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RHEUMATOLOGY LECTURES

CONNECTIVE TISSUE DISEASES

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) : is an autoimmune rheumatic disease of unclear etiology characterized by autoantibody production and protean organ system manifestations.

Autoantibodies in SLE are directed against intracellular targets; antinuclear antibodies (ANAs) are the most characteristic and are present in at least 95% of patients with SLE.
Anti–double stranded DNA (dsDNA), anti-smith (anti-Sm), anti-Ro, and anti-La antibodies are less common.

EPIDEMIOLOGY

primarily affects women of childbearing age.

the female-to-male ratio reaches a peak ratio of approximately 12 : 1.

lupus in men, though rarer, is more severe than that in women.

may develop at any age, although its peak incidence occurs during the childbearing years (15 to 45) in women.

RISK FACTORS

Complex interactions between genes and environmental exposures are probably necessary for the development of SLE.

Sibling risk ratio 8 fold to 29 fold higher than that in general population and a 10 fold increase in disease concordance in identical twins.
There is 24to 56 % concordance rate in monozygotic twins compared with 2-5 % risk in dizygotic twins.

Hormonal/reproductive factors .
Estrogen use in postmenopausal women appears to increase the risk of developing SLE.

Cigarette smoking and silica dust may increase the risk of developing SLE.

Nutritional factors and vit d. deficiency has been implicated in autoimmunity and the development of rheumatic diseases including SLE.

Ultraviolet light stimulates keratinocytes ,which leads not only to overexpression of nuclear ribonucleoproteins on their cell surface but also to secretion of cytokines that stimulate increased autoantibody production.

Photosensitivity is clearly a precipitant pf skin disease.

Infections.

CLINICAL FEATURES

GENERAL MANIFESTATIONS

Constitutional complaints such as malaise, fatigue, fever, anorexia, frailty, and weight loss are commonly seen in patients with SLE.

These may be the initial features or may be caused by later complications of the disease.

Fatigue occurs frequently and is a disabling symptom for many patients with SLE.

Its strongest correlation is with depressive (mood changes) features, and it is frequently independent of serologic or other clinical manifestations of lupus

Fever in patients with SLE is a challenging clinical problem.

About 42% of patients with SLE have fever as a manifestation of active lupus.

Fever may also result from infections, reaction to medications, or malignancies.

Lupus is a cause of fever of unknown origin (FUO) in fewer than 5% of patients, yet it is always on the list to consider when a patient is admitted to the hospital with an FUO.

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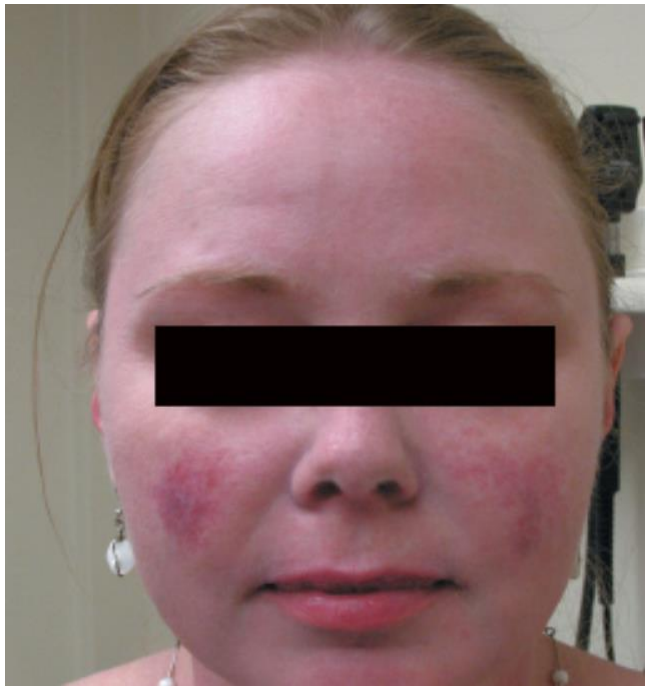
Mucocutaneous involvement (malar rash, alopecia, mucosal ulcers, discoid lesions, etc.)80-90%.

A. Acute cutaneous lupus erythematosus
Frequently associated with active SLE.
There are localized and generalized forms

- localized form like

Malar or butterfly rash, which refers to erythema,
flat or raised, over both cheeks, extend over the nasal bridge
sparing the nasolabial folds.
Present in up to 50% of SLE patients at the time of diagnosis.



These lesions are transient, sun induced and non scarring, persists for several days.

- Generalized form (rare),occurs above and below the neck, usually presents as an pruritic maculopapular photosensitive rash

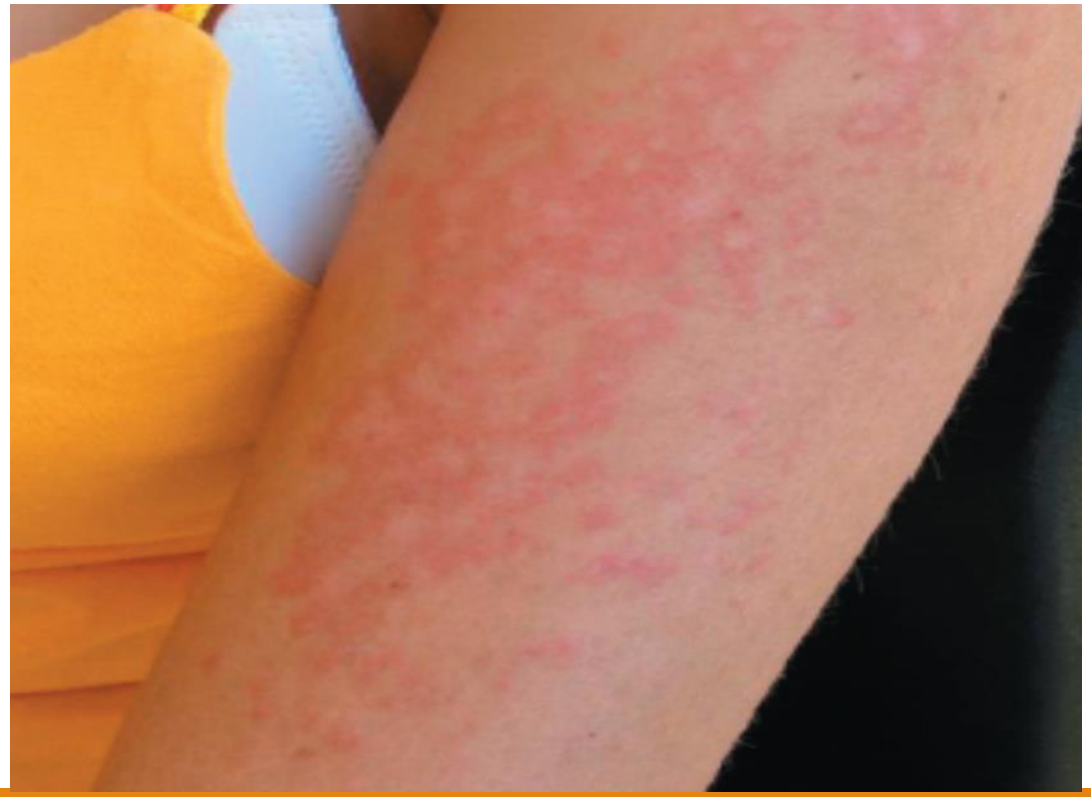
B. Subacute cutaneous lupus erythematosus(SCLE). 10%

SCLE lesions occur in sun exposed areas, upper back, chest, and extensor surfaces of the arms and forearms.
Central face and scalp are usually spared
Typically do not occur below the waist.
There is a strong association between SCLE and the presence of anti Ro (SSA),anti la antibodies.

There are 2 morphological variants(annular and papulosquamous)

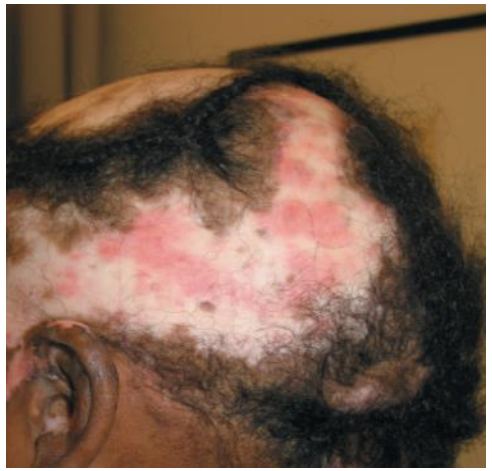
Annular type: scaly annular erythematous plaques, which tend to coalesce and produce polycyclic rash.
Papulosquamous variant: resemble eczema or psoriasis.

Subacute cutaneous
lupus erythematosus,
Papulosquamous variant.



C. Chronic cutaneous lupus erythematosus,(CCLE).25%

Discoid lupus erythematous :discoid lesions are the most common lesions of CCLE.
Well demarcated erythematous scaly macules that enlarge into indurated plaques with adherent scale and follicular plugging, atrophic scarring may occur in older lesions.



Typically the ear and scalp affected and when plaques involve the hair follicles a patchy alopecia develops, the arms and hands can also be involved.

About 5-10% of patients with discoid lupus actually develop SLE.

Rare forms of chronic cutaneous lupus include lupus profundus , chilblain lupus.

Other mucocutaneous manifestations like photosensitivity skin rash as a result of unusual reaction to sunlight, determined by patient history or physician observation.

Also Mucocutaneous lesions include ulcers of the mouth, nose, or genital area.
Nasal septal erosions occasionally lead to nasal septal perforation.

Alopecia is a common feature of SLE.
Hair loss may be diffuse or patchy.
Alopecia may be caused by lupus hairs, which are brittle, soft, lanugo-like, and break off easily, especially in the temporal and parietal areas of the scalp .
Alopecia areata occurs less frequently.
It may be associated with exacerbations of the disease, in which case hair tends to regrow when the disease is under control.
Alternatively, it may result from the extensive scarring of discoid lesions, in which case it is irreversible.
Alopecia may also be drug induced, for example, from corticosteroids or cytotoxic drugs.

Musculoskeletal involvement

arthritis/arthralgia, avascular necrosis, myositis, 80-90%.

Involvement of the joints as arthralgia, arthritis, or both is one of the earliest and most common initial manifestations of SLE.
inflammatory arthritis is found in 50% of patients at some point during the course of the disease.

it is important to note that patients experience pain out of proportion to the findings on physical examination largely because the inflammation may be confined to the joint capsule or tendon insertions.

Active arthritis, often associated with other features of a new lupus manifestation or active exacerbation, may include swollen inflamed joints with effusions or synovitis (or both) on physical examination.

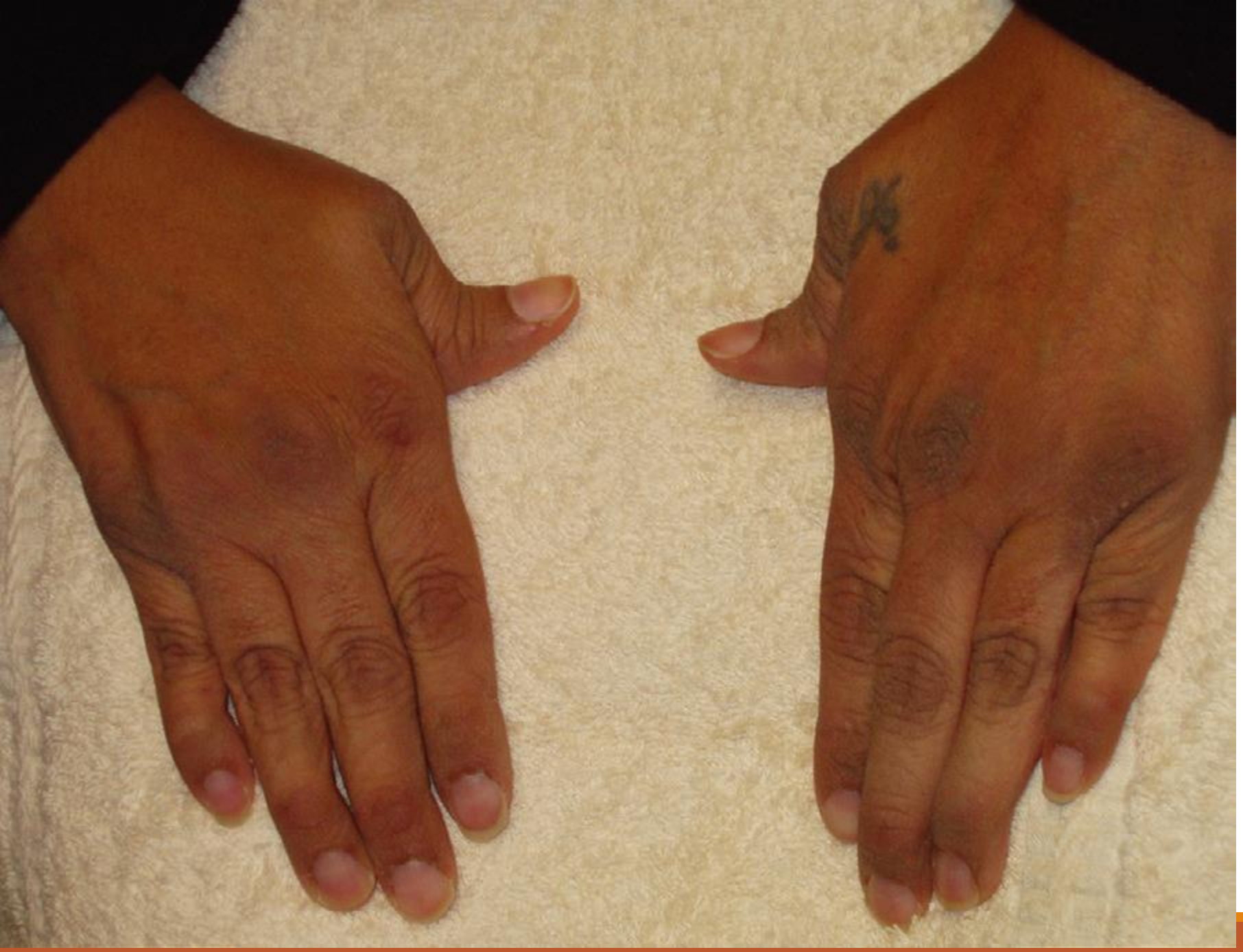
Deforming arthritis can occur in systemic lupus and can be categorized as a mild deforming polyarthritis, an erosive symmetric polyarthritis with RA-like deformities, or a non erosive Jaccoud arthropathy.

Jaccoud arthropathy is a generalized capsular and periarticular condition (resembling the arthritis of rheumatic fever) that affects the hands and results in ulnar drift with subluxation of the metacarpophalangeal joints because of joint instability secondary to lax joint capsules, tendons, and ligaments.

Jaccoud arthritis features can be distinguished from the arthritis of RA because the deforming findings are reversible, this unique form of arthritis is found in 10% of cases

Tenosynovitis is seen in 10% to 13% of patients with SLE

Patients with SLE may have muscle pain or weakness (or both) secondary to inflammatory myositis, drug-related myopathy, or fibromyalgia.



The deformities are reduced when the hands are placed on a flat surface.

Autoimmune cytopenia

Anemia, thrombocytopenia 20-30%

Hematologic involvement is common in SLE; all three blood cell lines can be affected
Anemia of chronic disease (ACD) is the most common anemia in SLE.

Autoimmune hemolytic anemia (AIHA) should be suspected in the setting of the following laboratory abnormalities:

increased serum unconjugated bilirubin, LDH, increased reticulocyte count, and reduced serum haptoglobin.
The direct Coombs test is typically positive and usually is mediated by warm-reacting IgG anti-erythrocyte antibodies.

Microangiopathic hemolytic anemia (MAHA), Blood loss, renal insufficiency, pure red
cell aplasia, and medication-induced myelotoxicity are additional potential causes of anemia in patients with SLE.

Leukopenia occurs in approximately 50% of patients with SLE and can occur secondary to lymphopenia and/or neutropenia.

Mild thrombocytopenia is noted in as many as 50% of patients with SLE, but severe thrombocytopenia can also occur.

Thrombocytopenia can be the result of immune mediated platelet destruction similar to immune thrombocytopenic purpura (ITP).

The platelet IIb/IIIa antigen is the primary target.
Thrombocytopenia can also be caused by a consumptive process such as TTP or splenomegaly.

Anti thrombopoietin antibodies have been found in the sera of some patients with SLE and have been correlated with lower platelet counts.

Lymphadenopathy commonly occurs in association with active SLE and is characterized by the presence of enlarged , soft nontender lymph nodes.

Lymphadenopathy can be focal or generalized; the cervical, axillary, and inguinal regions are typically involved.

The neurologic finding can be subdivided according to whether the central or peripheral nervous system is involved.

A truly unique lupus headache does not exist.

Migraine is statistically associated with lupus, Raynaud phenomenon, vasculopathy, and the presence of aPLs.

Tension-type headaches correlated with patients who have joint complaints and fibromyalgia and who use analgesics.
Some patients have been found to have increased intracranial pressure (pseudotumor cerebri).
Headaches of a severe nature may be a feature of the exceedingly rare case of CNS vasculitis or meningeal involvement.
An acute form of reversible meningitis in patients with SLE has been associated with ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs), especially ibuprofen.

Seizures in patients with SLE may be either focal or generalized.
Generalized tonic- clonic seizures occur much more frequently than other types of epilepsy,
They are associated with active SLE disease, but focal seizures may recur at any time irrespective of disease activity.

Cerebrovascular accidents (CVAs) can be caused by an occlusive process or embolic episodes.

Patients with a history of transient ischemic attacks or cardiac valvular lesions are at high (57% and 87%, respectively) risk for stroke.
Transverse myelitis, although rare, may be a catastrophic manifestation of SLE, It is associated with neuromyelitis Optica (NMO),spinal vasculature infarction, aPLs, or vasculitis.

Other rare but reported neurologic syndromes in patients with SLE include
aseptic meningitis, chorea, dementia .

posterior reversible leukoencephalopathy syndrome
(PRES), characterized by a rapid onset of headache, seizures, hypertension, blindness, altered mental status, and specific features on MRI.
Diffuse hyperintensities on T2-weighted and fluid-attenuated inversion recovery
(FLAIR) images in the white matter in posterior areas of the cerebral hemispheres are seen but are completely reversible with blood pressure and seizure control.
The overall prognosis is very good, with complete neurologic and radiologic recovery occurring within days.

Cranial and peripheral neuropathies have each been reported in about 10% of patients with SLE .

The most frequently involved cranial nerves are the sensory and motor nerves of the eye and the trigeminal nerve and the Patients may have visual defects, blindness, papilledema, nystagmus or ptosis, tinnitus, hearing loss, vertigo, or facial palsy.

Peripheral neuropathy may include motor, sensory (stocking or glove distribution), or mixed motor and sensory polyneuropathy or mononeuritis multiplex.

psychiatric manifestations of SLE:
Organic brain syndrome is defined as a state of diffuse cerebral dysfunction, sometimes with associated cerebral atrophy on imaging, and associated with a disturbance in consciousness, cognition, mood, and behavior in the absence of drugs, infection, or a metabolic cause.

Frank psychosis has long been recognized as a manifestation of SLE.

Pleuropulmonary Involvement

Pleuritis will develop in as many as 50% of patients with SLE.
Pleural effusion, Acute pneumonitis, Diffuse alveolar hemorrhage , ILD , alveolar hemorrhage , PAH.

Pleural effusions may occur and are generally small but can occasionally be massive.
They are also frequently bilateral.

When pleural effusions are significant, other causes of effusion such as infection must be ruled out by thoracocentesis before treatment is initiated.

The fluid is usually an exudate with a higher glucose concentration and lower LDH levels, and autoantibodies are present such as antinuclear and anti-dsDNA antibodies.
Effusions can be transudates (associated with nephrosis) or exudates (inflammatory, infectious, Malignancy

Lupus pneumonitis is a rare but serious manifestation and may initially be seen in either an acute or a chronic form.

Acute lupus pneumonitis usually occurs during a generalized multisystem lupus flare and is accompanied by fever, dyspnea, coughing, pleuritic chest pain, and, occasionally, hemoptysis.

Chronic lupus pneumonitis is manifested as interstitial lung disease and is characterized by dyspnea on exertion, nonproductive cough.

Shrinking lung syndrome occurs a subset of patients with SLE with unexplained dyspnea, small lung volumes with restrictive pulmonary function , and an elevated diaphragm.

Diffuse alveolar hemorrhage is a very rare but serious complication SLE, with mortality rates ranging from 50% to 90%.66 The characteristic finding is an abrupt onset of dyspnea, cough, fever, and infiltrates and a dramatic fall in hemoglobin.

Hemoptysis is present in only 50% of patients.

Cardiovascular Involvement

Cardiovascular disease is a frequent complication of SLE and may involve the pericardium, myocardium, valves, and coronary arteries.
Pericardial effusion secondary to pericarditis is the most commonly observed cardiac feature in SLE
Clinically, the findings may be classic for pericarditis, with precordial chest pain and a pericardial rub, or it may be painless and silent.

Pericardial fluid is usually transudative and rarely exudative if caused by lupus.

effusions in patients with SLE can also be caused by other conditions such as renal failure or bacterial and fungal infections.

Coronary artery disease is an important cause of morbidity in patients with SLE

Clinical myocarditis is seen in about 10% of patients with SLE , Myocarditis should be suspected in patients with arrhythmias or conduction defects, unexplained cardiomegaly with or without congestive heart failure, or unexplained tachycardia.

Valvular involvement is common in SLE, with vegetations noted on echocardiography in about 10% of patients.

Diffuse valvular thickening is the most commonly seen abnormality and involves either the mitral or aortic valve.

Verrucous vegetations, known as Libman -Sacks endocarditis, can be present within the left atrium .
on the aortic valve, these vegetations are usually seen on the vessel side.

Valvulitis can also involve the tricuspid valves and may progress to either hemodynamically significant stenosis or regurgitation requiring valve replacement.

Occasionally, multiple valves are involved in the same patient with Libman -Sacks endocarditis,
This endocarditis is associated with aPLs in about 50% of cases.

Gastrointestinal Involvement

Dysphagia 13% of patients, Decreased peristalsis is most commonly observed in the upper one-third of the esophagus.
Pancreatitis caused by SLE is uncommon and usually is associated with active SLE in other organs.

Mesenteric vasculitis is a very rare manifestation of SLE.
Liver test abnormalities have been described in as many as 60% of patients with SLE at some point during the course of their disease.

Ocular Involvement

The most is keratoconjunctivitis sicca Retinal abnormalities can be detected on ophthalmoscopic examination as retinal hemorrhages, vasculitic - appearing lesions, cotton wool spots , and hard exudates.

Episcleritis and scleritis can occur in SLE.
Uveitis is extremely rare.

Glomerulonephritis

Renal involvement is common in SLE and is a significant cause of morbidity and mortality.
It is estimated that as many as 90% of patients with SLE will have pathologic evidence of renal involvement on biopsy, but clinically significant nephritis will develop in only 50%.

The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria, to frank nephrotic syndrome, to rapidly progressive glomerulonephritis with loss of renal function.

International Society of Nephrology/Renal

Pathology Society Classification of Lupus Nephritis

Class I
Minimal Mesangial Lupus Nephritis
Class II
Mesangial Proliferative Nephritis
Class III
Focal Lupus Nephritis
Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis< involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class IV
Diffuse Lupus Nephritis

Active or inactive diffuse, segmental, or global endocapillary or extra capillary glomerulonephritis=involving =50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations.

This class is subdivided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G)lupus nephritis when =50% of the involved glomeruli have global lesions. Segmental is define as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases
with diffuse wire loop deposits, but with little or no glomerular proliferation

Class V

Membranous Lupus Nephritis
Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy
and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class V nephritis may occur in combination with class III or class IV, in which case both are diagnosed Class V nephritis may show advanced sclerotic lesions.

Class VI
Advanced Sclerotic Lupus Nephritis =90% of glomeruli globally sclerosed without residual activity

DIFFERENTIAL DIAGNOSIS

viral infections (parvovirus B19,EBV, Cytomegalovirus).

Malignancy, particularly non-Hodgkin's lymphoma.

autoimmune diseases such as RA, dermatomyositis, and Still's disease ,MCTD..

drug-induced lupus(minocycline, procainamide, hydralazine, isoniazid, IFN-α) Hydrochlorothiazide is associated with SCLE.

All of these drugs may cause a positive ANA.

Anti-histone antibodies are present in more than 95% of cases of drug-induced lupus
However, anti-histone antibodies cannot be used to confirm a diagnosis of drug-induced lupus because up to70 % - 80% of idiopathic patients with SLE will also produce anti-histone antibodies.

Diagnosis

The diagnosis is based on a combination of clinical features and laboratory abnormalities.

To fulfil the classification criteria for SLE, at least 4 of the 11 factors must be present or have occurred in the past.

Checking of ANAs, antibodies to ENAs and complement, routine hematology, biochemistry and urinalysis are mandatory.

Some rheumatologist believe that ANA-negative SLE occurs(e.g. in the presence of antibodies to Ro) but others regard SLE as necessarily ANA-positive.
Anti-dsDNA antibodies are positive in many, but not all, patients,(70%sensitivity).

Patients with active disease tend to have low levels of C3 due to complement consumption, but in some people low C3 and C4 may be the result of inherited complement deficiency in C1, C2 or C4 that predisposes to SLE .

A raised ESR, leucopenia and lymphopenia are typical of active SLE, along with anemia ,hemolytic anemia and thrombocytopenia.

CRP is often normal in active SLE, except in the presence of serositis; thus an elevated CRP may indicate infection.

Antibodies in SLE

Anti-nuclear Antibodies 95-100%

Anti-dsDNA 60% ,95% specificity for SLE, fluctuates with disease activity, associated with glomerulonephritis.

Anti-Smith ,20-30 , 99% specificity for SLE , associated with anti-U1RNP antibodies

Anti-U1RNP Antibody 30% associated with mixed connective tissue disease and lower frequency of glomerulonephritis.

Anti-Ro/SS-A 30% Associated with Sjogren's syndrome, photosensitivity, SCLE, neonatal lupus, congenital heart block

Anti-La/SS-B 20 %Associated with Sjogren's syndrome, SCLE, neonatal lupus, congenital heart block, anti-Ro/SS-A

Anti-histone 70% Also associated with drug-induced lupus
Anti-phospholipid 30% Associated with arterial and venous thrombosis, pregnancy morbidity.

ystemic Lupus

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scale and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, determined by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis-convincing history of pleuritic chest pain or rub heard by a physician or evidence of pleural effusions *or* pericarditis-documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria >0.5 g/day, >3+ if quantification not performed *or* cellular casts: may be red blood cell, hemoglobin, granular tubular, or mixed
Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, electrolyte imbalance) *or* Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, acidosis, electrolyte imbalance)
Hematologic disorder	Hemolytic anemia with reticulocytosis *or* Leukopenia $<4000/mm^3$ *or* Lymphopenia $<1500/mm^3$ *or* Thrombocytopenia $<100,000/mm^3$ in the absence of offending drugs
Immunologic disorder	Anti-DNA: antibody to native DNA in abnormal titer *or* anti-Smith: presence of antibody to Sm nuclear antigen *or* Positive finding of anti-phospholipid antibodies based on (1) abnormal serum concentration of immunoglobulin (Ig)G or IgM anti-cardiolipin antibodies, (2) positive test result for lupus anticoagulant by using a standard method, or (3) false-positive serologic test for syphilis known to be positive for at least 6 mo and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
Positive anti-nuclear antibody	An abnormal titer of anti-nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndromes

*The presence of four or more criteria is required for systemic lupus erythematosus classification. Exclude all other reasonable diagnoses.

SLICC† Classification Criteria for Systemic Lupus Erythematosus

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count i
   the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug

The new 2019 SLE European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria forsystemic lupus erythematosus (SLE) have been recently published.1 These criteria have been developed to find a better equilibrium between specificity and sensitivitycompared with the previous criteria (SLE ACR-1997 and SLE Systemic Lupus International Collaborating Clinics (SLICC).

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Management

The therapeutic goals are to educate the patient about the nature of the illness, to control symptoms and to prevent organ damage and maintain normal function.
Patients should be advised to avoid sun and ultraviolet light exposure and to employ sun blocks (sun protection factor 25–50)
Smoking cessation
Blood pressure control, lipid ,glucose.
Exercise.
Anti platelet or anticoagulants in antiphospholipid positive patients.

Mild to moderate disease:
Patients with mild disease restricted to skin and joints can sometimes be managed with analgesics, NSAIDs and hydroxychloroquine.
Frequently, however, glucocorticoids are also necessary (prednisolone 5–20 mg/day), often in combination with immunosuppressants such as methotrexate, azathioprine or mycophenolate mofetil (MMF).
Increased doses of glucocorticoids may be required for flares in activity or complications such as pleurisy or pericarditis.
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The monoclonal antibody belimumab, which targets the β-cell growth factor BLyS, has recently been shown to be effective in patients with active SLE who have responded inadequately to standard therapy

Severe and life-threatening disease

High-dose glucocorticoids and immunosuppressants are required for the treatment of renal, CNS and cardiac involvement.

A commonly used regimen is pulsed methylprednisolone (10 mg/kg IV) plus cyclophosphamide (15 mg/kg IV), repeated at 2–3-weekly intervals for six cycles.

Cyclophosphamide may cause hemorrhagic cystitis but the risk can be minimized by good hydration and co-prescription of mesna (2-mercaptoethane sulfonate), which binds its urotoxic metabolites.

Because of the risk of azoospermia and premature menopause, sperm or oocyte collection and storage need to be considered prior to treatment with cyclophosphamide.

MMF has been used successfully with high-dose glucocorticoids for renal involvement with results similar to those of pulsed cyclophosphamide but fewer adverse effects.
Belimumab in combination with standard therapy significantly decreases disease activity in SLE patients and is safe and well tolerated.

Rituximab has been reported as being effective in selected cases.

Maintenance therapy
Following control of acute disease, a typical maintenance regimen is oral prednisolone in a dose of 40–60 mg daily, gradually reducing to 10–15 mg/day or less by 3 months.
Azathioprine (2–2.5 mg/kg/day), methotrexate (10–25 mg/week) or MMF(2–3 g/day) should also be prescribed.

Cardiovascular risk factors, such as hypertension and hyperlipidemia, should be controlled and patients should be advised to stop smoking.
Patients with SLE and the antiphospholipid antibody syndrome, who have had previous thrombosis, require life-long warfarin therapy.

SLE patients are at risk of osteoporosis and hypovitaminosis D, and should be screened with biochemistry and DXA scanning accordingly.

Inflammatory Diseases of Muscles

Inflammatory muscle diseases are a heterogeneous group of systemic autoimmune rheumatic disorders characterized by chronic muscle weakness, muscle fatigue, and mononuclear cell infiltration into skeletal muscle.

EPIDEMIOLOGY

The onset of polymyositis (PM) is usually in the late teens or older: the mean patient age at onset is 50 to 60 years.

Dermatomyositis(DM) shows two peaks: 5 to 15 years and 45 to 65 years.

inclusion body myositis(IBM) is commonly seen in individuals older than 50 years and is rare in younger adults.

females are more commonly affected than males (ratio >2 : 1), whereas in IBM, the converse is true (again, >2 : 1 ratio).

CLINICAL FEATURES

Polymyositis and Dermatomyositis

The predominant symptoms in patients with PM or DM are muscle weakness and low muscle endurance.
The weakness is most pronounced in proximal muscle groups—typically in the neck, pelvic area, thigh, and shoulder muscles with a symmetric distribution.

Patients generally experience more problems with performing repetitive movements than with single-strength exercises, and they report difficulty walking uphill or upstairs, working with their arms above their shoulders, or rising from chairs. Also, distal muscles may be involved in PM and DM, affecting grip strength and health-related quality of life.

The onset of muscle weakness is often subacute, occurring during a few weeks, or it can be insidious, developing during several months.

Problems with swallowing and nutrition can occur as a result of impaired contractility of the throat muscles, potentially leading to aspiration pneumonia.

In rare cases, patients experience difficulty breathing because of weakness of the diaphragm or thoracic muscles, and they may require assisted ventilation.

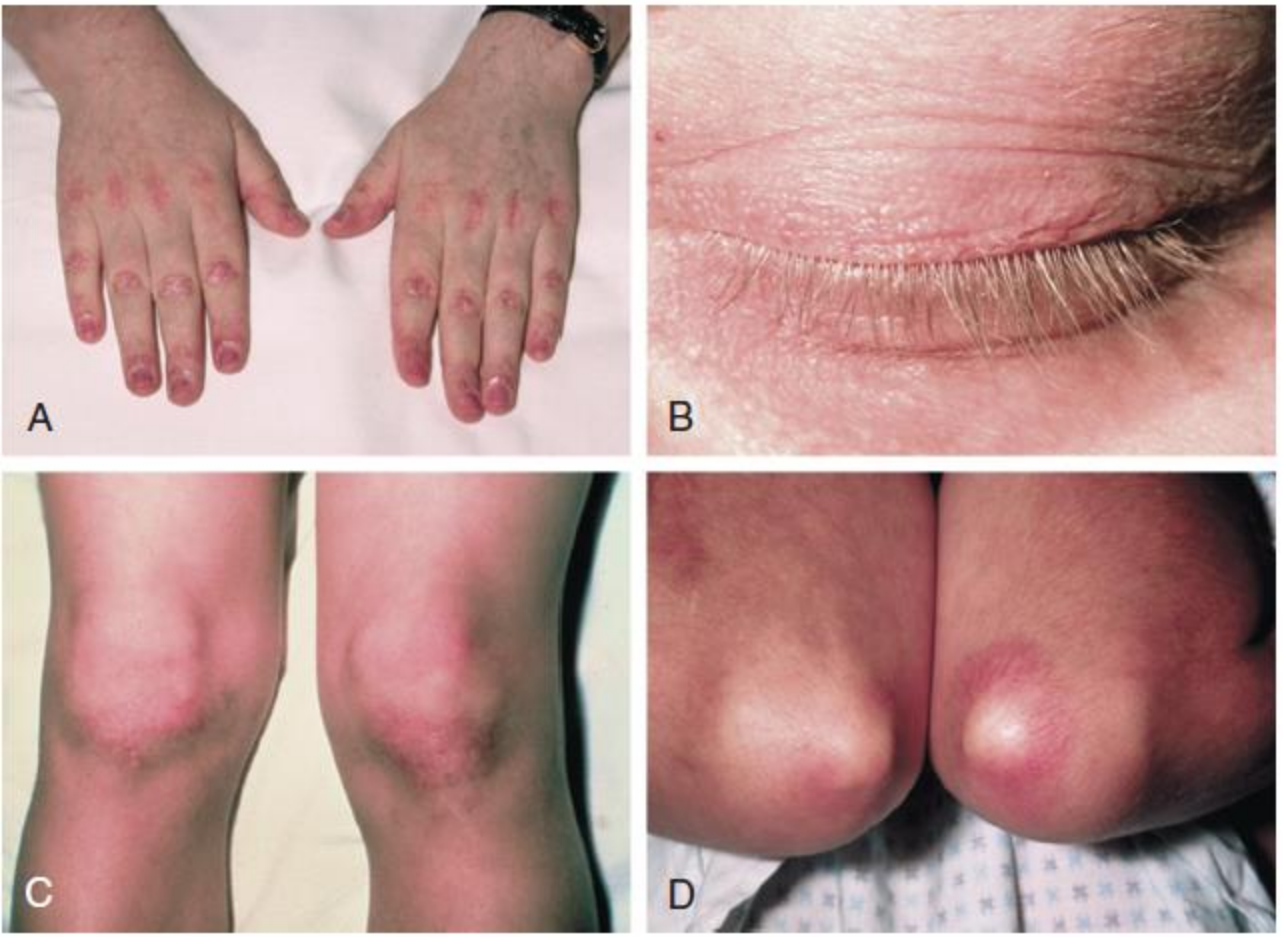
Other striated muscles may be involved, such as in the lower part of the esophagus (causing reflux problems) or the sphincter ani (causing incontinence).

skin

The most specific skin manifestations are Gottron's papules and the heliotrope rash .
Gottron's papules are slightly elevated, violaceous, pink, or dusky red papules located over the dorsal side of the metacarpal or interphalangeal joints, These papules may also occur over the extensor side of the wrist, elbow, or knee joints.

Gottron's papules are considered to be pathognomonic of DM.
A macular rash (without papules) with the same distribution as Gottron's papules is called Gottron's sign.

The heliotrope rash is a periorbital red or violaceous erythema of one or both eyelids, often with edema .



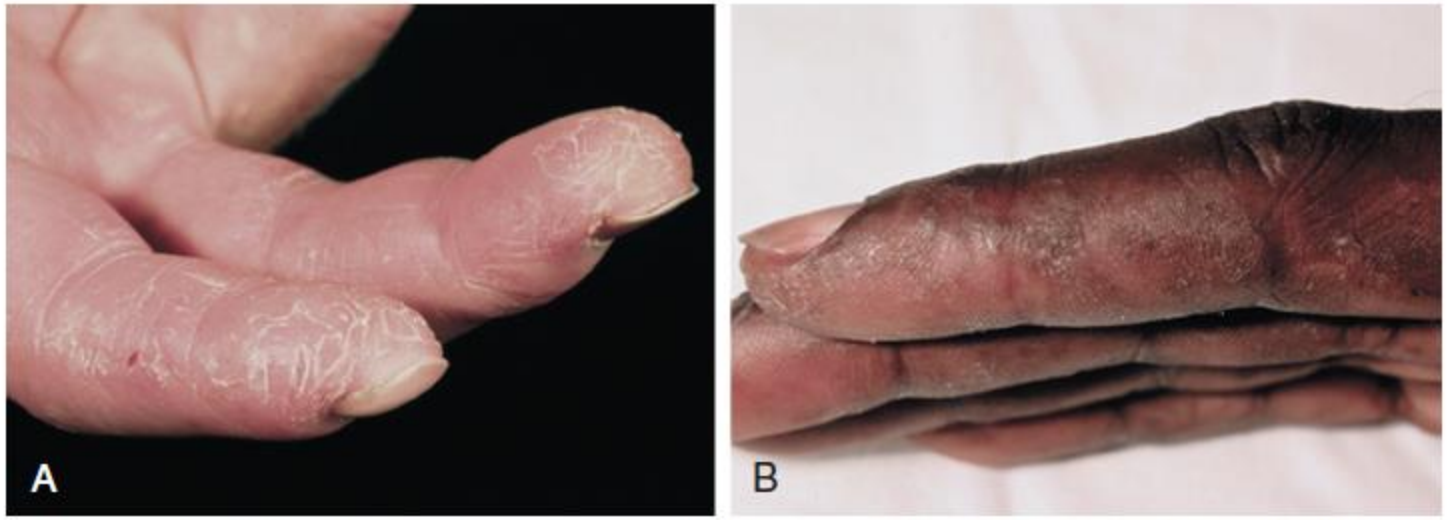
Characteristic features of dermatomyositis skin changes. A, Gottron’s papules. B, Heliotrope rash. C, Gottron’s sign on knee andD, elbow.

Linear erythema overlying the extensor surfaces of joints is also relatively specific to DM

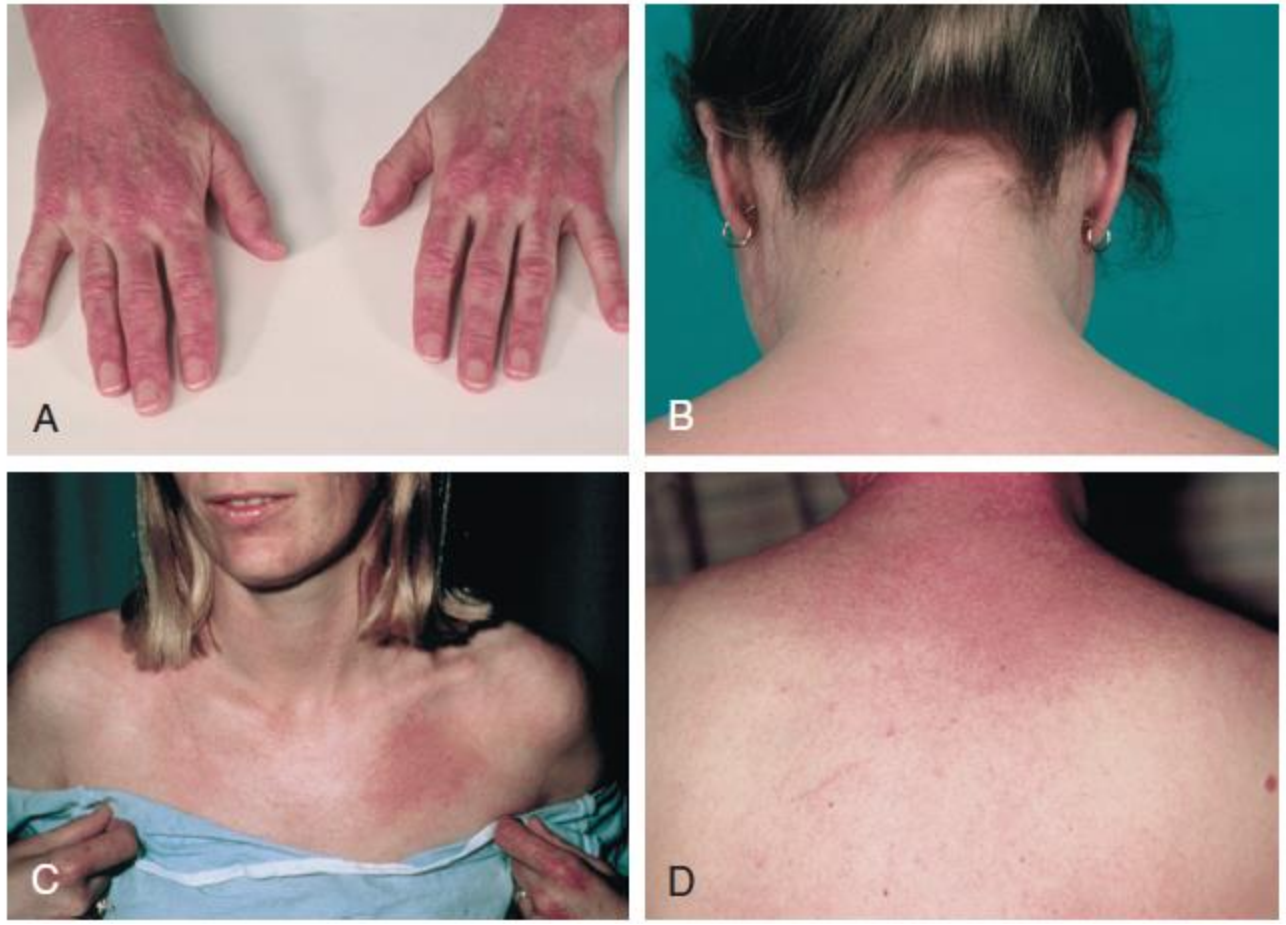
Many patients with DM have photosensitive rashes, typically found on the face or scalp or over the neck (the so-called V sign), although this rash is not specific to DM .

Another common rash in DM is located over the shoulders (shawl sign)or over the hips (holster sign).

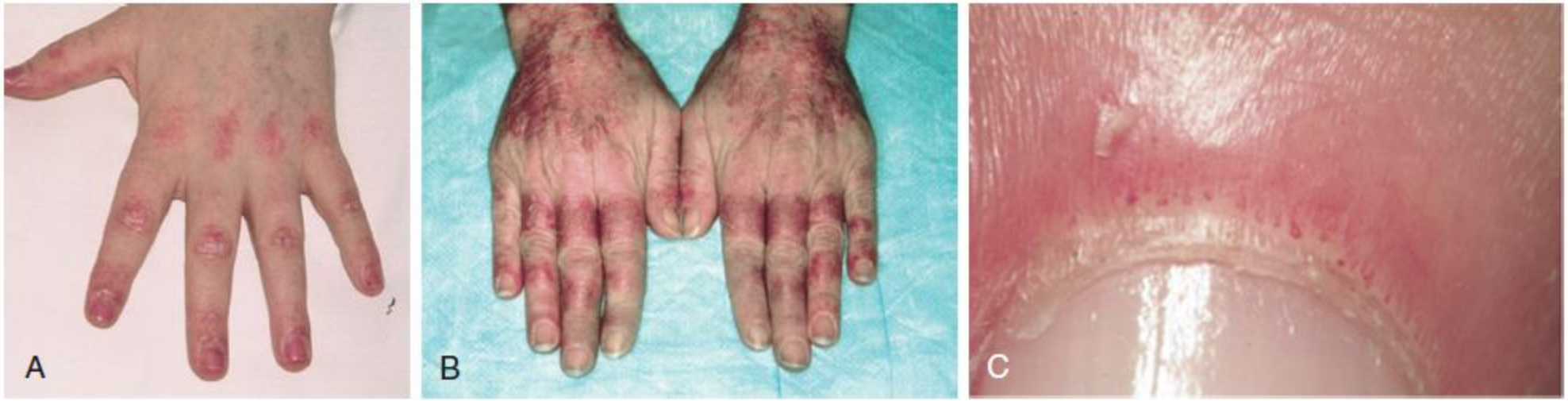
Another type of skin pathology seen in inflammatory myopathies is called mechanic's hands,
This rash is often associated with the presence of anti-synthetase autoantibodies and can be seen in both PM and DM.
The rash is a hyperkeratotic, scaling, fissuring of the fingers, particularly on the radial side of the index fingers.



Mechanic's hands in a white (**A**) and a black (**B**) patient. Note the characteristic skin changes on the lateral side of the fingers.



Characteristic features of dermatomyositis skin changes. A, Linear erythema. B, Scalp rash. C, V-like sign. D, Shawl sign



Erythematous rashes on the hand in dermatomyositis and systemic lupus erythematosus. A, Note the changes on the knuckles and dorsum of the hand in dermatomyositis (Gottron's sign). B, Rash is absent from the knuckles but present on the phalanges in lupus. C, Capillary nailfold changes in dermatomyositis.

Lungs

Lung involvement is frequent in PM and DM and is a major risk factor for morbidity and mortality.
Clinical symptoms such as dyspnea and cough are common.
Lung involvement can be caused by weakness of the respiratory muscles or inflammation of the lung tissue (ILD).

Arthritis

Joint pain and arthritis are common in patients with PM or DM.
The most common form of arthritis is a symmetric arthritis of the small joints of the hands and feet.

Heart

Cardiovascular disease is a risk factor for death among patients with PM and DM.
The most frequently reported subclinical manifestations are conduction abnormalities and arrhythmias detected by electrocardiogram.

Gastrointestinal Tract

Difficulty swallowing is frequent in patients with inflammatory myopathies, particularly those with IBM.
Muscle weakness occasionally becomes severe and causes problems with nutrition and aspiration pneumonia.

a Reflux occurring in 15% to 50% of patients.
Constipation, diarrhea, and stomach pain are common symptoms.
Vasculitis in the blood vessels of the GI tract is rare but may be complicated by intestinal bleeding.

Inclusion Body Myositis

IBM is distinguished from PM and DM on the basis of both clinical and histopathologic features.

In contrast to PM and DM, IBM is more frequent in men than in women, and it is seen mostly in individuals older than 50 years.
The onset is more insidious than that of PM or DM, Patients with IBM rarely have pain.

The most frequent initial symptoms are difficulty climbing stairs and walking uphill and frequent falls as a result of weakness in the knee extensor muscles, Muscle weakness may become prominent, and even walking across a threshold may become a problem.

Difficulty swallowing may also be an early clinical feature, reflecting the involvement of the pharyngeal muscles.

The course is slowly progressive, leading to muscle atrophy that can be striking, particularly in the thigh and forearm muscles.
Severe weakness may develop, and many patients become wheelchair-dependent, IBM is usually resistant to treatment with glucocorticoids and other immunosuppressive agents.

Diagnostic Features	Dermatomyositis	Polymyositis	Inclusion Body Myositis	Necrotizing Myopathy
Clinical features				
Age	Children and adults	Adults*	Adults >50 yr	Adults
Disease onset	Subacute	Subacute	Chronic	Subacute
Muscle weakness	Proximal	Proximal	Selective pattern†	Proximal
Symmetry	Symmetric	Symmetric	Asymmetric	Symmetric
Systemic features	Yes‡	Yes‡	Yes§	Yes§
Skin changes	Yes‖	No	No	No
Calcinosis	Yes¶	Rarely	No	No
Associated systemic autoimmune disease	Yes**	Yes**	Yes††	No
Associated malignancy‡‡	Yes	?	?	??
Laboratory features				
Serum enzymes§§	Normal to high	Normal to high	Normal to high	High
Abnormal EMG‖‖	Yes	Yes	Yes	Yes
Abnormal muscle biopsy	Perifascicular atrophy, capillary depletion, patchy class I MHC expression and microinfarcts	$CD8^+$ T cell invasion of non-necrotic fibers and class I MHC expression on fibers	$CD8^+$ T cell invasion, MHC expression, vacuolated fibers, and tubulofilamentous inclusions in fibers	Necrotic and regenerating fibers, upregulation of class I MHC

*Rarely in children.
†Early involvement of finger flexor, wrist flexor or wrist extensor weakness, and involvement of quadriceps femoris.
‡Some patients have dysphagia, synovitis, and interstitial lung disease.
§Some patients have dysphagia.
‖Gottron's sign and heliotrope rash.
¶Especially in children.
**Overlap with scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and mixed connective tissue disease.
††Associated with Sjögren's syndrome but less frequently associated with other connective tissue diseases.
‡‡Dermatomyositis is more frequently associated with cancer than are polymyositis and inclusion body myositis and not overrepresented in polymyositis or inclusion body myositis.
§§Serum creatine kinase, aspartate transaminase, lactate dehydrogenase, and aldolase vary from normal to very high levels.
‖‖Myopathic motor unit potentials with spontaneous discharges in dermatomyositis, with and without spontaneous discharges in polymyositis, and mixed pattern of short- and long-duration motor unit potentials in inclusion body myositis.
EMG, Electromyogram; MHC, major histocompatibility complex; ?, association between PM/IBM and malignance is not clear; ??, necrotizing myopathy (other than autoimmune necrotizing myopathy) can be associated with cancer.

LABORATORY FINDINGS

serum levels of muscle enzymes is an important part of the evaluation of patients with myositis.

Elevated levels of muscle-derived serum enzymes reflect ongoing
damage to the muscle parenchyma.

Histopathology
Muscle biopsy is the “gold standard” for the diagnosis of
inflammatory myopathies and a critical component of the definitive diagnosis of IIMs.

IMAGING:

Ultrasonography, CT, and MRI are the general imaging techniques used to evaluate skeletal muscle.

MRI can be helpful guides for muscle biopsy sampling.

Lungs

Radiography and high-resolution CT of the lungs are important for detecting lung involvement and should be considered at the time of myositis diagnosis because the prevalence of ILD is high.

PFT restrictive pattern.

ELECTROMYOGRAPHY

Electromyogram (EMG) changes are usually nonspecific but are a useful indicator of myopathic changes.

Autoantibodies	Clinical Disease/Features
Anti-synthetase autoantibodies*	More common in polymyositis than dermatomyositis; interstitial lung disease, arthritis, Raynaud's phenomenon, fevers, mechanic's hands
Signal recognition particle (SRP)†	Polymyositis; possible severe disease and cardiac involvement
Chromodomain helicase DNA binding proteins 3 and 4 (Mi-2α and β)‡	Dermatomyositis
Anti-MDA5/Anti-CADM-140	Dermatomyositis; mucocutaneous lesions; severe lung disease minimal muscle involvement
Anti-TIF1γ	Dermatomyositis; malignancy
Anti-nuclear matrix protein (NXP)-2/anti-MJ	Predominantly juvenile DM; joint contractures; calcinosis
Anti-HMG-CoA reductase	Statin-associated myopathy; necrotizing myopathy

ecific Antibodies

histidyl-tRNA synthetase (Jo-1), threonyl-tRNA synthetase (PL-7),alanyl-tRNA synthetase (PL-12), isoleucyl-tRNA synthetase (OJ), glycyl-tRNA synthetase (EJ), and asparaginyl-tRNA synthetase (KS), tyrosyl (Ha) and phenylalanyl (Zo).

HMG-CoA, 3-Hydroxy-3-methylglutaryl-coenzyme A; MDA, melanoma differentiation associated gene 5; TIF, transcriptional intermediary factor 1 gamma; SRP, signal recognition particle.

Management

Oral glucocorticoids (prednisolone 1 mg/kg daily) are the mainstay of initial treatment of PM and DM but high-dose intravenous methylprednisolone (1 g/day for 3 days) may be required in patients with respiratory or pharyngeal weakness.
If there is a good response, glucocorticoids should be reduced by approximately
25% per month to a maintenance dose of 5–7.5 mg.

Although most patients respond well to glucocorticoids, many need additional immunosuppressive therapy. Methotrexate and MMF are the first choices of many but azathioprine and ciclosporin are also used as alternatives.

Rituximab appears to show efficacy in a majority of patients.

In clinical practice, rituximab is an option for use with glucocorticoids, to maintain an early glucocorticoid-induced remission.
Intravenous immunoglobulin (IVIg) may be effective in refractory cases.
Mepacrine or hydroxychloroquine has been used for skin predominant disease in certain cases.
One risk of treatment is glucocorticoid-induced myopathy.
If the initial response to treatment is poor, further biopsy then shows type II fibre atrophy in glucocorticoid myopathy (compared with fibre necrosis and regeneration in active myositis).

Systemic sclerosis

Systemic sclerosis is a multisystem connective tissue disease affecting the skin and internal organs.

The disease process is characterized by chronic inflammation with variable degrees of collagen accumulation (fibrosis) in affected tissues and obliterative vasculopathy of the peripheral and visceral vasculature
The hallmarks of SSc are:

(1) autoimmunity
(2) inflammation
(3) functional and structural alterations in small blood vessels.
(4) widespread interstitial and vascular fibrosis affecting the skin and internal organs

EPIDEMIOLOGY

Incidence of approximately 18 to 20 cases per million population per year, prevalence of 100 to 300 cases per million population.

The average age at onset is between 35 and 50 years, and the disease is more common among women (3 to 7 : 1 female-to-male ratio).

ETIOLOGY

Neither the cause of SSc nor the precise contribution of genetic susceptibility is fully understood.
Evidence indicates that infectious agents, environmental toxins, and drugs, might be potential triggers.

Familial clustering of a disease is considered to be evidence of inherited disease susceptibility, but such clustering might be explained by shared environmental exposures, shared genetic background, or the interaction between genes and environment.

The risk of SSc is considerably increased among first-degree relatives of persons with SSc compared with the general population.

survival

Mortality among patients with scleroderma is high, with most deaths being attributed directly to disease manifestations.

Factors associated with poor prognosis include:

diffuse skin disease, the presence of pulmonary disease (particularly PAH), renal or cardiac involvement, severe GI failure, multisystem disease, older age at disease onset, and the presence of anemia.

CLINICAL FEATURES

Two major groups of patients can be identified based on the distribution of skin changes and associated clinical and laboratory outcomes.

Patients are considered to have diffuse skin disease if skin changes are found proximal to the elbows and/or knees or on the trunk, excluding the face.

These patients tend to have higher risk of multisystem disease and poor survival.

Patients are considered to have limited disease if skin changes occur distal to the elbows and/or knees and not on the trunk.

Facial skin thickening can be present in the limited group.

A subtype of disease with absence of skin fibrosis has been recognized and is referred to as scleroderma sine scleroderma.

TABLE 84-2 American College of Rheumatology/European League against Rheumatism Classification Criteria for the Classification of Systemic Sclerosis

Item	Sub-item(s)	Weight/Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	—	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers Sclerodactyly of the fingers (distal to the MCPs but proximal to the proximal interphalangeal joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia	—	2
Abnormal nailfold capillaries	—	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score 2)*	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	—	3
SSc-related autoantibodies *(maximum score is 3)*	ACA Scl-70 RNA Pol	3

*The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

ACA, Anticentromere; MCPs, metacarpophalangeal joints; RNA Pol, anti-RNA polymerase III; Scl-70, antitopoisomerase 1; SSc, systemic sclerosis.

Modified from van den Hoogen F, Khanna D, Fransen J, et al: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 65:2737–2747, 2013.

Raynaud's Phenomenon

RP is an exaggerated vascular response of the digital arterial circulation triggered by cold temperature and emotional stress.

The diagnosis of RP is based on a history of excessive cold sensitivity and recurrent events of sharply demarcated pallor and/or cyanosis of the skin of the digits Blanching reflects digital arterial vasospasm, and cyanosis occurs as a result of the deoxygenation of sluggish venous blood flow.

Some skin blushing (redness) may follow as a result of reactive hyperemia after regular blood flow has been restored.
RP occurs in 3% to 15% of the general population.

It is more common among females (3 to 4 : 1) and is likely to begin before age 20 years.

Primary RP occurs when no disease process is associated with recurrent vasospastic events.

Primary RP

Young age at onset (<20 years).
symmetric manifestations of symptoms.

mild to moderate severity.

no association with digital ulceration or tissue gangrene.

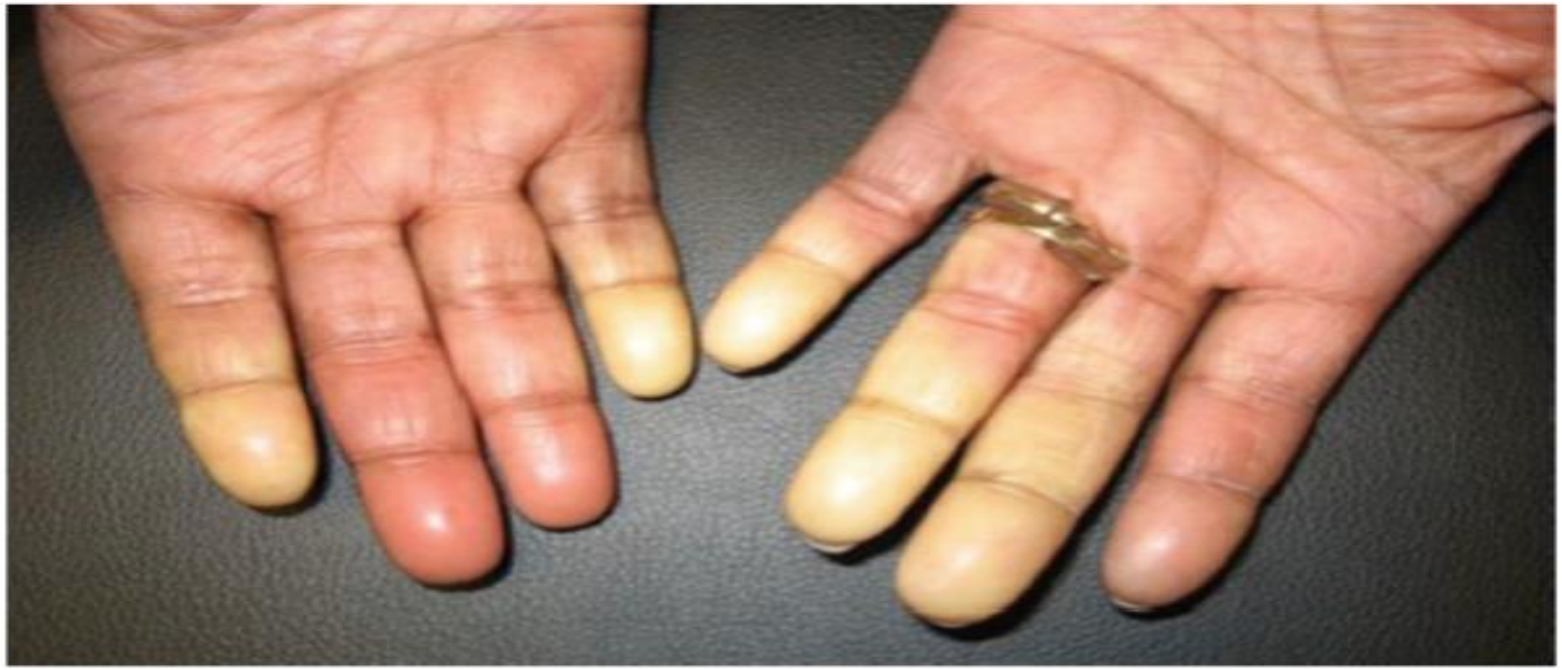
normal nail-fold capillary examination.

and a negative ANA titer are all indicative of primary RP.

Secondary RP occurs in a variety of settings, including connective tissues disorders and other rheumatic conditions, occupational trauma, the use of certain drugs (antimigraine agents, ergotamine derivatives, and bleomycin), increased blood viscosity, and compressive or obstructive vascular disease (e.g., thoracic outlet syndrome, atherosclerosis, and thromboangiitis obliterans).

Nail-fold capillaroscopy is the tool most commonly used at the bedside to distinguish patients with primary RP from those with scleroderma or another rheumatic disease.
Clinical features of scleroderma will develop in approximately 20% to 30% of patients with RP and abnormal nail-fold capillary changes, usually within a 2- to 3-year period.

Patients presenting with RP, nail-fold capillary changes, and the presence of a scleroderma-related autoantibody have a 70% to 80% chance of developing scleroderma within 2 to 3 years from presentation.



Active Raynaud’s phenomenon with well-demarcated pallor at the fingertips in a. patient with scleroderma

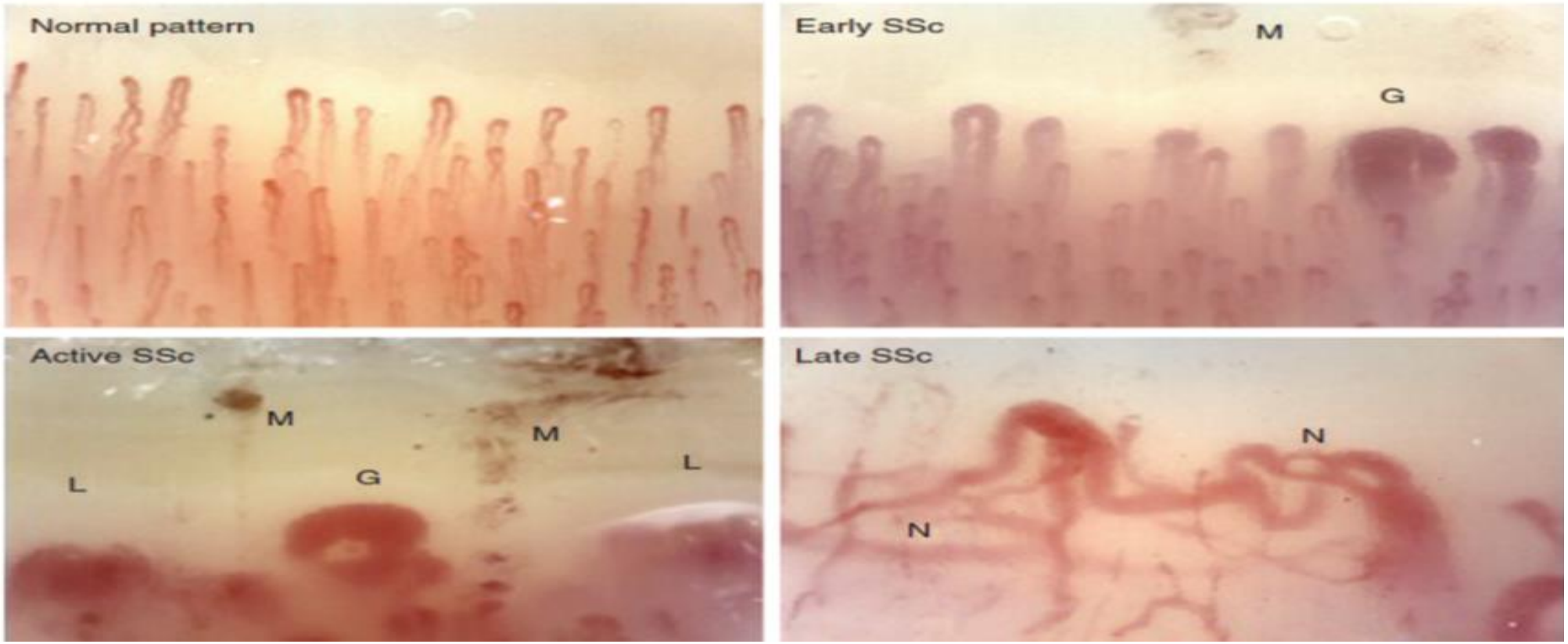
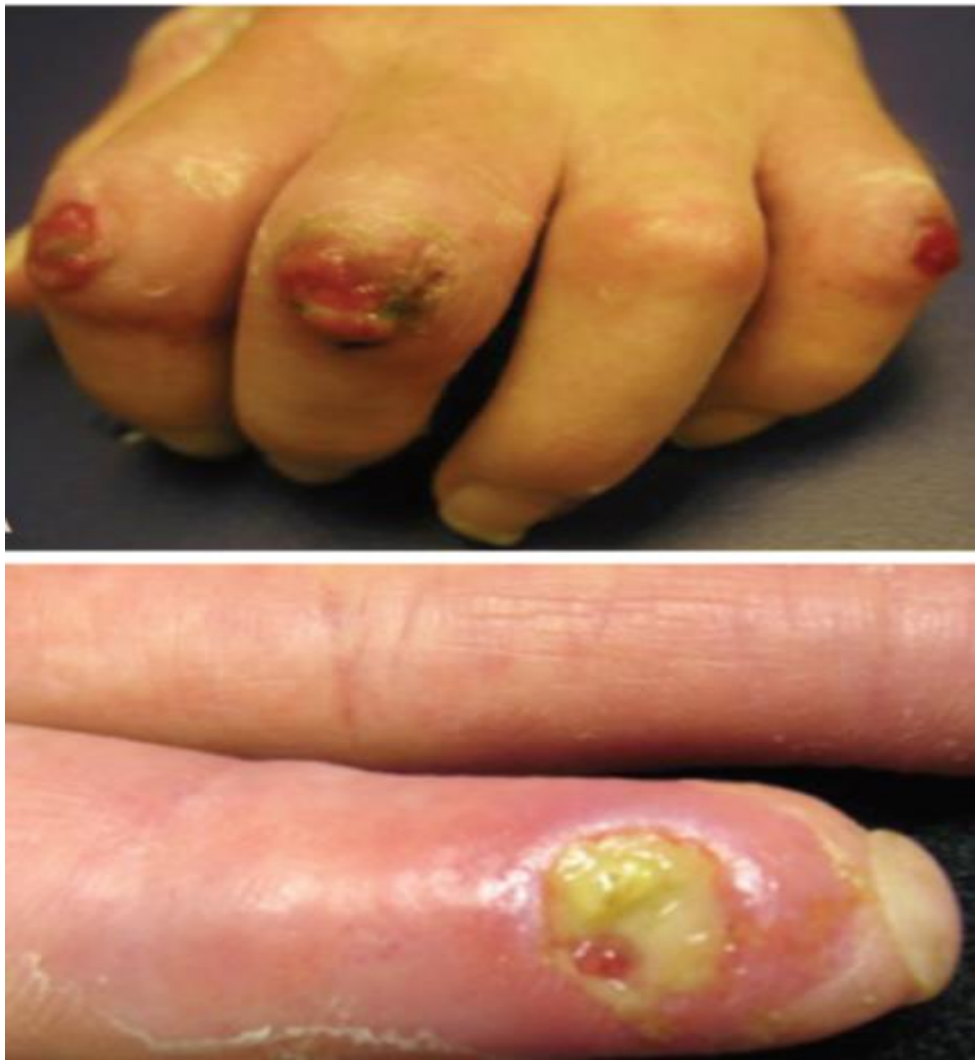


Figure 84-4 Patterns of nail-fold capillary abnormalities assessed by video capillaroscopy in patients with scleroderma. *Top right,* "Early pattern" shows the presence of few enlarged/giant capillaries, few capillary hemorrhages, and no evident loss or distortion of capillaries. *Bottom left,* "Active pattern" presents with frequent dilated capillary loops, frequent microhemorrhages, moderate loss of capillaries, and mild disorganization of the capillary architecture. *Bottom right,* "Late pattern" is characterized by severe loss of capillaries with avascular areas, ramified/bushy capillaries (neovascularization), and disorganization of the normal capillary architecture. G, Giant capillaries; L, loss of capillaries; M, microhemorrhages; N, neoangiogenesis; SSc, systemic sclerosis. *(Courtesy Professor Maurizio Cutolo.)*



TREATMENT OF RP AND GIGITAL ISCHEMIA

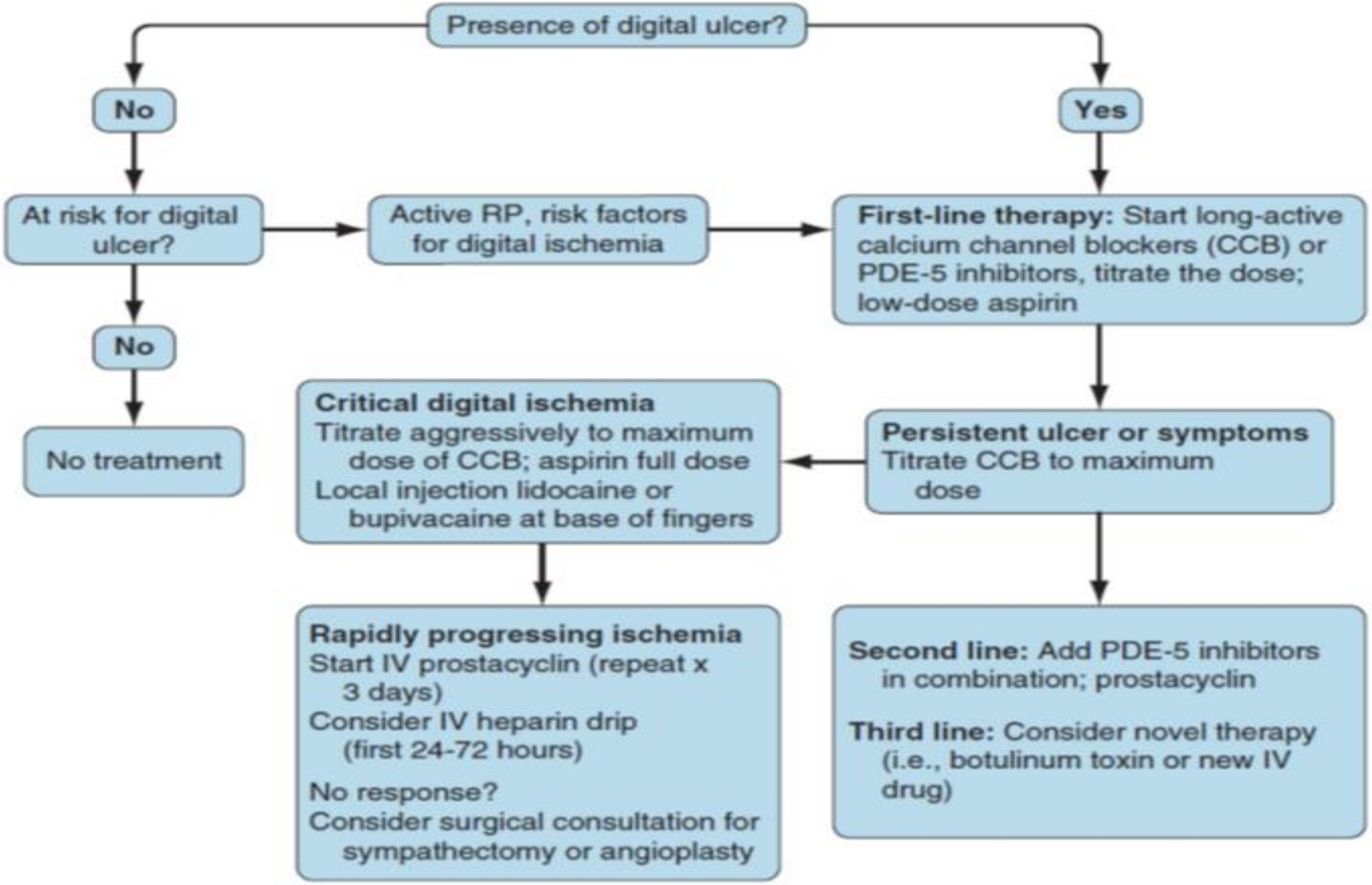


Figure 84-6 Approach to drug treatment of Raynaud's phenomenon (RP) and acute digital ischemia. CCB, Calcium channel blockers; IV, intravenous; PDE-5, phosphodiesterase-5; SSRI, selective serotonin reuptake inhibitor.

Skin Involvement

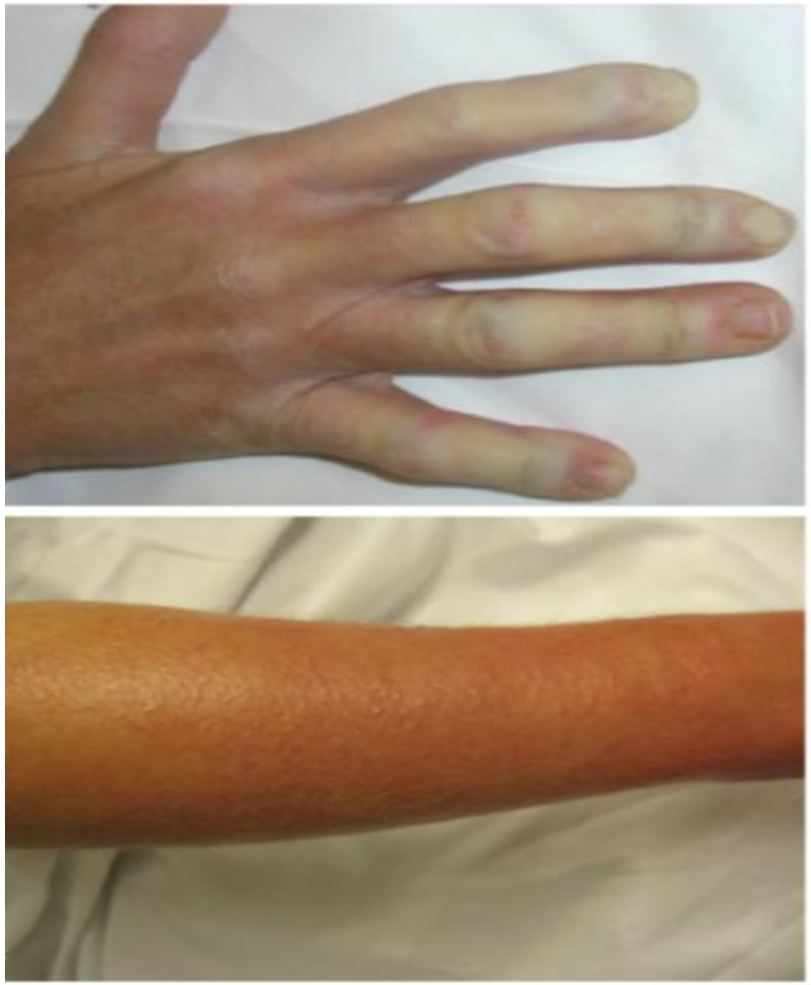
The most overt clinical manifestation of scleroderma is skin disease, Almost every patient with scleroderma presents with skin thickening and hardening due to increased collagen and extra-cellular matrix deposition in the dermis.

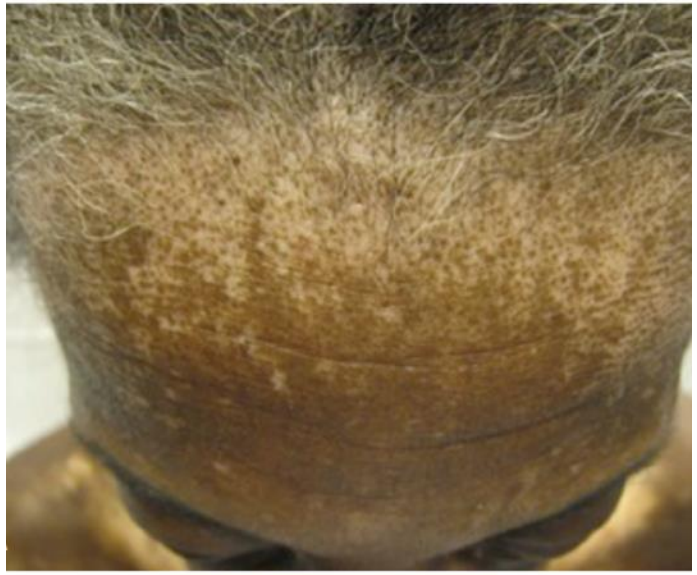
The distribution of skin changes is characteristic, with more frequent and intense involvement of fingers, hands, forearms, distal legs, feet, and the face, as well as, to a lesser degree, the proximal limbs and anterior trunk.

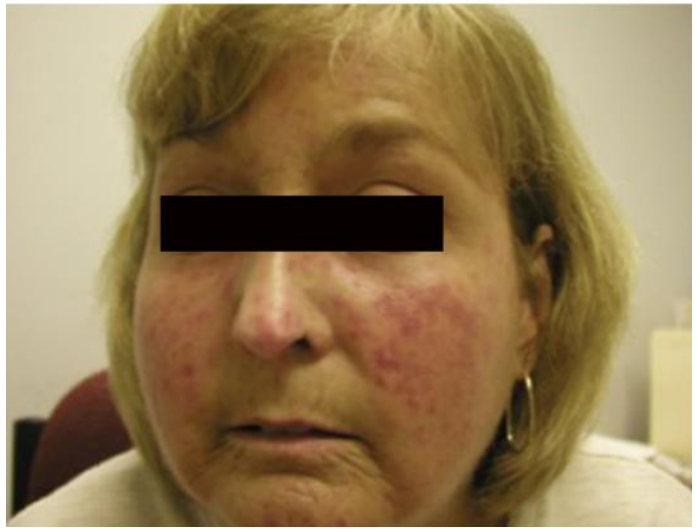
Scleroderma is classically subdivided into limited and diffuse cutaneous forms ,Limited scleroderma is defined by skin thickening that is restricted to the face and limbs distal to the elbows and knees.

Commonly, in this form of the disease, only the fingers and the face are involved.
In contrast, diffuse cutaneous involvement is characterized by widespread skin thickening, including proximal limbs and truncal areas.

Proximal skin involvement defines the diffuse cutaneous subset but may be absent in early stages of disease when signs of skin thickening are not prominent, other disease manifestations (e.g., RP and nail-fold capillary abnormalities) are more apparent, and evidence of internal organ involvement is still lacking.







Cutaneous involvement in scleroderma begins with clinical signs of inflammation, which is called the edematous phase because it is characterized by nonpitting edema of affected body areas.
In patients with limited scleroderma, this event is mild and is restricted to the digits, in the diffuse form of the disease, cutaneous swelling and edema can be widespread and so impressive in the limbs that it mimics a fluid overload state such as congestive heart failure.

Edema can also cause local tissue compression, For example, upon involvement of the wrist area, patients with scleroderma are not infrequently diagnosed with carpal tunnel syndrome (especially at disease onset) to explain hand and wrist discomfort.

Erythema of the skin and intense pruritus and pain are characteristic of advancing active diffuse skin disease.
This pain has a neuropathic quality with a reported “pins and needles” sensation.

The disease process leads to loss of skin appendages, as well as decreased hair growth and loss of sweat and exocrine glands; thus the skin surface becomes dry and uncomfortable.

The edematous phase continues for several weeks but eventually gives way to a fibrotic stage , with protracted activity that may last months or years.

During the fibrotic phase, acute inflammation is clinically less obvious, and deposition in the dermis of excessive collagen and other extra-cellular material thickens the skin, making it inflexible and causing further loss of skin appendages.

Fibrosis extends beyond the dermis into the deeper layers with loss of subcutaneous adipose tissue (lipodystrophy). In late stages of the disease, skin actually thins with atrophy and has a non-inflammatory bound down appearance.

Deeper tissue fibrosis causes permanent contractures around joints or may involve underlying muscle, causing a myopathy .

Patients with diffuse cutaneous scleroderma experience the most dramatic widespread skin changes,those with

limited skin disease may note only puffy fingers and digital thickening typical of sclerodactyly.

A masked facies, small oral and orbital apertures, and vertical furrowing of the perioral skin are consequences of skin and soft tissue fibrosis.
In some patients, gum atrophy and facial skin tightening make the front teeth appear more prominent.

Telangiectasias are erythematous matted skin lesions of vascular origin; for this reason, they blanch upon application of local pressure.

Telangiectasias develop primarily on the fingers, hands , face, and mucous membranes, but they also may be found on the limbs and trunk, They tend to become more numerous over time in both limited and diffuse types of skin disease and are more obvious in white patients with limited scleroderma.

The biologic mechanism leading to the development of telangiectasias in scleroderma is thought to be related to the underlying chronic tissue hypoxia that stimulates abnormal secretion of vascular growth factors(e.g., vascular endothelial growth factor).

Gastrointestinal Involvement

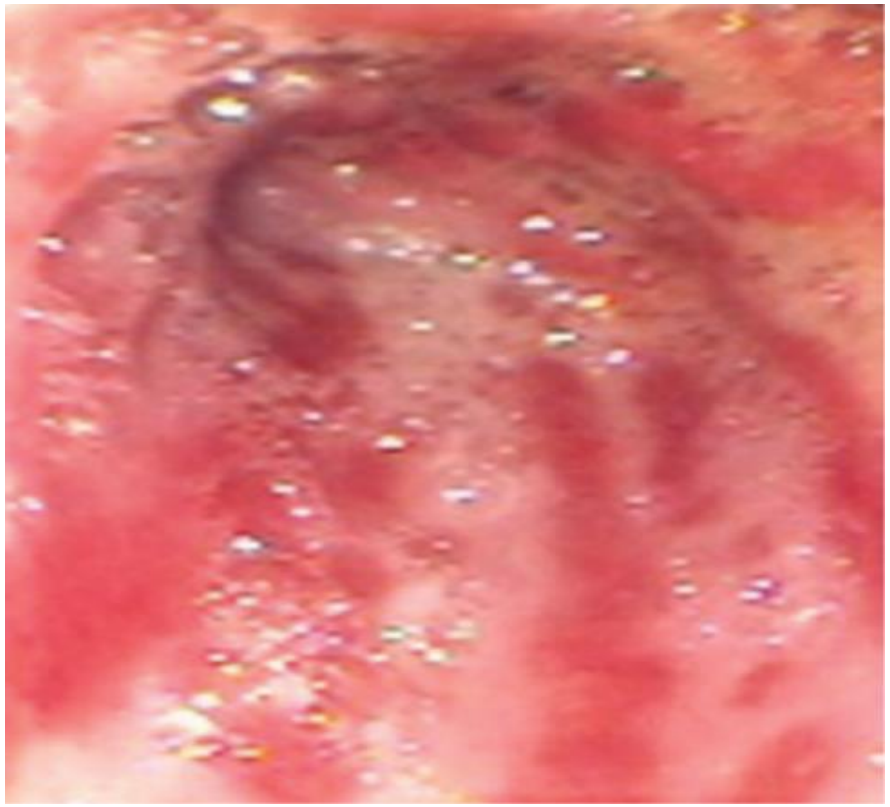
Almost every patient with scleroderma has symptoms of GI disease, ranging from mild gastroesophageal reflux disease (GERD) to severe bowel dysfunction, which can be life threatening, virtually any segment of the GI tract can be affected.

Dilation of the microvasculature in the gastric mucosa is found in a subset of patients.
This manifestation, also called gastric antral vascular ectasia (GAVE), is thought to be caused by an abnormal angiogenesis, leading to bizarre dilation of micro vessels and arterial-venous (A-V) malformations similar to the telangiectasias seen in the skin, lips, and oral mucous membranes.

Extensive clusters of A-V malformations lead to the presence of longitudinal red stripes in the inner lining of the stomach, converging to the pylorus and described on
endoscopy as “watermelon stomach,” based on their appearance.

GI MANIFESTATION OF SCLERODERMA

Site	Manifestation	Management
Oropharynx	Perioral tight skin Decreased oral aperture Periodontitis, gum disease Dry mouth Swallowing difficulties Coughing, aspiration	Regular dental and periodontal care Artificial saliva Targeted swallowing exercises and rehabilitation
Esophagus	Acid reflux (heartburn) Dysphagia Strictures Barrett's esophagus	Lifestyle modifications Proton pump inhibitors Prokinetics Endoscopic treatments and procedures
Stomach	Gastroparesis, dyspepsia Gastric antral vascular ectasia	Prokinetics Proton pump inhibitors, iron replacement Endoscopic laser or cryotherapy Transfusions Surgery
Small and large intestine	Hypomotility, constipation Bacterial overgrowth, diarrhea Pseudo-obstruction Pneumatosis intestinalis Malabsorption Colonic pseudodiverticula	Mild laxatives Promotility agents Rotational antibiotics Octreotide Avoidance of surgery Enteral or parenteral nutrition support
Anorectum	Sphincter incompetence	Biofeedback, sacral nerve stimulation, surgery



Upper endoscopy: gastric antral vascular ectasias presenting as “watermelon” stomach.

Pulmonary Involvement

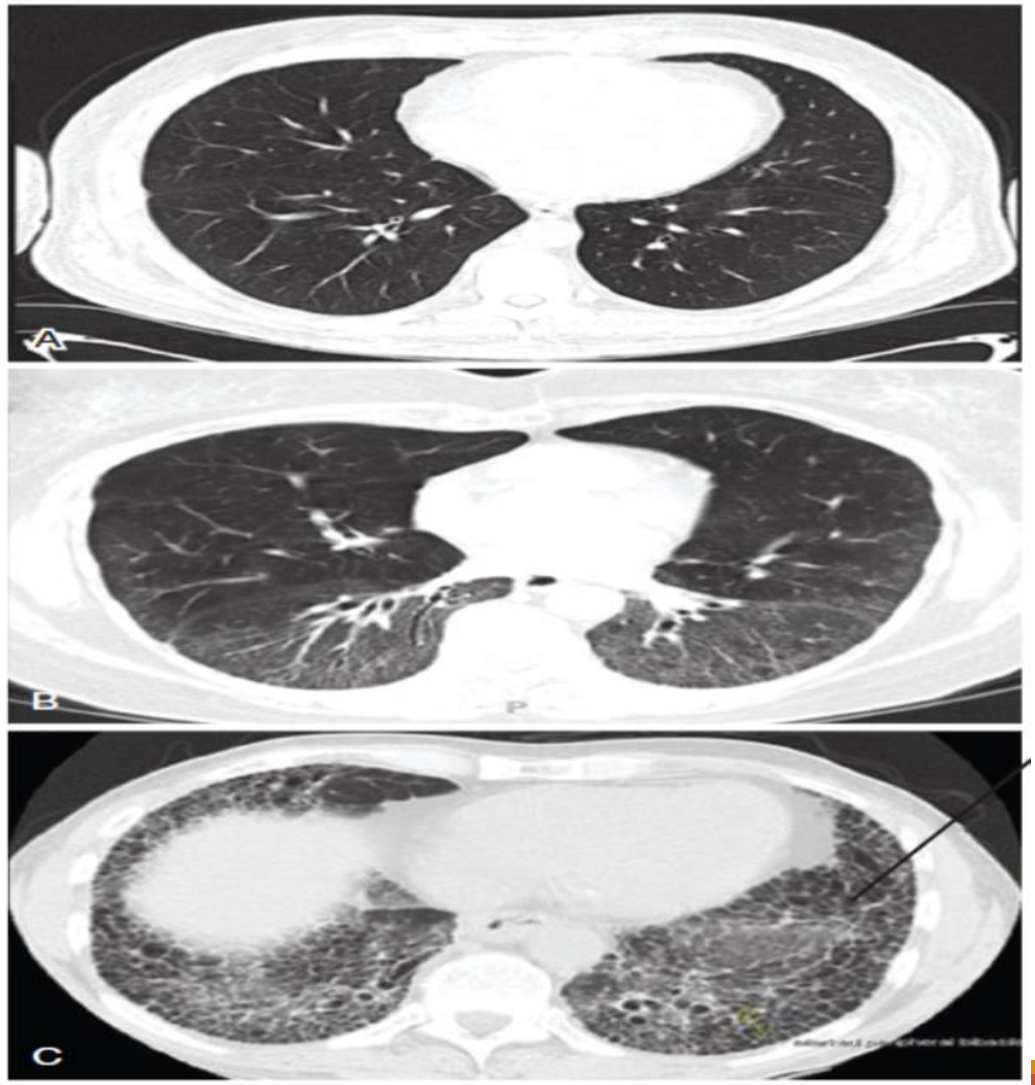
Lung disease is a major cause of morbidity and mortality in patients with scleroderma.
Pulmonary fibrosis occurs in both limited and diffuse subsets of scleroderma, and anti topoisomerase 1–positive patients generally have the worst prognosis.

Pulmonary function testing (spirometry and diffusing capacity) is helpful for screening and monitoring of ILD.
The degree of lung fibrosis on high-resolution computed tomography predicts outcome.
Current treatment for scleroderma-related ILD is limited to immunosuppression.

Risk factors for pulmonary arterial hypertension include late onset of scleroderma, limited phenotype, and the presence of numerous telangiectasias, Pulmonary involvement is found in most patients with scleroderma, ILD and pulmonary hypertension are recognized as the most common lung complications and are now regarded as the major cause of death in scleroderma.

The most common histologic pattern of fibrosing alveolitis in scleroderma is nonspecific interstitial pneumonia (NSIP), as opposed to usual interstitial pneumonia (UIP), which is the common presentation of idiopathic pulmonary fibrosis.

Scleroderma-related interstitial lung disease: high-resolution chest computed tomography scan showing (A) normal lung, (B) active alveolar inflammation (“ground glass” opacification), and (C) end-stage lung disease with honeycombing.



Pulmonary Hypertension

Pulmonary arterial vascular disease is a common manifestation of scleroderma and is usually a late manifestation.
Typical symptoms associated with clinically manifested PAH include dyspnea upon exertion, fatigue, and, less commonly, chest pain or syncope.
Physical examination may be normal during early stages of PAH, but as the disease progresses, a systolic murmur of tricuspid regurgitation, a loud pulmonic component, the S2, an S3 gallop, and signs of right heart failure (e.g., right-sided parasternal heave, prominent and elevated jugular venous pulse, hepatomegaly, and signs of fluid overload with peripheral edema)are seen.
Later in the disease, patients become dyspneic with little activity, have a resting tachycardia, and may appear cyanotic.
Sudden syncope or death can occur as a result of hypoxia and congestive heart failure.

Cardiac Involvement

The clinical manifestations of heart disease are highly variable, ranging from clinically silent cardiac involvement to frank heart failure.

The reported prevalence of heart disease varies from 10% to more than 50%.
Cardiac disease can occur in both diffuse and limited subtypes of scleroderma .

Along with pulmonary fibrosis and PAH, cardiac disease accounts for the majority of deaths in scleroderma.

Cardiac disease in scleroderma can be characterized by involvement of the endocardium, myocardium, and pericardium, separately or concomitantly.

As a consequence, pericardial effusion, ventricular arrhythmias, conduction disease, valvular regurgitation, myocardial ischemia, myocardial hypertrophy, and heart failure are all reported.

Renal Involvement

Scleroderma renal crisis (SRC) is a life-threatening condition that occurs in 5% to 10% of patients with scleroderma.

Risk factors for SRC include early diffuse skin disease, use of corticosteroids, and the presence of anti-RNA polymerase III antibodies.
Renal crisis is also associated with a positive ANA (speckled pattern) ,anti-U3-RNP and usually is not seen in patients with anticentromere antibodies.

Antibodies to RNA polymerase III were found in about 60% of patients with SRC .
Although anti topoisomerase I antibodies are prevalent in patients with diffuse skin disease,no association between their presence and SRC has been reported.

Early pharmacologic intervention with ACE inhibitors is crucial to control and possibly reverse the disease process.

Renal involvement in scleroderma is classically characterized by the abrupt onset of very high blood pressure (malignant hypertension), elevated plasma renin, and rising serum creatinine reflective of acute renal failure, along with a constellation of symptoms and clinical manifestations such as headaches, malaise, hypertensive retinopathy, encephalopathy, and pulmonary edema, usually referred to as scleroderma renal crisis (SRC).

Although SRC is the most recognized renal complication, abnormal renal function can be explained by factors other than intrinsic scleroderma renal disease such as medication adverse effects, comorbid conditions, or associated heart ,GI , or lung disease.

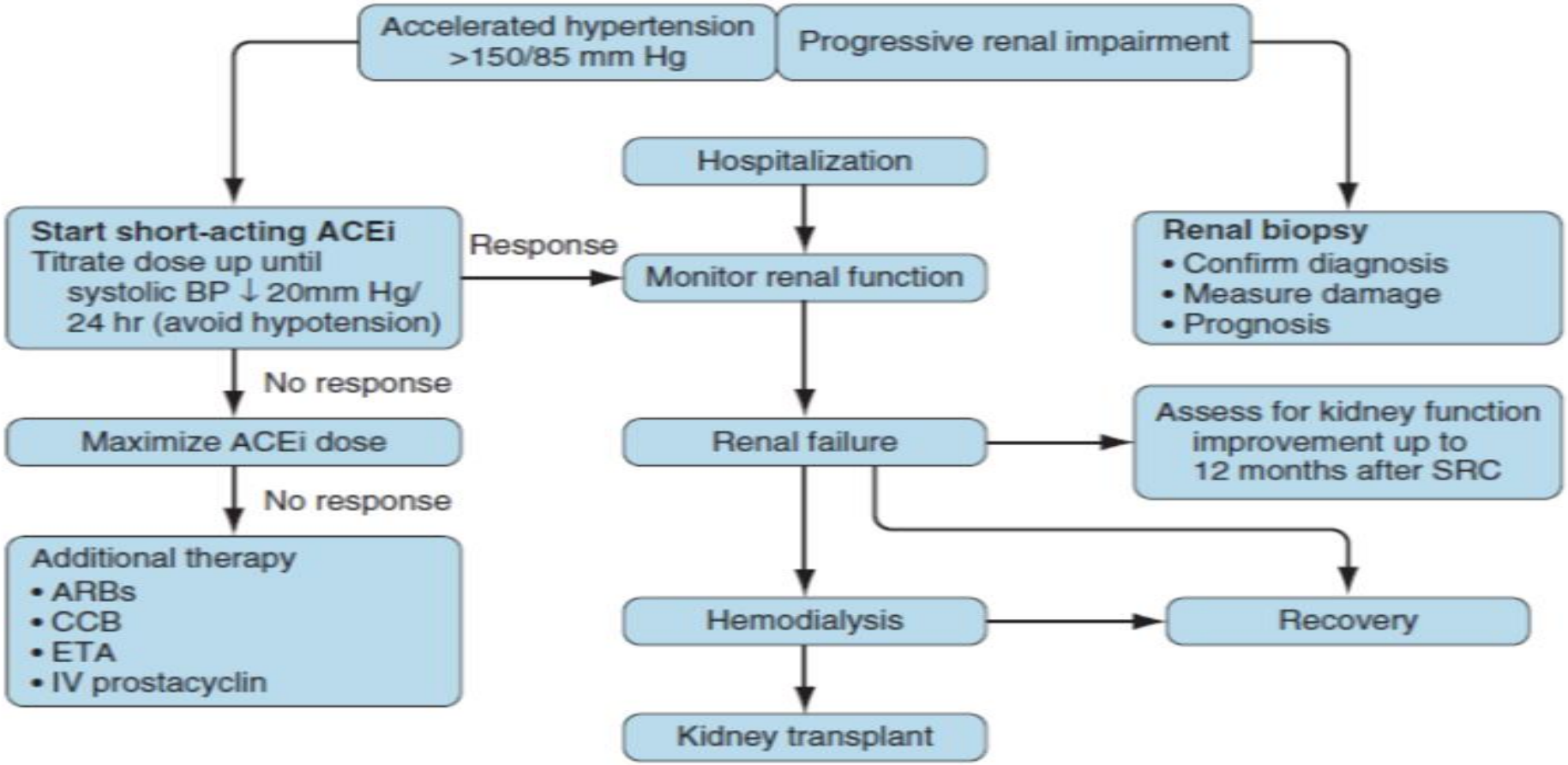


Figure 84-15 Management of scleroderma renal crisis. ACEi, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; ETA, endothelin receptor antagonist; IV, intravenous; SRC, scleroderma renal crisis.

Musculoskeletal Involvement

The most common symptoms are nonspecific pain, stiffness, and diffuse muscular discomfort that mimics a flu-like syndrome.

Impaired hand function, characterized by decreased hand mobility, reduced dexterity, and decreased grip force, is in particular a major source of difficulty in performing activities of daily living.

in early diffuse scleroderma, pain that is often widespread in areas of skin inflammation and advancing fibrosis can involve joint structures, tendons, subcutaneous tissue, and underlying muscle.

In later stage diffuse disease, joint contractures and muscle atrophy are often associated with pain and loss of function, causing significant disability

In patients with limited scleroderma, puffy fingers and loss of hand function and grip may be the only musculoskeletal symptoms throughout the disease course.

In the early edematous phase of diffuse scleroderma, patients often are diagnosed with carpal tunnel syndrome as a result of soft tissue swelling and inflammation in the hand and wrist area.

Erosive arthritis with joint space narrowing can be seen.

periarticular calcinosis are found in the fingers of patients with later stage diffuse scleroderma.

Contractures of the PIP and MCP joints are most common, and rarely, contractures of the distal interphalangeal joint occur

Tendon friction rubs can be felt as a coarse crepitus over joints or over the forearm or lower leg with adjacent joint movement.
These rubs are thought to be a result of low grade tenosynovitis, local edema, and fibrosis of the tendon sheath, fascia, and joint structures.
Friction rubs are seen primarily in patients with diffuse skin disease; when present, they are an indicator of a poor overall prognosis

Erosive arthritis is commonly associated with periarticular calcinosis

Measurement of the autoantibodies present in scleroderma can be helpful in determining the clinical features and prognosis of the disease, in that specific scleroderma related autoantibodies have been established as strong predictors of disease outcome and the pattern of organ Complications.

The three most frequently observed types of scleroderma-specific autoantibodies are anticentromere, antitopo isomerase I, and anti-RNA polymerase III antibodies.

Autoantibodies and Associated Phenotypes in Scleroderma

Antigen	Subtype	Clinical Phenotype
Topoisomerase 1 (Scl-70)	Diffuse	Pulmonary fibrosis, cardiac involvement
Centromere (protein B, C)	Limited	Severe digital ischemia, PAH, sicca syndrome, calcinosis
RNA polymerase III	Diffuse	Severe skin disease, tendon rubs, cancer, GAVE, renal crisis (±sine scleroderma)
U3-RNP (fibrillarin)	Diffuse or limited	Primary PAH; esophageal, cardiac, and renal involvement; muscular disease
Th/To	Limited	Pulmonary fibrosis, rare renal crisis, lower GI dysfunction
B23	Diffuse or limited	PAH, lung disease
Cardiolipin, β_2GPI	Limited	PAH, digital loss
PM/Scl	Overlap	Myositis, pulmonary fibrosis, acro-osteolysis
U1-RNP	Overlap	SLE, inflammatory arthritis, pulmonary fibrosis

GAVE, Gastric antral vascular ectasia; GI, gastrointestinal; GPI, glycoprotein I; PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein particle; SLE, systemic lupus erythematosus.

Management

No treatments are available that halt or reverse the fibrotic changes that underlie the disease.

The focus of management, therefore, is to slow the effects of the disease on target organs.

- Raynaud's phenomenon and digital ulcers.

Avoidance of cold exposure, use of thermal insulating gloves/socks and maintenance of a high core temperature all help.

If symptoms are persistent, calcium channel blockers, losartan, fluoxetine and sildenafil have efficacy.

Courses of intravenous prostacyclin are used for severe disease and critical ischemia (e.g. 6–8 hours daily for 5 days).

The endothelin-1 antagonist bosentan is licensed for treating ischaemic digital ulcers, and digital tip tissue health can be maintained with regular use of fucidin–hydrocortisone cream.

• Gastrointestinal complications.
Esophageal reflux should be treated with proton pump inhibitors and anti-reflux agents.
Rotating courses of antibiotics may be required for bacterial overgrowth (e.g. rifaximin, a tetracycline and metronidazole), while metoclopramide or domperidone may help patients with symptoms of dysmotility/ pseudo-obstruction.
• Hypertension. Aggressive treatment with ACE inhibitors is needed, even if renal impairment is present.
• Joint involvement.
This may be treated with analgesics and/or NSAIDs.
If synovitis is present and both RA (i.e. an overlap condition, which needs treatment on its own merit) and OA have been ruled out, low-dose methotrexate can be of value.

• Progressive pulmonary hypertension.

Early treatment with bosentan is required.
In severe or progressive disease , heart–lung transplant may be considered.

• Interstitial lung disease. Glucocorticoids and (pulse intravenous) cyclophosphamide are the mainstays of treatment in patients who have progressive interstitial lung disease.

Adult-onset Still’s disease

Is a rare systemic inflammatory disorder of unknown etiology , possibly triggered by infection, It presents with intermittent fever, rash and arthralgia, Splenomegaly, hepatomegaly and lymphadenopathy may be present.

Investigations

elevated CRP , with a markedly elevated serum ferritin.

Tests for RF and ANA are negative and so adult-onset Still’s disease may be better classified as an autoinflammatory rather than an autoimmune disease.

Most patients respond to glucocorticoids but immunosuppressants, such as azathioprine or MMF, can be added when response is inadequate.

interleukin(IL) 1 inhibitor like canakinumab or anakinra can be used for patients with resistant disease.

VASCULITIS

Vasculitis is characterized by inflammation and necrosis of blood-vessel walls, with associated damage to skin, kidney, lung, heart, brain and gastrointestinal tract.

Vasculitides are classified first by the size of blood vessel involved—small (capillaries and postcapillary venules),medium (muscular arteries and arterioles), or large (the aorta and its major branches) vessels vasculitis.

CLASSIFICATION

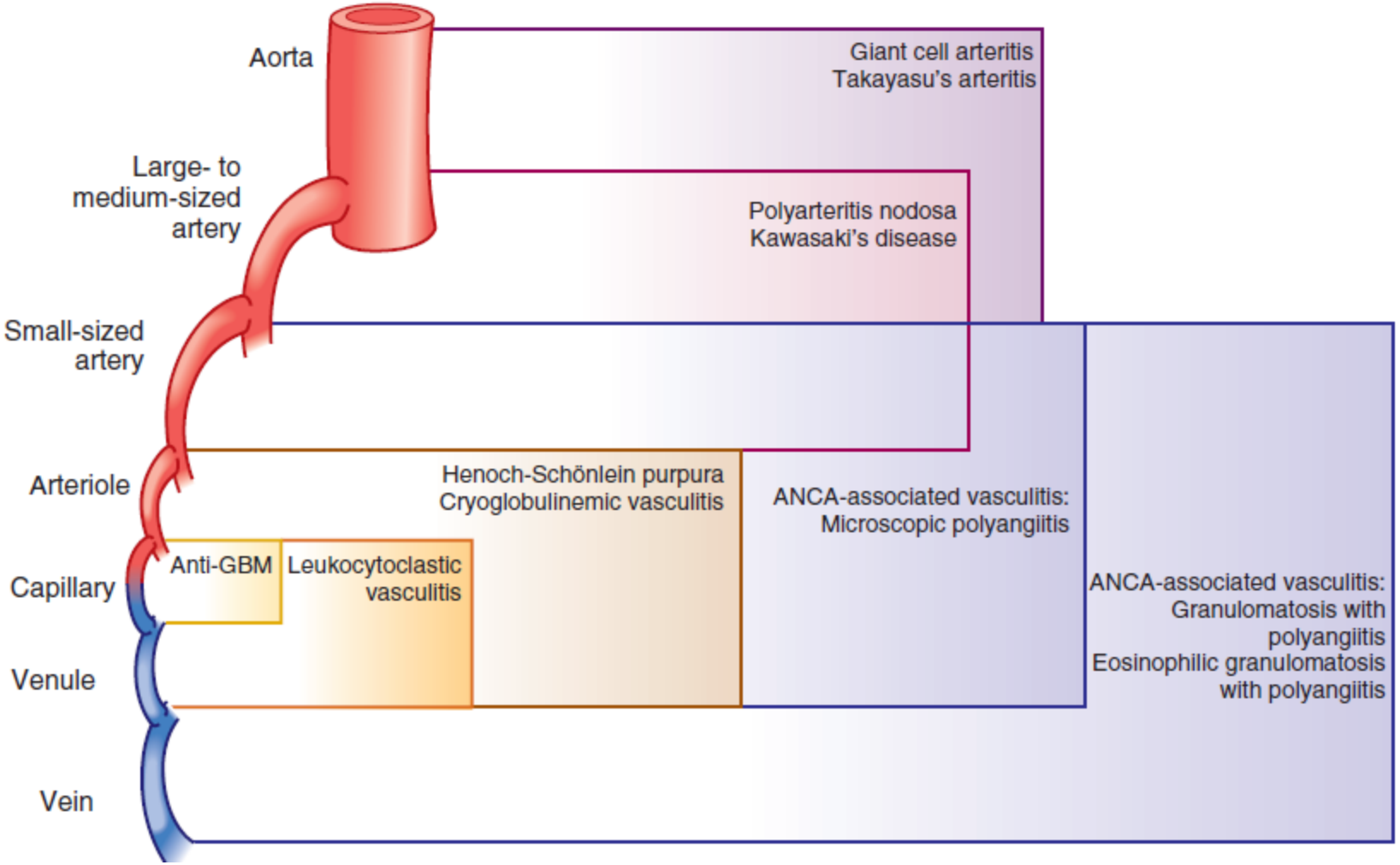
Large vessel vasculitis: generally denotes the aorta and its major branches (and the corresponding vessels in the venous circulation in some forms of vasculitis, e.g., Behcet's disease).

Medium vessel vasculitis: refers to vessels that are smaller than the major aortic branches yet still large enough to contain four elements:
an intima, a continuous internal elastic lamina, a muscular media, and an adventitia.
In clinical terms, medium-vessel vasculitis is generally macrovascular (i.e., it involves vessels large enough to be observed in gross pathologic specimens or visualized by angiography).

The large artery becomes a medium-sized artery when it penetrates a viscus, Thus, the renal artery is considered a large artery, but once it enters the kidney and separates into the smaller arcuate and interlobular arteries, these vessels are regarded as medium-sized arteries.

Small vessel vasculitis: which incorporates all vessels below macroscopic disease, includes capillaries, postcapillary venules, and arterioles.
Such vessels typically are all less than 500 μm in outer diameter.

Because glomeruli may be viewed simply as differentiated capillaries, forms of vasculitis that cause glomerulonephritis are considered to be small vessels vasculitis



Classification by blood vessel size. ANCA, Anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane

Many other considerations are important in the classification of vasculitis.
Such as the disease's tropism for particular organs, the presence or absence of granulomatous inflammation,
the participation of immune complexes in disease pathophysiology.
and the finding of characteristic autoantibodies in the patients serum (e.g., ANCAs, anti-GBM antibodies, or rheumatoid factor),the detection of certain infections known to cause specific forms of vasculitis

The organ tropisms of these disorders are illustrated by the following examples:

Granulomatosis with polyangiitis (GPA) classically involves the kidneys, upper airways, and lungs, In contrast, IgA vasculitis/Henoch-Schönlein purpura(HSP) often affects the kidneys, but never the nose or sinuses and almost never the lungs.

In contrast to both of these forms of vasculitis, Cogan's syndrome is defined by the simultaneous occurrence of ocular inflammation caused by a small-vessel vasculitis (most often interstitial keratitis) and sensorineural hearing loss (and, in 10% of cases, a large vessel vasculitis).

The histopathologic findings in these three disorders are equally distinctive, ranging from granulomatous inflammation of small to medium vessels (GPA) to IgA deposition in small vessels (HSP), to large vessel vasculitis centered on the adventitia (Cogan's syndrome).

Vasculitides Adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of vasculitides.

Large-Vessel Vasculitis
Takayasu's arteritis
Giant cell arteritis
Medium-Vessel Vasculitis
Polyarteritis nodosa
Kawasaki's disease
Small-Vessel Vasculitis
Anti-neutrophil Cytoplasmic Antibody–Associated Vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Immune Complex Small Vessel Vasculitis
Anti-glomerular basement membrane disease
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein purpura)
Hypocomplementemic urticarial vasculitis
Variable Vessel Vasculitis
Behçet's disease
Cogan's syndrome
Single-Organ Vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Vasculitis Associated with Systemic Disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others (e.g., IgG_4-related aortitis)
Vasculitis Associated with Probable Etiology
Hepatitis C virus–associated cryoglobulinemic vasculitis
Hepatitis B virus–associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

ANCA, Anti-neutrophil cytoplasmic antibody.

e-,Medium-, and Small-Vessel Involvement by Vasculitis.

Large
Limb claudication
Asymmetric blood pressures
Absence of pulses
Bruits
Aortic dilation
Renovascular hypertension

Medium
Cutaneous nodules
Ulcers
Livedo reticularis
Digital gangrene
Mononeuritis multiplex
Microaneurysms
Renovascular hypertension

Small
Purpura
Vesiculobullous lesions
Urticaria
Glomerulonephritis
Alveolar hemorrhage
Cutaneous extravascular necrotizing granulomas
Splinter hemorrhages
Uveitis/episcleritis/scleritis

Constitutional symptoms: fever, weight loss, malaise, arthralgias/arthritis (common to vasculitides of all vessel sizes).

Giant cell arteritis
Takayasu's arteritis
Cogan's syndrome
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Primary angiitis of the central nervous system*
Rheumatoid vasculitis

*Sometimes granulomatous.

ssociated with Granulomatous Inflammation.

There is a wide spectrum of involvement and severity, ranging from mild and transient disease affecting only the skin, to life-threatening fulminant disease with multiple organ failure.

The clinical features result from a combination of local tissue ischemia (due to vessel inflammation and narrowing) and the systemic effects of widespread inflammation.

Systemic vasculitis should be considered in any patient with fever, weight loss, fatigue, evidence of multisystem involvement, rashes, raised inflammatory markers and abnormal urinalysis.

Giant cell arteritis and polymyalgia rheumatica

Giant cell arteritis (GCA) is a granulomatous arteritis that affects any large (including aorta) and medium-sized arteries.
It is commonly associated with polymyalgia rheumatica (PMR), which presents with symmetrical, immobility-associated neck and shoulder girdle pain and stiffness.

Since many patients with GCA have symptoms of PMR, and many patients with PMR go on to develop GCA if untreated, many rheumatologists consider them to be different manifestations of the same underlying disorder
Both diseases are rare under the age of 60 years.
The average age at onset is 70, with a female-to-male ratio of about 3：1.
The overall prevalence is about 20 per 100 000 in those over the age of 50 years.

The greatest risk factor for GCA is aging.
the disease almost never occurs in individuals younger than 50 years, and its incidence rises steadily thereafter.
The highest incidence is found in Scandinavians and in Americans of Scandinavian descent,the lowest incidence of GCA is reported in Japanese, northern Indians, and African-Americans.

GCA is the most common form of systemic vasculitis in adults, the disease affects primarily the extracranial branches of the carotid artery in patients older than 50 years.

Because the cause of GCA is unknown, various names—including temporal arteritis, cranial arteritis, and granulomatous arteritis—have been used to highlight different salient features.

Genetic susceptibility to GCA was initially suggested by reports of GCA in families, and, more recently, an association with genes in the class II human leukocyte antigen (HLA) region.

sixty percent of GCA patients have HLA-DRB1*04 haplotype variants.

The existence of environmental risk factors has been suggested by the geographic clustering of GCA cases.

Smoking increases the risk for GCA six fold in women.

Circumstantial evidence links the development of GCA to a variety of infectious agents including Mycoplasma pneumoniae , varicella-zoster virus, parvovirus B19, and parainfluenza virus type I.

Having diabetes reduces the risk of GCA by 50% in women.

Although patients with GCA have an increased risk of developing thoracic aortic aneurysms, they do not have overall higher mortality rates.

PMR is two to three times more common than GCA.

PMR is associated with the same HLA-DR4 genes as GCA.

Pathology

In GCA, inflammation is found most often in medium sized muscular arteries that originate from the arch of the Aorta, The inflammation tends to affect the arteries in a segmental fashion (possibly leading to “skip lesions "within arteries), but long portions of arteries may be involved.

Early in the disease, collections of lymphocytes are confined to the region of the internal or external elastic lamina or adventitia.
The inflammation may be limited to the vasa vasorum in some cases.
Intimal thickening with prominent cellular infiltration is a hallmark of more advanced cases.
In heavily involved areas, all layers are affected .

Transmural inflammation of portions of the arterial wall (including the elastic laminae) and granulomas containing multinucleated histiocytic and foreign body giant cells, histiocytes , lymphocytes (which are predominantly CD4+ T cells), and some plasma cells and fibroblasts are found.

giant cells are seen in only approximately half of routinely examined specimens; therefore, they are not required to make the diagnosis if other features are compatible.

Clinical features

headache is the most common symptom in GCA, being present in nearly three quarters of patients.

The pain is typically described as boring in quality, of moderate severity, and most commonly appreciated in the temporal area, however, the description of the headache varies, It can be mild to so severe that the patient seeks immediate relief .

The headache, is often localized to the temporal or occipital region(because of involvement of the occipital artery) and may be accompanied by scalp tenderness.

The most consistent characteristic is that the patient experiences the headache as something new and unusual. In untreated patients, the headache may subside over weeks, even though the disease activity continues.

Abnormalities of the temporal artery—including enlargement, nodular swelling, tenderness, or loss of pulse manifest in only approximately half of patients , some patients note tenderness of the scalp, which can be aggravated by brushing or combing the hair.

Jaw claudication (Jaw pain develops in some patients, brought on by chewing or talking).

Visual symptoms are common in GCA, especially loss of vision and diplopia.

Visual disturbance can occur (most specifically amaurosis) and a catastrophic presentation is with blindness in one eye due to occlusion of the posterior ciliary artery.

Vision loss can be unilateral or (less commonly) bilateral, transient or permanent, and partial or complete.

Vision loss that lasts more than a few hours usually does not reverse.

Loss of vision often reflects an anterior ischemic optic neuropathy caused by occlusive arteritis of the posterior ciliary artery, the chief blood supply to the head of the optic nerve.

Less frequently, vision loss in GCA stems from a retinal artery occlusion.

Vision loss is less likely to develop in GCA patients who are seen with fever or other systemic symptoms, one possible explanation of this protective effect of fever and other systemic manifestations is that patients with prominent systemic inflammation demonstrate more extensive angiogenesis in temporal artery biopsies, the angiogenesis associated with increased inflammation may result in the development of collateral circulation that reduces the chance of ischemic events.

On fundoscopy, the optic disc may appear pale and swollen with hemorrhages, but these changes may take 24–36 hours to develop and the fundi may initially appear normal.

Rarely, neurological involvement may occur, with transient ischemic attacks, brainstem infarcts and hemiparesis.

American College of Rheumatology Classification Criteria for Giant Cell Arteritis

Criterion	Definition
Age at disease onset ≥50 yr	Development of symptoms or findings beginning at age 50 yr or older
New headache	New onset or new type of localized pain in the head
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
Elevated ESR	ESR ≥50 mm/hr by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis, characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For purposes of classification, a patient have giant cell (temporal) arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields with vasculitis is said to a sensitivity of 93.5% and a specificity of 91.2%.

Atypical Manifestations of Giant Cell Arteritis

Fever of unknown origin
Respiratory symptoms (especially cough)
Otolaryngeal manifestations Glossitis Lingual infarction Throat pain Hearing loss
Large artery disease Aortic aneurysm Aortic dissection Limb claudication Raynaud's phenomenon
Neurologic manifestations Peripheral neuropathy Transient ischemic attack, stroke Dementia Delirium
Myocardial infarction
Tumor-like lesions Breast mass Ovarian and uterine mass Syndrome of inappropriate anti-diuretic hormone secretion Microangiopathic hemolytic anemia

In GCA, constitutional symptoms, such as weight loss, fatigue, malaise and night sweats, are common.

With PMR, there may be stiffness and painful restriction of active shoulder movements on waking.

Polymyalgia Rheumatica is a syndrome characterized by aching in the proximal portions of the extremities and torso.

Because no specific diagnostic tests or pathologic findings exist, PMR is defined by its clinical features.

The features included in most definitions of PMR are as follows:
- aching and morning stiffness lasting half an hour or longer in the shoulder, hip girdle, neck, or a combination.
- duration of these symptoms for 1 month or longer.
- patient age older than 50 years, and
- laboratory evidence of systemic inflammation such as an elevated erythrocyte sedimentation rate (ESR).

Systemic manifestations such as malaise, low-grade fever, and weight loss are present in more than half of the patients, and may be the initial symptoms of disease, High spiking fevers are uncommon in PMR in the absence of GCA.

Arthralgias and myalgias may develop abruptly or evolve insidiously during weeks or months.
In most patients, the shoulder girdle is the first to become symptomatic ; in the remainder, the hip or neck is involved at the onset.

Muscles are not otherwise tender, and weakness and muscle-wasting are absent.
Other conditions that cause
PMR-like symptoms are spondylarthritis ,hyper -/hypothyroidism, psoriatic arthritis (enthesopathic),Inflammatory myopathy(particularly inclusion body myositis)….

Investigations

The typical laboratory abnormality is an elevated ESR, often with a normochromic, normocytic anemia.

Rarely, PMR and GCA can present with a normal ESR.

CRP may also be elevated and abnormal liver function can occur.
Liver function test results are mildly abnormal in approximately one-third of patients with GCA and in a slightly smaller number of those with PMR.
An increased alkaline phosphatase level is the most common abnormality, but increases in aspartate transaminase and prolonged prothrombin time may also be found.

More objective evidence for GCA should be obtained whenever possible.

There are three investigations to consider:
temporal artery biopsy, ultrasound of the temporal arteries and 19 fluorodeoxyglucose positron emission tomography (19FDG PET scan).
Characteristic biopsy findings are
fragmentation of the internal elastic lamina with necrosis of the media in combination with a mixed inflammatory cell infiltrate.

Temporal artery biopsy is the “gold standard” for diagnosing GCA.
Because GCA does not involve the artery in a continuous fashion, temporal artery biopsy should be directed to the symptomatic side.

Removing a small (1 to 2 cm) section of temporal artery is usually adequate in patients who have palpable abnormalities of the Vessel otherwise, the surgeon should try to excise a 4 to 6 cm sample.

The sensitivity of temporal artery biopsy is approximately 90% to 95%.

And the temporal artery biopsy can yield false negative results in up to 7%, this can be due to skip lesions and may results from corticosteroid treatment of GCA, and the longer the duration of treatment before biopsy the fewer positive results there will be, and positive biopsy may be found following corticosteroid treatment for GCA.

A negative biopsy does not exclude the diagnosis,

And bilateral temporal arteries biopsies do not increase the diagnostic yield in the majority of patients(99%).

Management of a patient with a negative unilateral biopsy depends on how strongly the patient's clinical picture suggests GCA , When GCA is still strongly suspected, a second biopsy or an imaging test should be considered.

Opting for a second temporal artery biopsy probably makes most sense in patients who have jaw claudication or diplopia.

Patients whose main symptom is occipital headache may be best diagnosed by biopsy of the occipital artery.

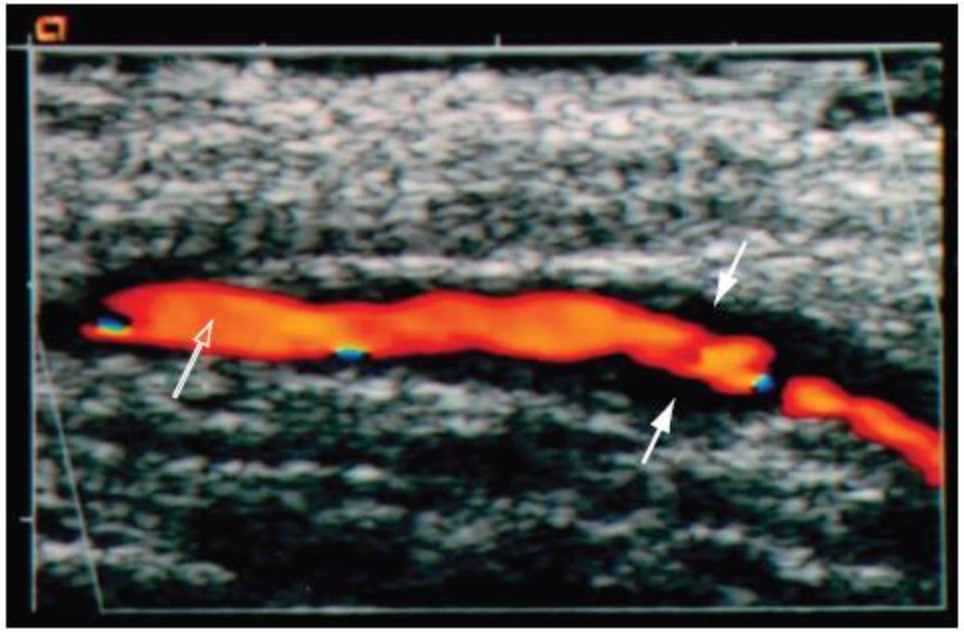
Patients who have signs of subclavian and axillary disease manifested by arm claudication, unequal arm blood pressures, and supraclavicular or axillary bruits may be diagnosed by angiogram, MRA, or CT scan.

Color duplex ultrasonography

The most specific and sensitive color duplex sonography sign for GCA is a concentric hypoechogenic mural thickening called the halo sign , which reflects vessel wall inflammatory edema.

The halo sign of temporal artery has a sensitivity of 75 % and a specificity of 83% for diagnosis of biopsy proven GCA, and an over all sensitivity of 68% and specificity of 91% for GCA diagnosed according to ACR criteria.

The specificity of the halo sign increase to 100% when the sign is bilateral.



Color duplex ultrasound examination of a swollen, tender temporal artery in a patient with giant cell arteritis. The variably thickened artery wall is visible as a clear “halo” (solid arrows) around the lumen in the center (open arrow).

High-resolution MRI

can demonstrate contrast enhancement and mural thickening of superficial cranial arteries in GCA.

PET

has shown promise in detecting occult involvement of the aorta and great vessels by GCA.
A strongly positive 19FDG PET scan is highly specific but sensitivity is low.
Caution is needed in interpreting weakly positive images.
Low-grade vascular uptake may occur in atheromatous arterial disease.

Treatment for Giant Cell Arteritis

Prednisolone should be commenced urgently in suspected GCA because of the risk of visual loss.

An initial dose of prednisone 40 to 60 mg/day or equivalent is adequate in nearly all cases.
If the patient does not respond promptly, the dose should be increased.
Osteoporosis prophylaxis measures (weekly bisphosphonates, vit .d , calcium supplements.)

Consider urgent ophthalmology examination and temporal artery biopsy in patients with visual symptoms.
Obtaining temporal artery ultrasound or 19FDG-PET scan.
Review within 1 week and adjust glucocorticoid doses according to clinical response and results of investigations

symptoms will completely resolve within 48–72 hours of starting therapy in virtually all patients.

the glucocorticoid dose should be progressively reduced, guided by symptoms and ESR, with the aim of reaching a dose of 10–15 mg by about 8 weeks.

Most patients need glucocorticoids for an average of 12–24 months.

Steroid sparing agents such as methotrexate can be used in combination with steroid.

Tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody, can be used in refractory cases.

Treatment for Polymyalgia Rheumatica

Patients with PMR without symptoms or signs or biopsy evidence of GCA are usually treated initially with prednisone 15 to 20 mg/day or equivalent, Prednisone therapy usually results in rapid (often overnight) and dramatic improvement of the musculoskeletal aching and stiffness and a more gradual return of the ESR and CRP level to normal.

Once the symptoms, signs, and laboratory abnormalities of PMR have resolved (usually after 2 to 3 weeks of therapy), the daily dose of prednisone can be slowly tapered.

minority of patients with PMR succeed in tapering off prednisone in less than 1 year. Many require at least 2 years of low-dose prednisone.

Some, but not all, studies suggest that oral methotrexate (10 mg once a week for 48 weeks) can reduce the long-term need for corticosteroids in patients with PMR.

TAKAYASU'S ARTERITIS

TA, also known as pulseless disease or occlusive thromboaortopathy, is a form of vasculitis of unknown cause that chiefly affects the aorta and its major branches, most frequently in young women.

It occurs most commonly in Japan, China, India, and Southeast Asia.
TA affects women eight times more frequently than men, the median patient age at onset is 25 years.

approximately 25% of cases begin before age 20, and 10% to 20% of patients are seen after age 40 years.

Clinical Features

Takayasu arteritis is characterized by granulomatous inflammation of the vessel wall, leading to occlusion or weakening of the vessel wall.
The most common presenting vascular symptoms were claudication (35%), reduced or absent pulse (25%), carotid bruit (20%), hypertension(20%), carotidynia (20%), lightheadedness (20%), and asymmetric arm blood pressures (15%).
Stroke, aortic regurgitation, and visual abnormalities were present at onset in less than 10% of patients.
Claudication affects the arms at least twice as frequently as the legs.

For many young women, arm claudication first reveals itself as arm pain or fatigue experienced while trying to hold a hair dryer.

Overall, bruit is the most common sign, eventually found in 80% of patients.
Bruit over the carotid artery is most frequent, it can also be found in supraclavicular, infraclavicular, axillary, flank, chest, abdominal, and femoral areas.

Unequal arm blood pressures eventually develop in half of all patients.

Aortic regurgitation develops in 20% of patients as a result of aortic root dilation.

Angina can develop as a result of coronary artery disease.

Myocarditis also occurs in TA and causes potentially reversible congestive heart failure.

Although TA of the pulmonary arteries is rare (appearing in less than 3% of patients), affected patients can be seen with cough, chest wall pain, dyspnea, or hemoptysis.

American College of Rheumatology Classification Criteria for Takayasu's Arteritis*

Onset before age 40 yr
Limb claudication
Decreased brachial artery pulse
Unequal arm blood pressure (>10 mm Hg)
Subclavian or aortic bruit
Angiographic evidence of narrowing or occlusion of aorta or its primary branches, or large limb arteritis

The presence of three or more of the six criteria is sensitive (91%) and specific (98%) for the diagnosis of Takayasu's arteritis.

Clinical Features of Takayasu's Arteritis

Feature	At Presentation (%)	Ever Present (%)
Vascular	50	100
Bruit		80
Claudication (upper extremity)	30	62
Claudication (lower extremity)	15	32
Hypertension	20	33
Unequal arm blood pressures	15	50
Carotidynia	15	32
Aortic regurgitation		20
Central nervous system	30	57
Lightheadedness	20	35
Visual abnormality	10	30
Stroke	5	10
Musculoskeletal	20	53
Chest wall pain	10	30
Joint pain	10	30
Myalgia	5	15
Constitutional	33	43
Malaise	20	30
Fever	20	25
Weight loss	15	20
Cardiac	15	38
Aortic regurgitation	8	20
Angina	2	12
Congestive heart failure	2	10

Laboratory Studies

The ESR is more frequently elevated (80%) than the CRP (~50%).

Mild anemia and hypergammaglobulinemia

The white blood cell count is usually normal or slightly elevated.

The platelet count is elevated in one-third of patients, and may exceed 500,000/µL in those with active disease.

The serum creatinine and urinalysis are usually normal.

Any renal abnormalities are usually secondary to hypertension.
TA rarely causes glomerulonephritis.

Imaging

Vascular abnormalities in TA can be imaged by conventional angiography, MRI, MRA, CT angiography, or ultrasonography.

The earliest detectable abnormality in TA is thickening of the vessel wall from inflammation.
MRI, ultrasonography, and, to a lesser degree, CT can detect this early vessel wall thickening.
Conventional angiography is invasive and provides the least sensitive method for visualizing wall thickness however, conventional angiography is the “gold standard” for precisely delineating the stenoses, occlusions, and aneurysms that characterize the latter stages of TA.

The most common sites of lesions in TA are the aorta (65%) and the left subclavian arteries (93%).

The left subclavian artery is affected slightly more frequently than the right.

Carotid, renal, and vertebral arteries are also commonly affected.

lesions may be stenotic(93%), occluded (57%), dilated (16%), or aneurysmal(7%).

Stenotic lesions are approximately four times more common than aneurysmal lesions.

Treatment

Corticosteroids are the cornerstone of treatment of active TA.

methotrexate with the initial dose not to exceed 15 mg/wk) is a moderately effective corticosteroid-sparing drug.

anti-TNF inhibitors (etanercept and infliximab) in treating patients with refractory TA.

Tocilizumab, which blocks the IL-6 receptor, has also been reported effective in individual patients.

Anti-neutrophil Cytoplasmic Antibody–Associated Vasculitis

(ANCA ASS0VIATED VASCULITIS)

(ANCA)-associated vasculitis are

granulomatosis with polyangiitis (GPA).
microscopic polyangiitis (MPA).
and eosinophilic granulomatosis with polyangiitis (EGPA).

They affect small- and medium-sized vessels and share clinical, pathologic, and diagnostic features.

These diseases are categorized together, given their association with antibodies directed against antigens in the cytoplasm of neutrophils—proteinase 3 (PR3) and myeloperoxidase(MPO)—and many overlapping clinical manifestations, diagnostic testing, and treatment strategies.

Chapel Hill Consensus Conference nomenclature*	
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). *Necrotizing glomerulonephritis is common.*
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). *Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.*
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels and associated with asthma and eosinophilia.

1990 American College of Rheumatology classification criteria for granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis †	
Granulomatosis with polyangiitis	**Eosinophilic granulomatosis with polyangiitis**
1. Nasal or oral inflammation Painful or painless oral ulcers, or purulent or bloody nasal discharge	**1. Asthma** History of wheezing or diffuse high-pitch rales on expiration
2. Abnormal chest radiograph Nodules, fixed infiltrates, or cavities	**2. Eosinophilia** Eosinophilia of >10% eosinophils on white blood cell differential count
3. Urinary sediment Microhematuria or red cell casts	**3. Mononeuropathy or polyneuropathy** Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to systemic vasculitis
4. Granulomatous inflammation on biopsy specimen Granulomatous inflammation within the wall of an artery or in the perivascular area	**4. Pulmonary infiltrates, nonfixed** Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates) attributable to systemic vasculitis
	5. Paranasal sinus abnormality History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
	6. Extravascular eosinophils Biopsy including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas

EPIDEMIOLOGY

These diseases are rare in childhood and the incidence increases with age, with the peak incidence occurring in persons between 65 and 74 years of age .

Granulomatosis with Polyangiitis

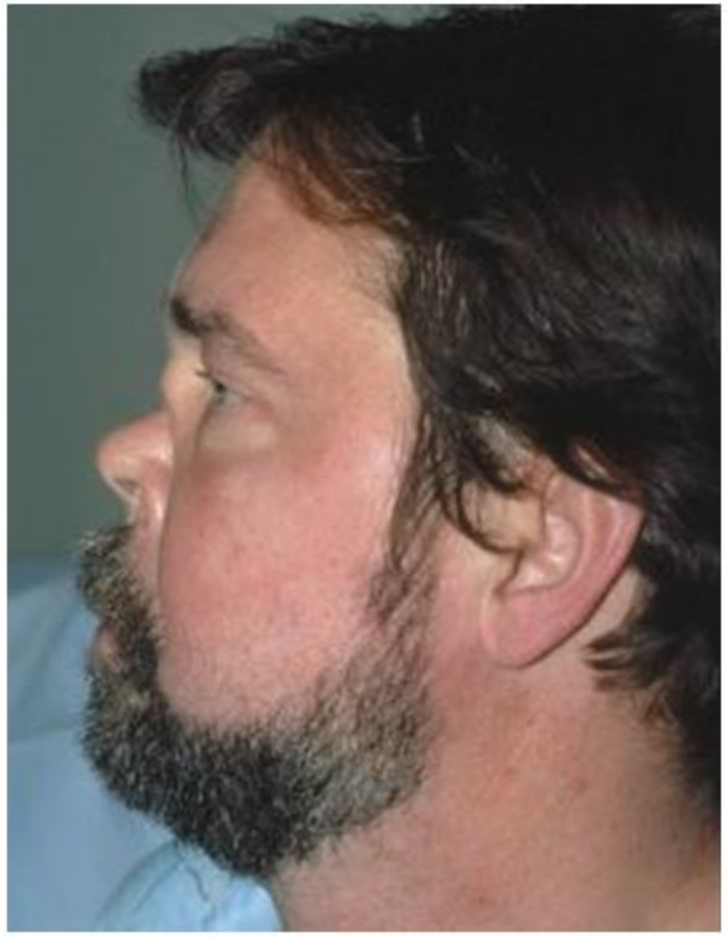
Is necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels (e.g., capillaries, venules, arterioles, arteries and veins)such as Necrotizing glomerulonephritis is common.

Constitutional symptoms and inflammation in the upper and/or lower airway may develop simultaneously with systemic vasculitis or may precede it by weeks, months, or years.

Inflammation in the upper airway is the most common initial symptom.

Frequent epistaxis and mucopurulent nasal discharge are common.

Inflammation of the paranasal sinuses causing pain is also common.
Ear congestion and conductive hearing loss can result from inflammation of the middle ear or the auditory tube or by obstruction of the tube at its entry into the nose.
Inflammation of the subglottic trachea occurs in approximately 15%, particularly in children and young adults.
Oral ulcers, gingivitis, and auricular chondritis are well-described but less frequent manifestations.



A is notable for its destructive potential, but permanent damage does not
e in its pace. The nasal septum is particularly at risk, and septal perforation can
teristic “saddle-nose” deformity

Saddle nose deformity in a patient with granulomatosis with polyangiitis.

Eye and orbital involvement
Conjunctivitis and episcleritis are the most common forms

Scleritis is usually painful, whereas conjunctivitis and episcleritis are not painful, but absence of pain does not rule out scleritis,
Retinal vasculitis, uveitis, oculomotor nerve palsy, and optic neuropathy are less common but well described

The lung is affected in several distinct ways, Pulmonary nodules, which are necrotizing and therefore frequently Cavitate, often occur prior to or in the absence of systemic vasculitis and thus are a common feature of "localized" or "limited" GPA.

Nodular disease is often asymptomatic or merely produces cough.

Alveolar hemorrhage, characterized by dyspnea and hemoptysis that can vary from mild to life-threatening

Musculoskeletal pain is common even in the early phases.

Monoarticular, oligoarticular, and polyarticular involvement are all seen.
Arthralgia is more common than inflammatory arthritis.

Myalgia also can occur

Cutaneous involvement in GPA includes the full range of presentations of cutaneous small-vessel vasculitis and, less commonly, vasculitis of small arteries.
Thus purpura, papules, vesicles/bullae, ulcers, digit ischemia, subcutaneous nodules, and livedo racemosa have all been reported.

Peripheral neuropathy can present either as a sensory polyneuropathy or a mononeuritis multiplex with both sensory and motor deficits

Glomerulonephritis (GN) is apparent in many patients at diagnosis and in more than half at some point during the course of disease.
On biopsy, the GN is characterized as pauci-immune and is frequently necrotizing and crescentic.

Cranial neuropathies are less frequent, with the exception of sensorineural hearing loss,
As with the CNS, patients with GPA will have cardiac problems and GI symptoms, but vasculitis of the heart muscle or the GI organs is very uncommon.

The classification criteria for GPA

1. Abnormal urinary sediment (red blood cell casts or >5 red blood cells/high-power field)
2. Abnormal findings on a chest radiograph (e.g.,nodules, cavities, or fixed infiltrates)
3. Oral ulcers or nasal discharge
4. Biopsy findings of granulomatous inflammation

The presence of two or more of these four criteria was associated with a sensitivity of 88.2% and a specificity of 92.0%.

Microscopic Polyangiitis

Necrotizing vasculitis with few or no immune deposits predominantly affecting small vessels (i.e., capillaries, venules, or arterioles).

Necrotizing arteritis involving small- and medium-sized arteries may be present.
Necrotizing glomerulonephritis is very common, Pulmonary capillaritis often occurs.

Granulomatous inflammation is absent.

GN is probably more common in MPA than in GPA, at least at diagnosis.

Cutaneous vasculitis, neuropathy, constitutional and musculoskeletal symptoms, and risk of alveolar hemorrhage are probably similar, Involvement of the eye is distinctly less common.
GI involvement and pulmonary fibrosis, CNS or myocardial vasculitis; subclinical myocardial abnormalities have been detected.

In addition to the constitutional symptoms.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

The hallmarks of EGPA are asthma and peripheral eosinophilia but other symptoms and findings are needed to make the diagnosis, as with MPA and GPA , constitutional and musculoskeletal symptoms are common.

Asthma itself is almost universal, often but not always severe, and highly variable in its onset relative to the onset of EGPA.
Upper airway involvement is common in EGPA, but in contrast to GPA, it is usually "allergic" in character and is seldom destructive.

GN and alveolar hemorrhage are uncommon and are highly associated with positive ANCA (usually anti-MPO) which is detected in only 35% to 40% of patients with EGPA overall

Skin involvement is at least as common in EGPA as in GPA but again includes “allergic” lesions such as urticaria, in addition to a wide range of presentations of cutaneous vasculitis.

clinically important cardiac involvement is clearly a greater risk in EGPA than in MPA or GPA, with about15% of patients having eosinophilic myocarditis severe enough to cause cardiomyopathy.

Neuropathy, is thought to be due to vasculitis rather than the neurotoxins of eosinophils, is more common in EGPA than in GPA or MPA.

A five-factor score (FFS) is used to classify EGPA patients according to the presence or absence of clinical manifestations associated with poor prognosis

(creatinine level of more than1.58 mg/dL [140 µmol/L], proteinuria of more than 1 g protein per day, cardiomyopathy, severe GI involvement, and CNS manifestations).
The presence of one or more of these features reflects severe disease and warrants aggressive treatment.

The classification criteria for EGPA .

1. Asthma
2. Eosinophilia greater than 10% on white blood cell count differential
3. Mononeuropathy (including multiplex) or polyneuropathy
4. Nonfixed pulmonary infiltrates on a chest radiograph
5. Paranasal sinus abnormality
6. A biopsy specimen containing a blood vessel with extravascular eosinophils

The presence of four or more of these six criteria was associated with a sensitivity of 85% and a specificity of 99.7%.3

Investigation

Non specific findings such as elevated WBC, platelets count or ESR .
CRP is typically raised
Liver or renal function may be abnormal
The presence of hyperesinophilia often more than 1500/cubic mm can suggest a diagnosis of EGPA , but rae there are other causes such as drug reactions .
Urine analysis for blood and protein in all patients with suspected vasculitis.

ANCA testing plays a major role in diagnosis, and positive results on ANCA assays are often helpful in suggesting the disease when presenting features are non specific.
the target antigen for the c-ANCA pattern was identified as PR3, and the antigen for the p-ANCA pattern was identified as MPO.
.

The majority of ANCAs directed against proteinase 3 in patients with GPA and against MPO in MPA although anti PR3 can be found.

ANCA antibodies are detected in 60% to 80% of patients with MPA
Anti MPO ANCAs are not specific for a diagnosis of MPA as anti PR3 ANCAs are for diagnosing GPA.

only 50% of patients with EGPA test positive for ANCA, usually anti-MPO.

GPA
Only 60% to 70% of patients with disease limited to the upper airway test positive for antibodies to PR3 or MPO(5%), in contrast to 90% or more with systemic vasculitis.

Some experts believe that a kidney biopsy should be performed whenever possible to confirm pauci-immune glomerulonephritis whereas other experts might argue that red blood cell casts in the urine in the setting of anti-PR3 or anti-MPO antibodies is sufficient.

Management for organ-threatening or acute–severe disease is with high-dose glucocorticoids (e.g. daily pulse intravenous methylprednisolone 0.5–1 g for 3 days, then oral prednisolone 0.5 mg/kg) and intravenous cyclophosphamide (e.g. 0.5–1 g every 2 weeks for 3 months), followed by maintenance therapy with lower-dose glucocorticoids and azathioprine, methotrexate or MMF.

Plasmapheresis should be considered for fulminant lung disease.

Rituximab in combination with high-dose glucocorticoids is equally effective as oral cyclophosphamide at inducing remission in AAV.

Glucocorticoids and methotrexate are an effective combination for treating limited AAV where there is indolent sinus, lung or skin disease.

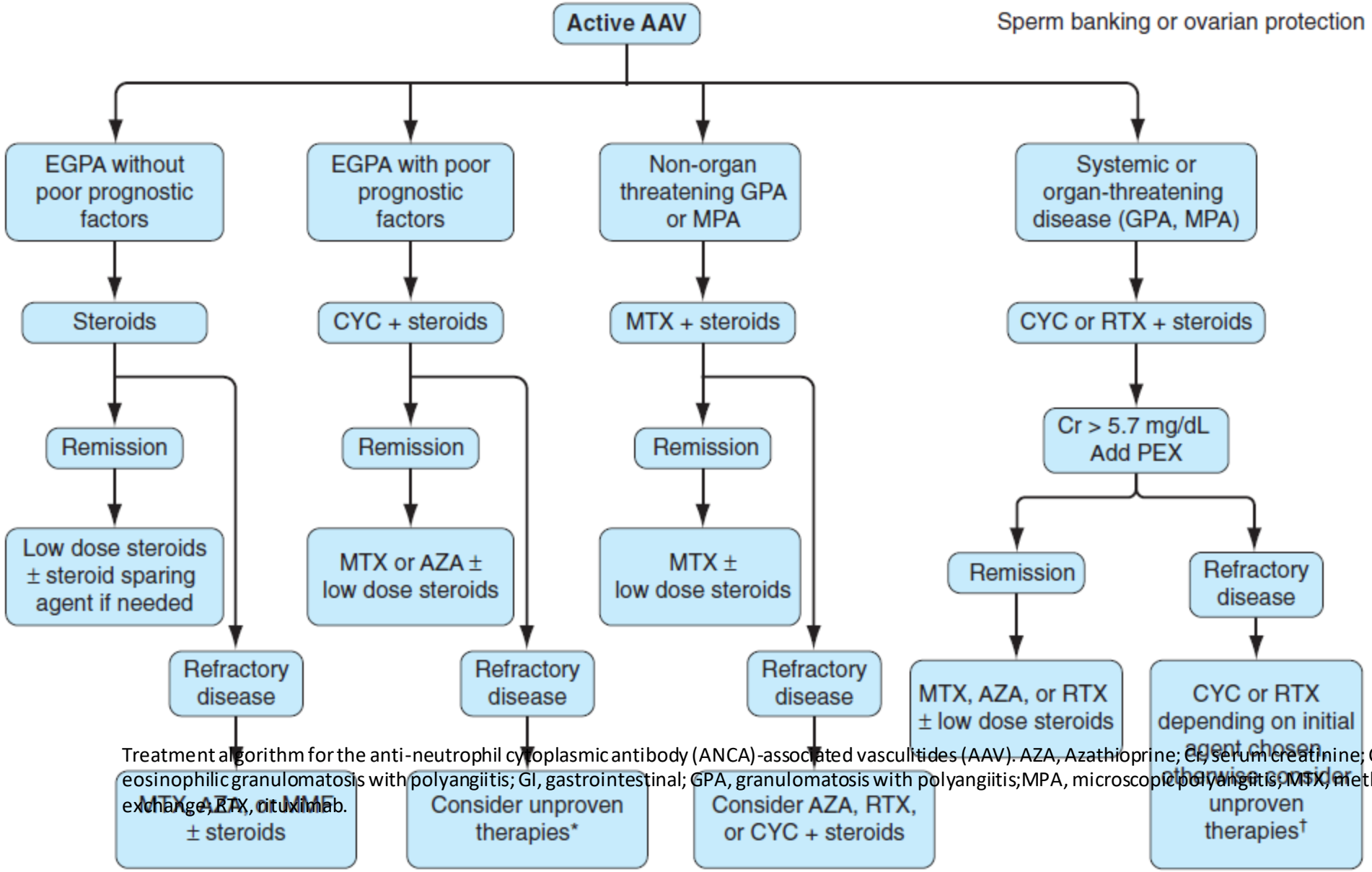
AAV has a tendency to relapse and patients must be followed on a regular and long-term basis, monitoring urinalysis for blood and protein, plasma creatinine, ESR, CRP, lung function and PR3 or MPO antibody titres .

For all patients, consider:

Pneumocystis jirovecii prophylaxis
Bone and GI protection

For patients on CYC, consider:

Sperm banking or ovarian protection



Treatment algorithm for the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). AZA, Azathioprine; Cr, serum creatinine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GI, gastrointestinal; GPA, granulomatosis with polyangiitis;MPA, microscopic polyangiitis; MTX, methotrexate; PEX, plasma exchange; RTX, rituximab.

Polyarteritis nodosa

Polyarteritis nodosa has a peak incidence between the ages of 40 and 50.

with a male-to-female ratio of 2 : 1.

Hepatitis B is an important risk factor

Presentation is with fever, myalgia, arthralgia and weight loss, in combination with manifestations of multisystem disease.
The most common skin lesions are palpable purpura , ulceration, infarction and livedo reticularis .

Pathological changes comprise necrotizing inflammation and vessel occlusion, and in 70% of patients arteritis of the vasa nervorum leads to neuropathy, which is typically symmetrical and affects both sensory and motor function.

Severe hypertension and/or renal impairment may occur due to multiple renal infarctions but glomerulonephritis is rare (in contrast to microscopic polyangiitis).

The diagnosis is confirmed by conventional or magnetic resonance angiography, which shows multiple aneurysms and smooth narrowing of mesenteric, hepatic or renal systems, or by muscle or sural nerve biopsy, which reveals the histological changes described above.

Treatment is with high-dose glucocorticoids and immunosuppressants.

Bechet's disease

This is a vasculitic multisystem inflammatory disorder characterized by relapsing oral and genital ulcers and bilateral posterior or pan uveitis as cardinal features.
Vasculitis of Bechet's disease involve all types and sizes of vessels

The venous side is more frequently involved with a thrombotic tendency, and arterial involvement usually results in pseudoaneurysms in pulmonary and less frequently in other arteries

It is rare in Western Europe but more common in ‘Silk Route’ countries, around the Mediterranean and in Japan, where there is a strong association with HLA-B51.

Oral ulcers are universal , unlike aphthous ulcers, they are usually deep and multiple, and last for 10–30 days.
Genital ulcers are also a common problem, occurring in 60–80% of cases.
The usual skin lesions are erythema nodosum or acneiform lesions but migratory thrombophlebitis and vasculitis also occur.

Ocular involvement is common and may include anterior or posterior uveitis or retinal vasculitis.

Neurological involvement occurs in 5% and mainly involves the brainstem, although the meninges, hemispheres and cord can also be affected, causing pyramidal signs, cranial nerve lesions, brainstem symptoms or hemiparesis.
Recurrent thromboses also occur.
Renal involvement is extremely rare.

The diagnosis is primarily made on clinical grounds but one characteristic feature that can be of diagnostic value is the pathergy test, which involves pricking the skin with a needle and looking for evidence of pustule development within 48 hours.

Criteria for the diagnosis of Bechet's disease

Recurrent oral ulceration: minor aphthous, major aphthous or herpetiform ulceration at least three times in 12 months plus two of the following:

- Recurrent genital ulceration
- Eye lesions: anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, retinal vasculitis
- Skin lesions: erythema nodosum, pseudo folliculitis, papulopustular lesions, acneiform nodules
- Positive pathergy test.

Treatment

Oral ulceration can be managed with topical glucocorticoid preparations (soluble prednisolone mouthwashes, glucocorticoid pastes).
Colchicine can be effective for erythema nodosum and arthralgia.
Thalidomide (100–300 mg per day for 28 days initially) is very effective for resistant oral and genital ulceration but is teratogenic and neurotoxic.
Glucocorticoids and immunosuppressants are indicated for uveitis and neurological disease

THANK YOU