IJPT
International Journal of Pharmacy & Technology

ISSN: 0975-766X

Available Online through
www.ijptonline.com

Review Article

ARTHRITIS - A REVIEW OF CLINICAL FEATURES, DIFFERENTIAL DIAGNOSIS AND TREATMENTS

D.Kilimozhi, V. Parthasarathy* and Kandaraboina Upendar
Department of Pharmacy, Annamalai University, Annamalai Nagar-608002,
Tamil Nadu, India
E.mail: vapartha123@gmail.com

Received On: 20-01-2010 ***Accepted On: 15-02-2010***

ABSTRACT

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology affecting both articular tissues and extraarticular organs. The disease is often progressive and results in pain, stiffness, and swelling of joints culminating in significant morbidity and increased mortality. This chapter discusses the epidemiology, possible etiology, clinical manifestations, diagnostic approach and treatment options of RA.

Keywords: Rheumatoid arthritis; autoimmune disease; Clinical manifestations; Lab testing; Imaging modalities; Treatment.

1.INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, usually progressive, systemic inflammatory condition of unknown cause. It is characterized by synovial proliferation and a symmetric, erosive arthritis of peripheral joints, but it may also cause systemic manifestations. RA is the most common autoimmune disease, affecting1–1.5% of the population worldwide [1–5]. Rheumatoid arthritis (RA) is characterized by synovitis and autoantibody formation (RF). The hallmark feature of the disease is persistent symmetric polyarthritis (synovitis) that affects the hands, wrists and feet, although almost all diarthrodial joints may become involved. In addition to articular manifestations, systemic involvement may cause constitutional symptoms, rheumatoid nodules, serositis and vasculitis. The severity of RA may fluctuate over time, but chronic RA most

commonly results in the progressive development of various degrees of joint destruction, deformity, significant decline in functional status and a premature death (6-7).

2. EPIDEMIOLOGY

The prevalence of arthritis is consistent world wide, affecting about 0.5-1%of the population. Although the disease affect the people all over the world, certain population demonstrate particularly low or high prevalence, as with other autoimmune conditions, women are affected more than men at the ratio of 3 :1.

The disease at occurs at any age, with the peak age of onset being around the fourth and fifth decade of life. The prevalence increase with the age but there is lower differential between the sexes in older patients.

High standardized mortality rate is have been observed in the arthritis population compared with a general population. In particular, recent studies suggest that the increased life expectancy observed in general population is not mirrored in arthritis patients(8-9). Throughout the world, ethnic groups like the North American Pima Indians and southeast Alaskan Indians have a much higher incidence of RA (10). The incidence of RA rises dramatically during adulthood and peaks in individuals aged 40–60 years. Patients, who are women, have a less formal education, greater number of affected joints and worse functional status appear to have worse morbidity and mortality (11).

3. ETIOLOGY

Although the etiology remains a mystery, several studies suggest environmental and genetic factors are responsible. Aho et al. showed the most compelling example for both by finding a 30% concordance in monozygotic twins, compared to 5% in fraternal twins and first degree relatives (12). Environmental factors must be related to RA development otherwise monozygotic twins would have a 100% concordance. A recognized RA genetic risk factor is the presence of the HLA-

DR4 or HLA-DRB1 class II MHC haplotypes (13–16). Associations have also been noted in the humeral system; in particular, the immunoglobulin kappa genotype appears to confer a risk of RA. Several environmental stimuli such as infections, vaccine inoculations, and emotional trauma have been implicated as inciting factors. Researchers have hypothesized a typical bacteria and viruses such as mycobacteria, mycoplasma, Epstein–Barr virus, parvovirus B-19, rubella and retroviruses, may infect an individual with the appropriate genetic background, and through some mechanism, the inflammatory response becomes focused on self antigens (17–19). Retrospective studies suggest a protective role of oral contraceptives, although the effect is probably very small and temporary (if it exists). Other endocrine influences, including corticotropin-releasing hormone, estrogen synthesis or nulliparity have been linked with RA. Although there are indications that certain diets (fish oils) may alleviate inflammation (20) in patients with RA, there are no data to implicate any diet or food additive as a potential cause or treatment of RA. Trauma, including surgery, may precipitate the initial symptoms and is often identified by patients in retrospect as a potential trigger. The perception has been held by many in the medical and lay community that RA is a relatively benign illness. However, this is far from the truth. There is an overall increased morbidity and mortality in patients with RA (21, 22, 23).

4. CLINICAL FEATURES

The diagnosis of RA is made using the patient's history and examination results in conjunction with laboratory and radiographic data. Patient characteristics, including age, gender, and ethnicity, are important, as they are related to disease risk and severity. Approximately 75% of patients with RA are women. RA with involvement limited to the hands and feet a sparing the more proximal joints, such as the shoulders, hips, and cervical spine are more common in women than in men (24). In contrast, there is a higher rate of large-joint involvement in men. Erosive disease is found in long-term follow-up in up to 73% of men and 55% of women (24). Although a higher percentage of men have erosive disease, women undergo almost twice as many orthopedic

surgeries as men, principally hand and foot joint procedures. This difference may be a consequence of increased small-joint involvement in women, but other factors may also contribute. The presence of a positive rheumatoid factor (RF) and of rheumatoid nodules is also risk factors for joint surgery (25).

The extraarticular manifestations, nodules, as well as lung and pericardial involvement, are more common in men, whereas the sicca syndrome occurs more frequently in women (24). Native Americans are at a higher risk for developing RA than Northern Europeans and often have early-onset seropositive disease with extraarticular manifestations (26). The incidence of disease-related complications increases with disease duration and patients with longer disease duration may not respond as well to treatment as those with early disease (27, 28). There are no specific laboratory findings in RA, although the RF is positive in approximately 60% of patients at diagnosis and 80% to 90% of patients with established disease (29).

To distinguish RA from other forms of arthritis, classification criteria were developed by the American Rheumatism Association (Table 1) (30).

Table.1 1987 Revised American Rheumatism Association Criteria for the Classification of Rheumatoid Arthritis

S.No	**Criterion**	**Definition**
1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 h.
2.	Arthritis in three or more joint areas	At least three 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
3.	Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint
4.	Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in Criterion 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5.	Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces or juxtaarticular regions observed by a physician
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.
7.	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on the posteroanterior hand and wrist radiographs, which must include erosions or unequivocal decalcification localized in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify).

MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

For classification purposes, a patient shall be said to have rheumatoid arthritis if he or she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

5.CLINICAL SYNDROMES OF EARLY RHEUMATOID ARTHRITIS

The majority of patients with RA have a slow onset of disease over several weeks to months. Uncommonly, patients present with acute onset of symptoms over days. The onset is polyarticular (more than sixjoints) in 75% of cases. The joints initially involved in RA are commonly the MCPs, PIPs, metatarsophalangeals (MTPs), ankles, and wrists in a symmetric distribution (31). However, in up to 25% of cases, the initial presentation is asymmetric or mono- or oligoarticular, or involves large joints such as the knees, hips, and shoulders.

5.1ARTICULAR

5.1.1 Overview

Although an attempt has been made to provide up-to-date information, long-term studies involving new therapies, such as tumor necrosis factor inhibitors, are not yet available. It appears likely that current therapeutic strategies will significantly modify the disease course of RA. The descriptions of joint involvement in RA will begin with the hands and cover the upper extremity joints, followed by the feet and lower extremity joints, and, finally, describe the spine and other axial joints.

5.1.2 Upper Extremity

5.1.2.1 WRIST AND HAND

The three major compartments of the wrist are the radiocarpal, midcarpal, and radioulnar. These compartments, as well as the overlying dorsal and volar tendon sheaths, are lined by synovium and

can be involved in RA. As with other joints, chronic synovitis in the wrist and hand eventually results in laxity of joint capsules and ligaments, allowing the tendons crossing the wrist to deform it. This eventually leads to ulnar and volar shifting of the carpus on the radius, dislocation of the radioulnar joint, radial deviation of the metacarpals at the wrist, and ulnar shift of the fingers at the MCP joints (32) (Fig.1). The forces involved with hand grip also pull the fingers in an ulnar direction and potentiate hand deformities in RA (33).

PIP and MCP joint involvement are common in RA, resulting in pain, swelling, and loss of finger motion. As the capsule of the MCP joints is weakened, volar migration of the fingers relative to the metacarpal bones occurs.

Swan-neck deformities are characterized by PIP joint hyperextension with concurrent flexion of the DIP joint. This deformity results from laxity of the joint capsule, volar plate, and collateral ligaments, with concurrent tightening of the dorsally displaced lateral bands and central extensor tendon. MCP joint hyperextension, PIP joint flexion, and DIP joint hyperextension characterize the deformity. This deformity results from stretching of the extensor mechanism, attenuation of the central slip over the PIP joint, and secondary contraction of the volarly displaced lateral bands (32). Extensor tendon rupture may result from wear against exposed jagged bone, usually over the distal ulna. Ulnar subluxation of the extensor tendons may cause them to slip between the metacarpal heads during flexion, causing a painful catching while attempting finger extension. Swelling in the region of the ulnar styloid and loss of wrist extension are early signs of RA. Later in the disease, rotation and subluxation of the wrist prevent the normal function of the extensor carpi ulnaris as a wrist extensor (33).

4.1.2.1 ELBOW

The elbow is frequently involved in RA with loss of extension. An effusion or synovitis is detected as a bulge between the head of the radius and the olecranon. The elbow region is the most common

site for subcutaneous rheumatoid nodules, which may be on the extensor aspect of the proximal ulna or within the olecranon bursa. Olecranon bursitis is also common.

5.1.2.1 Shoulder

Involvement of the shoulder joint in RA is variable. The rotator cuff may become inflamed and tear, causing pain and limitation of movement. Radiographically, the humeral head migrates up. Glenohumeral damage leads to pain both with motion and at rest and typically leads to severely restricted motion. The shoulder synovitis may lead to rupture of the long head of biceps. Acromioclavicular joint disease is frequently found and may cause shoulder pain.

5.1.3. Lower Extremity

5.1.3.1 Ankle and foot

Initial involvement with RA occurs as often in the feet as in the hands. The most frequently affected foot joints are the MTP, talonavicular, and ankle joints (34). Weight bearing results in greater dysfunction and pain in lower extremity joints, particularly the feet and ankles (34). Synovitis at the MTP joints causes laxity of the capsules and ligaments. In the presence of active forefoot synovitis, dorsiflexion of the toes during walking results in dorsal subluxation of the phalanges and plantar subluxation of the metatarsal heads (35). This condition may lead to painful callus formation under the metatarsal heads. Chronic cutaneous fistulas can develop from ulceration of the bursae under the metatarsal heads (33).

The midfoot consists of the navicular, the cuboid, and the cuneiform bones with their intertarsal and tarsometatarsal articulations. Forefoot deformities correlate with destruction of the midfoot joints, particularly the cuneonavicular and cuneometatarsal joints (36).

The hind foot consists of the talus and calcaneus and three articulations at the talonavicular, the talocalcaneal, and the calcaneocuboid. Of these, the talonavicular is most commonly affected in RA (37). The ankle is made up of the tibia, fibula, and talus with three articulation sac the

tibiotalar, the distal tibiofibular, and the fibulotalar. Hindfoot involvement and deformity become more prevalent after 5 years of disease duration, and ankle joint deformity probably results from the stress of talocalcaneal (subtalar) joint malalignment (33). Patients often are found to have pes planus with hind foot valgus deformity (Fig.3). Whether this is due to hind foot joint synovitis, posterior tibial tendon dysfunction, laxity of supporting ligaments, or a combination of these factors is controversial (39). Patients with RA may also develop Achilles tendonitis, retrocalcaneal bursitis, or ankle joint effusions.

5.1.3.2 Knee

Bilateral knee involvement is common in patients with RA. The presence of fluid in the knee may be confirmed by eliciting a bulge sign or by ballottement of the patella. The presence of fluid or synovitis limits knee flexion and may prevent full extension. Activation of nociceptors around the knee secondary to effusions and synovitis leads to quadriceps inhibition and secondary atrophy. Popliteal cysts are often present and best detected by observing the patient in the standing position from behind. Eventually, a valgus deformity with or without flexion contracture can develop, and these are often accompanied by pes planovalgus deformity of the feet.

5.1.3.3 Hip

Hip involvement occurs in well established disease and is manifested as pain in the groin, buttock, low back or referred to the knee on standing.

5.1.3.4 Spine

Involvement of the cervical spine with RA has been reported in 17% to 86% of patients and correlates with longer duration of disease, multiple joint involvement, extent of peripheral erosions, seropositivity, rheumatoid nodules, steroid use, and vasculitis (40). Spinal cord compression can result from atlantoaxial subluxation, basilar invagination, or subaxial subluxation. Atlantoaxial subluxation is defined as greater than 3 mm of space between the odontoid process of

second cervical vertebra (C-2) and the anterior arch of the atlas (C-1) (33). Subluxation greater than 10 mm greatly increases the risk of cervical myelopathy .

Up to 50% of patients with cervical spine involvement from RA do not have neck or occipital pain or any symptoms of neurologic impairment (41). Pain is the earliest and most common clinical manifestation, often experienced in the occipital or posterior neck areas. Suboccipital headaches may be due to synovitis at C1-2, bony disease, or compression of the greater occipital nerve. Degenerative disc disease, facet arthropathy, and subaxial subluxation can cause neck pain. Neurologic deficits have been reported in 11% of patients during an average follow-up of 10 years (41). Compression of the posterior aspect of the spinal cord and vertebrobasilar arteries may result in symptoms of tinnitus, vertigo, diplopia, or posterior column impingement with loss of proprioception. Rarely, rheumatoid pannus or reactive osteophyte formation of the cervical spine can compress the esophagus, causing dysphagia. Disc disease and cervical radiculopathy can occur at any level. Symptoms of cervical myelopathy can include weakness, numbness, clumsiness, and even respiratory embarrassment. Spasticity, sensory deficits, hyperreflexia, and upper motor neuron signs such as Babinski or Hoffmann may be present on physical examination (40).

5.1.3.5 Temporomal joint

Patients with RA more commonly report pain on palpation of and clicking of the TMJs than controls. Severe arthritic involvement of the TMJ has been associated with a higher incidence of upper-airway obstruction (42).

5.1.3.6 Cricoartenoid joint

Nearly 30% of the patients with RA have involvement of the cricoarytenoid joint; symptoms include hoarseness and inspiratory stridor and may require tracheostomy (43).

5.1.3.7 Middle ear

The incudomalleolar and incudostapedial joints are synovial joints and may be involved in RA. Abnormal middle-ear mechanics have been detected with multiple-frequency tympanometry in

40% of patients with RA, usually due to stiffness of the tympano-ossicular system (44). However, most middle-ear involvement is asymptomatic, and there is no difference in hearing acuity among patients with RA compared to control subjects.

5.1.3.8 Steroclavicular and sternomanubrial joints

Approximately one-third of RA patients have clinical manifestations of sternoclavicular involvement, as evidenced by asymmetry, swelling, crepitus, tenderness, hypertrophy, pain, or limitation of motion (45), and a similar percentage have erosions on tomography (46).

Synovitis of the sternomanubrial joint is also common, but, because of the relative immobility of this amphiarthrodial joint, symptoms are uncommon (47). Sternomanubrial joint arthritis should be considered in the differential diagnosis of chest pain in a patient with RA. Subluxation of the sternomanubrial joint is present in 2.5% of patients with RA (47). These patients tend to have severe erosive disease with cervical spine involvement.

6. EXTRAARTICULAR COMPLICATIONS OF RHEUMATOID ARTHRITIS

Extraarticular manifestations of RA occur in approximately 40% of patients and are associated with an overall mortality risk ratio of three times that of patients without these manifestations (48).

6.1 Skin

Nailfold infarcts and rheumatoid nodules are common findings in extraarticular RA, and both are suggestive of more severe disease. Rheumatoid neutrophilic dermatitis is a rare, nonvasculitic eruption of red-purple plaques and papules, sometimes with pustules or vesicles, occurring on extensor surfaces (49). Treatment-related skin pigmentation from drugs, such as minocycline, hydroxychloroquine, and gold (chrysiasis), can also occur.

6.2 Oral

There is an association between increased disease activity and decreased saliva production, and oral sicca symptoms have been reported in up to 50% of patients with RA (50). Secondary Sjogren's syndrome with reduced salivary flow can lead to difficulty swallowing, difficulty

speaking, oral burning, oral candidias is, difficulty with dentures, and increased caries. Periodontal disease, including loss of alveolar bone and teeth, occurs with an increased frequency in patients with longstanding RA. Nodules Rheumatoid nodules occur in approximately 30% of patients and are associated with seropositive, erosive, and more severe disease. Rheumatoid nodules should be distinguished from other types of nodules, including xanthomas and gouty tophi.

A very small subset of patients with multiple nodules, bone cysts without erosions on radiographs, elevated RF, and little active arthritis or synovitis are said to constitute a relatively benign variant of rheumatoid disease called rheumatoid nodulosis (51).

Patients tend to develop nodules in areas of increased friction or pressure, such as the extensor aspects of the elbow, olecranon bursae, finger joints, and Achilles tendons. In bedridden patients, the ischial, sacral, and occipital prominences can develop nodules (52). Nodules can occur not only in the skin and subcutaneous tissue, but also have been reported in the larynx, pericardium, heart valves, pleura, lung, peritoneum, eye, bridge of the nose, pinna of the ear, kidney, and meninges. Accelerated nodulosis can occur after the institution of methotrexate or antitumor necrosis factor alpha therapy (53).

Histological examination of the nodules reveals a central necrotic core surrounded by a corona of palisading mononuclear cells and an outer zone of fibroblasts, plasma cells, and lymphocytes (52)

(Fig.1)

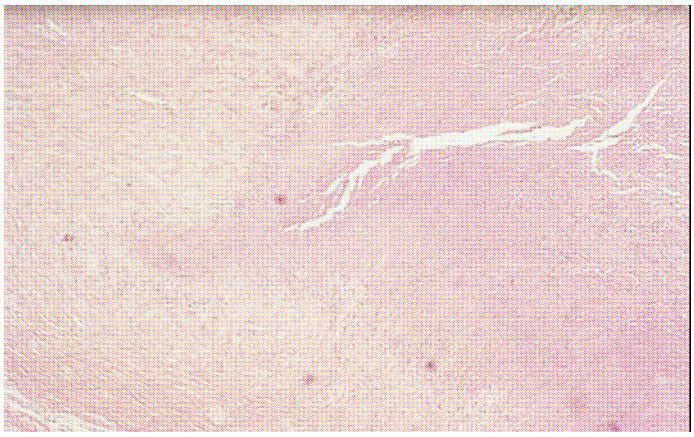

Figure 1. Histopathology of a rheumatoid nodule with central fibrinoid necrosis surrounded by a rim of palisading histiocytes and an outer zone of fibrosing connective tissue with fibroblasts, plasma cells, and lymphocytes .

6.3 Hematologic Abnormalities

Anemia is among the most common extraarticular manifestations of RA (54). The prevalence of anemia among patients with RA depends on the group sampled. In outpatients with RA, anemia has been found in up to 27%, and the average hemoglobin in that subset was 10.0 g per dL (55). Anemia of chronic disease is the most common type of anemia in RA, followed by iron deficiency and, less commonly, pure red cell aplasia and autoimmune hemolytic anemia. More than one type of anemia may be present simultaneously. Interpretation of the ferritin level in RA can be confusing, as the level may be elevated because of the acute phase response despite absent bone marrow iron stores. However, a ferritin of less than 50 ng per ml in patients with RA is always associated with iron deficiency (56).

Abnormalities of leukocyte counts in RA are likely to be related to medications. Corticosteroids cause a neutrophilic leukocytosis, whereas disease-modifying agents such as methotrexate and sulfasalazine can cause leukopenia. Leukopenia is also seen in Felty's syndrome. Eosinophilia is common in severe seropositive RA but may also be related to drug therapy with methotrexate, gold, or penicillamine.

Thrombocytosis often accompanies active RA and correlates well with other laboratory parameters of disease activity, such as erythrocyte sedimentation rate, C-reactive protein, and plasma fibrinogen. Elevation of the platelet count may represent the response of the bone marrow to stress or overcompensation by the marrow for shortened platelet survival time. Thrombocytopenia is usually secondary to drugs, FS, or splenomegaly. The increase in plasma proteins, fibrinogen, and immunoglobulins that occurs in RA results in an increased plasma viscosity that parallels increases in the sedimentation rate (57). Hyperviscosity syndrome, characterized by an insidious onset of

headache, retinal vein dilation, somnolence, and bleeding diathesis, has rarely been described in RA (58). Lymphadenopathy has been reported to occur in 19% to 96% of patients with RA, particularly those with active disease (59). The lymph nodes are usually small, mobile, nontender, and generally occur in the axillary, inguinal, and epitrochlear areas. The adenopathy resolves or decreases with improved disease control. Histologic examination usually reveals follicular hyperplasia (60). Even in the absence of FS, splenomegaly is clinically detectable in 5% to 10% of patients with RA (61).

6.4 Lymphedema

Lymphedema is an uncommon extraarticular feature of RA, presenting with gradual onset of uncomfortable swelling of a limb. Lymphoscintigraphy usually shows lymphatic obstruction not related to lymphadenopathy (62).

6.5 Amyloidosis

Clinically significant amyloidosis, of the AA type, is uncommon and has had a declining incidence in RA since the 1950s, which has been ascribed to more effective medical treatment (63). Serum amyloid-A protein levels are elevated by the increased cytokine production associated with active RA. Parenchymal organ amyloidosis occurs at a mean of 15 to 17 years of disease duration, presenting most commonly with proteinuria, diarrhea, or organomegaly. Amyloid is detected on tissue biopsy (usually fat aspirate) by Congo red stain and polarized microscopy. The prognosis for reactive AA amyloidosis is better than AL amyloidosis, although the 4-year survival rate is only 58% for the former (64).

6.6 Felty's Syndrome

The triad of RA, leukopenia, and splenomegaly is a rare extraarticular manifestation of RA, occurring in less than 1% of patients (65). The majority of cases are women, aged 55 to 65 years, with a disease duration of 10 to 15 years. Usually, these patients have had significantly worse articular disease than controls, although, at the time they develop FS, little or no active synovitis

may be present. The degree of neutropenia in FS is not related to the severity of splenomegaly. Patients with FS usually have high titers of RF and an increased incidence of other extraarticular features (66). The major complication and cause of mortality with FS is infection, which appears to be directly related to the degree of neutropenia. Hepatomegaly, abnormal liver function tests, and refractory leg ulcers are other manifestations of FS.

6.7 Pseudo-Felty's Syndrome

Pseudo-Felty's syndrome is a chronic lymphoproliferative disorder of large granular lymphocytes associated with neutropenia, splenomegaly, and recurrent pyogenic infections. It may be distinguished from FS by its onset earlier in the course of RA, paucity of erosive disease and other extraarticular features, lymphocytosis with lack of leukopenia, and T-cell gene rearrangement studies showing a clonally expanded population of large granular lymphocyte cells (65). Despite the fact that this is a clonal disorder, survival appears good, with 90% of patients alive after nearly 4 years of follow-up (67).

6.8 Ocular

Dry eyes occur in as many as 38% of patients with RA (68), but most authors have cited a prevalence of approximately 15% to 25%. Keratoconjunctivitis sicca is, thus, the most common ophthalmic manifestation of RA. Symptoms include dryness, burning, and sensation of a foreign body in the eyes. Severe dryness results in devitalization of corneal epithelial cells and punctate epithelial erosions, which are apparent with 1% rose-bengal staining. Decreased tear production may be detected by an abnormal Schirmer test

Inflammatory eye disease is much less common than keratoconjunctivitis sicca. Episcleritis does not affect visual acuity and usually correlates with the activity of RA and subsides spontaneously. It appears acutely as a red eye with mild, if any, associated discomfort. Necrotizing nodular scleritis is painful and associated with longstanding arthritis, active joint disease, and visceral vasculitis and can lead to scleromalacia perforans and blindness.

Retinal vasculitis is a rare complication in RA. Corticosteroid treatment places RA patients at higher risk of cataracts. Hydroxychloroquine treatment can uncommonly result in retinopathy.

Peripheral ulcerative keratitis is a severe form of keratitis that develops as an extension of scleritis and may lead to corneal thinning and perforation. Both necrotizing scleritis and peripheral ulcerative keratitis portend a high mortality in the absence of treatment, likely because of their association with underlying systemic vasculitis . Anterior uveitis commonly accompanies episcleritis or scleritis in RA patients, but seldom occurs in isolation (69).

6.9 Neurologic

Neurologic complications of RA include nerve compression from synovial proliferation, vasculitis, and sensory or sensorimotor neuropathies. Atlantoaxial subluxation, vertical subluxation with basilar invagination, and subaxial subluxation can result in spinal cord impingement or radiculopathy. Uncommonly, rheumatoid pannus formation from synovial facet joints in the spine can cause nerve root compression. Vasculitis of the central nervous system (CNS) is rare in RA and occurs in the setting of diffuse systemic vasculitis. As in other forms of CNS vasculitis, stroke, seizure, intracranial hemorrhage, and leptomeningitis can occur. Rheumatoid nodules rarely develop in the durra or choroid plexus and can impinge on the CNS, causing neurologic symptoms (70).

Some type of neuropathy affects up to one-third of RA patients (72). Carpal tunnel syndrome is the most common compressive neuropathy in RA, resulting from tenosynovitis of the flexor tendons of the fingers with pressure on the median nerve within the carpal tunnel. Patients may have numbness and tingling in the radial four fingers accompanied by a positive Tinel's, Phalen's, or carpal tunnel compression test. Less common is tarsal tunnel syndrome, which results from posterior tibial nerve compression by adjacent tenosynovitis of the posterior tibial tendon as both structures pass through the tarsal tunnel (formed by the medial malleolus and the flexor retinaculum) (70).

Clinically, tarsal tunnel syndrome may be asymptomatic, but it may cause pain, paresthesia, and burning in the toes and plantar aspect of the foot. Other compressive neuropathies are very rare, but include the anterior interosseous branch of the median nerve, the ulnar nerve at the wrist or elbow (cubital tunnel syndrome), the posterior interosseous branch of the radial nerve, and the common peroneal or tibial nerves (70). Very rarely, iliopsoas bursitis may cause unilateral femoral nerve palsy. Nerve conduction studies and electromyography can assist in the diagnosis of a compressive neuropathy. Treatment is usually aimed at controlling the responsible tenosynovial proliferation with medications, corticosteroid injections, or splinting, but, occasionally, decompressive surgery is needed.

Distal sensory neuropathy and combined sensorimotor neuropathy are more common than the compressive neuropathies in patients with RA (70,71). Distal sensory neuropathy has an insidious onset with symptoms of numbness, paresthesia, and burning in the feet. Often, this form of neuropathy remains stable over time or may even improve. In contrast, combined sensorimotor neuropathy can present acutely and has a poorer outcome. Mononeuritis multiplex is a form of combined sensorimotor neuropathy caused by vasculitis of epineural arteries and can present with acute foot or wrist drop. Such patients usually have severe longstanding RA with other extraarticular features. Pathologically, both sensory and sensorimotor neuropathy in RA are caused by epineural or perineural vasculitis, or both (72), resulting in axonal degeneration. The presence of multifocal neuropathy, low C-4 complement levels, and concomitant cutaneous vasculitis are associated with decreased survivorship (71).

6.10 Muscular

Myopathy in RA is usually due to disuse atrophy, corticosteroid therapy, or both. Hip and knee flexor and extensor strength are significantly reduced in RA patients compared with controls (73). Both hydroxychloroquine and penicillamine therapy may rarely cause a myopathy. Clinically

significant disease-related myositis is very rare. Denervation atrophy from peripheral neuropathy is another cause of muscle weakness.

6.11 Pulmonary Disease

Pleural disease is found in up to 73% of RA patients at autopsy (74). Rheumatoid pleural effusions can be transudates but are usually exudative with an increase in mononuclear cells, a high lactate dehydrogenase, high protein, and low glucose and pH (74). The low glucose is probably caused by impaired glucose transport into the pleural space (75). RF may be present in the fluid, and hemolytic complement levels may be low. Pleural effusions usually resolve over months with treatment of the underlying disease, but therapeutic and diagnostic aspiration may be required to confirm the fluid's relation to RA. Pulmonary rheumatoid nodules are usually asymptomatic and typically occur in seropositive patients who have subcutaneous nodules (76). The pulmonary nodules can be single or multiple but tend to be peripheral and upper lobe in location. Spontaneous pneumothorax can occur from rupture of a necrobiotic nodule into the pleural space and may cause secondary sterile empyema. Nodules can cavitate, erode into bronchi, and cause bronchopleural fistulas. Excisional biopsy may be required to exclude the possibility of neoplastic disease and granulomatous infection.

The most common pulmonary manifestation of RA is interstitial lung disease (ILD) (75). Male gender, high RF, more severe articular disease, and smoking are risk factors for this complication. In the majority of patients with ILD, joint involvement precedes lung involvement. ILD usually develops within 5 years of onset of joint disease (76). Bi-basilar interstitial infiltrates that may have honeycombing are seen on chest radiography or CT. CT has ten times the sensitivity of plain radiography for detecting ILD, and ILD may be found in as many as 47% of patients on high-resolution CT scanning (77). Clinically, findings are indistinguishable from idiopathic pulmonary fibrosis, although patients with RA are less likely to have digital clubbing (78). Bronchoalveolar

lavage usually demonstrates a neutrophilic alveolitis, which carries a worse prognosis than lymphocytic alveolitis (79).

Since the advent of high resolution CT scanning, bronchitis is detected in as many as 30% of patients with RA. The pathogenesis of bronchitis in RA is unknown but may relate to recurrent infections, underlying obstructive airway disease, or genetic susceptibility (75).

Bronchiolitis obliterans (BO) organizing pneumonia is another entity that can be idiopathic but may affect patients with RA. Its presenting symptoms include fever, cough, and dyspnea. Consolidative infiltrates are found on CT scan. The diagnosis usually requires lung biopsy, and prognosis is favorable with corticosteroid treatment (76).

Histopathologically, the disease results from peribronchial and submucosal fibrosis, which causes narrowing of the bronchiolar lumens with little active inflammation (80). There is an obstructive pattern on pulmonary function tests. Lung biopsy is often required for the diagnosis.

Primary pulmonary vasculitis in RA is extremely rare, as is primary pulmonary hypertension. Secondary pulmonary hypertension may result from underlying ILD (75).

Drugs such as gold, penicillamine, and methotrexate can rarely be the cause of lung problems in patients with RA. Pulmonary toxicity from methotrexate usually presents subacutely with interstitial pneumonitis, fever, cough, dyspnea, and eosinophilia (81). Prompt recognition of this syndrome and discontinuation of methotrexate may be life-saving.

6.12 Cardiac

Coronary artery disease and accelerated atherosclerosis are now recognized as perhaps the most common extraarticular manifestations of RA (82). Compared to patients those with RA have an increased prevalence of myocardial infarction, congestive heart failure, and stroke (83). There is an increased incidence of cardiovascular events in RA patients independent of traditional risk factors (84).

Inflammation plays a role in atherogenesis, as evidenced by the presence of inflammatory cells in atherosclerotic plaques. Certain T-cell populations are expanded in the blood of patients with RA (85). These same cells are found in ruptured coronary plaques of patients with unstable angina (86). At their first coronary angiogram, rheumatoid patients have an increased coronary atherosclerotic burden compared to control patients who required coronary angiography (87). Furthermore, elevated C-reactive protein levels, often detected in patients with RA, have been shown to carry an increased risk for coronary heart disease and portend a worse prognosis in patients with angina (88).

Although pericardial inflammation or effusion as detected by echocardiography and at autopsy is common, clinical signs and symptoms of pericarditis are not (89). Symptomatic pericarditis usually occurs in patients who have a positive RF and nodules and can result in pericardial tamponade or chronic constriction (90). In a review of 41 episodes, the median duration of RA among patients with pericarditis was 9 years. Typically, symptomatic patients present with dyspnea, orthopnea, and positional or pleuritic chest pain. On examination, tachycardia and tachypnea are common (91).

Myocarditis, when present, is usually asymptomatic and diagnosed at autopsy (89). If rheumatoid nodules and inflammation occur near the atrioventricular node, complete heart block can result (92). Nonspecific endocardial inflammation is not infrequently noted at autopsy, and valvular thickening can be seen on echocardiography. These are usually asymptomatic (90). Rheumatoid nodule formation within valve leaflets or extruding from the endocardium can rarely lead to valvular incompetence or mimic atrial myxoma (93,94). Coronary arteritis has been rarely described as the cause of myocardial infarction (95). Similarly, aortitis from RA is uncommon, can be fatal, and is seldom diagnosed before autopsy (96).

6.13 Rheumatoid Vasculitis

Isolated nailfold infarctions are not associated with a worse prognosis in patients with RA and, in isolation, are not an indication for intensification of therapy directed against vasculitis. However, the presence of these lesions should prompt a search for other dermatologic and systemic manifestations of rheumatoid vasculitis.

Clinically significant rheumatoid vasculitis most commonly presents with mononeuritis multiplex and skin involvement (97). The ischemic ulcers tend to affect the legs (Fig.6). Although leg ulcers are initiated by vasculitis, they are often potentiated by comorbid factors such as chronic venous insufficiency, occlusive arterial disease, peripheral edema, trauma, and friable skin from corticosteroid use.

Men who are seropositive and have nodular erosive disease of long duration are at greatest risk for developing rheumatoid vasculitis. Patients may have systemic constitutional symptoms and weight loss. Joint inflammation may be quiescent in these patients (97).

Patients with rheumatoid vasculitis typically have a high sedimentation rate, anemia of chronic disease, reactive thrombocytosis, hypoalbuminemia, high-titer RF and may have low C-3 and C-4 complement levels (99). Circulating immune complexes and activation of complement are believed to play a pathogenic role. Cryoglobulins may be present in one-third of patients (100). Angiography or biopsy of skin or nerve may be required to confirm the diagnosis. Leukocytoclastic vasculitis is the most common abnormality on skin biopsy (91).

6.14 Hepatic

Clinically significant liver disease related to RA is uncommon. Serum transaminases are usually normal, but alkaline phosphatase is not uncommonly elevated in active disease; in approximately two-thirds of cases, this is of hepatic origin (101).

Histological, liver biopsies obtained before starting methotrexate in RA patients reveal that 28% have mild portal triad inflammation and 38% have mild fatty infiltration (102). The liver is

frequently involved in amyloidosis. Patients with FS may develop nodular regenerative hyperplasia, portal fibrosis, portal hypertension, and bleeding esophageal varices (103). Hepatotoxicity is a known complication of many disease-modifying anti-rheumatic drugs and nonsteroidal anti-inflammatory agents.

6.15 Renal Disease

Although RA is not typically thought to cause renal disease, 17% of patients were found to have microscopic hematuria, elevated serum creatinine, or significant proteinuria in one prospective study (104).

Generally, renal disease in patients with RA is either secondary to drugs or related to RA and its complications. A raised serum creatinine or proteinuria is likely to be drug related, whereas isolated hematuria is associated with active rheumatoid disease (105). Numerous drugs used in the treatment of RA can cause renal disease, including nonsteroidal anti-inflammatory agents, gold, penicillamine, and cyclosporine. Clinically significant amyloidosis of the AA type, if it occurs in RA, almost invariably affects the kidneys, causing progressive proteinuria and decline in renal function. Renal involvement can occur in the setting of rheumatoid vasculitis, and membranous, membranoproliferative, and proliferative glomerulonephritis have been described in autopsy series (105). It is unclear whether the renal diseases associated with primary Sjogren's syndrome, such as interstitial nephritis and distal renal tubular acidosis, are seen with increased frequency in RA patients.

6.16 Infection

Infections are clearly increased in RA patients. Corticosteroid use, leukopenia, the presence of extraarticular features, and comorbid conditions such as diabetes, alcoholism, and chronic lung disease are all strong predictors of serious infection in this disease (106).

Malignancy

There are conflicting data regarding the overall risk of cancer in RA patients compared to the general population. Certainly, RA patients do have an increased risk of lymphoproliferative malignancies, and the risk is further increased by immunosuppressive medications used in treatment, including methotrexate, azathioprine, cyclosporine, and cyclophosphamide (107).

7. DIFFERENTIAL DIAGNOSIS

Other diseases must be considered which appear similar to RA([108) include.

7.1. Spondyloarthropathies:

• Enkylosing spondylitis,

• Enteric infections,

• Inflammatory bowel disease,

• Psoriatic arthritis,

• Reiter's arthritis,

• Whippet's disease;

7.2. Infectious causes:

• Acute rheumatic fever,

• Bacterial endocarditis,

• Gonococcal arthritis,

• Lyme disease,

• Viral infections (parvo-B 19, HIV, Hep.C);

7.3. Metabolic and endocrinecauses:

• Arthritis of thyroid disease,

• Gout,

• Hemochromotosis,

• Hemoglobinpathies,

• Pseudogout;

7.4. Connective tissue diseases:

• Acute relapsing symmetric seronegative synovitis,

• Dermatomyositis,

• Polymyalgia rheumatica,

• Polymyositis,

• Scleroderma,

• Still's disease,

• Systemic lupus erythematosus;

7.5. Other diseases that can mimic RA:

• Amyloidosis,

• Angioimmunoblastic lymphadenopathy,

• Arthritis associated with oral contraceptives,

• Malignancy,

• Sarcoidosis.

7.6 Laboratory work up

Serum protein abnormalities are often present. Rheumatoid factor (RF), an antibody directed against the Fc fragment of immunoglobulin G (IgG), is present in the sera of more than 75% of patients. High titers of RF are commonly associated with severe rheumatoid disease. Antinuclear antibodies are demonstrable in 20% of patients, though their titers are lower in RA than in SLE. However, the specificity of RF for RA is 74–98%. The amount of rheumatoid factor in blood can be measured as follows.

7.6.1 Agglutination tests

The most common method mixes the patient's blood with tiny latex beads covered with human antibodies (IgG). The latex beads clump or agglutinate if rheumatoid factor (IgM RF) is present. However, this method does not detect the presence of IgG or IgA RF.

7.6.2 Nephelometry test

This method mixes the patient's blood with antibodies that cause the blood to clump if rheumatoid factor is present. A light is passed through the tube containing the mixture and an instrument measures how much light is blocked by the mixture. Higher levels of rheumatoid factor create a cloudier sample and allow less light to pass through, measured in units. This method will detect all isotypes of RF. The presence of RF is not diagnostic of RA because of its lack of specificity for RA.

7.6.3 Anti-CCP

A new antibody against filaggrin may be a useful tool for the diagnosis of rheumatoid arthritis (RA). Anti-cyclic citrullinated peptide antibodies (Anti-CCP)-ELISA determination in early arthritis may be a good predictor of disease persistence and radiographic joint damage. The detection of anti-CCP antibody before the onset of the RA and the high concentration of autoantibodies in synovial fluid suggest a possible pathogenetic role of citrullination. The high specificity of anti-CCP antibody, its ability, to identify patients with early RA and distinguish it from other types of arthritis, potentially makes it a key serologic marker in the near future (109–112).

7.6.4 Imaging studies

Plain radiography of affected joints is essential in the evaluation of patients. The earliest changes occur in the wrists or feet and consist of soft-tissue swelling and juxta-articular demineralization. Later, the diagnostic changes of uniform joint-space narrowing are evident, and erosions develop. The erosions are often first evident at the fifth metatarsal head or ulnar styloid and at the juxta-

articular margins, where the bony surface is not protected by cartilage. These changes frequently take several years to develop.

7.6.5 MRI

Currently, magnetic resonance imaging is the best imaging modality to detect erosions. Specially designed magnetic resonance imaging (MRI) equipment called extremity MRI depicts soft-tissue changes and damage to cartilage and bone even better and at an earlier stage than does computed tomography. However, its cost precludes its widespread use.

7.6.6 ultrasound

Special ultrasound techniques called power Doppler ultrasonography (PDUS) or quantitative ultrasound (QUS) may be helpful in RA. Doppler ultrasound can aid in the initial diagnosis of RA even in the presence of minimal radiographic data on presentation. PDUS may be reliable for monitoring inflammatory activity in the joint. QUS, which is used for osteoporosis, has been used to detect bone loss in fingers, which may prove to be a good indicator of early RA. US are a sensitive method for assessing joint inflammatory activity but because it is a very new imaging modality in rheumatology, it is very operator dependent therefore is not a universally clinically relevant imaging tool for RA at this time. Doppler ultrasound is currently utilized by few rheumatologists in the academic setting, to follow up on patients with inflammatory arthritis (113, 114).

8. PHARMACOLOGIC THERAPY

Pharmacologic therapy is the therapeutic mainstay for all patients except those in remission. The drugs used either singly or in combination with each other include:

1. Analgesics/nonsteroidal anti-inflammatory drugs (NSAIDS), which primarily relieve pain,
2. DMARDS,
3. Biologics/anticytokines,
4. Immunoadsorption.

8.1 Medications used in treatment

Analgesics/ NSAIDS	DMARDS	Biologics/ anticytokines	Immunoadsorption
Acetaminophen	Azathioprine	Etanercept	Prosorba
Tramadol	d-penicillamine	Infliximab	
Cox 2 inhibitors	Hydroxychloroquine	Adalimumab	
Capsaicin	Methotrexate	Anakinra	
Narcotics	Sulfasalazine		
Ibuprofen	Leflunomide		
	Gold salts		

8.1.1Glucocorticoids

Prednisolone are most commonly used to suppress inflammation, and may be administered orally, intravenously, or by intraarticular injection. However, the use of glucocorticoids is very controversial because of its significant side effects and questionable joint preservation effects.

8.1.2 Combination drug therapy

Combinations of agents from the different classes are frequently employed in treatment However; concurrent use of two or more agents from within a drug class is usually reserved for DMARDs. Various combinations of DMARDS have been used to treat both active early RA and established disease. At present, it is unclear which combination is best, when they should be used, or which patients are more likely to benefit from combination versus single agent DMARD therapy.

8.1.3 Monitoring for drug toxicity

Anti-rheumatic drugs are potentially toxic substances, therefore, a balance must be struck between the side effects and the therapeutic effect. Therefore, all DMARDS have side effect monitoring recommendations. The recommended strategy by the American College of Rheumatology (ACR) for drug monitoring in the treatment of RA with DMARDS is to check serum transaminase, albumin, creatinine and complete blood counts every 4–8 weeks. However, if leflunomide and methotrexate are used together, monthly monitoring should be continued as long as the combination of these two drugs is used. The treatment of extraarticular manifestations of rheumatoid arthritis, such as interstitial lung disease, vasculitis, and others, is based upon an assessment of severity and activity. Most of the life threatening conditions are treated with DMARDS, high dose steroids and/or immunosuppressants. Management decisions require distinguishing between infections, underlying RA and drug side effects, which at times may be difficult. Rigorous antirheumatic treatment aiming at maximally suppressing disease activity will reduce extra-articular disease and complications. When joints are destroyed, patients should be referred to the orthopedic surgeon for reconstruction or replacement.

9. Summary

Armed with knowledge of the clinical features, examination findings, and differential diagnosis, the clinician is equipped to make an accurate and timely diagnosis of RA. Patients with RA then benefit from early introduction of effective therapies that lower the incidence and prevalence of many of the joint-specific and extraarticular disease complications described in this chapter.

REFERENCE

1. A.M. Wolfe, J.H. Kellgren, A.T. Masi, The epidemiology of rheumatoid arthritis: a review. II. Incidence and diagnostic criteria, Bull. Rheum. Dis. 19 (3) (1968) 524–529.
2. W.M. O'Brien, et al., A genetic study of rheumatoid arthritis and rheumatoid factor in Blackfeet and Pima Indians, Arthritis Rheum. 10 (3) (1967) 163–179.
3. A. Engel, J. Roberts, T.A. Burch, Rheumatoid arthritis in adults, Vital Health Stat. 1 11 (17) (1966) 1–43.
4. W.M. Mikkelsen, et al., Estimates of the prevalence of rheumatic diseases in the population of Tecumseh, Michigan, 1959–1960, J. Chronic. Dis. 20 (6) (1967) 351–369.
5. J.W. Wood, et al., Rheumatoid arthritis in Hiroshima and Nagasaki, Japan. Prevalence, incidence, and clinical characteristics, Arthritis Rheum. 10 (1) (1967) 21–31
6. J.P. Vandenbroucke, H.M. Hazevoet, A. Cats, Survival and cause of death in rheumatoid arthritis: a 25-year prospective follow-up, J. Rheumatol. 11 (2) (1984) 158–161.
7. R.S. Pinals, Survival in rheumatoid arthritis, Arthritis Rheum. 30 (4) (1987) 473–475.
8. LinosA Worthington JW,O Fallon WM, KurlandLT. The epidemiology of rheumatoid arthritis in Rochester, Minnoesta: a study of incidence, prevalence and motarlity. Ann J of Epidemiology 1980; 111.87.
9. Glennas A,Kvein TK Andrup O, karstensan B, Munthe E. recent arthritis in the elderly a five years longitudinal observational study. J of rheumatology 2000: 27 101-108.
10. A.J. Silman, et al., Twin concordance rates for rheumatoid arthritis: results from a nationwide study, Br. J. Rheumatol. 32 (10) (1993) 903–907.

11. Silman AJ, H.M., Epidemiology of the Rheumatic Diseases, 2nd ed., Oxford University Press, Oxford, 2001.

12. T. Pincus, L.F. Callahan, Formal education as a marker for increased mortality and morbidity in rheumatoid arthritis, J. Chronic. Dis. 38 (12) (1985) 973–984.

13. A.J. Silman, et al., Twin concordance rates for rheumatoid arthritis: results from a nationwide study, Br. J. Rheumatol. 32 (10) (1993) 903–907.

14. A.S. Rigby, et al., Investigating the HLA component in rheumatoid arthritis: an additive (dominant) mode of inheritance is rejected, a recessive mode is preferred, Genet. Epidemiol. 8 (3) (1991) 153– 175.

15. P. Stastny, Association of the B-cell alloantigen DRw4 with rheumatoid arthritis, N. Engl. J. Med. 298 (16) (1978) 869–871.

16. P.K. Gregersen, Genetics of rheumatoid arthritis: confronting complexity, Arthritis Res. 1 (1) (1999) 37–44.

17. H. Mu, et al., Tumor necrosis factor a microsatellite polymorphism is associated with rheumatoid arthritis severity through an interaction with the HLA-DRB1 shared epitope, Arthritis Rheum. 42 (3) (1999) 438–442.

18. T. Kouri, et al., Antibodies to synthetic peptides from Epstein–Barr nuclear antigen-1 in sera of patients with early rheumatoid arthritis and in preillness sera, J. Rheumatol. 17 (11) (1990) 1442–1449.

19. A.H. Hajeer, et al., Influence of previous exposure to human parvovirus B19 infection in explaining susceptibility to rheumatoid arthritis: an analysis of disease discordant twin pairs, Ann. Rheum. Dis. 53 (2) (1994) 137–139.

20. D.J. Walker, I.D. Griffiths, D. Madeley, Autoantibodies and antibodies to microorganisms in rheumatoid arthritis: comparison of histocompatible siblings, J. Rheumatol. 14 (3) (1987) 426–428.

21. D.J. Pattison, D.P. Symmons, A. Young, Does diet have a role in the aetiology of rheumatoid arthritis? Proc. Nutr. Soc. 63 (1) (2004) 137–143.

22. W.R. Finch, Mortality in rheumatoid disease, J. Insur. Med. 36 (3) (2004) 200–212.

23. S. Sihvonen, et al., Death rates and causes of death in patients with rheumatoid arthritis: a population-based study, Scand. J. Rheumatol. 33 (4) (2004) 221–227.

24. Weyand CM, Schmidt D, Wagner U, et al. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 1998; 41(5):817- 822.

25. Massardo L, Gabriel SE, Crowson CS, et al. A population based assessment of the assessment of the use of orthopedic surgery in patients with rheumatoid arthritis. J Rheumatol 2002; 29(1):52-56.

26. Peschken CA, Esdaile JM. Rheumatic diseases in North America's indigenous peoples. Semin Arthritis Rheum 1999; 28(6):368-391.

27. Anderson JJ, Wells G, Verhoeven AC, et al. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum 2000; 43(1):22-29.

28. Turesson C,Fallon WM, Crowson CS, et al. Incidence of extraarticular disease manifestations in a population based cohort of patients with rheumatoid arthritis. Arthritis Rheum 2000; 43(9S):S152.

29. Hakala M, Sajanti E, Ikaheimo I, et al. High prevalence of rheumatoid factor in community-based series of patients with rheumatoid arthritis meeting the new (1987) ARA criteria: RF-negative non-erosive rheumatoid arthritis is very rare. Scand J Rheumatol 1998; 27(5):368-372.

30. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31(3):315-324.

31. Fleming A, Benn RT, Corbett M, et al. Early rheumatoid disease. II. Patterns of joint involvement. Ann Rheum Dis 1976;35(4):361;364.

32. Rosen A, Weiland AJ. Rheumatoid arthritis of the wrist and hand. Rheum Dis Clin North Am 1998; 24(1):101-128.

33. Gordon DA, Hastings DE. Clinical features of early, progressive and late disease. In: Klippel JH, Dieppe PA, eds. Rheumatology, 2nd ed. Barcelona: Mosby, 1998:13.

34. Anderson RJ. Rheumatoid arthritis: clinical and laboratory features. In: Klippel JH, ed. Primer on the rheumatic diseases, 12th ed. Atlanta: Arthritis Foundation, 2001:221.

35. Burra G, Katchis SD. Rheumatoid arthritis of the forefoot. Rheum Dis Clin North Am 1998; 24(1):173-180.

36. Mizumura T, Momohara S, Tomatsu T, et al. Radiological evaluation of foot deformities in rheumatoid arthritis. Ryumachi 2000; 40(6):891-897.

37. Ritchie GW, Keim HA. Major foot deformities: their classification and x-ray analysis. J Can Assoc Radiol 1968; 19(3):155-166.

38. Spiegel TM, Spiegel JS. Rheumatoid arthritis in the foot and ankleâ€"diagnosis, pathology, and treatment. The relationship between foot and ankle deformity and disease duration in 50 patients. Foot Ankle Int 1982; 2(6):318-324.

39. Michelson J, Easley M, Wigley FM, et al. Posterior tibial tendon dysfunction in rheumatoid arthritis. Foot Ankle Int 1995; 16(3):156-161. P.24

40. Rawlins BA, Girardi FP, Boachie-Adjei O. Rheumatoid arthritis of the cervical spine. Rheum Dis Clin North Am 1998; 24(1):55-65.

41. Fujiwara K, Owaki H, Fujimoto M, et al. A long-term follow-up study of cervical lesions in rheumatoid arthritis. J Spinal Disord 2000; 13(6):519-526.

42. Redlund-Johnell I. Upper airway obstruction in patients with rheumatoid arthritis and temporomandibular joint destruction. Scand J Rheumatol 1988; 17(4):273-279.

43. I.A. Polisar, et al., Bilateral midline fixation of cricoarytenoid joints as a serious medical emergency, JAMA 172 (1960) 901–906

44. Colletti V, Fiorino FG, Bruni L, et al. Middle ear mechanics in subjects with rheumatoid arthritis. Audiology 1997; 36(3):136-146.

45. Yood RA, Goldenberg DL. Sternoclavicular joint arthritis. Arthritis Rheum 1980; 23(2):232-239.

46. Kalliomaki JL, Viitanen SM, Virtama P. Radiological findings of sternoclavicular joints in rheumatoid arthritis. Acta Rheumatol Scand 1968; 14(3):233-240.

47. Khong TK, Rooney PJ. Manubriosternal joint subluxation in rheumatoid arthritis. J Rheumatol 1982; 9(5):712-715.

48. Turesson C, Fallon WM, Crowson CS, et al. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002; 29(1):62-67.

49. Ichikawa MM, Murata Y, Higaki Y, et al. Rheumatoid neutrophilic dermatitis. Eur J Dermatol 1998; 8(5):347-349.

50. Uhlig T, Kvien TK, Jensen JL, et al. Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. Ann Rheum Dis 1999; 58(7):415-422.

51. Wisnieski JJ, Askari AD. Rheumatoid nodulosis: a relatively benign rheumatoid variant. Arch Intern Med 1981;141(5):615-619.

52. Palmer DG. The anatomy of the rheumatoid lesion. Br Med Bull 1995; 51 (2):286-295.

53. Segal R, Caspi D, Tishler M, et al. Accelerated nodulosis and vasculitis during methotrexate therapy for rheumatoid arthritis. Arthritis Rheum 1988; 31(9):1182-1185.

54. Cunnane G, Warnock M, Rehman Q, et al. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum 2001; 44(9):S373.

55. Baer AN, Dessypris EN, Krantz SB. The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis. Semin Arthritis Rheum 1990;19(4):209-223.

56. Bentley DP, Williams P. Serum ferritin concentration as an index of storage iron in rheumatoid arthritis. J Clin Pathol 1974; 27(10):786-788.

57. Harreby M, Danneskiold-Samsoe B, Kjer J, et al. Viscosity of plasma in patients with rheumatoid arthritis. Ann Rheum Dis 1987; 46(8):601-604.

58. Bach LA, Buchanan RR, Scarlett JD, et al. Hyperviscosity syndrome secondary to rheumatoid arthritis. Aust N Z J Med 1989; 19(6):710-712.

59. Kelly CA, Malcolm AJ, Griffiths I. Lymphadenopathy in rheumatic patients. Ann Rheum Dis 1987; 46(3):224-227.

60. Kondratowicz GM, Symmons DP, Bacon PA, et al. Rheumatoid lymphadenopathy: a morphological and immunohistochemical study. J Clin Pathol 1990; 43(2):106-113.

61. Isomaki H, Koivisto O, Kiviniitty K. Splenomegaly in rheumatoid arthritis. Acta Rheumatol Scand 1971; 17(1):23-26.

62. Georgescu L, Quinn GC, Schwartzman S, et al. Lymphoma in patients with rheumatoid arthritis: association with the disease state or methotrexate treatment. Semin Arthritis Rheum 1997; 26(6):794-804.

63. Sant SM, Tormey VJ, Freyne P, et al. Lymphatic obstruction in rheumatoid arthritis. Clin Rheumatol 1995; 14(4):445-450.

64. Husby G. Amyloidosis and rheumatoid arthritis. Clin Exp Rheumatol 1985;3(2):173-180.

65. Okuda Y, Takasugi K, Oyama T, et al. Amyloidosis in rheumatoid arthritisâ€”clinical study of 124 histologically proven cases. Ryumachi 1994; 34(6):939-946.

66. Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndromes. Semin Arthritis Rheum 1991; 21(3):129-142.

67. Dhodapkar MV, Li CY, Lust JA, et al. Clinical spectrum of clonal proliferations of T-large granular lymphocytes: a T-cell clonopathy of undetermined significance? Blood 1994; 84(5):1620-1627.

68. Foster CS, Forstot SL, Wilson LA. Mortality rate in rheumatoid arthritis patients developing necrotizing scleritis or peripheral ulcerative keratitis: effects of systemic immunosuppression. Ophthalmology 1984; 91(10):1253-1263.

69. Reddy SC, Rao UR. Ocular complications of adult rheumatoid arthritis. Rheumatol Int 1996; 16(2):49-52.

70. Chang DJ, Paget SA. Neurologic complications of rheumatoid arthritis. Rheum Dis Clin North Am 1993; 19(4):955-973.

71. Nadkar MY, Agarwal R, Samant RS, et al. Neuropathy in rheumatoid arthritis. J Assoc Physicians India 2001; 49:217-220.

72. Puechal X, Said G, Hilliquin P, et al. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis: a clinicopathologic and prognostic study of thirty-two patients. Arthritis Rheum 1995; 38(11):1618-1629.

73. Ekdahl C, Broman G. Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. Ann Rheum Dis 1992; 51(1):35-40.

74. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med 1998;19(4):667-685

75. Bywaters EG. The mechanism of low glucose concentration in rheumatoid pleural effusions: a primary transport defect? J Rheumatol 1981; 8(1):175-176.

76. Anaya JM, Diethelm L, Ortiz LA, et al. Pulmonary involvement in rheumatoid arthritis. Semin Arthritis Rheum 1995; 24(4):242-254.

77. Fujii M, Adachi S, Shimizu T, et al. Interstitial lung disease in rheumatoid arthritis: assessment with high-resolution computed tomography. J Thorac Imaging 1993; 8(1):54-62.

78. Rajasekaran BA, Shovlin D, Lord P, et al. Interstitial lung disease in patients with rheumatoid arthritis: a comparison with cryptogenic fibrosing alveolitis. Rheumatology (Oxford) 2001; 40(9):1022-1025.

79. Haslam PL, Turton CW, Heard B, et al. Bronchoalveolar lavage in pulmonary fibrosis: comparison of cells obtained with lung biopsy and clinical features. Thorax 1980; 35(1):9-18.

80. Muller NL, Miller RR. Diseases of the bronchioles: CT and histopathologic findings. Radiology 1995; 196(1):3-12.

81. Kremer JM, Alarcon GS, Weinblatt ME, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. Arthritis Rheum 1997; 40(10):1829-1837.

82. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002; 46(4):862-873.

83. Wolfe F, Straus WL. Increased prevalence of cardiovascular and cerebrovascular disease in rheumatoid arthritis compared with osteoarthritis. Arthritis Rheum 2000; 43:S133.

84. Del Rincon ID, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001; 44(12):2737-2745.

85. Warrington KJ, Takemura S, Goronzy JJ, et al. CD4+, CD28-T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. Arthritis Rheum 2001; 44(1):13-20.

86. Liuzzo G, Goronzy JJ, Yang H, et al. Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. Circulation 2000; 101(25):2883-2888.

87. Warrington KJ, Kent P, Nakajima T, et al. Rheumatoid arthritis is an independent risk factor for accelerated coronary artery disease. Arthritis Rheum 2001; 44:S378.

88. Haverkate F, Thompson SG, Pyke SD, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997; 349(9050):462-466.

89. Bonfiglio T, Atwater EC. Heart disease in patients with seropositive rheumatoid arthritis; a controlled autopsy study and review. Arch Intern Med 1969; 124 (6):714-719.

90. Bacon PA, Gibson DG. Cardiac involvement in rheumatoid arthritis. An echocardiographic study. Ann Rheum Dis 1974; 33 (1):20-24.

91. Hara KS, Ballard DJ, Ilstrup DM, et al. Rheumatoid pericarditis: clinical features and survival. Medicine (Baltimore) 1990; 69 (2):81-91.

92. Ahern M, Lever JV, Cosh J. Complete heart block in rheumatoid arthritis. Ann Rheum Dis 1983;42(4):389-397.

93. Chand EM, Freant LJ, Rubin JW. Aortic valve rheumatoid nodules producing clinical aortic regurgitation and a review of the literature. Cardiovasc Pathol 1999;8(6):333-338.

94. Webber MD, Selsky EJ, Roper PA. Identification of a mobile intracardiac rheumatoid nodule mimicking an atrial myxoma. J Am Soc Echocardiogr 1995;8(6):961-964

95. Voyles WF, Searles RP, Bankhurst AD. Myocardial infarction caused by rheumatoid vasculitis. Arthritis Rheum 1980; 23 (7):860-863.

96. Gravallese EM, Corson JM, Coblyn JS, et al. Rheumatoid aortitis: a rarely recognized but clinically significant entity. Medicine (Baltimore) 1989; 68(2):95-106.

97. Scott DG, Bacon PA, Tribe CR. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. Medicine (Baltimore) 1981; 60 (4):288-297.

98. Vollertsen RS, Conn DL. Vasculitis associated with rheumatoid arthritis. Rheum Dis Clin North Am 1990; 16(2):445-461.

99. Mongan ES, Cass RM, Jacox RF, et al. A study of the relation of seronegative and seropositive rheumatoid arthritis to each other and to necrotizing vasculitis. Am J Med 1969;47(1):23-35.

100. Weisman M, Zvaifler N. Cryoimmunoglobulinemia in rheumatoid arthritis. Significance in serum of patients with rheumatoid vasculitis. J Clin Invest 1975;56(3):725-739.

101. Sullivan S, Hamilton EB, Williams R. Rheumatoid arthritis and liver involvement. J R Coll Physicians Lond 1978;12(5):416-422.

102. Brick JE, Moreland LW, Al-Kawas F, et al. Prospective analysis of liver biopsies before and after methotrexate therapy in rheumatoid patients. Semin Arthritis Rheum 1989;19(1):31-44.

103. Thorne C, Urowitz MB, Wanless I, et al. Liver disease in Felty's syndrome. Am J Med 1982;73(1):35-40.

104. Koseki Y, Terai C, Moriguchi M, et al. A prospective study of renal disease in patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60(4):327-331.

105. Boers M, Croonen AM, Dijkmans BA, et al. Renal findings in rheumatoid arthritis: clinical aspects of 132 necropsies. Ann Rheum Dis 1987;46(9):658-663.

106. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46(9):2294-2300

107. Mikuls TR, Saag KG. Comorbidity in rheumatoid arthritis. Rheum Dis Clin North Am 2001;27(2):283-303.

108. G.S. Hoffman, Polyarthritis: the differential diagnosis of rheumatoid arthritis, Semin. Arthritis Rheum. 8 (2) (1978) 115–141.

109. O. Kasapcopur, et al., Diagnostic accuracy of anti-cyclic citrullinated peptide antibodies in juvenile idiopathic arthritis, Ann. Rheum. Dis.63 (12) (2004) 1687–1689.

110. K. Solanki, et al., Anti-cyclic citrullinated antibodies: complementary to IgM rheumatoid factor in the early diagnosis of rheumatoid arthritis, NZ Med. J. 117 (1203) (2004) U1097.

111. W.J. van Venrooij, E.R. Vossenaar, A.J. Zendman, Anti-CCP antibodies: the new rheumatoid factor in the serology of rheumatoid arthritis, Autoimmun. Rev. 3 (Suppl. 1) (2004) S17–S19.

112. M.H. Wener, et al., Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia, Arthritis Rheum. 50 (7) (2004) 2305–2308.

113. L. Casimiro, et al., Therapeutic ultrasound for the treatment of rheumatoid arthritis, Cochrane Database Syst. Rev. 3 (2002) CD003787.

114. J. Teh, et al., Power Doppler ultrasound of rheumatoid synovitis: quantification of therapeutic response, Br. J. Radiol. 76 (912) (2003) 875–879.

***Author for correspondence**
V.Parthasarathy
Phone: +91-9443512724
Fax: +91-4144-238080