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R E V I E W A R T I C L E

Review on Clinical features and Diagnosis of Rheumatoid arthritis

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A B S T R A C T

Rheumatoid arthritis is an autoimmune disease caused by chronic inflammation of unknown etiology makedby symmetric, peripheral polyarthritiswhich results in joint damage & physical disability. It is a progressive disease of synovial lining of peripheral joints characterized by symmetrical inflammation leading to potentially deforming polyarthritis. It is the most common systemic inflammatory disease characterized by symmetrical joint involvement. Extraarticular involvement, including rheumatoid nodules, vacuities, eye inflammation, neurologic dysfunction, cardiopulmonary disease, lymphadenopathy, and splenomegaly, can be manifestations of the disease. The joints affected most frequently by rheumatoid arthritis are the small joints of thehands, wrists, andfeet. In addition elbows, shoulders, hips, knees, and anklesmaybe involved. The pathogenetic advances described herein have paralleled the introduction of new, effective therapies and remarkable improvement in clinical outcomes.

Keywords: Rheumatoid arthritis, Inflammation, Joints, Poly arthritis, Autoimmune

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease. It causes joints to swell and can result in pain, stiffness, and progressive loss of function. In addition to joint pain and stiffness, people with RA may also have symptoms such as weight loss, low-grade fever, and fatigue. RA often affects pairs of joints (both hands, both feet, etc) and can affect more than one joint, including the small joints in the wrists and hands. Over time, other joints can be affected such as shoulders, elbows, knees, feet, and ankles. The pain, fatigue, and disability associated with RA result in a

significant reduction in health-related quality of life. Additionally, RA imposes a substantial economic burden upon patients, due to both increased cost of medical care and loss or reduction of employment, frequently during peak working years[1]. Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia ("swelling"), autoantibody production (rheumatoid factor and anti–citrullinated protein antibody [ACPA]), cartilage and bone destruction ("deformity"), and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders. These clinical features pose critical mechanistic questions: What genetic– environmental interactions must occur to facilitate autoimmunity a priori, and why does this beget articular localization? Why does synovial inflammation perpetuate? What drives local destruction leading to joint dysfunction? Why does rheumatoid arthritis cause systemic illness? We herein summarize key pathogenetic advances informing these issues[2].

Fig 1: Difference between healthy joint and RA joint

Etiology of Rheumatoid arthritis (RA)

Many factors are influence the rheumatoid arthritis. They are detailed in below.

Gender: Women before the menopause are affected three times more often than men with an equal sex incidence thereafter suggesting an etiological role for sex hormones.

Familial: There is an increased incidence in those with a family history of RA.

Genetic factors: Human leucocyte antigen (HLA)-DR4 and HLA-DRB1* 0404/0401 confer susceptibility to RA and are associated with development of more severe erosive disease.

Environmental factors: A variety of environmental factors have been implicated as potential triggers for RA. Hormonal influences on RA in women have been an area of active research, given that RA occurs more often in women. For example, in a case-control study, oral contraceptive use was not associated with a reduced risk of RA; however, breastfeeding for 13 or more months was associated with a reduced risk of RA compared with never breastfeeding (odds ratio, 0.46; 95% CI, 0.24-0.91)[3].

Antigen dependent activation of T-Lymphocytes: Among the genetic factors linked to RA susceptibility are differences in human leukocyte antigen (HLA)-DRB1 alleles, especially in patients who are positive for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA).11 The presence of a common amino acid motif (QKRAA) in these alleles seems to be associated with a particular susceptibility to RA and is referred to as the shared epitope.9 There is also evidence of gene-environment interactions; for example, there is an increased incidence of RA in HLA-DRB1 individuals who smoke cigarettes.12 Chromosome 6, which contains the genes for HLA-DRB1, also contains genes that influence a number of immune processes, including modulation of tumor necrosis factor (TNF)[4,5].

2. Pathophysiology of RA

There are two major subtypes of RA according to the presence or absence of anti-citrullinated protein antibodies (ACPAs). Citrullination is catalyzed by the calcium-dependent enzyme peptidylarginine-deiminase (PAD), changing a positively charged arginine to a polar but neutral citrulline as the result of a post-translational modification[6]. ACPAs can be detected in approximately 67% of RA patients and serve as a useful diagnostic reference for patients with early, undifferentiated arthritis and provide an indication of likely disease progression through to RA. The ACPA-positive subset of RA has a more aggressive clinical phenotype compared to ACPA-negative subset of RA.10 It is reported that ACPA-negative RA has different genetic association patterns11 and differential responses of immune cells to citrullinated antigens12 from those of ACPA-positive subset. In terms of treatment, less effective treatment response of methotrexate (MTX) or rituximab was observed in ACPA-negative subset. This suggests a requirement for future study on potential pathophysiology difference between these two subsets[7]. For the purpose of this review, we will focus on the ACPA-positive subset of RA and divide the progression of RA process into several distinct stages. It is noteworthy to mention, however, that these stages may occur sequentially or simultaneously.

Clinical manifestations of RA

Clinical manifestations consist of pain, swelling, and tenderness of the small joints of the hands. It is very important to take a detailed history of the joint symptoms, particularly on the mode of onset, whether gradual or acute, the pattern of joints involved, and any variance in symptoms according to time of day. Since RA is a systemic disease patients may therefore have accompanying symptoms like as fever, weight loss, and fatigue[8].

Onset:

The most common form of presentation is gradual and insidious onset of joint pain and swelling occurring over weeks to months. Some patients may present with an abrupt explosive onset polyarthritis. Still others may present with transient self-limited episodes of mono- or polyarthritis lasting days to weeks. This presentation is known as palindromic rheumatism. RA is classically a polyarticular disease but occasionally it may present as a monoarthritis; in such a situation more familiar causes of monoarthritis should be always ruled out like infectious arthritis, gout, and spondyloarthritis[9].

Morning stiffness:

Morning stiffness (i.e. difficulty in moving around) lasting for 1 hour or more is a characteristic feature of RA. A similar phenomenon can occur if a patient is inactive for a period during the day. This is probably due to the accumulation of edema fluid within inflamed synovial

tissues during sleep. The morning stiffness dissipates as edema and products of inflammation are absorbed by lymphatic's and venules and returned to the circulation by motion accompanying the use of muscles and joints.

Joint involvement: The joints most commonly involved in RA are the wrists, small joints of the hands and feet, i.e the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints of the fingers, interphalangeal joints of the thumbs, and metatarsalphalangeal (MTP) joints are most commonly affected. Distinctively the distal interphalangeal (DIP) joints are spared. As the disease progresses, larger joints such as the ankles, knees, elbows, and shoulders frequently become affected. The thoracic, lumbar and sacral spine are nearly always spared in RA. However cervical spine involvement is not rare. Cervical spine involvement is seen in established RA. There can be atlantoaxial subluxation, which manifests as neck pain, but passive range of movement of the cervical spine is often normal. The most dreaded complication of atlantoaxial subluxation is spaastic quadriparesis. The temporomandibular joint and sternoclavicular joints are also involved in varying proportions[10].

Pattern of arthritis: RA is a polyarthritis. Joint involvement is classically bilateral and symmetrical. The arthritis in RA is an "additive" form of arthritis, in that it is rare for symptoms to remit completely in one set of joints while developing in another. This is in contrast to rheumatic fever where the arthritis is migratory, in that symptoms in one joint subside completely before involving another. Asymmetrical joint involvement is seen when RA coexists with poliomyelitis, meningioma, encephalitis, neurovascular syphilis, strokes, and cerebral palsy. Joints on the paralyzed side are typically spared[11,12].

Physical examination: Patients with suspected or confirmed RA should undergo a thorough initial physical exam and the extent of articular and extra-articular involvement assessed. Patients should be followed every 2 to 4 months henceforth to monitor disease activity and response to treatment, the frequency depending upon the severity of the disease and the medication regimen. Joint examination reveals symmetrical swelling and tenderness of the joints. While palpating the joint, focus should be on the joint line to detect fullness and synovial tissue swelling (synovitis). This is important because the joint swelling could due to bony enlargement (hypertrophy) which is seen in osteoarthritis. Joint swelling is often confined to the joint capsule. While looking for joint swelling one must also look for joint tenderness, the range of motion of each joint, and any deformities of the joints. The presence of joint deformity, decreased range of motion, or mal-alignment suggests that the joint is damaged.

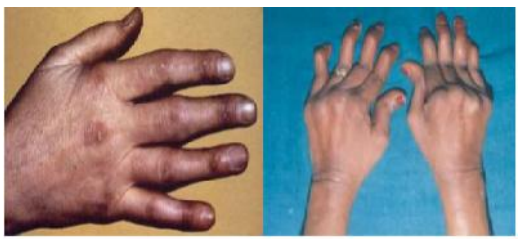

Fig 2: Hands of RA patients

Synovitis of the wrists and elbows is easy to appreciate. In advance stages of RA, there can be deformities like hyper flexion of the PIPs (boutonniere deformity), or hyperextension of the PIPs and flexion of the DIPs (swan neck deformity). Other deformities include ulnar deviation of the fingers and subluxation of the MCP joints. There can also be loss of full extension of the elbow and loss of flexion of the wrist. These deformities are less commonly seen these days because of early diagnosis and treatment. Physical examination of the MTPs in early disease reveals tenderness when the foot is squeezed. In more chronic disease, dorsal subluxation of the MTPs resulting in cock-up toe deformities, and hallux valgus (bunion) are commonly seen[13].

Extra-articular manifestations/complications of RA

Eye: The most common extra-articular manifestation of RA is Sjögren's syndrome, manifested by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), and occurring in approximately 23 - 35% of patients. Keratoconjunctivitis sicca (KCS) reflects lacrimal gland pathology and it is the most common ophthalmic manifestation of RA, occurring in up to 25% of patients. The cornea is involved secondarily to decrease tearing. Both episcleritis and scleritis can occur in RA. While episcleritis is benign, scleritis has a more ominous prognosis with respect to ocular morbidity and in some series is associated with more serious extra articular manifestations. These manifestations need to be detected early and managed accordingly in consultation with an ophthalmologist[14].

Rheumatoid nodules: Rheumatoid nodules are firm, non-tender swellings, which develop over extensor surfaces of the body especially the elbows, and are frequently adherent to the underlying periosteum. They occur in about 25% of established RA patients. They develop over pressure areas of the body most notably the elbows, Achilles tendons, fingers, scalp, and sacral areas. Patients with rheumatoid nodules are usually positive for rheumatoid factor (RF). Rarely, such nodules are present in the absence of obvious arthritis. A condition called rheumatoid nodulosis is characterized by the presence of multiple nodules on the hands, a positive test for RF, episodes of acute intermittent synovitis, and subchondral cystic lesions of small bones of the hands and feet.

3. Pulmonary disease

There are six recognized pattern of lung disease in RA. They are;

- Pleural disease
- Pulmonary fibrosis
- Nodules in the lung
- Bronchiolitis obliterans with organizing pneumonia
- Arteritis, with pulmonary hypertension
- Small airway disease

Pleuritisis a well-known manifestation of RA. It is commonly found on autopsy of patients with RA, but clinical disease during life is seen less frequently. Pleural effusions can sometime be significant to cause dyspnoea. Pleural effusions and pleurisy can be bilateral in up to 25% of the cases. The pleural fluid is exudative, with WBC

count ranging from 100 to 3500 cells/dL, which is lymphocytic predominant, low glucose, and high lactate dehydrogenase. The low glucose concentrations are of interest. Sepsis (particularly tuberculosis) is the only other condition that commonly has such a low pleural fluid glucose level. An impaired transport of glucose into the pleural space seems to be the cause of this. Pulmonary fibrosis can occur in RA, and is slowly progressive and the prognosis is not that bad when compared to idiopathic pulmonary fibrosis. The findings on auscultation of the lungs are fine, diffuse, dry rates. Plain radiographs of the chest show a diffuse reticular (interstitial) or reticulonodular pattern in both lung fields. Diagnosis is made by high resolution computed tomography (HRCT) scans of the chest which reveal usual interstitial pattern pneumonia. Pulmonary rheumatoid nodules may appear single or multiple and they can activate[15,16]. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure. Small airway disease characterized by reduced maximal midexpiratory flow rate is not uncommon in RA. Clinically asymptomatic mild pulmonary hypertension can be seen on transthoracic echocardiogram in up to 30% RA patients. Other rare lung manifestations are bronchiolitis.

Cardiac disease:

The most common cardiac manifestation is pericardial effusion and pericarditis, which is asymptomatic and is mostly found only on autopsies. It is increasingly recognized that the most common cause of death in patients with RA is cardiovascular disease. Patients with RA have a higher incidence of fatal and nonfatal cardiovascular events (myocardial infarction and stroke) than the general population, presumably due to accelerated atherosclerosis from chronic systemic and vascular inflammation. Congestive heart failure is also more common in RA patients than in the general population[17].

Renal disease:

Primary renal involvement by RA is unusual. However secondary amyloidosis can occur in longstanding RA.

Hematologic manifestations:

The most common hematologic abnormality is normocytic normochromic anemia. Although the cause of anemia is multifactorial, the most common cause is inflammation induced anemia of chronic disease. Another important cause of anemia is iron deficiency anemia, probably due to NSAIDs induced gastrointestinal blood loss.

Vascuities:

Small and medium vessel vasculitis is relatively uncommon complication of RA. Typically it occurs in patients with long-standing, erosive and seropositive RA. The organs involved are skin, digits, cardiac muscle, peripheral nerves and CNS leading to cutaneous ulcers, gangrene and necrosis of the digits, mononeuritis multiplex, pericarditis and coronary vasculitis. Patients can also have weight loss, fever, and fatigue. Perhaps the most common manifestation of vasculitis is nail fold infarcts, and splinter hemorrhages. Systemic rheumatoid vasculitis is a feared complication of RA.

Diagnostic investigations of RA

Routine blood investigations:

At initial patient evaluation complete blood count including ESR, liver function tests, kidney function tests, and CRP should be done. Anemia of a normocytic normochromic picture is seen in 25% patients, as mentioned above. The kidney function tests and liver function tests are usually normal. If the liver function tests are abnormal it suggest the presence of a concomitant disease process, and this may preclude the use of methotrexate (MTX) and leflunomide (LF). Abnormal kidney functions will warrant caution in the use of NSAIDs. Sometime serum albumin can be low, which is a sign of on-going systemic inflammation[18]. There can also be increased gamma globulin production by B cells (hypergammaglobulinemia), leading to elevated serum levels of non-albumin protein (socalled protein gap or gamma gap).

ESR and CRP:

ESR and CRP are the two most important biomarkers of inflammation in RA. These markers are usually elevated in RA patients with active disease and decline with treatment. High ESRand CRP at the onset of disease are predictive of more aggressive disease and potentially worse prognosis. The inflammatory markers ESR and CRP along with the patients' symptoms, the number of swollen joints, the number of tender joints are incorporated in to a score called as disease activity score (DAS) and is very useful to monitor disease activity over time.

Rheumatoid factor (RF):

RF are antibodies against the Fc portion of IgG and can be of any immunoglobulin subclass (IgA, IgG, and IgM) but are most commonly IgM. RFs can be estimated in the laboratory by enzyme-linked immune absorbent assay (ELISA), or by nephelometry or by latex fixation. The cut off value for a positive RF varies depending on the methodology used in the local laboratory, but a common cutoff point is greater than 45 IU/mL ELISA or laser nephelometry, or greater than a titer of 1:80 by latex fixation. RF is detectable during the course of disease in approximately 75% to 85% of patients with RA. RF is approximately 69% sensitive and 85% specific for the diagnosis of RA[19]. The result of a positive RF should be carefully interpreted in the light of clinical findings. RF in low titres is positive in elderly individuals, in chronic infections like chronic hepatitis C and bacterial endocarditis, cryoglobulinemia, primary biliary cirrhosis. RF is also positive in other rheumatic diseases. High titres of RF are associated with aggressive, destructive joint disease and extra-articular complications of RA, such as interstitial lung disease and rheumatoid vasculitis.

Anti-citrullinated peptide antibodies (ACPA):

ACPA are antibodies directed against the citrullinated residues of proteins. Citrulline is a non-naturally occurring amino acid generated by de-amination of arginine residues on proteins by enzymes called peptidylarginine deiminases. Deiminated recombinant fillagrin protein in cyclic form is a particularly useful substrate to detect these auto antibodies. Newer assays detect non-cyclic citrullinated peptides. ACPA are commonly detected in the laboratory by ELISA. They are more specific than RF for diagnosis of early RA. Their sensitivity is 70% and specificity approaches 96% for

diagnosis of established RA. They have also been found to be present in the sera at least 10 years before the diagnosis of RA. The presence of high titres of ACPA in sera of patients with RA predicts a more erosive joint disease and radiographic joint destruction.

Radiology: Plain radiographs of the hands, wrists, and feet posterior anterior (PA) view should be obtained at baseline in patients with RA, and can be repeated periodically to ensure that additional damage is not occurring in the face of apparently effective treatment. The earliest change on radiographs of the hands and feet is periarticular osteopenia. More typical changes of RA are juxta-articular bony erosions and symmetrical joint space narrowing. Erosions usually begin at the bare area of the joint not covered by cartilage, such as the intracapsular articular margins. Bony erosions often begins very early (in the 1st year) and progresses rapidly within the first years from symptoms onset if disease activity is not controlled effectively.Late radiographic findings include subluxation and loss of joint alignment, due to bone and cartilage destruction and also due to laxity of the ligaments and tendons surrounding the joint[20].

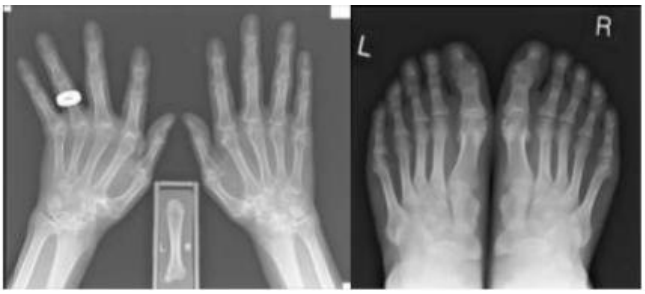

Fig 3: Radiographs of hands and feet showing typical features

Pharmacological therapy of RA

Disease-modifying antirheumatic drugs (DMARDs):

Commonly used are methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. The biologic agents that have disease-modifying activity.

Anti-Cytokine Agents:

Anti-TNF drugs include etanercept, infliximab, adalimumab

IL-1 receptor antagonist anakinra:

Costimulationmodulator, abatacept, and rituximab, which depletes peripheral B cells.

Immunosuppressive Therapy:

Less frequently used, azathioprine, D-penicillamine, gold (including auranofin), minocycline, cyclosporine and cyclophosphamide. This is due to either less efficacy, high toxicity, or both.

Combination therapy with two or more DMARDs may be effective:

Cyclosporine+methotrexate, methotrexate+sulfasalazineand hydroxychloroquine.

Glucocorticoids (lowdose): Prednisone

4. Conclusion

RA, a common autoimmune disease, is associated with inflammation and swelling of the synovium of the joint and, if left untreated, often results in destruction of both the bony and cartilaginous elements of the joint and resultant disability. Severe disease manifestations, such as vasculitis, nodule formation, scleritis, and amyloidosis, that are associated with persistent, uncontrolled inflammation have become rare. The clinical diagnosis of RA is largely based on signs and symptoms of a predominantly symmetrical inflammatory arthritis with involvement of hands and feet, with laboratory and radiographic results to support the diagnosis.Any discussion of rheumatoid arthritis will be limited by space, as it is the prototypic autoimmune disease. It is in many ways the crossroadof autoimmunity.

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