematologic tests often reveal a mild to moderate anemia of chronic disease with
   ① Normocytic, normochromic indices ② low hematocrit
2. Thrombocytosis Platelet counts rise and fall in direct correlation with disease activity in many patients.
3. The erythrocyte sedimentation rate is usually elevated.

The erythrocyte sedimentation rate and C-reactive protein are very nonspecific
4. Rheumatoid factor (IgM) is present in 60% to 70% of patients with rheumatoid arthritis.
5. Anti-cyclic citrullinated peptide antibody being found in 50% to 85% of patients with the disease, but is more specific (90% to 95%) and is detectable

Citrullination or deimination is the conversion of the amino acid arginine in a protein into the amino acid citrulline. Citrullination is a normal process, required for normal skin formation and other physiologic functions. However, in rheumatoid arthritis an autoimmune response develops against citrullinated peptides detected as anti-citrullinated peptide antibodies (ACPA).
6. Antinuclear antibodies are detected in 25% of patients with rheumatoid arthritis.
7. Serum complement is usually normal
8. Synovial fluid
   a. Synovial fluid usually is less viscous, turbid comparing to normal joints fluid because of the large number of leukocytes (5,000 to 50,000/mm³) in inflammatory fluid.
   b. Complement concentrations of joint fluid often are depressed from consumption secondary to the inflammatory process.
   c. Glucose concentrations of joint fluid are normal or low compared with those in serum drawn at the same time as synovial aspirates.
Early radiographic manifestations of rheumatoid arthritis include
   a. soft-tissue swelling
   b. osteoporosis near the joint (periarticular osteoporosis).
   c. Joint space narrowing occurs as a result of cartilage degradation.
   d. Erosions tend to occur later in the course of the disease and usually are seen first in the metacarpophalangeal and proximal interphalangeal joints of the hands and the metatarsophalangeal joints of the feet.
Periodic joint radiographs are a useful way of evaluating disease progression.