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Rheumatoid Arthritis

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement. RA with symptom duration of fewer than six months is defined as early, and when the symptoms have been present for more than months, it is defined as established.[1][2][3]

There is no labortaory test that is pathognomonic for rheumatoid arthritis. The treatment of patients with rheumatoid arthritis requries both pharmacological and non-pharmacological agents. Today, the standard of care is early treatment with disease modifying anti-rheumatic drugs.

Etiology

The etiology of RA remains unknown. It is thought to result from the interaction between patients genotype and environment. Twin studies have shown a concordance rate of 15% to 30% among monozygotic twins and 5% among dizygotic twins. The heritability of rheumatoid arthritis is approximately 40% to 65% for seropositive rheumatoid arthritis and 20% for seronegative rheumatoid arthritis. The risk of developing rheumatoid arthritis has been associated with HLA-DRB1 alleles: HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a stretch of conserved five amino acid sequence, the shared epitope (SE), in the third hypervariable region of their DRB1 chain, which has been associated with the risk of developing RA.[4][5][6]

It has been suggested that polymorphism in signaling transducers and activators of transcription (STAT)-4 and interleukin (IL) -10 genes also confer susceptibility to RA. Single nucleotide polymorphism (SNP) in PSORS1C1, PTPN2 and MIR 146 A genes are associated with severe disease.

The term epigenetics refers to heritable changes without altering the DNA sequence; these changes may be present in chromatin or the DNA. These include DNA methylation, histone modification, noncoding RNA-mediated regulation. RA-FLS (fibroblast-like synoviocytes) overexpress tyrosine phosphatase SHP-2, coded by gene PTPN11 as compared to synoviocytes from osteoarthritis (OA) patients and this promotes invasive nature of RA-FLS. Enhancer region of the PTPN11 intron contained two hypermethylated sites, resulting in abnormal epigenetic regulation of the gene and alteration of function of RA-FLS.

Cigarette smoking is the strongest environmental risk factor associated with rheumatoid arthritis. Studies have shown

in ACPA (anti-citrullinated protein antibody) positive individuals; there is an interaction between genes and smoking that increases the risk of RA.

Changes in the composition and function of intestinal microbiome have been related to rheumatoid arthritis. The composition of gut microbiome is altered in patients with rheumatoid arthritis (dysbiosis), rheumatoid arthritis patients have decreased gut microbiome diversity when compared with healthy individuals. There is an increase in these genera: *Actinobacteria, Collinsella, Eggerthalla, Faecalibacterium*. *Collinsella* alters gut mucosal permeability and has been related with increased rheumatoid arthritis disease severity.

Epidemiology

Incidence rates of RA are higher in northern Europe and North America compared with southern Europe. Incidence is 29 cases/100,000 in northern Europe, 38/100,000 in North America, and 16.5/100,000 in southern Europe. In North America and northern Europe, RA affects 0.4% to 1% of the population, in southern Europe, it affects 0.3% to 0.7% of the population. Female to male ratio is 2-3:1 and the prevalence of RA increase with age.[7][8]

Pathophysiology

Rheumatoid arthritis patients contain antibodies to citrullinated proteins. Citrulline is an amino acid generated by post-translational modification of arginyl residues by peptidyl arginine deaminases. These antibodies are called anti-citrullinated protein antibodies (ACPA). ACPA can be IgG, IgM, or IgA isotypes. ACPA can bind citrullinated residues on self-proteins like vimentin, fibronectin, fibrinogen, histones and type 2 collagen. Binding of antibodies to proteins leads to complement activation. The presence of antibodies in rheumatoid arthritis is associated with severe disease, joint damage and an increase in mortality. ACPA can be present in the serum up to 10 years before the onset of clinical symptom, with time concentration of ACPA and serum cytokine level increases.

The synovium in rheumatoid arthritis is infiltrated by immune cells which include innate immune cells (monocytes, dendritic cells, mast cells) and adaptive immune cells (Th1 (T helper 1), Th17 (T helper 17), B cells and plasma cells. Cytokines and chemokines like tumor necrosis factor (TNF), interleukin-6 (IL-6), granulocyte-monocyte colony stimulating factors activate endothelial cells and attract immune cells within the synovial compartment. The fibroblast in the rheumatoid synovium changes to an invasive phenotype. Fibroblast and inflammatory cells lead to osteoclast generation resulting in bone erosion the hallmark feature of rheumatoid arthritis.[9]

Histopathology

During the early phase of the disease, influx of inflammatory cells into the synovial membrane is obvious. As the disease progresses, there is a proliferation of monocytes and thickening of the synovial membrane with small villous projections into the joint space. Rheumatoid nodules initially have small vessel vasculitis phenomenon followed by a chronic inflammatory granulomatous phase.

History and Physical

Most common clinical presentation of RA is polyarthritis of small joints of hands: proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints and wrist. Some patients may present with monoarticular joint involvement. Most commonly joint involvement occurs insidiously over a period of months, however, in some cases, joint involvement may occur over weeks or overnight. Other commonly affected joints include wrist, elbows, shoulders, hips, knees, ankles and metatarsophalangeal (MTP) joints. Stiffness in the joints in the morning may last up to several

hours, usually greater than an hour. The patient may have a "trigger finger" due to flexor tenosynovitis.

On examination, there may be swelling, stiffness, deformity, and tenderness of the PIP, MCP wrist, knee joints, referred to as synovitis, and there may be a decreased range of motion.

Rheumatoid nodules may be present in 20% of patients with rheumatoid arthritis; these occur over extensor surfaces at elbows, heals, and toes.

Late in the course of the disease patient may present with "boutonniere (flexion at PIP and extension at DIP), swan neck (flexion at DIP and extension at PIP) deformities, subluxation of MCP joints and ulnar deviation.

Other features may include the presence of carpal tunnel syndrome, tenosynovitis and finger deformities.

Rheumatoid arthritis can affect almost every organ in the body.

Evaluation

Lab evaluation of patients with rheumatoid arthritis consists of obtaining rheumatoid factor (antibody against the Fc portion of IgG). About 45% to 75% of patients with rheumatoid arthritis test positive for rheumatoid factor. However, the presence of rheumatoid factor is not diagnostic of rheumatoid arthritis. It may be present in connective tissue disease, chronic infections, and healthy individuals, mostly in low titers. Anti-citrullinated protein antibodies (ACPA) are found in about 50% of patients with early arthritis, which subsequently are diagnosed with rheumatoid arthritis. Acute-phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be elevated in the active phase of arthritis.

X-ray of both hands and feet are usually obtained for the presence of erosions, the pathognomonic feature of rheumatoid arthritis, however, plain radiograph does not show early changes of the disease. Magnetic resonance imaging (MRI) and ultrasound (USG) of joints detect erosions earlier than an x-ray. MRI and USG are more sensitive than clinical examination in identifying synovitis and joint effusion.[10][11][12]

Treatment / Management

A strategic approach is followed when managing rheumatoid arthritis, disease activity is assessed at regular intervals and treatment is changed as per the disease activity. Disease-modifying, anti-rheumatic drugs (DMARDs) are initiated as soon as the diagnosis of rheumatoid arthritis is made. Traditional or conventional DMARD include methotrexate, leflunomide, sulfasalazine, hydroxychloroquine. Biologic DMARDs include TNF (tumor necrosis factor): Adalimumab, Etanercept, Infliximab, Golilumab, Certolizumab. And non-TNF inhibitors: Tocilizumab (Interleukin-6 inhibitor), Abatacept (inhibits T-cell costimulation), Rituximab (anti-B cell).[13][14][15]

Disease activity is defined as low, moderate, or high. This is based on validated scales which are obtained from the tender joint count, swollen joint count, global patient assessment, physician global assessment, and/or maker of inflammation. These are:

- Simplified disease activity (SDAI) index: tender joint count, swollen joint count, patient global assessment, physician global assessment and c reactive protein in mg/dl
- Clinical disease activity index (CDAI): tender joint count, swollen joint count, patient global assessment, physician global assessment

- DAS28-ESR (disease activity score): tender joint count, swollen joint count, patient global assessment, and erythrocyte sedimentation rate in mm
- DAS-Crp (disease activity score): tender joint count, swollen joint count, patient global assessment, and c reactive protein in mg/dl.

According to the American College of Rheumatology, 2015 recommendations for the treatment of early (symptoms duration less than 6 months) RA include initiation of DMARD monotherapy (methotrexate is the preferred DMARD). It is recommended to use monotherapy over double or triple therapy. Along with methotrexate, glucocorticoids may be used as bridge therapy, usually for a period of three months when the DMARD becomes effective. If the disease activity remains moderate or high, despite the use of DMARD monotherapy, then to use a combination of DMARD which can be either traditional DMARD, TNF inhibitors or non-TNF inhibitors. For disease flares to use short-term glucocorticoids at the lowest dose for the shortest duration.

For the management of established rheumatoid arthritis (symptoms present for greater than six months), for a patient who has never taken a DMARD to use DMARD monotherapy (methotrexate is the preferred DMARD), to use monotherapy over double or triple therapy. If the disease activity remains moderate or high, despite the use of DMARD monotherapy, then to use a combination of DMARD: traditional DMARD, TNF inhibitors, or non-TNF inhibitors.

If the patient has used TNF inhibitor and the disease activity remains moderate or high despite the use of single TNF inhibitor then to use the non-TNF inhibitor biologic, this can be with or without methotrexate. Similarly, if a patient has failed two or multiple TNF inhibitors, use the non-TNF inhibitor biologic, with or without methotrexate. If using a non-TNF inhibitor is not feasible then to use tofacitinib with or without methotrexate.

For patients with congestive heart failure, avoid TNF inhibitor and use non-TNF inhibitor biologic, as TNF inhibitors may worsen the symptoms of congestive heart failure.

For patients with active hepatitis B infection who are receiving concomitant antiviral therapy, immunosuppressive medications may be used safely. For hepatitis B patients with immunity from prior exposure (hepatitis core antibody positive, normal liver function tests, hepatitis B surface antibody positive and hepatitis B surface antigen negative), can be treated similarly to unexposed patients, on a condition that viral load is regularly monitored.

For patients with hepatitis C infection who are receiving antiviral therapy to be treated like RA patients without hepatitis C.

For a patient with melanomatous and non-melanomatous skin cancer, to use DMARD over biologics. For patients with previously treated lymphoproliferative disorder to use rituximab over TNF inhibitors or to use DMARD in combination with abatacept or tocilizumab over TNF inhibitors. For previously treated solid organ malignancy to treat these patients as those without these conditions. For previous serious infections to use a combination DMARD over TNF inhibitors or to use abatacept over TNF inhibitors.[16]

Differential Diagnosis

- Lupus
- Chronic Lyme disease
- Osteoarthritis

- Septic arthritis
- Psoriatic arthritis
- Sjogren syndrome
- Sarcoidosis

Staging

Disease progression:

Stage 1: No destructive changes on x-rays

Stage 2: Presence of x-ray evidence of periarticular osteoporosis, subchondral bone destruction but no joint deformity

Stage 3: X-ray evidence of cartilage and bone destruction in addition to joint deformity and periarticular osteoporosis.

Stage 4: Presence of bony or fibrous ankylosis along with stage 3 features.

Prognosis

Rheumatoid arthritis has no cure and is a progressive disease. All individuals have multiple exacerbations and remissions. Close to 50% of patients with the disease become disabled within 10 years. Besides the joint disease, the individuals can suffer from many extra joint related problems which significantly alters the quality of life. However, the progression of disease does vary from individual to individual. In general, the following factors determine worse prognosis:

- Elevated serum titer of autoantibodies
- Presence of HLA-DRB1*04 genotype
- Involvement of many joints
- Extra-articular features
- Female gender
- Age of less than 30
- Insidious onset
- Presence of systemic symptoms

Rheumatoid arthritis is also associated with cardiovascular risk factors, infection, respiratory disease and development of malignancies. Patients with rheumatoid arthritis have 2-3 times higher risk of death compared to the general population.

Complications

- Infections
- Chronic anemia

- Gastrointestinal cancers
- Pleural effusions
- Osteoporosis
- Heart disease
- Sicca syndrome
- Felty syndrome
- Lymphoma

Consultations

- Rheumatologist
- Orthopedic surgeon
- Physical and occupational therapist
- Cardiologist
- Dentist
- Dermatologist
- Ophthalmologist

Enhancing Healthcare Team Outcomes

Rheumatoid arthritis is a chronic disorder that has no cure. All the currently available treatments are geared towards improving the symptoms and offering a better quality of life. Revealing the diagnosis of such a disabling disorder requires a team approach. In addition, one has to discuss the prognosis and types of treatment available. Patients need to be educated about the many misconceptions of the disease and be realistic.

Because the disorder affects many other organs, it is best managed with an interprofessional team. The key is patient education by nurses, pharmacists, and primary care providers. The nurse should inform the patient about the signs and symptoms of different organ systems and when to seek medical care. The patient should enroll in an exercise program to recover joint function. An occupational therapy consult can help the patient manage daily living activities. The pharmacist should educate the patient on types of drugs used to treat rheumatoid arthritis and their potential side effects.

At each clinic visit, clinicians and nurse should provide patient education and encourage the individual to stop smoking, maintain a healthy body weight, get the recommended vaccinations and eat a healthy diet.

The social worker should be involved in ensuring that the patient's home is liveable and the patient has ample support systems. The patient should be encouraged to join support groups.

Because the condition can lead to disability, chronic pain and a poor quality of life, many patients develop depression; hence a mental health nurse should see the patient regularly. Finally, the patient should not be offered false hopes but in

fact, a supportive environment where the quality of life can be improved.[17][18][19] (Level V)

Outcomes

The outcome of most patients with Rheumatoid arthritis is guarded. The disorder has frequent relapses and remissions, and at least 40% of patients will become disabled within ten years. While some patients do have mild disease, others may have a fulminant disease that severely affects the quality of life. Worse outcomes are usually seen in patients with a high titer of autoantibodies, HLA-DRB1 genotypes, age younger than 30, multiple joint involvement, female gender, and extra-articular involvement. In addition, the drugs used to treat rheumatoid arthritis also have potent side effects which often are not well tolerated. As the disease progresses, many patients will develop adverse cardiac events leading to death. The overall mortality in patients with rheumatoid arthritis is three times higher than in the general population. Despite advances in care, mortality from infection, cancer, and ongoing vasculitis remains unchanged.[20][21] (Level V)

Questions

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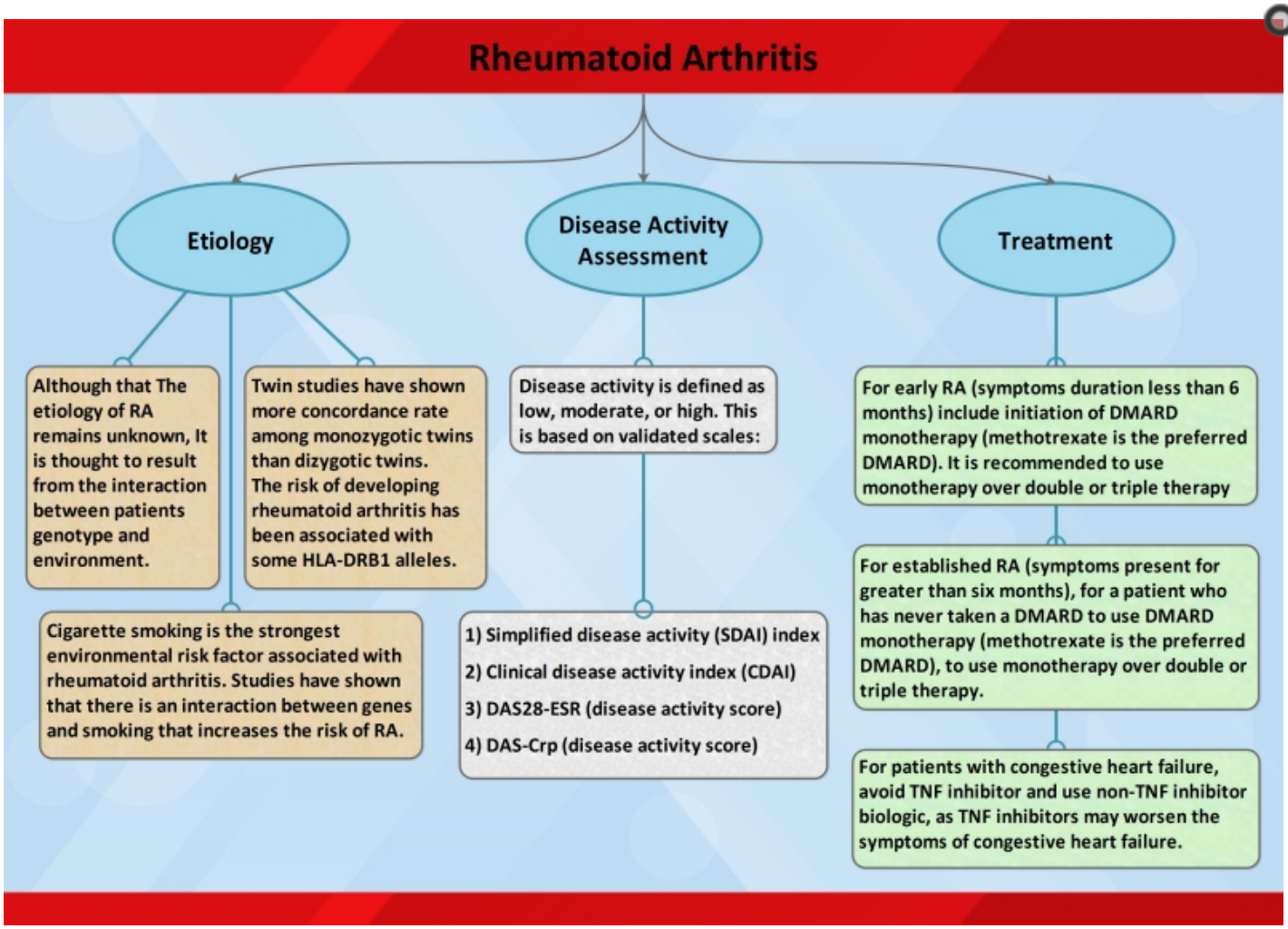
Figures



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