RHEUMATOID ARTHRITIS

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Introduction

- a chronic multisystem disease of unknown cause.
- persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution.
- 68% RA patients with positive Rheumatoid factor
- Pathologic change: chronic synovitis with pannus formation
- cartilage damage and bone erosion are the hallmarks of the disease

Epidemiology and Genetics

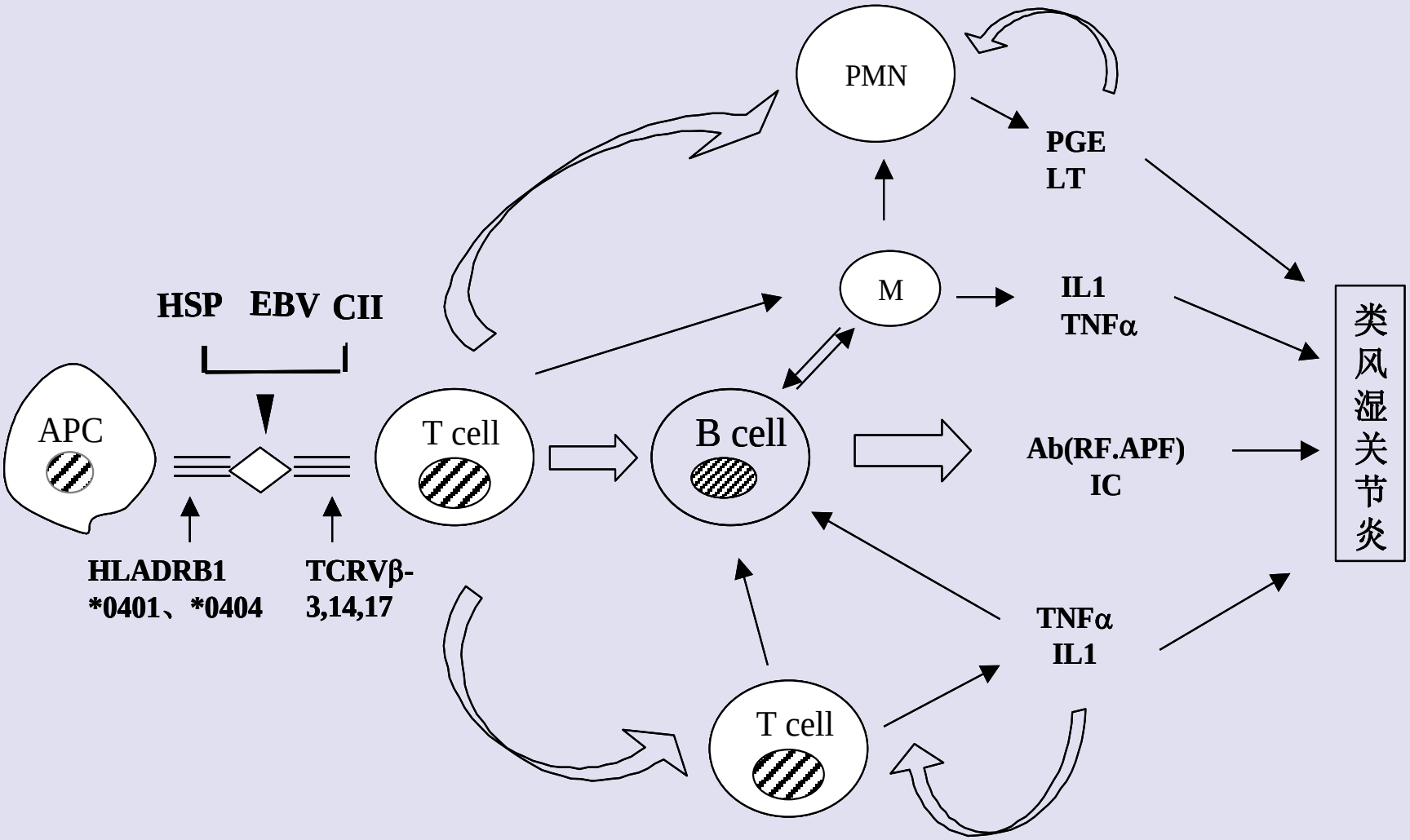
- The prevalence of RA in China is approximately 0.3% of the population
- women are affected approximately three times more often than men
- 80% of all patients develop the disease between the ages of 35 and 50.

Epidemiology and Genetics

- Family studies indicate a genetic predisposition.
- The class II major histocompatibility complex allele HLA-DR4 (DR ß1*0401) and related alleles are known to be major genetic risk factors for RA.

- Environmental factors also play a role in the etiology of the disease，such as stress, humidity, cold, infectious agent and cigarette smoking
- It has been suggested that developed RA might be a response to an incentive in a genetically susceptible host.

Pathology and Pathogenesis



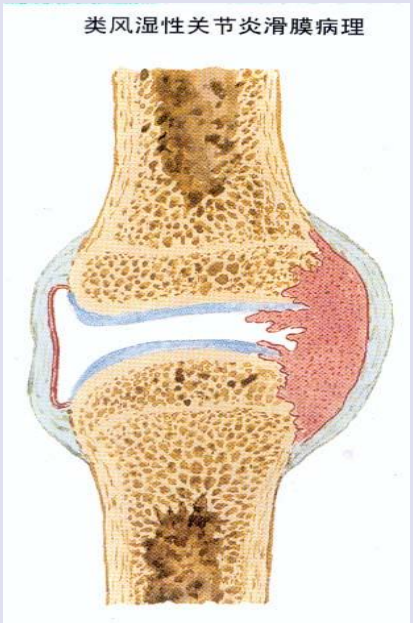
Pathology and Pathogenesis

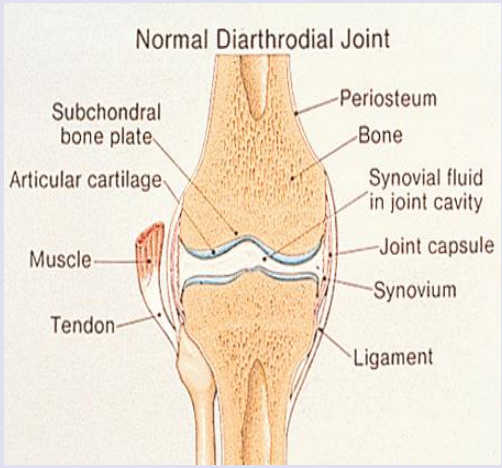
- Pathologic Finding： chronic synovitis

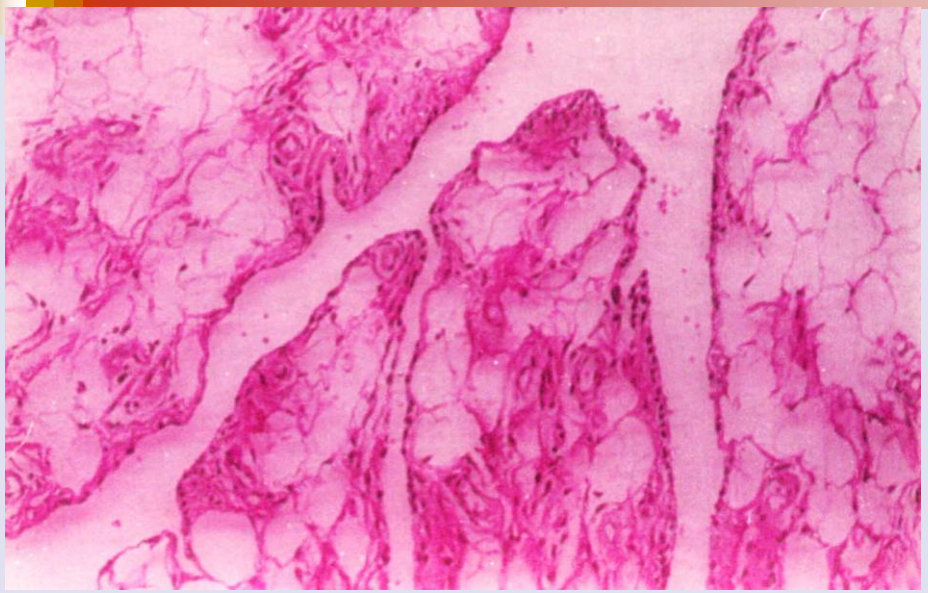
In acute phase: effusion and cell infiltration

In chronic phase: the number of synoviocyte, new capillary mononuclear cells remarkably increases

- the pannus(血管翳) protrudes into the joint cavity as villous
- Pannus erodes cartilage, bone, ligaments and tendons.



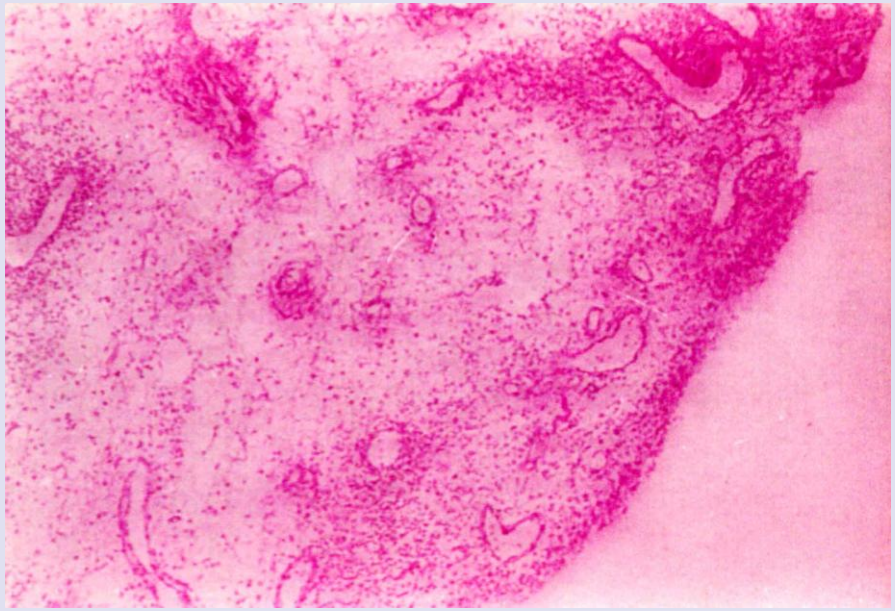




Normal synovium

RA：inflammatory synovium

- hyperplasia and hypertrophy of the synovial lining cells
- neovascularization
- infiltration with mononuclear cells



Clinical Manifestations

- **The usually age at onset is 35-50 years**
- **The ratio of female to male is 3:1**
- **The onset of RA is usually insidious**
- **Systemic symptoms of fatigue, fever, weight loss anorexia, generalized weakness may be seen**

articular manifestations

（1）morning stiffness（晨僵）

- **stiffness persisting for over 60 minutes is prominent in the morning or during rest and subsides after daytime activity**
- **The persisting length of morning stiffness is associated with the degree of articular inflammation.**

（2）**pain and tenderness： painful on rest**

location：small (PIP,MCP), symmetric joints

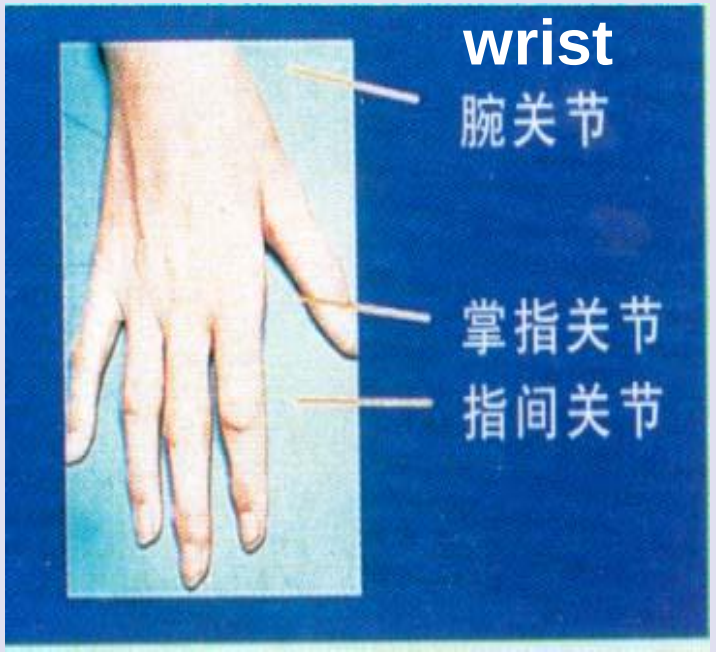
（3）swelling：synovial proliferation, effusion, swelling of soft tissue

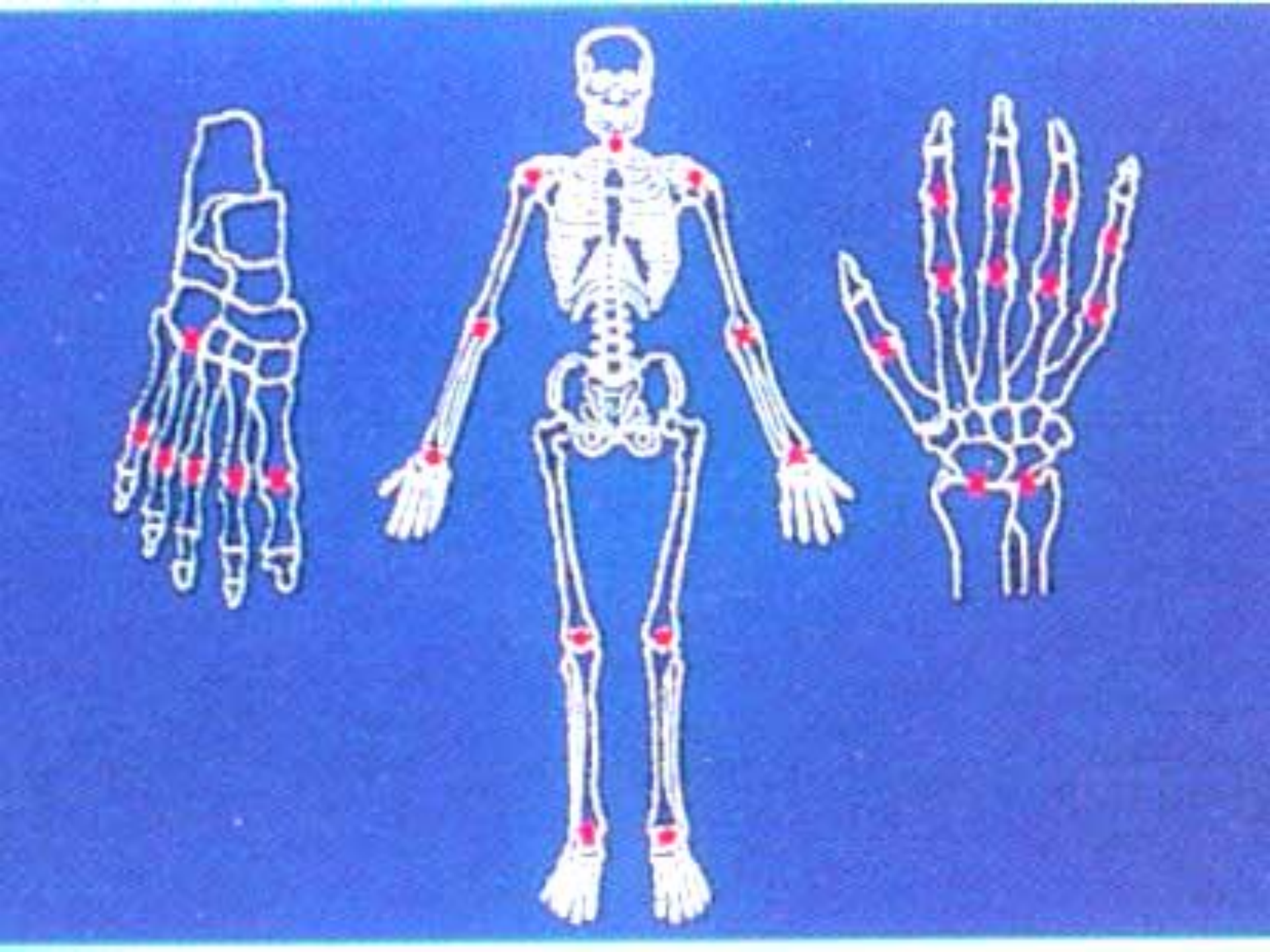
（4）articular deformity：ulnar deviation of the fingers, “swan-neck” deformity, atrophy of skin and muscle

（5）osteoporosis (骨质疏松)

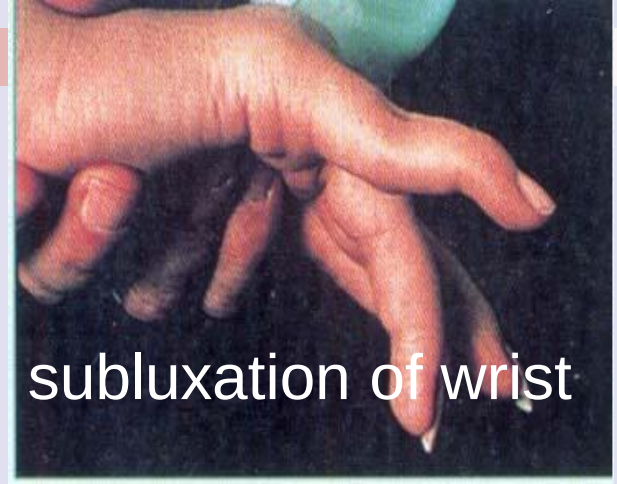
metacarpophalangeal joint

proximal interphalangeal joint

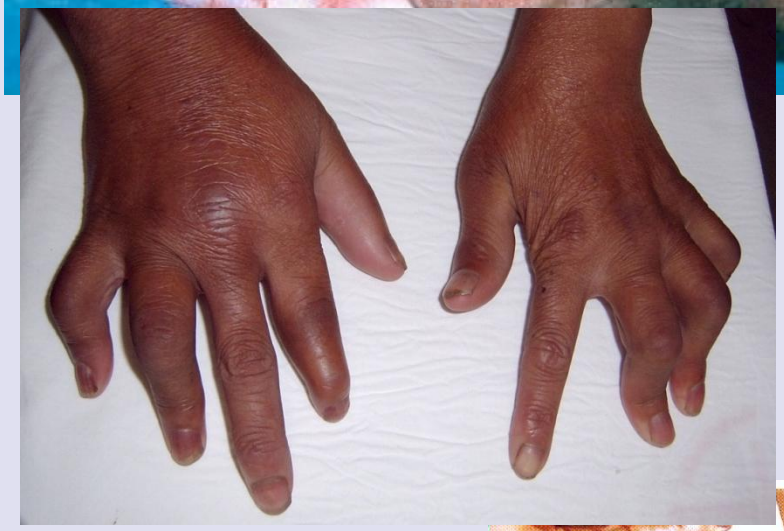


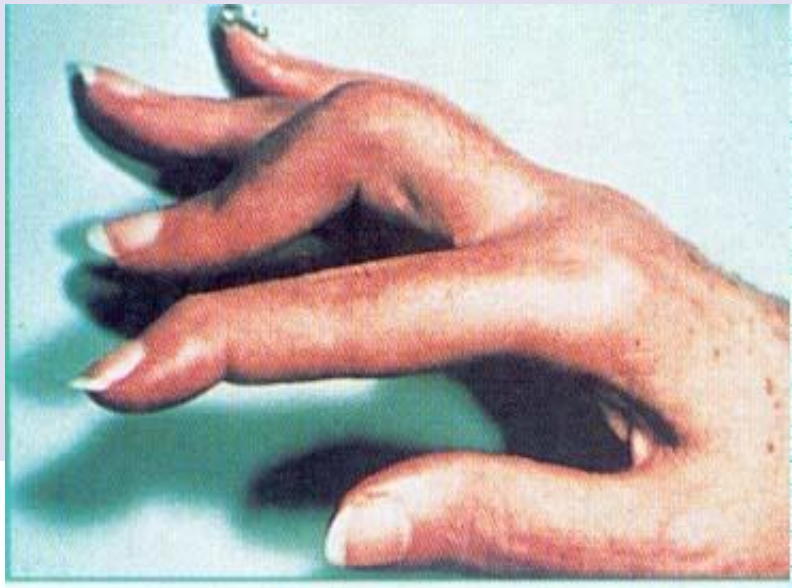


fusiformis swelling

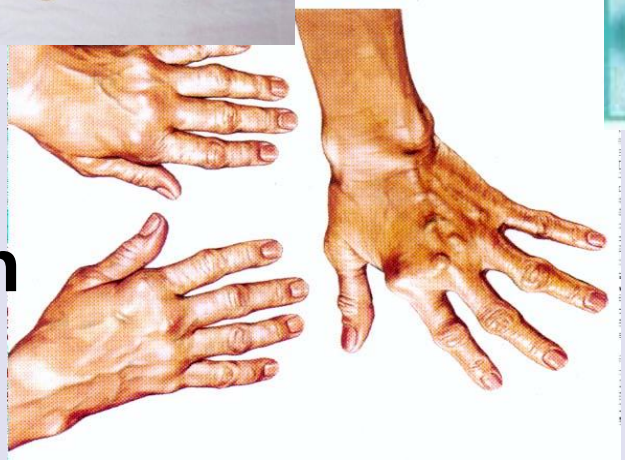


subluxation of wrist





ulnar deviation



boutonniere deformity

In conclusion

- Although the course of RA in different patient can be quite variable，the typical picture of bilateral symmetric inflammatory polyarthritis involving small joints in both the upper and lower extremities with sparing of the axial skeleton except the cervical spine suggests the diagnosis.

Extra-articular manifestations

（1）Rheumatoid nodules

- **20%-30% patients**
- on periarticular structures, extensor surfaces, or other areas such as the pleura and meninges.
- **The advent indicates that the disease is in the active phase**

（2）rheumatoid vasculitis**:** episcleritis, scleritis**,** peripheral neuropathy， multiplex, cutaneous ulceration and dermal necrosis

（3）Pleuropulmonary manifestation

- diffuse interstitial fibrosis: abnormal on CT scan, restrictive diffuse pattern（pulmonary function ）
- intrapulmonary nodules:：asymptomatic, infected, cavitate
- rheumatoid pleural disease：exudative, WBC<5 000/mm^3, lower level of glucose

(4) pericarditis: 30% pericardial effusion, asymptomatic

(5) gastrointestinal manifestation:

- nausea, loss of appetite

(6) kidney：drug-induced，amyloid degeneration

（7）**Neurologic manifestations：**

- **atlantoaxial subluxation: sensory abnormity and loss of strength**
- **peripheral neuropathies**

（8）**Felty’s syndrome ：** consists of chronic RA, splenomegaly, neutropenia, anemia and thrombocytopenia. It is most common in individuals with long-standing disease and high titers of rheumatoid factor.

Laboratory Findings

- No tests are specific for diagnosing RA
- rheumatoid factors（RF）are autoantibodies reactive with the Fc portion of IgG
- They are found in more than two-thirds of adults with the disease
- High titer of RF indicate patients at risk for severe systemic disease.

Laboratory Findings

- anti-CCP antibodies (against cyclic citrullinated peptide) have already proved useful in helping to establish the diagnosis of RA and in helping to predict in prognosis.
- Anti-CCP has become substantial part of The 2010 ACR-EULAR classification criteria for RA.

Laboratory Findings

- Elevated erythrocyte sedimentation rate and C-reactive protein correlate with disease activity

Radiographic Evaluation

- The radiographic findings is nonspecific in the diagnosis of RA.
  - symmetric involvement, osteopenia, soft tissue swelling, loss of articular cartilage and bone erosions.
- MRI is recommended on a new approach in the early diagnosis： marrow edema， synovitis，erosion

Diagnosis

Criterion （1988 Revised ARA Criteria ）

1.Morning stiffness

2.Arthritis of three

3.Arthritis of hand joints

4.Symmetric arthritis

5.Rheumatoid nodules

6.Serum rheumatoid factor

7.Radiographic changes

- As lack of biomarker, the typical symptom, subcutaneous nodules, the presence of rheumatoid factor, or Anti-CCP antibody, radiographic findings clinically support the diagnosis.

2010 ACR/EULAR

	Exact (0−100)	Rescaled (0−10)	Rounded to 0.5 (0−10)
1 large	0	0	0
>1−10 large, asymmetric	10.2	1.02	1
>1−10 large, symmetric	16.1	1.61	1.5
1−3 small	21.2	2.12	2
4−10 small	28.8	2.88	3
>10, including at least 1 small joint	50.8	5.08	5
Serology			
Negative RF and negative ACPA	0	0	0
Low-positive RF or low-positive ACPA	22.0	2.20	2
High-positive RF or high-positive ACPA	33.9	3.39	3.5
Acute-phase reactants			
Normal CRP and normal ESR	0	0	0
Abnormal CRP or abnormal ESR	5.9	0.59	0.5
Duration of symptoms			
<6 weeks	0	0	0
≥6 weeks	9.3	0.93	1

General Principles

- The goals of therapy of RA
  - relief of pain
  - reduction of inflammation and disease progression
  - protection of articular structures and
  - maintenance of function
  - Minimum of adverse events

Drugs

- NSAIDs (nonsteroidal anti-inflammatory drugs)
- Glucocorticoids
- DMARDs (disease modifying anti-inflammatory drugs)
- Anti-Cytokine Agents

NSAIDs

- have analgesic, anti-inflammatory, and antipyretic properties
- block the activity of the COX enzymes
- used as the first agent to relieve the pain and swelling at the initial course
- alone do not change the course of the disease or prevent joint destruction.

- the toxicities of the currently available NSAIDs are similar:
  - gastrointestinal disturbance， increased blood pressure, increase cardiovascular risks，platelet dysfunction, and exacerbation of allergic rhinitis and asthma，rash, liver function abnormalities, and bone marrow depression,

NSAIDs

- Isoforms of COX : COX-1 ,COX-2
- COX-1 is expressed constitutively in gastric mucosa, Kidney, platelets.
- COX-2 expression is inducible by inflammation and stress in macrophages, monocytes, synoviocytes.
- Selective COX-2 inhibitors exhibit safer GI profiles than conventional non-selective NSAIDs， but increase cardiovascular risks

3. Disease-Modifying Antirheumatic Drugs

- includes methotrexate, Leflunomide， gold compounds, D-penicillamine, the antimalarials, and sulfasalazine.
- actually retard the development of bone erosions
- The appearance of benefit is usually delayed for weeks or months
- early aggressive treatment with DMARDs should be proposed
- they cause a variety of toxic side effects, monitor should be done

MTX

- is recommend as the initial DMARD,
- better clinical responses and less toxicity
- Major toxicity includes gastrointestinal upset, oral ulceration, and liver function abnormalities ,drug-induced pneumonitis

Steroids Therapy

- have both anti-inflammatory and immunoregulatory activity
- recent evidence suggests that low-dose steroids therapy may retard the progression of bone erosion
  - are useful in early disease
  - patients with severe disease or systemic involvment
- the usual dose of predinisone is 5 to 10mg daily
- Side effects should be monitors.

Anti-Cytokine Agents

- TNF -a antagonist is remarkably effective
- to slow the rate of progression of joint damage
- the potential for an increased risk of serious infections.

- Surgery
  - Arthroplasties and total joint replacements
  - Open or arthroscopic synovectomy

Emphasis

- Typical manifestations of arthritis
- Drugs (classification of drugs, act of different drugs ，therapeutic strategies)

Thanks!

Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

- NSAIDs block prostaglandins by blocking Cox enzymes (specifically, Cox-1 and Cox-2 enzymes). This decreases inflammation and reduces pain and stiffness.
- The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen,
- NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present

Side effects

- vomiting
- nausea
- constipation
- diarrhea
- reduced appetite
- headache
- dizziness
- rash
- Drowsiness
- Ulcers bleeding
- kidney failure
- liver failure.

Disease-modifying antirheumatic drugs (DMARDs)

- are the standard treatments for RA.
- They are used either alone or in combination with newer biologic DMARDs.
- their use in RA slow down disease progression.

- NSAIDs (which refers to agents that treat the inflammation but not the underlying cause) and steroids (which blunt the immune response which are insufficient to slow down the progression of the disease.

DMARDs

- Methotrexate (considered to be the current standard of care)
- Leflunomide
- Hydroxychloroquine
- Sulfasalazine
- Gold
- Minocycline
- Azathioprine
- Cyclosporine

Corticosteroids

- work rapidly to control inflammation and pain. Long-time use, however, can have severe adverse effects.
- suppress the immune system and reduce inflammation and pain, and tissue damage throughout the body.

corticosteroids

- are most often used in combination with DMARDs, which significantly enhances the benefits of DMARDs.
- Oral corticosteroids are sometimes used in early stage-RA for patients who cannot tolerate NSAIDs.
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- High-dose corticosteroids are used to treat severe or life-threatening problems including: Kidney disease , vasculitis pleurisy , central nervous system

Side Effects

- cause a wide variety of side effects, some of which can be severe.
- The risk of side effects is especially high when corticosteroids are taken in high doses for long periods of time.

- edema
- Weight gain
- Rounding of facial features
- Mood swings, difficulty concentrating, insomnia, anxiety
- Easy bruising
- Increased risk
- Elevated blood pressure
- Gastritis, peptic ulcer
- Problems with blood sugar levels (diabetes)
- Muscle weakness
- Glaucoma

Biologic therapies

- **Target specific immune mediated processes: inhibitors of TNF-α (etanercept,infliximab,adalimumab) and the antagonist IL-1 receptor (Kineret)**
- **Others: a monoclonal antibody directed against CD20 (rituximab), a fusion protein (abatacept , modulated the CD80 or CD86-CD28)**

Key Points

- Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by features of persistent inflammatory synovitis, usually involving peripheral joints.
- The clinical feature of RA is chronic polyarthritis with joint pain, tenderness, swelling, and morning stiffness, particularly in the small joints of the hands and feet. In many patients, there is increasing joint damage and functional disability.
- Extra-articular manifestations often include rheumatoid nodules, vasculitis, pleural disease, interstitial pulmonary fibrosis, pleuro-pulmonary nodules, episcleritis, and scleritis.

Key Points

- A number of autoantibodies may be found in patients with RA besides rheumatoid factor, such as the antibodies against filaggrin, citrullinated proteins, and calpastatin etc.
- Imaging of RA provides a constellation of characteristic findings that reflect the underlying pathologic aberrations.
- Medical management of RA involves four general approaches, including nonsteroidal anti-inflammatory drugs, low-dose oral glucocorticoids, disease-modifying anti-rheumatic drugs and anti-cytokine agents.

Practices

- Please state the clinical features of RA.

- Please state the medical managements of RA.