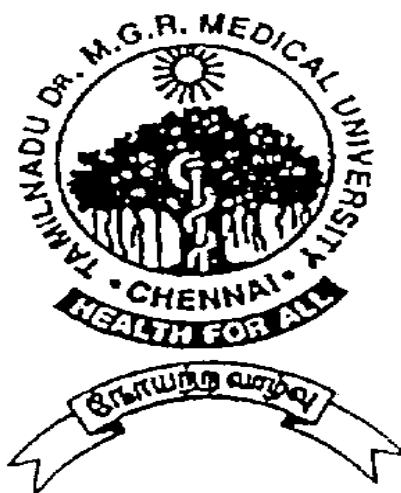


CLINICAL PROFILE OF RHEUMATOID ARTHRITIS

**M.D. – DEGREE EXAMINATION
BRANCH-I – GENERAL MEDICINE
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CERTIFICATE

This is to certify that the dissertation titled “**CLINICAL PROFILE OF RHEUMATOID ARTRITIS**” is the Bonafide original work of **Dr. B.SIVASUBRAMANIAM** in partial fulfillment of the requirement for M.D. Branch –I (General Medicine) examination of The Tamil Nadu Dr. M. G. R. Medical University to be held in March 2007. The period of study is from June 2005 to March 2006.

Prof. Dr S.Natarajan. M.D.
Prof. and Head of the Department
Department of Medicine
Govt. Stanley Medical College Hospital
Hospital

Prof. Dr. A.K. Geetha Devi M.D.
Professor of Medicine
Department of Medicine
Govt. Stanley Medical College

DEAN

Govt. Stanley Medical College Hospital
Chennai 600001

DECLARATION

I **Dr. B. SIVASUBRAMANIAM**, solemnly declare that the dissertation titled, “**CLINICAL PROFILE OF RHEUMATOID ARTRITIS**” was done by me at Govt. Stanley Medical College and Hospital during 2005 – 2006 under the guidance and supervision of my unit chief **Prof. Dr. A.K. GEETHA DEVI, M.D.**

The dissertation is submitted to Tamil Nadu Dr. M.G.R Medical University towards the partial fulfillment of requirement for the award of M.D Degree (Branch – I) in General Medicine.

Dr. B. SIVASUBRAMANIAM

Place:

Date:

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ANNEXURE

i) MASTER CHART

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of unknown cause. The characteristic feature of RA is persistent inflammatory synovitis usually involving the peripheral joints in a symmetric fashion. The hallmark of the disease is cartilage damage and bone destruction¹. Rheumatoid arthritis is the most common inflammatory arthritis, affecting 0.5% to 1% of general population worldwide. Because of its prevalence and ready accessibility of joint samples for laboratory investigation, rheumatoid arthritis has served as a useful model for the study of all inflammatory and immune mediated disease.

Rheumatoid arthritis patients can present with variety of clinical features, various articular and extra articular involvement. They may result in various complications which can impair the physical function in these patients. Pain in affected joints, aggravated by movement, is the most common manifestation of established RA. Generalized stiffness is frequent and is usually greatest after periods of inactivity.

Rheumatoid arthritis does not involve the same type of joints in all patients. In general the number and severity of articular features vary with the duration and severity of the disease. Articular manifestations (AM) can severely affect the functional quality of an individual due to various deformities, such as “Z” deformity, Swan neck deformity, boutonnière deformity and hallux valgus¹.

The Extra articular manifestations (EAM) may be due to formation of immune complexes. EAM includes the involvement of skin, eye, serosa, lung, heart, kidney, nervous system. The extra articular manifestations also depend upon the duration of the disease. If the duration is more the severity is also more. EAM are also associated with excessive mortality, since they affect major organs.

In two-third of the patients, RA begins insidiously with constitutional symptoms such as fever, loss of appetite, fatigability and generalized weakness. This also makes the patients to abstain from day-to-day routine activities.

AIM

The aim of the study is:

- a) To identify and analyze the common presenting complaints of rheumatoid arthritis patients like loss of appetite, fever and fatigability.
- b) To assess the various joint involvement and extent of damage due to the disease process in patients with proven rheumatoid arthritis and it's severity with the duration of the disease.
- c) To document EAM in patients with proven rheumatoid arthritis and its significance with the duration and severity of the disease.
- d) To establish beneficial effects of disease modifying anti rheumatic drugs.

REVIEW OF LITERATURE

MEDICAL HISTORY

Initial description of Rheumatoid arthritis made depressing reading indeed. SIR William Osler wrote:

“ARTHRITIS DEFORMANS

once established the disease is rarely curable. Too after it is a slow, but progressive crippling of the joints, with a disability that makes the disease one of the most terrible of human afflictions.”

-W.Osler,1909

Medical historians disagree about the first references to Rheumatoid arthritis in lay and medical writings. Some have concluded that Rheumatoid arthritis described only recently as a clear cut entity, whereas others contrast that cause can be traced at least to 1600's. Sir Alfred Garrod, an English clinician and Geneticist first introduced the term Rheumatoid arthritis in 1876 to the description of symmetrical inflammatory arthritis.

Although the natural course of RA has changed minimally, the changing is in the understanding of pathophysiology and newer therapies that has become available.

EPIDEMIOLOGY

Prevalence of RA in most population is around 1%, though there are a few exceptions. For instance in china, the incidence of RA is lower (0.3%) and substantially high in certain groups like Pima Indians in North America (about 50%) whereas in India the prevalence is 0.6- 1%.

Age

The incidence increases with age, and sex differences diminish in the older age group. The onset is most frequent during the fourth and fifth decades of life², with 80% of all patients developing the disease between the ages of 35 and 50. The incidence of RA is more than six times greater than in 60 to 64 year old women compared to 18-24 year old women. Recent data indicate that the incidence of RA may be diminishing¹.

Gender

The ratio of female to male patients is 2:1 to 4:1. The basis of this gender difference is probably due to the effect of the hormone milieu and immune function.

ETIOLOGY AND PATHOGENESIS

Despite intensive work only modest progress has been achieved in determining the cause of RA. Clues have been provided by studies of immuno genetics of the Class II Major Histo compatibility complex loci and the usage of specific RF genes. The role of small molecule mediators of inflammation (e.g. Arachadonic acid metabolite), cytokines, growth factors, chemokines, adhesion molecules and matrix metallo proteinases (MMP's) have been defined.

The etiology of RA is due to a blend of environmental and genetic factors.

GENETIC FACTORS

Family studies indicate genetic predisposition. The highest risk of concordance of RA is noted in Twins who have two HLA-DRB1 alleles known to be associated with RA³. The most compelling evidence of genetic component is in monozygotic twins where the occurrence is 30 to 50 % when one twin is affected. 10% of patients with RA will have an affected first degree relative.

Pregnancy is associated with remission of the disease in the last trimester⁴. Similarly, Oral contraceptives use shown decrease in severity of the disease⁵.

HLA DR susceptibility

The structure of CLASS II surface molecules on antigen presenting cells is of great importance in the susceptibility and severity of RA. Initiation of certain T- Cells immune response is dependent in part on the presence or absence of particular MHC (DR) allelic products. The genetic link between HLA DR and RA is due to shared epitopes on the chains of DR that predispose to RA. The susceptibility epitopes are glutamine, leucine, arginine, alanine, and alanine- (QKRAA) a sequence found in HLA DR4 and DW16 where RA is more prevalent. The DR4 β chains with greatest association with RA are DR β *0401, DR β *0101, and DR β 1*402. QKRAA epitope also predicts the severity of established RA.

HLA DR 2, DR 3, DR 5, DR 7 associations are protective against the development of RA. In Asian Indian and Israeli Jews HLA DR 1 (in stead of DR4) is associated with the development of RA. HLA DQ alleles, DQ β 1*0301, *0302 are also associated with RA. Early aggressive disease is related to DR β *0401 and DR β , *0404. Slowly progressive disease is associated with DR β *0101.

The genes outside of the HLA complex also contribute to the development of RA. These include genes controlling the expression of the antigen receptor on T cells and both immunoglobulin heavy and light chains.

Immunoglobulins

The class II MHC associations primarily implicate cellular immune response in RA. Deficient galactosylation of immunoglobulins is a risk factor for the development of RA. There is reduced galactosyl- transferase activity in RA β cells.

Cytokine polymorphism and other genetic associations

Single nucleotide polymorphisms (SNP's) in the promoter region or coding regions have been investigated in RA. The former could lead to altered gene regulations due to variable binding of transcription factors to promoters, while the latter directly changes the amino acid sequence of the encoded protein.

Several polymorphisms of the TNF- α promoter can alter gene transcription. Polymorphism of chemokines and inflammatory mediators like IL-1, CCR 5 and RANTES are associated with susceptibility.

ENVIRONMENTAL

Smoking is clearly associated with development of RA. Several environmental stimuli, viruses including Retro viruses infect an individual with the appropriate genetic background and through some unknown mechanism the inflammatory response is focused in the joints. After gaining a toe – hold, there the synovitis persists because of local autoimmunity and other influences that enable the disease to become self perpetuating.

Epidemiologic studies in Africa have indicated that climate and urbanization have a major impact on the incidence and severity of RA in groups of similar genetic background.

Infectious agents

Infectious agents implicated are:

- a) Bacteria like protein and acinobactor
- b) Mycobacteria
- c) Mycoplasma and Chlamydia
- d) Borrelia Burdorferi
- e) Viruses

Ebstein Barr Virus has been indirectly implicated in the pathogenesis as well as the etiology of RA through the mechanism of molecular mimicry. Parvovirus B 19, Rubella, Cytomegalovirus and Lenti virus⁶ are also implicated in causing RA.

Chronic inflammatory response is produced by these organisms in the synovial tissues which lead to damage of the articular structures. The response to the micro organism might induce an immune response to components of the joint by altering its integrity and revealing antigenic peptides.

PATHOGENESIS

Auto immunity

RA is an autoimmune disease where synovial inflammation was mediated by local immune complex formation and complement consumption.

Rheumatoid Factor (RF) is an autoantibody reactive with the Fc portion of IgG, which is found in more than two-thirds of adults with the disease, and precedes the onset of RA by many years¹. Some patients are initially sero negative and subsequently converted to seropositive which occurs during the first few years of the illness.

RA patients with positive test have severe clinical disease and complications than seronegative patients. RF is also able to fix and activate complement by the classic pathway. Large quantities of IgG RF are produced by rheumatoid synovial tissue and forms complexes through self association. The propagation of RA is an immunologically mediated event, although the original initiating stimulus has not been characterized.

RF containing immune complexes is readily detected in RA synovial tissue as well as surface layers of cartilage. Enhanced helper T- cell function has been correlated with the spontaneous production of RF of IgM type. Natural killer (NK) and Il-6 also have nonspecific B cell activation. IgM RF and IgG RF are the most abundant and pathogenic in RA followed by IgA RF. IgE RF has been demonstrated in a few cases.

Autoimmunity to cartilage specific antigens

Certain joint specific antigens may play an etiologic or pathogenic role.

They are

A. Cartilage antigens

1. Type II Collagen
2. gp 39
3. Cartilage like protein
4. Proteoglycans
5. Aggrecans

B. Other proteins

1. Citrullinated peptides
2. Glucose 6 phosphate Isomerase
3. Heat shock Proteins
4. Heavy chain binding proteins (BIP)
5. Super Antigens

Propagation of RA is an immunologically mediated event. Evidence for this

includes:

1. The predominance of CD4+ T cells in the synovium.
2. Increase in IL-2 receptors, a product of activated T cells, in the blood and synovial fluid.
3. Amelioration of the disease by removal of T cells by thoracic duct drainage.

PATHOLOGY

The primary site of immune activation in RA is the synovium. Infiltration of synovium with mononuclear cells especially T- cells and macrophages and synovial intimal hyperplasia are the hallmarks of the disease.

Synovial intimal lining

The synovial intimal lining in normal joint is 1-2 cell layers deep. Whereas in RA it is 4 -10 layers deep. Two major cells are found in the lining. They are a macrophage like cell known as Type A synoviocyte and a Fibroblast like cell called Type B synoviocyte.

There is absolute increase in both cell types in RA although the percentage increase in macrophage like cells is greater. PDGF, TGF β , TNF α and Il-1 along with Arachadonic acid metabolites induce proliferation of cells. Light microscopic examination of joint disclose hyperplasia and hypertrophy of the synovial lining cells, segmental vascular changes, thrombosis and neovascularization, edema and infiltration with mononuclear cells¹.

Synovial T- lymphocytes

In chronic RA the synovium contains a collection of T- Lymphocytes that resemble a lymphnode. The distribution varies from discrete lymphoid aggregate to diffuse sheets of mononuclear cells with the most predominant for T-cells along the perivascular region. These collections consists of small CD4 memory T-cells with scanty cytoplasm.

The presence of granulomatous lesions might be associated with EAM and products of both Th1 and Th2 cytokines in the synovium. T-cells consists 80% of cells in RA synovium and most are CD4 and 55 are B cells or plasma cells. The B cells are located primarily within reactive lymphoid centers whereas plasma cells and macrophages are often found outside the centers. This arrangement is consistent with T-cell dependent B lymphocyte activation.

Synovial B lymphocytes

Synovial B-Lymphocytes and plasma cell hyperactivity are participants in the perpetuation and initiation of phases of RA.

Other cell types

Dendritic cells are potent antigen presenting cells and are detected in synovial tissues and synovial effusions of patients with RA. NK cells and mast cells are also found in the synovial lining. Increased numbers of activated mast cells are also found in the Rheumatoid Synovium.

T-cell Cytokines

Helper T-Cells has been divided into specific subsets. They are primarily Th1 and Th2 cells. Th1 associated cytokines are Interferon (IFN) γ , Interleukin IL-1 and IL-6 are implicated in RA. Th2 associated cytokines are IL-4, IL-5, IL-10, IL-17. Some produce both TNF α , IL-3 and Granulocyte Monocyte Colony stimulating factors (GM-CSF).

Under production OF suppressor cytokines and Cytokines Antagonist like IL-4, IL-10 and TNF β are also responsible for the synovial proliferation.

The activity of chemokines and cytokines appear to account for many of the features of rheumatoid synovitis including the synovial tissue inflammation, synovial fluid inflammation, synovial proliferation and cartilage damage, as well as the systemic manifestation of RA.

PDGF and fibroblast growth factor

Both are chemo tactic and mitogenic for fibroblast. It is the most potent stimulation of growth of synovial cells.

Cartilage and bone destruction

RA cartilage is often covered by a layer of tissue composed of mesenchymal cells which might represent the progenitor of the aggressive mature pannus. In the established lesions numerous areas are seen in which macrophage like and fibroblast like cells penetrated into cartilage matrix.

Cartilage is destroyed by both enzymatic and mechanical process. Matrix Metallo proteinases (MMP) are family of enzymes that participate in extra cellular matrix degradation and remodeling. MMP are collagenases, gelatinases, serine proteases and cathepsins.

Prostaglandin E2 produced by fibroblast and macrophages may also contribute to bone demineralization. Osteoclasts are also prominent at sites of bone erosion. Rheumatoid synovium is characterized by the presence of number of secreted products of activated lymphocytes, macrophages, and fibroblasts. Increased numbers of activated mast cells are also found in rheumatoid synovium.

Activated mesenchymal stromal cells, similar to those found in normal bone marrow, can sometimes also found in the rheumatoid synovium.

Increased number of a separate population of T cell found in the rheumatoid synovium. The major population of t cells composed of Cd4+ memory cells. Besides the accumulation of T cells, rheumatoid synovitis is also characterized by the infiltration of variable numbers of B cells and antibody producing plasma cells.

The synovial fibroblasts in RA manifest evidence of activation in that they produce lot of enzymes such as collagenases and cathepsins that can degrade the components of the articular matrix.

CLINICAL FEATURES

ONSET

The onset of symptoms is more frequent in winter than summer. Usually RA patients have insidious slow onset over weeks to months. Initial symptoms may be systemic or articular. Patients may present with fatigue, malaise, diffuse musculo skeletal pain, generalized weakness, fever, loss of appetite and in some cases with loss of weight also. May be first non specific complaints followed by articular manifestations.

In 10% of individuals, the onset is more acute, with a rapid development of polyarthritis often accompanied by constitutional symptoms including fever, lymphadenopathy, splenomegaly. Morning stiffness may appear before pain due to accumulation of edema fluid within the inflamed tissue during sleep and should persist at least 30-45 minutes before disappearing.

Joint pain predominantly originates from joint capsule which is abundantly supplied with pain fibers. Affected joint is held in flexed posture to maximize the joint volume to minimize the stretching of the capsule. Rheumatoid arthritis can affect any type of diarthrodial joint. Symmetrical Joint involvement is due to bilateral release of neuropeptides (substance P) at terminal nerve endings in Joints.

Low grade fever and weight loss was seen in a few cases. A small percentage of patients present with an acute onset of the symptoms.

Joint involvement

Most commonly involved joints are Metacarpophalangeal joint (MCP), Proximal interphalangeal joint (PIP), Metacarpophalangeal joint (MTP) and wrists. Large joints such as elbow, hip, knee, and ankle become symptomatic after the small joints. Cervical joint involvement and temporomandibular joint involvement also occur. In one study which was conducted in south India showed significant involvement of temporomandibular joint.

Involvement of specific joints

Hand and wrist

Dorsal swelling on the wrist within the tendon sheath of the extensor muscle is one of the earlier sign of disease. As the synovial proliferation develops within the wrist integrity of the distal radio ulnar joint is lost. Ulnar head springs into distal prominence.

Hyper plastic synovia can compress the median nerve cause carpal tunnel syndrome often bilaterally. Progression of the disease is characterized by loss of joint space and bony ankylosis. Weakness of extensor carpi ulnaris leads to radial deviation of the wrist and ulnar deviation of the fingers (Zigzag deformity).

Swan neck Deformity is flexion of the DIP and MIP and hyperextension of the DIP joint due to shortening of the interosseous muscles and tendons. In chronic inflammation of PIP, Boutonnière Deformity occurs in which DIP joint is hyper extended.

In resorptive arthropathy there is severe disruption of bone that begins at the articular cartilage and spreads along the diaphysis of involved phalanges. Tenosynovitis of flexor tendon sheath is another common manifestation. Rheumatoid nodules may develop within the tendon sheaths and lock the fingers causing fixed flexion deformity.

Elbow

Involvement of elbow is common in 20-68%, as the disease progresses disability can be severe.

Shoulder

Involvement causes weakness of rotator cuff, chronic subacromial bursitis. Sterno clavicular and manubrio sternal joints are involved and cause symptoms in few cases.

Crico Arytenoid Joints

Crico arytenoid joints may become inflamed and cause hoarseness of voice in some cases. Ossicles of the ear are rarely involved causing difficulty in hearing.

Cervical spine

This is manifested as osteochondral destruction in RA. The atlantoaxial joint is prone to subluxation⁷. The earliest symptom is pain radiating to occiput. The clinical features are slowly progressive spastic quadri paresis and partial sensory loss in limbs. Transient episodes of medullary dysfunction are due to vertebral artery compression. Thoracic, lumbar and sacral spines are usually spared.

Hip

Less frequently involved and presents as pain lower back or groin pain on lateral aspect of hip and it is due to trochanteric bursitis.

Knees

Synovial inflammation and proliferation are common. Quadriceps atrophy is seen in few individuals. Popliteal or Baker's cyst is also common. In few cases, chronic effusion and ligament laxity were also seen in knee joint involvement.

Ankle and Foot

Ankle involvement is rare. Achilles tendon nodules can develop & its spontaneous rupture can occur. Involvement of subtalar joint leads to Rocker Bottom foot. Metatarso phalangeal joints are commonly involved. Downward subluxation of metatarsal heads occur producing cock up toe deformity of PIP joints. Hallux Valgus, bunion or callus formation can occur.

Other characteristic patterns of joint involvement are observed in

Adult onset still's disease

Palindromic pattern⁸

Old age of onset above 60 years

Asymmetric disease

Arthritis Robustus

Felty's syndrome consists of chronic RA, splenomegaly, neutropenia, and, on occasion, anemia and thrombocytopenia. These patients frequently have high titers of Rheumatoid factor, subcutaneous nodules, and other manifestations of systemic rheumatoid disease.

EXTRA ARTICULAR MANIFESTATIONS OF RA (EAM)

In general the number and severity of EAM vary with the duration and severity of the disease. A number of these features may be related to extra articular foci of an immune response based on the evidence of independent and qualitatively different production of RA in the pleural space, pericardium, muscles and meninges. EAM of RA is associated with excess mortality⁹.

1. Muscle

Degeneration of muscle fibers were found in all RA patients termed nodular myositis. There are 5 stages of muscle disease.

- a) Diminution in muscle bulk with atrophy of type II fibers.
- b) Peripheral mononeuropathy due to mononeuritis multiplex.
- c) Steroid Myopathy
- d) Active myositis and muscle necrosis
- e) Chronic Myopathy

2. Skin

The most frequent skin lesion in RA is rheumatoid nodules. The overlying skin of hands and finger become thin and atrophic. Palmar erythema is common. Raynolds phenomenon is rare. Evidence of vasculitis can range from nail fold infarcts to pyoderma gangrenosum. Palpable purpura and Livedo reticularis are due to deep dermal vasculopathy.

3. Eye

Kerato conjunctivitis sicca is a component of Sjogren's syndrome. Scleritis and episcleritis occur in less than 1% of RA. Tearing is due to gritty discomfort. There is no discharge. Secondary cataracts or keratitis can cause vision loss. Scleritis causes severe ocular pain and dark red discoloration.

It can be localized, generalized or necrotizing. Granulomatous resorption can cause scleromalacia perforans. Perilimbic ischemic ulcer can be cause by cryoproteins IgG complexes and results in perforation of anterior chamber.

4. Rheumatoid nodules

It has a central core necrosis rimmed by corona of pallsading fibroblast which is surrounded by a collagenous capsule with perivascular collection of chronic inflammatory cells. The earliest nodules are less than 4 mm in size as the disease progresses, they increase in size. They are found in extensor surfaces e.g. over the olecranon and proximal tibia. They are also seen in occiput. Incidence is 20-35%¹⁰. They are subcutaneous, attached firmly to periostium, mobile and vary in consistency.

Rheumatoid nodule over the vocal cord cause progressive hoarseness. They can be found in the heart, lungs, sclera, leptomeniges, and vertebral bodies. RF is always found in serum of patients with rheumatoid nodules. Rarely nodules are present in the absence of obvious arthritis.

The presence of multiple nodules over the hands and a positive test for RF is associated with episodes of acute intermittent synovitis; subchondral cystic lesions of small bones of the hands and foot represent a condition called rheumatoid nodulosis.

Methotrexate therapy down regulates the synovitis but the existing nodules may enlarge and may increase in number¹.

Differential diagnosis of rheumatoid nodules is,

1. Benign nodules
2. Granuloma annulare
3. Xanthomatosis
4. Tophi
5. Miscellaneous- Yaws, Pinta, Leprosy, Basal cell carcinoma,
Reticulo Histiocytosis.

Fistula development

Fistula can develop in long standing RF positive patients. Cutaneous sinuses near joints may develop. They are either sterile or septic. They usually connect the skin surface with a joint or with a bursa.

6. Hematological abnormalities

The majority of patients with RA have mild normocytic normochromic anemia that correlated with ESR elevation and activity of the disease⁹. Three quarters of RA patients have anemia of chronic disease whereas one quarter will respond to iron therapy¹¹. Both groups have superimposed vitamin B12 or folate deficiency. Anemia of chronic disease is associated with significantly higher ferritin concentration than in iron deficiency anemia. Folate and iron deficiency can mask iron deficiency by increasing MCV and MCHC.

ESR correlates inversely with hemoglobin levels. Erythropoietin levels are elevated in patients with iron deficiency than in anemia of chronic disease. Eosinophilia and thrombocytopenia are seen in RA. Eosinophilia (5% of TC) seen in patients with severe seropositive cases. Thrombocytosis is also seen in some patients¹².

Some patients have increased number of large granular lymphocytes (LGL) in the peripheral blood, bone marrow, and liver. Paraproteinemia and monoclonal gammopathy has poor prognosis in RA patients.

7. Vasculitis

Factors associated with increased incidence of vasculitis are¹³

- a) Male gender
- b) High titers of RF in serum
- c) Joint erosions
- d) Subcutaneous nodules
- e) Circulatory cryoglobulins
- f) Steroid therapy

Clinical vasculitis manifest as

1. Distal arteritis- ranging from splinter hemorrhage to gangrene
2. Cutaneous ulceration
3. Peripheral neuropathy
4. Palpable purpura
5. Arteritis of viscera (e.g.) Heart, lungs, kidneys, liver spleen
pancreas & testes.

The pathologic finding in vasculitis is panarteritis¹⁴. All layers of vessel wall are infiltrated with mononuclear cells. Fibrinoid necrosis and intimal proliferation can predispose to thrombosis. The incidence is 1% and more common in men. Obliterative endarteritis of finger is one of the most common manifestations of vasculitis.

8. Neuro vascular disease

This may be the only manifestations of vasculitis in some cases.

The few common clinical patterns are:

1. Mild distal sensory neuropathy
2. Severe sensory motor neuropathy

Symptoms of mild form are paraesthesia or burning feet and decreased touch and pain sensation distally.

Rheumatoid pachy meningitis is a rare complication of RA. Autonomic nervous disturbances can also occur. RA patients with vasculitis should be treated vigorously.

9. Renal disease

Renal involvement is rare in RA. Drugs which are used in RA like salicylates and phenacetin can cause renal papillary necrosis. Membranous nephropathy is associated with gold salts and penicillamine.

10. Pulmonary disease

There are six forms of the disease

1. Pleural disease
2. Interstitial fibrosis
3. Nodular lung disease
4. Bronchiolitis
5. Pulmonary hypertension
6. Small airway disease.

a) Pleural disease

This occurs in 20% of patients. Pleuritic pain is the main complaint. Effusion can be large enough to cause difficulty in breathing¹⁵.

The characteristics of effusion are

- i. Low glucose (10-50 mg/dl)
- ii. Protein >4g/dl
- iii. Cells are mononuclear
- iv. LDH is elevated
- v. CH50 decreased

b) Interstitial Fibrosis and pneumonitis

The increased activity of the mesenchymal cells in RA is the cause for pulmonary fibrosis. Clinical findings are fine, diffuse, dry rales. X-Ray shows diffuse reticular or reticulonodular pattern in both lung fields. HRCT shows lattice network. Smoking increases the risk. BAL shows increased number of lymphocytes.

c) Nodular lung disease

Nodules may be single or multiple. Single one appears as coin lesions. Caplan's syndrome is RA and pneumoconiosis¹⁶. Nodules may cavitate creating Brochopleural fistula. Malignant transformation to bronchogenic carcinoma is very rare¹⁷.

d) Bronchiolitis

It is a rare complication in RA patients. Proteinaceous exudate in bronchioles is characteristic¹⁸. It can cause respiratory insufficiency and death.

e) Pulmonary Hypertension

This occurs in 30% of patients. Most of them are asymptomatic.

f) Small airway disease

This occurs in 50% of RA patients. It is a part of generalized exocrinopathic process of the disease as in Sjogren's syndrome¹⁹.

11. Cardiac complications

Cardiac complication is due to granulomatous proliferation as vasculitis. 70% of nodular patients and 40% non-nodular patients have some cardiac involvement.

a) Pericarditis

Pericardial involvement is seen in 50 % of patients at autopsy. 31% of RA had echo features of pericardial Effusion. Cardiac tamponade and constrictive pericarditis²⁰ are rare. Most of the patients are RF positive and half of them have nodules.

b) Myocarditis

It may be granulomatous or interstitial myocarditis. Granulomatous process resembles subcutaneous nodules and specific for the disease.

c) Endocardial involvement like mitral regurgitation and aortic regurgitation are reported²¹. In some cases aortic valve regurgitation may be rapid²².

d) Conduction defects

AV Block, CHB is due to granulomatous involvement of AV node bundle of HISS. Rarely amyloidosis causes heart block.

e) Coronary Arteries

RA patients with vasculitis who develop myocardial infarction are likely to have coronary arteries involvement.

12) Entrapment Neuropathy

RA patients develop entrapment neuropathy like carpal tunnel syndrome.

DIAGNOSIS

Diagnosis is based on clinical examination / laboratory investigations and diagnosis that exclude it. Objective evidence of synovitis must be present for at least 6 weeks before the diagnosis. The diagnosis should be confirmed within two months after the onset of synovitis. The diagnosis is confirmed only if the patients fulfill the American college of rheumatology (ACR) criteria. The following table clearly depicts the ACR guidelines.

**1987 REVISED AMERICAN RHEUMATOID ASSOCIATION CRITERIA FOR
DIAGNOSIS OF RHEUMATOID ARTHRITIS.**

CRITERION	DEFINITION
1. Morning Stiffness	Morning stiffness in and around the joints lasting at least 1 hour before maximal improvement
2. Arthritis of three or more joint Areas	At least three joint areas simultaneously having soft tissue swelling or fluid observed by a physician (14 possible joints are Right or Left PIP, MCP, Wrist, Elbow, knee, Ankle and MTP joints)
3. Arthritis of hand joints	At least one joint area swollen as above in Wrist, MCP or PIP joint
4. Symmetric Arthritis	Simultaneous involvement of the same joint areas on both sides of the body (bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry)

CRITERION	DEFINITION
5. Rheumatoid Nodules	Subcutaneous nodules over bony prominences or extensor surfaces or in juxta articular regions observed by a physician
6. Serum Rheumatoid factor	Demonstrated by abnormal amounts of serum "Rheumatoid Factor" by any method has been positive in less than 5% of normal control subjects
7. Radiographic Changes	Changes typical of RA on PA hand and wrist radiograph which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints.

A patient is said to have RA if she/he has satisfied at least four of the seven criteria.

One to four must be present for at least 6 weeks.

Laboratory Investigations

1. Slight Leucocytosis with normal DC count.
2. Thrombocytosis.
3. Slight Anemia (Hb 10gm /dl) normochromic normocytic or microcytic.
4. Normal Urine Analysis.
5. ESR 30mm/hr or more.
6. CRP > 0.7 pg/ml.
7. Normal Renal, Hepatic, Metabolic function.
8. Positive Rheumatoid factor test.
9. Autoantibodies to flaggerin, Citrullinated proteins, calpastalin, components of spliceosome (RA-33) and an unknown Ag Sa.
10. ANA is positive in 40% of RA cases.
11. Increased Alpha1 and Alpha 2 globulin.
12. A normal or elevated serum complements level.

13. Synovial fluid analysis.

- Straw colored.
- Clot Forms in fluid left.
- 5000 to 25000 WBC/mm³ and 80% or polymorphs.
- Complement levels C2 and C4 are decreased, C3 is normal
- Glucose normal or reduced.

14. High resolution ultra sonogram is useful in picking up early synovitis, effusion and erosions²³.

15. Magnetic resonance imaging of joints (MRI): It is also useful in detecting early RA²³.

16. Radiographic changes: X-ray hand and wrist radiographs show erosion and juxta-articular osteoporosis.

MATERIALS AND METHODS

Patients with symptoms suggestive of Rheumatoid arthritis who represented the Medical OPD and Rheumatology OPD, Government Stanley medical college hospital during a period from July 2005 to June 2006 were included in this study. A total number of 100 patients who met the inclusion criteria below were included in this study.

Inclusion Criteria:

- a. Patients who presented with typical clinical features based on the Modified American College of rheumatology criteria.
- b. Patients above 16 years of age.
- c. Patients already diagnosed to have RA

Exclusion Criteria:

- a. Patients with mono articular involvement.
- b. Patients below 16 years
- c. Patients who did not fulfilled the ACR criteria.

Patients who fulfilled the four of the seven criteria defined by the American College of Rheumatology (Modified ACR criteria) were included in the study. Detailed History of clinical features also obtained from the patients.

The RA patients thus selected were screened for various common clinical features, articular and extra articular manifestations using a structured Proforma designed for this study.

These patients were clinically examined for evidence of articular and extra articular manifestations like skin, skeletal, eye, serosal vascular, nervous and respiratory system involvement.

The patients on DMARDs also were included in the study to know the efficacy of these drugs in controlling the symptoms

These patients were subjected to investigations:

- a. Hematological: Hb%, TC, DC, PCV, Peripheral smear study and platelet count.
- b. Acute phase reactants: ESR, C - reactive protein.
- c. Urine analysis for sugar, protein & deposits.

- d. Immunological: Rheumatoid Factor and anti nuclear antibody.
- e. Metabolic: Renal function test (RFT), Liver function Test (LFT).
- f. Radiological: X- Ray chest, X-Ray hands & X- Ray of the involved joints.
- g. Electrocardiogram (ECG): In relevant cases.
- h. Ultra sonogram (USG): In selected patients.
- i. Echocardiography: In relevant cases.
- j. HRCT lung: In relevant cases.

At the end of the study the proportion of articular and extra articular manifestations in 100 Rheumatoid arthritis patients screened were calculated and expressed as percentage.

The severity and frequency of these articular and extra articular manifestations were correlated with the duration of the illness and serological status.

OBSERVATIONS AND RESULTS

A total number of hundred patients were included in this study in the age group ranging from 18-74years. The mean age is being 41.6

1. The Total number of cases screened - 100

2. Gender

* No. of male RA patients screened - 18

* No. of female RA patients screened - 82

3. Age group distribution of RA patients

Age	Males	Females
16-24	3	6
25-34	2	17
35-44	4	30
45and above	9	29

4. Sero Positivity – RF

RF POSITIVE - 63 CASES		NEGATIVE – 37 CASES	
MALE	FEMALE	MALE	FEMALE
7	56	11	26

5. Clinical Features

1. Common constitutional symptoms observed were,

SYMPTOMS	MALE	FEMALE	TOTAL
Fever	14	77	91
Loss of weight	3	38	41
Fatigability	9	43	52

2. Articular Manifestations

The common articular manifestations observed were as follows:

S.No	Joints involved	Percentage
a)	Cervical Joint	3 %
b)	Elbow	48 %
c)	Wrist	82%
d)	Hands(PIP&MCP)	100%
e)	Hip	7%
f)	Knee	7%
g)	Ankle	45%
h)	Foot (MTP&PIP)	37%

3. Extra Articular Manifestations (EAM)

The common EAM observed were as follows:

S.no	EAM	Percentage
a)	Anemia	-20%
b)	Rheumatoid Nodules	- 4%
c)	Eye Involvement	- 4%
d)	Serosal Involvement	- 2%
e)	Lung	- 1%
f)	Cardiac Involvement	- 2%
g)	Vasculitis	-1%
h)	Secondary Sjogren's	- 4%
i)	Neural	-1%

8. Duration of Symptoms and EAM

The extra articular manifestations with the duration of the disease observed were:

Duration of Symptoms	0-2 years		>2-5 years		> 5 years	
	Male	Female	Male	Female	Male	Female
EAM	1	14	1	8	0	10

DISCUSSION

CONSTITUTIONAL SYMPTOMS

In this study three common symptoms such as Weight Loss, Fatigability and Fever were studied. 41 % of patients manifested with loss of weight and they have showed improvement in weight after starting the treatment.

Fatigability was observed in 91% of the patients. In our OPD, majority of the RA patients presented with joint pain along with fatigue, which has incapacitated them from day to day activities.

Fever was present in 52% of patients diagnosed to have RA for the first time. Fever was also present when the patient gets acute attack of RA.

ARTICULAR MANIFESTATIONS

The commonest joints involved are proximal inter phalangeal joints (PIP) and metacarpophalangeal (MCP) joints. They are almost affected in all patients presented with RA. For example a study conducted in south India (Chandrasekar, Radhakrishnan et al)²⁴, the involvement of PIP is 85%, MCP is 68% which shows the predilection for those joints in RA. The next common joint involved in wrist which was involved in 82% of RA patients.

The cervical joints are involved in three patients and among them one patient had it in the form of Atlanto axial subluxation. In a study conducted by D Chellapandian, C Rajendran Panchapakesa et al, showed 42% involvement of cervical spine²⁵. 20% of them had Atlanto axial subluxation^{24, 25}. The patient in this study was presented with gradual onset of quadriparesis. The other patients had cervical spine tenderness and limited mobility of cervical joint.

The other joints affected are

1. Elbow - 48%
2. Hip - 7%
3. Knee - 57%
4. Ankle - 45%
5. Foot - 31%
6. TMJ - 1%

Multiple joint involvements apart from upper limb joints are usually associated with chronic duration of the disease. The involvement of large joints occurred late.

EXTRA ARTICULAR MANIFESTATIONS

Anemia

In this study 22% of patients were manifested with anemia and 6 % of them were seronegative, whereas 16% cases were sero positive. Normochromic Normocytic anemia was seen in 12 %. In various studies the manifestation of anemia was in the range of 25-35%.^{9, 11, 24}

Hypochromic microcytic anemia was observed in 10%. Hemoglobin levels are ranged from 7.5 – 8.5%.

Rheumatoid nodules

Usually this occurs in 20 % to 30% of RA patients^{9, 10}. In this study 4% of cases diagnosed to have rheumatoid nodules. Among them 3 were Sero positive and one was Sero Negative. They were seen over the elbow.

Secondary SJOGREN's

This can develop in 10-15% of long-term rheumatoid patients¹⁹. In this study secondary Sjogren's was observed in 4% of patients.

Eye involvement

In this study, 4 patients showed evidence of Scleritis and episcleritis.

Serosal involvement

Pleural involvement is normally seen in 20% of patients. In this study one patient showed pleural effusion and pericardial effusion was seen in one patient¹⁵.

Pulmonary involvement

Interstitial lung disease was found in one patient who presented with dyspnoea and on examination had bilateral rales. Radiography showed Reticulonodular pattern and confirmed by HRCT. Pulmonary function test showed restrictive pattern.

Cardiac involvement

Mitral valve prolapse and mild mitral regurgitation was seen in one patient and aortic regurgitation was seen in one patient. And it was confirmed with echocardiography.

Vasculitis

Incidence of vasculitis is 1%. In this study one patient showed vasculitis feature and he was presented with cutaneous ulcer in the legs. It is usually seen in males.

Neural involvement

In this study one patient presented with insidious onset of quadriplegia due to the compression of spinal cord, because of atlantoaxial subluxation.

Response to Treatment

In this study, 85% of patients required disease modifying anti rheumatic drugs (DMARD) to control their symptoms and all of them had the disease for more than a year except for 3% of patients in whom the duration is less than 1 year. In a study conducted by Goldbach-Mansky R, Lipsky PE et al, it is shown that early institution of DMARDs is highly beneficial for patients with RA even at their first visit to rheumatologist²⁶. Fifteen percentages of patients were not on DMARDs and the duration of the disease in them was less than a year. Patients who were on DMARD had a good pain relief and it has improved the functional quality of life in those patients.

CONCLUSION

1. Fatigability, Loss of weight and Fever were observed in 91%, 41% & 52% of patients respectively.
2. All patients showed involvement of PIP& MCP joints. The next common joint involved was wrist in 82% of patients.
3. Cervical joint involvement is seen in three patients and one of them had neurological deficit in the form of atlantoaxial subluxation resulting in quadriplegia.
4. Extra articular manifestations (EAM) were found in 41%of patients studied.

Among the EAM, anemia was the predominant manifestation and seen in 22% of patients.

5. The frequency of complications was well correlated with duration of the disease.

Those who were having the disease more than two years showed evidence of joint damage and extra articular manifestations.

6. Majority of the patients with EAM were seropositive. And seropositive patients presented with joint damage earlier than seronegative patients.

7. DMARD is required in 85% of patients to overcome the symptoms.

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CLINICAL PROFILE OF RHEUMATOID ARTHRITIS

PROFORMA

NAME

AGE

SEX

OP/IP NUMBER

OCCUPATION

ADDRESS

PRESENTING COMPLAINTS:

H/O PRESENTING ILLNESS:

FAMILY HISTORY:

PERSONAL HISTORY:

PAST HISTORY:

GENERAL EXAMINATION:

EXAMINATION OF JOINTS:

SYSTEMIC EXAMINATION:

OPHTHALMIC

DERMATOLOGICAL

CVS

RS

CNS

MUSCLES

GASTROINTESTINAL

GENITOURINARY

INVESTIGATION:

URINE

Albumin Sugar deposits

HEMATOLOGY

TC DC ESR HB Platelets.

Peripheral smear

BLOOD CHEMISTRY:

SUGAR
LFT
RFT
Uric Acid.

IMMUNOLOGICAL TESTS:

RF
CRP
ASO
ANA

RADIOLOGY:

X ray Chest PA view

X ray hand and foot AP view in selected patients

Others

ECG

Echocardiography

HRCT lung

OTHER:

Summary of constitutional symptoms, articular manifestations and extra articular manifestations