RHEUMATOLOGY

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CHAPTER 10

The wolf, I'm afraid, is inside tearing up the place.

Flannery O'Connor (1925–1964)
Novelist afflicted with systemic lupus erythematosus (letter)

1. Give an operational definition of rheumatic diseases.

Syndromes of pain or inflammation or both in articular or periarticular tissues.

2. How common are the rheumatic diseases?

Fairly common. Forty-six million (22%) adults have self-reported doctor-diagnosed arthritis according to data from the National Health Interview Survey (2003–2005). By the year 2030, 67 million (25%) adults will have doctor-diagnosed arthritis. Overall, 2% of the general population has an inflammatory arthritis, and half of those have rheumatoid arthritis (RA).

Centers for Disease Control and Prevention: *Arthritis*. Available at: http://www.cdc.gov/arthritis.

SIGNS AND SYMPTOMS

3. What are key points in assessing a rheumatic history?

- Pain location
- Symmetry of symptoms
- Presence of morning stiffness
- Effect of exercise
- Additional constitutional symptoms (fatigue, low-grade fever, and weight loss)
- Daily function
- Family history (such as positive human leukocyte antigen [HLA]-B27 in ankylosing spondylitis)

4. What is the "squeeze test"?

A physical examination maneuver that assesses the possible presence of inflammatory arthritis. The metacarpophalangeal (MCP) squeeze test is performed by squeezing all four MCPs together to elicit tenderness. The metatarsophalangeal (MTP) squeeze test elicits tenderness across the four MTP joints.

5. What is Finkelstein's test?

A maneuver to demonstrate de Quervain's tenosynovitis in which a fist is made around the thumb and the wrist is moved toward the ulnar side. In a positive test, a sharp pain is felt at the base of the thumb.

6. Define "Tinel's sign."

The sensation of focal pain and electrical sensations occurring when a nerve is tapped at the site of entrapment.

7. How do you elicit Phalen's sign?

Ask the patient to:

- Raise both arms to shoulder level.
- Press the back (dorsum) of the hands together.
- Slightly drop the elbows, causing maximal flexion of the wrist, and maintain for 30–60 seconds.

If the patient has carpal tunnel syndrome (CTS), the discomfort will be reproduced.

8. What does the Schober test detect?

Limited forward flexion of the lumbar spine. Schober's test is useful in the diagnosis of the spondyloarthropathies. Two points on the patient's lumbar spine (usually the lumbar sacral junction and a point 10 cm above) are marked while the patient is standing. The distance is remeasured after the patient bends to touch the toes (maximal forward flexion). An elongation < 5 cm suggests spine stiffness.

9. Straight leg raising (SLR) is a useful diagnostic maneuver in what common condition?

Back pain. If the pain is due to nerve root compression, the symptoms are reproduced with SLR. To perform the maneuver, lift the lower leg by the calcaneus with the knee remaining straight. The cross-table SLR test additionally brings the heel across the other leg and may increase the sensitivity of this maneuver.

10. What distinguishes Bouchard's nodes and Heberden's nodes?

The location of the bony enlargement. Bouchard's nodes involve the proximal interphalangeal (PIP) joints; Heberden's nodes, the distal interphalangeal (DIP) joints. Both are associated with osteoarthritis (OA) and women are affected more frequently than men in a 10:1 ratio. Heredity plays a particularly strong role in mothers, daughters, and sisters.

11. What is Jaccoud's deformity?

Deformities of the hands secondary to chronic inflammation of the joint capsule, ligaments, and tendons. The changes may mimic those of RA such as ulnar deviation of the fingers and MCP joint subluxation. Erosions are not present on x-ray, although after several recurrences, notches may be seen radiographically on the ulnar side of the metacarpal heads. Although originally described in rheumatic fever, this disorder has been extended to include the arthropathy of other conditions, most commonly systemic lupus erythematosus (SLE).

12. Name dermatologic findings associated with some rheumatic diseases.

See Table 10-1.

13. Which rheumatic syndromes have been associated with uveitis?

- Ankylosing spondylitis
- Juvenile idiopathic arthritis
- Reactive arthritis
- Sjögren's syndrome
- Psoriasis
- Sarcoidosis
- Inflammatory bowel disease
- Behçet's disease (BD)
- Kawasaki disease (KD)
- Relapsing polychondritis

TABLE 10-1. DERMATOLOGIC FINDINGS IN RHEUMATIC DISEASES

Dermatologic Finding	Description	Disease
Malar rash	Butterfly appearance on face which spares the nasolabial folds	Systemic lupus erythematosus
Palpable purpura	Slightly elevated purpuric rash over one or more areas of the skin	Vasculitis
Erythema nodosum	Reddish/violet subcutaneous nodules that tends to develop in a pretibial location	Sarcoidosis, inflammatory bowel disease, tuberculosis, streptococcal infection
Keratoderma blennorrhagicum	Hyperkeratotic skin lesions on soles and palms	Reactive arthritis
Heliotrope rash	Violaceous eruption on the upper eyelids	Dermatomyositis
Gottron's papules	Erythematous rash extensor on the regions of MCP and IP joints	Dermatomyositis
Erythema chronicum migrans	Reddish, central clearing known as a "target lesion"	Lyme disease
Morphea	Small area(s) of skin fibrosis	Systemic sclerosis
Linear scleroderma	Band-like lesion which may expand across dermatomes	Systemic sclerosis
"En coup de sabre"	Specific curvilinear band that resembles a dueling scar that occurs across the face	Systemic sclerosis

IP = interphalangeal; MCP = metacarpophalangeal.

14. Describe Raynaud's phenomenon.

The presence of color changes (usually white, blue, then red) in the hands (or any distal part of the body) incited by exposure to cold or intense emotion. Raynaud's phenomenon may present without the classic triphasic color response. When one inquires about Raynaud's, it is sometimes difficult not to suggest a positive answer. Preferably, one should ask, "While grocery shopping, do you notice any problems in the frozen food section?" or "If you look at your hands when you get cold, do they look any different to you?"

15. Distinguish between primary and secondary Raynaud's phenomenon.

Primary Raynaud's phenomenon or *Raynaud's disease* occurs without association with another condition. Raynaud's occurring in association with another condition is usually termed *Raynaud's syndrome* or *secondary Raynaud's phenomenon.* The primary/secondary designation seems much easier to remember.

16. Which rheumatic conditions are typically associated with Raynaud's phenomenon?

Systemic lupus erythematosus (SLE)
Antiphospholipid antibody (APA) syndrome
CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome
Drug-induced lupus
Reflex sympathetic dystrophy
Systemic sclerosis
Idiopathic Raynaud's phenomenon
Carcinoid syndrome
Connective tissue disease
Polymyositis
Sjögren's syndrome
Cold agglutinin disease
Cryoglobulinemia
Systemic vasculopathies
Cholesterol emboli
Drug-induced (especially beta blockers)

17. What factors predict the development of a systemic autoimmune disease in a patient presenting with Raynaud's phenomenon?

Positive antinuclear antibodies (ANAs) (positive predictive value 30%), abnormal nail bed capillaries (positive predictive value 47%), or abnormal pulmonary function studies. One study showed that 12.6% of patients presenting with Raynaud's phenomenon went on to develop a rheumatic disease.

Spencer-Green G: Outcomes in primary Raynaud's phenomenon: With meta-analysis of frequency rates and predictions of transformation to secondary diseases, *Arch Intern Med* 158:595–600, 1998.

18. What is erythromelalgia?

Intense burning pain, pronounced erythema, and increased skin temperature often in response to mild thermal stimuli or exercise. Erythromelalgia is often thought of as the opposite to Raynaud's phenomenon. The condition is believed to arise from vasomotor abnormalities resulting in abnormal blood flow to the extremities.

LABORATORY AND RADIOGRAPHIC EVALUATION

19. When is an arthrocentesis (joint aspiration) indicated?

When joint infection is suspected. Synovial fluid analysis on patients with a mono- or polyarticular arthropathy of unclear etiology may be helpful in determining the etiology.

20. Which studies should generally be performed on synovial fluid after arthrocentesis?

- Gram stain and bacterial culture
- Total leukocyte count and differential
- Crystal evaluation by polarized light microscopy
- Culture for mycobacteria or fungi, if suspected

21. What are rice bodies?

Aggregates of fibrin frequently found in the synovial fluid of patients with RA.

22. What is the erythrocyte sedimentation rate (ESR)?

A measurement of the distance in millimeters that red blood cells travel in a Westergen or Wintrobe tube over 1 hour that is an indirect measurement of acute-phase reactants in systemic inflammation.

23. Describe the clinical utility of C-reactive protein (CRP).

To monitor disease progression and therapy response in inflammatory conditions. CRP is an acute-phase reactant protein that is synthesized in response to tissue injury. CRP rises within 4–6 hours with a peak in 24–72 hours and normalization within 1 week.

24. What are rheumatoid factors (RFs)?

Antibodies directed at the Fc portion of the immunoglobulin G (IgG) molecule. Although IgM RFs are the most common, all immunoglobulin isotypes have been reported. IgG RFs are associated with a greater likelihood of vasculitis.

25. Which conditions are associated with circulating RFs?

- Hepatitis C, occurring in 70% of patients with active disease. Because chronic hepatitis can also produce achiness and occasionally a mild synovitis, hepatitis C should be excluded before establishing a diagnosis of RA, even if serum transaminase levels are normal.
- Bacterial endocarditis
- Viral infections (parvovirus B19)
- Sarcoidosis
- Primary biliary cirrhosis
- SLE

26. Do all patients with RA have circulating RF?

No. RF may be detectable in 50% of RA patients in the first 6 months of diagnosis and 85% in the first 2 years; however, up to 25% of patients with clinical RA have no circulating RF. The titer has little prognostic value in an individual patient, and remeasurements provide little added information.

KEY POINTS: SIGNIFICANCE OF LABORATORY VALUES IN RHEUMATIC DISEASE

1. ANA titers are not associated with intensity of disease.
2. Mixed connective tissue disease is a specific diagnosis which may have associated features of SLE, scleroderma, Sjögren's and/or polymyositis in association with anti-RNP antibodies.
3. Joint fluid analysis includes cell count, gram stain, culture, and crystals.
4. A patient with low positive RF and arthralgia should be checked for hepatitis C, which can produce synovitis and cryoglobulins (which can produce a false-positive RF).

ANA = antinuclear antibody; RF = rheumatoid factor; SLE = systemic lupus erythematosus.

27. What are anti-CCP antibodies?

Anti-cyclic citrullinated peptide (anti-CCPs) antibodies, which are directed against the citrullinated residue of certain molecules (such as filaggrin and fibrin). These antibodies are found in the sera of patients with RA.

28. What is the sensitivity and specificity of RF and anti-CCP antibodies?

- **RF:** 66% sensitivity, 70% specificity
- **Anti-CCP antibodies:** 82% sensitivity, 95% specificity

Measurement of anti-CCP antibodies is superior in specificity compared with RF alone, but the diagnostic yields of both tests are very good in patients suspected with RA. High titers of either RF or anti-CCP antibodies correlate with more severe disease including erosive disease and extra-articular manifestations.

29. What is the ANA?

Antinuclear antibody (ANA) refers to any autoantibody that reacts to certain nuclear antigens (e.g., histones, ribonucleoproteins, DNA, or centromere). With the development of immunofluorescence microscopy techniques, different staining patterns were discovered, and it became clear that many different nuclear antigens can elicit an antibody response. Thus, many antibodies can be classified as ANA (Table 10-2). Detecting the specific antibody reaction requires more refined techniques.

TABLE 10-2. ANTIGENS AND ANTINUCLEAR ANTIBODIES

Antigen	Antibody
Deoxyribose phosphate backbone of DNA	Anti-DNA (double-stranded or native)
Purine and pyrimidine bases	Anti–single-stranded DNA
H1, H2A, H2B, H3, H2A/H2B complex, H3/H4 complex	Antihistones
DNA topoisomerase I	Anti–SCL-70
Histidyl tRNA transferase	Anti–Jo-1
Kinetochore	Anticentromere
RNA polymerase I	Antinucleolar
Y1–Y5 RNA and protein	Anti-Ro
U1–6 RNA and protein	Anti-RNP (includes anti-Sm)

Adapted from von Mühlen CA, Tan EM: Autoantibodies in the diagnosis of systemic rheumatic diseases. Semin Arthritis Rheum 24:323–358, 1995.

30. What is the significance of a positive ANA in a patient who is otherwise healthy?

Uncertain. ANA positivity is common and may not carry any significance. In 1997, the ANA Subcommittee of the International Union of Immunological Societies (IUIS) Standardization Committee completed a multicenter study with the objective of identifying the range of ANA titers in normal individuals and in patients with certain rheumatic diseases. The study found that a positive ANA can be found in 31.7% of healthy individuals at 1:40 serum dilution, 13.3% at 1:80, 5.0% at 1:160, and 3.3% at 1:320. Despite these frequencies, the ANA titer may be useful in determining the presence of disease. Setting a low cutoff of 1:40 (high sensitivity, low specificity) could aid in diagnosis because it would classify most patients who have SLE, systemic sclerosis (SSc), or Sjögren's syndrome. Conversely, setting a high cutoff at 1:160 serum dilution (high specificity, low sensitivity) could be useful to confirm the presence of disease and would likely exclude 95% of normal individuals

Tan EM, Feltkamp TE, Smolen JS, et al: Range of antinuclear antibodies in "healthy" individuals, *Arthritis Rheum* 40:1601–1611, 1997.

31. Do ANA staining patterns detect specific ANAs? What is their clinical relevance?

No. The fluorescence test for ANA is performed by incubating the patient's serum with a fixed monolayer of human larynx epithelioma cancer (HEp-2) cell lines. If ANAs are present in the serum, they bind to the nuclear component of the substrate. Next, fluorescent anti-Ig is added, which binds to antibodies (if present) in the test serum. With the fluorescent tag, the ANA can be directly visualized under fluorescent light. Different patterns of staining occur, and although they may provide some information, they do not identify the specific antibody present, nor are they specific for a disease entity or clinically relevant. For example, the rim or peripheral pattern (usually associated with antibodies directed against nuclear membrane proteins) may be obscured if another autoantibody (staining a homogeneous pattern) is present.

KEY POINTS: DIAGNOSING RHEUMATIC DISEASES

1. Inflammatory arthritis tends to involve small joints, has a morning stiffness component, and improves with activity.
2. Joint arthrocentesis is most useful in evaluating for joint infection.
3. Rheumatoid factor and anti-CCP antibodies help improve sensitivity and specificity in diagnosing rheumatoid arthritis.
4. Although ANA positivity may occur in normal patients, its titer and its presence with other autoantibodies are useful in diagnosing connective tissue diseases.
5. The HLA B27 association with arthritis is highest in ankylosing spondylitis and reactive arthritis but lower with the spondylitis associated with psoriasis and inflammatory bowel disease.

ANA = antinuclear antibody; HLA = human leukocyte antigen.

32. Why is it helpful to know which specific ANA is present in a given patient?

To increase the diagnostic likelihood of a specific rheumatic diagnosis and provide prognosis.

33. What rheumatic diseases are associated with specific ANAs?

See Table 10-3.

TABLE 10-3. SPECIFIC ANTINUCLEAR ANTIBODIES AND DISEASE ASSOCIATION

Antibody	Associated Diseases
Ro/SSA	SLE, neonatal lupus syndrome, subacute lupus, Sjögren's syndrome, RA
dsDNA	SLE (with nephritis)
Sm	SLE
Jo-1	Polymyositis (pulmonary involvement)
Centromere	CREST syndrome (limited scleroderma)
SCL-70	Systemic sclerosis
Histone	SLE, drug-induced lupus

(continued)

TABLE 10-3. SPECIFIC ANTINUCLEAR ANTIBODIES AND DISEASE ASSOCIATION—*(continued)*

Antibody	Associated Diseases
RNP	SLE, MCTD
Ribosomal P	SLE (with psychosis)
Cardiolipin	SLE (with thromboembolic events), antiphospholipid syndrome

CREST = calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; MCTD = mixed connective tissue disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

34. What are antineutrophil cytoplasmic antibodies (ANCAs)?

Antibodies directed against enzymes (proteinase-3 [PR-3] and myeloperoxidase) found in primary granules of neutrophils and lysosomes of monocytes. Immunofluorescence detects two principal staining patterns: (1) a fine granular cytoplasmic staining (c-ANCA) and (2) a perinuclear collection of antibody (p-ANCA).

35. Which diseases are associated with soft tissue calcification on plain x-rays?

Calcific tendinitis
Chondrocalcinosis
Dermatomyositis
Diabetes
Ehlers-Danlos syndrome
Neoplasia
Neuropathic arthropathy
Parathyroid disease
Renal osteodystrophy
Sarcoidosis
Scleroderma
Trauma

36. Describe typical radiographic features of inflammatory arthritis in early and progressive disease.

Soft tissue swelling and juxta-articular osteoporosis in early disease and more diffuse osteoporosis with uniform loss of cartilage in chronic disease. Further inflammation will lead to synovial hypertrophy and erosions with marginal areas of the synovium.

37. List five classic radiographic findings of OA.

- Subchondral cyst formation
- New bone formation (osteophytes)
- Bone sclerosis
- Joint space narrowing
- Lack of osteoporosis

38. Describe the role of magnetic resonance imaging (MRI) and peripheral ultrasound (US) in inflammatory arthritis.

To detect subtle bony abnormalities that may not be seen on plain radiographs. MRI is able to detect early bony erosions. Peripheral US is also a sensitive test for detecting erosions. US is less expensive than MRI but accurate results are dependent upon the operator's skill.

RHEUMATOID ARTHRITIS

39. What is the basis for the revised RA classification criteria established in 2010 by the ACR and European League Against Rheumatism (EULAR)?

Definite RA is based on:

- Presence of synovitis in at least 1 joint

- Absence of an alternative diagnosis to explain the synovitis
- Achievement of a total score $\geq$ 6 from individual scores from 4 domains:
  - Number and site of involved joints (score range 0-5)
  - Serologic abnormalities (score range 0-5)
  - Elevated acute-phase response (score range 0-1)
  - Symptom duration (2 levels; range 0-1)

Aletaha D, Neogi T, Silman AF, et al: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum* 62(9):2569–2581, 2010.

40. What is the advantage of these new criteria?

To identify patients with new symptoms of inflammatory synovitis who are likely to develop persistent or erosive joint disease as seen in RA.

41. What is the differential diagnosis of RA?

- Connective tissue disease (SLE, SSc, Sjögren's disease)
- Psoriatic arthritis
- IBD
- Polyarticular gout
- Lyme-related arthropathy
- Viral-induced arthropathies (parvovirus B19, hepatitis C)

42. Describe the epidemiology of RA.

RA occurs in up to 1% of the general population worldwide with lower prevalence in parts of Africa (0.1%) and China (0.3%) and higher prevalence in Pima and Chippawa Indians (5%). Peak incidence is in the fourth and fifth decades of life, but almost any age can be affected.

43. What are the genetic associations in RA?

First-degree relatives of patients with RA have a 1.5-fold increased risk of developing RA compared with the general population. Monozygotic twin studies found a concordance rate for RA of 12–15%. An increased prevalence of RA is present in a subset of populations with the presence of HLA-DR4 (Western European descent) and HLA-DR1 or HLA-DR10 (Spanish, Basque, and Israeli descent). RA susceptibility is associated with the third hypervariable region of DR1β-chains from amino acids 70–74 referred to as the "shared epitope" (QKRAA, QRRAA or RRRAA) and is associated with both susceptibility and severity of RA.

Nepom GT, Byers P, Seyfried C, et al: HLA gene association with RA: Identification of susceptibility alleles using specific oligopeptide probes, *Arthritis Rheum* 32:15, 1989.

44. Explain the influence of gender in RA.

Females have a two to three times increased likelihood of developing RA compared with males. Estrogen has been shown to inhibit T suppressor cell function and enhance T helper function, leading to stimulatory effects on the immune system. In addition, null parity increases RA risk. The last trimester of pregnancy is associated with decreased RA disease activity. Men with RA tend to have lower testosterone levels than other men and later disease onset than women.

45. What are nongenetic risk factors for RA?

Smoking and infections (bacterial and viral). A 25 pack-year or more history of tobacco use is associated with more severe disease with greater seropositivity, nodules, and radiographic changes. Bacterial infections have been implicated in initiation of RA through activation of Toll-like receptors on mast cells and stimulation of innate immunity. Viruses have also been considered in etiology of RA. Epstein-Barr virus (EBV), parovirus B19, and retroviruses have similar amino acid sequences to the shared epitope and may trigger an autoimmune response leading to inflammation.

46. What is the synovium?

A 1- to 2-cell-thick lining of the joint made up of two types of synoviocytes: type A (macrophage-like cells probably derived from bone marrow) and type B (fibroblast-like cells that are probably of mesenchymal origin). The subsynovium constitutes the second layer of normal synovium.

47. How does RA affect the synovium?

By inducing intimal lining hyperplasia and subsynovial infiltration with mononuclear cells (especially CD4-negative T cells, macrophages, and B cells). Increased numbers of type A and type B synoviocytes are added to the synovial lining. The lining is the main source of the inflammatory cytokines and proteases thought to lead to the joint destruction in RA. Activated chondrocytes and osteoclasts may also be involved. In addition, other cell types including plasma cells, T and B lymphocytes, and dendritic cells may also accumulate in RA synovium. Synovial fluid has elevated polymorphonuclear leukocytes (PMNs) with lesser cell types including lymphocytes, macrophages, natural killer cells, and fibroblasts present.

48. What is pannus?

A term to describe the area of proliferating synovium that can erode the adjacent cartilage and bone. (***Pannus*** means cloth in Latin.) Angiogenesis allows the synovium to hypertrophy leading to enlargement of pannus and an influx of inflammatory cells.

49. How does pannus contribute to joint destruction in RA?

Pannus tissue adheres to articular cartilage, and the cells within the pannus produce proteinases that can destroy cartilage. The marginal erosions on radiographs are likely due to bone invasion by pannus. Synovial tissue analysis also reveals inflammatory mediators including cytokines, enzymes, adhesion molecules, and transcription factors. Notable examples include interleukin-1 (IL-1), tumor necrosis factor-alpha (TNA-alpha), IL-6, IL-8, IL-17, matrix metalloproteinases, cathepsins, and other proteases. Receptor activator for nuclear factor kappa-B ligand (RANK-L) production leads to osteoclast activation, which may be involved in the bone loss in RA.

50. Which joints are most commonly involved in RA?

Multiple diarthrodial joints (with free motion) in a symmetrical distribution. In early disease, the MCP, PIP, wrist, and MTP joints are involved. Larger joints of the upper and lower extremities, such as the elbows, shoulders, ankles, and knees, are also commonly affected, although symptoms may appear later. Less common are cervical spine, temporomandibular, and sternoclavicular joint involvement. Joints that are very uncommon in RA include the distal interphalangeal (DIP) joints and thoracic and lumbar spine.

51. Describe the typical late joint deformities in RA.

- Swan neck deformity typically results from inflammation and flexor contraction of the MCP joints, which causes flexion at the MCP and DIP joints with hyperextension of the PIP joints.
- Boutonnière deformity is due to flexion contracture at the PIP joint with extension of the DIP joint due to injury or weakening of the extrinsic extensor tendon.
- Ulnar deviation is due to MCP joint subluxation.
- The “piano key sign” is characterized by softening of the ulnar styloid due to destruction of the ulnar collateral ligamaent.
- In the feet, late deformities include claw toe or hammer toe, which is due to subluxation of the metatarsal heads.

52. Describe cervical spine involvement in RA.

Initial symptoms include pain with motion in the neck and occipital headache. Risk factors for cervical spine disease include high RF seropositivity, later onset, active synovitis, and

rapid progression of erosive disease. Significant laxity at the atlantoaxial joint with subluxation makes patients prone to slowly progressive, spastic quadriparesis. If this laxity is present, the hyperextension of the neck that occurs during intubation for general anesthesia can produce quadriplegia. Therefore, patients with neck pain or longstanding disease should undergo cervical spine evaluation before any surgical procedure.

53. What are rheumatoid nodules?

Firm, usually movable nodules ranging in size from a few millimeters to 2 cm found over pressure areas. The classic rheumatoid nodule has a central area of necrosis surrounded by a rim of palisading fibroblasts surrounded by a collagenous capsule with perivascular collections of chronic inflammatory cells. Rheumatoid nodules occur in 20–35% of patients with RA and can be found at the elbow, knuckles, wrist, soles, Achilles tendon, head, bridge of the nose (if pressure area from glasses), and sacrum. RF is usually positive, as are anti-CCP antibodies. Accelerated nodule formation has been described in patients receiving methotrexate treatment for RA, even when methotrexate shows efficacy at calming the arthritis and the patient has had no previous nodule formation. Nodulosis goes away when methotrexate is discontinued.

54. What factors suggest an aggressive disease course in RA?

- Acute onset of disease with involvement of multiple joints
- High titers of RF
- Positive ANA
- Presence of nodules
- Lower socioeconomic status
- Fewer years of formal education.

55. List some extra-articular manifestations of RA.

See Table 10-4.

TABLE 10-4. EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

Organ System	Extra-Articular Manifestation
Constitutional	Fever, fatigue, weight loss
Skin	Rheumatoid nodules
Pulmonary	Pulmonary nodules, pleural thickening, pleural effusions, diffuse interstitial lung disease, BOOP
Ophthalmologic	Keratoconjunctivitis sicca, episcleritis, scleritis
Vascular	Small vessel vasculitis
Neurologic	Cervical spine subluxation causing cervical myelopathy, nerve entrapments
Cardiac	Pericarditis, coronary atherosclerosis
Muscular	Muscle atrophy
Hematologic	Anemia of chronic disease, thrombocytosis, lymphoma

BOOP = bronchiolitis obliterans with organizing pneumonia.

56. What is Felty's syndrome?

The triad of RA, splenomegaly, and leukopenia. Felty's occurs in 1% of RA patients with severe disease who typically have RF positivity, rheumatoid nodules, and other extra-articular manifestations. Leukopenia predominantly affects neutrophils with white blood cell (WBC) count $< 2000/mm^3$. Patients are more susceptible to bacterial infections and have a higher risk of development of non-Hodgkin's lymphoma. Patients with Felty's also are susceptible to large granular lymphocyte (LGL) syndrome with CD2, 3, 8, 16, and 57 markers and susceptibility to infections.

57. What is Caplan's syndrome?

The development of lung inflammation and scarring in patients with RA and pneumoconiosis from mining dust exposure. Multiple perihilar lung nodules with pathology similar to rheumatoid nodules are also found. These patients can develop massive fibrosis and are at increased risk of tuberculosis.

58. Why is functional capacity so important in patients with RA?

Because functional status may be one of the best predictors of premature mortality.

59. Why is early treatment of RA so important?

Because the joints can be significantly structurally damaged early in the disease if not treated. The structural damage produces mechanical derangements in the joint leading to deformity and profoundly impaired joint function.

60. How does pregnancy affect RA?

Usually with improvement. Signs and symptoms of RA subside in approximately 70% of women during pregnancy. No data suggest that RA has a detrimental effect on the fetus; however, arthritis should be assessed before pregnancy, if possible, because anesthesia and intubation (if needed) can be problematic and even dangerous when cervical spine disease is present. Delivery also can be difficult if arthritis limits hip motion. Postpartum flares of disease occur in approximately 90% of women who experience improvement during pregnancy.

Griffin J: Rheumatoid arthritis: Biological effects and management. In Scott JS, Bird HA, editors: *Pregnancy, Autoimmunity and Connective Tissue Disorders*, Oxford, 1990, Oxford University Press, pp 140–162.

61. Describe the basic mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs).

Inhibition of production of prostaglandins (and other inflammatory cytokines) through competition with arachidonic acid for cyclooxygenase (COX) binding. There are two main subtypes of COX. COX-1 is often described as a "housekeeping" enzyme and has been associated with regulating normal cellular processes such as gastric cellular protection, platelet aggregation, and kidney function. COX-2 is expressed in the brain, kidney, bone, and possibly, the cardiovascular system. COX-2 seems to be involved more specifically in the synthesis of inflammatory mediators than COX-1. Without COX, there are fewer circulating prostaglandins and, therefore, less inflammation and pain.

62. What is the advantage of selective COX-2 inhibition over nonselective COX inhibition?

Decreased risk of gastrointestinal (GI) injury. COX-1 is known to be involved in gastric cellular protection, so selective inhibition of COX-2 would theoretically lead to less gastric and duodenal injury. Clinical studies do show this, but toxicity still may occur with COX-2 inhibition. Although improved GI tolerance has been shown, there has been no significant improvement in efficacy with selective COX-2 inhibition. Patients at risk of peptic ulcer disease (PUD) who use NSAIDs chronically should be evaluated for proton pump inhibitor (PPI) prophylaxis. (See Chapter 2, General Medicine and Ambulatory Care.)

63. What side effects are found in both NSAIDs and COX-2 inhibitors?

- **Renal:** hypertension, acute renal failure, and papillary necrosis
- **Hepatic:** elevated transaminases and rarely acute hepatic injury
- **Nervous system:** dizziness, headache, and cognitive dysfunction

Also see Chapter 2, General Medicine and Ambulatory Care.

64. How do the effects of aspirin on platelets differ from those of other NSAIDs?

Acetylated salicylates (such as aspirin) **irreversibly** destroy the COX enzyme that leads to decreased platelet aggregation. Other NSAIDs (including nonacetylated salicylates) allow the return of normal enzyme function once the drug level has decreased. Because COX-2 does not regulate platelet aggregation, newer COX-2 NSAIDs have little effect on platelet function.

65. What is the role of glucocorticoids (GCs) in the management of RA?

Mainly for managing disease flares and bridging therapies. GCs reduce synthesis of enzymes involved in the production of prostaglandins and proinflammatory cytokins such as IL-1, IL-6, TNA-alpha. Because of more specific, safer agents, GCs are currently used less often in the long-term management of RA. The relatively quick onset of action (hours to days) make GCs a good agent for disease flare-ups. Low-dose GCs are also used as bridging therapy concurrently with disease-modifying antirheumatic drug (DMARD) therapy.

66. What are common adverse side effects from long-term use of GCs?

- Osteoporosis (secondary)
- Hyperglycemia
- Increased incidence of cardiovascular disease
- Cushing's syndrome
- Increased risk of cataracts
- Increased risk of infection

67. What are DMARDs and how are they used in the treatment of RA?

Disease-modifying antirheumatic drugs are thought to alter the natural history of RA, lessening the likelihood of joint destruction and deformity. Nonbiologic DMARDs are typically oral and have been used clinically for many years. Biologic DMARDs are structurally engineered versions of already natural molecules such as monoclonal antibodies and have more specific targets in the inflammatory cascade of disease.

KEY POINTS: TREATMENT OF RHEUMATIC DISEASE

1. COX-2 selective inhibition is safer from GI toxicities than from traditional NSAIDs, but are no more efficacious and may have a higher cardiovascular risk.
2. Patients taking chronic NSAIDs who are at risk of PUD may benefit from prophylactic treatment with PPIs to prevent PUD.
3. Disease-modifying medications including the biologic agents have improved clinical outcomes in rheumatoid arthritis.
4. Although glucocorticoid treatments are common in managing several rheumatic diseases, there are many untoward side effects including osteoporosis, increased cardiovascular disease, elevated glucose, and increased risk of infection.

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors; PUD = peptic ulcer disease.

68. Name the most commonly used nonbiologic DMARDs, list mechanism of action, and name common side effects.
See Table 10-5.

TABLE 10-5. MECHANISM OF ACTION AND SIDE EFFECTS OF NONBIOLOGIC DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Nonbiologic DMARDs	Mechanism of Action	Common Side Effects
Methotrexate	Inhibits dihydrofolate reductase, which leads to anti-inflammatory effects and down-regulation of cytokines, although the exact mechanism is still unclear	Nausea, stomatitis, alopecia, fatigue, elevated liver transaminases, bone marrow suppression, pneumonitis
Sulfasalazine	Suppresses lymphocyte and leukocyte functions	Nausea, rash, leukopenia
Hydroxychloroquine	Accumulation in lysosomes raises the intravesical pH and interferes with antigenic peptides	Nausea, rash, hyperpigmentation, retinopathy
Leflunomide	Inhibits pyrimidine synthesis which inhibits T-cell function	Nausea, stomatitis, alopecia, fatigue, elevated liver transaminases, bone marrow suppression

DMARDs = disease-modifying antirheumatic drugs.

69. Name other less common nonbiologic DMARDs.
Minocycline has shown efficacy in small clinical trials. Gold compounds were used more frequently in the past, but much less frequently now because of high levels of toxicity. Cyclosporine, tacrolimus, and azathioprine have been shown to have efficacy as well.

70. Name current biologic DMARD therapies, list mechanism of action, and name common side effects.
See Table 10-6.

SYSTEMIC LUPUS ERYTHEMATOSUS

71. What is SLE?
An autoimmune inflammatory disease that can affect many organ systems with protean manifestations. The pathogenesis of lupus is largely unknown, but immunologic abnormalities can give rise to excessive autoantibody production that can cause tissue damage.

TABLE 10-6. MECHANISM OF ACTION AND SIDE EFFECTS OF BIOLOGIC DISEASE MODIFYING ANTIRHEUMATIC DRUGS

Biologic DMARDs	Class	Mechanism of Action and Route of Administration	Common Side Effects
Infliximab	TNF-α inhibitor	Chimeric monoclonal antibody that binds to both soluble and membrane bound TNF-α; intravenous administration	Infection (including reactivation of TB and fungal infection), infusion reaction, lymphoma, demyelinating disorder, drug-induced lupus
Entanercept	TNF-α inhibitor	Soluble receptor fusion protein that binds to soluble TNF-α; subcutaneous administration	Infection (including reactivation of latent TB and fungal infection), injection site reaction, lymphoma, demyelinating disorder, drug-induced lupus
Adalimumab	TNF-α inhibitor	Fully humanized monoclonal antibody that binds to both soluble and membrane bound TNF-α; subcutaneous administration	Infection (including reactivation of latent TB and fungal infection), injection site reaction, lymphoma, demyelinating disorder, drug-induced lupus
Golimumab	TNF-α inhibitor	Fully humanized monoclonal antibody that binds to both soluble and membrane bound TNF-α; subcutaneous administration	Infection (including reactivation of latent TB and fungal infection), injection site reaction, lymphoma, demyelinating disorder, drug-induced lupus
Certolizamab pegol	TNF-α inhibitor	Pegulated humanized antibody Fab fragment chemically linked to polyethylene glycol and binds to soluble and membrane bound TNA-α and does not contain an Fc portion unlike the other monoclonal antibodies to TNF-α; subcutanous administration	Infection (including reactivation of latent TB and fungal infection), injection site reaction, lymphoma, demyelinating disorder, drug-induced lupus, pancytopenia

(continued)

TABLE 10-6. MECHANISM OF ACTION AND SIDE EFFECTS OF BIOLOGIC DISEASE MODIFYING ANTIRHEUMATIC DRUGS—*(continued)*

Biologic DMARDs	Class	Mechanism of Action and Route of Administration	Common Side Effects
Abatacept (CTLA-4Ig)	T-cell inhibitor	Recombinent fusion protein that binds to CD80/CD86 on the surface of APC and prevents binding onto CD28 on T cells (blocks T-cell second signals); intravenous administration	Infection, infusion reaction, malignancy, COPD exacerbations
Rituximab	B-cell inhibitor	Chimeric anti-CD20 monoclonal antibody that involves inhibition of T cell activation through reduction of antigen presentation by B cells; intravenous administration	Infection, infusion reactions, headache, fever
Tocilizumab	IL-6 inhibitor	Humanized IL-6 receptor antibody. IL-6 has proinflammatory effects and activates T cells, B cells, and macrophages	Infection, infusion reaction, elevated hepatic function tests, elevated total cholesterol, neutropenia

APC = antigen presenting cell; COPD = chronic obstructive pulmonary disease; DMARDs = disease-modifying antirheumatic drugs; IL = interleukin; TB = tuberculosis; TNF = tumor necrosis factor.

72. What are the ACR classification criteria for SLE?

See Table 10-7.

TABLE 10-7. AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS*

Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration usually painless, observed by physician

(continued)

TABLE 10–7. AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS* — *(continued)*

Nonerosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Pleuritis or pericarditis	a. Pleuritis: convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion *or* b. Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria $>$ 0.5 g/day or $>$ 3+ if quantitative not performed *or* b. Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
Seizures or psychosis	a. Seizures: in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance) b. Psychosis: in the absence of offending drugs or known metabolic derangement (e.g., uremia, ketoacidosis, electrolyte imbalance)
Hematologic disorder	a. Hemolytic anemia with reticulocytosis *or* b. Leukopenia: $<4000/mm^3$ on two occasions *or* c. Lymphopenia: $<1500/mm^3$ on two occasions *or* d. Thrombocytopenia: $<100{,}000/mm^3$ in the absence of offending drugs
Immunologic disorder	a. Anti-DNA: antibody to native DNA in abnormal titer *or* b. Anti-Sm: presence of antibody to Sm nuclear antigen *or* c. Positive findings of antiphospholipid antibodies based on: 1. An abnormal serum concentration of IgG or IgM anticardiolipin antibodies 2. A positive test for lupus anticoagulant using standard method *or* 3. A false-positive test for at least 6 mo and confirmed by *Treponema palladium* immobilization fluorescent treponemal antibody absorption test
Positive ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drug

ANA = antinuclear antibody; Ig = immunoglobulin; SLE = systemic lupus erythematosus.
*Four of these criteria must be present in order for the patient to enroll in a SLE research study.
Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 40:1725, 1997.

73. How are these criteria used for the diagnosis of SLE in an individual patient?

The ACR classification criteria were proposed to identify SLE patients for enrollment into clinical trial, providing a uniform base for which studies can be conducted in lupus patients. The ACR criteria are intended to reflect the major clinical features of the disease (e.g., dermatologic, renal, neurologic, articular, hematologic, and immunologic findings). Although these criteria may be helpful in aiding the diagnosis of lupus, patients who do not fulfill the classification criteria may still have the disease. The diagnosis of SLE in clinical practice is based upon autoantibody analysis, symptoms, laboratory tests of involved organ systems, and physical examination findings.

74. What are common laboratory and clinical findings in SLE?

See Table 10-8.

TABLE 10-8. FREQUENCIES OF VARIOUS MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS BY DISEASE STAGE

Manifestation	Early Disease (%)	Late Disease (%)
Arthritis	46–53	83–95
Rash	9–11	81–88
Fever	3–5	77
Mucosal ulcers	—	7–23
Alopecia	—	37–45
Serositis	5	63
Pulmonary inflammation	—	9
Liver function test abnormalities	1	—
Vasculitis	—	21–27
Myositis	—	5
Osteoporosis	—	High
Osteonecrosis	—	7–24
Leukopenia	41–66	41–66
Thrombocytopenia	2	19–45
Anemia	2	57–73
CNS abnormalities	3	55–59
Nephritis	6	31–53
Renal failure	<1	20

CNS = central nervous system.
From Lahita RG: The clinical presentation of systemic lupus erythematosus in adults. In Lahita RG (ed): Systemic Lupus Erythematosus, 4th ed. San Diego, CA, Academic Press, 2004, p 435.

75. When is the peak incidence of SLE?

15–44 years of age, which is believed to be related to the hormonal changes that occur during puberty and the childbearing years. The incidence of SLE in prepubertal females is similar to that of postmenopausal females.

Masi AT, Kaslow RA: Sex effects in systemic lupus erythematosus: A clue to pathogenesis, *Arthritis Rheum* 21:480–484, 1978.

76. How can cutaneous lupus be categorized?

- Acute cutaneous lupus erythematosus (ACLE)
- Subacute cutaneous lupus erythematosus (SCLE)
- Chronic cutaneous lupus erythematosus (CCLE)

77. Compare and contrast the typical rashes of ACLE with SCLE.

The prototypical lesion of ACLE is the malar or butterfly rash, which is an erythematous rash that can be flat or raised. The rash spans the bridge of the nose and extends over the malar eminences. Ultraviolet (UV) light may exacerbate the lesion; hence, the nasolabial folds are often spared because these regions receive less UV rays. The rash of SCLE is also photosensitive and is often located in the upper chest, shoulders, and neck. SCLE may start as erythematous, scaly papules or plaques, often progressing into larger papulosquamous or annular polycyclic lesions that can then coalesce to produce large confluent areas with central hypopigmentation. Neither ACLE nor SCLE results in dermal scarring.

78. What are some examples of CCLE?

- Lupus tumidus
- Lupus profundus
- Chilblain lupus
- Discoid lupus erythematosus (DLE).

79. Describe DLE and explain the relationship between SLE and DLE.

Discrete erythematous plaques covered by scales that extend into hair follicles, causing follicular plugging. The plaques can occur over the face, scalp, pinnae and conchae bowl of the ear, neck, and in areas that may not be exposed to the UV rays. DLE can exist in patients with SLE or in isolation. About 10% of patients with discoid lesions will have SLE.

Walling HW, Sontheimer RD: Cutaneous lupus erythematosus: Issues in diagnosis and treatment, *Am J Clin Dermatol* 10:365–381, 2009.

80. What are other cutaneous manifestations of lupus?

Raynaud's phenomenon	Bullae	Livedo reticularis
Periungual telangiectasia	Livedo reticularis	Alopecia
	Petechiae	
	Vasculitis	

81. List the differential diagnoses of a lupus patient who presents with musculoskeletal complaints.

Synovitis	Myopathy	Septic arthritis
Fibromyalgia	Osteonecrosis	Adrenal insufficiency
Myositis	Fractures	

Some of these disorders are related to the disease itself, whereas others may be related to medication side effects or existing comorbid conditions.

82. What is the prevalence of lupus nephritis and how is nephritis categorized?

About 50%. The Society of Pathology/Renal Pathology Society (ISN/RPS) in 2003 revised the World Health Organization (WHO) classification of lupus nephritis by adding chronicity and activity scores. Classification is based on biopsy:

- **Class I:** minimal mesangial lupus nephritis
- **Class II:** mesangial proliferative lupus nephritis
- **Class III:** focal lupus nephritis, subcategorized as proliferative with activity (class III-A), proliferative and sclerosis with activity and chronicity (class III-A/C), or sclerosing with chronicity (class III-C)

- **Class IV:** diffuse lupus nephritis, subcategorized as segmental and active [class IV-S(A)], global proliferative and active [class IV-G(A)], segmental with activity and chronicity [class IV-S(A/C)], global proliferative with activity and chronicity [class IV–G(A/C)], segmental with chronicity [class IV–S(C)], or global proliferative with chronicity [class IV–G(C)]
- **Class V:** membranous lupus nephritis
- **Class VI:** advanced sclerosis lupus nephritis

Weening JJ, D'Agati VD, Schwartz MM, et al: The classification of glomerulonephritis in systemic lupus erythematosus revisited, *J Am Soc Nephrol* 15:241–250, 2004.

83. What happens to lupus activity in patients with renal failure?

Oftentimes, lupus becomes quiescent with the onset of uremia and dialysis. Several studies note the ability to discontinue GCs without a return of extrarenal manifestations once dialysis has been initiated. Although there are reports of subsequent disease exacerbations, disease activity usually does not recur in transplanted kidneys.

84. How commonly does SLE affect the GI tract?

Frequently. GI manifestations may be present in up to 50% of patients with SLE. Anorexia, nausea, and vomiting are among the most common symptoms. Oral ulcerations (most commonly painless buccal erosions) were identified in 40% of one group of patients. Esophageal involvement such as esophagitis, esophageal ulceration, or esophageal dysmotility seems to correlate with the presence of Raynaud's phenomenon. Intestinal involvement results in abdominal pain, diarrhea, and occasionally, hemorrhage. Intestinal ischemia may be present and may progress to infarction and perforation. Pneumatosis intestinalis in SLE is usually benign and transient but may represent an irreversible necrotizing enterocolitis. In addition, pancreatitis and abdominal serositis are well-recognized. Abnormal liver functions also occur. A vasculitic process has been implicated in the pathogenesis of GI manifestations.

85. What is the most common pathologic abnormality in patients with lupus central nervous system (CNS) disease?

Small infarcts and hemorrhages. Vasculitis is suggested by such commonly used designations as "lupus cerebritis" and occurs in $< 15\%$ of patients.

Johnson RT, Richardson EP: The neurological manifestations of systemic lupus erythematosus, *Medicine* 47:337–369, 1968.

86. What are the neuropsychiatric manifestations of SLE?

- Psychosis
- Cranial, autonomic, and peripheral neuropathies
- Migraine headaches
- Seizure
- Aseptic meningitis
- Pseudotumor cerebri
- Chorea
- Cerebral infarction
- Transverse myelitis (rare)
- Posterior reversible encephalopathy syndrome (PRES)
- Organic brain syndrome (delirium, mild memory loss, and impaired concentration)

Because of the difficulty in establishing an unequivocal diagnosis, rates of CNS features in SLE cross a broad range. Neuropsychiatric manifestations of lupus may occur in approximately 70% of patients. The more subtle features of cognitive dysfunction may be the most common CNS finding. Abnormal single-photon emission computed tomography (SPECT) or positron-emission tomography (PET) scanning and decreasing intellectual

function, as measured by a standard battery of neurocognitive function tests, are present. The cause for this problem is not known, but cytokines are believed to play an important role.

87. What is PRES?

Posterior reversible encephalopathy syndrome, which is a rare neurologic manifestation that has recently been described in patients with SLE. PRES is often associated with acute hypertension and renal failure. Diagnosis is based on presenting symptoms of headaches, seizures, altered mental status, cortical blindness, focal neurologic deficits, and typical MRI findings of posterior cerebral edema.

Leroux G, Sellam J, Costedoat-Chalumeau N, et al: Posterior reversible encephalopathy syndrome during systemic lupus erythematosus: Four new cases and review of the literature, *Lupus* 17:139–147, 2008.

88. Describe the pulmonary manifestations of lupus.

Pleurisy or pleural effusion is most common. Up to 60% of patients may have pleuritic pain over the course of their illness. Effusions can be either transudative or exudative and, in rare cases, are the presenting feature. The so-called shrinking lung syndrome describes dyspnea associated with diaphragmatic dysfunction, probably secondary to chronic pleural scarring. Pulmonary parenchymal involvement or lupus pneumonitis has been described, as have pulmonary hemorrhage, pulmonary emboli, and pulmonary hypertension. Emboli and hypertension are more common when APAs are also present.

89. Which drugs are commonly associated with the development of a clinical syndrome of lupus and a positive ANA?

Hydralazine	Methyldopa	D-penicillamine
Procainamide	Minocycline	Chlorpromazine
Quinidine	Isoniazid	TNF inhibitors
Diphenylhydantoin	Sulfasalazine	Diltiazem

So-called slow acetylators more commonly develop clinical symptoms, which typically include fever, rash, and arthritis. The clinical features usually regress fairly promptly, although the laboratory abnormality may persist (sometimes indefinitely) when the drug is discontinued. The clinical features commonly present in drug-induced lupus rarely, if ever, include CNS disease or nephritis. There are numerous published reports of many other drugs inducing lupus symptoms on a small number of patients.

90. What antibody is often touted to be diagnostic for drug-induced lupus?

Antihistone. Although antihistone antibody is present in as many as 90% of the cases of drug-induced lupus, the antibody is also present in nearly 75% of patients with SLE, and its presence is not diagnostic for drug-induced lupus.

91. Summarize the mortality rate associated with SLE.

Death rates from SLE have declined significantly over the last half of the 20th century. The 5-year survival rate in the 1950s was only 50%, whereas it is now $>$ 90%. Survival in those with late-onset disease seems to be reduced compared with survival among those patients afflicted at an earlier age.

92. List some factors that may contribute to the morbidity or mortality of patients with SLE.

- Nonadherence to medical advice and treatment
- Presence of active disease
- Medication toxicity
- Infection
- Cardiovascular events

Death early in the course of disease is usually related to the disease itself. Nephritis and CNS disease are the most ominous prognostic factors. Of the causes of death not directly related to active disease, infection is most common, followed by myocardial infarction, stroke, and other atherosclerotic complications. Two recent studies have shown the presence of accelerated atherosclerosis in SLE.

Asanuma Y, Oeser A, Shintani AK, et al: Premature coronary-artery atherosclerosis in systemic lupus erythematosus, *N Engl J Med* 349:2407–2415, 2003.

Roman MJ, Shanker BA, Davis A, et al: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus, *N Engl J Med* 349:2399–2340, 2003.

93. Discuss the interaction of pregnancy and SLE.

Fertility is unaffected by the disease (i.e., patients become pregnant just as readily as women without lupus), and disease exacerbations can occur during pregnancy. Recent data suggest, though, that pregnant patients with lupus do not have disease flares more frequently than nonpregnant patients. Because such flares can be severe, pregnant patients with SLE should be considered at high risk for complications. Preeclampsia, premature births, spontaneous abortions, intrauterine growth delay, and intrauterine fetal deaths are higher in lupus patients. Active disease during the antecedent 3–6 months may increase the risk of flare during the pregnancy. Pregnancy outcome is optimal if the disease has been under control for at least 6–12 months.

Lockshin MD: Pregnancy does not cause systemic lupus erythematosus to worsen, *Arthritis Rheum* 32:665–670, 1989.

94. How does neonatal lupus occur?

Through transplacental passage of maternal Anti-SSA/Ro antibodies to the fetus. These antibodies have been linked to direct tissue injury. Babies born with neonatal lupus can exhibit cutaneous lesions as SCLE, hematologic aberrations, hepatic abnormalities, or congenital heart block (CHB), which potentially can be fatal.

95. What is the incidence of CHB in neonatal lupus?

1–2%; it is typically identified between 16 and 24 weeks of gestation. The risk for recurrence is 10 times higher in subsequent pregnancies.

Buyon JP, Hiebert R, Copel J, et al: Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry, *J Am Coll Cardiol* 31:1658–1666, 1998.

96. What drugs are approved by the FDA for the treatment of SLE?

- Low-dose aspirin
- GCs
- Hydroxychloroquine

97. Describe the APA syndrome?

A symptom complex that occurs in approximately 40% of SLE patients and includes one or more of the following: multiple miscarriages, arterial or venous thrombosis, and thrombocytopenia in association with a laboratory finding of APAs. These antibodies can be specific (such as anticardiolipin antibodies), or they may be identified by their effect on the clotting cascade (lupus anticoagulant). Common laboratory tests indicating the presence of antibodies to various phospholipids include prolonged partial thromboplastin time, false-positive Venereal Disease Research Laboratory (VDRL) test for syphilis, or positive anticardiolipin antibodies. A less common example is the dilute Russell viper venom clotting time. APA syndrome may occur by itself (primary APA syndrome) or in association with an underlying connective tissue syndrome, primarily lupus (secondary APA syndrome).

98. What is Hughes syndrome?

Antiphospholipid syndrome. Graham R. V. Hughes, a rheumatologist, originally described antiphospholipid syndrome in 1983.

99. Describe catastrophic APA syndrome.

Sudden overwhelming vascular occlusion mediated by APAs. Clinical features result from widespread thrombosis of small vessels and the systemic inflammatory response which may include ischemic bowel, pulmonary emboli, acute respiratory distress syndrome (ARDS), infarctive skin lesions, encephalopathy with altered consciousness, seizure, myocardial infarction, and cardiac valvular lesions. Renal involvement is present in the majority of cases.

100. What factors increases the risk of catastrophic APA syndrome?

- Presence of other diseases, such as SLE or BD, even if treated
- Infections
- Vaccination
- Flare of underlying disease
- Withdrawal of anticoagulation

Mortality $>$ 50% even with prompt intervention.

101. How is catastrophic APA syndrome treated?

- Anticoagulation
- GCs
- Treatment of underlying conditions such as infection
- IV immunoglobulin
- Plasma exchange
- Cytotoxic agents

Petri M: Management of thrombosis in antiphospholipid antibody syndrome, *Rheum Dis Clin North Am* 27:633–641, 2001.

SYSTEMIC SCLEROSIS

102. What is scleroderma?

A connective tissue disease is characterized by abnormal collagen deposition into the skin and other organs. The term "scleroderma" is derived from two Greek words: ***skleros***, meaning hard, and ***derma***, meaning skin. Disease pathogenesis is believed to occur as a consequence of aberrant immune activation causing endothelial damage, followed by fibroblast activation that results in obliterative vasculopathy and fibrosis. Of note, the disease is heralded by a vasculopathy, **not** vasculitis. The term "scleroderma" is being phased out and replaced by the term "systemic sclerosis (SSc)" with subcategories of localized sclerosis (morphea, linear scleroderma) or systemic sclerosis (diffuse SSc or limited SSc).

103. Describe CREST syndrome.

Calcinosis, **R**aynaud's, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasias. CREST is often found in patients with limited SSc but can be present in diffuse SSc.

104. Compare and contrast diffuse SSc and limited SSc.

Patients with diffuse SSc have truncal skin involvement, higher mortality rates, and greater risks of developing pulmonary fibrosis, tendon friction rubs, and scleroderma renal crisis than those with limited SSc. Anti-Scl 70 antibodies are more often found in diffuse SSc. Patients with limited SSc have a higher incidence of pulmonary hypertension and anticentromere antibodies.

105. Summarize the genetic component of SSc.

Family members of SSc patients have a significantly greater risk of developing scleroderma than someone with no family history. One likely culprit is an abnormality in the fibrillin gene. This has been elegantly shown in a population study of Choctaw Indians, in whom a genetic defect has been traced to a single common ancestor.

Tan FK, Arnett FC: Genetic factors in the etiology of systemic sclerosis and Raynaud's phenomenon, *Curr Opin Rheumatol* 12:511–519, 2000.

106. List the noncutaneous features of SSc.

- Arthralgia
- Inflammatory muscle disease
- GI dysmotility with malabsorption
- Pulmonary interstitial fibrosis with or without pulmonary hypertension
- Scleroderma renal crisis

107. Do specific autoantibodies help predict the form of SSc a patient may develop?

Yes. Although $>$ 80% of patients with scleroderma have a positive ANA, this test adds little specificity. Antitopoisomerase 1 (anti–Scl-70) has a positive predictive value of 70% for developing scleroderma. Centromere antibodies have a positive predictive value of 88% for the development of CREST.

Spencer-Green G: Tests preformed in systemic sclerosis: Anticentromere antibody and anti Scl-70 antibody, *Am J Med* 103:242–248, 1997.

108. What is scleroderma renal crisis?

A life-threatening aspect of diffuse SSc manifested by sudden onset of malignant hypertension, hemolytic anemia, hyperreninemia, and renal failure. Angiotensin-converting enzyme inhibition therapy has been shown to improve clinical outcomes.

109. What are the risk factors for scleroderma renal crisis?

- Diffuse skin involvement
- Rapid progression of skin thickening
- Disease duration $<$ 4 years
- Anti-RNA-polymerase III antibodies
- New-onset anemia
- New-onset cardiac involvement
- High-dose corticosteroid therapy
- Pregnancy

Steen VD, Medsger TA Jr, Osial TA Jr, et al: Factors predicting development of renal involvement in progressive systemic sclerosis, *Am J Med* 1976:779–786, 1984.

110. What part of the GI tract can SSc affect?

Anywhere from mouth to anus. Patients may have small oral aperture, dry mucosal membranes with periodontal disease, esophageal dysmotility, reflux, esophagitis, stricture, dysphagia, delayed stomach emptying, pseudo-obstruction of the small intestines, bacterial overgrowth, malabsorption, wide mouth diverticuli, and fecal incontinence due to rectal sphincter fibrosis.

111. What abnormalities on pulmonary function testing can be seen with SSc?

- Decreased diffusing capacity for carbon monoxide (DLCO) (earliest marker of pulmonary hypertension)
- Increased A-a gradient with exercise activity
- Decreased vital capacity and increased forced expiratory volume in 1 second–to–forced vital capacity (FEV_1/FVC) ratio (restrictive pattern)

112. How does SSc affect the heart?

- Myocardial fibrosis
- Dilated cardiomyopathy
- Cor pulmonale
- Arrhythmias
- Pericarditis
- Myocarditis
- Heart failure with preserved ejection fraction (diastolic heart failure)
- Myocardial infarction

113. Are scleredema and scleromyxedema related to SSc?

No. Scleredema is a dermatosis of unknown etiology characterized by symmetrical truncal skin induration and thickening, sometimes with erythema. A high proportion of cases are associated with diabetes, malignancies, and infections. Skin biopsy of a patient with scleredema may reveal thickened dermal collagen with a mild infiltration of mucin in the deeper regions of the dermis. Scleromyxedema (also called "papular mucinosis") is characterized by raised pale, waxy papules that result from excessive mucin deposition distributed over the face, fingers, arms, and legs. This condition is associated with paraproteins, particularly IgG lambda. Cases of scleromyxedema have been described in patients with multiple myeloma, amyloidosis, and human immunodeficiency virus (HIV) infection. Patients with scleredema and scleromyxedema do not typically exhibit Raynaud's phenomenon and positive autoantibodies as would be found in SSc.

IDIOPATHIC INFLAMMATORY MYOPATHIES

114. What are the idiopathic inflammatory myopathies (IIMs)?

Polymyositis, dermatomyositis, and inclusion body myositis (IBM).

115. What are the diagnostic criteria for polymyositis and dermatomyositis?

- Symmetrical proximal weakness
- Elevated muscle enzymes (creatine phosphokinase [CPK], aldolase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH])
- Myopathic electromyography (EMG) abnormalities
- Typical changes on muscle biopsy
- Typical dermatologic features (Gottron's sign, heliotropic rash)

To make a definite diagnosis of dermatomyositis, three of four criteria plus the rash must be present. For a definite diagnosis of polymyositis, four criteria must be present without the rash. Note that the criteria do not distinguish polymyositis from inclusion body myositis (IBM).

Bohan A, Peter JB: Polymyositis and dermatomyositis, *N Engl J Med* 292:344–347, 1975.

116. Compare and contrast polymyositis with dermatomyositis.

Both polymyositis and dermatomyositis are characterized by muscle weakness and abnormal muscle findings, but the disorders differ significantly. In dermatomyositis, the inflammation is perivascular (e.g., surrounding the fascicles) with a predominance of CD4+ cells; whereas in polymyositis, CD8+ lymphocytes invade the muscle fiber (e.g., endomysial infiltration). Dermatomyositis can be associated with cancer and may overlap with SSc or mixed connective tissue disease (MCTD). Sclerotic thickening of the dermis, contractures, esophageal hypomotility, microangiopathy, and calcium deposits may be present in dermatomyositis but typically are not seen with polymyositis.

Dalakas MC, Hohlfeld R: Polymyositis and dermatomyositis, *Lancet* 362:971–982, 2003.

117. List some of the characteristic features of IBM.

- Usually occurs in older people.
- Insidious onset.
- Incidence greater in men than women.
- Muscle involvement may be focal or diffuse with asymmetry.
- Can involve both proximal and distal muscles.
- CPK normal (25%) or only slightly elevated.
- Light microscopy shows ragged red fibers, atrophic fibers, and intracellular lined vacuoles.
- Electron microscopy shows intracytoplasmic, intranuclear tubular or filamentous inclusions.

118. What is Gottron's sign?

An erythematous rash that is frequently scaly and occurs over the MCP and IP joints in a symmetrical pattern.

119. Where does the term "heliotropic" rash come from?

A South American plant with clusters of rich purple flowers, whose scent is similar to cherry pie, named "heliotrope." The heliotropic rash refers to the violaceous coloration similar to that of the plant seen along the eyelids of a patient with dermatomyositis.

120. What percentage of patients who have an IIM have normal muscle enzymes?

$\leq$33%.

121. Give examples of myositis-associated/-specific antibodies.

Patients with IIM and anti-Jo-1 can present with arthritis, interstitial lung disease, and Raynaud's phenomenon. Anti-SRP is typically found in patients with polymyositis, and its presence portends a poor prognosis. IIM patients with anti-U1RNP may have myositis overlap with MCTD. Anti-Mi-2 is found in patients with classic dermatomyositis; these patients have good prognoses and will respond well to treatment.

122. What is the antisynthetase syndrome?

A subcategory of the IIM defined by the presence of autoantibodies to aminoacyl-tRNA synthetases. Specific clinical manifestations include myositis, interstitial lung disease, arthritis, Raynaud's phenomenon, fever, and mechanics hands. Antibodies to Jo-1, PL-12, OJ, EJ, PL-7, KS, and Zo have been reported.

123. What further evaluation for an occult malignancy should be undertaken in an adult diagnosed with dermatomyositis?

Because of the increased risk of malignancy in patients with myositis, particularly dermatomyositis, age-appropriate cancer screening should be pursued. (See Chapter 2, General Medicine and Ambulatory Care.)

SPONDYLOARTHROPATHIES

124. What is a spondyloarthropathy?

A group of inflammatory diseases of uncertain etiology that affect the spine and sacroiliac joints characterized by the absence of RF autoantibodies and a high association with class 1 major histocompatability antigen, HLA-B27. Other unifying features include peripheral oligoarthropathy, enthesopathy, and extra-articular foci of inflammation such as uveitis. Diseases classified as spondyloarthropathies include:

Ankylosing spondylitis
Reactive arthritis
Juvenile spondyloarthritis
SAPPHO (synovitis, severe acne, palmoplantar pustulosis, hyperostosis, and osteitis)
Psoriatic arthritis
Enteropathic arthritis
Arthritis associated with Whipple's disease

Arnett FC: Seronegative spondyloarthritis. In Nabel EG, editor: *ACP Medicine*, New York, 2010, BC Decker, www.acpmedicine.com.

125. What mechanisms may explain the association of HLA-B27 with arthropathy?

Although the exact mechanism is unknown, one hypothesis suggests that B27 presents an arthritogenic peptide or alters immune repertoire through its antigen presentation role. Another possibility is that the B27 peptide itself may be prone to misfolding, forming homodimers that subsequently trigger an inflammatory response. Lastly, B27 may serve as a surface ligand for other immunomodulatory receptor families, such as KIRs (killer cell immunoglobulin receptors). In addition, we know that individuals who are homozygous for B27 are three times more likely to develop ankylosing spondylitis than heterozygotes, suggesting a gene dosage effect.

Melis L, Elewaut D: Progress in spondylarthritis. Immunopathogenesis of spondyloarthritis: which cells drive disease? *Arthritis Res Ther* 11:233–238, 2009.

126. Describe the principal clinical features of ankylosing spondylitis.

- Occurs more often in men than in women in a 3:1 ratio.
- Begins in later adolescence.
- Presents with inflammatory low back pain and stiffness.
- Has inflammatory pain pattern that improves with activity and worsens with rest.
- Has predominantly lower limb peripheral joint involvement.

127. Name the extra-articular features of ankylosing spondylitis.

- Anterior uveitis (occurring in ~25%)
- Aortitis (often progressing to aortic valve insufficiency)
- Cardiac conduction defects
- Pulmonary fibrosis (<1%)

128. What is the difference between a syndesmophyte and an osteophyte?

Syndesmophytes represent ossification of the outer layers of the annulus fibrosus (Sharpey's fibers), creating an osseous bridge across vertebra at the discovertebral junction. The syndesmophyte is a characteristic radiographic finding in ankylosing spondylitis, though it may be seen in any of the spondyloarthropathies. Spinal **osteophytes** are triangular ossifications, continuous with the vertebral bodies, forming at either the margins of a vertebral body or a few millimeters from the margin of the discovertebral junction. Osteophytes are often associated with degenerative disc disease.

Brower AC: The "phytes" of the spine. In Brower AC, Flemming DJ, editors: *Arthritis in Black and White*, ed 2, Philadelphia, 1997, WB Saunders, pp 175–191.

129. Describe the mucocutaneous manifestations of reactive arthritis.

- Small painless areas of **desquamation on the tongue** that may be unnoticed by the patient
- **Circinate balanitis** usually affecting the glans penis that can range from small erythematous macules to large areas of dry, flaking skin
- **Keratoderma blennorrhagica,** a thickening and keratinization of the skin that generally involves the feet, hands, and nails that resemble psoriasis clinically and on histopathology

130. List the five patterns of joint involvement found in psoriatic arthritis and their relative frequencies.

- **DIP joints of hands and/or feet:** 8%
- **Peripheral asymmetrical oligoarthropathy:** 8%
- **Symmetrical polyarthritis resembling RA:** 18%
- **Arthritis mutilans** ("opera glass hands"): 2%
- **Sacroiliitis with or without higher levels of spinal involvement:** 24%

Arnett FC: Seronegative spondyloarthropathies, *Bull Rheum Dis* 37:1–12, 1987.

131. What are the treatment options for ankylosing spondylitis?

NSAIDs, either nonselective or selective COX-2 inhibitors. Anti-TNF treatment such as etanercept, infliximab, adalimumab, or golimumab may be considered for those with persistent disease activity. Unlike RA, conventional DMARDs such as methotrexate and sulfasalazine do not have any demonstrable effect on axial disease, though they may have some benefit for peripheral arthritis. Nonpharmacologic treatment, including patient education and exercise programs, should also be part of the treatment approach.

Zochling J, van der Heijde D, Burgos-Vargas R, et al: ASAS/EULAR recommendations for the management of ankylosing spondylitis, *Ann Rheum Dis* 65:442–452, 2006.

VASCULITIS

132. What is vasculitis?

A varied group of disorders that share a common underlying pathology of inflammation of a single blood vessel or blood vessels. Vasculitis occurs as a primary disorder or secondary to a variety of diseases or drugs.

133. How are vasculitides classified?

By the predominant sizes of the involved blood vessels (large, medium, and small). The presence or absence of ANCA is a more recent addition to proposed classification criteria; however, there is substantial overlap among different vasculitides.

134. What are the possible immune-pathogenic mechanisms of vasculitis?

- Deposition of circulating antigen-antibody complexes or in situ formation of immune complexes within the vessel wall
- Cell-mediated hypersensitivity
- Granulomatous tissue reaction

135. What is polymyalgia rheumatica (PMR)?

An inflammatory condition that causes pain or stiffness, usually in the neck, shoulder girdle, and hip girdle with sudden onset and occurrence in patients older than 50 years. Patients typically have elevated ESR or CRP or both, which suggests a systemic inflammatory process.

136. What are the types of large vessel vasculitis?

Giant cell arteritis (GCA) and Takayasu's disease (TD).

137. What is the association between PMR and GCA?

Approximately 15% of patients with PMR develop GCA, and approximately 50% of patients with GCA have associated PMR.

138. How does the distribution of blood vessels involved in GCA affect the symptoms?

If the *extracranial* branches of the aorta (with sparing of the intracranial vessels) are involved, the classic manifestations of blindness, headache, scalp tenderness, and jaw claudication are seen. Vasculitis of the vertebral arteries can impair the posterior cerebral circulation and

cause stroke, transient ischemic attacks, vertigo, and dizziness. Involvement of the subclavian, axillary, and proximal brachial arteries leads to the aortic arch syndrome of claudication of the arms and absent or asymmetric pulses.

139. What is TD?

A large vessel vasculitis affecting blood vessels with elastic lamina. The populations at highest risk include women who are adolescent or in the second and third decades of life. The syndrome is most commonly seen in Japan, Southeast Asia, India, and Mexico. Clinical manifestations range from asymptomatic disease with nonpalpable pulses to catastrophic neurologic impairment (stroke, postural dizziness, seizures, and amaurosis).

140. What are the medium vessel vasculitides?

- Polyarteritis nodosa (PAN)
- KD
- Primary CNS vacuities

141. What is PAN?

A vasculitis characterized by necrotizing inflammation of medium-sized or small arteries. Patients typically present with systemic symptoms involving the kidneys, skin, joints, muscles, nerves, and GI tract.

142. Which are the characteristics of KD?

Fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, rash, extremity changes, and lymphadenopathy. The most serious complication is severe coronary aneurysmal dilations. KD is one of the most common vasculitides of childhood and usually occurs in children $<$ 5 years old.

143. Compare the common clinical presentations and laboratory findings of GCA, TD, KD, and PAN.

See Table 10-9.

144. With which diseases are ANCAs associated?

- Wegener's granulomatosis (WG)
- Microscopic polyarteritis (MPA)
- A pauci-immune (meaning lack of immune complex deposition or complement consumption) crescentic glomerulonephritis, limited to the kidneys

TABLE 10-9. CHARACTERISTICS OF GIANT CELL ARTERITIS, TAKAYASU'S DISEASE, KAWASAKI'S DISEASE, AND POLYARTERITIS NODOSA

	Vessels Affected	Clinical Manifestations	Laboratory Data
GCA	Large extracranial vessels	Visual changes, headache, scalp tenderness and jaw claudication	Elevated ESR and CRP
TD	Large blood vessels with elastic lamina	From asymptomatic to severe neurological impairment	Elevated ESR
KD	Medium vessel vasculitis	Fever, rash, conjunctivitis, erythema (lips/mucosa), LAD	Elevated ESR

(continued)

TABLE 10-9. CHARACTERISTICS OF GIANT CELL ARTERITIS, TAKAYASU'S DISEASE, KAWASAKI'S DISEASE, AND POLYARTERITIS NODOSA— *(continued)*

	Vessels Affected	Clinical Manifestations	Laboratory Data
PAN	Predominantly medium-sized venules	Systemic symptoms, HTN, renal insufficiency, abdominal pain, neurologic dysfunction	Possible hepatitis B Aneurysms on angiography

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; HTN = hypertension; KD = Kawasaki disease; LAD = lymphadenopathy; PAN = polyarteritis nodosa; TD = Takayasu's disease.

- Churg-Strauss syndrome (CSS)
- Drug-induced vasculitis: propylthiouracil, hydralazine, minocycline, and others
- Inflammatory rheumatic disease: RA, SLE, Sjögren's syndrome, SSc, inflammatory myopathies, and APA syndrome
- Autoimmune gastrointestinal disorders: ulcerative colitis and primary sclerosing cholangitis

145. What is WG?

One of the systemic necrotizing vasculitis characterized by granulomatous inflammation of the small vessels of the upper respiratory tract, lungs, and kidneys commonly associated with c-ANCA. Over 80–90% of WG patients have PR3-ANCA.

146. Which organs are primarily affected in WG?

Respiratory tract (upper and/or lower) and kidneys. Respiratory tract involvement can manifest as recurrent sinusitis, otitis media, tracheobronchial inflammation and erosions, lung nodules, or pneumonitis with cavitation. Renal involvement occurs in the form of a pauci-immune glomerulonephritis.

147. What are other symptoms in WG?

- Arthritis
- Neurologic symptoms including polyneuritis, meningitis and mononeuritis multiplex
- Skin ulcerations in the distal portions of arms or legs
- Eye inflammation due to contiguous granulomatous sinus disease (nasolacrimal duct obstruction, proptosis, and ocular muscle or optic nerve involvement) or due to focal vasculitis (conjunctivitis, episcleritis, scleritis, corneoscleral ulceration, uveitis, and granulomatous vasculitis of the retina and optic nerve).

148. What is CSS?

A granulomatous small vessel vasculitis that involves mainly the blood vessels of the lungs, GI system, and peripheral nerves and is associated with p-ANCA (myeloperoxidase) antibodies. The heart, skin, and kidneys may also be affected, and eosinophilia and severe asthma are very characteristic.

149. How is MPA characterized?

By pauci-immune necrotizing small vessel vasculitis of the lungs and kidneys without clinical or pathologic evidence of necrotizing granulomatous inflammation. MPA is the most common pulmonary-renal syndrome. Other organs involved include the skin, musculoskeletal system, and GI tract. Over 80% of patients with MPA are ANCA-positive, most often p-ANCA (MPO-ANCA).

150. What is cryoglobulinemic vasculitis (CV)?

Small vessel vasculitis caused by the localization of mixed cryoglobulins in vessel walls, which incites acute inflammation. The most frequent manifestations are purpura, arthralgias, and nephritis. Mixed cryoglobulins and RF are often positive. Most patients have an associated infection with hepatitis C virus.

151. Define "Henoch-Schönlein purpura (HSP)"?

As a small vessel vasculitis characterized by vascular deposition of IgA-dominant immune complexes. Purpura, arthralgias, and colicky abdominal pain are the most frequent manifestations. Approximately half the patients have hematuria and proteinuria, but only 10–20% have renal insufficiency. HSP is the most common vasculitis in childhood and has an excellent prognosis.

152. Compare the common clinical presentations and laboratory findings of MPA, WG, CSS, CV, and HSP.

See Table 10-10.

TABLE 10-10. CHARACTERISTICS OF MICROSCOPIC POLYANGIITIS, WEGENER GRANULOMATOSIS, CHURG-STRAUSS SYNDROME, CRYOGLOBULINEMIC VASCULITIS, AND HENOCH–SCHÖNLEIN PURPURA

		Characteristics		
Disease	Vessel Size Affected	Clinical Feature	Frequency (%)	Laboratory
MPA	Small to medium-sized vessels	Glomerulonephritis	>90	Usually p-ANCA (anti-MPO)
		Pulmonary and skin	50	
		Neurologic, GI	Less common	
WG	Small to medium-sized vessels	Pulmonary, ENT	90	Usually c-ANCA (anti-PR3)
		Glomerulonephritis	80	
		Neurologic, GI and skin	50	
CSS	Small to medium-sized vessels	Pulmonary and peripheral nerve.	70–80 50	Eosinophilia Usually p-ANCA (anti-MPO)
		Skin, ENT, GI, renal and musculoskeletal		
CV	Small vessels	Skin	90	Cryoglobulins, RF
		Musculoskeletal	70	
		Renal	55	
		Neurologic, GI	30–40	
HSP	Small vessels	Skin	90	IgA deposition
		Musculoskeletal	75	
		GI	60	

c-ANCA = cytoplasmic antineutrophil cytoplasmic antibody; CSS = Churg-Strauss syndrome; CV = cryoglobulinemic vasculitis; ENT = ear, nose, and throat; GI = gastrointestinal; HSP = Henoch-Schönlein purpura; MPA = microscopic polyangiitis; MPO = myeloperoxidase; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; RF = rheumatoid factor; WG = Wegener's granulomatosis.

153. What is BD?

A systemic vasculitic disorder of unknown etiology, characterized by relapsing episodes of oral aphthous ulcers, genital ulcers, skin lesions, and ocular lesions (retinal vasculitis, anterior and posterior uveitis). Other symptoms include arthralgia/arthritis, CNS vasculitis, meningitis, thrombosis, and GI ulcerations. BD affects blood vessels of all sizes and is most common along the "Old Silk Route," which spans the region from Japan and China in the Far East to the Mediterranean Sea, including countries such as Turkey and Iran.

154. What are the skin lesions of BD?

- Folliculitis
- Acneiform lesions
- Erythema nodosum lesions that may ulcerate
- Pathergy (pustular reaction to skin injury)
- Palpable purpura
- Pyoderma gangrenosum type lesions

155. What are the ocular findings associated with BD?

- Retinal vasculitis
- Anterior and posterior uveitis
- Hypopyon (severe anterior uveitis with purulent material in the anterior chamber)
- Cataracts
- Glaucoma
- Neovascularization
- Conjunctival ulceration

156. What treatments are available for the management of vasculitis?

Corticosteroids and immunosuppressive medications. The treatment choices for vasculitis will be determined by the type and severity of the manifestations of the disease. Some commonly used immunosuppressants include cyclophosphamide, azathioprine, and methotrexate.

OSTEOARTHRITIS

157. Is OA a genetic disease?

Yes, in that there is a hereditary component. Perhaps the most recognized inherited feature is the presence of Heberden's nodes in mothers and sisters of affected patients. Studies have uncovered a mutation in a type II collagen gene (Arg519 to Cys) that predisposes to early OA.

Pun YL, Moskowitz RW, Lie S, et al: Clinical correlations of osteoarthritis associated with a single-base mutation (arginine 519 to cysteine) in type II procollagen gene: A newly defined pathogenesis, *Arthritis Rheum* 37:264–269, 1994.

158. Compare the biochemical changes of the aged joint with the osteoarthritic joint.

See Table 10-11.

159. What is spinal stenosis syndrome?

The progressive narrowing of the spinal canal, most commonly from OA of the lumbar or cervical spine. With cervical disease, patients typically present with pain and limitation of motion. Hyperreflexia is common. Other signs may include muscle weakness, spastic gait, and Babinski's sign. In the lumbar region, the clinical manifestations are mostly those of neurogenic claudication and compression of the cauda equina when severe.

TABLE 10-11. BIOCHEMICAL DIFFERENCES BETWEEN THE AGING JOINT AND OSTEOARTHRITIS

	Aging Joint	Osteoarthritis
Bone	Osteoporosis	Thickened cortices, osteophytes, subchondral cysts, remodeling
Chondrocyte activity	Normal	Increased
Collagen	Increased cross-linking of fibrils	Irregular weave Smaller fibrils
Water	Slight decrease	Significant increase
Proteoglycan	Normal total content Decreased chondroitins Increased keratin Normal aggregation	Decreased total proteoglycan component Increased chondroitins Decreased keratin Decreased aggregation

From Brandt KD, Fife RS: Aging in relation to the pathogenesis of osteoarthritis. Clin Rheum Dis 12:117–130, 1986.

160. What is DISH?

Diffuse idiopathic skeletal hyperostosis characterized by extensive ossification of tendinous and ligamentous attachments to the bone. Spine involvement with flowing calcification over the anterior longitudinal ligament is among the most common findings. Extraspinal manifestations also are reported. DISH has been associated with obesity, increased waist circumference, hypertension, dyslipidemia, diabetes mellitus, hyperuricemia, metabolic syndrome, and an increased risk for cardiovascular diseases.

161. What radiographic features help to distinguish DISH from ankylosing spondylitis, degenerative spine disease, and spondylosis deformans?

- Flowing calcification along the anterolateral aspect of at least four contiguous vertebral bodies
- Relative preservation of intervertebral disc height in the involved vertebral segment and absence of extensive radiographic changes of "degenerative" disc disease (disc space narrowing with vacuum phenomena, vertebral body marginal sclerosis)
- Absence of apophyseal joint ankylosis and sacroiliac joint erosion, sclerosis, and intra-articular osseous fusion

162. What is the vacuum phenomenon?

A radiographic finding seen in degeneration of the intervertebral disc that has the appearance of a radiolucent stripe in an intervertebral disc. Radiolucencies represent gas or nitrogen that appears at the site of negative pressure produced by abnormal spaces of clefts.

INFECTIOUS ARTHRITIS

163. What is the mechanism for acute rheumatic fever?

Antibody formation to group A streptococcus that occurs after pharyngeal infection, which may be asymptomatic. The antibodies cross-react with human antigens, leading to a

persistent autoimmune reaction with tissue destruction (molecular mimicry) and development of immune complexes. Arthritis is one of the earliest manifestations of rheumatic fever and has a migratory pattern.

164. What is St. Vitus' dance?

A neurologic disorder consisting of abrupt, purposeless involuntary movements that disappear during sleep. The disorder is found in patients with rheumatic fever and is also called "Syndenham's chorea" or "chorea minor."

165. What viral illnesses may be associated with arthropathy?

- Hepatitis B and C
- Parvovirus B19
- EBV
- Cytomegalovirus (CMV)
- Enteroviruses (ECHO [enteropathic cytopathogenic human orphan], coxsackievirus)
- HIV
- Mumps
- Rubella
- Smallpox (vaccinia)
- Group A arboviruses (Ross River virus, chikungunya, o'ynong-nyong, sindbis, Mayaro)

Naides SJ: Viral arthritis including HIV, *Curr Opin Rheumatol* 7:337–342, 1995.

166. What arthropathy is associated with chronic hepatitis B infection?

Polyarteritis nodosa, likely associated with persistent circulating hepatitis B antigen.

167. What are the articular manifestations of hepatitis C infection?

- Arthropathy
- Nondestructive RA-like arthritis
- Monoarthritis
- Oligoarthritis

Hepatitis C can also be part of the mixed cryoglobulinemia syndrome.

168. What arthropathy is associated with active parvovirus infection?

Nondestructive RA-like picture with positive RF. The arthropathy clears with no chronic or destructive sequelae.

169. Summarize the association of rubella infection with arthropathy.

Joint symptoms usually begin within 1 week of the onset of the rash of rubella and include arthralgia and arthritis, especially in adult women. In the past, arthritis and arthralgias often were seen after rubella vaccination, but they are less common because a less arthrogenic strain of virus is used for the vaccine.

170. What are the common articular problems experienced by patients infected with HIV?

- Arthralgia
- Reactive arthritis associated with HLA-B27 (but axial disease and sacroiliitis are unusual)
- Psoriatic arthritis with asymmetrical polyarticular inflammatory arthritis that may be more severe than in non-HIV patients
- "Painful articular syndrome" describing an exquisitely painful, asymmetrical, minimally inflammatory arthritis involving the large joints of the lower extremities
- Septic arthritis, typically *Staphylococcus aureus* but also with *Streptococcus, Salmonella,* atypical *Mycobacteria,* and other opportunistic infections

Solomon G, Brancato L, Winchester R: An approach to the human immunodeficiency virus–positive patient with a spondyloarthropathic disease, *Rheum Dis Clin North Am* 17:43–58, 1991.

171. What are the specific muscle problems encountered by patients infected with HIV?

- IIM (polymyositis and dermatomyositis)
- Nemaline rod myopathy with findings of nemaline rods without inflammation on muscle biopsy
- Noninflammatory myopathy associated with severe wasting
- Pyomyositis or direct muscle infection with small muscle abscesses frequently caused by *S. aureus*, *Mycobacterium avium,* cryptococci, *Microsporidia,* and other organisms
- Medication-associated myopathy seen with zidovudine (AZT) and other nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)

172. What is DILS?

Diffuse infiltrative lymphocytosis syndrome, a condition occurring in 3–8% of HIV-infected patients, producing prominent salivary gland involvement and sicca symptoms due to CD8 infiltration. In addition to salivary glands, other organs may be involved in DILS resulting in neuropathy, interstitial pneumonitis, interstitial nephritis, and hepatitis.

173. Is DILS the same as Sjögren's syndrome?

No. DILS is a distinct entity with different immunogenetics and pathophysiology from Sjögren's syndrome. DILS is a predominantly CD8 disease whereas Sjögren's syndrome is a CD4 disease. In addition, African American DILS sufferers show a high incidence of HLA-DR8, whereas DR6 and DR7 are more prevalent in Caucasians. By contrast, in patients with Sjögren's syndrome, HLA-DR2 and DR3 predominate.

174. Which bacterial pathogens are most commonly responsible for septic arthritis?

- *Neisseria gonorrhoeae*
- *Staphylococcus* spp.
- *Streptococcus* spp.
- Gram-negative bacilli

175. What are the common clinical manifestations of gonococcal arthritis?

Migratory tenosynovitis and macular or papular rash on a distal extremity. Gonococcal arthritis occurs in approximately 0.1–0.5% of patients with gonorrhea, but synovial fluid cultures are positive in $<$ 50% of cases.

176. What are the clinical manifestations of Lyme disease and the time of their occurrence in the untreated disease course?

Early localized:

- Erythema chronicum migrans (ECM)
- Flulike illness

Early disseminated:

- Neurologic findings (meningitis, cranial neuropathies such as Bell's palsy, peripheral neuropathy)
- Cardiac findings (arteriovenous block, myopericarditis)

Late:

- Inflammatory arthritis with chronic inflammatory synovitis

177. What is the classic skin manifestation of Lyme disease?

ECM, an expanding erythematous ring (often asymptomatic) with central clearing beginning at the sight of the tick bite. The *Borrelia* organism can be cultured from the margin of the lesion. In endemic regions, ECM is the most common presenting feature of early Lyme disease. Other skin manifestations include benign lymphocytoma and acrodermatitis chronica atrophicans.

178. Is chronic arthritis of Lyme disease produced by active joint infection?

Likely not. Live spirochetes have rarely been documented. In addition, spirochetal DNA has not been reliably discovered after amplification with polymerase chain reaction (PCR) technology.

CRYSTAL ARTHROPATHY

179. What three principal crystals are associated with joint inflammation?

- Urate (gout)
- Calcium pyrophosphate (CPP; "pseudogout")
- Hydroxyapatite

Dieppe P, Calvert P: *Crystals and Joint Disease*, London, 1983, Chapman & Hall.

180. What conditions have been associated with calcium pyrophosphate dihydrate (CPPD) disease?

Hemochromatosis	Hypophosphatasia	Hypomagnesemia
Hypothyroidism	Amyloidosis (likely)	Gout
Aging	Trauma, including surgery	
Hyperparathyroidism		
Gene mutations (ANKH)	OA (likely)	

181. Why is the polarizing microscope important in the diagnosis of rheumatic diseases?

To analyze synovial fluid and identify the specific etiologies of inflammatory arthritis, in particular crystal-induced arthritis. The microscopy operates on the relatively simple observation that some crystals refract light into fast and slow rays (i.e., they are birefringent). Polarized light passing through a crystal is no longer parallel to light not passing through the crystal. If a second polarizer is added so that its axis is rotated 90° (extinction) to the light as it emerges from the first polarizer but after some light is bent (rotated) by the crystal in between the polarizers, the only light reaching the observer's eye is the light that the crystal has rotated. Monosodium urate crystals have a strongly negative birefringent appearance on polarized light microscopy and appear yellow when oriented parallel to the axis of the compensator. Calcium pyrophosphate crystals are weakly positively birefringent and appear blue when oriented parallel to the axis of the compensator. Polarized microscopy requires operator expertise for accuracy.

Rosenthal AK, Mandel N: Identification of crystals in synovial fluids and joint tissues, *Curr Rheumatol Rep* 3:11–16, 2001.

182. Where is chondrocalcinosis commonly demonstrated roentgenographically?

In the joint cartilages. The cartilages appear punctate or stippled with linear densities within the articular hyaline or fibrocartilage in knee menisci, radiocarpal joints, annulus fibrosus of intervertebral discs, and symphysis pubis. When present in peripheral joints, the findings are usually bilateral. The prevalence in the general population (as assessed by multiple radiologic studies) is 10–15% in people aged 65–75 years but rises above 40% in people older than 80 years.

183. What are the four stages of gout?

- **Stage 1:** asymptomatic hyperuricemia
- **Stage 2:** acute gouty arthritis
- **Stage 3:** intercritical gout or the period between attacks
- **Stage 4:** chronic tophaceous gout

184. Describe stage 1 gout.

Elevated serum urate levels in the absence of symptomatic articular disease or nephrolithiasis. Not all patients with asymptomatic hyperuricemia progress to gout, but the higher the serum level, the greater the likelihood of developing articular disease. With serum urate $>$ 9 mg/dL, the annual incidence of gout is 4.9%, with 5-year incidence of 22%. In most cases, 20–30 years of sustained hyperuricemia pass before an attack of nephrolithiasis or arthropathy.

Campion EW, Glynn RJ, DeLabry LO: Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study, *Am J Med* 82:421–426, 1987.

185. Describe the characteristics of the first attack of acute gouty arthritis (stage 2).

Exquisite pain usually occurring in a single joint (monoarticular). Fever, swelling, erythema, and skin sloughing may be associated findings, suggesting cellulitis. Fifty percent of initial attacks occur as podagra (involving the great toe or MTP joint), and 90% of patients with gout have podagra at some stage of disease without treatment. Typical sites of acute gout attacks include feet, ankles, knees, and less commonly, upper extremity joints such as elbows, wrists, and fingers.

186. What are the symptoms of stage 3 gout?

None. Stage 3 gout refers to the asymptomatic period between attacks. However, 62% of patients have a second attack of articular disease within 1 year of the first attack, 16% within 1–2 years, 11% within 2–5 years, 4% after 5–10 years, and 7% after $>$ 10 years.

187. What is chronic tophaceous gout (stage 4)?

Chronic arthritis with extra-articular tissue deposition of urate. Gout flares in this stage are often polyarticular, with longer duration and severity. In some cases, chronic tophaceous gout may have an appearance mimicking RA (pseudorheumatoid pattern), with chronic, nearly symmetrical arthritis with nodules (tophi in gout). The principal determinant of the rate of urate deposition is the serum urate concentration. Tophi are often observed on finger pads, olecranon bursae, pinnae of the ear, and pressure points.

Teng GG, Nair R, Saag KG: Pathophysiology, clinical presentation and treatment of gout, *Drugs* 66:1547–1563, 2006.

188. What are the treatment options for acute gout flares?

NSAIDs, colchicine, and corticosteroids, either oral or intra-articular. Ideally, acute gout flares are treated within 12 hours of symptom onset to reduce the severity. Oral NSAIDs can be given at high dose for 2–3 days, then tapered off within 5–7 days. NSAIDs have potential GI and renal toxicities, especially in elderly patients and those with comorbidities such as congestive heart failure or anticoagulation use. Oral colchicine at lower doses (1.2 mg initially, followed by 0.6 mg 1 hr later) was shown in a recent randomized study to have equal efficacy but better tolerability than traditional higher dose colchicines (1.2 mg initially, then 0.6 mg every hour for 6 hr) for acute gout flares. Severe diarrhea, nausea, and vomiting are among the common side effects of colchicine, especially with a higher dose regimen.

Terkeltaub R: Update on gout: New therapeutic strategies and options, *Nat Rev Rheumatol* 6:30–38, 2010.

189. What are the treatment options for chronic gout?

Allopurinol, probenecid, and febuxostat. New evidence-based guidelines focus on treating chronic gout to a target uric acid level $<$ 6 mg/dL. Allopurinol is commonly used in uric acid overproducers and undersecreters. Uricosuric agents similar to probenecid are

limited to undersecreters with normal renal function. Allopurinol can be initiated at a dose of 100 mg daily, titrating higher to a maximum approved dose of 800 mg/day. Allopurinol dosing should be more cautious in patients with renal insufficiency (CrCl $<$ 50 mL/min) or elderly patients. Febuxostat, a nonpurine inhibitor of xanthine oxidase, could be used for treatment in those patients with allopurinol hypersensitivity, intolerance, or treatment failure. Febuxostat is dosed at 40 mg daily, or 80 mg daily for those who do not attain adequate uric acid suppression at the lower dose. Chronic urate-lowering therapy should not be started during acute gout flares, but can be continued through acute flares in those already taking urate-lowering treatment. Also, it is not uncommon for patients starting chronic urate-lowering therapy to have more frequent acute gout flares due to mobilization and destabilization of urate deposits in tissues and joints. These patients should receive acute gout prophylaxis with low-dose daily colchicine (0.6 mg daily or twice daily) or NSAIDs for the first 6 months of therapy.

Teng GG, Nair R, Saag KG: Pathophysiology, clinical presentation and treatment of gout, *Drugs* 66:1547–1563, 2006.

Terkeltaub R: Update on gout: New therapeutic strategies and options, *Nat Rev Rheumatol* 6:30–38, 2010.

SOFT TISSUE RHEUMATISM

190. What is fibromyalgia (FM)?

A chronic nondestructive illness characterized by fatigue, generalized pain, sleep disturbance (sometimes termed "nonrestorative" sleep), and tender points in a characteristic distribution (see Fig. 10-1). Eighteen reproducible tender points have been established, and diagnosis of FM requires the presence of at least 11. Patients may have FM alone or in association with other diseases such as RA, OA, Lyme disease, and sleep apnea. The disease is often mimicked by hypothyroidism.

Wolfe F, Smythe HA, Yunus MB, et al: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee, *Arthritis Rheum* 33:160–172, 1990.

191. What other symptoms and syndromes may be associated with FM?

- IBS
- Tension headaches
- Irritable bladder (daytime urinary frequency, nocturia, dysuria, urgency, urge incontinence)
- Chronic cough

192. How is FM treated?

With muscle reconditioning (slow but consistent physical training), restoration of more normal sleep patterns, and pain control. Low-dose tricyclic antidepressants may help with sleep and non-narcotic medications such as NSAIDs or acetaminophen may be used for pain control. Biofeedback may also be of use. More recent U.S. Food and Drug Administration (FDA)–approved medications include duloxetin, pregabalin, and milnacipran.

193. Define the following disorders named after occupations.

- **Housemaid's knee:** prepatellar bursitis
- **Tailor's seat** (also called "weaver's bottom"): inflammation of the ischial bursa (the bursa that separates the gluteus maximus from the ischial tuberosity)

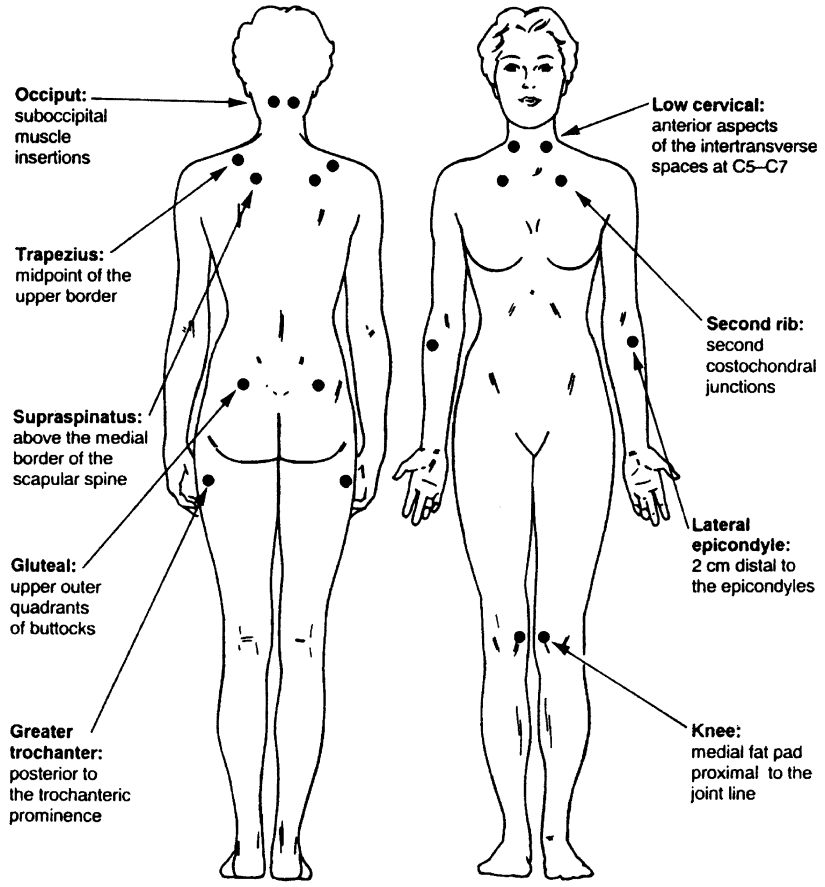

Figure 10-1. Location of tender points in fibromyalgia. (From Freundlich B, et al: The fibromyalgia syndrome. In Schumacher HR Jr, et al [eds]: Primer on Rheumatic Diseases, 10th ed. Atlanta, Arthritis Foundation, 1993, p 247, with permission.)

194. Define the following disorders named after specific sports and activities.

- **Little Leaguer's shoulder:** separation of the proximal humeral epiphysis, probably secondary to the repetitive motion associated with pitching
- **Tennis elbow:** lateral epicondylitis
- **Golfer's elbow:** medial epicondylitis
- **Jumper's knee:** Sinding-Larsen-Johannson (SLJ) syndrome or patellar tendinopathy usually seen in basketball and volleyball athletes but also in ballet dancers

195. What is deQuervain's tenosynovitis?

Inflammation of the synovial lining and subsequent narrowing of the membrane (stenosing tenosynovitis) of the abductor pollicis longus and extensor pollicis brevis tendons at the radial styloid.

196. What is patellofemoral syndrome (PFS)?

Knee pain that worsens with activity, while descending stairs and after long periods of inactivity. PFS occurs when the patella does not move or "track" in a correct fashion when the knee is being bent and straightened. This movement can lead to damage of the surrounding tissues, such as the cartilage on the underside of the patella itself, which can lead to pain in the region. This injury is quite common in people who play sports, in particular adolescent girls.

OTHER RHEUMATIC CONDITIONS

197. What is pyoderma gangrenosum?

Skin lesions that begin as pustules or erythematous nodules and break down to form spreading ulcers with necrotic, undermined edges. Pyoderma gangrenosum is frequently associated with inflammatory bowel disease (IBD) but also occurs in chronic active hepatitis, seropositive RA (without evidence of vasculopathy), leukemia, and polycythemia vera. Differential diagnosis of the lesions includes necrotizing vasculitis, bacterial infection, and spider bites.

198. What is Sjögren's syndrome?

An exocrinopathy manifested by sicca (dryness) symptoms. The lacrimal and salivary glands are primarily affected, but the urogenital and GI systems may be involved as well.

199. What are the revised ACR criteria for Sjögren's syndrome?

I. Presence of ocular symptoms (dry eyes, recurrent feeling of sand or gravel in the eyes, or use of tear substitutes more than three times a day)
II. Presence of oral symptoms (feeling of dry mouth daily, recurrent or persistent swollen salivary glands, frequent use of liquids to help swallow dry food)
III. Objective evidence of ocular dryness (e.g., the Schirmer's test or rose Bengal score)
IV. Objective evidence of salivary gland involvement (e.g., sialogram, salivary scintigraphy or salivary flow test)
V. Positive histopathology on salivary gland biopsy
VI. Presence of Sjögren's specific autoantibodies, SSA/Ro or SSB/La.

Patients are considered to have Sjögren's if:

1. Four out of six criteria are present and either V or VI is present or
2. Three out of four objective criteria are present (III, IV, V, and VI).

Vitali C, Bombardieri S, Jonsson R, et al: Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group, *Ann Rheum Dis* 61:554–558, 2002.

200. How do you treat Sjögren's syndrome?

Primarily with symptom relief using ductal plugs, preservative-free artificial tears, and cholinergic agonists or other secretagogues There is limited evidence to support the use of immunomodulatory agents in treating primary Sjögren's syndrome, but anecdotal published reports have reported that hydroxychloroquine may help with the arthralgias and dermatologic conditions. Patients benefit from regular dental and ophthalmologic evaluation.

201. What is undifferentiated connective tissue disease (UCTD)?

A syndrome with clinical and laboratory features that are suggestive of an autoimmune etiology but the diagnosis is unable to be confirmed. An exact diagnosis of a rheumatic disease is not always possible at initial presentation. The clinical manifestations of a given rheumatic disease may not develop at once but may unfold over time, and many features are shared among different rheumatic diseases. Myositis, for example, can be found as a primary condition (polymyositis) or as part of other systemic diseases (e.g., dermatomyositis, SSc, and SLE). In addition to shared clinical features, rheumatic diseases may have shared serologic features.

The most obvious example is ANA, which may be found in various diseases, including SLE, SSc, Sjögren's syndrome, inflammatory myopathies, Hashimoto's thyroiditis, and IBD. When clinical and laboratory features suggest an autoimmune etiology but clinical and serologic heterogeneity make the diagnosis uncertain, the designation UCTD may be used.

KEY POINTS: SPECIFIC RHEUMATIC DISEASES

1. Rheumatoid arthritis is a chronic, symmetrical inflammatory disease that will lead to joint damage and destruction. Early diagnosis and early initiation of disease-modifying treatment lead to better outcomes.
2. SLE is a heterogeneous, autoimmune disease more common in premenopausal females and is associated with ANA autoantibodies.
3. Undifferentiated connective tissue disease is a description commonly applied to a patient with signs and symptoms definitive enough to be clearly autoimmune and inflammatory in nature, but not sufficient to render a more exact diagnosis.
4. Spondyloarthropathies are characterized by inflammatory symptoms of the axial skeleton and have associated symptoms of enthesopathy and uveitis.

ANA = antinuclear antibody; SLE = systemic lupus erythematosus.

202. How is UCTD different from MCTD?

MCTD is defined by specific characteristics and was first described as a separate entity in 1972. MCTD is used specifically when features of SLE and SSc are present with high titers of antibody to U_1RNP.

203. What diseases are associated with complement deficiencies?

See Table 10-12.

TABLE 10-12. CLINICAL MANIFESTATIONS OF COMPLEMENT COMPONENT DEFICIENCY

Deficient Component	Clinical Syndrome*
Classic Pathway	
C1q	SLE, infections
C1r/C1s	SLE, infections
C4	SLE, infections
C2	SLE, infections
Lectin Pathway	
MBL	Infections
Central component	
C3	Severe infections, GN, SLE
Membrane attack component	
C5, C6, C7, C8 or C9	*Neisseria* infections

(continued)

TABLE 10-12. CLINICAL MANIFESTATIONS OF COMPLEMENT COMPONENT DEFICIENCY—*(continued)*

Deficient Component	Clinical Syndrome*
Alternative Pathway	
Properdin, factor D	*Neisseria* infections

GN = glomerulonephritis; MBL = mannan-binding lectin; SLE = systemic lupus erythematosus.
*With early component deficiencies of the classic pathway (C1, C4, or C2), infections are caused by the commonly encountered pyogenic organisms. With a late component (C5–9) or an alternative pathway component deficiency, *Neisseria* infections predominate, especially meningococcal infections.
From Atkinson JD: Complement system. In Firestein GS, Budd RS, Harris ED, et al (eds): Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.

204. Describe Still's disease.

A syndrome characterized by high spiking fevers ($\leq$104°F), polyarthritis, evanescent rash typically on the trunk, leukocytosis, and elevated inflammatory markers and ferritin that occurs in children and adults. Fevers may occur only once or twice a day and patients typically have a negative RF and ANA.

205. What is sarcoidosis?

A systemic inflammatory disease characterized by a noncaseating granulomatous reaction in affected organs. The lungs are most commonly affected, but the skin (typically as erythema nodusum), eyes (potentially all compartments), joints (arthralgias or synovitis), upper respiratory tract (nasal congestion), and lymph nodes (enlargement) are also affected. Asymptomatic sarcoid granulomas have been found in muscle biopsy and may occur in bones, appearing radiographically as cysts. Osteolysis also has been described.

206. What is Löfgren's syndrome?

An acute presentation of sarcoidosis that consists of fever, bilateral hilar adenopathy, erythema nodosum, symmetrical polyarthritis, and uveitis. This syndrome is more common in Scandinavians.

207. What is Ehlers-Danlos syndrome?

A group of disorders characterized by hyperextensibility of skin and hypermobility of joints, predisposing to early development of osteoarthritis.

208. Distinguish between Legg-Calvé-Perthes disease and Osgood-Schlatter disease.

- **Legg-Calvé-Perthes disease:** idiopathic osteonecrosis of the femoral capital epiphysis usually in boys ages 3–8 that may result in a large flat femoral head
- **Osgood-Schlatter disease** (also called "tibial tubercle apophysitis"): inflammation at the site where the patellar tendon inserts onto the tibial tubercle that is probably due to a repetitive motion injury, usually occurring in adolescents

209. Describe RS3PE syndrome.

Remitting **s**eronegative **s**ymmetrical **s**ynovitis with **p**itting **e**dema (RS3PE). Mostly affecting men older than 70 years, the syndrome is characterized by an acute onset of severe synovitis of the small joints with pitting edema of the dorsal aspect of the hand. Symptoms respond to low-dose prednisone and the syndrome can mimic conditions like RA and PMR.

210. Define "Cogan's syndrome."

An unusual vasculopathy associated with interstitial keratitis, sensorineural hearing loss, tinnitus, and vertigo. Systemic features such as fever, weight loss, and fatigue are present in about one half of patients.

211. What is pigment villonodular synovitis (PVNS)?

A proliferative disorder of unknown etiology characterized by inflammation and hemosiderin of the synovium. The knee is most commonly affected, and clinically, the patient presents with monoarticular joint swelling. MRI is the diagnostic modality of choice because it may detect the hemosiderin that will show nodular foci.

212. Describe Paget's disease of bone.

A chronic disorder of bone remodeling in which there is increased osteoclast-mediated bone resorption leading to increased bone formation; however, this reorganization leads to a disorganized bone matrix and mechanical weakness of the bone. Patients are older than 40 years with a 2:1 incidence in men compared with women. Most patients are asymptomatic, but bone pain and joint pain at night tends to occur. Paget's disease is typically found through serendipitous testing such as an elevated alkaline phosphatase or noted on x-rays ordered for other reasons. Radionuclide bone scan can show the extent of disease. Treatments include analgesics, bisphosphonates, and calcitonin.

213. What conditions are associated with avascular necrosis of bone?

- Trauma (femoral head fracture)
- Gaucher's disease
- Hemoglobinopathies
- Pregnancy
- Exogenous or endogenous overproduction of glucocorticoids
- SLE
- Alcoholism
- Lymphoproliferative diseases
- HIV
- Anticardiolipin antibody
- Kidney transplantation

214. What mechanisms contribute to bone loss with the use of GCs?

Inhibition of osteoblast proliferation and stimulation of osteoblast and osteocyte apoptosis (physiologic cell death). Increased bone resorption also occurs by increasing osteoclast proliferation via stimulating production of receptor activator of nuclear factor kappa-B (RANK) leading to osteoclastogenesis. Corticosteroids have also been shown to decrease intestinal absorption of calcium and increase urinary calcium excretion. The calcium loss stimulates parathyroid hormone (PTH) production and PTH levels are often elevated. The severity of bone loss parallels the dose and duration of treatment. Patients at doses of > 7.5 mg/day will generally have some bone loss, usually in trabecular bone.

Sambrook PN, Jones G: Corticosteroid osteoporosis, *Br J Rheum* 34:8–12, 1995.

Khosla S: Minireview: The OPG/RANKL/RANK system, *Endocrinology* 2:5050–5055, 2001.

215. Describe nephrogenic systemic fibrosis (NSF).

Large areas of hardened skin in patients with chronic kidney disease that is likely associated with gadolinium-based MRI contrast agents. Histopathology reveals disruption of normal collagen bundles with increased dermal mucin deposition.

ACKNOWLEDGMENT

The editor gratefully acknowledges contributions by Dr. Richard A. Rubin that were retained from the previous edition of *Medical Secrets*.

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