Rheumatoid Arthritis

Module –I

Clinical Features and Diagnosis

Dr Ved Chaturvedi MD, DM
Senior Consultant Rheumatologist, Army Medical Corps
President, Indian Rheumatology Association

Dr Vinod Ravindran MD, FRCP
Assistant Professor of Rheumatology
MES Medical College, Perinthalmanna, Kerala

Dr Molly Thabah MD
Assistant Professor of Medicine
JIPMER, Puducherry
Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects mainly the small joints of the hands and feet. RA is one of the most common inflammatory joint diseases and causes premature mortality, disability and compromised quality of life.

Burden of RA

RA is widely prevalent throughout the world. The overall worldwide prevalence is 0.8% and steadily increases to 5% in women over the age of 70. RA is two to three times more common in women compared to men. In India the prevalence has been estimated to be 0.7%.

Basic pathology

The inflammatory process primarily affects the lining of the synovium, in contrast to osteoarthritis which primarily involves the cartilage. The inflamed synovium leads to erosions of the cartilage and bone and if the inflammatory process is unchecked leads to joint deformity.

Clinical (Articular) Manifestations

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.

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.

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 lymphatics 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 spastic quadriparesis. The temporomandibular joint and sternoclavicular joint are also involved in varying proportions.

**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 paralysed side are typically spared.

**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.

**Hand joints in early and established RA [Figures]**

Synovitis of the wrists and elbows is easy to appreciate. In advance stages of RA, there can be deformities like hyperflexion 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.

Shoulder synovitis can be difficult to assess because the joint lies deep and is covered by muscle. But there can be painful range of motion. Similarly hip joint involvement is difficult to examine clinically. Knee joint effusion is commonly observed in RA.

Large knee effusions may herniate posteriorly, creating a popliteal (Baker’s) cyst that can dissect or rupture into the calf, causing calf pain, swelling, pitting edema, which closely mimic deep venous thrombosis but ultrasonography can differentiate the two entities. Synovitis in the ankle may be due to inflammation in the tibiotalar joint (which mediates flexion and extension) or in the joints of the hind foot (which mediate inversion and eversion of the ankle). Range of motion of the tibiotalar joint is usually fairly well preserved early on, while diminished inversion and eversion are more common.
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.

The cervical spine involvement in RA causes headache, neck pain, giddiness, paraesthesias, weakness, and bowel bladder symptoms. The development of any of these clinical manifestations in patients with RA warrants a neurological examination followed by an MRI to look for anatomical derangements of the cervical spine. Among the joints of the cervical spine the atlanto-axial joint is most prone to subluxation. Chronic synovitis may result in bony erosion and ligamentous laxity that result in instability and subluxation. Risk factors for development of cervical subluxation include older age at onset of RA, longer duration of RA, active synovitis, high CRP, and early peripheral joint subluxations.

**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.

**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.
Cutaneous vasculitis and episcleritis and scleritis (Figures)

Pulmonary disease

There are six recognized patterns 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

Pleuritis is 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 sometimes 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 rales. 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 cavitate. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure.

Small airway disease characterised 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 recognised 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.

**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.

Another hematologic abnormality associated with RA is thrombocytosis.

**Felty syndrome**
This syndrome consists of RA, neutropenia, splenomegaly and occasionally anemia and thrombocytopenia. Felty syndrome is an uncommon complication of RA and occurs in about 1% of RA patients. It occurs typically in patients with longstanding disease. It also is associated with erosive, deforming disease, high RF, high ESR and the presence of other extra articular manifestations like subcutaneous nodules and vasculitis.
Neutropenia (absolute neutrophil count below 2000/µL) is asymptomatic, it is often incidentally detected during routine blood counts. Bone marrow examination usually reveals moderate hypercellularity with a paucity of mature neutrophils. The diagnosis of Felty’s syndrome may be masked in patients who present with infection, because active bacterial infection can raise the white blood cell count to a normal or even slightly elevated level; the neutropenia typically reappears within a short time after successful treatment of the infection. Other causes of neutropenia and splenomegaly like drug induced neutropenia, lymphoma, amyloidosis, HIV infection, should be ruled out.

**Vasculitis**

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.

**INVESTIGATIONS**

**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. There can also be increased gamma globulin production by B cells (hypergammaglobulinemia), leading to elevated serum levels of non-albumin protein (so-called 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 ESR
and 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 immunoabsorbent 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. 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 begin very early (in the 1st year) and progresses rapidly within the first years from symptoms onset if disease activity is not controlled effectively.

**Radiographs of hands and feet showing typical features (Figures)**

![Radiographs](image)

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.

**DIAGNOSIS AND CLASSIFICATION CRITERIA**

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. The Revised 1987 American Rheumatism Association now the American College of Rheumatology (ACR) Criteria for the classification of RA in **table-1**, basically captures all the clinical features of established RA.

In the past 15-20 years, there has been a better understanding of the pathophysiology of RA. This has resulted in the use of agents that target cytokines such TNF-alpha, interleukin-1, interleukin-6, B cell and the co-stimulatory molecule which has revolutionized RA therapy. It is also understood that damage to the joint appears in the first 2 years.

- Therefore early diagnosis and treatment are important.
• The therapeutic window of opportunity is estimated to be at 1st two years of disease onset.
• Several landmark clinical trials have shown that early intervention leads to improved patient outcomes.
• The use of disease-modifying anti-rheumatic drugs (DMARDs) in combination is highly effective.

In the light of all these advancements, in 2010 a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy (Table-2).

The criteria consists of 4 domains including the types of joints involved, presence of auto-antibodies, laboratory markers of inflammation (ESR and CRP), and symptom duration. Application of the newly revised criteria yields a score of 0–10, patients are considered to have definite RA if they have a score of 6.

The new classification criteria differ in several ways from the older criteria set. The new criteria include a positive test for serum ACPA, which is more specific for RA diagnosis. The new criteria do not include rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA.

To summarize the ACR/EULAR 2010 classification criteria are target early RA diagnoses. Patients with long-standing disease who previously satisfy the 1987 criteria but currently have inactive disease or have erosions on radiographs will still be classified as having RA.

**Differential diagnosis**

The most common causes of symmetrical inflammatory polyarthritis that may be confused with RA are the other systemic connective tissue disorders like systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, psoriatic arthritis, and Sjögren’s syndrome. Viral induced arthritis can also present with symmetrical polyarthritis of short duration. The RF is often positive in very high titres in Sjögren’s syndrome. Chronic hepatitis C should also be ruled out. The skin should also be examined carefully for psoriasis.
Source

Table-1. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1 Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement</td>
</tr>
<tr>
<td>2 Arthritis of 3 or more joint areas</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 left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints</td>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>5 Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular 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/she has satisfied at least 4 or these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded.

### Table-2. 2010 Rheumatoid Arthritis Classification Criteria.

<table>
<thead>
<tr>
<th>Target population (Who should be tested?): Patients who</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. have at least 1 joint with definite clinical synovitis (swelling)*</td>
<td></td>
</tr>
<tr>
<td>2. with the synovitis not better explained by another disease</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥6/10 is needed for classification of a patient as having definite RA)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td><strong>Joint involvement</strong> *</td>
</tr>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2- 10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>Serology (at least 1 test result is needed for classification)#</strong></td>
</tr>
<tr>
<td>Negative RF and ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF or low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF or high positive ACPA</td>
<td>3</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td><strong>Acute-phase reactants (at least 1 test result is needed for classification)</strong></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td><strong>Duration of symptoms</strong></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt;6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

* Large joints refer to shoulders, elbows, hips, knees, and ankles. Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

# Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.