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The clinical features of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations. Tendon and bursal involvement are frequent and often clinically dominant in early disease. RA can affect any joint, but it is usually found in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as in the wrists and knee. Articular and periarticular manifestations include joint swelling and tenderness to palpation, with morning stiffness and severe motion impairment in the involved joints. The clinical presentation of RA varies, but an insidious onset of pain with symmetric swelling of small joints is the most frequent finding. RA onset is acute or subacute in about 25% of patients, but its patterns of presentation also include palindromic onset, monoarticular presentation (both slow and acute forms), extra-articular synovitis (tenosynovitis, bursitis), polymyalgic-like onset, and general symptoms (malaise, fatigue, weight loss, fever). The palindromic onset is characterized by recurrent episodes of oligoarthritis with no residual radiologic damage, while the polymyalgic-like onset may be clinically indistinguishable from polymyalgia rheumatica in elderly subjects. RA is characteristically a symmetric erosive disease. Although any joint, including the cricoarytenoid joint, can be affected, the distal interphalangeal, the sacroiliac, and the lumbar spine joints are rarely involved. The clinical features of synovitis are particularly apparent in the morning. Morning stiffness in and around the joints, lasting at least 1 h before maximal improvement is a typical sign of RA. It is a subjective sign and the patient needs to be carefully informed as to the difference between pain and stiffness. Morning stiffness duration is related to disease activity. Hand involvement is the typical early manifestation of rheumatoid arthritis. Synovitis involving the metacarpophalangeal, proximal interphalangeal and wrist joints causes a characteristic tender swelling on palpation with early severe motion impairment and no radiologic evidence of bone damage. Fatigue, feveret, weight loss, and malaise are frequent clinical signs which can be associated with variable manifestations of extra-articular involvement such as rheumatoid nodules, vasculitis, hematologic abnormalities, Felty's syndrome, and visceral involvement. Although there is no laboratory test to exclude or prove the diagnosis of rheumatoid arthritis, several laboratory abnormalities can be detected. Abnormal values of the tests for evaluation of systemic inflammation are the most typical humoral features of RA. These include: erythrocyte sedimentation rate, acute phase proteins and plasma viscosity. Erythrocyte sedimentation rate and C-reactive protein provide the best information about the acute phase response. The C-reactive protein is strictly correlated with clinical assessment and radiographic changes. Plain film radiography is the standard investigation to assess the extent of anatomic changes in rheumatoid arthritis patients. The radiographic features of the hand joints in early disease are characterized by soft tissue swelling and mild juxtaarticular osteoporosis. In the the past 10 years, ultrasonography has gained acceptance for studying joint, tendon and bursal involvement in RA. It may improve the early clinical assessment and the follow-up of these patients, showing such details as synovial thickening even within finger joints. Other imaging techniques, such as magnetic resonance, computed tomography and scintigraphy may provide useful information about both the features and the extent for anatomic damage in selected rheumatoid arthritis patients. The natural history of the disease is poorly defined; its clinical course is fluctuating and the prognosis unpredictable. RA is an epidemiologically relevant cause of disability. An adequate early treatment of RA may alter the disease course.

Keywords: Chronic inflammatory diseases; Connective tissue diseases; Rheumatoid arthritis; Clinical features of rheumatoid arthritis

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology and complex multifactorial pathogenesis affecting joints and other tissues. The natural history of RA is poorly defined, its clinical course is fluctuating and the prognosis unpredictable.

RA affects up to 1–3% of the population, with a 3:1 female preponderance disappearing in older age. There is evidence of a genetic predisposition to the disease.

RA is characterized by progressive and irreversible damage of the synovial-lined joints causing loss of joint space, of bone and of function, as well as deformity. Extracellular matrix degradation is a hallmark of RA which is responsible for the typical destruction of cartilage, ligaments, tendons, and bone.

RA is characteristically a symmetric arthritis. Articular and periarticular manifestations include joint swelling and tenderness to palpation, with morning stiffness and severe motion impairment in the involved joints.

Extra-articular signs can involve pulmonary, cardiovascular, nervous, and reticuloendothelial systems (Table 1) [1–4].

The clinical presentation of RA varies, but an insidious onset of pain with symmetric swelling of the small joints is the most frequent finding. RA onset is acute or subacute in about 25% of patients, but its patterns of presentation also include palindromic onset, monoarticular presentation (both slow and acute forms), extra-articular synovitis (tenosynovitis, bursitis), polymyalgic-like onset, and general symptoms (malaise, fatigue, weight loss, fever).

The palindromic onset is characterized by recurrent episodes of oligoarthritis with no residual radiologic damage, while the polymyalgic-like onset may be clinically indistinguishable from polymyalgia rheumatica in elderly subjects.

Early RA is characterized by symmetric polyarthritis involving the small joints of the hands and feet with no radiologic changes (Fig. 1). RA most frequently affects the metacarpophalangeal, proximal interphalangeal and wrist joints.

Although any joint, including the cricoarytenoid joint, can be affected, the distal interphalangeal, the sacroiliac and the lumbar spine joints are rarely involved, which is peculiar because these are some of the most typical targets of seronegative spondylarthropathies, such as psoriatic arthritis and ankylosing spondylitis.

Simultaneous involvement of the same joint areas on both sides of the body should always be investigated even when it is not apparent.

The clinical manifestations of RA vary, depending on the involved joints and the disease stage.

The clinical features of synovitis are particularly apparent in the morning. Morning stiffness in and around the joints, lasting at least 1 h before maximal improvement is a typical sign of RA. It is a subjective sign and the patient needs to be carefully informed as to the difference between pain and stiffness. Morning stiffness duration is related to disease activity [5].

Table 1
Rheumatoid arthritis: extra-articular manifestations

Constitutional symptoms
Fever
Asthenia
Weight loss
Malaise
Anorexia
Rheumatoid nodules
Subcutaneous
Lung parenchymal
Cardiovascular
Vasculitis (coronary arteritis)
Pericardial inflammation and effusion
Myocarditis
Mitral valve disease
Conduction defects
Pulmonary
Pleural effusions
Pulmonary nodules
Interstitial fibrosis
Pneumonitis
Arteritis
Ocular
Keratoconjunctivitis sicca
Episcleritis
Scleritis
Conjunctivitis
Neurologic
Compression neuropathy (such as carpal tunnel syndrome)
Mononeuritis multiplex
Cervical myelopathy
Central nervous system disease (stroke, seizure, hemorrhage, encephalopathy, meningitis)
Skin
Distal leg ulcers
Palmar erythema
Cutaneous vasculitis
Hematologic
Anemia
Thrombocytosis
Granulocytopenia
Eosynophilia
Cryoglobulinemia
Hyperviscosity
Renal
Glomerulonephritis
Vasculitis
Secondary amyloidosis
Hepatic
Elevated liver enzymes

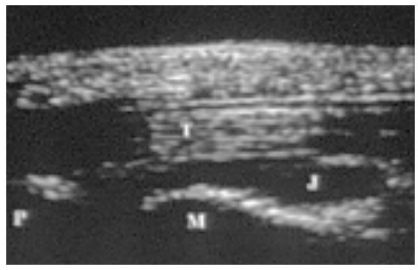

Fig. 1. Early rheumatoid arthritis. Longitudinal volar scan of a metacarpophalangeal joint shows capsular enlargement with homogeneous anechoic joint cavity widening. M, metacarpal head; P, phalanx; J, fluid collection; T, flexor tendons.

To better define the clinical syndrome, some classification criteria have been developed. Table 2 lists the 1987 American Rheumatism Association revised criteria for RA classification. A patient is said to have RA if at least 4 criteria are present for at least 6 weeks. These criteria are useful for several purposes such as the classification of groups of patients, the assessment of disease frequency, and diagnosis [6].

2. The clinical features of joint, tendon, and bursal involvement

2.1. The hand

Hand involvement is the typical early sign of RA. Synovitis involving the metacarpophalangeal, proximal interphalangeal and wrist joints causes a characteristic tender swelling on palpation with early severe motion impairment and no radiologic evidence of bone damage. Several deformities can occur in late disease. Such terms as 'boutonniere deformity' and 'swan neck deformity' are commonly used to describe associated damage and dislocation of finger joints and tendons. Metacarpophalangeal and proximal interphalangeal joints are early and typical sites of erosions (Fig. 2). Small, discrete, pocketed erosions develop near the capsular insertion.

Table 2
American Rheumatism Association revised criteria for rheumatoid arthritis classification

1. Morning stiffness
2. Arthritis of three or more joint areas
3. Arthritis of hand joints
4. Symmetric arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes

Criteria 1–4 must have been present for at least 6 weeks.

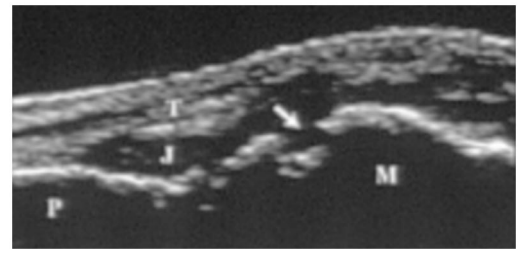

Fig. 2. Rheumatoid arthritis. Chronic synovitis of a metacarpophalangeal joint. Longitudinal dorsal scan shows enlarged joint cavity and marked erosion of the metacarpal head. M, metacarpal head; P, phalanx; J, synovial fluid; T, extensor tendon; arrow indicates erosion.

2.2. The foot

Synovitis of the metatarsophalangeal joints is an early sign of RA and one of the first joint areas with unequivocal radiographic changes, i.e. erosions and bone decalcification. Metatarsophalangeal joint involvement is painful and disabling. Valgus deformities and flat foot are frequent findings in late disease.

2.3. The knee

The knee is a common site for RA, being affected in 70–80% of patients. Although not an early target of the disease, the knee can be prominently involved in later stages. Muscle atrophy, flexion contractures, large Baker's cysts, valgus instability and inability to walk are typical late manifestations of aggressive synovitis. A thrombophlebitis-like syndrome can be caused by popliteal cyst rupture. Erosions are relatively late manifestations.

2.4. The hip

Early involvement of the hip joint is rare, but can cause severe disability in 50% of the established RA patients where it is found. The radiologic features of rheumatoid coxitis include periarticular osteopenia and concentric articular cartilage narrowing. Destructive synovitis can cause the so-called protrusio acetabuli. Hip pain in RA patients may be due to bursal involvement, i.e. in the trochanteric, iliac, or ischial bursae. Advanced synovitis of the hip causes severe disability because the patient cannot walk and perform all the daily living activities based on hip rotation and abduction.

2.5. The shoulder

The shoulder is often involved in both early and late disease. Many different patterns of shoulder involvement can be observed according to disease target, i.e.

the glenohumeral joints, various bursae, the biceps tendon, the acromioclavicular joint. Several patterns may be associated, resulting in heterogeneous combinations of joint disease. Rotator cuff damage is a relevant and often insidious cause of morbidity which can be observed in about 50% of patients; however, sudden rotator cuff tears have been described with pain and inflammation so severe as to mimic sepsis. Tendon rupture may be precipitated by local steroids injection.

2.6. The elbow

Although the elbow is relatively commonly affected in RA, its clinical involvement is usually not severe in early RA. The loss of full extension is one of the first signs of elbow involvement, while loss of supination indicates radial head damage.

2.7. The spine

Cervical spine dislocation is a relatively frequent complication in RA patients with long-standing, severe involvement of peripheral joints. Atlantoaxial joint subluxation is a serious complication which can cause spinal cord compression. The clinical features of cervical spine dislocation can be rather variable, including paresthesia, weakness, numbness, sensory impairment, spastic paralysis, paraplegia, tetraplegia, syncope, loss of bladder control, fecal incontinence and sudden death. Most patients can be asymptomatic at the time of diagnosis. Other patients complain of mild to severe neck pain with or without neurologic signs. Acute cervical myelopathy can be caused by neck hyperextension due to anesthesia or car crashes. Clinically relevant involvement of the dorsolumbar spine is rare.

2.8. Temporomandibular joints

Temporomandibular joints are frequently affected in RA. Painful mouth opening, ear, face or temple pain and palpable crepitus are the typical clinical features. Arthritis of the temporomandibular joints hardly ever interferes with mastication.

2.9. Cricoarytenoid joints

Hoarseness, upper airway obstruction, pain in the throat, dysphagia, and stridor are the clinical features of arthritis in the crycoarytenoid joints.

2.10. Tendon involvement

Tenosynovitis of finger flexor and extensor tendon sheaths is one of the earliest signs of RA. It usually develops insidiously over weeks to months, but may be slowly progressive over years or occasionally more acute with rapid onset of swelling and clinically relevant motion impairment, i.e. finger and wrist flexion. Entrapment neuropathies due to nerve compression by enlarged tendon sheaths (e.g. carpal and tarsal tunnel syndromes) may complicate tenosynovitis. As the disease progresses, the tendon may rupture. Tendon weakening and rupture contribute to the development of joint instability, severe joint dislocation, and deformities. Spontaneous tendon rupture of the finger extensor tendons is the most frequent complication of advanced tendon damage. Ultrasonography (US) of the hand is a very important tool for RA studies since the typical features of tendon involvement appear early and rather distinctly in this anatomic region and US shows them clearly. Different patterns of tendon damage, including tendon sheath enlargement, loss of normal fibrillar echotexture, irregular tendon margins and tendon tears [7] are easily and quickly demonstrated by high frequency transducers (10, 13, 15, and 20 MHz).

2.11. Bursal involvement

Bursitis can be a major cause of pain and functional impairment. Enlarged inflamed bursae can develop abnormal communications with adjacent joints. Olecranon bursitis is common in early RA.

3. Extra-articular involvement

3.1. Constitutional manifestations

Fatigue, fever, weight loss, and malaise are frequent clinical signs which can be associated with variable manifestations of extra-articular involvement such as rheumatoid nodules, vasculitis, hematologic abnormalities, Felty's syndrome, and visceral involvement—cardiac, pulmonary, renal, ocular, and neurologic or hepatic.

3.2. Rheumatoid nodules

Nodules are one of the most typical diagnostic features of RA. Subcutaneous rheumatoid nodules are found in 20–30% of the patients with a positive test for rheumatoid factor; they usually occur on extensor surfaces and pressure areas, i.e. finger joints, the olecranon process, the proximal ulna, Achilles tendon, and sacral prominences.

3.3. Rheumatoid vasculitis

Rheumatoid vasculitis, mostly involving small vessels, has heterogeneous clinical presentation including nailfold infarcts, cutaneous ulcerations, rash, gangrene, palpable purpura, constitutional symptoms, sensorymo-

tor neuropathy, and visceral arteritis. Systemic vasculitis is rare, while necrotizing vasculitis is associated with severe disease and relevant mortality [8].

3.4. Muscular involvement

Muscle weakness and atrophy are frequently found in RA patients. They may be due to motion impairment, long standing compression of the peripheral nerves, and corticosteroid therapy. Active 'patchy' myositis, focal necrosis, chronic myopathy with similar features to a dystrophic process may also occur.

3.5. Bone involvement

Periarticular osteopenia and diffuse bone loss are common features in RA patients.

3.6. Felty's syndrome

Felty's syndrome is characterized by the association of RA, splenomegaly, and leukopenia. It usually occurs in patients with long standing disease. Other features of Felty's disease include anemia, thrombocytopenia, leg ulcers, peripheral neuropathy, and infections.

3.7. Cardiac involvement

Although pericardial involvement is a frequent autoptic finding in RA patients, symptomatic pericarditis and other manifestations of clinical heart disease are unusual. On rare occasions, coronary arteritis, myocarditis, endocarditis and valve damage can be clinically apparent.

3.8. Pulmonary involvement

Pulmonary involvement is relatively frequent in RA. Clinical findings closely reflect the pathologic changes and include pleural effusions, obliterative bronchiolitis, interstitial fibrosis, pulmonary nodules, and pulmonary arteritis. Pulmonary involvement may be insidious and escape clinical recognition.

4. Laboratory tests

Although there is no laboratory test to diagnose or rule out RA, several laboratory abnormalities can be detected. Abnormal values of systemic inflammation tests are the most typical humoral features of RA. They include erythrocyte sedimentation rate, acute phase proteins (C-reactive protein, fibrinogen, haptoglobin, α-1-acid glycoprotein, α-1-antitrypsin, *S*-amyloid-A protein) and plasma viscosity. Erythrocyte sedimentation rate and C-reactive protein provide the best information about the acute phase response. The C-reactive protein is strictly correlated with clinical assessment and radiographic changes. Thrombocytosis, low serum iron and low hemoglobin levels also indicate active disease.

Rheumatoid factors are anti-immunoglobulins that characterize RA, even though they can be found in other conditions, such as other connective tissue diseases, viral infections, sarcoidosis, infective endocarditis, liver diseases, and tuberculosis.

Normocytic, hypochromic anemia, leukocytosis, high γ-globulin and α-2-globulin levels are the other usual findings which, however, are not diagnostic. Antinuclear antibodies may be detected in several patients.

5. Imaging techniques

Plain radiography is the standard investigation to assess the extent of anatomic changes in RA patients. The radiographic features of the hand joints in early disease are characterized by soft tissue swelling and mild juxtaarticular osteoporosis. However, conventional radiology is of limited value in soft tissue studies, even though mammography may markedly improve the resolution of the radiologic images.

Tiny bone erosions at the joint margin with minimal bone formation may develop over a few months in patients with active synovitis. The most common sites of early involvement include the ulnar styloid, I–III metacarpophalangeal joints, and II–III proximal interphalangeal joints.

Regular radiologic studies are of relevant value in following the course of RA [9].

In the past ten years, US has gained acceptance for studying joint, tendon and bursal involvement in RA patients; it may improve the early clinical assessment and the follow-up of RA patients, showing such details as synovial thickening (Fig. 3) even within finger joints (Fig. 4) [10].

Other imaging techniques, such as magnetic resonance, computed tomography and scintigraphy may provide useful information about both the features and the extent of anatomic damage in selected RA patients.

6. Differential diagnosis

A detailed history, the careful assessment of joints and periarticular soft tissue structures, and laboratory and imaging findings are all needed to diagnose RA correctly.

RA is usually easy to diagnose if the typical clinical features of the disease are integrated with laboratory and radiologic findings of chronic active synovitis. Conversely, it can often be difficult to distinguish early RA

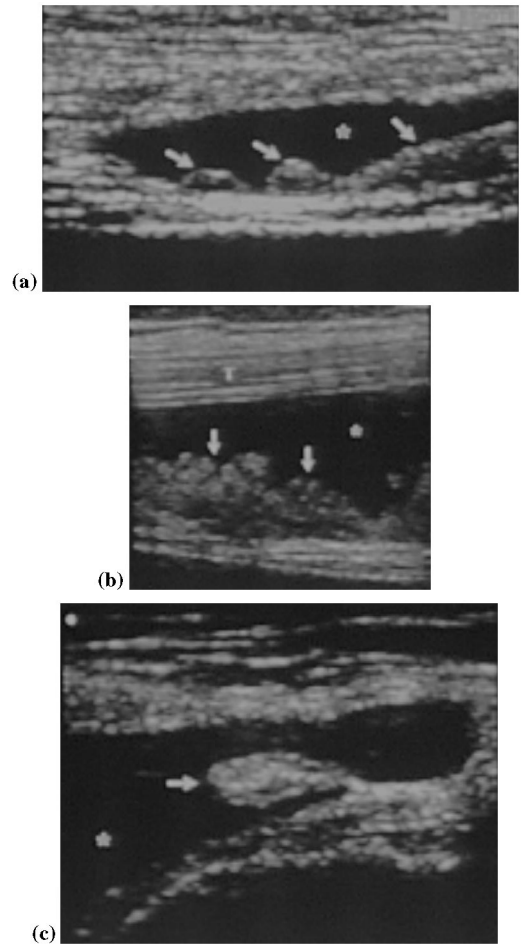

Fig. 3. Rheumatoid arthritis. Different features of synovial hyperthrophy: (a) bushy pattern; (b) hilly pattern; (c) polypoid pattern. *, joint fluid; arrows indicate synovial hyperthrophy; T, tendon.

from a wide spectrum of diseases characterized by clinically prominent synovitis, such as viral, reactive and psoriatic arthritis, and enteroarthritis. In such cases, the differential diagnosis is primarily made by exclusion, as there is no specific test for RA.

Longitudinal follow-up is a useful 'test' to make an unquestionable diagnosis.

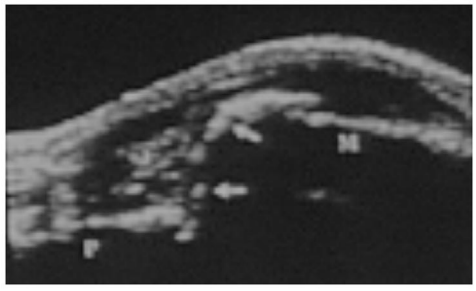

Fig. 4. Late rheumatoid arthritis. Longitudinal dorsal scan of a metacarpophalangeal joint shows the joint dislocation and capsular distension. The echoes within the joint space indicate synovial hypertrophy.

Table 3
Rheumatoid arthritis: unfavorable prognostic markers

Male gender
Low socioeconomic status
Lack of formal education
Subcutaneous nodules
Systemic manifestations
Severity of initial clinical disease activity
Persistent synovitis
Thrombocytosis
Eosinophilia
Elevated ESR
Elevated CRP
High rheumatoid factor titer
Antinuclear antibodies
Cryoglobulins
Circulating immune complex
Elevated C1q levels
Complement activation
Presence of HLA-DR4
Early erosive changes

7. The course of rheumatoid arthritis

The clinical course of RA is mostly progressive, with remission and worsening but continuing disease activity. Slow progression of joint symptoms is typical in RA. Several clinical, laboratory, and imaging findings can indicate the disease process and may play a relevant role in predicting good or poor patient outcome and patient risk stratification (Table 3). The erythrocyte sedimentation rate and acute phase reactants, i.e. C-reactive protein, best reflect disease activity fluctuations.

The main prognostic signs that may help identify the patients with more severe disease include several swollen joints, high serum levels of acute phase reactants or IgM rheumatoid factor, and early radiographic and functional abnormalities [11–13].

The radiologic progression is unpredictable and varies among patients.

Long-term disability is associated with hand function loss and failure of the larger weight-bearing joints.

An adequate early treatment of RA may alter the disease course [14].

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