NOTES
INFLAMMATORY CONNECTIVE TISSUE DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Chronic autoimmune disorders characterized by inflammation; primarily affect connective tissue
- Production of autoantibodies → deposition of immune complexes → complement activation → tissue destruction
- Inflammatory cytokines stimulate fibroblasts → increased collagen deposition (fibrosis)
- Affects multiple organ systems
  - Skin, heart, respiratory system, urinary, gastrointestinal (GI) tract

CAUSES

- Genetic, environmental factors

COMPLICATIONS

- Skin necrosis; renal, cardiac failure; pulmonary insufficiency; GI reflux/bleeding

SIGNS & SYMPTOMS

- Constitutional symptoms
  - Low grade fever, fatigue, weight loss
- Specific to disease, organ systems affected
  - "Butterfly skin rash" specific to systemic lupus erythematosus (SLE)

DIAGNOSIS

DIAGNOSTIC IMAGING

Barium swallow X-ray

- GI involvement

LAB RESULTS

- Blood tests
  - Hematologic abnormalities, increased inflammatory markers, complications (e.g. increased creatinine reflecting renal failure)
- Serological tests
  - Antibodies, confirm diagnosis

OTHER DIAGNOSTICS

- Physical examination (e.g. characteristic skin rashes)
- Pulmonary function tests
  - Pulmonary involvement

TREATMENT

- Usually symptomatic (e.g. analgesics)

MEDICATIONS

- Steroids/other immunosuppressive agents
  - Reduce inflammation

CREST SYNDROME

osms.it/CREST-syndrome

PATHOLOGY & CAUSES

- Form of limited systemic sclerosis
- Composed of five features; see mnemonic
  - *Calcinosis:* deposition of calcium under skin
  - *Raynaud's syndrome:* episodic, dramatic constriction of arteries in hands
  - *Esophageal dysmotility:* atrophied muscle in esophagus without significant inflammation/fibrosis
  - *Sclerodactyly:* fibrosis of skin of digits
  - *Telangiectasia:* dilation of small blood vessels
- Caused by chronic autoimmune inflammation triggered mainly by anticentromere antibodies (ACAs)
- More benign clinical course than other forms of sclerosis

MNEMONIC: CREST

Features of CREST syndrome

Calcinosis
Raynaud's syndrome
Esophageal dysmotility
Sclerodactyly
Telangiectasia

COMPLICATIONS

- Ischemic ulcers, gangrene, predisposition to chronic skin infections (due to sclerosis, severe ischemia of skin)
- Upper GI bleeding (due to mucosal telangiectasias)

SIGNS & SYMPTOMS

- Calcific nodules under the skin
- White-blue-red transitions in skin color in response to triggers (e.g. low temperature, stress)
- Dysphagia (due to esophageal dysmotility)
- Sclerodactyly
- Telangiectasias (esp. hands, face)

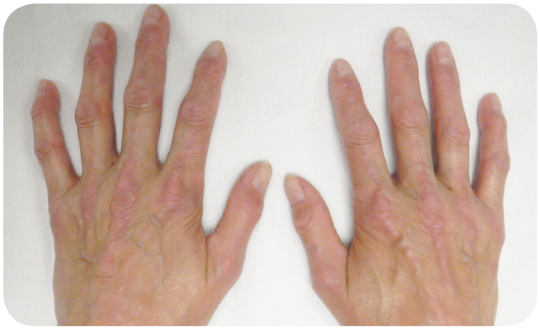

Figure 112.1 Sclerodactyly in an individual with CREST syndrome.

DIAGNOSIS

LAB RESULTS

- Serum blood tests
  - ↑ ANAs: sensitive for systemic sclerosis
  - ↑ ACAs: highly specific (limited systemic sclerosis); confirm diagnosis

OTHER DIAGNOSTICS

- Clinical history, physical examination

TREATMENT

MEDICATIONS

- Steroids
- If sclerosis progresses, stronger immunosuppressants (e.g. cyclosporine)

FIBROMYALGIA

osms.it/fibromyalgia

PATHOLOGY & CAUSES

- Chronic condition of central sensitization; hypersensitivity to pain, sleep disturbances
  - ↓ serotonin (inhibits pain signals)
  - ↑ substance P, ↑ nerve growth factor (involved in propagating pain signals)
  - Predominance in individuals who are biologically female

CAUSES

- Genetic factors
- Environmental factors (child abuse)
- Negative emotions (depression, anxiety, negative beliefs) can amplify pain

SIGNS & SYMPTOMS

- Low threshold to pain
- Widespread muscle pain
- Extreme tenderness in various parts of body
- Sleep disturbances → fatigue, headache
- Difficulty concentrating, remembering things; AKA "fibro fog"

DIAGNOSIS

OTHER DIAGNOSTICS

Diagnostic Criteria

- Pain in ≥ seven areas of body with symptom severity (SS) of ≥ 5 (of 12)/pain in ≥ five areas of body with SS of ≥ 9 (of 12)
- Final score between 0–12
- Symptoms present ≥ three months
- Pain not due to another disorder

Symptom severity (SS) measures

- Fatigue; waking unrefreshed; cognitive symptoms; somatic symptoms
  - *0:* no problem
  - *1:* slight/mild/intermittent
  - *2:* moderate/considerable/often present
  - *3:* severe, continuous, life disturbing

TREATMENT

MEDICATIONS

- If non-pharmacologic measures fail, drug therapy
- Antidepressants
  - Inhibit pain by elevating levels of serotonin, norepinephrine
  - *Tricyclic antidepressants (TCAs):* amitriptyline first line treatment
  - *Serotonin-norepinephrine reuptake inhibitors (SNRIs):* milnacipran
- Anticonvulsants
  - Slow nerve impulses, relieve sleep disturbances

PSYCHOTHERAPY

- Cognitive behavioral therapy (CBT)
  - Manage pain, change negative feelings

OTHER INTERVENTIONS

- Physical therapy, relaxation techniques, sleep hygiene to reduce pain, fatigue

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

osms.it/mixed-connective-tissue-disease

PATHOLOGY & CAUSES

- Overlap autoimmune syndrome; constellation of SLE, systemic sclerosis, polymyositis; may not occur simultaneously
- Can evolve into classic SLE/systemic sclerosis

COMPLICATIONS

- Pulmonary hypertension; interstitial lung disease; renal disease

SIGNS & SYMPTOMS

- Arthralgias (due to polyarthritis)
- Myalgias (due to mild myositis)
- Swollen hands with puffy fingers (due to synovitis)
- Sclerodactyly
- Early development of Raynaud phenomenon
- Fatigue
- Low-grade fevers

DIAGNOSIS

- Confirmation requires characteristic clinical presentation

LAB RESULTS

- High serum levels of anti-U1 ribonucleoprotein (anti-U1-RNP) antibodies
- High ANAs, RF, anti dsDNA, anti Sm, anti Ro

TREATMENT

- Depends on predominant autoimmune disease

MEDICATIONS

- Corticosteroids
  - Suppress immune system

POLYMYALGIA RHEUMATICA (PMR)

osms.it/polymyalgia-rheumatica

PATHOLOGY & CAUSES

- Immune-mediated rheumatic condition affecting joints, sparing muscles
- Most commonly affects shoulder, hip joints
- Usually occurs in individuals who are biologically female > 50; mean age 70
- Strongly associated with giant-cell arteritis, AKA temporal arteritis
- Can regress without treatment after 1–2 years/remain chronic

CAUSES

- *Genetic defects:* specific allele of human leukocyte antigen (HLA)-DR4
- *Environmental factors:* exposure to adenovirus/human parvovirus B19

SIGNS & SYMPTOMS

- Joint pain, stiffness (shoulder, hip joints)
  - Often starts unilaterally, progresses to bilateral within few weeks
  - More severe after prolonged inactivity (e.g. morning)
  - Typically lasts > one hour
  - Affects nearby nerves in muscle → muscle pain (referred pain)
- Constitutional symptoms
  - Low grade fever (interleukins act as pyrogens)
  - Fatigue
  - Loss of appetite → weight loss
- If severe headache, jaw pain, vision problems
  - Temporal arteritis

DIAGNOSIS

LAB RESULTS

- Increased serum inflammatory markers
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
- Biopsy
  - Inflammation in joints

OTHER DIAGNOSTICS

- Physical examination
  - Decreased passive range of motion of affected joints

TREATMENT

MEDICATIONS

- Low dose of corticosteroids
  - Suppress immune response

RAYNAUD'S DISEASE

osms.it/raynauds-disease

PATHOLOGY & CAUSES

- Vasospasm of skin arteries in response to triggers, resulting in skin color transitions
- Exposure to trigger → stimulation of sympathetic nerves in arteriole walls → vasospasm of arterioles → decrease in blood flow
- Usually affects hands, fingers, toes; can affect nose, ears, lips
- Common triggers
  - Emotional stress; low temperatures; nicotine; caffeine; medications that affect sympathetic nervous system (e.g. pseudoephedrine)

TYPES

Primary: Raynaud phenomenon/disease

- Common in pregnant individuals, people who work in jobs involving vibration (e.g. jackhammer)

Secondary: Raynaud syndrome

- Connective tissue disorders
  - Systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease
- Disorders affecting blood vessels
  - Buerger's disease, Takayasu's arteritis, thromboangiitis obliterans
- Medications
  - Beta blockers, nicotine

COMPLICATIONS

- Ulceration, infarction, tissue necrosis, gangrene (if severe)

SIGNS & SYMPTOMS

- Vasospasm → changes in skin color of hands, fingers, toes
  - *White:* ischemia
  - *Blue:* hypoxia after prolonged ischemia
  - *Red:* reactive hyperemia (vasospasm ends, oxygenated blood rushes into tissue)
- Raynaud phenomenon
  - Affects hand fingers, toes symmetrically; severity remains constant
- Raynaud syndrome
  - Asymmetrical; progressive severity
- Swelling, numbness, tingling, pain (due to reactive hyperemia)

DIAGNOSIS

- Based upon description of episodes

DIAGNOSTIC IMAGING

- Nailfold capillary microscopy to examine finger capillaries
  - *Normal appearance:* Raynaud phenomenon
  - *Damaged appearance:* Raynaud syndrome

TREATMENT

MEDICATIONS

- Vasodilators (e.g. calcium channel blockers)

SURGERY

- If severe, surgery to cut sympathetic nerve fibers supplying affected areas

OTHER INTERVENTIONS

- Avoid triggers

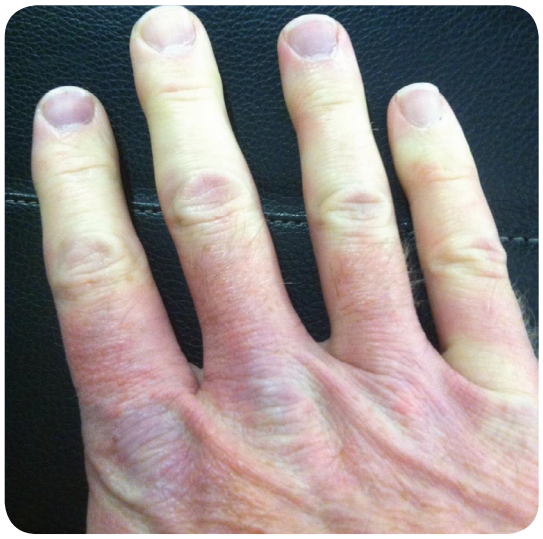

Figure 112.2 A hand with pale fingers caused by Raynaud's disease.

SCLERODERMA

osms.it/scleroderma

PATHOLOGY & CAUSES

- AKA systemic sclerosis
- Chronic inflammatory autoimmune disease, can result in widespread damage to small blood vessels, excessive fibrosis
  - T helper cells activated by unknown antigen → release cytokines → stimulate inflammatory cells, fibroblasts → chronic inflammation, excessive collagen deposition
  - Mediators released by inflammatory cells → damage microvasculature → ischemic injuries, scarring
- Primarily affects skin, can involve visceral organs
  - GI tract, kidneys, heart, muscles, lungs

TYPES

Limited (80%)

- Skin involvement limited to fingers, forearms, face
- Late visceral involvement
- Some individuals develop CREST syndrome
  - Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia
- Associated with anticentromere antibodies
- Relatively benign

Diffuse (20%)

- Widespread skin involvement
- Early visceral involvement
- Rapid progression
- Associated with anti-DNA topoisomerase I antibodies
- Poor prognosis

RISK FACTORS

- More common in individuals who are biologically female (3:1 ratio)
- Average age of onset: 35–50
- Genetic factors
- Environmental factors (e.g. viruses, toxins, drugs)

COMPLICATIONS

- Excessive skin fibrosis → painful ulcers, disfigurement, disability
- Severe internal organ involvement → renal, cardiac failure; pulmonary insufficiency; intestinal malabsorption

SIGNS & SYMPTOMS

- Raynaud phenomenon
  - Precedes other symptoms, present in almost all individuals
- Cutaneous changes of face, extremities
  - Skin thickening, tightening, sclerosis (most common); edema, erythema (precede sclerosis)
- GI involvement
  - Esophageal fibrosis → dysphagia, GI reflux
  - Small intestine involvement → abdominal pain, obstructions, constipation, diarrhea, malabsorption syndrome (weight loss, anemia)
- Pulmonary involvement with interstitial fibrosis
  - Right-sided cardiac dysfunction/ pulmonary hypertension
- Cardiac involvement
  - Pericardial effusions, myocardial fibrosis → congestive heart failure, arrhythmias
- Renal involvement (diffuse disease) → fatal hypertensive crisis (rare)

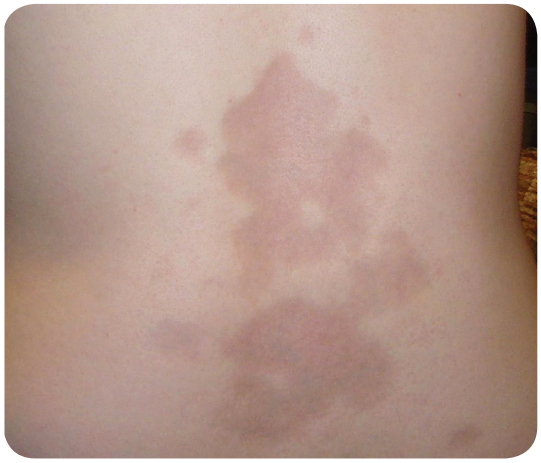

Figure 112.4 A rash on the back of an individual with a form of localised scleroderma known as morphea.

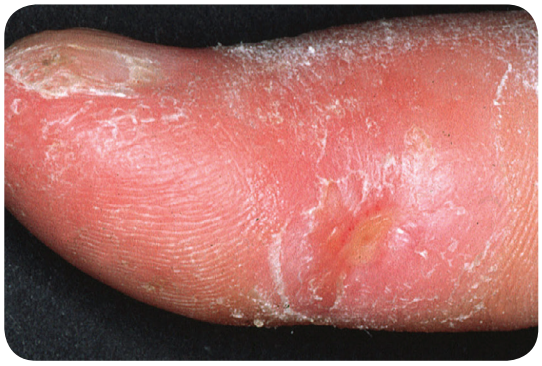

Figure 112.3 The finger of an individual with systemic sclerosis showing sclerosis, erythema and ulcer formation.

DIAGNOSIS

DIAGNOSTIC IMAGING

- Upper endoscopy
  - Esophageal fibrosis/reflux esophagitis

LAB RESULTS

- Serologic tests
  - ↑ ANAs in almost all individuals with systemic sclerosis; low specificity
  - ↑ ACAs highly specific (limited)
  - Anti-topoisomerase I antibodies (anti-Scl-70) highly specific (diffuse)
- Complete blood count (CBC)
  - Anemia due to malabsorption, increased serum creatinine due to renal dysfunction

OTHER DIAGNOSTICS

- Clinical presentation
  - Skin thickening, swollen fingers, Raynaud's phenomenon, GI reflux
- Pulmonary function tests
  - Restrictive ventilatory defect due to pulmonary interstitial fibrosis

TREATMENT

- Depends on disease subset, severity of internal organ involvement

MEDICATIONS

- Usually symptomatic
  - Analgesics for musculoskeletal pain
  - Proton pump inhibitors for gastroesophageal reflux
  - Calcium channel blockers for Raynaud's phenomenon
  - Angiotensin converting enzyme (ACE) inhibitors for renal hypertensive crisis
- *Immunosuppressive therapy initiation:* diffuse skin/severe internal organ involvement

SJOGREN'S SYNDROME (SS)

osms.it/sjogrens-syndrome

PATHOLOGY & CAUSES

- Chronic autoimmune inflammatory disease; lymphocytic infiltration, destruction of exocrine glands of eyes, mouth
- Proposed mechanisms
  - Immune reactions against antigens of viral infection of exocrine glands
  - Autoimmune T cell reaction against unknown self antigen expressed in salivary, lacrimal glands
- Variety of extraglandular manifestations may occur
- Usually occurs in individuals who are biologically female, 50–60 years

CAUSES

- *Primary:* sicca syndrome
- *Secondary* (to other autoimmune diseases)*:* rheumatoid arthritis (most common)

COMPLICATIONS

- Periodontal complications; oral infections; mucosal associated lymphoid tissue (MALT) lymphoma

SIGNS & SYMPTOMS

- Dry eyes
  - Irritation, itching, foreign body sensation, keratoconjunctivitis
- Oral dryness reflecting salivary hypofunction
- Salivary gland enlargement (parotid, submandibular, etc.)
- Extraglandular manifestations
  - Musculoskeletal symptoms (arthralgias, arthritis); rashes; interstitial nephritis, vasculitis

DIAGNOSIS

- *Clinical presentation:* persistent dry eyes/mouth, parotid gland enlargement

DIAGNOSTIC IMAGING

Parotid gland MRI

- Honeycomb pattern

Salivary gland ultrasound

- Multiple hypoechoic areas

LAB RESULTS

- CBC
  - Leukopenia, thrombocytopenia, anemia
- ↑ ESR
- Urinalysis

- Proteinuria/hematuria reflecting glomerulonephritis
- Labial salivary gland biopsy (confirm diagnosis)
  - Focal lymphocyte foci (collections of tightly aggregated lymphocytes)
- Serologic tests (support diagnosis)
  - ↑ antinuclear antibodies (ANAs) in 95% of individuals
  - ↑ rheumatoid factor (RF) in 50–75% of individuals with/without rheumatoid arthritis
  - Anti-Sjögren syndrome A (SSA) (Ro), Anti-Sjögren syndrome B (SSB) (La) specific to SS, found elevated only in 55%, 40% of individuals, respectively

OTHER DIAGNOSTICS

Tear deficiency tests

- Schirmer test
  - Measures reflex tear production; wetting of test paper < 5mm indicative of tear deficiency
  - Ocular surface staining with Rose Bengal stain and slit-lamp examination—assess tear break-up time (TBUT); TBUT < 10 seconds indicative of tear deficiency
- Salivary gland tests
  - *Salivary gland scintigraphy:* low uptake of radionuclide characteristic of SS
  - *Sialometry:* low volume of saliva indicative of salivary gland hypofunction

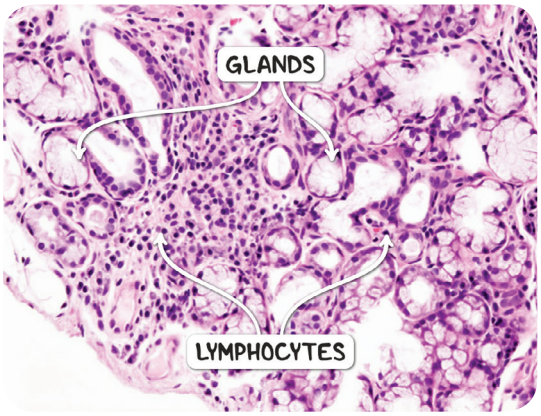

Figure 112.5 A lymphocytic infiltrate in a minor salivary gland excised from an individual with Sjögren's syndrome.

TREATMENT

MEDICATIONS

- Mild SS
  - Secretagogues
  - Local treatment for ocular, oral dryness (e.g. artificial tears)
- Moderate to severe SS
  - Immunosuppressive treatment

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

osms.it/systemic-lupus-erythematosus

PATHOLOGY & CAUSES

- Chronic systemic autoimmune disorder; wide range of clinical, serological features
- Periods of flare-ups, remittance
- Environmental triggers damage DNA → apoptosis → release of nuclear bodies
- Clearance of apoptotic bodies ineffective due to genetic defects → increased amount of nuclear antigens in bloodstream → initiates immune response → production of antinuclear antibodies → bind to antigens, form immune complexes
- Complexes deposit in tissues (e.g. kidneys, skin, joints, heart) → Type III hypersensitivity reaction
- Individuals may develop antibodies targeting molecules (e.g., phospholipids) of red, white blood cells → marking them for phagocytosis → Type II hypersensitivity reaction

RISK FACTORS

- Genetic defects associated with SLE
- UV radiation
- Smoking
- Viral, bacterial infections
- Medications (e.g. procainamide, hydralazine, isoniazid, estrogens)
- More common in individuals who are biologically female, of reproductive age

COMPLICATIONS

- Cardiovascular disease
  - Libman–Sacks endocarditis, myocardial infarction (MI)
- Serious infections; renal failure; hypertension
- Antiphospholipid syndrome
  - Hypercoagulable state; individuals prone to develop clots (e.g. deep vein thrombosis, hepatic vein thrombosis, stroke)

SIGNS & SYMPTOMS

- Fever, joint pain, rash in sun-exposed areas
- Typical rashes
  - *Malar rash (butterfly rash):* over cheeks
  - *Discoid rash:* plaque-like/patchy redness, can scar
  - *General photosensitivity:* typically lasts few days

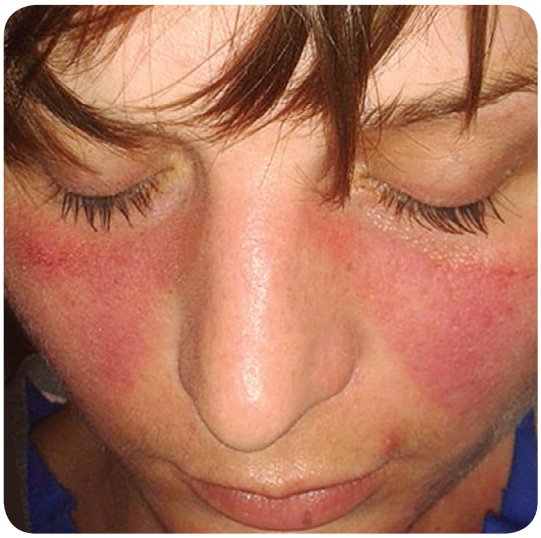

Figure 112.6 A butterfly rash on the face of an individual with systemic lupus erythematosus.

- Weight loss
- Ulcers in oral/nasal mucosa
- Serositis (e.g. pleuritis/pericarditis)
- Libman–Sacks endocarditis: formation of nonbacterial vegetations on ventricular, atrial valve surfaces; mitral, aortic valves (most common)
- Myocarditis
- Renal disorders
  - Abnormal levels of urine protein, diffuse proliferative glomerulonephritis
- Neurologic disorders
  - Seizures, psychosis
- Hematologic disorders
  - Anemia, thrombocytopenia, leukopenia

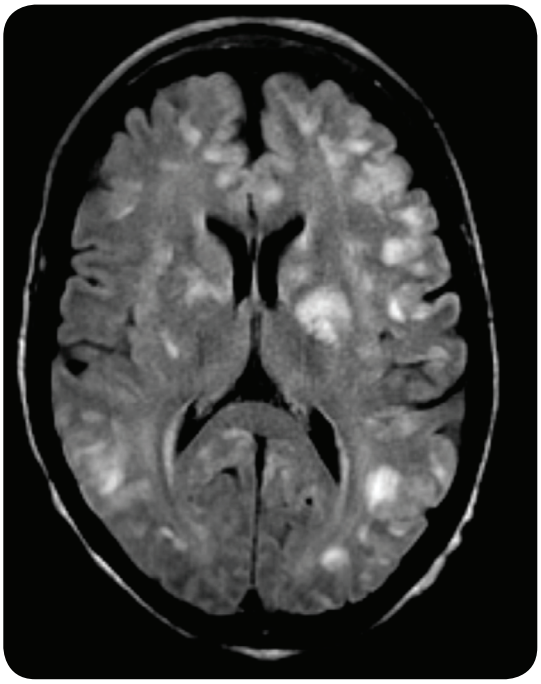

Figure 112.7 An MRI scan of the head of an individual with SLE who presented with altered mental status and seizures. There a numerous small infarcts suggestive of cerebral vasculitis. The individual improved after treatment with steroids.

DIAGNOSIS

OTHER DIAGNOSTICS

Diagnostic criteria (4 of 11)

- Malar rash
- Discoid rash
- General photosensitivity
- Oral/nasal ulcers
- Serositis
- Arthritis in ≥ two joints
- Renal disorders
- Neurologic disorders
- Hematologic disorders
- Antinuclear antibodies
  - Very sensitive, not specific
- Other antibodies
  - *SLE specific:* anti-Smith, anti-dsDNA
  - *Anti-phospholipid:* anticardiolipin (false-positive test for syphilis); lupus anticoagulant (lupus antibody); anti-beta 2 glycoprotein I

TREATMENT

- *Goal:* prevent relapses, limit severity

MEDICATIONS

- Long term therapy
  - Antimalarial agents
- Mild to moderate manifestations
  - Non-steroidal anti-inflammatory drugs (NSAIDs), low doses of corticosteroids
- Severe/life-threatening manifestations
  - High doses of corticosteroids, intensive immunosuppressive drugs

OTHER INTERVENTIONS

- Avoid sun exposure
- Physical exercise
- Balanced diet
- Smoking cessation
- Immunizations

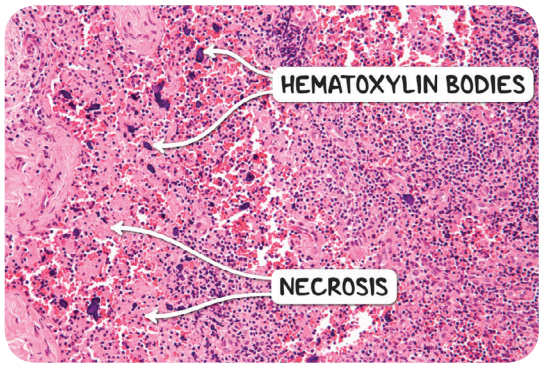

Figure 112.8 A histological section of a lymph node from an individual with lupus lymphadenopathy. There is necrosis, with an absence of neutrophils, and large numbers of hematoxylin bodies.

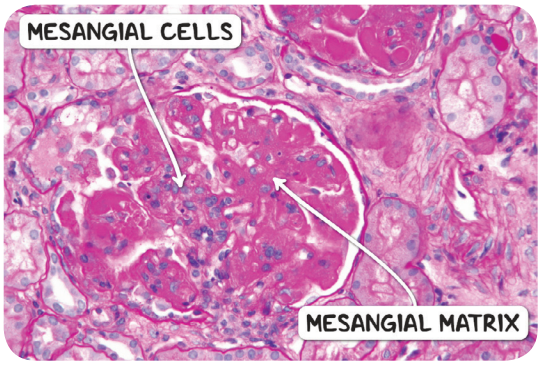

Figure 112.9 Histological appearance of the glomerulus in a case of lupus nephritis. There is global mesangial cell proliferation and abundant mesangial matrix.