Polyarthritis skin rashes and mild anemia

A 32-year-old nurse presents to your office with a complaint of **intermittent** episodes of **pain, stiffness, and swelling in both hands and wrists** for approximately 1 year. The episodes last for several weeks and then resolve. More recently, she noticed similar symptoms in her **knees** and **ankles**. Joint pain and stiffness are making it harder for her to get out of bed in the morning and are interfering with her ability to perform her duties at work. The **joint stiffness usually lasts for several hours before improving**. She also reports malaise and easy fatigability for the past few months, but she denies having fever, chills, skin rashes, and weight loss. Physical examination reveals a well-developed woman, with *blood pressure* 120/70 mm Hg, heart rate 82 bpm, and respiratory rate 14 breaths per minute. She has **nodules** and **skin rashes** over the extensor surface of arms. Head, neck, cardiovascular, chest, and abdominal examinations are normal. There is *no hepatosplenomegaly*. The joint examination reveals the presence of **bilateral swelling, redness, and tenderness of most proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, the wrists, and the knees**. Laboratory studies show a **mild anemia** with hemoglobin 11.2 g/dL, hematocrit 32.5%, mean corpuscular volume (MCV) 85.7 fL, white blood cell (WBC) count 7.9/mm3 with a normal differential, and platelet count 300 000/mm3. The *urinalysis is clear with no protein and no red blood cells* (RBCs). The **erythrocyte sedimentation rate (ESR) is 75 mm/h (n.r. 0-20)**, and the kidney and liver function tests are normal.

What is your most likely diagnosis?
What is your next diagnostic step?

CFIM n°22

RHEUMATIC DISEASES

DEFINITION: disorders of connective tissue characterized by general or localized inflammation.

CLINICAL FEATURES

- Pain: peripheral joints, spine, or muscles.
- Constitutional syntoms : stiffness, fever, anemia, fatigue or weight loss
- Extra-musculoskeletal manifestations: skin rashes, renal dysfunction, sierositis, etc.

For most rheumatic disorders, the underlying molecular mechanisms through which environmental triggers and genetic susceptibility factors collaborate to result in a particular rheumatic disease in an individual remain to be fully elucidated.

These diseases can be broadly considered as those that are primarily degenerative, with inflammation occurring secondarily, and those in which inflammation is the primary mediator of the disease. In the latter, the pathogenesis can be mediated through aberrant immune responses or as a result of metabolic abnormalities.

rheumatic diseases

cancer

infection

Mimics of rheumatic diseases in infection and malignancy

DEGENERATIVE DISEASES OF BONES AND JOINTS	SYSTEMIC AUTOIMMUNE DISEASES	SERONEGATIVE SPONDYLOARTHROPATHIES	VASCULAR RHEUMATIC DISEASES	AUTOINFLAMMATORY DISEASES	PAIN DISORDERS
Osteoarthritis	Rheumatoid arthritis	Ankylosing spondylitis	ANCA- associated vasculitis	Adult-onset Still's disease	Regional myofascial pain syndromes
DISH	Systemic lupus erythematosus	Psoriatic arthritis	Temporal artery vasculitis	Crystal diseases	Tendonitis/bursitis
Degenerative disc disease	Sjögren's syndrome	Reactive arthritis	Polymyalgia rheumatica	Pediatric periodic fever syndromes	Adhesive capsulitis
Spinal stenosis	Inflammatory myopathies (polymyositis, dermatomyositis)	Enteropathic arthritis	Behçet's disease		Reflex sympathetic dystrophy
Osteoporosis	Systemic sclerosis				Pain with hypermobility syndromes
					Fibromyalgia*

*The only pain disorder that has not been associated primarily with inflammation.
ANCA = antineutrophil cytoplasmic antibody; DISH = diffuse idiopathic sclerosing hyperostosis (also linked to metabolic factors, including elevated growth hormone).

Classification of Rheumatic Diseases according to pathogenesis

(1) those associated with **degeneration of connective tissues** attributable to (a) trauma, (b)structural/mechanical imbalances, or (c) inherent early demise of cellular components;

(2) those associated with **systemic autoimmunity**, often linked with measurable autoantibodies that can manifest primarily with (a) synovitis, (b) widespread organ involvement, (c) inflamed blood vessels, or (d) inflammation of muscle;

(3) other inflammatory connective tissue diseases involving more dense tissues, not associated with the formation of autoantibodies and hence termed **seronegative rheumatic diseases** or spondyloarthropathies;

(4) diseases in which **inflammation of the vasculature**, particularly small, medium, or large arteries, is the predominant feature;

(5) **Autoinflammatory diseases** that can be associated with crystal deposition or genetic mutations involving cytokine pathways;

(6) **pain syndromes** that must often be considered in the context of these diseases, in which some appear to be comorbid and closely linked to the underlying rheumatic disease, such as diffuse pain associated with Sjögren's syndrome, hypermobility of connective tissue, or those regional pain syndromes that are anatomically linked to mechanical disruption. Patients presenting with generalized pain syndromes require investigation to exclude a connective tissue disease.

PREVALENCE OF RHEUMATIC DISEASES

- Rheumatoid arthritis (RA) — 0.5 per 100
- Sieronegative spondyloarthropathy (SpA) — 0.5 per 100
- Sjögren's syndrome (SS) — 0.5 per 100
- Systemic lupus erythematosus (SLE) — 0.05 per 100
- Systemic sclerosis (SSc) — 0.01 per 100
- Vasculitis — 0.05 per 100

DISEASE	EUROPE
RA	200-900 (2-7)
SLE	20-70 (2-7)
SSc	<10-15 (<2)
SpA	100-850 (2-9)
SS	200-600 (4-5)

*Prevalence (annual incidence) per 100,000

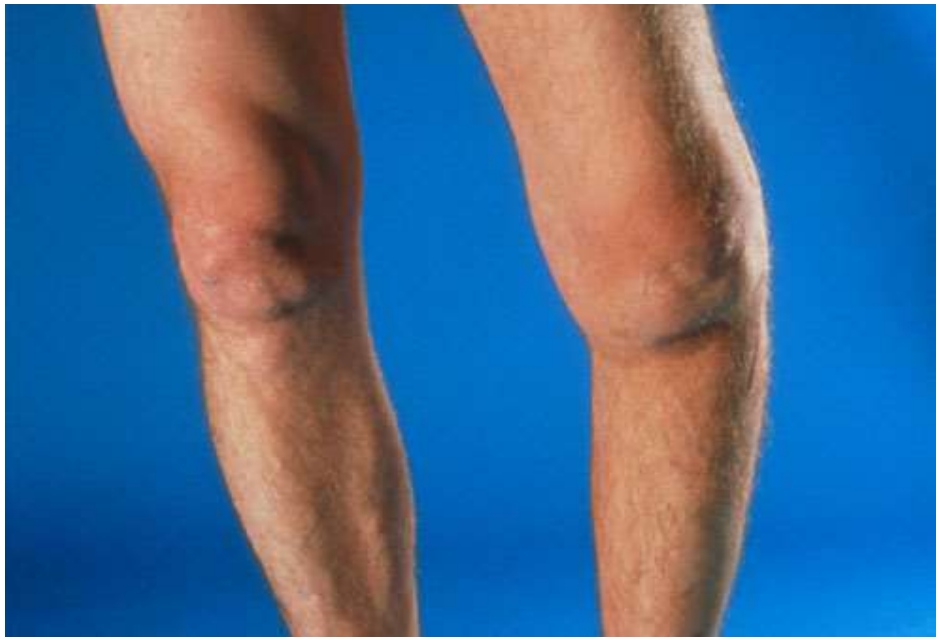
Table 20–7. Frequency (%) of autoantibodies in rheumatic diseases.[1]

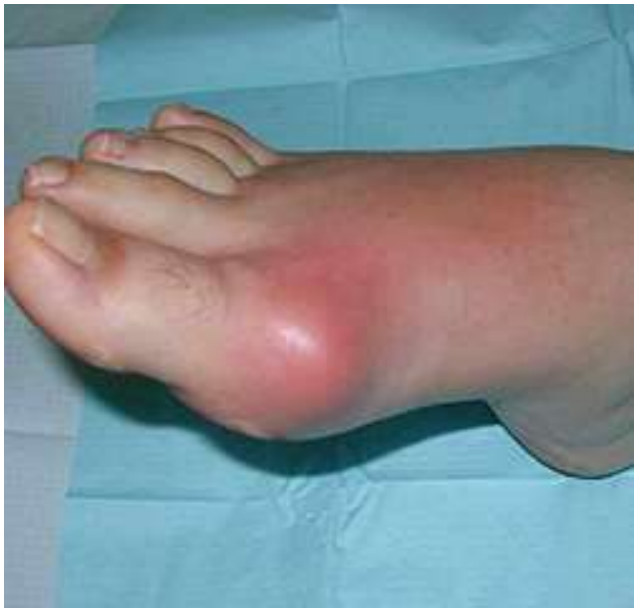
	ANA	Anti-Native DNA	Rheumatoid Factor	Anti-Sm	Anti-SS-A	Anti-SS-B	Anti-SCL-70	Anti-Centromere	Anti-Jo-1	ANCA
Rheumatoid arthritis	30–60	0–5	70	0	0–5	0–2	0	0	0	0
Systemic lupus erythematosus	95–100	60	20	10–25	15–20	5–20	0	0	0	0–1
Sjögren syndrome	95	0	75	0	65	65	0	0	0	0
Diffuse scleroderma	>95	0	30	0	0	0	33	1	0	0
Limited scleroderma (CREST syndrome)	>95	0	30	0	0	0	20	50	0	0
Polymyositis/ dermatomyositis	80	0	33	0	0	0	0	0	20–30	0
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	0–15	0	50	0	0	0	0	0	0	93–96[1]

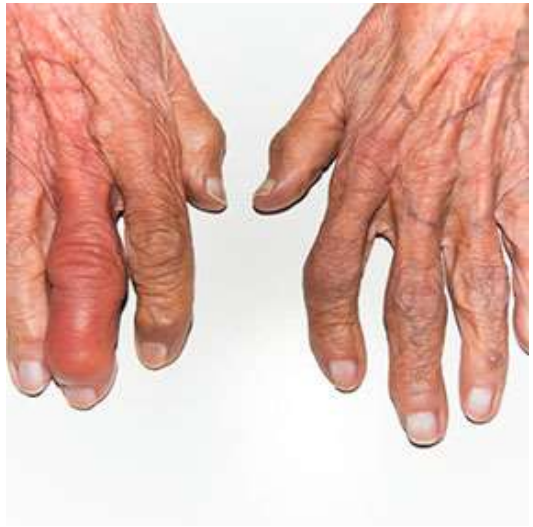
[1]Frequency for generalized, active disease.

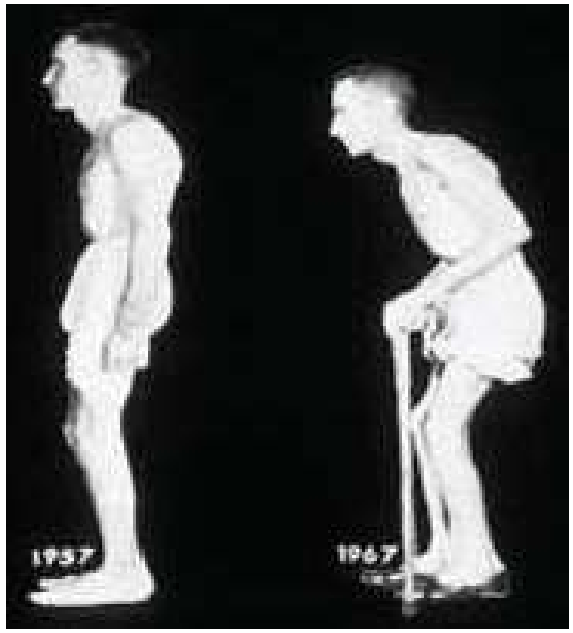
ANA, antinuclear antibodies; Anti-Sm, anti-Smith antibody; anti-SCL-70, anti-scleroderma antibody; ANCA, antineutrophil cytoplasmic antibody; CREST, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia.

CONSTITUTIONAL SYMPTOMS








1937
1967

Patterns of presentation of arthritis

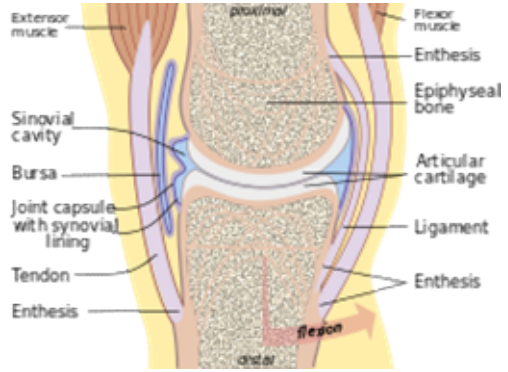
Monoarthritis	Oligoarthritis (≤5 joints)	Polyarthritis (>5 joints involved)	
Septic arthritis	Crystal arthritis	*Symmetrical:*	*Asymmetrical:*
Crystal arthritis (gout, CPPD)	Psoriatic arthritis	Rheumatoid arthritis	Reactive arthritis
Osteoarthritis	Reactive arthritis, eg *Yersinia, Salmonella, Campylobacter*	Osteoarthritis	Psoriatic arthritis
Trauma, eg haemarthrosis	Ankylosing spondylitis	Viruses (eg hepatitis A, B & C; mumps)	
	Osteoarthritis	Systemic conditions[1] (can be either)	

1 Connective tissue disease (eg SLE and relapsing polychondritis), sarcoidosis, malignancy (eg leukaemia), endocarditis, haemochromatosis, sickle-cell anaemia, familial Mediterranean fever, Behçet's.

►► Exclude septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h (p546). Inflammation may be less overt if immunocompromised (eg from the many immunosuppressive drugs used in rheumatological conditions) or if there is underlying joint disease. Joint aspiration (p543) is the key investigation, and if you are unable to do it, find someone who can.

Radiology Look for erosions, calcification, widening or loss of joint space, changes in underlying bone of affected joints (eg periarticular osteopenia, sclerotic areas, osteophytes). Characteristic X-ray features for various arthritides are shown in figs 1–3. Irregularity of the lower half of the sacroiliac joints is seen in spondyloarthritis. Ultrasound and MRI are more sensitive in identifying effusions, synovitis, enthesitis and infection than plain radiographs—discuss further investigations with a radiologist. Do a CXR for RA, vasculitis, TB and sarcoid.

Fig 1. X-ray features of osteoarthritis.



The enthesis is the connective tissue between tendon or ligament and bone.

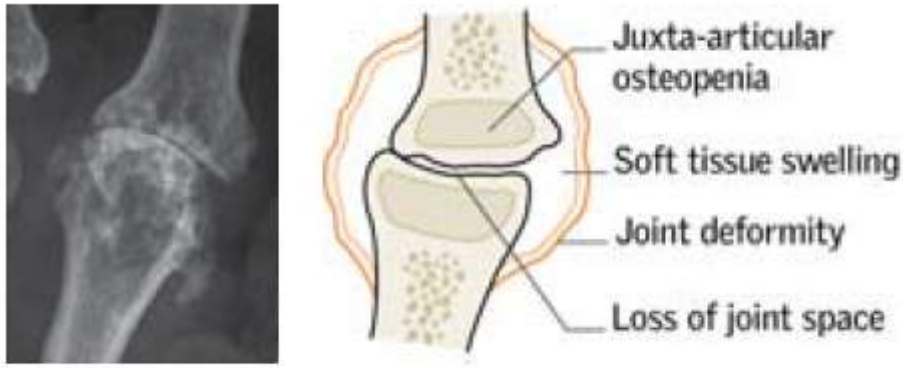


Fig 2. X-ray features of rheumatoid arthritis (MCPJ).

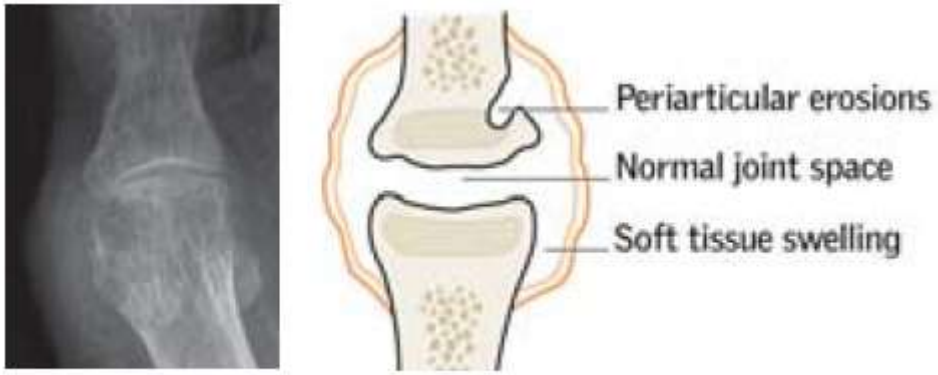


Fig 3. X-ray features of gout (1st MTPJ).

Joint Symptoms as a Common Presenting Feature

Almost all rheumatic diseases can manifest with joint-related symptoms as a significant and frequently presenting feature. This can include symptoms of pain, stiffness, swelling, and erythema, as in the case of autoinflammatory diseases such as gout or pseudogout. The pattern of joint involvement, particularly duration and timing of maximal symptoms, can help the health care provider identify patients who present with spondyloarthropathy or any inflammatory arthritis, regardless of pathogenetic classification. For instance, joint pain that is worse in the morning, is associated with prolonged stiffness, and improves with activity is a classic presentation of inflammatory pain. On the contrary, pain that is worse with activity, better with rest, and associated with a very short period of stiffness signals that the category is degenerative. Location provides a clue to broad classification. Patients describing "pain all over" may have a primary pain syndrome. However pain with an inflammatory pattern localized to the spine or an enthesis (site of ligament insertion) is more likely to indicate a seronegative spondyloarthropathy. A patient noting an inflammatory pattern of symptoms in small joints of the hands and feet suggests the presence of one of the autoimmune rheumatic diseases associated with either a positive antinuclear antibody (ANA) or rheumatoid factor (RF). Thus, joint symptom patterns become central to the evaluation of any rheumatic disease.

Skin manifestations of systemic diseases

Erythema nodosum (fig 1) Painful, blue-red, raised lesions on shins (± thighs/arms). *Causes:* sarcoidosis, drugs (sulfonamides, the Pill, dapsone), streptococcal infection. *Less common:* Crohn's/UC, BCG vaccination, leptospirosis, *Mycobacterium* (TB, leprosy), *Yersinia* or various viruses and fungi. Cause unknown in 30–50%.

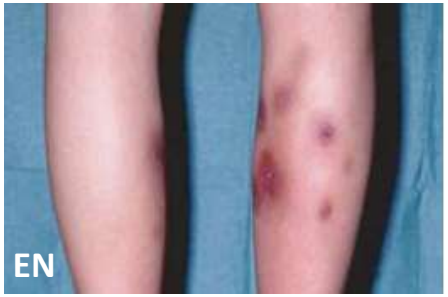
Erythema multiforme (see *OHCS* p588) (fig 3) 'Target' lesions: symmetrical ± central blister, on palms/soles, limbs, and elsewhere. *Stevens–Johnson syndrome* (p724): a rare, severe variant with fever and mucosal involvement (mouth, genital, and eye ulcers), associated with a hypersensitivity reaction to drugs (NSAIDs, sulfonamides, anti-convulsants, allopurinol) or infections (herpes, *Mycoplasma*, orf—). Also seen in collagen disorders. 50% of cases are idiopathic. Get expert help in severe disease.

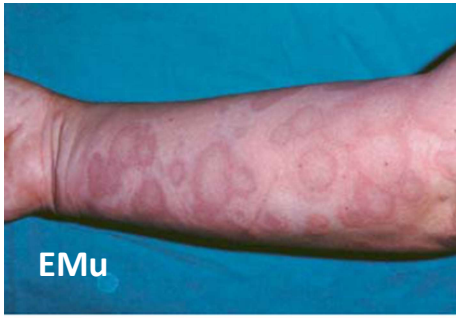
Erythema migrans (fig 7) Presents as a small papule at the site of a tick bite which develops into a spreading large erythematous ring, with central fading. It lasts from 48h to 3 months and there may be multiple lesions in disseminated disease. *Cause:* The rash is pathognomonic of Lyme disease and occurs in ~80% of cases (p430).

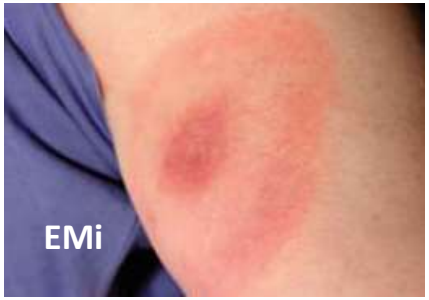
Erythema marginatum Pink coalescent rings on trunk which come and go. It is seen in rheumatic fever (or rarely other causes, eg drugs). See fig 1, p137.

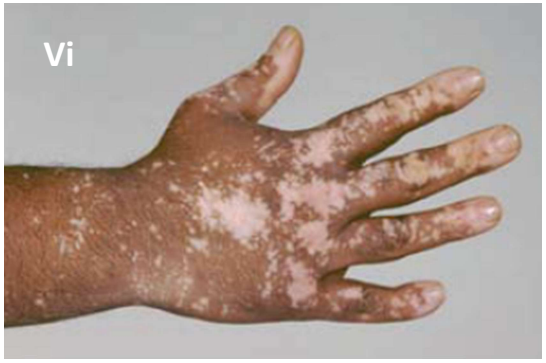
Pyoderma gangrenosum (fig 2) Recurring nodulo-pustular ulcers, ~10cm wide, with tender red/blue overhanging necrotic edge, purulent surface, and healing with cribriform scars on leg, abdomen, or face. *Associations:* UC/Crohn's, autoimmune hepatitis, Wegener's*, myeloma, neoplasia. ♀>♂. *Treatment:* Get help. Oral steroids ± ciclosporin should be 1st-line therapy.[78]

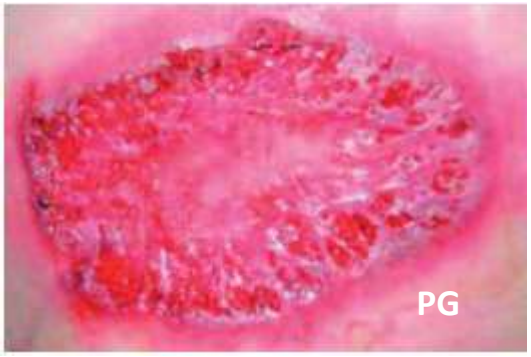
Vitiligo (fig 4) *Vitellus* is Latin for *spotted calf:* typically white patches ± hyperpigmented borders. Sunlight makes them itch. *Associations:* autoimmune disorders; premature ovarian failure. Treat by camouflage cosmetics and sunscreens (± steroid creams ± dermabrasion). UK Vitiligo Society: 0800 018 2631.

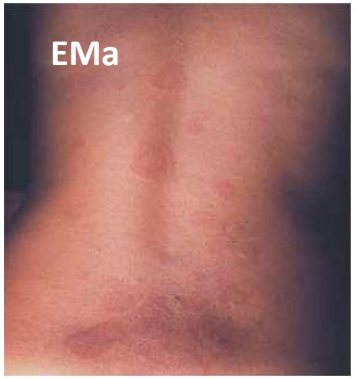












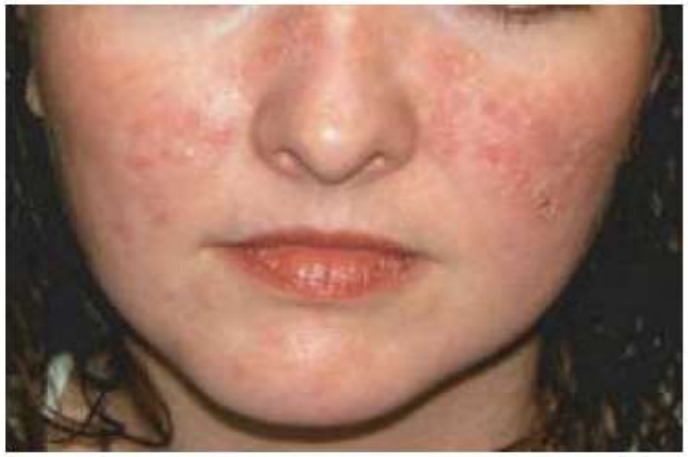


Fig 1. Malar rash, with sparing of the nasolabial folds.

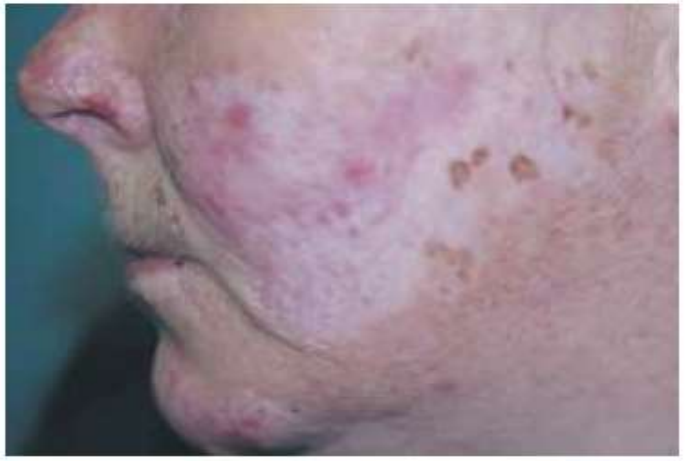
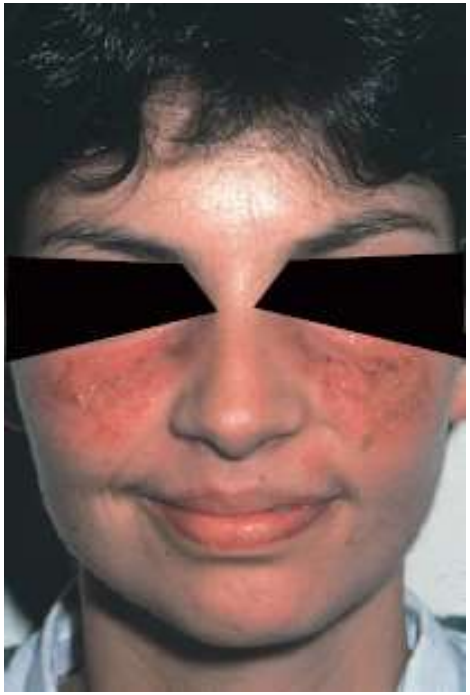


Fig 2. Discoid rash.



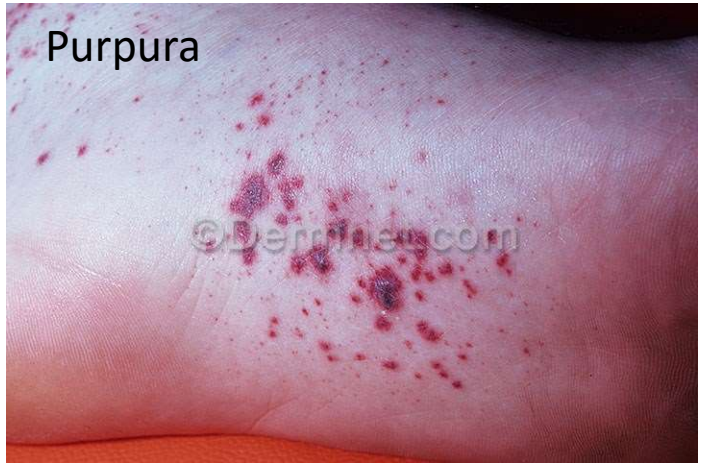
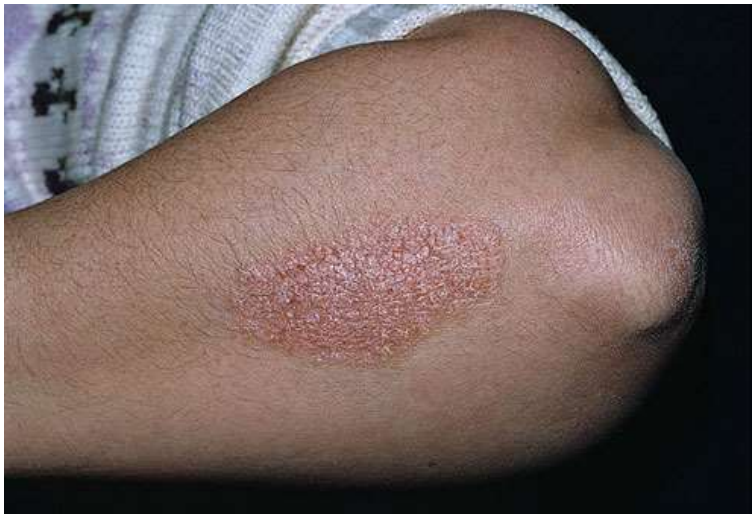
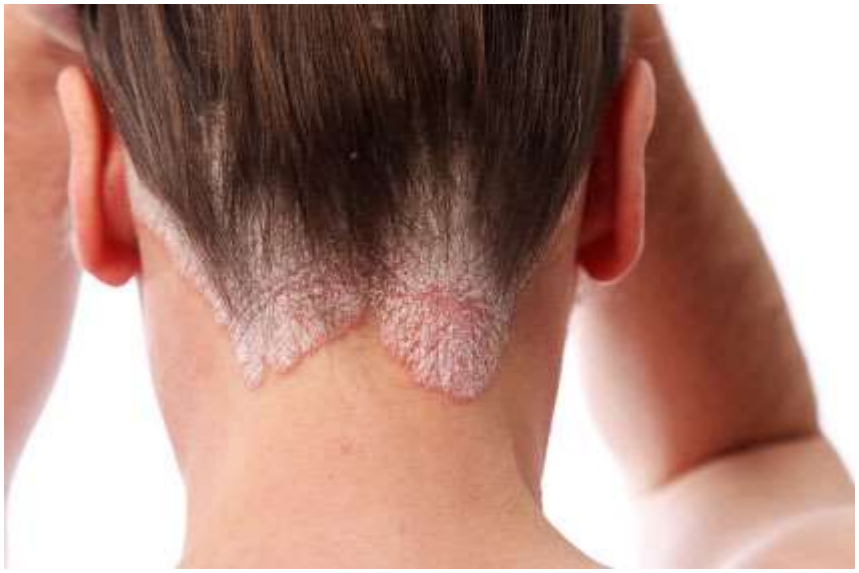


FIGURE 266-2. Malar rash in a patient with systemic lupus erythematosus. Note that the rash does not cross the nasolabial fold. (From Gladman DD, Urowitz MB. Systemic

PSORIASIS

Psoriasis is one of the most common dermatologic diseases, affecting up to 2% of the world's population. It is an immune-mediated disease clinically characterized by erythematous, sharply demarcated papules and rounded plaques covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis (the *Koebner* or isomorphic phenomenon). In addition, other external factors may exacerbate psoriasis, including infections, stress, and medications (lithium, beta blockers, and antimalarial drugs).





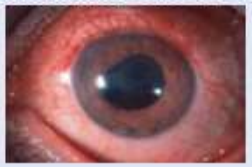
Cutaneous Manifestations

Although cutaneous manifestations are frequent in patients with seropositive autoimmune diseases, particularly SLE, they are important manifestations of all autoimmune diseases. A nonblanching purpuric rash can indicate a vasculitis, and rashes involving specific extensor regions are common to dermatomyositis. In cases of SLE or dermatomyositis, rashes are triggered or worsened by exposure to ultraviolet light and occur in a light-exposed distribution. Rashes of vasculitic origin can indicate either the presence of an autoimmune disease such as SLE or an inflammatory vascular disease such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. These tend to be present for days and are often palpable, and a tissue biopsy of the lesions will be very helpful in diagnosis. Rashes can be transient. In adult-onset Still's disease (an adult form of systemic inflammatory arthritis classified as an autoinflammatory disease), patients present with daily spiking fevers, peaking late in the day, associated with a salmon-colored evanescent blanching rash lasting only 1 to 2 hours. The specific location of a rash aids in diagnosis. A facial rash that spares the nasolabial folds is classic for lupus. A rash that does not spare the nasolabial folds suggests rosacea. Psoriasis is almost always present in psoriatic arthritis (a spondyloarthropathy variant). Although psoriasis is often widespread, involving extensor surfaces, it can be missed if there are very few lesions or if it is located in areas that are not easily seen (intertriginous regions, such as in the ear, umbilicus, buttock creases, or scalp) or if it only involves the nails. The rash of psoriasis can be seen in any of the variants of the spondyloarthropathies. Occasionally RA will manifest with nodules over the extensor surfaces or rashes in the same areas, but this is increasingly rare. However, the presence of nodules over extensor surfaces may also indicate gouty tophi. In SSc, distal tightening of the skin, presence of telangiectasias, and digital ulcers can be seen. These should also be sought in the context of Raynaud's syndrome, characterized by vascular spasm in the hands.

Nonspecific Clinical Presentations

All of the rheumatic diseases can be associated with joint involvement. However, joint symptoms are not always present in many of these diseases. Thus, a working knowledge of other patterns of presentation is important. Fever or cutaneous manifestations, including rashes, are common in vasculitis and in the presentation of SLE. Sicca symptoms are pathognomonic of Sjögren's syndrome. Both Sjögren's syndrome and inflammation of blood vessels can occur concurrently in patients with SLE. Systemic features such as myalgias or fatigue are common to almost all rheumatic diseases regardless of their classification, whereas true weakness may be the only presenting complaint of an inflammatory myopathy. Renal involvement is common to seropositive systemic autoimmune diseases and vasculitis and can present with anasarca if proteinuria is severe or prolonged. Consequently, specific and nonspecific features associated with various connective tissue diseases must be identified to correctly develop a differential diagnosis that fits within the classification described in Table 256-1. Features may present sequentially over time; thus, rheumatic diseases from more than one category must often be considered in a patient whose disease has not yet been diagnosed, leaving the patient with a label of a nonspecific or undifferentiated connective tissue disease. Most rheumatic diseases have specific classification criteria. When these are not yet met, features are considered in the context of the broad classifications, and terms such as *undifferentiated inflammatory polyarthritis* or *undifferentiated spondyloarthropathy* may be used in the interim to aid in diagnosis and management. When a patient's disease is not yet diagnosed, investigations and monitoring over time, as indicated in Figure 256-1, can help to ultimately identify an emerging rheumatic disease.

Differential diagnosis of a red eye

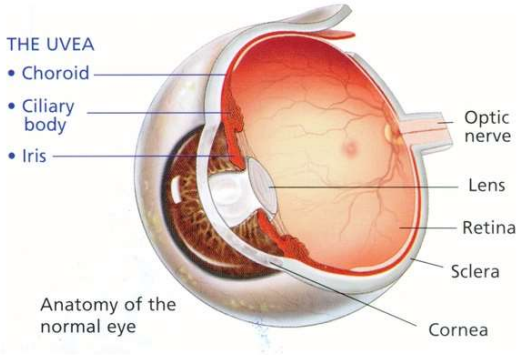
	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	Treatment	Appearance
Acute glaucoma	Both ciliary and conjunctival vessels injected. Entire eye is red. See *OHCS* p430.	Injected	Dilated, fixed, oval	Steamy, hazy	Very shallow	Very high	Refer. IV acetazolamide + pilocarpine drops (miotic); Peripheral iridotomy.	
Anterior uveitis (iritis)	Redness most marked around cornea, which doesn't blanch on pressure. Usually unilateral. *Causes:* AS, RA, Reiter's▪, sarcoidosis, herpes simplex, herpes zoster, and Behçet's disease. NB: a similar scleral appearance but without papillary or anterior chamber involvement may be *scleritis* (eg RA, SLE, vasculitis).	Injected	Small, irregular due to adhesions between the anterior lens and the pupil margin	Normal	Turgid	Normal	Refer. Steroid eye drops (eg 0.5% prednisolone) + mydriatic (eg cyclopentolate 0.5%).	
Conjunctivitis	Often bilateral. Conjunctival vessels injected, greatest toward fornices, but blanching on pressure. Mobile over sclera. Purulent discharge.	Normal	Normal	Normal	Normal	Normal	Most do not require treatment. Consider chloramphenicol ointment or drops.	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus. *Causes:* BP↑; leptospirosis; bleeding disorders; trauma; snake venom; haemorrhagic fevers.	Normal	Normal	Normal	Normal	Normal	Looks alarming but resolves spontaneously. Check BP if elderly; Refer if traumatic; On warfarin?	

oston. Images courtesy of Prof. Jonathan Trobe and ADB.

Granulomatous disorders Syphilis, TB, sarcoidosis, leprosy, brucellosis, and toxoplasmosis may inflame either the front chamber (anterior uveitis/iritis) or back chamber (posterior uveitis/choroiditis). Refer to an ophthalmologist.

Systemic inflammatory diseases may manifest as iritis in ankylosing spondylitis and Reiter's▪; *conjunctivitis* in Reiter's; *scleritis* or *episcleritis* in RA, vasculitis and SLE. Scleritis in RA and Wegener's▪ may damage the eye. Refer urgently if eye pain. Giant cell arteritis causes optic nerve ischaemia presenting as sudden blindness.

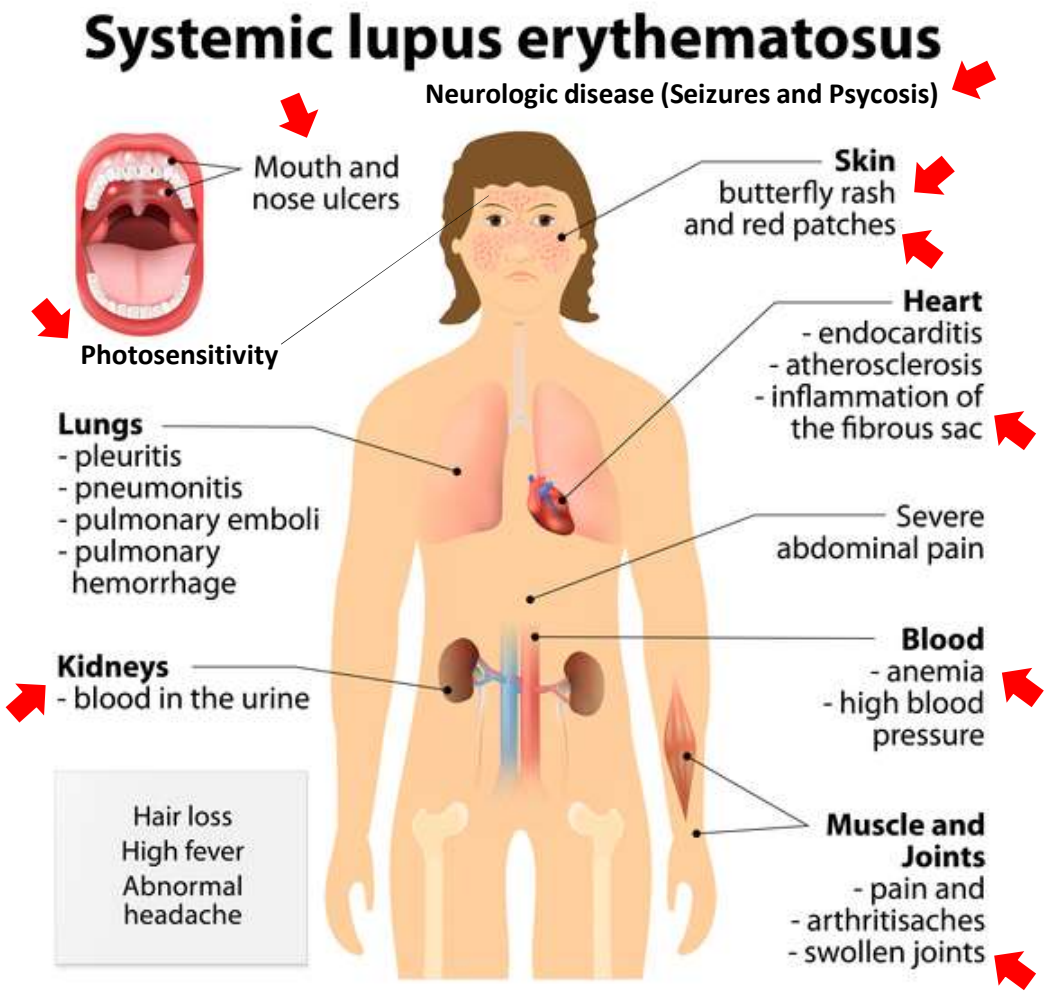
Keratoconjunctivitis sicca is a reduction in tear formation, tested by the Schirmer filter paper test (<5mm in 5min). It causes a gritty feeling in the eyes, and a dry mouth (xerostomia from ↓ saliva production). It is found on its own (Sjögren's syndrome), or with other diseases, eg SLE, RA, sarcoidosis. *℞:* artificial tears/saliva (eg Tears Naturale®, hypromellose drops, Saliveze® oral spray).



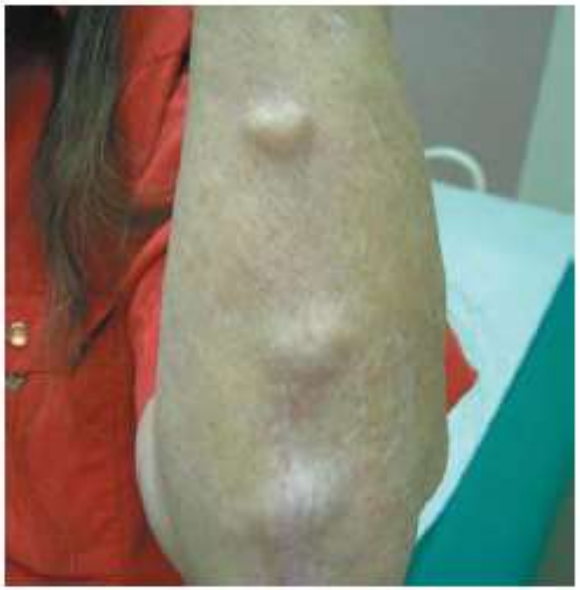
Anatomy of the normal eye

Criteria for the classification of SLE. (A patient is classified as having SLE if any 4 or more of 11 criteria are met.)

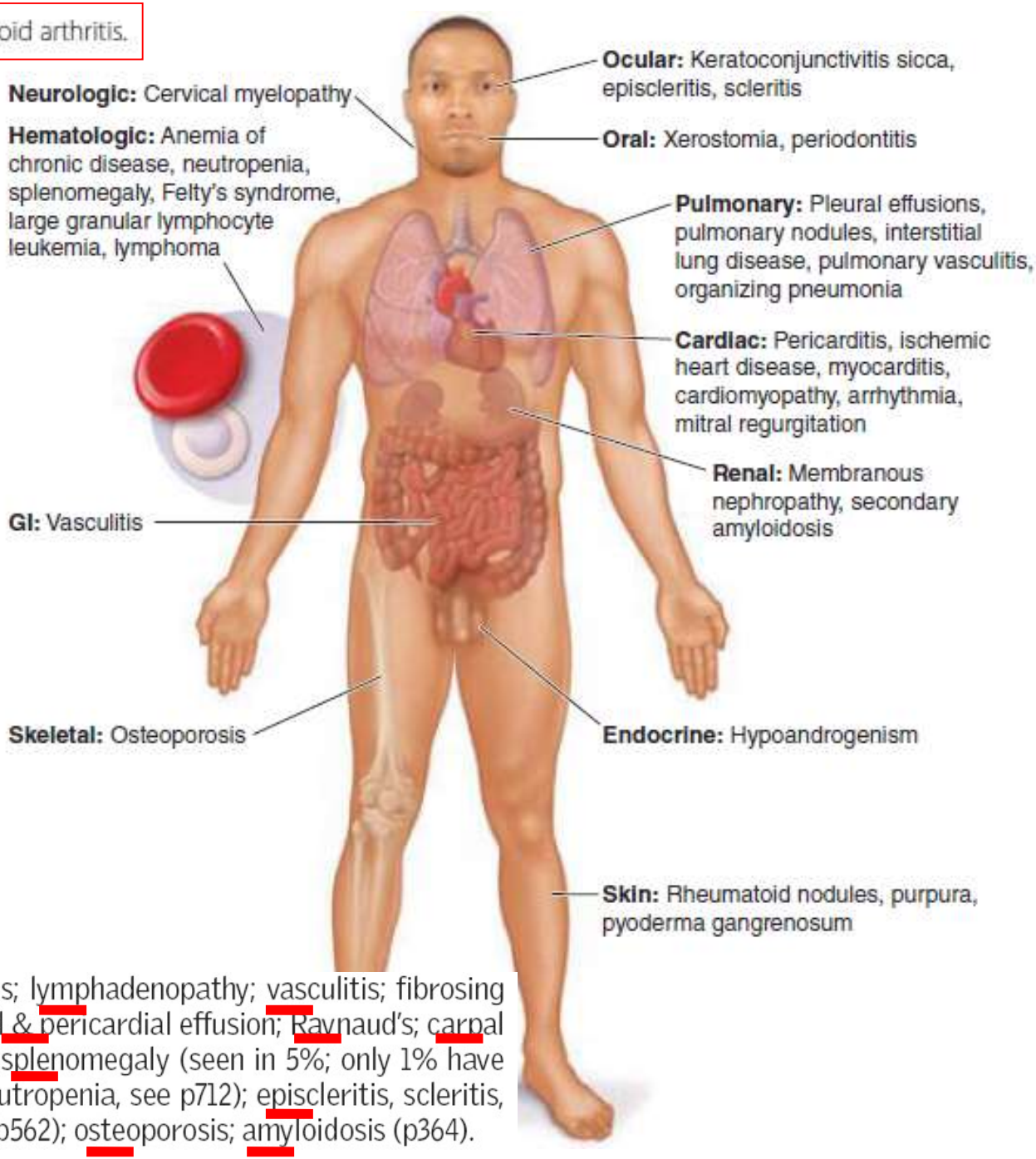
1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Arthritis
6. Serositis
7. Kidney disease
   a. > 0.5 g/d proteinuria, or
   b. ≥ 3+ dipstick proteinuria, or
   c. Cellular casts
8. Neurologic disease
   a. Seizures, or
   b. Psychosis (without other cause)
9. Hematologic disorders
   a. Hemolytic anemia, or
   b. Leukopenia (< 4000/mcL), or
   c. Lymphopenia (< 1500/mcL), or
   d. Thrombocytopenia (< 100,000/mcL)
10. Immunologic abnormalities
    a. Antibody to native DNA, or
    b. Antibody to Sm, or
    c. Antibodies to antiphospholipid antibodies based on (1) IgG or IgM anticardiolipin antibodies, (2) lupus anticoagulant, or (3) false-positive serologic test for syphilis
11. Positive ANA



Extraarticular manifestations of rheumatoid arthritis.

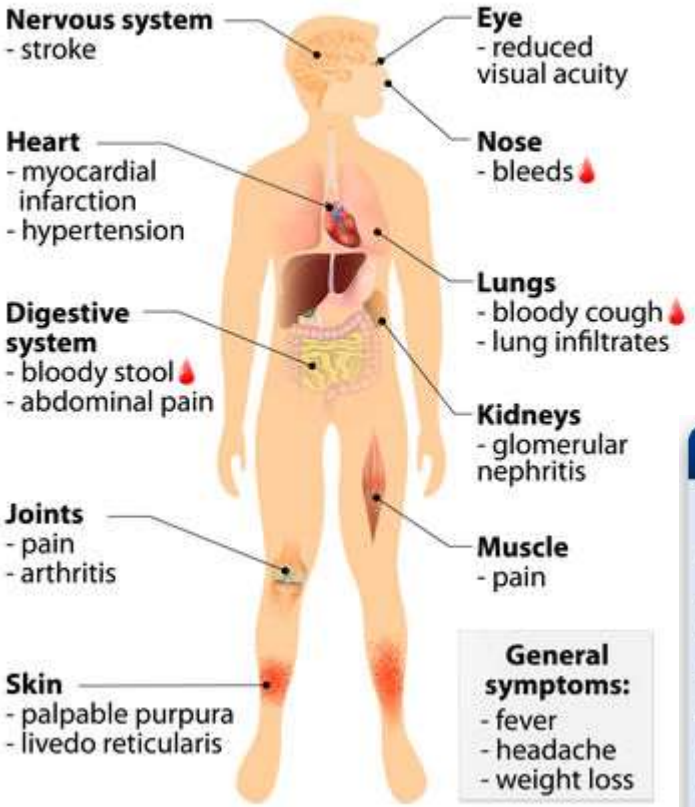


▲ **Figure 20–4.** Rheumatoid nodules over the extensor surface of the forearm (Reproduced with permission, from Richard P. Usatine, MD).



Extra-articular Nodules—elbows & lungs; lymphadenopathy; vasculitis; fibrosing alveolitis, obliterative bronchiolitis; pleural & pericardial effusion; Raynaud's; carpal tunnel syndrome; peripheral neuropathy; splenomegaly (seen in 5%; only 1% have Felty's syndrome: RA + splenomegaly + neutropenia, see p712); episcleritis, scleritis, scleromalacia, keratoconjunctivitis sicca (p562); osteoporosis; amyloidosis (p364).

VASCULITIS



Vasculitis is defined as an inflammatory disorder of blood vessel walls, causing destruction (aneurysm/rupture) or stenosis. It can affect the vessels of any organ, and presentation depends on which organs are involved. It may be a primary condition or secondary to other diseases, eg SLE, RA, hepatitis B & C, HIV. It is categorized according to the main size of blood vessel affected:

- *Large:* Giant cell arteritis, Takayasu's arteritis (see p726).
- *Medium:* Polyarteritis nodosa, Kawasaki disease (*OHCS* p646).
- *Small:* •ANCA +ve vasculitis has a predilection for respiratory tract and kidneys. It includes p-ANCA associated microscopic polyangiitis, glomerulonephritis and Churg-Strauss syndrome (p710) and c-ANCA associated Wegener's granulomatosis (p728).
- ANCA –ve vasculitis includes Henoch-Schönlein purpura (p716), Goodpasture's syndrome (p714) and cryoglobulinaemia.

Features of vasculitis

The presentation of vasculitis will depend on the organs affected:

Systemic: fever, malaise, weight loss, arthralgia, myalgia.
Skin: purpura, ulcers, livedo reticularis (fig 1), nailbed infarcts, digital gangrene.
Eyes: episcleritis, scleritis, visual loss.
ENT: epistaxis, nasal crusting, stridor, deafness.
Pulmonary: haemoptysis and dyspnoea (due to pulmonary haemorrhage).
Cardiac: Angina or MI (due to coronary arteritis), heart failure and pericarditis.
GI: Pain or perforation (infarcted viscus), malabsorption (chronic ischaemia).
Renal: Hypertension, haematuria, proteinuria, casts, and renal failure (renal cortical infarcts; glomerulonephritis in ANCA +ve vasculitis).
Neurological: Stroke, fits, chorea, psychosis, confusion, impaired cognition, altered mood. Arteritis of the vasa nervorum (arterial supply to peripheral nerves) may cause mononeuritis multiplex or a sensorimotor polyneuropathy.[63]
GU: Orchitis—testicular pain or tenderness.

Tests: ESR/CRP↑. ANCA may be +ve. ↑Creatinine if renal failure. Urine: proteinuria, haematuria, casts on microscopy. Angiography ± biopsy may be diagnostic.

Degenerative Rheumatic Diseases

These refer to rheumatic diseases commonly associated with advancing age. Degenerative joint disease (DJD) is usually thought to include osteoarthritis (OA) and degenerative disc disease (DDD). DJD is heralded by breakdown of articular collagenous structures (cartilage or intervertebral discs) and development of bony hypertrophy. Controversy remains as to which occurs first. As collagenous structures degrade, associated inflammation commonly occurs. Resultant pain from varying causes contributes to immobility, secondary comorbidities, and disability. DJD represents, by far, the most common of the rheumatic diseases and is described in detail in Chapter 262. In general, these diseases are not associated with rashes or nonspecific constitutional symptoms.

Polyarthritis skin rashes and mild anemia

A 32-year-old nurse presents to your office with a complaint of **intermittent** episodes of **pain, stiffness, and swelling in both hands and wrists** for approximately 1 year. The episodes last for several weeks and then resolve. More recently, she noticed similar symptoms in her **knees** and **ankles**. Joint pain and stiffness are making it harder for her to get out of bed in the morning and are interfering with her ability to perform her duties at work. The **joint stiffness usually lasts for several hours before improving**. She also reports malaise and easy fatigability for the past few months, but she denies having fever, chills, skin rashes, and weight loss. Physical examination reveals a well-developed woman, with *blood pressure* 120/70 mm Hg, heart rate 82 bpm, and respiratory rate 14 breaths per minute. She has **nodules** and **skin rashes** over the extensor surface of arms. Head, neck, cardiovascular, chest, and abdominal examinations are normal. There is *no hepatosplenomegaly*. The joint examination reveals the presence of **bilateral swelling, redness, and tenderness of most proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, the wrists, and the knees**. Laboratory studies show a **mild anemia** with hemoglobin 11.2 g/dL, hematocrit 32.5%, mean corpuscular volume (MCV) 85.7 fL, white blood cell (WBC) count 7.9/mm3 with a normal differential, and platelet count 300 000/mm3. The *urinalysis is clear with no protein and no red blood cells* (RBCs). The **erythrocyte sedimentation rate (ESR) is 75 mm/h (n.r. 0-20)**, and the kidney and liver function tests are normal.

What is your most likely diagnosis?
What is your next diagnostic step?

CFIM n°22

Polyarthritis and mild anemia

A 32-year-old nurse presents to your office with a complaint of **intermittent** episodes of **pain, stiffness, and swelling in both hands and wrists** for approximately 1 year. The episodes last for several weeks and then resolve. More recently, she noticed similar symptoms in her **knees** and **ankles**. Joint pain and stiffness are making it harder for her to get out of bed in the morning and are interfering with her ability to perform her duties at work. The **joint stiffness usually lasts for several hours before improving**. She also reports malaise and easy fatigability for the past few months, but she denies having fever, chills, skin rashes, and weight loss. Physical examination reveals a well-developed woman, with *blood pressure* 120/70 mm Hg, heart rate 82 bpm, and respiratory rate 14 breaths per minute. She has nodules and skin rashes over the extensor surface of arms. Head, neck, cardiovascular, chest, and abdominal examinations are normal. There is *no hepatosplenomegaly*. The joint examination reveals the presence of **bilateral swelling, redness, and tenderness of most proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, the wrists, and the knees**. Laboratory studies show a **mild anemia** with hemoglobin 11.2 g/dL, hematocrit 32.5%, mean corpuscular volume (MCV) 85.7 fL, white blood cell (WBC) count 7.9/mm3 with a normal differential, and platelet count 300 000/mm3. The *urinalysis is clear with no protein and no red blood cells* (RBCs). The **erythrocyte sedimentation rate (ESR) is 75 mm/h (n.r. 0-20)**, and the kidney and liver function tests are normal.

What is your most likely diagnosis? Rheumatoid arthritis (RA).
Tipical polyarticular presentation (symmetrical involvement of small joints) and progression (additive and centripetal involvement of larger joints). Constitutional symptoms (stiffness, anemia, fatigue, ↑ESR). No apparent extra-musculoskeletal manifestations.

What is your next diagnostic step?
Rheumatoid factor,
anti cyclic citrullinated peptide antibody,
antinuclear antibody titer

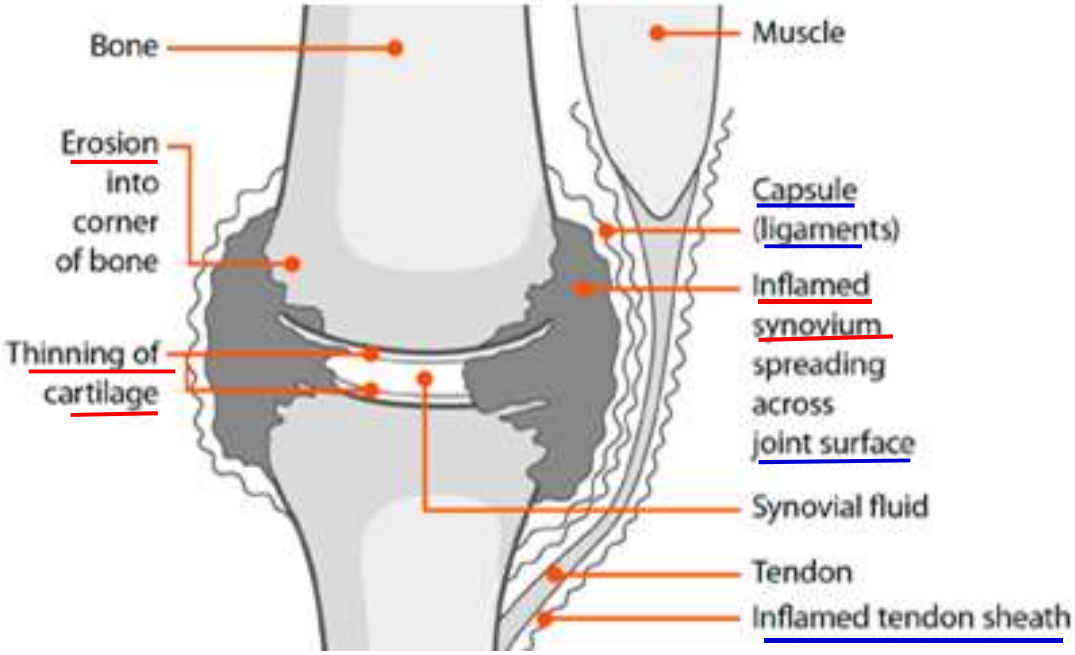
2010 ACR/EULAR

CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2 ■
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (≤3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3 ■
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1 ■
Duration of symptoms	<6 weeks	0
	≥6 weeks	1 ■

Who should be tested? Those with ≥1 joint with definite swelling which is not better explained by another disease. Add total A-D score. Scores ≥6/10 are diagnostic.

Rheumatoid arthritis

- The exact pathogenesis of RA is still unclear.
- It is believed to be due to an **autoimmune inflammatory process of synovial membrane** that leads to proliferation of synovial cells and formation of inflammatory granulation tissue (**pannus**).
- The **inflammatory process secondarily involves underlying connective tissue** with **cartilage destruction, bony erosions, soft tissues swelling, tenosynovitis, bursitis, tendinitis and entesitis** .
- This destructive process is believed to be driven by overproduction of proinflammatory cytokines such as **TNF-a**, **IL-1** and **IL-6.**
- **Later, iuxta-articular osteopenia, loss of joint space, subluxation, ankylosis, joint destruction, deformity**,.



CLINICAL FEATURES

- Arthritis
- Constitutional syntoms : stiffness, fever, anemia, fatigue or weight loss
- Extra-musculoskeletal manifestations

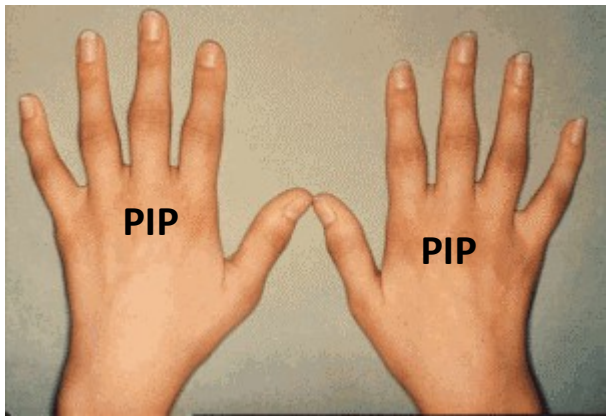
RA is a chronic systemic inflammatory disease, characterized by a symmetrical, deforming, peripheral polyarthritis. *Epidemiology:* Prevalence is ~1% (↑ in smokers). ♀:♂ >2:1. Peak onset: 5th–6th decade. HLA DR4/DR1 linked (associated with ↑ severity).

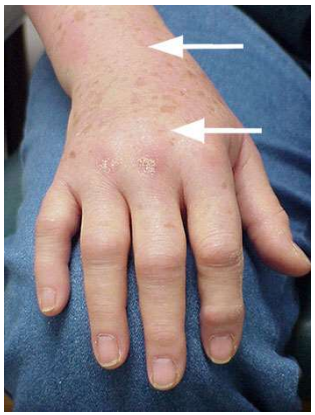
- **Presentation: symmetrical involvement of small joints**
- **Progression: additive and centripetal involvement of larger joints**

Presentation *Typically:* symmetrical swollen, painful, and stiff small joints of hands and feet, worse in the morning. This can fluctuate and larger joints may become involved. *Less common presentations*: •Sudden onset, widespread arthritis; •Recurring mono/polyarthritis of various joints (*palindromic RA*);[1] •Persistent monoarthritis (often knee, shoulder or hip); •Systemic illness with extra-articular symptoms, eg fatigue, fever, weight loss, pericarditis and pleurisy, but initially few joint problems (commoner in ♂); •Polymyalgic onset—vague limb girdle aches; •Recurrent soft tissue problems (eg frozen shoulder, carpal tunnel syndrome, de Quervain's tenosynovitis).

1 In rheumatological palindromes, arthritis lasting hours or days runs to and fro, visiting and revisiting 3 or more sites, typically knees, wrists, and MCP joints. It may presage RA, SLE, Whipple's, or Behçet's disease. Remissions are (initially) complete, leaving no radiological mark.

Signs *Early* (inflammation, no joint damage): swollen MCP, PIP, wrist, or MTP joints (often symmetrical). Look for tenosynovitis or bursitis.

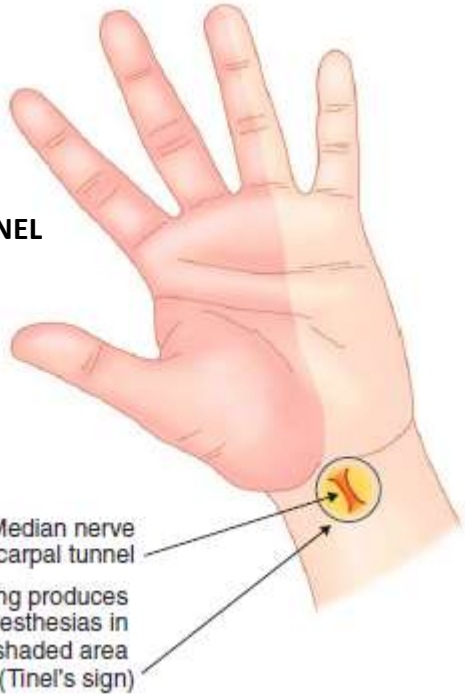


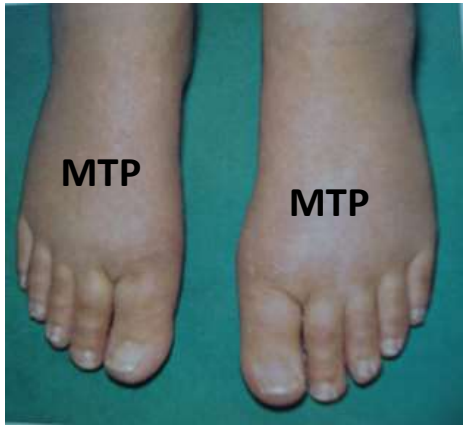


WRIST

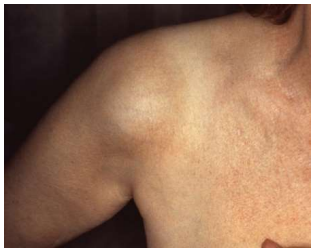
MCP

CARPAL TUNNEL SYNDROME

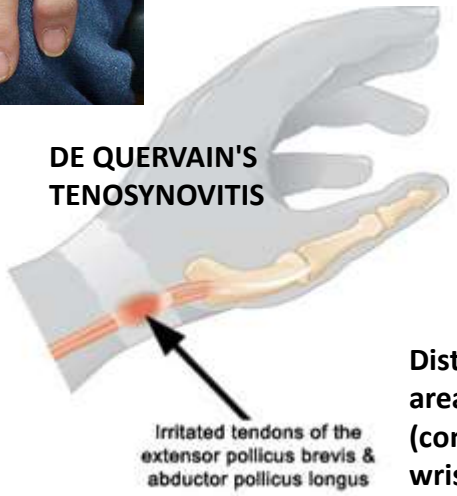




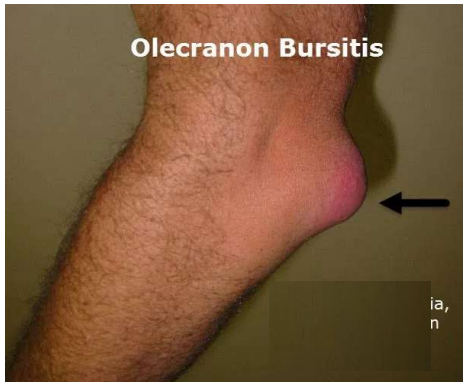
BURSITIS IN THE SHOULDER

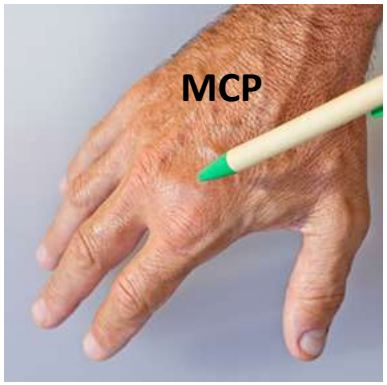


DE QUERVAIN'S TENOSYNOVITIS

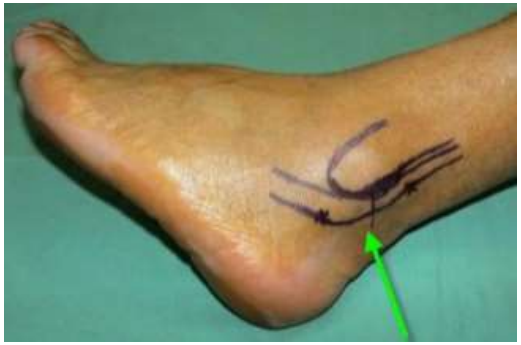


Distribution of pain and/or paresthesias (shaded area) when the median nerve is compressed (compression neuropathy) by swelling in the wrist (carpal tunnel)

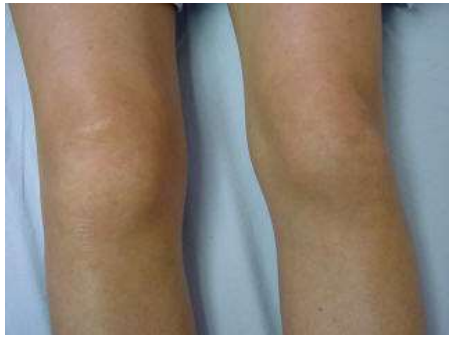




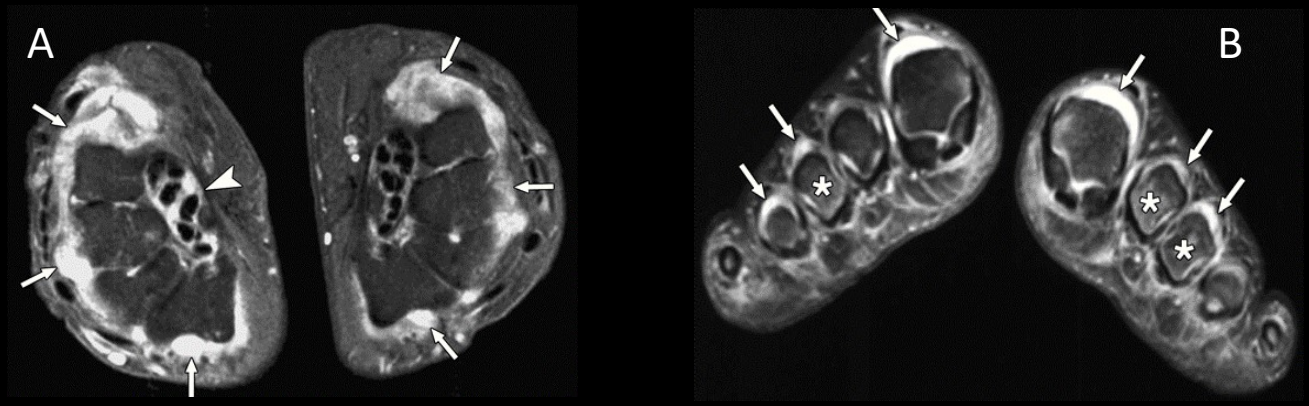
PERONEAL TENOSYNOVITIS



KNEES

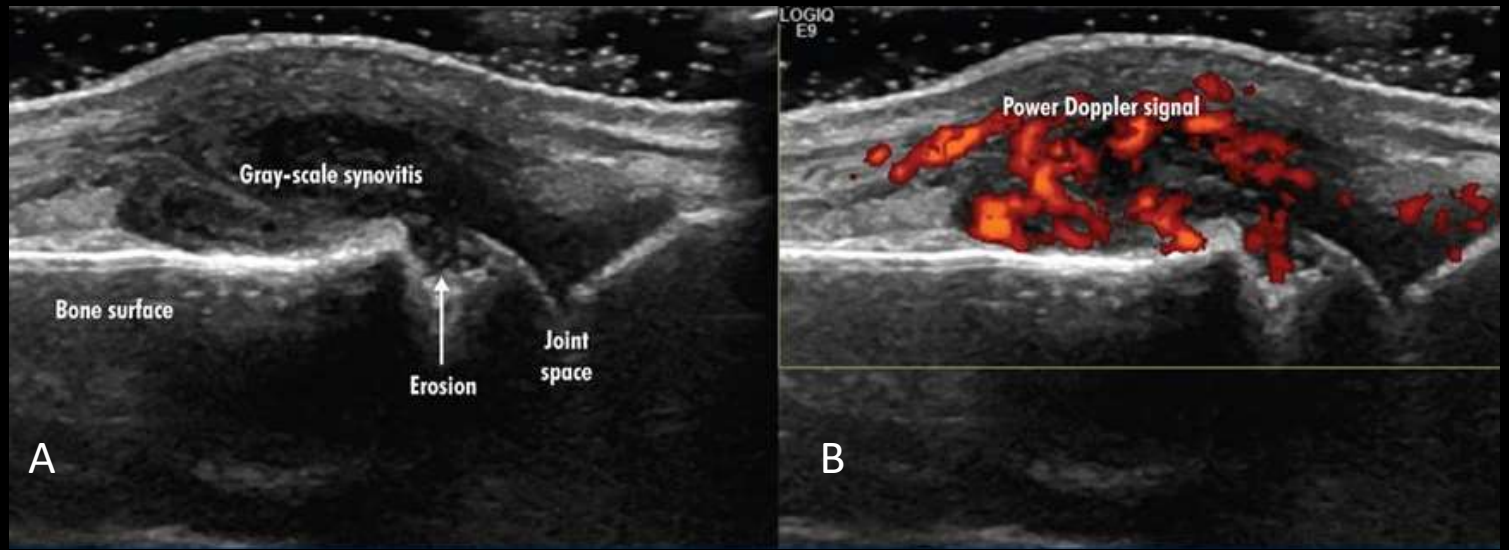


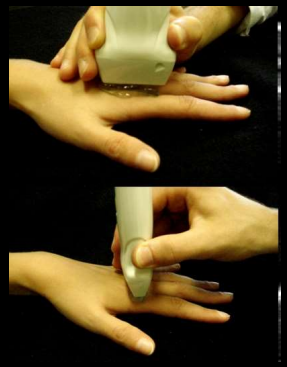
MUSCULOSKELETAL MRI AND ULTRASOUND IN EARLY RHEUMATOID ARTHRITIS



MRI. 34-year-old woman with early rheumatoid arthritis and synovitis. Transverse fat-suppressed gadolinium-enhanced T1-weighted spin-echo MR images show bilateral synovitis (arrows) in wrist (A) and metatarsophalangeal joints (B). Note also bone marrow edema signal intensity changes (asterisks, B), which precede frank bone erosions, and flexor digitorum tenosynovitis (arrowhead, A).

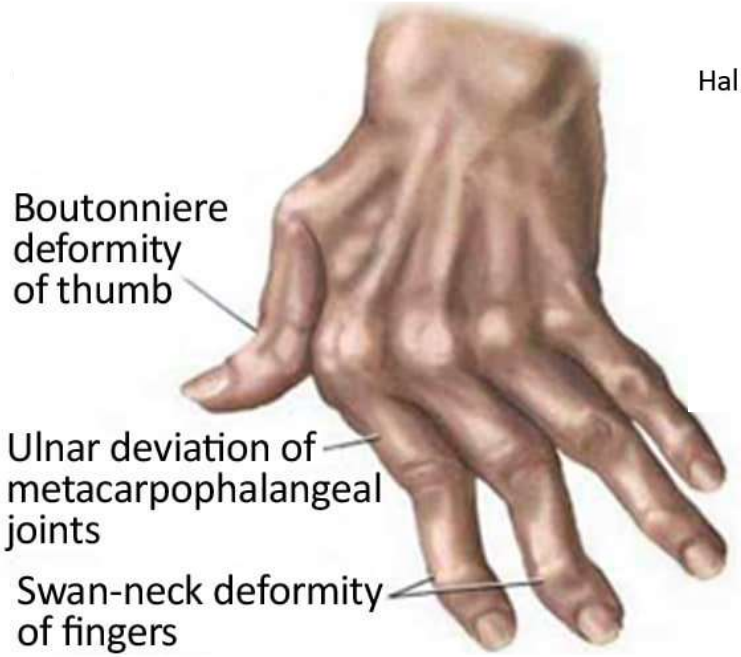
ULTRASOUND. Metacarpophalangeal joint synovitis in a rheumatoid arthritis patients. A: Gray.scale synovial thickening and erosion; B: Power Doppler synovitis

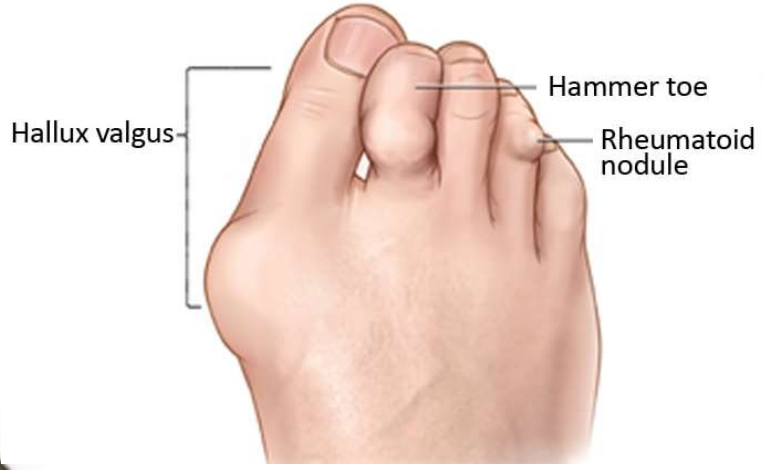


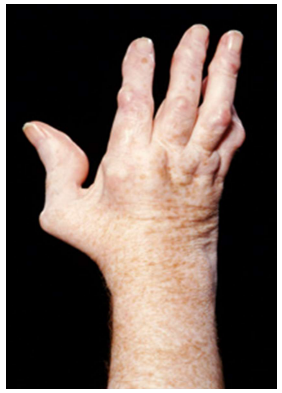


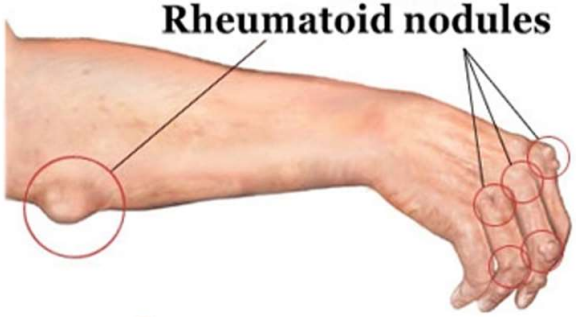
Signs

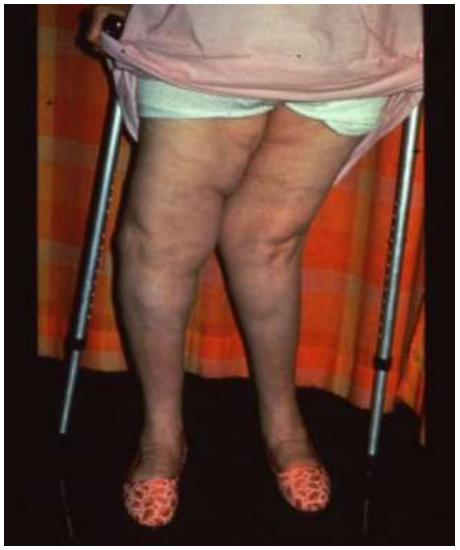
Later (joint damage, deformity): ulnar deviation of the fingers and dorsal wrist subluxation. Boutonnière and swan-neck deformities of fingers (fig 1 on p540) or z-deformity of thumbs occur. Hand extensor tendons may rupture. Foot changes are similar. Larger joints can be involved.







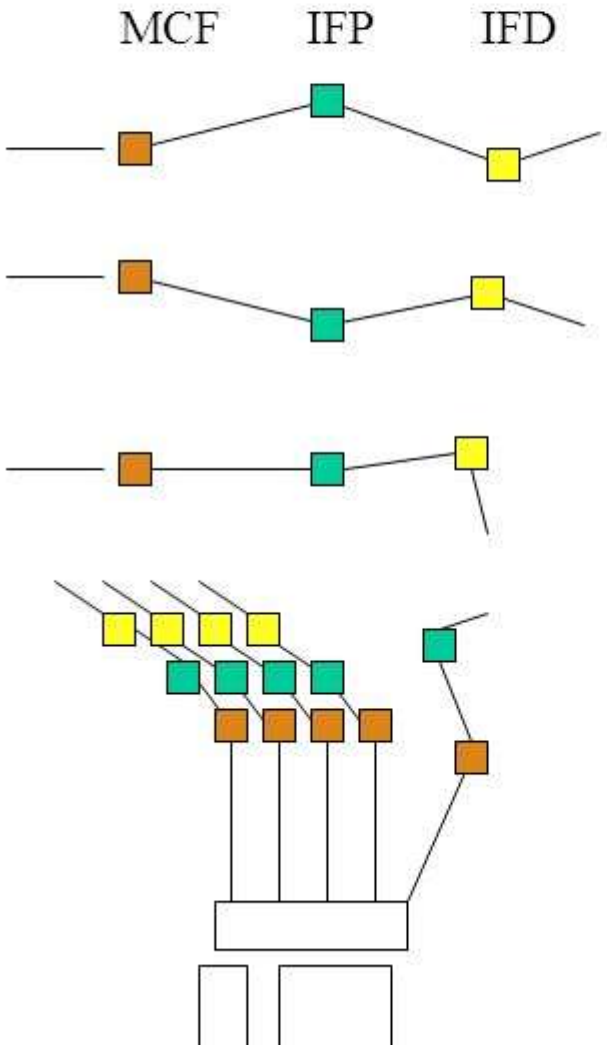




Swan neck deformity of fingers
Hyperextension of PIP joints with flexion of DIP joint

Boutonniere deformity of fingers: Hyperextension of DIP & MCP joints with flexion of PIP joints

Rappresentazione schematica delle principali deformità della mano reumatoide nel corso della malattia non efficacemente trattata

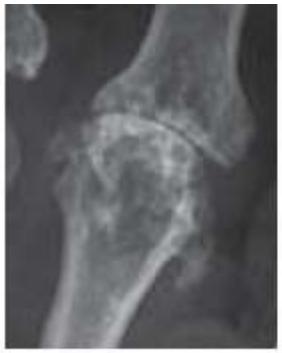


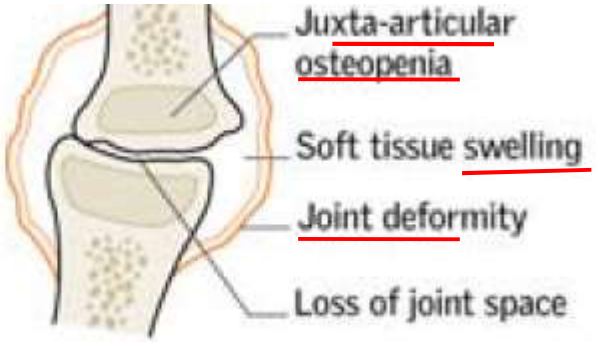
"en boutonniere" (ad asola)

"swan neck" (collo di cigno)

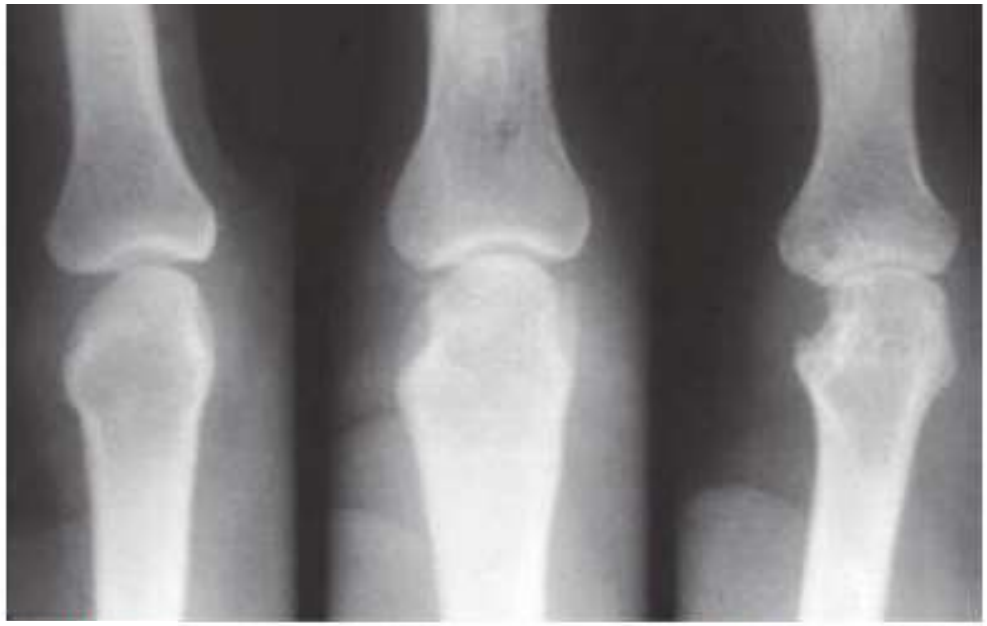
dito "a martello"

Deviazione ulnare "a colpo di vento" e "pollice a Z"

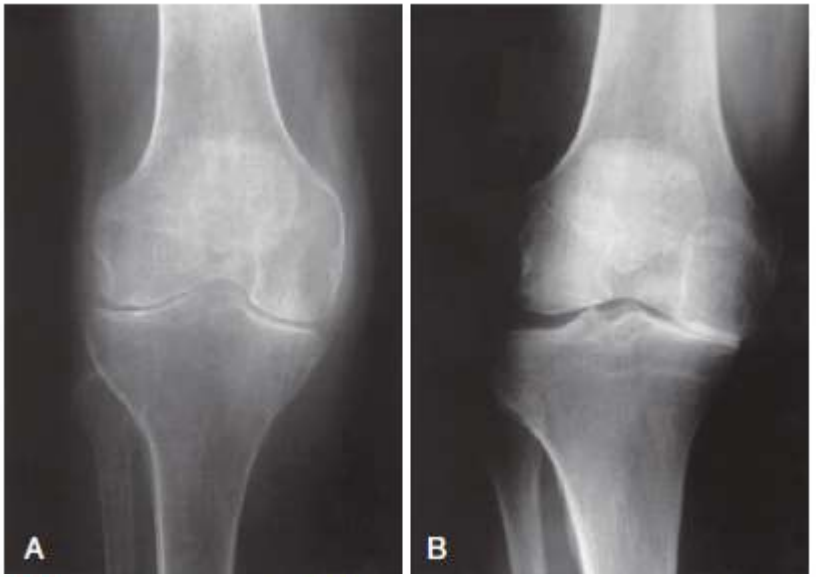




. X-ray features of rheumatoid arthritis (MCPJ).



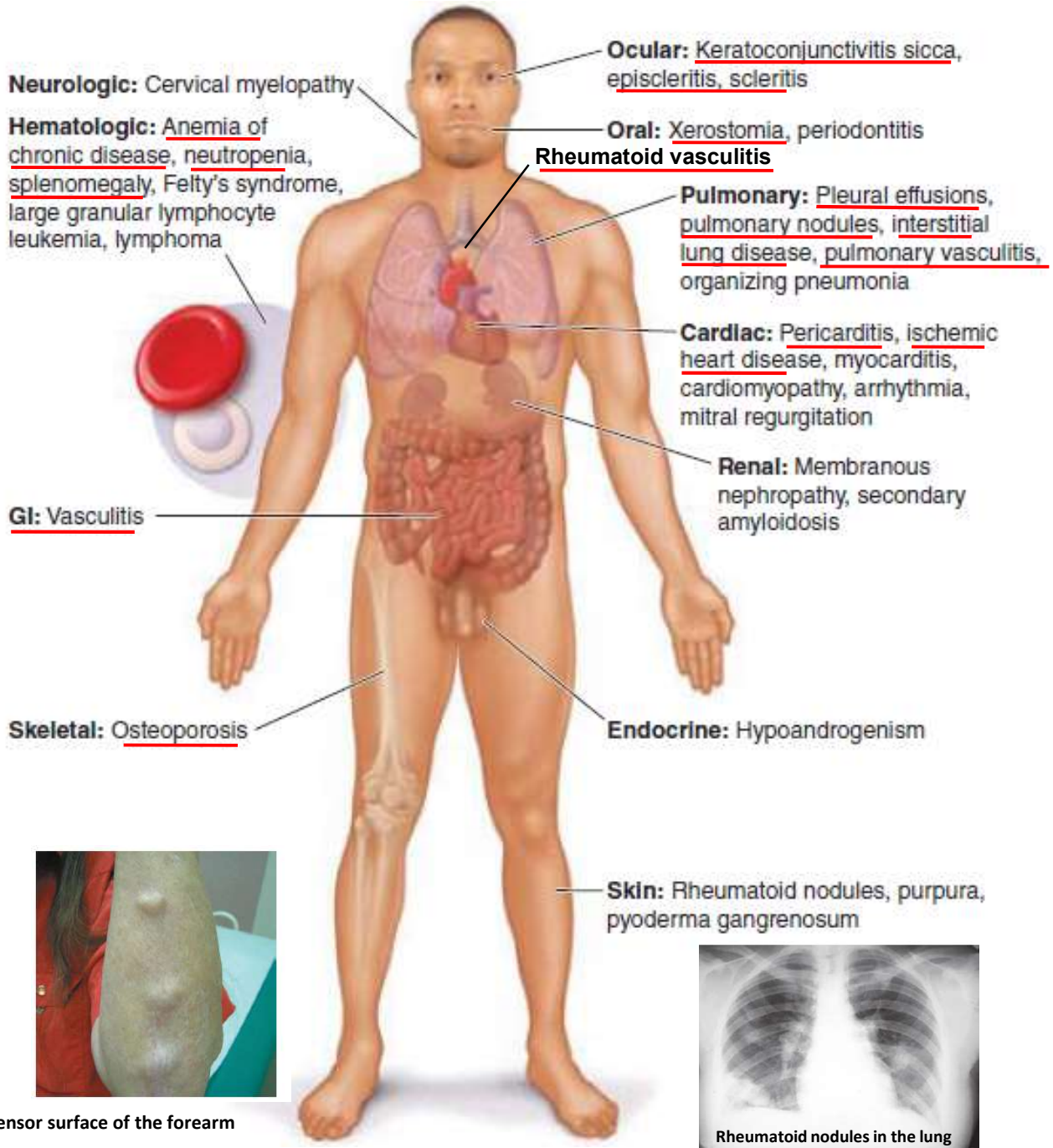
X-ray demonstrating progression of erosions on the proximal interphalangeal joint.



Radiographs of the knees in the two most common forms of arthritis: rheumatoid arthritis and osteoarthritis. A, Severe involvement in rheumatoid arthritis, with almost complete symmetrical loss of joint space in both the medial and the lateral compartments, but with little subchondral sclerosis or osteophyte formation. B, Typical osteoarthritis, with severe, near-total loss of joint space of one compartment and a normal or actually increased joint space of the other compartment. Note also the significant subchondral sclerosis in the involved area, typical of osteoarthritis.

EXTRAARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

- Nodules—elbows & lungs
- Lymphadenopathy
- Vasculitis
- Fibrotising alveolitis, obliterative bronchiolitis
- Pleural & pericardial effusion
- Raynaud's
- Carpal tunnel syndrome
- Peripheral neuropathy
- Splenomegaly (seen in 5%; only 1% have Felty's syndrome: RA + splenomegaly + neutropenia)
- Episcleritis, scleritis, scleromalacia keratoconjunctivitis sicca
- Osteoporosis
- Amyloidosis



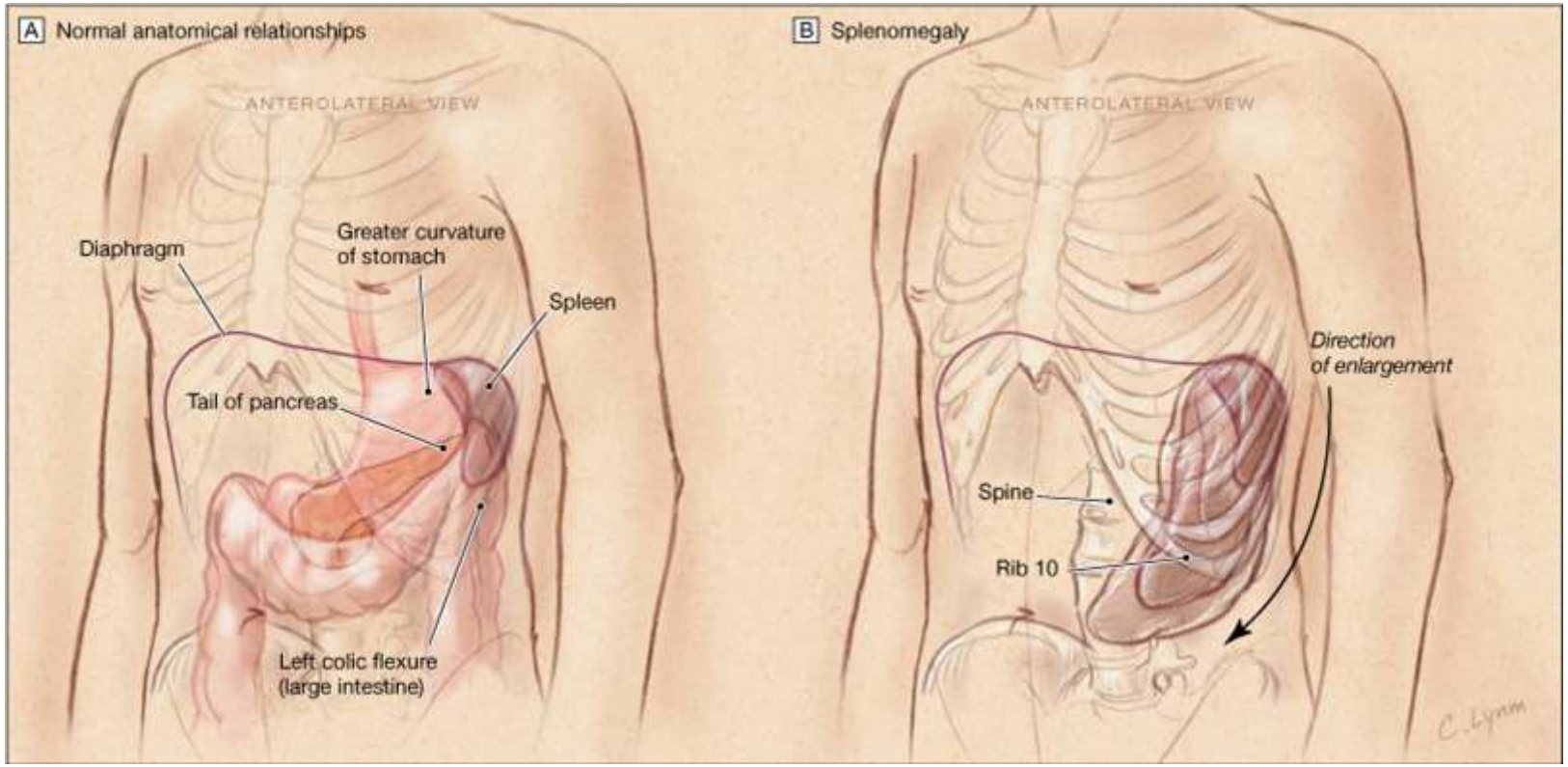
Rheumatoid nodules over the extensor surface of the forearm

Rheumatoid nodules in the lung

Felty's syndrome A triad of rheumatoid arthritis + WCC↓ + splenomegaly (±hypersplenism, causing anaemia and ↓platelets), recurrent infections, skin ulcers and lymphadenopathy. 95% are Rh factor +ve. Splenectomy may raise the wcc. ℞: DMARDs (p549) ± *rituximab* if refractory.[47]

Augustus Roi Felty, 1895–1964 (US physician)

Leukopenia: WCC < 4000/mcL
Neutropenia: Neutrophils < 2000/mcL
Severe Neutropenia: Neutrophils < 500/mcL



Investigations Rheumatoid factor (RhF) is positive in ~70% (p555). A high titre is associated with severe disease, erosions and extra-articular disease. Anticyclic citrullinated peptide antibodies (ACPA/anti-CCP) are highly specific (~98%) for RA. There is often anaemia of chronic disease. Inflammation causes ↑platelets, ↑ESR, ↑CRP. *X-rays* show soft tissue swelling, juxta-articular osteopenia and ↓joint space. Later there may be bony erosions, subluxation or complete carpal destruction (see fig 2 on p543). Ultrasound and MRI can identify synovitis more accurately, and have greater sensitivity in detecting bone erosions than conventional x-rays.[18]

Frequency (%) of autoantibodies in rheumatic diseases

	ANA	Anti-Native DNA	Rheumatoid Factor	Anti-Sm	Anti-SS-A	Anti-SS-B	Anti-SCL-70	Anti-Centromere	Anti-Jo-1	ANCA
Rheumatoid arthritis	30–60	0–5	70	0	0–5	0–2	0	0	0	0
Systemic lupus erythematosus	95–100	60	20	10–25	15–20	5–20	0	0	0	0–1
Sjögren syndrome	95	0	75	0	65	65	0	0	0	0
Diffuse scleroderma	>95	0	30	0	0	0	33	1	0	0
Limited scleroderma (CREST syndrome)	>95	0	30	0	0	0	20	50	0	0
Polymyositis/dermatomyositis	80	0	33	0	0	0	0	0	20–30	0
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	0–15	0	50	0	0	0	0	0	0	93–96[1]

Immunologic Markers Found in Rheumatic Diseases

Disease	Immunologic Markers
Systemic lupus erythematosus (SLE)	ANA (95% of patients) Anti-dsDNA antibodies (60% of patients) Anti-Sm antibodies False-positive RPR or VDRL (syphilis test)
Drug-induced lupus	Antihistone antibodies ANA
Rheumatoid arthritis (RA)	RF (75% of patients) ACPA ANA (<50% of patients) HLA-DR4 common
Polymyositis or dermatomyositis	ANA Anti-Jo-1 antibodies
Ankylosing spondylitis	HLA-B27 (90% of patients)
Psoriatic arthritis	Possible HLA-B27
Scleroderma	Anti-scl-70 ANA
CREST syndrome	Anticentromere antibodies
Mixed connective tissue disease (MCTD)	Anti-RNP ANA
Sjögren syndrome	Anti-Ro (anti-SSA) ANA Anti-La (anti-SSB) ANA

ANA, antinuclear antibodies; CREST, calcinosis, Raynaud, esophageal dysmotility, sclerodactyly, and telangiectasias; dsDNA, double-stranded DNA; RF, rheumatoid factor; RPR, rapid plasma reagin. ACPA, anti-citrullinated peptide antibodies

Plasma autoantibodies (Abs): disease associations 1

Rheumatological Rheumatoid factor (RhF) positive in:

Sjögren's syndrome	≤100%	Mixed connective tissue disease	50%
Felty's syndrome	≤100%	SLE	≤40%
RA	70%	Systemic sclerosis	30%
Infection (SBE/IE; hepatitis)	≤50%	Normal	2–10%

Anticyclic citrullinated peptide Ab (anti-CCP):[1] Rheumatoid arthritis (~96% specificity)

Antinuclear antibody (ANA) positive by immunofluorescence in:

SLE	>95%	Systemic sclerosis	4%
Autoimmune hepatitis	75%	RA	30%
Sjögren's syndrome	68%	Normal	0–2%

ANA titres are expressed according to dilutions at which antibodies can be detected, ie 1:160 means antibodies can still be detected after the serum has been diluted 160 times. Titres of 1:40 or 1:80 may not be significant. The pattern of staining may indicate the disease (although these are not specific):

• *Homogeneous*	SLE	• *Nucleolar*	Systemic sclerosis
• *Speckled*	Mixed CT disease	• *Centromere*	Limited systemic sclerosis

Anti-double-stranded DNA (dsDNA): SLE (60% sensitivity, but highly specific).

Antihistone Ab: Drug-induced SLE (~100%).

Antiphospholipid Ab (eg anti-cardiolipin Ab): antiphospholipid syndrome, SLE.

Anticentromere Ab: limited systemic sclerosis.

Anti-extractable nuclear antigen (ENA) antibodies (usually with +ve ANA):

• Anti-Ro (SSA)	SLE, Sjögren's syndrome, systemic sclerosis. Associated with congenital heart block.
• Anti-La (SSB)	Sjögren's syndrome, SLE (15%).
• Anti-Sm	SLE (20–30%).
• Anti-RNP	SLE, mixed connective tissue disease.
• Anti Jo-1; Anti-Mi-2	Polymyositis, dermatomyositis.
• Anti-Scl70	Diffuse systemic sclerosis.

1 Most centres now use anti-CCP antibodies for the initial workup of suspected RA.

Plasma autoantibodies (Abs): disease associations 2

Gastrointestinal (for liver autoantibodies, see p268).
Antimitochondrial Ab (AMA): Primary biliary cirrhosis (>95%), autoimmune hepatitis (30%), idiopathic cirrhosis (25–30%).
Anti-smooth muscle Ab (SMA): Autoimmune hepatitis (70%), primary biliary cirrhosis (50%), idiopathic cirrhosis (25–30%).
Gastric parietal cell Ab: Pernicious anaemia (>90%), atrophic gastritis (40%), 'normal' (10%).
Intrinsic factor Ab: Pernicious anaemia (50%).
α-gliadin Ab, antitissue transglutaminase, anti-endomysial Ab: Coeliac disease.
Endocrine Thyroid peroxidase Ab: Hashimoto's thyroiditis (~87%), Graves' (>50%).
Islet cell Ab (ICA), glutamic acid decarboxylase (GAD) Ab: Type 1 diabetes mellitus (75%).

Patterns of presentation of arthritis

Monoarthritis	Oligoarthritis (≤5 joints)	Polyarthritis (>5 joints involved)	
Septic arthritis	Crystal arthritis	*Symmetrical:*	*Asymmetrical:*
Crystal arthritis (gout, CPPD)	Psoriatic arthritis	Rheumatoid arthritis	Reactive arthritis
Osteoarthritis	Reactive arthritis, eg *Yersinia, Salmonella, Campylobacter*	Osteoarthritis	Psoriatic arthritis
Trauma, eg haemarthrosis	Ankylosing spondylitis	Viruses (eg hepatitis A, B & C; mumps)	
	Osteoarthritis	Systemic conditions[1] (can be either)	

▶▶ Exclude septic arthritis in any acutely inflamed joint, as it can destroy a joint in under 24h (p546). Inflammation may be less overt if immunocompromised (eg from the many immunosuppressive drugs used in rheumatological conditions) or if there is underlying joint disease. Joint aspiration (p543) is the key investigation, and if you are unable to do it, find someone who can.

1 Connective tissue disease (eg SLE and relapsing polychondritis), sarcoidosis, malignancy (eg leukaemia), endocarditis, haemochromatosis, sickle-cell anaemia, familial Mediterranean fever, Behçet's.

Clinical distinction between rheumatoid arthritis and osteoarthritis

Feature	Rheumatoid arthritis	Osteoarthritis
Primary joints affected	Metacarpophalangeal	Distal interphalangeal
	Proximal interphalangeal	Carpometacarpal
Heberden's nodes	Absent	Frequently present
Joint characteristics	Soft, warm, and tender	Hard and bony
Stiffness	Worse after resting (eg, morning stiffness)	If present, worse after effort, may be described as evening stiffness
Laboratory findings	Positive rheumatoid factor	Rheumatoid factor-negative
	Positive anti-CCP antibody	Anti-CCP antibody-negative
	Elevated ESR and CRP	Normal ESR and CRP

CCP: cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Confirming a diagnosis of rheumatoid arthritis: Differential diagnosis

Diagnosis	Sex	Age	Lab tests	Comments
Undifferentiated seronegative polyarthritis	F > M	35-65	10-15 percent RF+	Chronic seronegative inflammatory polyarthritis, atypical of RA or fails to meet classification criteria for RA. Up to 20 percent of cases may evolve into RA; nearly 50 percent will go into remission.
Psoriatic arthritis	M = F	30-55	<20 percent RF+	10 percent of those with psoriatic arthritis will have an RA-like distribution (MCPs, PIPs, wrists). Cutaneous psoriasis will be evident in the vast majority of cases.
Tophaceous gout	M > F	25-70 M	95 percent RF–	Intermittent inflammatory arthritis during the onset, with evolution of tophi and chronic inflammatory polyarthritis. Elevated serum urate and tophi help distiguish from RA.
	F	>45	>95 percent ↑ serum urate	
Erosive inflammatory OA	F > M	>60	RF– (or normal for age)	Chronic polyarthritis with intermittent or sustained inflammation affecting PIP and DIP joints. Radiographs demonstrate distinctive erosions and evidence of OA.
Pseudogout	F = M	>60	5-10 percent RF+	5 percent of patients will have "rheumatoid-like" inflammatory arthritis with stiffness, fatigue, synovitis, and elevated ESR, often lasting four weeks to several months.
Reactive arthritis (formerly known as Reiter's syndrome)	M > F	16-50	95 percent RF–; 50-80 percent HLA-B27+	See criteria for spondyloarthropathies; often associated with low back pain, ocular, genitourinary, or GI symptomatology and enthesitis (heel pain).
Enteropathic arthritis	M = F	All ages	95 percent RF–	20 percent of patients with Crohn's disease or ulcerative colitis will develop peripheral arthritis. Diagnosis may be difficult until GI involvment becomes apparent. Associated with oral ulcerations, GI symptoms or other features of spondyloarthropathy.
Systemic lupus erythematosus	F > M	15-40	10-15 percent RF+; usually ANA+	Chronic nondeforming inflammatory polyarthritis associated with ANA positivity and other features of SLE.
Polymyositis/ dermatomyositis	F > M	30-60	95 percent RF–; 50 percent ANA+; 70 percent ↑ CK	Chronic inflammatory arthritis uncommonly occurs early in course of PM/DM. Features of proximal muscle weakness, bulbar dysphagia, muscle enzyme elevation, or skin involvement (ie, Gottron's papules) should be sought.
Scleroderma	F > M	30-50	95 percent RF–; >90 percent ANA+	Chronic inflammatory polyarthritis may predominate over skin changes early in the disease. Associated with Raynaud's phenomenon, sclerodactyly, dysphagia, hypertension, or renal abnormalities.
Sarcoid arthritis	F > M	20-40	25 percent RF+	15 percent of patients with sarcoidosis will develop arthritis. Early in the disease a chronic inflammatory oligo or polyarthritis lasting weeks to months may develop and typically involve the ankles and knees. Other features of sarcoidosis (ie, erythema nodosum, hilar adenopathy) are usually apparent.
Parvovirus B19-associated arthritis	F > M	Any age	<10 percent RF+; >80 percent anti-B19 IgM antibodies (acutely)	Adults manifest a flu-like picture, seldom develop the "slapped-cheek" rash; arthralgias are more common than arthritis. Arthritis is an acute inflammatory polyarthritis with an RA-like distribution lasting two weeks. Less than 10 percent develop a chronic inflammatory arthritis.
Polymyalgia rheumatica	F > M	>50	90 percent RF–; >95 percent ↑↑ ESR	Proximal girdle pain and stiffness without synovitis.

The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA

2010 ACR/EULAR classification criteria for newly presenting patients

	Score
Target population (who should be tested?): patients who	
1) have at least one joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
One large joint‖	0
Two to 10 large joints	1
One to three small joints (with or without involvement of large joints)¶	2
Four to 10 small joints (with or without involvement of large joints)	3
> 10 joints (at least one small joint)**	5
B. Serology (at least one test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low positive RF *or* low positive ACPA	2
High positive RF *or* high positive ACPA	3
C. Acute phase reactants (at least one test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or normal ESR	1
D. Duration of symptoms§§	
< six weeks	0
≥ six weeks	1

ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis.

**—The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with long-standing disease, including those whose disease is inactive (with or without treatment), who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.*

†—Differential diagnoses differ in patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

‡—Although patients with a score of less than 6 out of 10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

§—Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

‖—"Large joints" refers to shoulders, elbows, hips, knees, and ankles.

¶—"Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

***—In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).*

††—Negative refers to international unit values that are less than or equal to the upper limit of normal for the laboratory and assay; low positive refers to international unit values that are higher than the upper limit of normal but three or less times the upper limit of normal for the laboratory and assay; high positive refers to international unit values that are more than three times the upper limit of normal for the laboratory and assay. When rheumatoid factor information is only available as positive or negative, a positive result should be scored as low positive for rheumatoid factor.

‡‡—Normal/abnormal is determined by local laboratory standards.

§§—Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Adapted with permission from Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published correction appears in Ann Rheum Dis. *2010;69(10):1892].* Ann Rheum Dis. *2010;69(9):1583.*

A 41 year old woman presents with **pain** in the **joints of both hands** for 8 weeks; this was associated with **morning stiffness** which subsides over several hours. She has particular trouble with fine movements of the hand, mainly due to the pain. She recalls that her left **wrist was swollen and tender** about 3 months ago; this resolved spontaneously. Her medical and drug histories are unremarkable.

Select Relevant Investigations

♦ACPA + Rheumatoid Factor

Rheumatoid factor: weakly positive Anti-citrullinated protein antibodies (ACPA): weakly positive

♦ESR & CRP

ESR: 32 mm/1h (<20) CRP: 6 mg/dL (0-1.0)

♦ANA

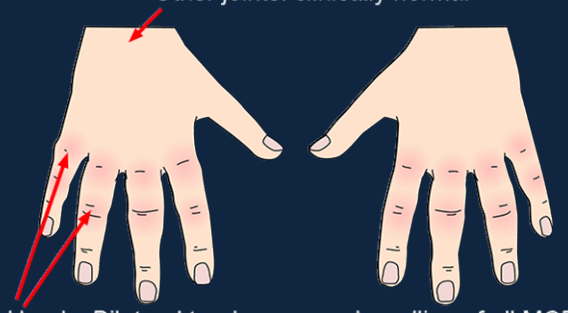
Antinuclear Antibodies (ANA): negative

♦X-Rays B/L Hands & Feet

X-rays of both hands and feet are obtained and are found to be normal.

Afebrile
Vital signs: stable
General examination: normal

Wrists: mild tenderness noted bilaterally.
Other joints: clinically normal



Hands: Bilateral tenderness and swelling of all MCP and PIP joints of 2nd to 5th fingers.
No joint deformities noted.

Heart, Lungs, Abdomen, CNS: no abnormalities

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA

	Score
Target population (who should be tested?): patients who	
1) have at least one joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
One large joint‖	0
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B. Serology (at least one test result is needed for classification)††	
Negative RF *and* negative ACPA	0
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High positive RF *or* high positive ACPA	3
C. Acute phase reactants (at least one test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or normal ESR	1
D. Duration of symptoms§§	
< six weeks	0
≥ six weeks	1

SCORE = 9/10

AR ≥ 6/10

Select Relevant Management

- NSAIDs are the first line agents for pain relief; their anti-inflammatory effects may also help in disease control
- Methotrexate disease-modifying antirheumatic drugs (DMARDs) are key towards preventing future joint damage and should be started as soon as possible. Methotrexate is the first line agent used in most patients.
- Infliximab is a biologic DMARD, it is only indicated in patients unresponsive to conventional therapy; it should not be started as a first-line agent.
- Physiotherapy is an essential non-pharmacological intervention, and is key towards maintaining good joint function and improving quality of life.

Diagnosis and reasoning

Joint pain is the hallmark symptom of clinical rheumatology, being encountered in almost every rheumatological disease, as well as many non-rheumatological conditions.

Fortunately, many of these diseases tend to give rise to characteristic patterns of joint involvement; thus, a meticulous examination technique combined with analytic 'pattern matching' is often capable of arriving at a good differential diagnosis.

In this respect, the most important characteristics are the number of joints involved, the type of joints affected, and the presence or absence of symmetricity.

Thus, evaluation of this patient's findings reveals the following:

- The joints involved are those of the hands and wrists - i.e. the peripheral joints.
- More than 5 joints are involved, i.e. this is a polyarthritis.
-The joint involvement is symmetrical.
-In summary, this is a symmetrical, peripheral polyarthritis.

Note also the presence of morning stiffness which gradually recedes over the day; this is strongly suggestive of an inflammatory etiology.

Rheumatoid arthritis (RA) is the most common cause of (inflammatory) symmetrical peripheral polyarthritis in this age group; note that involvement of the proximal interphalangeal joints (PIP) and metacarpophalangeal joints (MCP) is strongly suggestive of this diagnosis.

Connective tissue diseases are the other key possibility here - particularly systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), or scleroderma; these can be extremely difficult to differentiate from RA, particularly in the early stages.

It is particularly important to note that the absence of extra-articular manifestations does not necessarily exclude this possibility; however, the presence of a negative antinuclear antibody (ANA) assay in this patient argues against the presence of a connective tissue disease.

Psoriatic arthritis can also present as a symmetrical peripheral polyarthritis; while the absence of psoriatic skin manifestations makes this diagnosis clinically less likely, it does not rule it out, as arthritis can develop before any dermatological manifestations.

While viral processes can also give rise to a similar pattern of findings, this rarely lasts longer than 6 weeks.

All individuals with suspected RA should be matched against the 2010 classification criteria released by the The American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR).

Note that the criteria make use of both clinical findings as well as biochemical test results - i.e. seropositivity for rheumatoid factor and/or anti-citrullinated protein antibody (ACPA), and ESR and C-Reactive protein (CRP) levels; these are then matched against a score-based algorithm, with a score of 6 out of 10 or more being sufficient to diagnose RA.

Thus, matching the relevant clinical findings against the algorithm: >10 small joints are affected (+5 points); and symptoms have been present for >6 weeks (+1 point).

Reviewing her biochemical test results: she is weakly seropositive for both rheumatoid factor and ACPA (+ 2 points); and both CRP and ESR are abnormal (+1 point).

Thus, her score is 9 out of 10 points; when considered along with the fact that there is no other diagnosis that would better explain the joint swelling in this patient, this is sufficient to diagnose RA. X-rays of both hands and feet should be obtained to determine if any erosive changes are present, and to establish a baseline for future comparison.

NSAIDS are the first line agents for pain relief; their anti-inflammatory effects may also help in disease control.

However, disease-modifying antirheumatic drugs (DMARDs) are key towards preventing future joint damage and should be started as soon as possible. Methotrexate is the first line agent used in most patients. While Infliximab is a biologic DMARD, it is only indicated in patients unresponsive to conventional therapy; it should not be started as a first-line agent. Physiotherapy is an essential non-pharmacological intervention, and is key towards maintaining good joint function and improving quality of life.

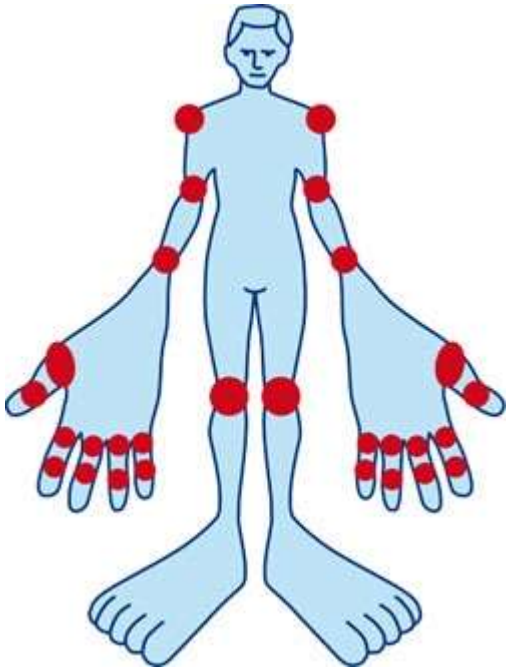
The primary objectives in treating rheumatoid arthritis are reduction of inflammation and pain, preservation of function, and prevention of deformity. Success requires early, effective pharmacologic intervention. Disease-modifying antirheumatic drugs (DMARDs) should be started as soon as the diagnosis of rheumatoid disease is certain and then adjusted with the aim of suppressing disease activity. NSAIDs provide some symptomatic relief in rheumatoid arthritis but do not prevent erosions or alter disease progression. They are not appropriate for monotherapy and should only be used in conjunction with DMARDs, if at all. The American College of Rheumatology recommends using standardized assessments, such as the Disease Activity Score 28 Joints (DAS28), to gauge therapeutic responses, with the target of mild disease activity or remission by these measures. In advanced disease, surgical intervention may help improve function of damaged joints and to relieve pain.

DAS 28 - Disease Activity Score Calculator for Rheumatoid Arthritis

DAS28-CRP = 0.56*sqrt(Tender Joints C28) + 0.28*sqrt(Swollen Joints C28) + 0.36*ln(CRP mg/l +1) + 0.014*Global Health (0 best→100 worst) + 0.96

Tender Joints = 0
Swollen Joints =6
CRP= 10
Global Health = 20
DAS28-CRP = 2.79

Tender Joints = 6
Swollen Joints =6
CRP= 20
Global Health = 30
DAS28-CRP = 4.57



- Disease activity is measured using the DAS28.[2] Aim to reduce score to <3.

Management ►Refer early to a rheumatologist (before irreversible destruction).

- Disease activity is measured using the DAS28.[2] Aim to reduce score to <3.
- Early use of DMARDs and biological agents improves long-term outcomes (see BOX).
- Steroids rapidly reduce symptoms and inflammation. Avoid starting unless appropriately experienced. They are useful for treating acute exacerbations ('flares'), eg IM depot *methylprednisolone* 80–120mg. Intra-articular steroids have a rapid but short-term effect (*OHCS* p708–711). Oral steroids (eg *prednisolone* 7.5mg/d) may control difficult symptoms, but side-effects preclude routine long-term use.
- NSAIDs (see p547) are good for symptom relief, but have no effect on disease progression. Paracetamol and weak opiates are rarely effective.
- Offer specialist physio- and occupational therapy, eg for aids and splints.
- Surgery may relieve pain, improve function and prevent deformity.
- There is ↑ risk of cardiovascular and cerebrovascular disease, as atherosclerosis is accelerated in RA.[19] Manage risk factors (p87). Smoking also ↑ symptoms of RA.

Patients want to live as unencumbered by the disease as possible. Depressive symptoms and pain are better predictors of quality of life than disease markers or radiological damage. Assess impact on relationships, work and hobbies. Psychological interventions (eg relaxation, cognitive coping skills) may help. There is little evidence for the long-term efficacy of complementary therapies but don't prejudice patients who may decide to try.

Influencing biological events in RA

The chief biological event is inflammation. Over-produced cytokines and cellular processes erode cartilage and bone, and produce the systemic effects seen in RA.

Disease-modifying antirheumatic drugs (DMARDs) are 1st-line for treating RA and should ideally be started within 3 months of persistent symptoms. They can take 6–12 weeks for symptomatic benefit. Best results are often achieved with a combination of methotrexate, sulfasalazine and hydroxychloroquine.[21] Other DMARDs include leflunomide and IM gold (now rarely used). The role of penicillamine, azathioprine and ciclosporin is less clear.

► *Immunosuppression* is a potentially fatal SE of treatment (especially in combination with methotrexate) which can result in pancytopenia, ↑susceptibility to infection and neutropenic sepsis (p346). Regular FBC monitoring is required.[22]

Other SE: • Methotrexate—pneumonitis (get urgent respiratory help), oral ulcers, hepatotoxicity • Sulfasalazine—rash, ↓sperm count, oral ulcers • Leflunomide—teratogenicity (♂ and ♀), oral ulcers, ↑BP, hepatotoxicity • Hydroxychloroquine—irreversible retinopathy (request annual ophthalmology review).[23]

typical RA patient should be started on methotrexate monotherapy, and, if not controlled after 3 months on maximum methotrexate, advanced to triple therapy. If the patient does not achieve adequate control after 3 to 6 months on triple therapy, either a TNF inhibitor or abatacept should be added to methotrexate.

Biological agents and NICE guidance: There are 4 approaches, which should be initiated under specialist supervision:

1 *TNFα inhibitors*, eg Infliximab (p275), etanercept, adalimumab, certolizumab-pegol and golimumab. All are approved by NICE (usually in combination with methotrexate) as 1st-line biological agents for active RA after failure to respond to 2 DMARDs and with a DAS28 >5.1.[24,25,26] Where methotrexate is contraindicated, adalimumab and etanercept can be used as monotherapy. Clinical response can be striking, with improved function and health outcomes, although some patients may have inadequate or unsustained response.[24]

2 *B cell depletion*, eg Rituximab, used in combination with methotrexate and approved by NICE for severe active RA where DMARDs and a TNFα blocker have failed.[28]

3 *IL-1 and IL-6 inhibition*, eg Tocilizumab (IL-6 receptor blocker), approved by NICE in combination with methotrexate for patients where both a TNFα blocker and rituximab have failed (or are contraindicated).[29] Anakinra (IL-1 receptor inhibitor) is not recommended. Cochrane review shows less clinical improvement in comparison to other agents.[30]

4 *Disruption of T cell function*, eg Abatacept—used infrequently for patients with severe active RA who have not responded to DMARDs, a TNFα blocker or rituximab.[31]

SEs of biological agents: Serious infection, including reactivation of TB (∴ screen and consider prophylaxis) and hepatitis B; worsening heart failure; hypersensitivity; injection-site reactions and blood disorders. Neutralizing antibodies may ↓ efficacy with infliximab and adalimumab; ANA and reversible SLE-type illness may evolve. Long-term safety is unknown (no clear evidence for ↑ risk of cancer).

The anaemia of chronic disease (secondary anaemia)

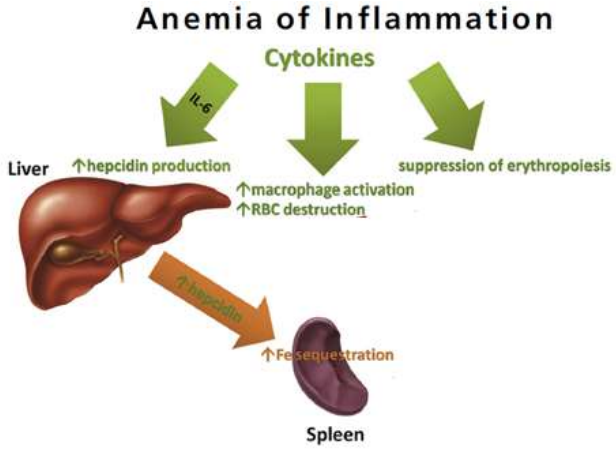
It is the commonest anaemia in hospital patients (the 2nd commonest anaemia, after IDA, worldwide).[3] *3 problems* (in which the polypeptide, hepcidin, plays a key role): 1 Poor use of iron in erythropoiesis 2 Cytokine-induced shortening of RBC survival 3 ↓Production of and response to erythropoietin.

Causes: Many, eg chronic infection, vasculitis, rheumatoid, malignancy, renal failure.

Tests: Mild normocytic anaemia (eg Hb >80g/L), ferritin normal or ↑. Do blood film, B_{12}, folate, TSH and tests for haemolysis (p330) as anaemia is often multifactorial.[4]

Treatment: Treating the underlying disease more vigorously may help (eg in 60% of patients with RA). Erythropoietin (p296) is effective in raising the haemoglobin level (SE: flu-like symptoms, hypertension, mild rise in the platelet count and thromboembolism). It is also effective in raising Hb and improving quality of life in those with malignant disease.[5] Iron given parenterally can safely overcome the functional iron deficiency. Inhibitors of hepcidin and inflammatory modulators show promise.[6]

- Mild or moderate normocytic or microcytic anemia.
- Normal or increased ferritin and normal or reduced transferrin.
- Underlying chronic disease.



TRANSFERRINA Siero v.n. 200 - 360 mg/dL

Total iron-binding capacity (TIBC, 250–370 µg/dL) or sometimes transferrin iron-binding capacity is a medical laboratory test that measures the **blood's capacity to bind iron** with transferrin. It is performed by drawing blood and measuring the maximum amount of iron that it can carry, which **indirectly measures transferrin** since transferrin is the most dynamic carrier. TIBC is less expensive than a direct measurement of transferrin.

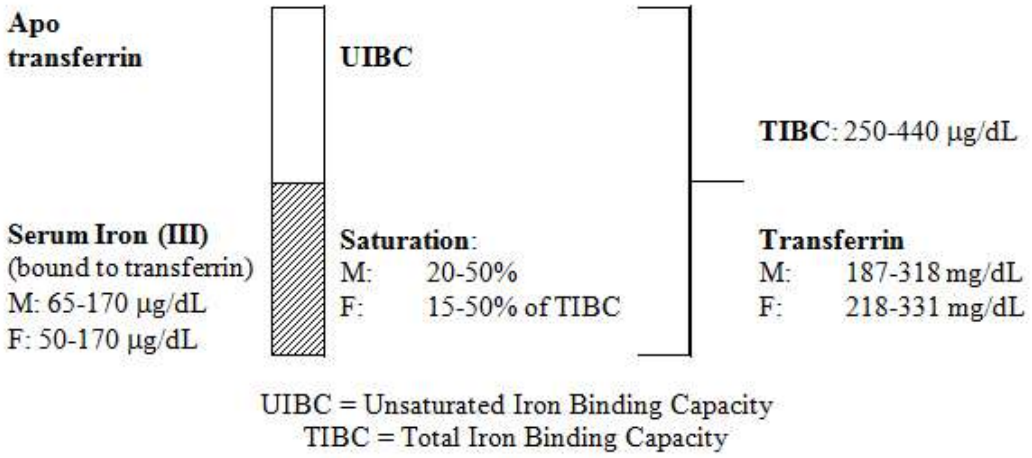
SIDEREMIA Siero v.n. M: 59 – 158; F: 37 - 135 µg/dL

SATURAZIONE DELLA TRANSFERRINA

= Sideremia/TIBC

= [Sideremia/(Transferrina x 1,42)] x 100

v.n. 20-50%



FERRITINA Siero v.n. M: 14 – 300; F: 10 - 280 µg/L

<100 µg/L

Potenziale deplezione marziale: eseguire sideremia, transferrina e saturazione della transferrina

3 Interpreting laboratory blood test results to assess iron status*

Diagnosis	Haemoglobin	Mean cell volume and mean cell haemoglobin	Serum ferritin µg/L	Transferrin or total iron binding capacity	Transferrin saturation†	Soluble transferrin receptor	Serum iron‡
Tissue iron deficiency without anaemia	Normal	Normal or low	< 15–30	Normal or high	Low-normal or low	High-normal or high	Low
Iron deficiency anaemia (IDA)	Low	Low (or normal in early IDA)	< 15–30 adult < 10–12 child	High	Low	High	Low
Anaemia of chronic disease or inflammation	Low	Normal (may be mildly low)	Normal or elevated (elevated ferritin does not imply elevated iron stores)	Normal	Low	Normal	Low
IDA with coexistent chronic disease or inflammation	Low	Low	Low or normal, but usually < 60–100 µg/L	Normal or high	Low	High	Low
Thalassaemia minor§	Low (or normal)	Low (or normal)	Normal or elevated	Normal	Normal or elevated	Normal or elevated	Normal
Iron overload	Normal	Normal	Elevated (correlates with body iron stores)	Normal to low	High	Normal	Normal to elevated

* Compared with laboratory reference range for age, sex and gestation if applicable. † Ideally performed on fasting morning sample.
‡ Serum iron is markedly labile with a significant diurnal variation, is low in both iron deficiency and inflammation, and should not be used to diagnose iron deficiency.
§ Includes β-thalassaemia minor and single or two alpha gene deletion thalassaemia minor. A thalassaemic condition and iron deficiency may coexist, particularly in pregnancy.

◆

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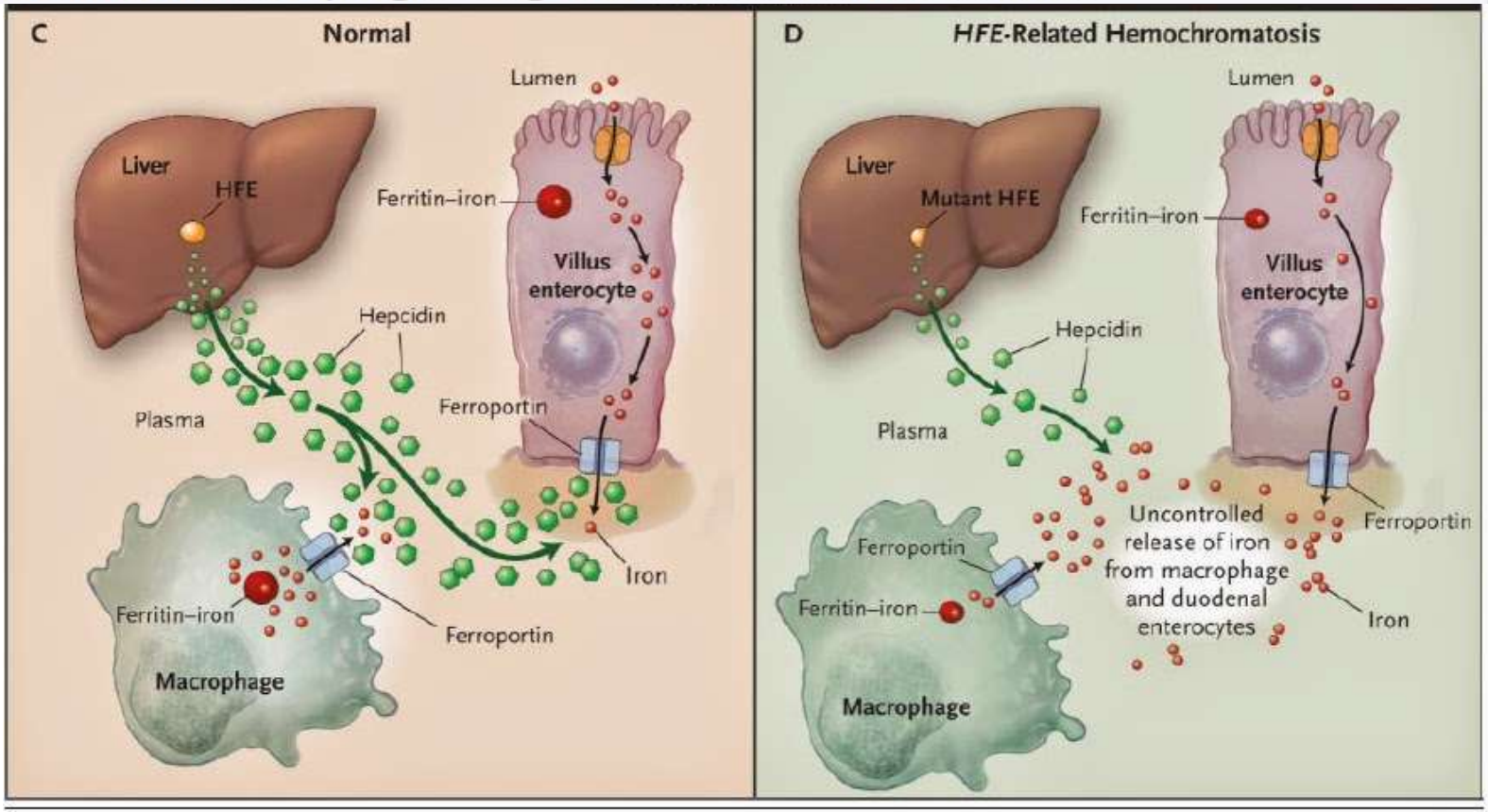
Hepcidin, a peptide synthesized in hepatocytes, secreted in plasma, is a negative regulator of gut iron absorption and haeme iron recycling by macrophages. Hepcidin synthesis is stimulated by iron and repressed by iron deficiency and by ↑marrow erythropoiesis[141] (eg in anaemia, bleeding, haemolysis, dyserythopoiesis or erythropoietin injections). A defect in activation of hepcidin normally triggered by iron excess causes haemochromatosis whereas a defect in hepcidin repression is responsible for an iron refractory iron deficiency anaemia.

In HH the total body iron is up to 10-fold that of a normal person, with loading found particularly in the liver and pancreas (×100). Hepatic disease classically starts with fibrosis, progressing to cirrhosis as a late feature.



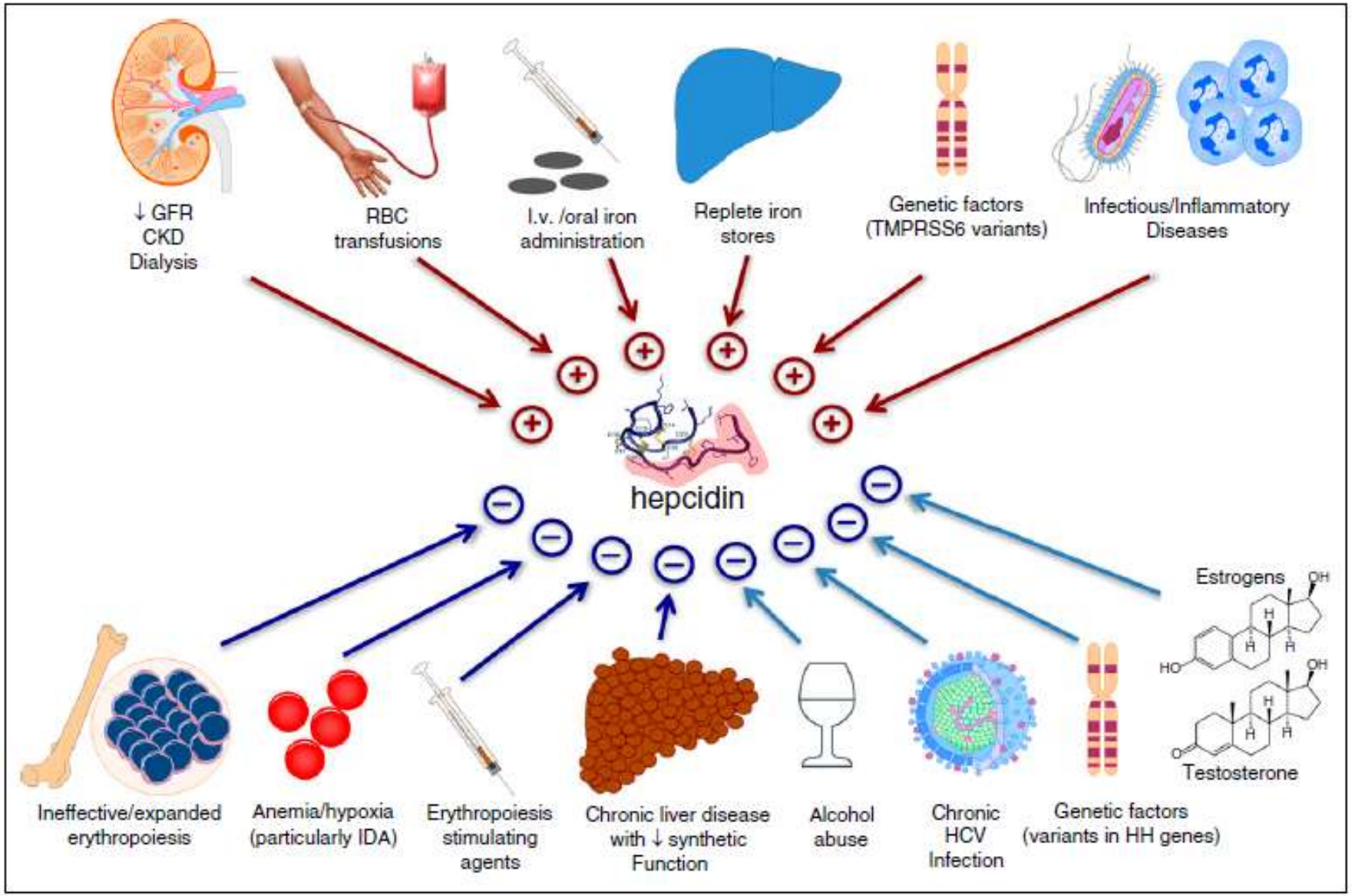


Figure 1. Clinical conditions known to influence circulating hepcidin levels. Clinically relevant conditions include CKD,[11,16] RBC transfusions,[27] iron administration,[28,29] replete iron stores,[1] *TMPRSS6* variants,[30,31] infections/inflammatory disorders,[32-34] ineffective erythropoiesis,[3,49] hypoxia,[35,36] administration of erythropoietic stimulating agents,[37] chronic liver diseases,[38] alcohol abuse,[39] HCV,[40] hemochromatosis-related mutations,[1,28,41,42] and administration of the sex hormones testosterone[43] and estrogens.[44,45] CKD, chronic kidney disease; GFR, glomerular filtration rate; HCV, hepatitis C virus; HH, hereditary hemochromatosis; IDA, iron deficiency anemia; RBC, red blood cell; *TMPRSS6* (transmembrane protease serine 6), the gene encoding for matriptase-2.