4 - Musculoskeletal and Connective Tissue Disorders

Chapter 32. Approach to the Patient With Joint Disease

Introduction

Some musculoskeletal disorders affect primarily the joints, causing arthritis. Others affect primarily the bones (eg, fractures, Paget's disease, tumors), muscles or other extra-articular soft tissues (eg, fibromyalgia), or periarticular soft tissues (eg, polymyalgia rheumatica, bursitis, tendinitis, sprain). Arthritis has myriad possible causes, including infection, autoimmune disorders, crystal-induced inflammation, and noninflammatory tissue degeneration (eg, osteoarthritis). Arthritis may affect single joints (monarthritis) or multiple joints (polyarthritis) in a symmetric or asymmetric manner. Joints may suffer fractures or sprains (see elsewhere in THE MANUAL).

History

The clinician should focus on systemic and extra-articular symptoms as well as joint symptoms. Many symptoms, including fever, chills, malaise, weight loss, Raynaud's syndrome, mucocutaneous symptoms (eg, rash, eye irritation or pain, photosensitivity), and GI or cardiopulmonary symptoms, can be associated with various joint disorders.

Pain is the most common symptom of joint disorders. The history should address the character, location, severity, factors that aggravate or relieve pain, and time frame (new-onset or recurrent). The clinician must determine whether pain is worse when first moving a joint or after prolonged use and whether it is present upon waking or develops during the day. Usually, pain originating from superficial structures is better localized than pain originating from deeper structures. Pain originating in small distal joints tends to be better localized than pain originating in large proximal joints. Joint pain can be referred from extra-articular structures or from other joints. Arthritis often causes aching pain, whereas neuropathies often cause burning pain.

Stiffness may mean weakness, fatigue, or fixed limitation of motion to patients. The clinician must separate the inability to move a joint from reluctance to move a joint because of pain. Characteristics of stiffness may suggest a cause, as in the following:

- Discomfort that occurs with motion when attempting to move a joint after a period of rest occurs in rheumatic disease. Duration of stiffness after beginning joint motion reflects its severity.

- The theater sign (stiffness upon standing that necessitates walking slowly after sitting for several hours) is common in osteoarthritis.

- Stiffness is more severe and prolonged in inflammatory joint disorders.

- Morning stiffness in peripheral joints that lasts > 1 h can be an important early symptom of RA (see Table 32-1).

- In the low back, morning stiffness that lasts > 1 h may reflect spondylitis.

Fatigue is a desire to rest that reflects exhaustion. It differs from weakness, inability to move, and reluctance to move due to pain with movement.

Instability (buckling of a joint) may suggest weakness of the ligaments or other structures that stabilize the joint, which are assessed by stress testing. Buckling occurs most often in the knee and most often results from an internal joint derangement.

Physical Examination

Each involved joint should be inspected and palpated, and the range of motion should be estimated. With polyarticular disease, certain nonarticular signs (eg, fever, wasting, rash) may reflect systemic disorders.

The rest position of joints is noted, along with any erythema, swelling, deformity, and skin abrasions or punctures. Involved joints are compared with their uninvolved opposites or with those of the examiner.

Joints are gently palpated, noting the presence and location of tenderness, warmth, and swelling. Determining whether tenderness is present along the joint line or over tendon insertions or bursae is particularly important. Soft masses, bulges, or tissues that fill normal concavities or spaces (representing joint effusion or synovial proliferation) are noted. Palpation of

[**Table 32-1.** Distinguishing Inflammatory vs Noninflammatory Features in Joint Disease by Features]

swollen joints can sometimes differentiate among joint effusion, synovial thickening, and capsular or bony enlargement. Small joints (eg, the acromioclavicular, tibiofibular, radioulnar) can be the source of pain that was initially believed to arise from a nearby major joint. Bony enlargement (often due to osteophytes) is noted.

Active range of motion (the maximum range through which the patient can move the joint) is measured first, using a goniometer; limitation may reflect weakness, pain, or stiffness as well as mechanical abnormalities. Then passive range of motion (the maximum range through which the examiner can move the joint) is assessed; passive limitation generally reflects mechanical abnormalities (eg, scarring, swelling, deformities) rather than weakness or pain. Active and passive movement of an inflamed joint (eg, due to infection or gout) may be very painful.

Patterns of joint involvement should be noted. Symmetric involvement of multiple joints is common in systemic diseases (eg, RA); monarticular (involving one joint) or asymmetric oligoarticular (involving ≤ 4) joint involvement is more common in osteoarthritis and psoriatic arthritis. Small peripheral joints are commonly affected in RA, and the larger joints and spine are affected more in spondyloarthropathies. However, a pattern of involvement may not be apparent in early disease.

Crepitus, a palpable or audible grinding produced by motion, is noted. It may be caused by roughened articular cartilage or by tendons; crepitus-causing motions should be determined and may suggest which structures are involved.

Specific features should be sought at each joint.

Elbow: Synovial swelling and thickening caused by joint disease occur in the lateral aspect between the radial head and olecranon, causing a bulge. Full 180° extension of the joint should be attempted. Although full extension is possible with nonarthritic or extra-articular problems such as tendinitis, its loss is an early change in arthritis. The area around the joint is examined for swellings. Rheumatoid nodules are firm, occurring especially along the extensor surface of the forearm. Tophi are sometimes visible under the skin as cream-colored aggregates and indicate gout. Swelling of the olecranon bursa occurs over the tip of the olecranon, is cystic, and does not limit joint motion; infection, trauma, gout, and RA are possible causes. Epitrochlear nodes occur above the medial epicondyle; they can result from inflammation in the hand but can also suggest sarcoidosis or lymphoma.

Shoulder: Because pain can be referred to areas around the shoulder, shoulder palpation should include the glenohumeral, acromioclavicular, and sternoclavicular joints, the coracoid process, clavicle, acromion process, subacromial bursa, biceps tendon, and greater and lesser tuberosities of the humerus, as well as the neck. Glenohumeral joint effusions may cause a bulge between the coracoid process and the humeral head. Possible causes include RA, osteoarthritis, septic arthritis, Milwaukee shoulder (see p. 355), and other arthropathies.

Limited motion, weakness, pain, and other disturbances of mobility caused by rotator cuff impairment can be quickly identified by having the patient attempt to abduct and raise both arms above the head and then to slowly lower them. Muscle atrophy and neurologic abnormalities should be sought.

Knee: At the knee, gross deformities such as swelling (eg, joint effusion, popliteal cysts), quadriceps muscle atrophy, and joint instability may be obvious when the patient stands and walks. With the patient

supine, the examiner should palpate the knee, identifying the patella, femoral condyles, tibial tuberosity, tibial plateau, fibular head, medial and lateral joint lines, popliteal fossa, and quadriceps and patellar tendons. The medial and lateral joint lines correspond to locations of the medial and lateral menisci and can be located by palpation while slowly flexing and extending the knee. Tender extra-articular bursae such as the anserine bursa below the medial joint line should be differentiated from true intra-articular disturbances.

Detection of small knee effusions is often difficult and is best accomplished using the bulge sign. The knee is fully extended and the leg slightly externally rotated while the patient is supine with muscles relaxed. The medial aspect of the knee is stroked to express any fluid away from this area. Placement of one hand on the suprapatellar pouch and gentle stroking or pressing on the lateral aspect of the knee can create a fluid wave or bulge, visible medially when an effusion is present. Larger effusions can be identified visually or by balloting the patella. Joint effusion can result from many joint diseases, including RA, osteoarthritis, gout, and trauma.

Full 180° extension of the knee is attempted to detect flexion contractures. The patella is tested for free, painless motion.

Hip: Examination begins with gait evaluation. A limp is common in patients with significant hip arthritis. It may be caused by pain, leg shortening, flexion contracture, muscle weakness, or knee problems. Loss of internal rotation (often the earliest change in hip osteoarthritis or any hip synovitis), flexion, extension, or abduction can usually be demonstrated. Placement of one hand on the patient's iliac crest detects pelvic movement that might be mistaken for hip movement. Flexion contracture can be identified by attempting leg extension with the opposite hip maximally flexed to stabilize the pelvis. Tenderness over the femoral greater trochanter suggests bursitis (which is extra-articular) rather than an intra-articular disorder. Pain with passive range of motion (assessed by internal and external rotation with the patient supine and the hip and knee flexed to 90°) suggests intra-articular origin. However, patients may have simultaneous intra-articular and extra-articular disorders.

Other: Hand examination is discussed elsewhere (see p. 385 and Polyarticular Joint Pain on p. 292). Foot and ankle examination is discussed in Ch. 44. Examination of the neck and back is discussed on p. 379.

Testing

Laboratory testing and imaging studies often provide less information than do the history and physical examination. While some testing may be warranted in some patients, extensive testing is often not.

Blood tests: Some tests, although not specific, can be helpful in supporting the possibility of certain systemic rheumatic diseases, as for the following:

- Antinuclear antibodies (ANA) and complement in SLE
- Rheumatoid factor and anticitrullinated peptide (CCP) in RA
- HLA-B27 in spondyloarthropathy (occasionally useful)
- Antineutrophil cytoplasmic antibodies (ANCA) in certain vasculitides (occasionally useful)

Tests such as WBC count, ESR, and C-reactive protein may help determine the likelihood that arthritis is inflammatory due to infectious or other systemic disorders, but these tests are not highly specific or sensitive. For example, an elevated ESR or C-reactive protein level suggests inflammation or may be due to aging or a large number of nonarticular inflammatory conditions (eg, infection, cancer). Also, such markers may not be elevated in all inflammatory disorders.

Imaging studies: Imaging studies are often unnecessary. Plain x-rays in particular reveal mainly bony abnormalities, and most joint disorders do not affect bone primarily. However, imaging may help in the initial evaluation of relatively localized, unexplained persistent or severe joint and particularly spine

abnormalities; they may reveal primary or metastatic tumors, osteomyelitis, bone infarctions, periarticular calcifications (as in calcific tendinitis), or other changes in deep structures that may escape physical examination. If chronic RA, gout, or osteoarthritis is suspected, erosions, cysts, and joint space narrowing with osteophytes may be visible. In pseudogout, Ca pyrophosphate deposition may be visible in intra-articular cartilage.

For musculoskeletal imaging, plain x-rays may be obtained first, but they are often less sensitive, particularly during early disease, than MRI, CT, or ultrasonography. MRI is the most accurate study for fractures not visible on plain x-rays, particularly in the hip and pelvis, and for soft tissues and internal derangements of the knee. CT is useful if MRI is contraindicated or unavailable. Ultrasonography, arthrography, and bone scanning may help in certain conditions, as can biopsy of bone, synovium, or other tissues.

Arthrocentesis: Arthrocentesis is the process of puncturing the joint with a needle to withdraw fluid. If there is an effusion and arthrocentesis is done correctly, fluid can generally be withdrawn. Examination of synovial fluid is the most accurate way to exclude infection, diagnose crystal-induced arthritis, and otherwise determine the cause of joint effusions. It is indicated in all patients with severe or unexplained monarticular joint effusions and in patients with unexplained polyarticular effusions.

Arthrocentesis is done using strictly sterile technique. Infection or other rash over the site used to enter the joint is a contraindication. Preparations for collecting samples should be made before doing the procedure. Local anesthesia, with lidocaine or difluoroethane spray, is often used. Many joints are punctured on the extensor surface to avoid nerves, arteries, and veins, which are usually on the joint's flexor surface. A 20-gauge needle can be used for most larger joints. Smaller joints of the upper and lower extremities are probably easier to access using a 22- or 23-gage needle. As much fluid as is possible should be removed. Specific anatomic landmarks are used (see
Figs. 32-1,
32-2, and
32-3).

Metacarpophalangeal joints, metatarsophalangeal joints, and interphalangeal joints of the hands and feet are punctured similarly to each other, using a 22- or 23-gauge needle. The needle is inserted dorsally, to either side of the extensor tendon. Distraction of the joint is sometimes useful to open the joint space and allow easier access.

[**Fig. 32-1.** Arthrocentesis of the shoulder.]

Synovial fluid examination: At the bedside, gross characteristics of the fluid are assessed, such as its color, turbidity, and viscosity. Viscosity can be assessed using the string sign. The length of a viscous string of joint fluid dropped from the syringe is normally > 3 cm. Inflammation decreases viscosity, shortening the length of the string.

Gross characteristics allow many effusions to be tentatively classified as noninflammatory, inflammatory, or infectious (see
Table 32-2). Effusions can also be hemorrhagic. Each type of effusion suggests certain joint diseases (see
Table 32-3). So-called noninflammatory effusions are actually mildly inflammatory but tend to suggest diseases such as osteoarthritis, in which inflammation is not severe.

Laboratory tests commonly done on joint fluid include cell count, leukocyte differential, Gram stain and culture (if infection is a concern—see p. 365), and wet drop examination for cells and crystals. However, the exact tests often depend on which diagnoses are suspected.

Microscopic examination of a wet drop preparation of synovial fluid for crystals (only a single drop of fluid from a joint is needed), using polarized light, is essential for definitive diagnosis of gout, pseudogout, and other crystal-induced arthritides (see p. 349). A polarizer over the light source and another polarizer between the specimen and the examiner's eye allow visualization of crystals with a shiny white birefringence. Compensated polarized light is provided by inserting a first-order red plate, as is found in

commercially available microscopes. The effects of a compensator can be reproduced by placing 2 strips of clear adhesive tape on a glass slide and placing this slide over the lower polarizer. Such a homemade system should be tested against a commercial polarizing microscope. The most common crystals seen are those diagnostic of gout (monosodium urate, negatively birefringent needle-shaped crystals) and pseudogout (Ca pyrophosphate, positively birefringent square-ended crystals). If crystals appear atypical in a wet drop, several less common crystals (cholesterol, liquid lipid crystals, oxalate, cryoglobulins) or artifacts (eg, depot corticosteroid crystals) should be considered.

Other synovial fluid findings that occasionally make or suggest a specific diagnosis include the following:

• Specific organisms (identifiable by Gram or acid-fast stain)

• Marrow spicules or fat globules (caused by fracture)

• Reiter's cells (monocytes on Wright's-stained smears that have phagocytized PMNs), which appear most often in reactive arthritis

• Amyloid fragments (identifiable by Congo red stain)

• Sickled RBCs (caused by sickle cell hemoglobinopathies)

[Fig. 32-2. Arthrocentesis of the elbow.]

[Table 32-2. Classification of Synovial Effusions]

Monarticular Joint Pain

Monarticular pain may originate from the joint itself or surrounding structures. There may be pain (arthralgia) or also inflammation (arthritis) with redness, warmth, and swelling. Pain may occur only with use, suggesting a mechanical problem (eg, osteoarthritis, tendinitis), or also at rest, suggesting inflammation (eg, crystal disease, septic arthritis). There may or may not be fluid within the joint (effusion). Prompt assessment is essential to exclude infection. It is important to remember that acute monarticular arthritis is sometimes the initial manifestation of some types of polyarticular arthritis (eg, psoriatic arthritis, RA).

Pathophysiology

Monarticular pain may originate

• Within a joint (intra-articular)

• Around a joint (periarticular)

Intra-articular disorders may be inflammatory (eg, infectious, rheumatoid, crystal deposition arthritis) or noninflammatory (eg, osteoarthritis, internal derangement).

Periarticular disorders include bursitis and tendinitis.

Crystal-induced arthritis is usually caused by monosodium urate crystals (gout) or Ca pyrophosphate dihydrate crystals (pseudogout).

Etiology

At all ages, injury is the most common cause of acute monarticular joint pain; history of trauma is usually obvious.

[Fig. 32-3. Arthrocentesis of the knee.]

[**Table 32-3.** Differential Diagnosis Based on Synovial Fluid Classification*†]

Among young adults, the most common nontraumatic causes are the following:

• Disseminated gonococcal infection

• Periarticular syndromes

Among older adults, the most common nontraumatic causes are the following:

• Osteoarthritis

• Crystal-induced disease (gout or pseudogout)

• Periarticular syndromes

The most dangerous cause at any age is acute infectious arthritis, because it requires acute operative intervention (saline washout of the joint) and antibiotics to minimize permanent damage to the joint and to prevent sepsis and death.

At all ages, rare causes include adjacent osteomyelitis, avascular necrosis, pigmented villonodular synovitis, hemarthrosis (eg, in hemophilia or coagulopathies), and tumors (see Table 32-4).

Evaluation

Acute monarticular joint pain requires especially rapid diagnosis because some of its causes, particularly infectious (septic) arthritis and crystal-induced arthritis, require rapid treatment.

[**Table 32-4.** Some Causes of Monarticular Joint Pain]

Evaluation should determine whether the joint or periarticular structures are the cause of symptoms and whether there is inflammation. If inflammation is present or the diagnosis is unclear, symptoms and signs of polyarticular and systemic disorders should be sought and all joints should be examined.

History: History of present illness should focus on the acuity of onset (eg, abrupt, gradual), whether the problem is new or recurrent, and whether other joints have caused pain in the past. Also, temporal patterns (eg, diurnal variation, persistent vs intermittent), exacerbating and mitigating factors (eg, cold weather, activity), and any recent or past trauma to the joint should be noted. Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection), tick bites, and residence in or travel to an area where Lyme disease is endemic.

Review of systems should seek symptoms of causative disorders, including fever (infection), urethritis (gonococcal arthritis), and previous unexplained illness with rash (Lyme arthritis).

Past medical history should identify known joint disorders (particularly gout, osteoarthritis) and any known conditions that may cause monarticular joint pain (eg, coagulopathy, bursitis, tendinitis, hemoglobinopathy). Drug history should be reviewed for any use of anticoagulants or diuretics and for chronic corticosteroid use. A family history should also be obtained.

Physical examination: Vital signs are reviewed for fever. Examination of the head, neck, and skin should note any signs of conjunctivitis, psoriatic plaques, mucosal lesions, ecchymoses, or malar rash. Genital examination should note any discharge or other findings consistent with sexually transmitted diseases.

Joints are inspected for deformities, erythema, and swelling. Range of motion is assayed, first actively and then passively; any crepitus on joint motion is noted.

Palpation is done to detect warmth, identify any effusion, and localize the area of tenderness. Of particular importance is whether the tenderness is directly over the joint line or adjacent to it (helping to differentiate an intra-articular from a periarticular disorder). Sometimes, compression of the joint without flexing or extending it (eg, pushing on the end of the great toe for patients with pain in the 1st metatarsophalangeal joint), sometimes with slight rotation, also helps differentiate intra-articular from periarticular disorders; this maneuver is not particularly painful for patients with tendinitis or bursitis but is quite painful for those with arthritis. If the patient can tolerate it, the joint is stressed with various maneuvers to identify disruption of cartilage or ligaments (eg, in the knee, valgus and varus tests, anterior and posterior drawer tests, Lachman's test, and McMurray's test). Comparison with the contralateral unaffected joint often helps detect more subtle changes.

Large effusions in the knee are typically readily apparent. The examiner can check for minor knee effusions by pushing the suprapatellar pouch inferiorly and then pressing medially on the lateral side of the patella on an extended knee. This maneuver causes swelling to appear on the medial side.

Periarticular structures also should be examined to look for discrete soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

Red flags: The following findings are of particular concern:

• Erythema, warmth, effusion, and decreased range of motion

• Fever

• Acute-onset joint pain in a sexually active young adult

• Skin breaks with cellulitis adjacent to the affected joint

• Underlying bleeding disorder, hemoglobinopathy, or anticoagulation

• Extra-articular or systemic symptoms

Interpretation of findings: Antecedent trauma suggests a fracture, meniscal tear, or hemarthrosis. In the absence of trauma, history and physical examination may suggest a cause, but testing is often necessary to rule out serious causes.

Acuteness of onset is a very important feature. Severe joint pain that develops over hours suggests crystal-induced arthritis or, less often, infectious arthritis. A previous attack of crystal-induced arthritis with development of similar symptoms suggests recurrence. Gradual onset of pain is typical of RA or noninfectious arthritis but can result from certain infectious arthritides (eg, mycobacterial, fungal).

Pain during rest and on initiating activity suggests inflammatory arthritis, whereas pain worsened by movement and relieved by rest suggests mechanical disorders (eg, osteoarthritis).

Pain worse with active than with passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely.

Increased warmth and erythema suggest inflammation, but erythema is often absent during inflammation. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause.

Although gout can involve many different single joints or combinations of joints, acute, painful monarticular arthritis of the metatarsophalangeal joint of a great toe (podagra) is especially suggestive.

The presence of systemic findings can help narrow the diagnosis. Urethritis can suggest gonococcal infection (although gonococcal arthritis often develops in patients without symptoms of urethritis). Fever is

indicative of septic joint, crystal-induced arthropathy, or osteomyelitis. Symptoms indicating dermatologic, cardiac, or pulmonary involvement suggest diseases that are more commonly associated with polyarticular joint pain.

Testing: Joint aspiration (arthrocentesis) should be done in patients with an effusion or other signs of inflammation (eg, erythema, warmth, fever). Studies of the joint fluid should include WBC count with differential (to determine whether the effusion is bloody or inflammatory), Gram stain and cultures, and microscopic examination for crystals. Finding crystals in synovial fluid confirms crystal-induced arthritis but does not rule out coexisting infection. A noninflammatory synovial fluid (eg, < 2000/µL WBCs or < 75% neutrophils) should lead to consideration of osteoarthritis, soft-tissue injury, or viral infection.

X-rays usually are done unless the cause is clearly a flare-up of a known disorder (eg, gout) or is a clinically obvious bursitis or tendinitis, which can often be diagnosed without further testing.

Other imaging tests (eg, CT, MRI, bone scan) are adjunctive and are done depending on what diagnoses are being considered (see Table 32-4).

Blood tests (eg, ESR, antinuclear antibodies, rheumatoid factor, anticyclic citrullinated peptide [CCP] antibody, HLA-B27 testing) may help support an early diagnosis of a noninfectious inflammatory arthritis.

Treatment

Overall treatment is directed at the underlying disorder.

Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints. Cold therapy may be analgesic in inflammatory joint diseases.

Physical therapy after the acute symptoms have lessened is useful to maintain range of motion and strengthen surrounding muscles.

Key Points

- Atraumatic joint pain should prompt consideration of degenerative disease, crystal-induced arthropathy, infection, or cancer.
- Arthrocentesis is mandatory to rule out infection in a joint that is red, warm, and swollen.
- Disseminated gonococcal infection is the most common cause of acute nontraumatic monarthritis in young adults, whereas osteoarthritis is the most common cause in older adults.
- Crystals in synovial fluid confirm crystal-induced arthritis but do not rule out coexisting infection.
- Joint pain that is still unexplained after arthrocentesis and x-ray should be evaluated with MRI to rule out uncommon etiologies (eg, occult fracture, avascular necrosis, pigmented villonodular synovitis).

Polyarticular Joint Pain

Joints may simply be painful (arthralgia) or also inflamed (arthritis), with redness, warmth, and swelling. Pain may occur only with use or also at rest, and there may or may not be fluid within the joint (effusion).

A useful initial distinction is whether pain is present in one joint (monarticular) or multiple joints (polyarticular). When multiple joints are affected, different terms can be used:

- Arthritis involving ≤ 4 joints, particularly when it occurs in an asymmetric fashion, is oligoarticular or pauciarticular arthritis.

• Arthritis involving > 4 joints, usually in a symmetric fashion, is polyarticular arthritis.

Pathophysiology

Polyarticular arthralgia can originate from arthritis or from extra-articular disorders (eg, polymyalgia rheumatica, fibromyalgia). Pain caused by intra-articular disorders may be secondary to an inflammatory arthritis (eg, infection, RA, crystal deposition) or a noninflammatory process (eg, osteoarthritis).

Inflammatory arthritis may involve peripheral joints only (eg, hands, knees, feet) or both peripheral and axial joints (eg, sacroiliac, apophyseal, discovertebral, costovertebral).

Etiology

Peripheral oligoarticular and polyarticular arthritis have specific, likely causes (see Table 32-5); the presence or absence of axial involvement helps limit possibilities. However, in many patients, arthritis is often transient and resolves without diagnosis or may not fulfill the criteria for any defined rheumatic disease.

Acute polyarticular arthritis is most often due to the following:

• Infection (usually viral)

• Flare of a rheumatic disease

[**Table 32-5.** Some Causes of Polyarticular Joint Pain]

Chronic polyarticular arthritis in adults is most often due to the following:

• RA (inflammatory)

• Osteoarthritis (noninflammatory)

Chronic polyarticular arthritis in children is most often due to the following:

• Juvenile idiopathic arthritis

Evaluation

Evaluation should determine whether the joints or periarticular structures are the cause of symptoms and whether there is inflammation or effusion. If inflammation is present or the diagnosis is unclear, symptoms and signs of systemic disorders should be sought.

History: History of present illness should identify the acuity of onset (eg, abrupt, gradual), temporal patterns (eg, diurnal variation, persistent vs intermittent), chronicity (eg, acute vs longstanding), and exacerbating factors (eg, cold weather, activity). Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection) and tick bites or residence in a Lyme-endemic area.

Review of systems should seek symptoms and signs of causative disorders (see Tables 32-5 and 32-6).

[**Table 32-6.** Some Suggestive Findings in Polyarticular Joint Pain]

Past medical history and family history should identify known rheumatic disorders and other conditions capable of causing joint symptoms (see Table 32-5).

Physical examination: Vital signs are reviewed for fever.

Examination of the head, neck, and skin should note any signs of conjunctivitis, iritis, mucosal lesions,

sinonasal abnormalities, lymphadenopathy, ecchymoses, skin ulcers, psoriatic plaques, purpura, or malar rash.

Cardiopulmonary examination should note any signs of acute inflammatory disease or serositis (eg, murmur, pericardial rub, muffled heart sounds, bibasilar dullness consistent with pleural effusion).

Genital examination should note any discharge, ulcers, or other findings consistent with sexually transmitted diseases.

Musculoskeletal examination should note muscular point tenderness associated with fibromyalgia. Joint examination begins with inspection for deformities, erythema, swelling, or effusion and then proceeds to palpation and estimation of pain and crepitus with active and passive range of motion. Comparison with the contralateral unaffected joint often helps detect more subtle changes. Examination should note whether the distribution of affected joints is symmetric.

Periarticular structures also should be examined for discrete, soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

Red flags: The following findings are of particular concern:

• Hot, swollen, red joints

• Any extra-articular symptoms (eg, fever, rash, plaques, ulcers, conjunctivitis, iritis, murmur, purpura)

Interpretation of findings: An important initial element is whether pain originates in the joints, spine, or both or in other structures such as bones, tendons, bursae, muscles, other soft-tissue structures, or nerves. Pain that worsens with active rather than passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause. Pain that is diffuse and described inconsistently or vaguely may result from fibromyalgia or functional disorders.

If the joints, spine, or both are involved, differentiating inflammatory from noninflammatory disorders may help. Clinical findings of prominent morning stiffness, nontraumatic joint swelling, and fever or weight loss are suggestive of an inflammatory disorder, but testing is often helpful.

Examination of the hand joints may yield other clues (see Table 32-6) and may help differentiate osteoarthritis from RA (see
Table 32-7).

Back pain with arthritis suggests ankylosing spondylitis a reactive or psoriatic arthritis, or fibromyalgia.

[**Table 32-7.** Differential Features of the Hand in RA and Osteoarthritis]

Testing: The following tests are of particular importance:

• Arthrocentesis

• Serologic testing

• Usually ESR

Arthrocentesis is mandatory in most patients with a new effusion and can help rule out infection and crystal arthropathy as well as distinguish between an inflammatory and noninflammatory process. Other tests may be needed to identify specific disorders (see Table 32-5).

If the specific diagnosis cannot be established clinically and if determining whether arthritis is inflammatory may help determine the diagnosis, ESR and C-reactive protein may be done. A low ESR makes inflammatory causes (eg, rheumatic disease, gout, infection, vasculitis) less likely but does not rule them out. Elevated results argue more strongly for inflammation, but they are very nonspecific, particularly in older adults.

Once a diagnosis of a systemic disease is thought to be most likely, supportive serologic testing for antinuclear antibodies, double-stranded DNA, rheumatoid factor, anticyclic citrullinated peptide, and antineutrophil cytoplasmic antibodies may assist in making the diagnosis.

Treatment

The underlying disorder is treated. Systemic diseases may require either immunosuppression or antibiotics as determined by the diagnosis. Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints, and cold therapy may be analgesic in inflammatory joint diseases. For cases of chronic arthritis, continued physical activity is encouraged.

Geriatrics Essentials

Osteoarthritis is by far the most common cause of arthritis in older people. RA most commonly begins between ages 30 and 40, but in up to one third of patients, it develops after the age of 60. Because paraneoplastic phenomena also can cause inflammatory polyarthritis, cancer should be considered in older adults in whom new-onset RA is suspected.

Key Points

- The differential diagnosis of polyarticular joint pain can be narrowed by considering how many joints are affected, whether inflammation is present, and whether any extra-articular signs are present.
- Chronic arthritis is most often caused by juvenile idiopathic arthritis in children and osteoarthritis and RA in adults.
- Acute polyarticular arthritis is most often due to infection, gout, or a flare of rheumatic disease.
- Arthrocentesis is mandatory in most cases of a new effusion and can help rule out infection and crystal-induced arthropathy as well as distinguish between an inflammatory and noninflammatory process.

Chapter 33. Autoimmune Rheumatic Disorders

Introduction

Autoimmune rheumatic disorders include eosinophilic fasciitis, mixed connective tissue disease, polymyositis and dermatomyositis, relapsing polychondritis, Sjogren's syndrome, SLE, and systemic sclerosis. RA and the spondyloarthropathies and their variants (see Ch. 35) are also immune mediated. The triggers and precise pathophysiology remain unknown for all these disorders, although many aspects of pathogenesis are becoming clearer. Patients with most autoimmune rheumatic disorders are at increased risk of atherosclerosis.

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is an uncommon disorder characterized by symmetric and painful inflammation, swelling, and induration of the arms and legs. Diagnosis is by biopsy of skin and fascia. Treatment is with corticosteroids.

The cause of EF is unknown. The disorder occurs mostly in middle-aged men but can occur in women and children.

Symptoms and Signs

The disease often begins after strenuous physical activity (eg, chopping wood). The initial features are pain, swelling, and inflammation of the skin and subcutaneous tissues, followed by induration, creating a characteristic orange-peel configuration most evident over the anterior surfaces of the extremities. The face and trunk are occasionally involved. Restriction of arm and leg movement usually develops insidiously. Contractures commonly evolve, secondary to induration and thickening of the fascia, but the process may also involve tendons, synovial membranes, and muscle. Typically, EF does not involve the fingers and toes (acral areas). Muscle strength is unimpaired, but myalgia and arthritis may occur. Carpal tunnel syndrome may also occur.

Fatigue and weight loss are common. Rarely, aplastic anemia, thrombocytopenia, and lymphoproliferative processes develop.

Diagnosis

• Biopsy

EF should be suspected in patients with typical symptoms. The cutaneous manifestations may suggest systemic sclerosis; however, patients with systemic sclerosis usually also have Raynaud's syndrome, acral involvement, telangiectasia, and visceral changes (eg, esophageal dysmotility). All of these are absent in EF.

Diagnosis is confirmed by en bloc biopsy, which should be deep enough to include fascia and adjacent muscle fibers. Characteristic findings are inflammation of the fascia, with or without eosinophils.

Blood tests are not diagnostic, but CBC shows eosinophilia (in early active disease), and serum protein electrophoresis shows polyclonal hypergammaglobulinemia. CBC should be done in all patients because the presence of eosinophilia helps in the diagnosis. Autoantibodies are usually absent. MRI, although not specific, can show thickened fascia, the increased signal intensity in the superficial muscle fibers correlating with the inflammation.

Prognosis

Although the long-term outcome varies, EF is often self-limited and uncomplicated.

Treatment

• Oral prednisone

Most patients respond rapidly to high doses of prednisone (40 to 60 mg po once/day followed by gradual reduction to 5 to 10 mg/day as soon as the fascitis resolves). Continued low doses may be required for 2 to 5 yr. Some patients require longer courses and possibly other drugs (eg, hydroxychloroquine, cyclosporine). NSAIDs and H_2 blockers (eg, cimetidine) also have been used to treat EF.

Monitoring with CBCs is advised because of the occasional hematologic complications.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is an uncommon, specifically defined, overlap syndrome characterized by clinical features of SLE, systemic sclerosis, and polymyositis with very high titers of circulating antinuclear antibody to a ribonucleoprotein antigen. Hand swelling, Raynaud's syndrome, polyarthralgia, inflammatory myopathy, esophageal hypomotility, and pulmonary dysfunction are common. Diagnosis is by the combination of clinical features, antibodies to ribonucleoprotein, and absence of antibodies specific for other autoimmune diseases. Treatment varies with disease severity and organ involvement but usually includes corticosteroids and sometimes additional immunosuppressants.

MCTD occurs worldwide and in all races, with a peak incidence in the teens and 20s. About 80% of people who have this disease are women. The cause is unknown. In some patients, the disorder evolves into classic systemic sclerosis or SLE.

Symptoms and Signs

Raynaud's syndrome may precede other manifestations by years. Frequently, the first manifestations resemble early SLE, systemic sclerosis, polymyositis, dermatomyositis, or even RA. Whatever the initial manifestation, limited disease tends to progress and become widespread, and the clinical pattern changes over time.

The most frequent finding is swelling of the hands that eventually causes a sausage-like appearance of the fingers. Skin findings include lupus or dermatomyositis-like rashes. Diffuse systemic sclerosis-like skin changes and ischemic necrosis or ulceration of the fingertips may occasionally develop.

Almost all patients have polyarthralgias, and 75% have frank arthritis. Often the arthritis is nondeforming, but erosive changes and deformities similar to those in RA (eg, boutonniere and swan-neck deformities) may be present. Proximal muscle weakness with or without tenderness is common.

Renal disease occurs in about 10% and is often mild but occasionally causes morbidity or mortality. Sometimes pulmonary involvement is the most serious complication. Heart failure can occur. Sjogren's syndrome may develop. A trigeminal sensory neuropathy develops more frequently in MCTD than in other systemic autoimmune diseases. It may be the presenting feature and is considered the most frequent CNS manifestation.

Diagnosis

• Testing for antinuclear antibodies (ANA), extractable nuclear antigen (ENA), and ribonucleoprotein (RNP)

• Organ involvement determined as clinically indicated

MCTD should be suspected when additional overlapping features are present in patients appearing to have SLE, systemic sclerosis, polymyositis, or RA.

Tests for ANA and antibody to ENA and RNP antigen are done first. If results of these tests are compatible with MCTD (eg, RNP antibodies very high, positive ANA), tests for rheumatoid factors, anti Jo-1 (anti-histidyl t-RNA synthetase), antibodies to the ribonuclease-resistant Smith (Sm) component of ENA,

and double-stranded DNA are done to exclude other possible diagnoses.

Further evaluation depends on symptoms and signs; manifestations of myositis, renal involvement, or pulmonary involvement prompt tests of those organs (eg, CK, MRI, electromyogram, or muscle biopsy for diagnosis of myositis).

Almost all patients have high titers (often > 1:1000) of fluorescent ANA that produce a speckled pattern. Antibodies to ENA are usually present at very high titers (> 1:100,000). Antibody to RNP is present, whereas antibody to the ribonuclease-resistant Sm component of ENA is absent.

Rheumatoid factors are frequently positive, and titers are often high. The ESR is frequently elevated.

Prognosis

The overall 10-yr survival rate is 80%, but prognosis depends largely on which manifestations predominate. Patients with features of systemic sclerosis and polymyositis have a worse prognosis. Patients are at increased risk of atherosclerosis. Causes of death include pulmonary hypertension, renal failure, MI, colonic perforation, disseminated infection, and cerebral hemorrhage. Some patients have sustained remissions for many years without treatment.

Treatment

• NSAIDs or antimalarials for mild disease

• Corticosteroids for moderate to severe disease

• Sometimes other immunosuppressants

General management and initial drug therapy are tailored to the specific clinical problem and are similar to those of SLE. Most patients with moderate or severe disease respond to corticosteroids, particularly if treated early. Mild disease is often controlled by NSAIDs, antimalarials, or sometimes low-dose corticosteroids. Severe major organ involvement usually requires higher doses of corticosteroids (eg, prednisone 1 mg/kg po once/day) and additional immunosuppressants. If patients develop features of myositis or systemic sclerosis, treatment is as for those diseases.

All patients should be closely monitored for atherosclerosis. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are uncommon systemic rheumatic disorders characterized by inflammatory and degenerative changes in the muscles (polymyositis) or in the skin and muscles (dermatomyositis). The most specific skin signs are Gottron's papules over the knuckles and a periorbital heliotropic rash. Manifestations include symmetric weakness, some tenderness, and later atrophy, principally of the proximal limb girdle muscles. Complications can include visceral involvement and cancer. Diagnosis is by clinical findings and abnormalities on muscle tests, which may include muscle enzymes, MRI, electromyography, and muscle biopsy. Treatment is with corticosteroids, sometimes combined with immunosuppressants or IV immune globulin.

The female:male ratio is 2:1. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15.

Etiology

The cause seems to be an autoimmune reaction to muscle tissue in genetically susceptible people. Familial clustering occurs, and HLA subtypes DR3, DR52, DR6 seem to be the genetic predisposition. Possible inciting events include viral myositis and underlying cancer. Picornavirus-like structures have

been found in muscle cells, but their significance is not known, and viruses can trigger similar disorders in animals. The association of cancer with dermatomyositis (much less so with polymyositis) suggests that a tumor may incite myositis as the result of an autoimmune reaction against a common antigen in muscle and tumor.

Pathophysiology

Pathologic changes in both disorders include cellular damage and atrophy, with variable degrees of inflammation. Muscles in the hands, feet, and face are affected less than other skeletal muscles. Involvement of visceral muscles in the pharynx and upper esophagus and occasionally the heart, stomach, or intestines can impair the functions of those organs. High blood levels of myoglobin from rhabdomyolysis can damage the kidneys. Inflammation may occur in joints and lungs, especially in patients with antisynthetase antibodies.

Dermatomyositis is characterized by immune complex deposition in the vessels and is considered a complement-mediated vasculopathy. In contrast, the main pathophysiologic abnormality in polymyositis is direct T cell-mediated muscle injury.

Classification

Myositis has been divided into several subtypes:

- Primary idiopathic polymyositis can occur at any age and does not involve the skin.
- Primary idiopathic dermatomyositis is similar to primary idiopathic polymyositis but also involves the skin.
- Polymyositis or dermatomyositis associated with cancer can occur at any age but is most common among older adults; the cancer can develop up to 2 yr before or after the myositis.
- Childhood dermatomyositis can be associated with systemic vasculitis.
- Polymyositis or dermatomyositis can occur with an associated disorder such as progressive systemic sclerosis, mixed connective tissue disease, RA, SLE, or sarcoidosis.

Inclusion body myositis is a separate disorder that has clinical manifestations similar to chronic idiopathic polymyositis; however, it develops at an older age, frequently involves distal muscles (eg, hand and feet muscles), has a longer duration, responds poorly to therapy, and has a different histologic appearance.

Symptoms and Signs

Onset of polymyositis may be acute (particularly in children) or insidious (particularly in adults). Polyarthralgias, Raynaud's syndrome, dysphagia, pulmonary symptoms, and constitutional complaints (notably fever, fatigue, and weight loss) may also occur.

Muscle weakness may progress over weeks to months. However, it takes destruction of 50% of muscle fibers to cause symptomatic weakness (ie, muscle weakness indicates advanced myositis). Patients may have difficulty raising their arms above their shoulders, climbing steps, or rising from a sitting position. Patients may become wheelchair-bound or bedridden because of weakness of pelvic and shoulder girdle muscles. The flexors of the neck may be severely affected, causing an inability to raise the head from the pillow. Involvement of pharyngeal and upper esophageal muscles may impair swallowing and predispose to aspiration. Muscles of the hands, feet, and face escape involvement. Limb contractures may eventually develop.

Joint manifestations include polyarthralgia or polyarthritis, often with swelling, effusions, and other characteristics of nondeforming arthritis, which occur in about 30% of patients. However, joint manifestations tend to be mild. They occur more often in a subset with Jo-1 or other antisynthetase antibodies.

Visceral involvement (except that of the pharynx and upper esophagus) is less common in polymyositis than in some other rheumatic disorders (eg, SLE, systemic sclerosis). Occasionally, and especially in patients with antisynthetase antibodies, interstitial pneumonitis (manifested by dyspnea and cough) is the most prominent manifestation. Cardiac arrhythmias (including conduction disturbances and abnormal systolic time intervals) can occur but are often asymptomatic. GI symptoms, more common among children with associated vasculitis, may include hematemesis, melena, and ischemic bowel perforation.

Skin changes, which occur in dermatomyositis, tend to be dusky and erythematous. Periorbital edema with a purplish appearance (heliotrope rash) is specific for dermatomyositis. The rash may be slightly elevated and smooth or scaly; it may appear on the forehead, V of the neck and shoulders, chest and back, forearms and lower legs, elbows and knees, medial malleoli, and radiodorsal aspects of the proximal interphalangeal and metacarpophalangeal joints (Gottron's papules—also a relatively specific finding). The base and sides of the fingernails may be hyperemic or thickened. Desquamating dermatitis with splitting of the skin may evolve over the radial aspects of the fingers. The primary skin lesions frequently fade completely but may be followed by secondary changes (eg, brownish pigmentation, atrophy, scarring, vitiligo). Subcutaneous calcification may occur, particularly in children.

Diagnosis

• Clinical criteria

• Muscle biopsy (definitive)

Polymyositis should be suspected in patients with proximal muscle weakness with or without muscle tenderness. Dermatomyositis should be suspected in patients with a heliotropic rash or Gottron's papules, even without polymyositis, and in patients with symptoms of polymyositis and any skin findings compatible with dermatomyositis. Polymyositis and dermatomyositis share certain clinical findings with systemic sclerosis or, less frequently, with SLE or vasculitis. Establishing the diagnosis requires as many as possible of the following 5 criteria:

• Proximal muscle weakness

• Characteristic rash

• Elevated serum muscle enzymes (CK, or if this is not elevated, aminotransferases or aldolase)

• Characteristic electromyographic or MRI abnormalities

• Muscle biopsy changes (the definitive test)

Muscle biopsy excludes some similar conditions such as inclusion body myositis and postviral rhabdomyolysis. Biopsy findings can be variable, but chronic inflammation and muscle degeneration and regeneration are typical. A definite diagnosis made by muscle biopsy is recommended before treatment of polymyositis to exclude other muscle disorders. To increase the sensitivity of the biopsy results, the biopsy sample should be obtained from a muscle that has one or more of the following characteristics:

• Weakness on clinical examination

• Inflammation identified on MRI

• Contralateral pair of a muscle shown to be abnormal on electromyography

Laboratory studies can increase or decrease suspicion for the disorder, assess its severity, identify overlaps, and help detect complications. Autoantibodies should be tested. Antinuclear antibodies are positive in up to 80% of patients. Detailed testing of the antinuclear antibodies (ANA), when present, is important in identifying other overlap syndromes, most often those with another autoimmune disorder. About 30% of patients have myositis-specific autoantibodies: antibodies to aminoacyl-tRNA synthetases (anti-synthetase antibodies), including anti-Jo-1; antibodies to signal recognition particle (SRP—anti-SRP

antibodies); and antibodies to Mi-2, a nuclear helicase. The relationship between these autoantibodies and disease pathogenesis remains unclear, although antibody to Jo-1 is a significant marker for fibrosing alveolitis, pulmonary fibrosis, arthritis, and Raynaud's syndrome.

Periodic measurement of CK is helpful in monitoring treatment. However, in patients with widespread muscle atrophy, levels are occasionally normal despite chronic, active myositis. Muscle biopsy, MRI, or high CK levels can often differentiate a relapse of polymyositis from corticosteroid-induced myopathy. Aldolase is a less specific marker for muscle injury than CK.

Cancer screening is recommended by some authorities for any adult who has dermatomyositis or for patients ≥ 60 yr who have polymyositis because these patients often have unsuspected cancers. Screening should include a physical examination that includes breast, pelvis, and rectum (with occult blood testing); CBC; biochemical profile; mammogram; carcinoembryonic antigen; urinalysis; chest x-ray; and any other tests appropriate based on patient's age. Additional investigation should be based on history and physical examination findings. Some authorities recommend CT of the chest, abdomen, and pelvis. Younger patients without symptoms of cancer need not undergo screening.

Prognosis

Long remissions (even apparent recovery) occur in up to 50% of treated patients within 5 yr, more often in children. Relapse, however, may still occur at any time. Overall 5-yr survival rate is 75% and is higher in children. Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. Polymyositis tends to be more severe and resistant to treatment in patients with cardiac or pulmonary involvement. Death in children may be a result of bowel vasculitis. Cancer, if present, generally determines the overall prognosis.

Treatment

• Corticosteroids

• Sometimes immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin)

Physical activities should be modestly curtailed until the inflammation subsides. Corticosteroids are the drugs of choice initially. For acute disease, adults receive prednisone ≥ 40 to 60 mg po once/day. Serial measurements of CK provide the best early guide of therapeutic effectiveness, falling toward or reaching normal in most patients in 6 to 12 wk, followed by improved muscle strength. Once enzyme levels have returned to normal, prednisone can be gradually reduced. If muscle enzyme levels rise, the dose is increased. Patients who seem to recover can have treatment gradually withdrawn with close monitoring, but most adults require chronic maintenance with prednisone (up to 10 to 15 mg/day). Children require initial doses of prednisone of 30 to 60 mg/m^2 once/day. In children, it may be possible to stop prednisone after ≥ 1 yr of remission.

Occasionally, patients treated chronically with high-dose corticosteroids become increasingly weak because of a superimposed corticosteroid myopathy.

If a patient does not to respond to corticosteroids, depends on a high to moderate dose of corticosteroids, or develops a corticosteroid myopathy or another complication that necessitates stopping or decreasing prednisone, immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin) should be tried. Some patients have received only methotrexate (generally in higher doses than used for RA) for ≥ 5 yr. IV immune globulins can be effective in some patients refractory to drug treatment, but the prohibitive cost has precluded comparative trials. Some clinicians combine prednisone with an immunosuppressant. Other possible emerging therapies include anti-tumor necrosis factor (TNF) agents and rituximab.

Myositis associated with tumors, metastatic disease, or inclusion body myositis usually is more refractory to corticosteroids. Cancer-associated myositis may remit if the tumor is removed.

People with an autoimmune disorder are at higher risk of atherosclerosis and should be closely monitored. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Relapsing Polychondritis

Relapsing polychondritis is an episodic, inflammatory, and destructive disorder involving primarily cartilage of the ear and nose but also potentially affecting the eyes, tracheobronchial tree, heart valves, kidneys, joints, skin, and blood vessels. Diagnosis is by a combination of clinical, laboratory, imaging, and sometimes biopsy findings. Treatment usually requires prednisone and other immunosuppressants.

Relapsing polychondritis affects men and women equally; onset typically is in middle age. An association with RA, systemic vasculitis, SLE, and other connective tissue disorders suggests an autoimmune etiology.

Symptoms and Signs

Acute pain, erythema, and swelling most commonly affect the pinna cartilage. Nasal cartilage inflammation is the next most common, followed by arthritis that varies from arthralgias to symmetric or asymmetric nondeforming arthritis involving large and small joints, with a predilection for the costochondral joints. The next most common manifestations, in decreasing order of frequency, are inflammation of the eye (eg, conjunctivitis, scleritis, iritis, keratitis, chorioretinitis); cartilaginous tissue of the larynx, trachea, or bronchi (causing hoarseness, cough, and tenderness over the laryngeal cartilage); internal ear; cardiovascular system (eg, aortic regurgitation, mitral regurgitation, pericarditis, myocarditis, aortic aneurysms, aortitis); kidney; and skin. Bouts of acute inflammation heal over weeks to months, with recurrences over several years. Various rashes can develop.

Advanced disease can lead to destruction of supporting cartilage, causing floppy ears; saddle nose; pectus excavatum; and visual, auditory, and vestibular abnormalities. Tracheal narrowing can lead to dyspnea, pneumonia, or even tracheal collapse. Coexisting systemic vasculitis (leukocytoclastic vasculitis or polyarteritis nodosa), myelodysplastic syndrome, or cancer is possible.

Diagnosis

• Clinical criteria

• Sometimes biopsy

Diagnosis is established if the patient develops at least 3 of the following:

• Bilateral chondritis of the external ears

• Inflammatory polyarthritis

• Nasal chondritis

• Ocular inflammation

• Respiratory tract chondritis

• Auditory or vestibular dysfunction

Biopsy of involved cartilage, most often the pinna, is helpful if clinical diagnosis is not clear-cut.

Laboratory tests are done. They are not specific but may help to exclude other disorders. Synovial fluid analysis reveals mild inflammatory changes that are nonspecific but help to rule out an infectious process. Blood tests may show normocytic-normochromic anemia, leukocytosis, elevated ESR or γ-globulin levels, and occasionally positive rheumatoid factor, antinuclear antibodies (ANA), or, in up to 25%, antineutrophil

cytoplasmic antibodies (ANCA). Abnormal renal function may indicate an associated vasculitis. A positive c-ANCA test (ANCA that are reactive mainly to proteinase-3) suggests Wegener's granulomatosis, which can cause similar findings (see p. 329).

The upper and lower airways should be evaluated, including complete spirometric testing and chest CT, when the diagnosis is made.

Prognosis

Mortality after 5 yr is 30%, from collapse of laryngeal and tracheal structures or from cardiovascular complications such as large-vessel aneurysm, cardiac valvular insufficiency, or systemic vasculitis.

Treatment

- NSAIDs or dapsone for mild ear disease
- Corticosteroids
- Sometimes methotrexate or other immunosuppressants (eg, cyclosporine, cyclophosphamide, azathioprine)

Mild recurrent ear disease may respond to NSAIDs in anti-inflammatory doses, or dapsone (50 to 100 mg po once/day). However, most patients are treated with prednisone 30 to 60 mg po once/day, with tapering of the dose as soon as there is a clinical response. Some patients require chronic use. In such patients, methotrexate 7.5 to 20 mg po once/wk can reduce the requirement for corticosteroids. Very severe cases may require other immunosuppressants, such as cyclosporine, cyclophosphamide, or azathioprine (see p. 337). None of these therapies has been tested in controlled trials or has been shown to decrease mortality. If tracheal narrowing causes stridor, a tracheostomy or stent may be needed. More extensive tracheobronchial collapse may require tracheal reconstruction. Eye disease may sometimes be recalcitrant to treatment, especially when involving the sclera, and carries a poor prognosis.

All patients should be closely monitored for atherosclerosis given the risk of premature atherosclerosis in systemic vasculitides. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Sjogren's Syndrome

Sjogren's syndrome (SS) is a relatively common chronic, autoimmune, systemic, inflammatory disorder of unknown cause. It is characterized by dryness of the mouth, eyes, and other mucous membranes due to lymphocytic infiltration of the exocrine gland and secondary gland dysfunction. Sjogren's syndrome can affect various exocrine glands or other organs. Diagnosis is by specific criteria relating to eye, mouth, and salivary gland involvement, autoantibodies, and (occasionally) histopathology. Treatment is symptomatic.

SS occurs most frequently among middle-aged women. SS is classified as primary when there is no other associated disease. In about 30% of patients with autoimmune disorders such as RA, SLE, systemic sclerosis, mixed connective tissue disease, Hashimoto's thyroiditis, primary biliary cirrhosis, or chronic autoimmune hepatitis, SS develops and, in such cases, is classified as secondary. Genetic associations have been found (eg, HLADR3 antigens in whites with primary SS).

Pathophysiology

Salivary, lacrimal, and other exocrine glands become infiltrated with CD4+ T cells and with some B cells. The T cells produce inflammatory cytokines (eg, IL-2, interferon-γ). Salivary duct cells also produce cytokines, eventually damaging the secretory ducts. Atrophy of the secretory epithelium of the lacrimal glands causes desiccation of the cornea and conjunctiva (keratoconjunctivitis sicca—see p. 592). Lymphocytic infiltration and intraductal cellular proliferation in the parotid gland cause luminal narrowing and in some cases formation of compact cellular structures termed myoepithelial islands; atrophy of the

gland can result. Dryness and GI mucosal or submucosal atrophy and diffuse infiltration by plasma cells and lymphocytes may cause symptoms (eg, dysphagia).

Symptoms and Signs

Glandular manifestations: SS often affects the eyes or mouth initially and sometimes exclusively. Dry eyes can cause irritation and photosensitivity. In advanced cases, the cornea is severely damaged, epithelial strands hang from the corneal surface (keratitis filiformis), and vision can be impaired. Diminished saliva (xerostomia) results in difficulty chewing and swallowing, secondary *Candida* infection, tooth decay, and calculi in the salivary ducts. Taste and smell may be diminished. Dryness may also develop in the skin and in mucous membranes of the nose, throat, larynx, bronchi, vulva, and vagina. Dryness of the respiratory tract may cause cough. Alopecia may occur. Parotid glands enlarge in 33% of patients and are usually firm, smooth, and mildly tender. Chronic salivary gland enlargement is rarely painful unless there is obstruction or infection.

Extraglandular manifestations: Joint disease in SS is typically nonerosive and nondeforming. Arthralgias occur in about 50% of patients. Arthritis occurs in about 33% of patients and is similar in distribution to RA but is not erosive.

Other common extraglandular manifestations include generalized lymphadenopathy, Raynaud's syndrome, parenchymal lung involvement (which is common but infrequently serious), and vasculitis. Vasculitis can occasionally affect the peripheral nerves (causing peripheral polyneuropathy or mononeuritis multiplex) or CNS or cause rashes (including purpura) and glomerulonephritis. Kidney involvement can cause renal tubular acidosis, impaired concentrating ability, kidney stones, or interstitial nephritis. Pseudolymphoma, malignant lymphoma, or Waldenstrom's macroglobulinemia can develop; patients develop non-Hodgkin lymphoma at 40 times the normal rate. Chronic hepatobiliary disease and pancreatitis (exocrine pancreatic tissue is similar to that of salivary glands) may also occur.

Diagnosis

• Eye symptoms, oral symptoms, and eye and salivary gland testing

• Autoantibodies

• Sometimes salivary gland biopsy

SS should be suspected in patients with gritty or dry eyes or dry mouth, enlarged salivary glands, peripheral neuropathy, purpura, or unexplained renal tubular acidosis. Such patients should receive diagnostic tests that can include evaluation of the eyes and salivary glands and serologic tests. Different criteria have been proposed for classification of SS. The latest modifications to the American-European classification criteria for SS were proposed in 2002. These criteria were not developed for use in routine clinical practice, and not every patient who receives a clinical diagnosis of SS fulfills the proposed criteria (usually > 3 of 6 manifestations). The 6 manifestations are eye symptoms, oral symptoms, positive eye tests, salivary gland involvement, autoantibodies, and histopathology.

Eye symptoms are ≥ 3 mo of either dry eyes or use of tear substitutes ≥ 3 times/day; slit-lamp examination may also confirm dry eyes.

Oral symptoms are > 3 mo of daily dry mouth sensation, daily use of liquids to aid in swallowing, or swollen salivary glands.

Eye signs include evaluation by Schirmer's test, which measures the quantity of tears secreted in 5 min after irritation from a filter paper strip placed under each lower eyelid. A young person normally moistens 15 mm of each paper strip. Most people with SS moisten < 5 mm, although about 15% of test results are false-positive and 15% are false-negative. Ocular staining with an eyedrop of rose bengal or lissamine green solution is highly specific. Slit-lamp examination showing a fluorescein tear breakup in < 10 sec is also suggestive.

Salivary gland involvement can be confirmed by abnormally low saliva production (≤ 1.5 mL/15 min) as measured by salivary flow, sialography, or salivary scintiscanning, although these tests are used less often.

Autoantibodies (serologic criteria) have limited sensitivity and specificity. They include antibodies to Ro (SS-A autoantibodies—see Systemic Lupus Erythematosus on p. 305) or to nuclear antigens (termed La or SS-B autoantibodies), antinuclear antibodies, or an elevated level of antibodies against γ-globulin. Rheumatoid factor is present in > 70% of patients. ESR is elevated in 70%, 33% have anemia, and up to 25% have leukopenia.

Histopathology is assessed by biopsy of minor salivary glands in the buccal mucosa. Salivary gland biopsy is usually reserved for patients in whom the diagnosis cannot be established by autoantibody testing or when a major organ is involved. Histopathologic involvement is confirmed if labial minor salivary glands show multiple large foci of lymphocytes with atrophy of acinar tissue.

Most common causes of dry eyes and dry mouth (sicca symptoms) are aging and drugs, but when parotid enlargement occurs in addition to sicca symptoms, diseases such as hepatitis C, HIV, bulimia, and sarcoidosis should be differentiated from SS.

Prognosis

SS is chronic, and death may occasionally result from pulmonary infection and, rarely, from renal failure or lymphoma. Associated systemic autoimmune disorders may dictate prognosis.

Treatment

• Symptomatic treatment for sicca symptoms

• Avoidance of aggravating factors

• Occasionally oral corticosteroids or cyclophosphamide

SS should be initially managed by topical therapy of dry eyes and dry mouth. Other systemic manifestations of SS should be treated depending on the severity and the involved organ. Recognition of therapies for other conditions that can exacerbate dryness complaints is crucial. Hydroxychloroquine 200 to 400 mg po once/day is usually given to halt the progression of the disease and for the treatment of arthralgias.

Dry eyes should be treated with lubricating eye preparations (initially drops such as hypromellose or methylcellulose and an OTC ointment at bedtime). Other treatments include drainage (punctal) duct closure and topical cyclosporine. Skin and vaginal dryness can be treated with lubricants.

Mouth dryness may be avoided by sipping fluids throughout the day, chewing sugarless gum, and using a saliva substitute containing carboxymethylcellulose as a mouthwash. Drugs that decrease salivary secretion (eg, antihistamines, antidepressants, other anticholinergics) should be avoided. Fastidious oral hygiene and regular dental visits are essential. Stones must be promptly removed, preserving viable salivary tissue. The pain of suddenly enlarged salivary glands is generally best treated with warm compresses and analgesics. Pilocarpine 5 mg po tid to qid or cevimeline HCl 30 mg po tid can stimulate salivary production but should be avoided in patients with bronchospasm and closed-angle glaucoma.

Aggressive systemic treatment is occasionally indicated. It is usually reserved for patients with associated diseases (eg, severe vasculitis or visceral involvement); corticosteroids (eg, prednisone 1 mg/kg po once/day) or cyclophosphamide 5 mg/kg po once/day may be used.

Systemic Lupus Erythematosus

(Disseminated Lupus Erythematosus)

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory disorder of autoimmune etiology, occurring predominantly in young women. Common manifestations may include arthralgias and arthritis; malar and other skin rashes; pleuritis or pericarditis; renal or CNS involvement; and hematologic cytopenias. Diagnosis requires clinical and serologic criteria. Treatment of severe ongoing active disease requires corticosteroids, often hydroxychloroquine, and sometimes immunosuppressants.

Of all cases, 70 to 90% occur in women (usually of child-bearing age). SLE is more common among blacks and Asians than whites. It can affect patients of any age, including neonates. Increased awareness of mild forms has resulted in a worldwide rise in reported cases. In some countries, the prevalence of SLE rivals that of RA. SLE may be precipitated by currently unknown environmental triggers that cause autoimmune reactions in genetically predisposed people. Some drugs (eg, hydralazine, procainamide, isoniazid) cause a reversible lupus-like syndrome.

Symptoms and Signs

Clinical findings vary greatly. SLE may develop abruptly with fever or insidiously over months or years with episodes of arthralgias and malaise. Vascular headaches, epilepsy, or psychoses may be initial findings. Manifestations referable to any organ system may appear. Periodic exacerbations (flares) may occur.

Joint manifestations: Joint symptoms, ranging from intermittent arthralgias to acute polyarthritis, occur in about 90% of patients and may precede other manifestations by years. Most lupus polyarthritis is nondestructive and nondeforming. However, in long-standing disease, deformities without bone erosions may develop (eg, the metacarpophalangeal and interphalangeal joints may rarely develop ulnar drift or swan-neck deformities without bony or cartilaginous erosions [Jaccoud's arthritis]).

Skin and mucous membrane manifestations (see also p. 309): Skin lesions include malar butterfly erythema (flat or raised) that generally spares the nasolabial folds. The absence of papules and pustules helps distinguish SLE from rosacea. A variety of other erythematous, firm, maculopapular lesions can occur elsewhere, including exposed areas of the face and neck, upper chest, and elbows. Skin blistering and ulceration are rare, although recurrent ulcers on mucous membranes (particularly the central portion of the hard palate near the junction of the hard and soft palate, the buccal and gum mucosa, and the anterior nasal septum) are common. Generalized or focal alopecia is common during active phases of SLE. Panniculitis can cause subcutaneous nodular lesions. Vasculitic skin lesions may include mottled erythema on the palms and fingers, periungual erythema, nail-fold infarcts, urticaria, and palpable purpura. Petechiae may develop secondary to thrombocytopenia. Photosensitivity occurs in most patients.

Cardiopulmonary manifestations: Cardiopulmonary symptoms commonly include recurrent pleurisy, with or without pleural effusion. Pneumonitis is rare, although minor impairments in pulmonary function are common. Severe pulmonary hemorrhage occasionally occurs. Prognosis has traditionally been poor but seems to be improving, possibly because of better early, aggressive, critical care. Other complications include pulmonary emboli, pulmonary hypertension, and shrinking lung syndrome. Cardiac complications include pericarditis (most commonly), pericardial effusion, and myocarditis. Serious, rare complications are coronary artery vasculitis, valvular involvement, and Libman-Sacks endocarditis. Accelerated atherosclerosis is an increasing cause of morbidity and mortality. Congenital heart block can develop in neonates.

Adenopathy and splenic manifestations: Generalized adenopathy is common, particularly among children, young adults, and blacks. Splenomegaly occurs in 10% of patients. The spleen may develop periarterial fibrosis.

Neurologic manifestations: Neurologic symptoms can result from involvement of any part of the central or peripheral nervous system or meninges. Mild cognitive impairment is common. There may also be headaches, personality changes, ischemic stroke, subarachnoid hemorrhage, seizures, psychoses, organic brain syndrome, aseptic meningitis, peripheral neuropathies, transverse myelitis, or cerebellar dysfunction.

Renal manifestations: Renal involvement can develop at any time and may be the only manifestation of SLE. It may be benign and asymptomatic or progressive and fatal. Renal lesions can range in severity from a focal, usually benign, glomerulitis to a diffuse, potentially fatal, membranoproliferative glomerulonephritis. Common manifestations include proteinuria (most often), an abnormal urinary sediment manifested by RBC casts and leukocytes, hypertension, and edema.

Obstetric manifestations: Obstetric manifestations include early and late fetal loss. In patients with antiphospholipid antibodies, the risk of recurrent miscarriages is increased. Pregnancy can be successful (see p. 2636), particularly after 6 to 12 mo of remission, but SLE flares are common during pregnancy. Pregnancy should be timed for when disease is in remission. During pregnancy, the patient should be monitored closely for any disease flare or thrombotic events by a multidisciplinary team that includes a rheumatologist, an obstetrician who specializes in high-risk pregnancies, and a hematologist.

Hematologic manifestations: Hematologic manifestations include anemia (often autoimmune hemolytic), leukopenia (usually lymphopenia, with < 1500 cells/µL,), and thrombocytopenia (sometimes life-threatening autoimmune thrombocytopenia). Recurrent arterial or venous thrombosis, thrombocytopenia, and a high probability of obstetric complications occur in patients with antiphospholipid antibodies. Thromboses probably account for many of the complications of SLE, including obstetric complications.

GI manifestations: GI manifestations can result from bowel vasculitis or impaired bowel motility. In addition, pancreatitis can result from SLE or from its treatment with corticosteroids or azathioprine. Manifestations may include abdominal pain from serositis, nausea, vomiting, manifestations of bowel perforation, and pseudo-obstruction. SLE rarely causes parenchymal liver disease.

Diagnosis

• Clinical criteria

• Cytopenias

• Autoantibodies

SLE should be suspected in patients, particularly young women, with any of the symptoms and signs. However, early-stage SLE can mimic other connective (or nonconnective) tissue disorders, including RA if arthritic symptoms predominate. Mixed connective tissue disease can mimic SLE but also may involve features of systemic sclerosis, rheumatoid-like polyarthritis, and polymyositis or dermatomyositis. Infections (eg, bacterial endocarditis, histoplasmosis) can mimic SLE and may develop as a result of treatment-caused immunosuppression. Disorders such as sarcoidosis and paraneoplastic syndromes can also mimic SLE.

Laboratory testing differentiates SLE from other connective tissue disorders. Routine testing should include the following:

• Antinuclear antibodies (ANA)

• CBC

• Urinalysis

• Chemistry profile including renal and liver enzymes

The diagnosis is especially likely if ≥ 4 of the criteria in Table 33-1 are present at any time but is still possible if < 4 criteria are present. If the diagnosis is suspected but not established, additional testing for autoantibodies can be useful. Establishing the diagnosis may require repeated evaluations over months or years.

Fluorescent ANA: The fluorescent test for ANA is the best screen for SLE; positive ANA tests (usually in high titer: > 1:80) occur in > 98%. However, positive ANA tests can also occur in RA, other connective tissue disorders, cancers, and even in the general population. The false-positive rate varies from about 3% for ANA titers of 1:320 to about 30% for ANA titers of 1:40 among healthy controls. Drugs such as hydralazine, procainamide, and tumor necrosis factor (TNF)-α antagonists can produce positive ANA results as well as a lupus-like syndrome; the ANA eventually becomes negative if the drug is stopped. Positive ANA should prompt more specific testing such as anti-double-stranded DNA antibodies; high titers are highly specific for SLE but occur in only 25 to 30% of people with SLE.

Other ANA and anticytoplasmic antibodies: The ANA test is very sensitive, but it is not specific for SLE; thus, evidence of other autoantibodies is needed to establish the diagnosis. They include Ro [SSA], La [SSB], Smith [Sm], ribonucleoprotein [RNP], and double-stranded DNA. Ro is predominantly cytoplasmic; anti-Ro antibodies are occasionally present in ANA-negative SLE patients presenting with chronic cutaneous lupus. Anti-Ro is the causal antibody for neonatal lupus and congenital heart block. Anti-Sm is highly specific for SLE but, like anti-double-stranded DNA, is not sensitive. Anti-RNP occurs in patients with SLE, mixed connective tissue disease, and occasionally other systemic autoimmune disorders and systemic sclerosis.

[Table 33-1. Criteria for the Classification of SLE*]

Other blood tests: Leukopenia (usually lymphopenia) is common. Hemolytic anemia may occur. Thrombocytopenia in SLE may be difficult or impossible to differentiate from idiopathic thrombocytopenic purpura except that patients have other features of SLE. False-positive serologic tests for syphilis occur in 5 to 10% of SLE patients. These test results may be associated with the lupus anticoagulant and a prolonged PTT. Abnormal values in one or more of these assays suggest the presence of antiphospholipid antibodies (eg, anticardiolipin antibodies), which should then be measured directly by enzyme-linked immunosorbent assay (ELISA). Antiphospholipid antibodies are associated with arterial or venous thrombosis, thrombocytopenia, and, during pregnancy, spontaneous abortion or late fetal death but may be present in asymptomatic patients.

Other tests help monitor disease severity and determine the need for treatment. Serum complement levels (C3, C4) are often depressed in active disease and are usually lowest in patients with active nephritis. ESR is elevated frequently during active disease. C-reactive protein levels are not necessarily elevated.

Renal involvement: Screening for renal involvement begins with urinalysis. RBC and WBC casts suggest active nephritis. Urinalysis should be done at regular intervals, even for patients in apparent remission, because kidney disease may be asymptomatic. Renal biopsy is usually not necessary for diagnosis of SLE or to confirm renal involvement but is helpful in evaluating the status of renal disease (ie, active inflammation vs postinflammatory scarring) and guide therapy. Patients with chronic renal insufficiency and mostly sclerotic glomeruli are not likely to benefit from aggressive immunosuppressive therapy.

Prognosis

The course is usually chronic, relapsing, and unpredictable. Remissions may last for years. If the initial acute phase is controlled, even if very severe (eg, with cerebral thrombosis or severe nephritis), the long-term prognosis is usually good. The 10-yr survival in most developed countries is > 95%. Improved prognosis is in part due to earlier diagnosis and more effective therapies. More severe disease requires more toxic therapies, which increase risk of mortality. Examples of such complications include infection from immunosuppression or osteoporosis from long-term corticosteroid use. Increased risk of coronary artery disease can contribute to premature death.

Treatment

• NSAIDs and often antimalarials for mild disease

• Corticosteroids and often immunosuppressants for severe disease

To simplify therapy, SLE should be classified as mild (eg, fever, arthritis, pleurisy, pericarditis, headache, rash) or severe (eg, hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial involvement, significant renal damage, acute vasculitis of the extremities or GI tract, florid CNS involvement).

Mild or remittent disease: Little or no therapy may be needed. Arthralgias are usually controlled with NSAIDs. Antimalarials help, particularly when joint and skin manifestations are prominent. Hydroxychloroquine 200 mg po once/day or bid reduces the frequency of SLE flares. Alternatives include chloroquine 250 mg po once/day and quinacrine 50 to 100 mg po once/day. Hydroxychloroquine can rarely cause retinal toxicity. The eyes should be examined at 12-mo intervals.

Severe disease: Corticosteroids are first-line therapy. A combination of prednisone and immunosuppressants is recommended in active, serious CNS lupus, vasculitis especially affecting viscera or nerves, or active lupus nephritis. Prednisone is usually given in doses of 40 to 60 mg po once/day, but the dose may vary according to the manifestation of SLE. Oral azathioprine 1 to 2.5 mg/kg once/day or oral cyclophosphamide 1 to 4 mg/kg once/day can be used as an immunosuppressant. For renal involvement, cyclophosphamide is usually given in intermittent IV pulses instead of daily oral doses; eg, about 500 mg to 1 g/m^2 IV (together with mesna and fluid loading to protect the bladder) monthly for 6 mo and then once q 3 mo for 18 mo (less frequently if there is renal or hematologic toxicity—see Table 33-2).

In CNS lupus or other critical crises, methylprednisolone 1 g by slow (1-h) IV infusion on 3 successive days is often the initial treatment, followed by IV cyclophosphamide, as mentioned previously. Mycophenolate mofetil is an alternative to cyclophosphamide therapy for patients with active kidney disease who have preserved kidney function. IgG 400 mg/kg IV once/day for 5 consecutive days may be useful for refractory thrombocytopenia. Patients

[**Table 33-2.** Protocol for Chemotherapy with Cyclophosphamide and IV Mesna]

with end-stage renal disease can undergo kidney transplantation, as an alternative to dialysis, with a successful outcome, especially if their disease has been in remission.

Improvement of severe SLE often takes 4 to 12 wk. Thrombosis or embolism of cerebral, pulmonary, or placental vessels requires short-term treatment with heparin and longer treatment with warfarin, if the diagnosis of antiphospholipid syndrome is confirmed. The target INR is usually 3.

Suppressive therapy: For most patients, the risk of flares can be decreased without prolonged high-dose corticosteroids. Chronic disease should be treated with the lowest dose of corticosteroids and other drugs that control inflammation (eg, antimalarials, low-dose immunosuppressants). Treatment should be guided by clinical features primarily, although anti-double-stranded DNA antibody titers or serum complement levels may be followed. Other pertinent blood and urine tests may be used to assess specific organ involvement. Anti-double-stranded DNA antibody titers or serum complement levels may not parallel nonrenal disease flares. If a patient needs long-term high-dose corticosteroids, alternative oral immunosuppressants should be considered. Ca, vitamin D, and bisphosphonate therapy should be considered in patients taking corticosteroids long term.

Focal complications and coexisting medical conditions: All patients should be closely monitored for atherosclerosis. Long-term anticoagulation is vital in patients with antiphospholipid antibodies and recurrent thrombosis (see p. 2228).

If a pregnant patient has antiphospholipid antibodies, thrombotic complications can be limited with corticosteroids (prednisone ≤ 30 mg po once/day), low-dose aspirin, or anticoagulation with heparin. Daily heparin given subcutaneously with or without one baby aspirin throughout the 2nd and 3rd trimesters may be the most successful prophylactic measure.

Variant Forms of Lupus

Discoid lupus erythematosus (DLE): DLE, also sometimes called chronic cutaneous lupus

erythematosus, is a set of skin changes that can occur as part of lupus, with or without systemic involvement. Skin lesions begin as erythematous plaques and progress to atrophic scars. They cluster in light-exposed areas of the skin, such as the face, scalp, and ears. Untreated, lesions extend and develop central atrophy and scarring. There may be widespread scarring alopecia. Mucous membrane involvement may be prominent, especially in the mouth.

Patients presenting with typical discoid lesions should be evaluated for SLE. Antibodies against double-stranded DNA are almost invariably absent in DLE. Although it does not differentiate DLE from SLE, biopsy can rule out other disorders (eg, lymphoma or sarcoidosis). Biopsy should be done from the active margin of a skin lesion.

Early treatment can prevent permanent atrophy. Exposure to sunlight or ultraviolet light should be minimized (eg, using potent sunscreens when outdoors). Topical corticosteroid ointments (particularly for dry skin) or creams (less greasy than ointments) tid to qid (eg, triamcinolone acetonide 0.1 or 0.5%, fluocinolone 0.025 or 0.2%, flurandrenolide 0.05%, betamethasone valerate 0.1%, and, particularly betamethasone dipropionate 0.05%) usually cause involution of small lesions; they should not be used excessively or on the face (where they cause skin atrophy). Resistant lesions can be covered with plastic tape coated with flurandrenolide. Alternatively, intradermal injection with triamcinolone acetonide 0.1% suspension (< 0.1 mL per site) may resolve lesions, but secondary atrophy frequently follows. Antimalarials (eg, hydroxychloroquine 200 mg po once/day or bid) can help, including for facial lesions. In resistant cases, combinations (eg, hydroxychloroquine 200 mg/day plus quinacrine 50 to 100 mg po once/day) may be required for months to years.

Subacute cutaneous lupus erythematosus (SCLE): SCLE is a variant form of SLE in which skin involvement is prominent. Patients with SCLE develop extensive recurring rashes. Annular or papulosquamous lesions may develop on the face, arms, and trunk. Lesions are usually photosensitive and can develop hypopigmentation but rarely scar. Arthritis and fatigue are common in SCLE, but neurologic and renal manifestations are not. Patients may be ANA-positive or ANA-negative. Most have antibodies to Ro (SSA). Infants whose mothers have Ro antibodies may have congenital SCLE or congenital heart block. SCLE should be treated similarly to SLE.

Systemic Sclerosis

(Scleroderma)

Systemic sclerosis (SSc) is a rare chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lungs, heart, and kidneys). Common symptoms include Raynaud's syndrome, polyarthralgia, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers. Lung, heart, and kidney involvement accounts for most deaths. Diagnosis is clinical, but laboratory tests help with confirmation. Specific treatment is difficult, and emphasis is often on treatment of complications.

SSc is about 4 times more common among women than men. It is most common among people aged 20 to 50 and is rare in children. SSc can develop as part of mixed connective tissue disease.

Etiology

Immunologic mechanisms and heredity (certain HLA subtypes) play a role in etiology. SSc-like syndromes can result from exposure to vinyl chloride, bleomycin, pentazocine, epoxy and aromatic hydrocarbons, contaminated rapeseed oil, or L-tryptophan.

Pathophysiology

Pathophysiology involves vascular damage and activation of fibroblasts; collagen and other extracellular proteins in various tissues are overproduced.

In SSc, the skin develops more compact collagen fibers in the reticular dermis, epidermal thinning, loss of

rete pegs, and atrophy of dermal appendages. T cells may accumulate, and extensive fibrosis in the dermal and subcutaneous layers develops. In the nail folds, capillary loops dilate and some microvascular loops are lost. In the extremities, chronic inflammation and fibrosis of the synovial membrane and surfaces and periarticular soft tissues occur.

Esophageal motility becomes impaired, and the lower esophageal sphincter becomes incompetent; gastroesophageal reflux and secondary strictures can develop. The intestinal muscularis mucosa degenerates, leading to pseudodiverticula in the colon and ileum. Interstitial and peribronchial fibrosis or intimal hyperplasia of small pulmonary arteries can develop; if long-standing, pulmonary hypertension can result. Diffuse myocardial fibrosis or cardiac conduction abnormalities occur. Intimal hyperplasia of interlobular and arcuate arteries can develop within the kidneys, causing renal ischemia and hypertension.

SSc varies in severity and progression, ranging from generalized skin thickening with rapidly progressive and often fatal visceral involvement (SSc with diffuse scleroderma) to isolated skin involvement (often just the fingers and face) and slow progression (often several decades) before visceral disease develops. The latter form is termed limited cutaneous scleroderma or CREST syndrome (calcinosis cutis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasias). In addition, SSc can overlap with other autoimmune rheumatic disorders—eg, sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

Symptoms and Signs

The most common initial symptoms and signs are Raynaud's syndrome and insidious swelling of the distal extremities with gradual thickening of the skin of the fingers. Polyarthralgia is also prominent. GI disturbances (eg, heartburn, dysphagia) or respiratory complaints (eg, dyspnea) are occasionally the first manifestations.

Skin and nail manifestations: Swelling of the skin is usually symmetric and progresses to induration. It may be confined to the fingers (sclerodactyly) and hands, or it may affect most or all of the body. The skin eventually becomes taut, shiny, and hypopigmented or hyperpigmented; the face becomes masklike; and telangiectases may appear on the fingers, chest, face, lips, and tongue. Subcutaneous calcifications may develop, usually on the fingertips (pulps) and over bony eminences. Trophic ulcers are common, especially on the fingertips, overlying the finger joints, or over calcinotic nodules. Abnormal capillary and microvascular loops in the nails can be seen with an ophthalmoscope or dissecting microscope.

Joint manifestations: Polyarthralgias or mild arthritis can be prominent. Flexion contractures may develop in the fingers, wrists, and elbows. Friction rubs may develop over the joints, tendon sheaths, and large bursae.

GI manifestations: Esophageal dysfunction is the most frequent visceral disturbance and occurs in most patients. Dysphagia (usually retrosternal) usually develops first. Acid reflux can cause heartburn and stricture. Barrett's esophagus occurs in one third of patients and predisposes to complications (eg, stricture, adenocarcinoma). Hypomotility of the small bowel causes anaerobic bacterial overgrowth that can lead to malabsorption. Air may penetrate the damaged bowel wall and be visible on x-rays (pneumatosis intestinalis). Leakage of bowel contents into the peritoneal cavity can cause peritonitis. Distinctive wide-mouthed diverticula can develop in the colon. Biliary cirrhosis may develop in patients with CREST syndrome.

Cardiopulmonary manifestations: Lung involvement generally progresses indolently, with substantial individual variability, but is a common cause of death. Lung fibrosis can impair gas exchange, leading to exertional dyspnea and restrictive disease with eventual respiratory failure. Acute alveolitis (potentially responsive to therapy) can develop. Esophageal dysfunction can lead to aspiration pneumonia. Pulmonary hypertension may develop, as can heart failure, both of which are poor prognostic findings. Pericarditis with effusion or pleurisy can occur. Cardiac arrhythmias are common.

Renal manifestations: Severe, often sudden renal disease (renal crisis) may occur, most commonly in the first 4 to 5 yr and in patients with diffuse scleroderma. It is usually heralded by sudden, severe

hypertension.

Diagnosis

• Clinical evaluation

• Usually antinuclear antibodies (ANA), Scl-70 (topoisomerase I), and anticentromere antibodies

SSc should be considered in patients with Raynaud's syndrome, typical musculoskeletal or skin manifestations, or unexplained dysphagia, malabsorption, pulmonary fibrosis, pulmonary hypertension, cardiomyopathies, or conduction disturbances. Diagnosis can be obvious in patients with combinations of classic manifestations, such as Raynaud's syndrome, dysphagia, and tight skin. However, in some patients, the diagnosis cannot be made clinically, and confirmatory laboratory tests can increase the probability of disease but do not rule it out.

Serum ANA and Scl-70 antibody should be obtained. ANA are present in ≥ 90%, often with an antinucleolar pattern. Antibody to centromeric protein (anticentromere antibody) occurs in the serum of a high proportion of patients with CREST syndrome and is detectable on the ANA. Scl-70 antigen is a DNA-binding protein sensitive to nucleases. Patients with diffuse scleroderma are more likely than those with CREST to have anti-Scl-70 antibodies. Rheumatoid factor also is positive in one third of patients.

If lung involvement is suspected, pulmonary function testing, chest CT, and echocardiography can begin to define its severity. Acute alveolitis is often detected by high-resolution chest CT.

Prognosis

The course depends on the type of SSc but is often unpredictable. Typically, progression is slow. Overall 10-yr survival is about 65%. Most patients with diffuse skin disease eventually develop visceral complications, which are the usual causes of death. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present early. Heart failure may be intractable. Ventricular ectopy, even if asymptomatic, increases the risk of sudden death. Acute renal insufficiency, if untreated, progresses rapidly and causes death within months. Patients with CREST syndrome may have disease that is limited and nonprogressive for long periods; visceral changes (eg, pulmonary hypertension caused by vascular disease of the lung, a peculiar form of biliary cirrhosis) eventually develop, but the course is often remarkably benign.

Treatment

• Treatment directed at symptoms and dysfunctional organs

No drug significantly influences the natural course of SSc overall, but various drugs are of value in treating specific symptoms or organ systems. NSAIDs can help arthritis. Corticosteroids may be helpful if there is overt myositis or mixed connective tissue disease but may predispose to renal crisis. Penicillamine, long used for treatment of skin thickening, has not shown clear efficacy in recent trials.

Various immunosuppressants, including methotrexate, azathioprine, and cyclophosphamide, may help pulmonary alveolitis. Successful lung transplantation has been reported. Epoprostenol (prostacyclin) and bosentan may be helpful for pulmonary hypertension. Ca channel blockers, such as nifedipine 20 mg po tid or as an extended-release formulation, or angiotensin receptor blockers, such as losartan 50 mg po once/day, may help Raynaud's syndrome. Patients should dress warmly. IV infusions of prostaglandin E1 (alprostadil) or epoprostenol or sympathetic blockers can be used for digital ischemia. Reflux esophagitis is relieved by frequent small feedings, high-dose proton pump inhibitors, and sleeping with the head of the bed elevated. Esophageal strictures may require periodic dilation; gastroesophageal reflux may possibly require gastroplasty. Tetracycline 500 mg po bid or another broad-spectrum antibiotic can suppress overgrowth of intestinal flora and may alleviate malabsorption symptoms. Physiotherapy may help preserve muscle strength but is ineffective in preventing joint contractures. No treatment affects calcinosis.

For acute renal crisis, prompt treatment with an ACE inhibitor can dramatically prolong survival. Blood pressure is usually, but not always, controlled. The mortality rate of renal crisis remains high. If end-stage renal disease develops, it may be reversible, but dialysis and transplantation may be necessary.

Chapter 34. Vasculitis

Introduction

Vasculitis is inflammation of blood vessels, often with ischemia, necrosis, and occlusive changes. It can affect any blood vessel—arteries, arterioles, veins, venules, or capillaries. Most damage results when inflammation narrows vessels and causes tissue necrosis. Clinical manifestations of specific vasculitic disorders are diverse and depend on the size of the involved vessels and the organs affected by ischemia.

Etiology

Vasculitis may be primary or secondary. Primary vasculitis results from an inflammatory response that targets the vessel walls and has no known cause. Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.

Pathophysiology

Histologic description of an affected vessel should include the following:

- A description of vessel wall damage
- The nature of the inflammatory infiltrate in the vessel wall (eg, granulomatous, nongranulomatous, leukocytoclastic vasculitis)
- A description of healing responses (eg, intimal hypertrophy, fibrosis)

Certain features (eg, predominant inflammatory cells, location of inflammation) suggest particular vasculitic processes and may aid in the diagnosis (see Table 34-1). For example, in many acute lesions, the predominant inflammatory cells are PMNs; in chronic lesions, lymphocytes predominate.

Inflammation may be segmental or involve the entire vessel. At sites of inflammation, varying degrees of cellular inflammation and necrosis or scarring occur in one or more layers

[**Table 34-1.** Histologic Clues to Diagnosis of Vasculitic Disorders]

[
Table 34-2. Classification of Vasculitic Disorders]

of the vessel wall. Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina.

Leukocytoclastic vasculitis is a histopathologic term used to describe findings in small-vessel vasculitis. It refers to breakdown of inflammatory cells that leaves small nuclear fragments (nuclear debris) in and around the vessels. Inflammation is transmural, rarely necrotizing, and nongranulomatous. PMNs predominate early; later, lymphocytes predominate. Resolution of the inflammation tends to result in fibrosis and intimal hypertrophy. Intimal hypertrophy or secondary clot formation can narrow the arterial lumen and accounts for tissue ischemia or necrosis.

Classification

Vasculitic disorders can be classified according to the size of the predominant vessel affected (see Table 34-2). However, there is often substantial overlap.

Symptoms and Signs

Size of the affected vessels helps determine clinical presentation (see Table 34-2).

Regardless of the size of the vessels involved, patients can present with symptoms and signs of systemic inflammation (eg, fever, night sweats, fatigue, anorexia, weight loss, arthralgias, arthritis). Some manifestations are life- or organ-threatening and require immediate treatment. They include alveolar hemorrhage, rapidly progressive glomerulonephritis, mesenteric ischemia, orbital pseudotumor threatening the optic nerve (in Wegener's granulomatosis), and vision loss in patients with giant cell arteritis.

Diagnosis

• Clinical evaluation

• Antineutrophil cytoplasmic antibodies (ANCA) tests

• Biopsy

• Angiography

Systemic vasculitis is suspected in patients with the following:

• Symptoms or signs characteristic of vasculitis (eg, mononeuritis multiplex, leukocytoclastic vasculitis)

• Ischemic manifestations (eg, ischemic stroke, limb claudication, mesenteric ischemia) out of proportion to a patient's risk factors for atherosclerosis

• Unexplained combinations of symptoms in more than one organ system that are compatible with vasculitis (eg, hypertension, myalgias), particularly when symptoms of a systemic illness are present

Primary vasculitic disorders are diagnosed based on the presence of characteristic symptoms, physical findings, compatible laboratory test results, and exclusion of other causes (ie, secondary vasculitis). Histologic examination is done whenever possible and may point to a particular vasculitic disorder (see Table 34-1).

Routine laboratory tests are done. Most results are nonspecific but can help support the diagnosis. Tests usually include CBC, ESR or C-reactive protein, serum albumin and total protein, and tests for ANCA. Often, patients present with elevated ESR or C-reactive protein, anemia due to chronic inflammation, elevated platelets, and low serum albumin and total protein. Freshly voided urine must be tested for RBCs, RBC casts, and protein to identify renal involvement. Serum creatinine levels should be checked and monitored. Leukopenia and thrombocytopenia are uncommon.

Detection of ANCA may support the diagnosis of Wegener's granulomatosis, Churg-Strauss syndrome, or microscopic polyangiitis. Standardized tests for ANCA include immunofluorescence staining and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence staining of ethanol-fixed neutrophils can detect the cytoplasmic pattern of cANCA or the perinuclear pattern of pANCA. Then solid-phase ELISA is used to check for antibodies specific for the major autoantigens: proteinase-3 (PR3), which correlates with the cANCA staining pattern, or myeloperoxidase (MPO), which correlates with the pANCA staining pattern. Because false-positives occur, ANCA should be measured only when one of these vasculitic disorders is clinically suspected.

Other useful laboratory tests include hepatitis B and C serologic testing, testing for the presence of cryoglobulins, and complement levels to diagnose viral or cryoglobulinemic vasculitis. Further testing is determined by clinical findings. A chest x-ray should be done to check for infiltrates, but high-resolution noncontrast CT of the chest may be needed to check for subtle findings, such as small nodules or cavities. Bilateral diffuse infiltrates suggest possible alveolar hemorrhage, which requires immediate diagnosis and treatment. Other imaging tests may be required. For example, magnetic resonance angiography of large blood vessels and the aorta is useful for diagnosis and monitoring when such vessels appear affected. If symptoms suggest mononeuritis multiplex, electromyography is done.

Because vasculitic disorders are rare and treatment may have severe adverse effects, tissue biopsy is done to confirm the diagnosis whenever possible. Usually, clinical findings suggest the best site for biopsy. For example, if clinical and electromyographic findings suggest mononeuritis multiplex with dysfunction of a specific peripheral nerve, tissue around arteries supplying the nerve is biopsied. Usually, biopsies of unaffected tissue are much less likely to provide positive results.

Because vasculitis is often segmental or focal, biopsy may not show inflammation even when a vessel is affected. Sampling from multiple areas or long segments of a vessel may increase diagnostic sensitivity.

Treatment

- Corticosteroids and cyclophosphamide to induce remission of life- or organ-threatening disorders

- Tapering or elimination of corticosteroids and substitution of methotrexate or azathioprine to maintain remission

Treatment depends on the etiology and extent and severity of disease. For secondary vasculitic disorders, removing the cause (eg, infection, drug, cancer) can help.

For primary vasculitic disorders, treatment aims to induce and maintain remission. Remission is induced by using cytotoxic immunosuppressants and high-dose corticosteroids, usually for 3 to 6 mo, until remission occurs or disease activity is acceptably reduced. Adjusting treatment to maintain remission usually takes longer, on average > 1 or 2 yr. During this period, the goal is to eliminate corticosteroids or reduce their dose and to use less potent immunosuppressants as long as needed.

Induction of remission: For less severe forms of vasculitis, low doses of corticosteroids and less potent immunosuppressants (eg, methotrexate, azathioprine, mycophenolate mofetil) may be used.

Severe, rapidly progressive and life- or organ-threatening vasculitis (eg, causing alveolar hemorrhage, rapidly progressive glomerulonephritis, or mesenteric ischemia) is a medical emergency requiring hospital admission and immediate treatment. Treatment consists of the following:

- **Corticosteroids:** High-dose corticosteroids (also called pulse corticosteroids) are often prescribed. Methylprednisolone 15 mg/kg or 1 g IV once/day for 3 days may be used. Oral prednisone is given concurrently. A dose of 1 mg/kg once/day is given for about 4 wk until patients improve. The dose is then tapered slowly, as tolerated, usually by 10 mg every week to 40 mg/day, by 5 mg every 2 wk to 20 mg/day, by 2.5 mg every 2 wk to 10 mg/day, and by 1 mg every month from there on until the drug is stopped. Changes in this tapering schedule may be necessary if the patient fails to improve or relapses.

- **Cyclophosphamide:** A dose of 2 mg/kg po once/day is usually recommended for at least 3 mo or until remission occurs. The WBC count must be closely monitored, and the dose must be adjusted to avoid leukopenia. (WBC count should be maintained at > 3500/µL.) If patients cannot tolerate oral cyclophosphamide, are unlikely to take oral drugs as directed, or have a high risk of bladder cancer, IV cyclophosphamide may be used. The recommended cumulative dose of cyclophosphamide is 0.75 to 1 g/m^2 monthly. The dose should be reduced in patients with significant renal insufficiency. Patients taking cyclophosphamide should also be given prophylactic treatment against *Pneumocystis jirovecii*.

Acrolein, a product of cyclophosphamide degradation, is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. For patients who have taken cyclophosphamide long term, risk of cystitis is increased, and some develop transitional cell carcinoma of the bladder. During cyclophosphamide therapy, careful hydration is needed to reduce the risk of bladder hemorrhage, cystitis, and bladder cancer. Mesna binds acrolein and is mixed together with the IV cyclophosphamide infusion. One milligram of mesna is added for each milligram of cyclophosphamide. Recurrence of hematuria, especially without casts and dysmorphic red cells, should prompt a referral for urologic evaluation. Cystoscopy and renal imaging should be done to exclude cancer.

Remission maintenance: Corticosteroids are tapered to zero or to the lowest dose that can maintain remission. Usually, methotrexate (with folate) or azathioprine is prescribed to replace cyclophosphamide

because these drugs have a better adverse effects profile. The duration of this treatment varies, from one year to several years. Patients with frequent relapses may need to take immunosuppressants indefinitely.

Long-term use of corticosteroids can have significant adverse effects. Patients who are taking such therapy should be given Ca and vitamin D supplements and bisphosphonates to help prevent or minimize osteoporosis; bone density should be monitored yearly.

Behcet's Syndrome

Behcet's syndrome is a multisystem, relapsing, chronic vasculitic disorder with prominent mucosal inflammation. Common manifestations include recurrent oral ulcers, ocular inflammation, genital ulcers, and skin lesions. The most serious manifestations are blindness, neurologic or GI manifestations, venous thromboses, and arterial aneurysms. Diagnosis is clinical, using international criteria. Treatment is mainly symptomatic but may involve corticosteroids for acute severe ocular or neurologic manifestations or immunosuppressants for severe chronic lesions.

Behcet's syndrome involves small and large arteries and veins. Arterial thrombosis and superficial and deep venous thrombosis often occur.

The syndrome occurs nearly equally in men and women, typically beginning during their 20s. Occasionally, the syndrome develops in children. Incidence varies by location. Behcet's syndrome is most common along the silk route from the Mediterranean to China; it is uncommon in the US.

The cause is unknown. Immunologic (including autoimmune) and viral or bacterial triggers have been suggested, and HLA-B51 is associated with cases from Turkey, Iran, China, Korea, and Japan.

Neutrophil infiltration is detected in biopsy specimens from oral aphthous ulcers and erythema nodosum and pathergy lesions, but no histologic changes are pathognomonic.

Symptoms and Signs

Mucocutaneous: Almost all patients have recurrent painful oral ulcers resembling those of aphthous stomatitis; in most, these ulcers are the first manifestations. The ulcers are round or oval, 2 to 10 mm in diameter, and shallow or deep with a central yellowish necrotic center; they can occur anywhere in the oral cavity, often in clusters. Ulcers last 1 to 2 wk. Similar ulcers occur on the penis and scrotum, on the vulva where they are painful, or in the vagina where they may cause little or no pain.

Cutaneous lesions are common and may include acneiform lesions, nodules, erythema nodosum, superficial thrombophlebitis, pyoderma gangrenosum-type lesions, and palpable purpura.

Pathergy (an erythematous papular or pustular response to local skin injury) is defined as a papule > 2 mm that appears 24 to 48 h after oblique insertion of a 20- to 25-gauge needle into the skin. Pathergy has occurred in many parts of the world but is less common among North American and northern European patients than among Middle Eastern and Asian patients.

Ocular: The eyes are affected in 25 to 75% of patients. The following may occur:

- Relapsing uveitis or iridocyclitis (most common) often manifests as pain, photophobia, and red eye.
- Hypopyon (a layer of pus visible in the anterior chamber) may occur.
- Uveitis is typically bilateral and episodic, often involves the entire uveal tract (panuveitis), and may not resolve completely between episodes.
- Choroiditis, retinal vasculitis, vascular occlusion, and optic neuritis may irreversibly impair vision and even progress to blindness.

Musculoskeletal: Relatively mild, self-limiting, and nondestructive arthralgias or frank arthritis, especially in the knees and other large joints, occur in 50% of patients. Sacroiliac inflammation can occur.

Vascular: Superficial and deep venous thromboses are common. Large vessels are affected in about one third of patients. Perivascular and endovascular inflammation may lead to hemorrhage, stenosis, aneurysms, and thrombosis in arteries and veins. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, and other venous obstructive lesions can also occur.

Disease of the aorta and large blood vessels may be life threatening. Hemoptysis may occur if fistulas between the pulmonary artery and bronchus develop.

Neurologic and psychiatric: CNS involvement is less common but is serious. Onset may be sudden or gradual. The first manifestations may be parenchymal involvement with pyramidal signs, small-vessel disease with a multiple sclerosis-like pattern, aseptic meningitis or meningoencephalitis, or dural sinus thrombosis.

Psychiatric disorders including personality changes and dementia may develop years later. Peripheral neuropathy, common in other vasculitic disorders, is uncommon in Behcet's syndrome.

GI: Abdominal discomfort, abdominal pain, and diarrhea with intestinal ulcers, occurring primarily in the ileum and colon and closely resembling Crohn's disease, may occur.

Diagnosis

• Clinical criteria

Behcet's syndrome should be suspected in young adults with recurrent oral aphthous ulcers, unexplained ocular findings, or genital ulcers. Diagnosis is clinical and may require months because many of the manifestations are nonspecific and can be insidious.

International criteria for diagnosis include recurrent oral ulcers (3 times in 1 yr) and 2 of the following:

• Recurrent genital ulcers

• Eye lesions

• Skin lesions

• Positive pathergy test with no other clinical explanation

Laboratory tests (eg, CBC, ESR or C-reactive protein, serum albumin and total protein levels) are done. Results are nonspecific but characteristic of inflammatory disease (elevated ESR, C-reactive protein, and α_2- and γ-globulins; mild leukocytosis).

Differential diagnosis includes reactive arthritis, SLE, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and herpes simplex infection. Behcet's syndrome has no single pathognomonic finding but may be distinguished by its combinations of relapsing symptoms with spontaneous remissions and multiple organ involvement, particularly in patients with recurrent, deep mucosal ulcers.

Prognosis

Behcet's syndrome typically has a waxing and waning course characterized by exacerbations and remissions. Mucocutaneous and ocular lesions and arthralgias are often worse early in the disease. CNS and large-vessel manifestations, if they develop, typically occur later. Occasionally, the syndrome results in death, usually due to neurologic, vascular (eg, aneurysms), or GI manifestations. Many patients eventually go into remission.

Treatment

• Colchicine, thalidomide, etanercept, and interferon for mucosal disease

• Azathioprine or cyclosporine for eye disease

• Cyclophosphamide and chlorambucil for refractory or life-threatening disease

Treatment depends on the clinical manifestations.

Mucosal disease can be managed symptomatically. Colchicine 0.6 mg po bid may decrease the frequency and severity of oral or genital ulcers and may be effective for erythema nodosum and arthralgias. Thalidomide 100 to 300 mg po once/day may be used to treat oral, genital, and skin lesions, but lesions may recur when treatment is stopped. Etanercept 50 mg sc once/wk or 25 mg sc twice/wk may suppress mucocutaneous lesions. Etanercept can be given if colchicine is ineffective. Interferon alfa-2a 6 million units sc 3 times/wk can also be given if colchicine is ineffective.

Azathioprine 2.5 mg/kg po once/day helps preserve visual acuity and prevent new eye lesions. Azathioprine is also useful for mucocutaneous lesions and arthralgia. Cyclosporine 5 to 10 mg/kg po once/day may be reserved for patients with severe ocular manifestations and may be used with azathioprine to treat refractory uveitis. Interferon alfa-2a 6 million units sc 3 times/wk and infliximab (a tumor necrosis factor inhibitor) 3 to 10 mg/kg IV at 0, 2, 4, and then every 8 wk show promise for patients with ocular manifestations.

Cyclophosphamide and chlorambucil are used in patients with refractory disease, life-threatening conditions (eg, pulmonary aneurysms), or CNS manifestations.

The efficacy of corticosteroids is unsubstantiated, despite their wide use. Topical corticosteroids may temporarily relieve ocular manifestations and most oral lesions. However, topical or systemic corticosteroids do not alter the frequency of relapses. A few patients with severe uveitis or CNS manifestations respond to high-dose systemic corticosteroids (eg, prednisone 60 to 80 mg po once/day).

Whether immunosuppressants should be added to anticoagulation therapy when patients have thromboses has not been established.

Churg-Strauss Syndrome

(Allergic Angiitis and Granulomatosis)

Churg-Strauss syndrome is a pulmonary and systemic small-vessel necrotizing vasculitis, characterized by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils. It tends to occur in people with adult-onset asthma, allergic rhinitis, nasal polyposis, or a combination. Diagnosis is best confirmed by biopsy. Treatment is primarily with corticosteroids and, for severe disease, addition of other immunosuppressants.

Churg-Strauss syndrome occurs in about 3 people/million. Mean age at onset is 48.

Churg-Strauss syndrome is characterized by extravascular necrotizing granulomas (usually containing eosinophilic infiltrates), eosinophilia, and tissue infiltration by eosinophils. However, these abnormalities rarely coexist. The vasculitis typically affects pulmonary and systemic arteries and veins. Any organ can be affected, but the lungs, skin, cardiovascular system (eg, as coronary artery vasculitis), kidneys, peripheral nervous system, sinuses, joints, and GI tract are most commonly affected. Occasionally, pulmonary capillaritis may cause alveolar hemorrhage.

Etiology

The cause is unknown. However, an allergic mechanism, with tissue directly injured by eosinophils and neutrophil degranulation products, may be involved. Activation of T lymphocytes seems to help maintain eosinophilic inflammation. The syndrome occurs in patients who have adult-onset asthma, allergic rhinitis,

nasal polyposis, or a combination. Antineutrophil cytoplasmic autoantibodies (ANCA) are sometimes present.

Symptoms and Signs

The syndrome has 3 phases, which may overlap:

- Prodromal: This phase may persist for years. Patients have allergic rhinitis, nasal polyposis, asthma, or a combination.

- 2nd phase: Peripheral blood and tissue eosinophilia is typical. Clinical presentation, which may resemble Loffler's syndrome, includes chronic eosinophilic pneumonia and eosinophilic gastroenteritis.

- 3rd phase: Potentially life-threatening vasculitis develops. Systemic symptoms (eg, fever, malaise, weight loss, fatigue) are common.

However, the phases do not necessarily follow one another consecutively, and the time interval between them varies greatly.

Various organs and systems may be affected:

- **Respiratory:** Asthma, often with onset during adulthood, occurs in most patients. Sinusitis is common, typically without severe necrotizing inflammation. Sinusitis causes facial pain and increases nasal discharge. Patients may be short of breath. Cough and hemoptysis, due to alveolar hemorrhage, may be present. Transient patchy pulmonary infiltrates are common.

- **Neurologic:** Neurologic manifestations are common. Mononeuritis multiplex occurs in up to three fourths of patients. CNS involvement is rare but can include confusion, seizures, and coma, with or without cranial nerve palsies or evidence of cerebral infarction.

- **Cutaneous:** The skin is affected in about one half of patients. Nodules and papules appear on extensor surfaces of extremities. They are caused by extravascular palisading granulomatous lesions with central necrosis. Purpura or erythematous papules, due to leukocytoclastic vasculitis with or without prominent eosinophilic infiltration, may develop.

- **Musculoskeletal:** Occasionally, arthralgias, myalgias, or even arthritis can occur, usually during the vasculitic phase.

- **Cardiac:** Heart failure, MI, coronary artery vasculitis (possibly with MI), valvular disorders, or pericarditis may develop. The predominant histopathologic finding is eosinophilic myocarditis.

- **GI:** Up to one third of patients present with GI symptoms (eg, abdominal pain, diarrhea, bleeding) due to eosinophilic gastroenteritis or mesenteric ischemia due to vasculitis.

- **Renal:** The kidneys are affected less often than in other vasculitic disorders associated with ANCA. Typically, pauci-immune (few if any immune complexes), focal segmental necrotizing glomerulonephritis with crescent formation is present; eosinophilic or granulomatous inflammation of the kidneys is rare.

Renal, cardiac, or neurologic involvement indicates a worse prognosis.

Diagnosis

- Clinical criteria

- Routine laboratory tests

- Biopsy

Criteria for classification from the American College of Rheumatology consist of the following:

• Asthma

• Eosinophilia of > 10% in peripheral blood

• Paranasal sinusitis

• Pulmonary infiltrates, sometimes transient

• Histologic evidence of vasculitis with extravascular eosinophils

• Mononeuritis multiplex or polyneuropathy

If ≥ 4 criteria are present, sensitivity is 85%, and specificity is 99.7%.

Testing aims to establish the diagnosis and the extent of organ involvement and to distinguish Churg-Strauss syndrome from other eosinophilic disorders (eg, parasitic infections, drug reactions, acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, idiopathic hypereosinophilic syndrome). Diagnosis is suggested by clinical findings and results of routine laboratory tests but should usually be confirmed by biopsy of lung or other affected tissue.

Blood tests and chest x-rays are done, but results are not diagnostic. CBC with differential is done to check for eosinophilia. Peripheral blood eosinophilia is also a marker of disease activity. IgE and C-reactive protein levels and ESR are determined periodically to evaluate inflammatory activity. Electrolyte levels are measured and urinalysis is done to check for evidence of renal involvement and to follow its severity.

Serologic testing is done. It detects ANCA in up to 50%; if ANCA is detected, enzyme-linked immunosorbent assay (ELISA) is done to check for specific antibodies. Perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase is the most common result, but ANCA is not specific for Churg-Strauss syndrome.

Chest x-ray often shows transient patchy pulmonary infiltrates.

Biopsy of the most accessible affected tissue should be done if possible.

Treatment

• Corticosteroids

Systemic corticosteroids are the mainstay of treatment. When to add other immunosuppressants is not clear, but Churg-Strauss syndrome is generally treated the same way as Wegener's granulomatosis (see p. 329) or microscopic polyangiitis (see p. 322). Recombinant interferon alfa-2a 3 million units sc daily has been used when the syndrome is refractory to other drugs or when eosinophilic inflammation is difficult to control.

Cutaneous Vasculitis

Cutaneous vasculitis affects small or medium-sized vessels in the skin and subcutaneous tissue. This disorder may be limited to the skin or be part of systemic vasculitis. Purpura, ulcers, livedo reticularis, or nodules may develop. Diagnosis requires biopsy. Treatment depends on etiology and extent of disease.

Common causes include serum sickness, infections (eg, hepatitis C), cancers, rheumatologic or other autoimmune disorders, and hypersensitivity to drugs.

Vessel inflammation often results from immune complex deposition, but other pathogenetic mechanisms

may be involved. Predominantly cutaneous vasculitis is a leukocytoclastic vasculitis, so-called because inflammation disrupts leukocytes, resulting in deposition of nuclear debris (leukocytoclasis) in the vessel wall.

Symptoms and Signs

Patients may present with skin symptoms such as lesions, including palpable purpura, urticaria, ulcers, livedo reticularis, and nodules. If cutaneous vasculitis occurs as part of a systemic vasculitis, symptoms may also include fever, arthralgias, other organ involvement, or a combination.

Diagnosis

- Exclusion of systemic vasculitis clinically and by routine tests (eg, CBC, ESR, urinalysis, chest x-ray, serum creatinine)

- Biopsy

- Tests for the cause of vasculitis (eg, cryoglobulins, antineutrophil cytoplasmic antibodies [ANCA], hepatitis B and C antibodies, complement levels)

A diagnosis of vasculitis limited to the skin requires a complete history and physical examination, focusing on excluding manifestations of inflammation or vasculitis in other organs, as in the following:

- Lungs: Shortness of breath, cough, hemoptysis, and signs of consolidation

- Kidneys: New-onset hypertension or edema

- Nerves: New-onset asymmetric weakness or paresthesias

- Intestine: New-onset abdominal pain, diarrhea, and bloody stools

Urinalysis should exclude blood, protein, and RBC casts. A chest x-ray is needed to check for infiltrates (suggesting alveolar hemorrhage). CBC and other blood tests are needed to check for anemia, to determine platelet count and serum creatinine level, and to check for elevated levels of acute-phase reactants (eg, ESR, C-reactive protein).

A skin biopsy is done, optimally within 24 to 48 h after vasculitic lesions appear. Diagnostic yield depends on the depth of the biopsy. Generally, punch biopsy or excision biopsy into the subcutis is preferred; these biopsies can sample small and medium-sized vessels. Shave biopsy is usually inadequate.

If histologic examination detects the following, cutaneous vasculitis is confirmed:

- Infiltration of the vessel wall by inflammatory cells, resulting in disruption and destruction of the vessel wall

- Intramural and intraluminal fibrin deposition (fibrinoid necrosis)

- Extravasation of RBCs

- Nuclear debris (leukocytoclasis)

Direct immunofluorescence staining is needed to check for IgA, IgM, and IgG and complement deposition in and around the vessel wall, which suggests an immune complex-mediated process and supports the diagnosis. Further testing to establish the cause of vasculitis includes checking for cryoglobulins, ANCA, and hepatitis B and C antibodies, measuring complement levels, and tests for any clinically suspected disorders that can cause vasculitis.

Treatment

• Antihistamines and sometimes low-dose corticosteroids to treat skin lesions

• Trial of colchicine, hydroxychloroquine, or dapsone to prevent recurrences

Treatment is first directed at any identified cause. If no cause is identified and vasculitis is limited to the skin, treatment is minimal and conservative. Support hose and antihistamines may be sufficient. If this treatment is ineffective, low-dose corticosteroids can be tried.

If lesions recur, colchicine, hydroxychloroquine, or dapsone may prevent further recurrences. Rarely, stronger immunosuppressants (eg, azathioprine, methotrexate) are used, particularly if lesions ulcerate.

Giant Cell Arteritis

(Temporal Arteritis; Cranial Arteritis; Horton's Disease)

Giant cell arteritis involves predominantly the thoracic aorta, large arteries emerging from the aorta in the neck, and extracranial branches of the carotid arteries. Simultaneous polymyalgia rheumatica is common. Focal symptoms and signs may include headaches, visual disturbances, temporal artery tenderness, and pain in the jaw muscles during chewing. Fever, weight loss, malaise, and fatigue are also common. ESR and C-reactive protein are typically elevated. Diagnosis is clinical and confirmed by temporal artery biopsy. Treatment with high-dose corticosteroids and aspirin is usually effective and prevents vision loss.

Giant cell arteritis is a relatively common form of vasculitis in the US and Europe. Incidence varies depending on ethnic background. Autopsy studies suggest that the disorder may be more common than is clinically apparent. Women are affected more often. Mean age at onset is about 70, with a range of 50 to > 90. About 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. The intracranial vessels are usually not affected.

Pathophysiology

Vasculitis may be localized, multifocal, or widespread. The disorder tends to affect arteries containing elastic tissue, most often the temporal, cranial, or other carotid system arteries. The aortic arch branches, coronary arteries, and peripheral arteries can also be affected. Mononuclear cell infiltrates in the adventitia form granulomas containing activated T cells and macrophages. Multinucleated giant cells, when present, cluster near the disrupted elastic lamina. The intimal layer is markedly thickened, with concentric narrowing and occlusion of the lumen.

Symptoms and Signs

Symptoms may begin gradually over several weeks or abruptly.

Patients may present with systemic symptoms such as fever (usually low-grade), fatigue, malaise, unexplained weight loss, and sweats. Some patients are initially diagnosed as having FUO. Eventually, most patients develop symptoms related to the affected arteries.

Severe, sometimes throbbing headache (temporal, occipital, frontal, or diffuse) is the most common symptom. It may be accompanied by scalp pain elicited by touching the scalp or combing the hair.

Visual disturbances include diplopia, scotomas, ptosis, blurred vision, and loss of vision (which is an ominous sign). Brief periods of partial or complete vision loss (amaurosis fugax) in one eye may be rapidly followed by permanent irreversible loss of vision. If untreated, the other eye may also be affected. However, complete bilateral blindness is uncommon. Vision loss is caused by arteritis of branches of the ophthalmic artery or posterior ciliary arteries, which leads to ischemia of the optic nerve. Funduscopic findings may include ischemic optic neuritis with pallor and edema of the optic disk, scattered cotton-wool patches, and small hemorrhages. Later, the optic nerve atrophies. Rarely, central blindness results from infarction in the occipital cortex caused by arterial lesions in the distal cervical region or base of the brain.

Intermittent claudication (ischemic muscle pain) may occur in jaw muscles and muscles of the tongue or extremities. Jaw claudication is noted especially when firm foods are chewed.

Neurologic manifestations, such as strokes and transient ischemic attacks, can result when the carotid or vertebrobasilar arteries or branches are narrowed or occluded.

Thoracic aortic aneurysms and dissection of the aorta are serious, often late, complications.

Diagnosis

• ESR, C-reactive protein, and CBC

• Biopsy, usually of the temporal artery

Giant cell arteritis is suspected in patients > 55 if any of the following develops, especially if they also have symptoms of systemic inflammation:

• A new type of headache

• Any new symptom or sign compatible with ischemia of an artery above the neck

• Jaw pain during chewing

• Temporal artery tenderness

• Unexplained subacute fever or anemia

The diagnosis is more likely if patients also have symptoms of polymyalgia rheumatica.

Physical examination may detect swelling and tenderness, with or without nodularity or erythema, over the temporal arteries. Temporal arteries can become prominent. A temporal artery that rolls under the examiner's fingers, rather than collapses, is abnormal. The large arteries of the neck and limbs and the aorta should be evaluated for bruits.

If the diagnosis is suspected, ESR, C-reactive protein, and CBC are determined. In most patients, ESR and C-reactive protein are elevated; anemia of chronic disease is common. Occasionally, platelets are elevated, and serum albumin and total protein, measured for other reasons, are low. Mild leukocytosis is commonly detected but is nonspecific.

If the diagnosis is suspected, biopsy of an artery is recommended. Because inflamed segments often alternate with normal segments, a segment that appears abnormal should be sampled if possible. Usually, the temporal artery is biopsied, but the occipital artery can also be biopsied if it appears abnormal. The optimal length of the temporal artery to remove is unclear, but 5 cm is recommended if possible. Treatment should not be delayed to do the biopsy. Biopsy can be done up to 2 wk or perhaps more after treatment is started because the inflammatory infiltrate is slow to resolve.

If patients have pulse deficits, the aorta and its branches are imaged (see Table 34-3 on p. 328).

Treatment

• Corticosteroids

• Low-dose aspirin

Treatment should be started as soon as giant cell arteritis is suspected, even if biopsy is going to be delayed for several days.

Corticosteroids are the cornerstone of treatment. Corticosteroids rapidly reduce symptoms and prevent vision loss in most patients. The optimal initial dose, tapering schedule, and total length of treatment are debated. For most patients, an initial dose of prednisone 40 to 60 mg po once/day (or equivalent) for 4 wk, followed by gradual tapering, is effective. If patients have visual disturbances, an initial dose of IV methylprednisolone 500 to 1000 mg once/day for 3 to 5 days can be tried in an attempt to help prevent further decline in vision, particularly in the contralateral eye.

If symptoms lessen, prednisone can be tapered gradually from doses of up to 60 mg/day based on the patient's response, usually as follows: by 5 to 10 mg/day every week to 40 mg/day, by 2 to 5 mg/day every week to 10 to 20 mg/day, then by 1 mg/day every month thereafter until the drug is stopped. ESR alone should not be used alone to evaluate patient response (and disease activity). Clinical symptoms must also be used.

Most patients require at least 2 yr of treatment with corticosteroids. Long-term use of corticosteroids can have significant adverse effects and thus should be limited if possible. More than one half of patients taking these drugs have drug-related complications. Consequently, alternative therapies are being studied. If patients cannot tolerate corticosteroids or if symptoms return when the dose is tapered, methotrexate 0.3 mg/kg/wk may be useful.

Tumor necrosis factor inhibitors have not been shown to be effective.

Low-dose aspirin (100 mg po once/day) may help prevent ischemic events and should be prescribed for all patients unless contraindicated.

Henoch-Schonlein Purpura

Henoch-Schonlein purpura is vasculitis that affects primarily small vessels. It occurs most often in children. Common manifestations include palpable purpura, arthralgias, GI symptoms and signs, and glomerulonephritis. Diagnosis is clinical in children but usually warrants biopsy in adults. Disease is usually self-limited. Corticosteroids can relieve arthralgias and GI symptoms but do not alter the course of the disease. Progressive glomerulonephritis may require high-dose corticosteroids and cyclophosphamide.

In Henoch-Schonlein purpura, IgA-containing immune complexes are deposited in small vessels of the skin and other sites, with consequent activation of complement. Possible inciting antigens include viruses that cause URIs, streptococcal infection, drugs, foods, insect bites, and immunizations. Focal, segmental proliferative glomerulonephritis is typical but mild.

Symptoms and Signs

The disease begins with a sudden palpable purpuric rash typically occurring on the feet, legs, and arms and as a strip across the buttocks. The purpura may start as small areas of urticaria that become indurated and palpable. Crops of new lesions may appear over days to several weeks. Many patients also have fever and polyarthralgia with periarticular tenderness and swelling of the ankles, knees, hips, wrists, and elbows.

GI symptoms are common and include colicky abdominal pain, abdominal tenderness, and melena. Intussusception occasionally develops in children. Stool may test positive for occult blood.

Symptoms usually remit after about 4 wk but often recur at least once after a disease-free interval of several weeks. In most patients, the disorder subsides without serious sequelae; however, some patients develop chronic renal failure.

Diagnosis

• Biopsy of skin lesions

The diagnosis is suspected in patients, particularly children, with typical skin findings. It is confirmed by biopsy of skin lesions when leukocytoclastic vasculitis with IgA in the vessel walls is identified. Biopsy is unnecessary if clinical diagnosis is clear in children. Urinalysis is done; hematuria, proteinuria, and RBC casts indicate renal involvement. CBC and renal function tests are done.

If renal function is deteriorating, renal biopsy may help define the prognosis. Diffuse glomerular involvement or crescent formation in most glomeruli predicts progressive renal failure.

Treatment

• Primarily corticosteroids and symptomatic measures

If the cause is a drug, it has to be stopped. Otherwise, treatment is primarily symptomatic. Corticosteroids (eg, prednisone 2 mg/kg up to a total of 50 mg po once/day) may help control abdominal pain and are occasionally needed to treat severe joint pain or renal disease. Pulse IV methylprednisolone followed by oral prednisone and cyclophosphamide can be given to attempt to control inflammation when the kidneys are severely affected. However, the effects of corticosteroids on renal manifestations are not clear.

Microscopic Polyangiitis

Microscopic polyangiitis is a systemic pauci-immune necrotizing vasculitis that affects mainly small vessels. It may begin as a pulmonary-renal syndrome with rapidly progressing glomerulonephritis and alveolar hemorrhage, but the pattern of disease depends on the organs affected. Diagnosis is by biopsy. Treatment, which depends on disease severity, includes corticosteroids and immunosuppressants.

Microscopic polyangiitis is rare (about 13 to 19 cases/million). Pathogenesis is unknown. Like immune complex-associated vasculitis (eg, SLE, cryoglobulinemia, serum sickness, Henoch-Schonlein purpura), microscopic polyangiitis affects small vessels. Polyarteritis nodosa can cause some manifestations similar to the small vessel vasculitides, such as mononeuritis multiplex and bowel ischemia. Microscopic polyangiitis can be distinguished from immune complex-associated vasculitis and polyarteritis nodosa by the following:

• Microscopic polyangiitis affects predominantly small vessels, unlike polyarteritis nodosa, which affects medium-sized muscular arteries.

• Microscopic polyangiitis, unlike polyarteritis nodosa, may cause glomerulonephritis and may affect the lungs and cause alveolar hemorrhage.

• Immune complex deposits are scarce or absent (ie, pauci-immune) in contrast to immune complex-associated vasculitis.

Clinical manifestations resemble those of Wegener's granulomatosis except that granulomatous destructive lesions are absent and the upper respiratory tract is usually not severely affected. In both disorders, antineutrophil cytoplasmic antibodies (ANCA) may be present. Microscopic polyangiitis can occur in patients with viral hepatitis B or C.

Symptoms and Signs

Usually, a prodromal illness with systemic symptoms of fever, weight loss, myalgia, and arthralgia occurs. Other symptoms depend on which organs and systems are affected:

• **Renal:** The kidneys are affected in up to 90% of patients. Hematuria, proteinuria (sometimes > 3 g/24 h), and RBC casts are present. Without prompt diagnosis and treatment, renal failure may follow rapidly.

• **Cutaneous:** About one third of patients have a purpuric rash at the time of the diagnosis. Nail bed infarcts and splinter hemorrhages may occur; digital ischemia occurs rarely.

- **Respiratory:** If the lungs are affected, alveolar hemorrhage may occur, followed by pulmonary fibrosis. Rapid-onset dyspnea and anemia, with or without hemoptysis and bilateral patchy infiltrates (seen on chest x-ray) may be due to alveolar hemorrhage, a medical emergency that requires immediate treatment. Mild symptoms of rhinitis, epistaxis, and sinusitis may occur; however, if the upper respiratory tract is severely affected, the cause is more likely to be Wegener's granulomatosis.

- **GI:** GI symptoms include abdominal pain, nausea, vomiting, diarrhea, and bloody stools.

- **Neurologic:** If the nervous system is affected, mononeuritis multiplex that affects peripheral or cranial nerves usually occurs. Cerebral hemorrhage, infarction, seizures, or headache rarely results from cerebral vasculitis.

- **Cardiac:** Rarely, the heart is affected.

- **Ocular:** If the eyes are affected, episcleritis usually results.

Diagnosis

- Clinical findings

- Tests for ANCA and C-reactive protein and routine laboratory tests

- Biopsy

Microscopic polyangiitis may mimic many other disorders because its manifestations vary. The disorder should be suspected in patients who have unexplained combinations of GI symptoms or signs, alveolar hemorrhage, episcleritis, and peripheral neuropathy. Laboratory tests and sometimes x-rays are done, but the diagnosis is usually confirmed by biopsy.

Tests include CBC, ESR, C-reactive protein, urinalysis, serum creatinine, and tests for ANCA. ESR, C-reactive protein levels, and WBC and platelet counts are elevated, reflecting systemic inflammation. Anemia of chronic disease is common. An acute drop in Hct suggests alveolar hemorrhage or hemorrhage in the GI tract. Urinalysis (to check for hematuria, proteinuria, and cellular casts) should be done, and serum creatinine should be measured periodically to check for renal involvement.

Immunofluorescence staining can detect ANCA; this test is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. At least 60% of patients have ANCA, usually perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase.

Biopsy of the most accessible involved tissue should be done to confirm vasculitis. Renal biopsy may detect focal segmental pauci-immune necrotizing glomerulonephritis with fibrinoid necrosis of the glomerular capillary wall, leading to formation of cellular crescents.

In patients with respiratory symptoms, chest x-ray is done to check for infiltrates. Bilateral patchy infiltrates suggest alveolar hemorrhage even in patients without hemoptysis.

If patients have dyspnea and bilateral infiltrates, bronchoscopy should be done immediately to check for alveolar hemorrhages. Blood coming from both lungs and all bronchi, with more blood coming as the bronchoscope goes deeper in the airways, indicates active alveolar hemorrhage. Hemosiderin-laden macrophages appear within 24 to 72 h after onset of hemorrhage and may persist for up to 2 mo.

Treatment

- When vital organs are affected, corticosteroids plus cyclophosphamide

- For less severe cases, corticosteroids plus azathioprine or methotrexate

Treatment is similar to that of Wegener's granulomatosis. Cyclophosphamide given daily plus corticosteroids improves survival when vital organs are affected. However, induction and maintenance regimens vary, and adjunctive therapies such as plasma exchange and pulse IV methylprednisolone may or may not be used.

Less severe cases may be managed with corticosteroids plus azathioprine or methotrexate.

Polyarteritis Nodosa

(Polyarteritis; Periarteritis Nodosa)

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries and occasionally affects small muscular arteries, resulting in secondary tissue ischemia. The kidneys, skin, joints, muscles, peripheral nerves, and GI tract are most commonly affected, but any organ can be. However, the lungs are usually spared. Patients typically present with systemic symptoms (eg, fever, fatigue). Diagnosis requires a biopsy or arteriography. Treatment with corticosteroids and immunosuppressants is often effective.

PAN is rare (about 2 to 33 cases/million). It affects mainly middle-aged adults, and incidence increases with aging, peaking in people in their 50s.

Etiology

Most cases are idiopathic. About 20% of patients have hepatitis B or C.

The cause is unknown, but immune mechanisms appear to be involved. The variety of clinical and pathologic features suggests multiple pathogenic mechanisms. Drugs may be a cause. Usually, no predisposing antigen is identified. Patients with certain lymphomas and leukemias, RA, or Sjogren's syndrome may develop a systemic vasculitis similar to PAN.

Pathophysiology

PAN is characterized by segmental, transmural necrotizing inflammation of muscular arteries, most commonly at points of bifurcation. Unlike other vasculitic disorders, PAN does not involve postcapillary venules or veins. Lesions in all stages of development and healing are usually present. Early lesions contain PMNs and occasionally eosinophils; later lesions contain lymphocytes and plasma cells. Granulomatous inflammation does not occur. Intimal proliferation with secondary thrombosis and occlusion leads to organ and tissue infarction. Weakening of the muscular arterial wall may cause small aneurysms and arterial dissection. Healing can result in nodular fibrosis of the adventitia.

Mostly commonly affected are the kidneys, skin, peripheral nerves, joints, muscles, and GI tract. Often affected are the liver and heart. Renal ischemia and infarction occur, but glomerulonephritis is not a feature of PAN. Purpura is not a characteristic of PAN.

Symptoms and Signs

PAN mimics many disorders. The course may be acute and prolonged, subacute and fatal after several months, or insidious, chronic, and debilitating. Symptoms depend mainly on location and severity of the arteritis and extent of secondary ischemia. Only one organ or organ system may be affected.

Patients typically present with fever, fatigue, night sweats, loss of appetite, weight loss, and generalized weakness. Myalgias with areas of focal ischemic myositis and arthralgias are common. Affected muscles are tender and weak. Arthritis may occur.

Symptoms and signs vary, depending on organ or organ system predominantly affected:

- **Peripheral nervous system:** Patients usually present with asymmetric peripheral neuropathy, such as mononeuritis multiplex with signs of motor and sensory involvement of the peroneal, median, or ulnar

nerves. As additional nerve branches are affected, patients may appear to have a distal symmetric polyneuropathy.

- **CNS:** Headache and seizures can result. In a few patients, ischemic stroke and cerebral hemorrhage occur, sometimes resulting from hypertension.

- **Renal:** If small and medium-sized arteries in the kidneys are affected, patients may have hypertension, oliguria, uremia, and a nonspecific urinary sediment with hematuria, proteinuria, and no cellular casts. Hypertension may worsen rapidly. Rupture of renal arterial aneurysms can cause perirenal hematomas. In severe cases, multiple renal infarcts with lumbar pain and gross hematuria may occur. Renal ischemia and infarction can lead to renal failure.

- **GI:** Vasculitis of the liver or gallbladder causes right upper quadrant pain. Perforation of the gallbladder with acute abdomen may occur. Vasculitis of medium-sized mesenteric arteries causes abdominal pain, nausea, vomiting (with or without bloody diarrhea), malabsorption, intestinal perforation, and acute abdomen. Aneurysms may develop in hepatic or celiac arteries.

- **Cardiac:** Some patients have coronary artery disease, which is usually asymptomatic, but may cause angina. Heart failure may result from ischemic or hypertensive cardiomyopathy

- **Cutaneous:** Livedo reticularis, skin ulcers, tender erythematous nodules, bullous or vesicular eruptions, infarction and gangrene of fingers or toes, or a combination may occur. The nodules in PAN resemble erythema nodosum (inflammation of subcutaneous fat), but in PAN, necrotizing vasculitis occurs within the walls of medium-sized arteries, usually located in the deep dermis and subcutaneous fat.

- **Genital:** Orchitis with testicular pain and tenderness can occur.

Diagnosis

- Clinical findings

- Biopsy

- Arteriography if no clinically involved tissue is available for biopsy

PAN may be suspected in patients with unexplained fever, abdominal pain, renal failure, hypertension, arthralgia, muscle tenderness or weakness, subcutaneous nodules, skin ulcers, pain in the abdomen or extremities, or rapidly developing hypertension. If patients have insidious, nonspecific symptoms, diagnosis is much more difficult. The diagnosis is further clarified when clinical findings are combined with certain laboratory results and other causes are excluded. PAN is also suspected in patients with systemic symptoms or signs and peripheral (usually multiple) neuritis involving major nerve trunks (eg, radial, peroneal, sciatic) in a bilaterally symmetric or asymmetric fashion (mononeuritis multiplex).

Diagnosis is confirmed by biopsy showing necrotizing arteritis or by arteriography showing the typical aneurysms in medium-sized arteries. Magnetic resonance angiography may show microaneurysms, but some abnormalities may be too small for it to detect. Thus, magnetic resonance angiography is not the test used primarily for diagnosis. Biopsy of clinically uninvolved tissue is usually useless because the disease is focal; biopsy should target sites suggested by clinical evaluation. Samples of subcutaneous tissue, sural nerve, and muscle, if thought to be involved, are preferred to samples from the kidneys or liver. If clinical findings are absent or minimal, electromyography and nerve conduction studies may help select the site of muscle or nerve biopsy. If skin lesions are present, surgical skin biopsies that include deeper dermis and subcutaneous fat should be done. (Punch biopsies of the skin that sample the epidermis and superficial dermis miss the lesions of PAN.) Even though microscopic lesions in the testes are common, testicular biopsy should not be done if testicular symptoms are absent and if other possible sites are accessible because the yield is low. Also, men may be reluctant to have testicular biopsy.

Laboratory tests are nonspecific. Leukocytosis up to 20,000 to 40,000/µL, proteinuria, and microscopic hematuria are the most common abnormalities. Patients may have thrombocytosis, markedly elevated

ESR, anemia caused by blood loss or renal failure, hypoalbuminemia, and elevated serum immunoglobulins. AST and ALT are often mildly elevated. Testing for hepatitis B and C should be done. Other testing (eg, antineutrophil cytoplasmic antibodies [ANCA], rheumatoid factor, anticyclic citrullinated peptides [CCP], antinuclear antibodies [ANA], C3 and C4 complement levels, cryoglobulin levels, nuclear antigens and antibodies to extractable nuclear antigens such as anti-Smith, anti-Ro/SSA, anti-La/SSB, and anti-RNP) is done if the clinical presentation suggests other diagnoses, such as RA, SLE, or Sjogren's syndrome.

Prognosis

Without treatment, 5-yr survival is < 15%. With treatment, 5-yr survival is > 80% but may be lower for patients with hepatitis B. Prognosis is better if disease remission is achieved within 18 mo after diagnosis.

The following findings are associated with a poor prognosis:

• Renal insufficiency

• GI involvement

• Neurologic involvement

Treatment

• Corticosteroids alone or with cyclophosphamide, methotrexate, or azathioprine, depending on disease severity

• Addition of lamivudine and plasma exchange for patients with hepatitis B

Treatment depends on the severity of the disease. For systemic symptoms but no serious neurologic, renal, GI, or cardiac manifestations, corticosteroids may be sufficient, at least initially. For severe disease with neurologic, renal, GI, or cardiac manifestations, cyclophosphamide plus corticosteroids may improve outcome. For moderate disease, corticosteroids plus methotrexate or azathioprine can be used. Hypertension should be treated aggressively; ACE inhibitors are effective.

Hepatitis B-related PAN: Treatment aims at rapidly suppressing inflammation, then eliminating the virus and inducing seroconversion via plasma exchange. A short course of corticosteroids is used for a few weeks. Lamivudine 100 mg po once/day is given for a maximum of 6 mo. A lower dose is used in patients with renal insufficiency. Plasma exchanges are scheduled as follows: 3 times/wk for 3 wk, 2 times/wk for 2 wk and once/wk until hepatitis B e antigen (HBeAg) converts to hepatitis B e antibody (anti-HBe) or until clinical recovery is sustained for 2 to 3 mo. Although this approach has not been proved to improve survival when compared with immunosuppressive therapy only, it may reduce the risk of long-term complications of hepatitis B and suppress the side effects of long-term treatment with corticosteroids and immunosuppressants.

Traditional treatment with corticosteroids, sometimes with cytotoxic immunosuppressants (mainly cyclophosphamide), was often effective in the short term but did not prevent relapses and complications (eg, chronic hepatitis, cirrhosis) due to persistence of the hepatitis B virus.

Polymyalgia Rheumatica

Polymyalgia rheumatica is a syndrome closely associated with giant cell (temporal) arteritis. It affects adults > 55. It typically causes severe pain and stiffness in proximal muscles, without weakness or atrophy, and nonspecific systemic symptoms. ESR is markedly elevated. Diagnosis is clinical. Treatment with low-dose corticosteroids is effective.

Polymyalgia rheumatica affects adults > 55; the female:male ratio is 2:1.

Because polymyalgia rheumatica is closely associated with giant cell arteritis (see p. 319), some

authorities consider the two disorders to be different phases of the same process. Polymyalgia rheumatica appears to be more common. A few patients with polymyalgia rheumatica develop giant cell arteritis, but 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. Polymyalgia rheumatica may precede or occur simultaneously with giant cell arteritis.

Etiology and pathogenesis are unknown. Whether symptoms result from vasculitis is unclear; they probably result from low-grade axial synovitis and bursitis.

Symptoms and Signs

Polymyalgia rheumatica is characterized by bilateral proximal aching of the shoulder and hip girdle muscles and the back (upper and lower) and neck muscles. Stiffness in the morning is typical. Shoulder symptoms may reflect proximal bursitis (eg, subdeltoid, subacromial) and less often bicipital tenosynovitis or joint synovitis. Discomfort is worse in the morning and is occasionally severe enough to prevent patients from getting out of bed and from doing simple activities. The pain may make patients feel weak, but objective muscle weakness is not a feature of the disorder.

Diagnosis

• Clinical findings

• Exclusion of other causes

Polymyalgia rheumatica is suspected in elderly patients with typical symptoms, but other possible causes must be excluded. Tests include ESR, CBC, thyroid-stimulating hormone levels, and CK. In > 80 % of patients, ESR is markedly elevated, often > 100 mm/h, usually > 50 mm/h (Westergren method). Electromyography, biopsy, and other tests (eg, rheumatoid factor), which are normal in polymyalgia rheumatica, are sometimes done to rule out other clinically suspected diagnoses.

The following findings in polymyalgia rheumatica distinguish it:

• From RA: Chronic small joint synovitis (although some joint swelling may be present), erosive or destructive lesions, rheumatoid nodules, and rheumatoid factor are absent.

• From polymyositis: Pain rather than weakness predominates; muscle enzyme levels and electromyography and muscle biopsy results are normal.

• From hypothyroidism: Thyroid function test results and muscle enzyme levels are normal.

• From multiple myeloma: Monoclonal gammopathy is absent.

• From fibromyalgia: Symptoms are more localized, and ESR is typically elevated.

Treatment

• Prednisone

Prednisone started at 15 to 20 mg po once/day results in dramatic improvement. If giant cell arteritis is thought to be present, the dose should be higher, and temporal artery biopsy should be done. As symptoms subside, corticosteroids are tapered to the lowest clinically effective dose, regardless of ESR. Some patients are able to stop corticosteroids in ≤ 1 yr; others require small doses for years. NSAIDs are rarely sufficient.

In elderly patients, physicians should watch for and treat complications of corticosteroid use (eg, diabetes, hypertension). Patients taking prednisone long term should be given a bisphosphonate to prevent osteoporosis.

Because patients may develop giant cell arteritis, they should be instructed to immediately report

headache, muscle pain during chewing, and, particularly, visual disturbances to their physician.

Takayasu's Arteritis

(Pulseless Disease; Occlusive Thromboaortopathy; Aortic Arch Syndrome)

Takayasu's arteritis is an inflammatory disease affecting the aorta, its branches, and pulmonary arteries. It occurs predominantly in young women. Etiology is unknown. Vascular inflammation may cause arterial stenosis, occlusion, dilation, or aneurysms. It causes asymmetric pulses and symptoms and signs of arterial obstruction. Diagnosis is by aortic arteriography or magnetic resonance angiography. Treatment is with corticosteroids and, for organ-threatening ischemia, vascular interventions such as bypass surgery.

Takayasu's arteritis is rare. It is more common among Asians but occurs worldwide. Female:male ratio is 8:1, and age at onset is typically 15 to 30. In North America, annual incidence is estimated to be 2.6 cases/million.

Etiology

The cause is unknown. Cell-mediated immune mechanisms may be involved and may be similar to those in giant cell arteritis.

Pathophysiology

Takayasu's arteritis affects primarily large elastic arteries. The most commonly affected are the innominate and subclavian arteries, aorta (mainly the ascending aorta and the arch), common carotid arteries, and renal arteries. Most patients have stenoses or occlusions. Aneurysms occur in about one third of patients. Usually, the wall of the aorta or its branches thickens irregularly, with intimal wrinkling. When the aortic arch is affected, orifices of the major arteries emerging from the aorta may be markedly narrowed or even obliterated by intimal thickening. In one half of patients, pulmonary arteries are also affected.

Histologically, early changes consist of adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum. Later, intense mononuclear inflammation of the media may occur, sometimes accompanied by granulomatous changes, giant cells, and patchy necrosis of the media. Morphologic changes may be indistinguishable from those of giant cell arteritis. Panarteritic inflammatory infiltrates cause marked thickening of the affected artery and subsequent luminal narrowing and occlusion.

Symptoms and Signs

Most patients present with only focal symptoms that reflect hypoperfusion of the affected organ or limb. Takayasu's arteritis may have 3 stages:

- Systemic disease, usually with systemic, nonspecific symptoms (eg, fever, malaise, night sweats, weight loss, arthralgias, fatigue)

- Vascular inflammatory phase, with ischemic manifestations that may wax and wane

- Inactive (burned-out) disease, sometimes with acute or progressive occlusion (including thrombosis)

Only one third of patients have systemic symptoms at presentation or recall having had such symptoms.

Repetitive arm movements and sustained arm elevation may cause pain and fatigue. Arterial pulses in arms and legs may be diminished and asymmetric. Bruits are often audible over the subclavian arteries, brachial arteries, carotid arteries, abdominal aorta, or femoral arteries. Reduced BP in one or both arms is common.

When the carotid and vertebral arteries are affected, cerebral blood flow decreases, leading to dizziness,

syncope, orthostatic hypotension, headaches, transient visual disturbances, transient ischemic attacks, or strokes. Stenotic lesions in a subclavian artery near the origin of a patent vertebral artery can cause posterior circulation neurologic symptoms or syncope when the arm is used (called subclavian steal syndrome). Retrograde flow through the vertebral artery supplies the subclavian artery distal to the stenosis, and vasodilation of the arterial bed in the upper limb during exercise compromises posterior cerebral blood flow.

Angina pectoris or MI may result from narrowing of the coronary artery orifice due to aortitis or coronary arteritis. Aortic regurgitation may occur if the ascending aorta is markedly dilated. Heart failure can develop.

Obstruction of the descending thoracic aorta sometimes causes signs of aortic coarctation (eg, hypertension, headache, leg claudication). Renovascular hypertension may develop if the abdominal aorta or renal arteries are narrowed.

Pulmonary arteries are often affected, sometimes causing pulmonary hypertension. Because Takayasu's arteritis is chronic, collateral circulation can develop. Thus, ischemic ulcerations or gangrene due to obstruction of the arteries to the extremities is rare.

Diagnosis

• Aortic arteriography or magnetic resonance angiography

• Monitoring of disease activity

The diagnosis is suspected when symptoms suggest ischemia of organs supplied by the aorta or its branches or when peripheral pulses are decreased or absent in patients at low risk of atherosclerosis and other aortic disorders, especially in young women. In these patients, arterial bruits and right-left or upper extremity-lower extremity discrepancies in pulses or in BP also suggest the diagnosis. Confirmation of the diagnosis requires aortic arteriography or magnetic resonance angiography to evaluate all branches of the aorta. Characteristic findings include stenosis, occlusion, irregularities in arterial lumens, poststenotic dilation, collateral arteries around obstructed vessels, and aneurysms.

BP is measured in both arms. However, measurement can be difficult. If both subclavian arteries are severely affected, systemic BP can be accurately measured only in the legs. If the disorder affects both subclavian arteries in patients with coarctation of the descending aorta or involvement of both iliac or femoral arteries, BP cannot be accurately measured. Then, central arterial pressure must be measured via angiography to detect occult hypertension, which can cause complications.

Laboratory tests are nonspecific and not helpful in diagnosis. Common findings include anemia of chronic disease, elevated platelet levels, occasionally elevated WBC counts, and elevated ESR and C-reactive protein.

Once Takayasu's arteritis is diagnosed, disease activity must be monitored to look for the following:

• New systemic symptoms, which may reflect active arthritis or infection (secondary to immunosuppression therapy)

• Evidence of inflammation detected by blood tests (although markers of inflammation may miss active arteritis)

• Development of stenosis, aneurysms, or ischemic symptoms in previously unaffected arteries, as assessed with periodic imaging (usually magnetic resonance angiography)

Periodic imaging of the aorta and large arteries is important (see Table 34-3) because the disorder may progress silently, without clinical symptoms or evidence of inflammation in blood. Once the disorder is diagnosed, BP should be measured periodically in an unaffected limb because hypertension must be controlled.

Disorders that mimic Takayasu's arteritis must be excluded. They include inherited connective tissue disorders (eg, Ehlers-Danlos or Marfan syndrome), vascular infections (tuberculous, fungal, or syphilitic), fibromuscular

[Table 34-3. Imaging Tests Used in Takayasu's Arteritis]

dysplasias, disorders causing arterial thrombosis (eg, hypercoagulable states), and idiopathic inflammatory conditions (eg, ankylosing spondylitis with aortitis, Cogan's or Behcet's syndrome, Kawasaki disease, sarcoidosis); all can affect large vessels.

Prognosis

For 20% of patients, the course is monophasic. For the rest, the course is relapsing and remitting or chronic and progressive. Even when symptoms and laboratory abnormalities suggest quiescence, new lesions occur and are evident on imaging studies. A progressive course and the presence of complications (eg, hypertension, aortic regurgitation, heart failure, aneurysms) predict a less favorable prognosis.

Treatment

• Corticosteroids

• Sometimes immunosuppressants

• Antihypertensives

• Vascular interventions

Drugs: Corticosteroids are the cornerstone of treatment. The optimal dose, tapering schedule, and length of treatment have not been determined. Treatment with corticosteroids alone induces remission in most patients. Prednisone is usually used. The starting dose is 1 mg/kg po once/day for 1 to 3 mo; the dose is then tapered slowly over several months. Lower starting doses may also induce remission. About one half of patients relapse when the drug is tapered or stopped, despite initial response.

Methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, and tumor necrosis factor inhibitors (eg, etanercept, infliximab) have been used in some patients. They can be tried if corticosteroids are insufficiently effective or cannot be tapered. Methotrexate is given with a corticosteroid. Often, the starting dose is 0.3 mg/kg once/wk, which is increased up to 25 mg/wk. Mycophenolate mofetil can also be tried. Cyclophosphamide should be considered in patients with coronary vasculitis or other serious complications thought to be due to active arteritis.

An antiplatelet drug (eg, aspirin 325 mg po once/day) is frequently used because platelet-mediated occlusion cannot be excluded. Hypertension should be treated aggressively; ACE inhibitors may be effective.

Procedures: Vascular intervention, usually a bypass procedure, may be needed to reestablish blood flow to ischemic tissues if drug therapy is ineffective. Indications include the following:

• Severe hypertension that is refractory to medical management because renal artery stenosis is present (although reocclusion and thrombosis of grafts is common)

• Ischemia in the extremities that interferes with daily activities

• Ischemia of cerebral arteries

• New York Heart Association (NYHA) class II heart failure secondary to a discrete coronary artery stenosis or occlusion

• Cardiac ischemia caused by stenosis of the coronary arteries

• Coarctation of the aorta

• Dissection or enlargement of an aortic aneurysm

Bypass grafting preferably with an autologous graft has the best patency rates. The anastomosis should be made at disease-free sites of the affected arteries to help prevent aneurysm formation and occlusion.

Percutaneous transluminal coronary angioplasty (PTCA) has few risks and may be effective for short lesions. But long-term restenosis rates seem much higher than those with bypass grafting. Vascular stenting is usually not recommended because the restenosis rate is high.

For aortic regurgitation, valvular surgery with aortic root replacement may be necessary.

Wegener's Granulomatosis

Wegener's granulomatosis is characterized by necrotizing granulomatous inflammation, small and medium-sized vessel vasculitis, and focal necrotizing glomerulonephritis, often with crescent formation. Typically, the upper and lower respiratory tract and the kidneys are affected, but any organ may be. Symptoms vary depending on the organs and systems affected. Patients may present with upper and lower respiratory tract symptoms (eg, recurrent nasal discharge or epistaxis, cough), followed by hypertension and edema, or with symptoms reflecting multiorgan involvement. Diagnosis usually requires biopsy. Treatment is with corticosteroids plus an immunosuppressant. Remission is usually possible, although relapses are common.

Wegener's granulomatosis occurs in about 1/25,000 people; it is most common among whites but can occur in all ethnic groups and at any age. Mean age at onset is 40.

The cause is unknown, although immunologic mechanisms play a role. Most patients with active generalized disease have antineutrophil cytoplasmic antibodies (ANCA).

Pathophysiology

Characteristically, granulomas form with histiocytic epithelioid cells and often with giant cells. Plasma cells, lymphocytes, neutrophils, and eosinophils are present. Inflammation affects tissues as well as vessels; vasculitis may be a small or large component of the disease. Micronecrosis, usually with neutrophils (microabscesses), occurs early. Micronecrosis progresses to macronecrosis. A central area of necrosis (called geographic necrosis) is rimmed by lymphocytes, plasma cells, macrophages, and giant cells. A zone of fibroblastic proliferation with palisading histiocytes may surround the area.

Nonspecific chronic inflammation and tissue necrosis occurs in the nose. The lungs are most likely to display the full spectrum of histopathologic abnormalities. In the kidneys, the most common finding is a proliferative crescentic focal glomerulonephritis with necrosis and thrombosis of individual loops or larger segments of the glomerulus. Vasculitic lesions and disseminated granulomas occur only occasionally.

Symptoms and Signs

Onset may be insidious or acute; the full spectrum of the disease may take years to evolve. Some patients present initially with upper and lower respiratory tract symptoms; at some point later, the kidneys are affected. In other patients, onset of systemic manifestations is relatively acute; several organs and systems, such as the upper respiratory tract, peripheral nervous system (causing mononeuritis multiplex), kidneys (causing glomerulonephritis), and lower respiratory tract (causing hemorrhage, lung nodules, cavities, or a combination), are simultaneously affected.

• **Upper respiratory tract:** Sinus pain, serosanguineous or purulent discharge, and epistaxis may occur. The mucosa appears granular (like cobblestones) and is friable; ulcers, thick dark crusts, and septal

perforation are common. Nasal chondritis can occur with swelling, pain, and collapse of the nasal bridge (saddle nose). Patients may report recurrent sinusitis that has responded inadequately to multiple antibiotic regimens and has required one or more sinus operations before diagnosis. Secondary infections (eg, due to *Staphylococcus aureus*) may develop. Subglottic stenosis may develop, causing symptoms such as pain in the larynx, hoarseness, dyspnea, wheezing, and stridor.

- **Ears:** Otitis, sensorineural hearing loss, vertigo, and chondritis may occur. The middle ear, inner ear, and mastoids are often affected.

- **Eyes:** Eyes may appear red and swollen. Nasolacrimal duct inflammation and obstruction may affect the eye; conjunctivitis, scleritis, uveitis, or retinal vasculitis may also occur. Inflammatory infiltrates in the retro-orbital space (orbital pseudotumor) can cause proptosis, compression of the optic nerve, and blindness. Extension into the extraocular muscles leads to diplopia. If serious eye symptoms develop, evaluation and treatment are required immediately to prevent permanent vision loss.

- **Lower respiratory tract:** Respiratory manifestations are common. Inflammation of the major bronchi and branches can cause localized wheezing, postobstructive pneumonia, and atelectasis. Single or multiple pulmonary nodules, with or without cavitation, and parenchymal infiltrates, sometimes cause symptoms, such as chest pain, shortness of breath, and productive cough. Dyspnea with bilateral infiltrates, with or without hemoptysis, may indicate alveolar hemorrhage, and must be evaluated immediately.

- **Heart:** Coronary artery disease may occur, but rarely.

- **Musculoskeletal system:** Patients may present with myalgias, arthralgias, or nonerosive inflammatory arthritis.

- **Skin:** Leukocytoclastic vasculitis, tender subcutaneous nodules, papules, livedo reticularis, or pyoderma gangrenosum may develop.

- **Nervous system:** Vasculitis may cause ischemic peripheral neuropathy, brain lesions, or extension of lesions from contiguous sites. Lesions that originate in the sinuses or middle ear may extend directly to the retropharyngeal area and base of the skull, leading to cranial neuropathy, proptosis, diabetes insipidus, or meningitis.

- **Kidneys:** Symptoms and signs of glomerulonephritis develop. Urinary sediment may be abnormal, and serum creatinine may increase rapidly. Edema and hypertension may result. Rapidly progressive glomerulonephritis, which is life threatening, can develop.

- **Other organs:** Occasionally, an inflammatory mass occurs in the breasts, kidneys, prostate, or other organs.

Diagnosis

- Routine laboratory tests, including urinalysis

- Tests for ANCA

- Biopsy for definitive diagnosis

Wegener's granulomatosis should be suspected in patients with chronic, unexplained respiratory symptoms and signs (including otitis media in adults), particularly if manifestations in other organ systems, especially the kidneys, also suggest the disorder. Routine laboratory tests are done, but ANCA testing and biopsy yield the most specific findings.

Routine laboratory tests include ESR or C-reactive protein, CBC with differential, serum albumin and total protein, serum creatinine, urinalysis, 24-h urine protein, and chest x-ray. In most patients with active disease, ESR and C-reactive protein are elevated, and serum albumin and total protein are decreased;

anemia, thrombocytosis, and mild to moderate eosinophilia are detected. Dysmorphic RBCs and RBC casts, detected during urinalysis, indicate glomerular involvement. Proteinuria may be detected. Serum creatinine may be increased.

Serologic testing to detect ANCA is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. Most patients with active disease have cytoplasmic ANCA (cANCA), with antibodies against proteinase-3 (PR3); these findings plus characteristic clinical findings suggest Wegener's granulomatosis.

Some patients with other disorders (eg, bacterial endocarditis, TB) test positive for ANCA. If characteristic clinical findings are absent, a positive ANCA result does not confirm Wegener's granulomatosis. ANCA testing should not be used to guide treatment. During apparent remission, ANCA may increase or ANCA test results may change from negative to positive. In some of these patients, symptoms do not recur; in others, symptoms recur or worsen soon after the test is done or during the next few weeks, months, or sometimes years.

Biopsy should be done if possible to confirm the diagnosis. Clinically abnormal sites may be biopsied first, but lung biopsy is most likely to detect characteristic findings. Open thoracotomy provides the best access to affected tissue. Biopsies of lung or sinus tissue are cultured to exclude infection. Renal biopsy may be necessary to confirm the diagnosis and to exclude other causes, especially if serum creatinine is elevated. Biopsy results may also provide histologic information that can help guide treatment (eg, renal fibrosis, which is irreversible with immunosuppressive treatment).

Differential diagnosis includes other vasculitic disorders that affect small and medium-sized vessels. Polyarteritis nodosa is unlikely if lung involvement is prominent and glomerulonephritis is present. Infections, especially due to slow-growing fungi or acid-fast organisms should be ruled out by staining and by culture of the sampled tissues. RA should not be diagnosed based only on the presence of rheumatoid factor, which is present in one half of patients with Wegener's granulomatosis.

Prognosis

Prognosis depends on the extent of the disorder—whether it is limited to nasal and pulmonary lesions, with little or no systemic involvement, or it affects many organs, causing severe systemic vasculitis.

Use of immunosuppressants for severe disease has dramatically improved prognosis. With treatment, complete remission is possible for about 70% of patients, but about one half of them eventually relapse; relapse may occur when treatment is stopped or many years after it is stopped. Resuming or increasing treatment can usually control the disorder. However, the disease or treatment causes significant morbidity in 90% of patients.

Treatment

• Emergency treatment with corticosteroids and cyclophosphamide for severe disease

• Corticosteroids and methotrexate for less severe disease

• Kidney transplantation if necessary

Treatment depends on the severity of disease. A multidisciplinary approach is required for multiorgan disease; a rheumatologist, an otorhinolaryngologist, a pulmonologist, and sometimes a nephrologist may be included.

Patients who have severe life- or organ-threatening manifestations (eg, alveolar hemorrhage, rapidly progressive glomerulonephritis, mononeuritis multiplex with motor involvement) require immediate treatment and hospital admission. These patients require high-dose corticosteroids and cyclophosphamide (see p. 314). The role of rituximab in severe or refractory disease is under study.

For less severe disease, corticosteroids and methotrexate are used. Methotrexate or azathioprine is used

to maintain remission.

Irrigation of sinuses with saline, with or without mupirocin 2% nasal ointment, helps minimize crusting and secondary staphylococcal infections.

Treatment of subglottic stenosis is difficult. Systemic immunosuppressants may not be effective. Intralesional injection of long-acting corticosteroids, with gentle progressive dilation, markedly improves outcomes and helps prevent unnecessary tracheostomies.

Patients should be taught about the disorder so that relapses can be detected early. Patients should learn how to test their urine for blood and protein and be instructed to notify their physician at the first sign of hematuria.

Kidney transplantation has been successful; the risk of relapse after transplantation is reduced compared with maintenance dialysis treatment (possibly in part due to use of immunosuppressants to prevent rejection).

Chapter 35. Joint Disorders

Introduction

Joint disorders may be inflammatory (RA, spondyloarthropathies, crystal-induced arthritis) or relatively less inflammatory (osteoarthritis, neurogenic arthropathy). Crystal-induced arthritis and infectious arthritis are discussed elsewhere in THE MANUAL.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily involves the joints. RA causes damage mediated by cytokines, chemokines, and metalloproteases. Characteristically, peripheral joints (eg, wrists, metacarpophalangeal joints) are symmetrically inflamed, leading to progressive destruction of articular structures, usually accompanied by systemic symptoms. Diagnosis is based on specific clinical, laboratory, and imaging features. Treatment involves drugs, physical measures, and sometimes surgery. Disease-modifying antirheumatic drugs help control symptoms and slow disease progression.

RA affects about 1% of the population. Women are affected 2 to 3 times more often than men. Onset may be at any age, most often between 35 yr and 50 yr, but can be during childhood (see Juvenile Idiopathic Arthritis on p. 339) or old age.

Etiology

Although RA involves autoimmune reactions, the precise cause is unknown; many factors may contribute. A genetic predisposition has been identified and, in white populations, localized to a shared epitope in the HLA-DR β_1 locus of class II histocompatibility antigens. Unknown environmental factors (eg, viral infections) are thought to play a role.

Pathophysiology

Prominent immunologic abnormalities include immune complexes produced by synovial lining cells and in inflamed blood vessels. Plasma cells produce antibodies (eg, rheumatoid factor [RF]) that contribute to these complexes, but destructive arthritis can occur in the absence of RF. Macrophages also migrate to diseased synovium in early disease; increased macrophage-derived lining cells are prominent along with vessel inflammation. Lymphocytes that infiltrate the synovial tissue are primarily CD4+ T cells. Macrophages and lymphocytes produce pro-inflammatory cytokines and chemokines (eg, tumor necrosis factors [TNF], granulocyte-macrophage colony-stimulating factor [GM-CSF], various ILs, interferon-γ) in the synovium. Release of inflammatory mediators probably contributes to the systemic and joint manifestations of RA.

In chronically affected joints, the normally thin synovium thickens and develops many villous folds. The synovial lining cells produce various materials, including collagenase and stromelysin, which contribute to cartilage destruction, and IL-1 and TNF-α, which stimulate cartilage destruction, osteoclast-mediated bone absorption, synovial inflammation, and prostaglandins (which potentiate inflammation). Fibrin deposition, fibrosis, and necrosis are also present. Hyperplastic synovial tissue (pannus) releases these inflammatory mediators, which erode cartilage, subchondral bone, articular capsule, and ligaments. PMNs on average make up about 60% of WBCs in the synovial fluid.

Rheumatoid nodules develop in about 30% of patients with RA. They are granulomas consisting of a central necrotic area surrounded by palisaded histiocytic macrophages, all enveloped by lymphocytes, plasma cells, and fibroblasts. Nodules and vasculitis can also develop in visceral organs.

Symptoms and Signs

Onset is usually insidious, often beginning with systemic and joint symptoms. Systemic symptoms include early morning stiffness of affected joints, generalized afternoon fatigue and malaise, anorexia, generalized

weakness, and occasionally low-grade fever. Joint symptoms include pain, swelling, and stiffness.

The disease progresses most rapidly during the first 6 yr, particularly the first year; 80% of patients develop some permanent joint abnormalities within 10 yr. The course is unpredictable in individual patients.

Joint symptoms are characteristically symmetric. Typically, stiffness lasts > 60 min after rising in the morning but may occur after any prolonged inactivity. Involved joints become tender, with erythema, warmth, swelling, and limitation of motion. The joints involved include the following:

• Wrists and the index and middle metacarpophalangeal joints (most commonly involved)

• Proximal interphalangeal joints

• Metatarsophalangeal joints

• Shoulders

• Elbows

• Hips

• Knees

• Ankles

However, virtually any joint except uncommonly the distal interphalangeal (DIP) joints may be involved. The axial skeleton is rarely involved except for the upper cervical spine. Synovial thickening is detectable. Joints are often held in flexion to minimize pain, which results from joint capsular distention.

Fixed deformities, particularly flexion contractures, may develop rapidly; ulnar deviation of the fingers with an ulnar slippage of the extensor tendons off the metacarpophalangeal joints is typical, as are swan-neck and boutonniere deformities (see
Fig. 43-2 on p. 387). Joint instability can also occur. Carpal tunnel syndrome can result from wrist synovitis compressing the median nerve. Popliteal (Baker's) cysts can develop, causing calf swelling and tenderness suggestive of deep venous thrombosis.

Extra-articular manifestations: Subcutaneous rheumatoid nodules are not usually an early sign but eventually develop in up to 30% of patients, usually at sites of pressure and chronic irritation (eg, the extensor surface of the forearm, metacarpophalangeal joints, occiput). Visceral nodules, usually asymptomatic, are common in severe RA. Other extra-articular signs include vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, pulmonary nodules, pulmonary infiltrates or fibrosis, pericarditis, myocarditis, lymphadenopathy, Felty's syndrome, Sjogren's syndrome, scleromalacia, and episcleritis. Involvement of the cervical spine can cause atlantoaxial subluxation (see p. 385) and spinal cord compression (see p. 1810); it may worsen with extension of the neck (eg, during endotracheal intubation).

Diagnosis

• Clinical criteria

• Serum rheumatoid factor (RF) or anticyclic citrullinated peptide antibody (anti-CCP)

• X-rays

RA should be suspected in patients with polyarticular, symmetric arthritis, particularly if the wrists and 2nd and 3rd metacarpophalangeal joints are involved. Criteria for the diagnosis of RA are listed in
Table 35-1. The presence of ≥ 4 criteria suggests the diagnosis. Other causes of symmetric polyarthritis,

particularly hepatitis C, must be excluded. Patients should have a serum RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes.

[Table 35-1. Diagnosing Rheumatoid Arthritis*]

RFs, antibodies to human γ-globulin, are present in about 70% of patients with RA. However, RF, often in low titers, occurs in patients with other diseases, including other connective tissue diseases (eg, SLE), granulomatous diseases, chronic infections (eg, viral hepatitis, subacute bacterial endocarditis, TB), and cancers. Low RF titers can also occur in 3% of the general population and 20% of the elderly. An RF titer measured by latex agglutination of > 1:80 or a positive anti-CCP test supports the diagnosis of RA.

Anti-CCP antibodies have high specificity (90%) and sensitivity (96%) for RA and, like RF, predict a worse prognosis.

X-rays show only soft-tissue swelling during the first months of disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may become visible. Erosions often develop within the first year but may occur any time. MRI seems to be more sensitive and detects earlier articular inflammation and erosions. In addition, abnormal subchondral bone signals (eg, bone marrow lesions, bone marrow edema) around the knee suggest progressive disease.

If RA is diagnosed, additional tests help detect complications and unexpected abnormalities. CBC with differential should be obtained. A normochromic (or slightly hypochromic)-normocytic anemia occurs in 80%; Hb is usually > 10 g/dL. If Hb is ≤ 10 g/dL, superimposed iron deficiency or other causes of anemia should be considered. Neutropenia occurs in 1 to 2% of cases, often with splenomegaly (Felty's syndrome). Acute-phase reactants (eg, thrombocytosis, elevated ESR, elevated C-reactive protein) reflect disease activity. A mild polyclonal hypergammaglobulinemia often occurs. ESR is elevated in 90% of patients with active disease.

Synovial fluid examination is necessary with any new-onset effusion to rule out other disorders and differentiate RA from other inflammatory arthritides (eg, septic and crystal-induced arthritis). In RA, during active joint inflammation, synovial fluid is turbid, yellow, and sterile, with reduced viscosity and usually 10,000 to 50,000 WBCs/μL; PMNs typically predominate, but > 50% may be lymphocytes and other mononuclear cells. Crystals are absent.

Differential diagnosis: Many disorders can simulate RA:

• Crystal-induced arthritis

• Osteoarthritis

• SLE

• Sarcoidosis

• Reactive arthritis

• Psoriatic arthritis

• Ankylosing spondylitis

RF can be nonspecific and is often present in several autoimmune diseases; the presence of anti-CCP antibodies is more specific for RA.

Some patients with crystal-induced arthritis may meet criteria for RA; however, synovial fluid examination should clarify the diagnosis. The presence of crystals makes RA unlikely. Joint involvement and subcutaneous nodules can result from gout, cholesterol, and amyloidosis as well as RA; aspiration or biopsy of the nodules may occasionally be needed.

SLE usually can be distinguished if there are skin lesions on light-exposed areas, hair loss, oral and nasal mucosal lesions, absence of joint erosions in even long-standing arthritis, joint fluid that often has < 2000 WBCs/μL (predominantly mononuclear cells), antibodies to double-stranded DNA, renal disease, and low serum complement levels. In contrast to RA, deformities in SLE are usually reducible because of the lack of erosions and bone or cartilage damage. Arthritis similar to RA can also occur in other rheumatic disorders (eg, polyarteritis, systemic sclerosis, dermatomyositis, or polymyositis) or there can be features of more than one disease, which suggests an overlap syndrome or mixed connective tissue disease.

Sarcoidosis, Whipple's disease, multicentric reticulohistiocytosis, and other systemic diseases may involve joints; other clinical features and tissue biopsy sometimes help differentiate these conditions. Acute rheumatic fever has a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin-O titer); in contrast, RA has an additive arthritis.

Reactive arthritis (see p. 343) can be differentiated by antecedent GI or GU symptoms; asymmetric involvement and pain at the Achilles insertion of the heel, sacroiliac joints, and large joints of the leg; conjunctivitis; iritis; painless buccal ulcers; balanitis circinata; or keratoderma blennorrhagicum on the soles and elsewhere.

Psoriatic arthritis (see p. 344) tends to be asymmetric and is not usually associated with RF, but differentiation may be difficult in the absence of nail or skin lesions. DIP joint involvement and severely mutilating arthritis (arthritis mutilans) is strongly suggestive, as is the presence of a diffusely swollen (sausage) digit. Ankylosing spondylitis (see p. 341) may be differentiated by spinal and axial joint involvement, absence of subcutaneous nodules, and negative RF test.

Osteoarthritis (see p. 345) can be differentiated by the joints involved; the absence of rheumatoid nodules, systemic manifestations, or significant amounts of RF; and synovial fluid WBC counts < 2000/μL. Osteoarthritis of the hands most typically involves the DIP and proximal interphalangeal joints. RA does not affect the DIP joints.

Prognosis

RA decreases life expectancy by 3 to 7 yr, with heart disease, infection, and GI bleeding accounting for most excess mortality; drug treatment, cancer, as well as the underlying disease may be responsible.

At least 10% of patients eventually are severely disabled despite full treatment. Whites and women have a poorer prognosis, as do patients with subcutaneous nodules, advanced age at disease onset, inflammation in ≥ 20 joints, early erosions, cigarette smoking, high ESR, and high levels of RF or anti-CCP.

Treatment

• Supportive measures (eg, nutrition, rest, physical measures, analgesics)

• NSAIDs

• Drugs that modify disease progression

Treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery.

Rest and nutrition: Complete bed rest is rarely indicated, even for a short time; however, a program including judicious rest should be prescribed. An ordinary nutritious diet is generally sufficient. Rarely, patients have food-associated exacerbations; no specific foods have been noted to exacerbate RA. Food and diet quackery is common and should be discouraged. Substituting ω-3 fatty acids (in fish oils) for dietary ω-6 fatty acids (in meats) may partially relieve symptoms by transiently decreasing production of inflammatory prostaglandins.

Physical measures: Joint splinting reduces local inflammation and may relieve severe symptoms. Cold may be applied to reduce pain from temporary worsening in one joint. Orthopedic or athletic shoes with good heel and arch support are frequently helpful; metatarsal supports placed posteriorly to painful metatarsophalangeal joints decrease the pain of weight bearing. Molded shoes may be needed for severe deformities. Self-help devices enable many patients with debilitating RA to perform activities of daily living.

Exercise should proceed as tolerated. During acute inflammation, passive range-of-motion exercise helps prevent flexion contractures. Heat therapy can be helpful. Range-of-motion exercises done in warm water are helpful because heat improves muscle function by reducing stiffness and muscle spasm. However, contractures can be prevented and muscle strength can be restored more successfully after inflammation begins to subside; active exercise (including walking and specific exercises for involved joints) to restore muscle mass and preserve range of joint motion should not be fatiguing. Flexion contractures may require intensive exercise, casting, or immobilization (eg, splinting) in progressively more stretched-open positions. Paraffin baths can warm digits and facilitate finger exercise. Massage by trained therapists, traction, and deep heat treatment with diathermy or ultrasonography may be useful.

Surgery: Surgery must always be considered in terms of the total disease and patient expectations. For example, deformed hands and arms limit crutch use during rehabilitation; seriously affected knees and feet limit benefit from hip surgery. Reasonable objectives for each patient must be determined, and function must be considered. Surgery may be done while the disease is active.

Arthroplasty with prosthetic joint replacement is indicated if damage severely limits function; total hip and knee replacements are most consistently successful. Prosthetic hips and knees cannot tolerate vigorous activity (eg, competitive athletics). Excision of subluxed painful metatarsophalangeal joints may greatly aid walking. Thumb fusions may provide stability for pinch. Neck fusion may be needed for C1-2 subluxation with severe pain or potential for spinal cord compression. Arthroscopic or open synovectomy can relieve joint inflammation but only temporarily unless disease activity can be controlled.

Drugs for RA

The goal is to reduce inflammation as a means of preventing erosions and progressive deformity. Disease-modifying antirheumatic drugs (DMARDs) are used early, often in combination. Other drug classes, including biologic agents, TNF-α antagonists, and IL-1 receptor antagonists, seem to slow the progression of RA. NSAIDs are of some help for the pain of RA but do not prevent erosions or disease progression. Sometimes low-dose systemic corticosteroids (prednisone < 10 mg daily) are added to control severe polyarticular symptoms, usually with the objective of replacement with a DMARD. Intra-articular depot corticosteroids can control severe monarticular or even oligoarticular symptoms. The optimal combinations of drugs are not yet clear. However, some data suggest that certain combinations of drugs from different classes (eg, methotrexate plus other DMARDs, a rapidly tapered corticosteroid plus a DMARD, methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist, a TNF-α antagonist or an IL-1 receptor antagonist plus a DMARD) are more effective than using DMARDs alone sequentially or in combination.

NSAIDs: Aspirin is no longer used for RA, as effective doses are often toxic. Only one NSAID should be given at a time (see
Table 35-2), although patients may also take aspirin at ≤ 325 mg/day for its antiplatelet cardioprotective effect. Because the maximal response for NSAIDs can take up to 2 wk, doses should be increased no more frequently than this. Doses of drugs with flexible dosing can be increased until response is maximal or maximum dosage is reached. All NSAIDs treat the symptoms of RA and decrease inflammation but do not alter the course of the disease.

NSAIDs inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins. Some prostaglandins under COX-1 control have important effects in

[**Table 35-2.** NSAID Treatment of Rheumatoid Arthritis]

many parts of the body (ie, they protect gastric mucosa and inhibit platelet adhesiveness). Other prostaglandins are induced by inflammation and are produced by COX-2. Selective COX-2 inhibitors, also called coxibs (eg, celecoxib), seem to have efficacy comparable to nonselective NSAIDs and are less likely to cause GI toxicity; however, they do not seem less likely to cause renal toxicity.

NSAIDs other than coxibs should be avoided in patients with previous peptic ulcer disease or dyspepsia. Other possible adverse effects of all NSAIDs include headache, confusion and other CNS symptoms, increased BP, worsening of hypertension, edema, and decreased platelet function. The effect of NSAIDs on cardiovascular risk is still unclear. Creatinine levels can rise reversibly because of inhibited renal prostaglandins; less frequently, interstitial nephritis can occur. Patients with urticaria, rhinitis, or asthma from aspirin can have the same problems with these other NSAIDs.

Traditional DMARDs: (See Table 35-3 for specific dosage information and adverse effects of other drugs used to treat RA.)

These drugs seem to slow the progression of RA and are indicated in nearly all patients with RA. They differ from each other chemically and pharmacologically. Many take weeks or months to have an effect. About two thirds of patients improve overall, but complete remissions are uncommon. Many result in evidence of decreased damage on imaging studies, presumably reflecting decreased disease activity. They have minimal immediate analgesic effects, so NSAIDs or low-dose corticosteroids must often be continued. Patients should be fully apprised of the risks of DMARDs and monitored carefully for evidence of toxicity.

Combinations of DMARDs may be more effective than single drugs. For example, hydroxychloroquine, sulfasalazine, and methotrexate together are more effective than methotrexate alone or the other two together. Also, combining a DMARD with another drug, such as methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist or a rapidly tapered corticosteroid, may be more effective than using DMARDs alone.

Methotrexate is a folate antagonist with immunosuppressive effects at high dose. It is anti-inflammatory at doses used in RA. It is very effective and has a relatively rapid onset (clinical benefit often within 3 to 4 wk). Methotrexate should be used with caution, if at all, in patients with hepatic dysfunction or renal failure. Alcohol should be avoided. Supplemental folate, 1 mg po once/day, reduces the likelihood of adverse effects. CBC, AST, ALT, and albumin and creatinine levels should be determined about every 8 wk. Rarely, a liver biopsy is needed if liver function test findings are persistently twice the upper limit of normal or more and the patient needs to continue to use methotrexate. Severe relapses of arthritis can occur after withdrawal of methotrexate. Paradoxically, rheumatoid nodules may enlarge with methotrexate therapy.

Hydroxychloroquine can also control symptoms of mild RA. Funduscopic examination should be done and visual fields should be assessed before and every 12 mo during treatment. The drug should be stopped if no improvement occurs after 9 mo.

Sulfasalazine can alleviate symptoms and slow development of joint damage. It is usually given as enteric-coated tablets. Benefit should occur within 3 mo. Enteric coating or dose reduction may increase tolerability. CBCs should be obtained after 1 to 2 wk and then about every 12 wk during therapy. AST and ALT should be obtained at about 6-mo intervals and whenever the dose is increased.

Leflunomide interferes with an enzyme involved with pyrimidine metabolism. It is about as effective as methotrexate but is less likely to suppress bone marrow, cause abnormal liver function, or cause pneumonitis.

Parenteral **gold compounds** are not commonly used anymore.

Corticosteroids: Systemic corticosteroids decrease inflammation and other symptoms more rapidly and to a greater degree than other drugs. They also seem to slow bone erosion. However, they do not prevent joint destruction, and their clinical benefit often diminishes with time. Furthermore, rebound often follows the withdrawal of corticosteroids in active disease. Because of their long-term adverse effects,

many doctors recommend that corticosteroids are given to maintain function only until another DMARD has taken effect.

Corticosteroids may be used for severe joint or systemic manifestations of RA (eg, vasculitis, pleurisy, pericarditis). Relative contraindications include peptic ulcer disease, hypertension, untreated infections, diabetes mellitus, and glaucoma. The risk of latent TB should be considered before corticosteroid therapy is begun.

Intra-articular injections of depot corticosteroids may temporarily help control pain and swelling in particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time. Triamcinolone acetonide and methylprednisolone acetate are also effective. No single joint should be injected with a corticosteroid more than 3 to 4 times a year, as too-frequent injections may accelerate joint destruction (although there are no specific data from humans to support this effect). Because injectable corticosteroid esters are crystalline, local inflammation transiently increases within a few hours in < 2% of injections. Although infection occurs in only < 1:40,000, it must be considered if pain occurs > 24 h after injection.

Immunomodulatory, cytotoxic, and immunosuppressive drugs: Treatment with azathioprine, cyclosporine (an immunomodulatory drug), or cyclophosphamide provides efficacy similar to DMARDs. However, these drugs are more toxic, particularly cyclophosphamide. Thus, they are used only for patients in whom treatment with DMARDs has failed or to decrease the need for corticosteroids. They are used infrequently unless there are extra-articular complications. For maintenance therapy with azathioprine, the lowest effective dose should be used. Low-dose cyclosporine may be effective alone or when combined with methotrexate. It may be less toxic than azathioprine and cyclophosphamide.

Biologic agents: Biologic response modifiers other than TNF-α antagonists can be used to target B cells or T cells.

Rituximab is an anti-CD 20 antibody that depletes B cells. It can be used in refractory patients. Response is often delayed but may last 6 mo. The course can be repeated in 6 mo. Mild adverse effects are common, and analgesia, corticosteroids, diphenhydramine, or a combination may need to be given concomitantly. Rituximab is given only to patients who have not improved after using a TNF inhibitor and methotrexate.

Abatacept, a soluble fusion cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) Ig, is indicated for patients with RA with an inadequate response to other DMARDs.

[Table 35-3. Other Drugs Used to Treat RA]

Other agents: Anakinra is a recombinant IL-1 receptor antagonist. IL-1 is heavily involved in the pathogenesis of RA. Infection and leukopenia can be a problem, particularly when given in combination with a TNF antagonist.

TNF-α antagonists (eg, adalimumab, etanercept, and infliximab) reduce the progression of erosions and reduce the number of new erosions. Although not all patients respond, many have a prompt, dramatic feeling of well being, sometimes with the first injection. Inflammation is often dramatically reduced.

Although there are some differences among agents, the most serious problem is infection, particularly with reactivated TB. Patients should be screened for TB with PPD. Etanercept, infliximab, and adalimumab can and probably should be used with methotrexate. High-dose infliximab should not be used in patients with severe heart failure.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a group of rheumatic diseases that begins at or before age 16. Arthritis, fever, rash, adenopathy, splenomegaly, and iridocyclitis are typical of some forms. Diagnosis is clinical. Treatment involves NSAIDs and disease-modifying antirheumatic drugs.

JIA is uncommon. The cause is unknown, but there seems to be a genetic predisposition and an autoimmune pathophysiology. JIA may be similar to adult RA (see p. 332), but most forms are slightly different.

Symptoms and Signs

Patients with JIA can have joint stiffness, swelling, effusion, pain, and tenderness. JIA may interfere with growth and development. Micrognathia (receded chin) due to early closure of mandibular epiphyses may occur. Iridocyclitis may develop, which may cause conjunctival injection, pain, and photophobia but can be asymptomatic; scarring and glaucoma with band keratopathy can result. The initial symptoms and signs of JIA tend to fall into 3 possible patterns.

Systemic onset (Still's disease) occurs in about 20% of patients. High fever, rash, splenomegaly, generalized adenopathy, and serositis with pericarditis or pleuritis are common. These symptoms may precede the development of arthritis. Fever (quotidian) is often highest in the afternoon or evening and may persist for up to 2 wk. A typical transient rash often appears with the fever or may be diffuse and migratory, with urticarial or macular lesions.

Pauciarticular onset is characterized by involvement of ≤ 4 joints. It occurs in about 40% of patients, usually young girls. Iridocyclitis is most common in pauciarticular JIA, developing in nearly 20%. Many affected older boys have the HLA-B27 allele. Most of these boys subsequently develop classic features of one of the spondyloarthropathies (eg, ankylosing spondylitis, psoriatic arthritis, reactive arthritis).

Polyarticular onset involves ≥ 5 joints, often ≥ 20. It occurs in the remaining 40% of patients and is often similar to adult RA. Arthritis tends to be symmetric and develop slowly.

Diagnosis

• Clinical criteria

• Rheumatoid factor (RF) and antinuclear antibodies (ANA)

JIA should be suspected in children with symptoms of arthritis, signs of iridocyclitis, generalized adenopathy, splenomegaly, or unexplained rash or fever lasting more than a few days. Diagnosis is primarily clinical. Patients suspected of having JIA should be tested for RF, ANA, and ESR because these tests may be helpful in diagnosing JIA and distinguishing its subtypes. In Still's disease, RF and ANA are absent. In pauciarticular-onset JIA, ANA are present in up to 75% and RF is absent. In polyarticular-onset JIA, RF usually is negative, but in some patients, mostly adolescent girls, it can be positive.

To diagnose iridocyclitis, slit-lamp examination should be done, even in the absence of ocular symptoms. A recently diagnosed patient with pauciarticular onset should have an eye examination every 3 to 4 mo, and a patient with polyarticular onset should have an eye examination about every 6 mo.

Prognosis

Complete remissions occur in 50 to 75% of treated patients. Patients with polyarticular onset and a positive RF have a less favorable prognosis.

Treatment

• Drugs that slow disease progression

• Usually NSAIDs

Similar to the therapy of patients with adult RA, disease-modifying antirheumatic drugs (DMARDs), particularly the biologic agents, have dramatically changed the therapeutic approach.

Symptoms may be reduced with NSAIDs. Naproxen 5 to 10 mg/kg po bid, ibuprofen 5 to 10 mg/kg po qid,

and indomethacin 0.5 to 1.0 mg/kg po tid are among the most useful. Salicylates are rarely used because of their possible role in causing Reye's syndrome (see p. 2937).

Except for severe systemic disease, systemic corticosteroids can usually be avoided. When necessary, the lowest possible dose is used (eg, oral prednisone, 0.0125 to 0.5 mg/kg qid, or the same daily dose given once or twice daily). Growth retardation, osteoporosis, and osteonecrosis are the major hazards of prolonged corticosteroid use in children. Intra-articular depot corticosteroids can be given. The dosage for children is adjusted based on weight. Children may need to be sedated for intra-articular injection.

Methotrexate is useful for pauciarticular and polyarticular disease. Adverse effects are monitored as in adults. Bone marrow depression and hepatic toxicity are monitored with CBC, AST, ALT, and albumin. Occasionally, sulfasalazine is used, especially in cases of suspected spondyloarthropathy. IM gold and penicillamine are rarely used.

Etanercept, used as in adults, blocks tumor necrosis factor-α (TNF-α) and is often effective; 0.4 mg/kg sc (up to a maximum of 25 mg) is given twice/wk. Anakinra is particularly effective in some patients with systemic-onset disease.

Physical therapy, exercises, splints, and other supportive measures help prevent flexion contractures. Adaptive devices can improve function and minimize unnecessary stresses on inflamed joints. Iridocyclitis is treated with ophthalmic corticosteroid drops and mydriatics (see p. 609).

Seronegative Spondyloarthropathies

(Seronegative Spondyloarthritides)

Seronegative spondyloarthropathies share certain clinical characteristics (eg, back pain, uveitis, GI symptoms, rashes). Some are strongly associated with the HLA-B27 allele. Clinical and genetic similarities suggest that they also share similar causes or pathophysiologies. Rheumatoid factor (RF) is negative in the spondyloarthropathies (hence, why they are called seronegative spondyloarthropathies). They include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and other disorders.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a systemic disorder characterized by inflammation of the axial skeleton, large peripheral joints, and digits; nocturnal back pain; back stiffness; accentuated kyphosis; constitutional symptoms; aortitis; cardiac conduction abnormalities; and anterior uveitis. Diagnosis requires showing sacroiliitis on x-ray. Treatment is with NSAIDs or tumor necrosis factor antagonists and physical measures that maintain joint flexibility.

AS is 3 times more frequent in men than in women and begins most often between ages 20 and 40. It is 10 to 20 times more common among 1st-degree relatives of AS patients than in the general population. The risk of AS in 1st-degree relatives with the HLA-B27 allele is about 20%. Increased prevalence of HLA-B27 in whites or HLA-B7 in blacks supports a genetic predisposition. However, the concordance rate in identical twins is only about 50%, suggesting that environmental factors contribute. The pathophysiology probably involves immune-mediated inflammation.

Symptoms and Signs

The most frequent manifestation is back pain, but disease can begin in peripheral joints, especially in children and women, and rarely with acute iridocyclitis (iritis or anterior uveitis). Other early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia.

Back pain—often nocturnal and of varying intensity—eventually becomes recurrent. Morning stiffness, typically relieved by activity, and paraspinal muscle spasm develop. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, kyphosis is common in untreated patients. Severe hip arthritis can eventually develop. In late stages, the patient has accentuated kyphosis, loss of lumbar

lordosis, and fixed bent-forward posturing, with compromised pulmonary function and inability to lie flat. There may be peripheral potentially deforming joint involvement, sometimes involving the digits (dactylitis). Achilles tendinitis can occur.

Systemic manifestations occur in one third of patients. Recurrent, acute anterior uveitis is common but usually self-limited; uncommonly it becomes protracted and severe enough to impair vision. Neurologic signs occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, or cauda equina syndrome (see p. 1806). Cardiovascular manifestations can include aortic insufficiency, aortitis, angina, pericarditis, and cardiac conduction abnormalities (which may be asymptomatic). Dyspnea, cough, or hemoptysis can result from nontuberculous fibrosis or cavitation of an upper lobe of the lung; secondary infection with *Aspergillus* can develop. Rarely, AS results in secondary amyloidosis. Subcutaneous nodules do not develop.

Diagnosis

• Lumbosacral spine imaging

• Blood tests (ESR, C-reactive protein, and CBC) or explicit clinical criteria (modified New York criteria)

AS should be suspected in patients, particularly young men, with nocturnal back pain and kyphosis, diminished chest expansion, Achilles tendinitis, or unexplained anterior uveitis. A 1st-degree relative with AS should heighten suspicion. Patients should generally be tested with ESR, C-reactive protein, and CBC. IgM, RF, and antinuclear antibodies are needed only if peripheral arthritis suggests other diagnoses. No laboratory test is diagnostic, but results can increase suspicion for the disorder or rule out other disorders than can simulate AS. If, after these tests, AS is still suspected, patients should undergo imaging of the lumbosacral spine; demonstration of sacroiliitis on x-ray strongly supports the diagnosis.

Alternatively, AS can be diagnosed by the modified New York criteria. Using these criteria, the patient must have imaging study evidence of sacroiliitis and one of the following:

• Restriction of lumbar spinal motion in both the sagittal (looking from the side) and frontal (looking from the back) planes

• Restriction of chest expansion, adjusted for age

• A history of inflammatory back pain

Historical features that distinguish inflammatory back pain from noninflammatory back pain include onset at ≤ 40 yr, gradual onset, morning stiffness, improvement with activity, and duration ≥ 3 mo before seeking medical attention.

ESR and other acute-phase reactants (eg, C-reactive protein) are inconsistently elevated in patients with active AS. Tests for RF and antinuclear antibodies are negative. The HLA-B27 genetic marker is not of diagnostic value.

The earliest x-ray abnormalities are pseudowidening from subchondral erosions, followed by sclerosis or later narrowing and eventually fusion in the sacroiliac joints. Changes are symmetric. Early changes in the spine are upper lumbar vertebral squaring with sclerosis at the corners; spotty ligamentous calcification; and one or two evolving syndesmophytes. Late changes result in a "bamboo spine" appearance, resulting from prominent syndesmophytes, diffuse paraspinal ligamentous calcification, and osteoporosis; these changes develop in some patients on average over 10 yr.

Changes typical of AS may not become visible on plain x-rays for years. CT and MRI show changes earlier, but there is no consensus regarding their role in routine diagnosis.

A herniated intervertebral disk can cause back pain and radiculopathy similar to AS, but the pain is limited to the spine, usually causes more sudden symptoms, and causes no systemic manifestations or

laboratory test abnormalities. If necessary, CT or MRI can differentiate it from AS. Involvement of a single sacroiliac joint suggests a different spondyloarthropathy, possibly infection. Tuberculous spondylitis can simulate AS (see p. 1313).

Diffuse idiopathic skeletal hyperostosis (DISH) occurs primarily in men > 50 yr and may resemble AS clinically and on x-ray. Patients uncommonly have spinal pain, stiffness, and insidious loss of motion. X-ray findings in DISH include large ossifications anterior to spinal ligaments (the calcification appears as if someone poured candle wax in front and on the sides of the vertebrae), bridging several vertebrae and usually starting at the lower thoracic spine, eventually affecting the cervical and lumbar spine. There is often subperiosteal bone growth along the pelvic brim and at insertion of tendons (such as the Achilles tendon insertion). However, the anterior spinal ligament is intact and frequently bulging, and sacroiliac and spinal apophyseal joints are not eroded. Additional differentiating features are stiffness that is not accentuated in the morning and a normal ESR.

Prognosis

AS is characterized by mild or moderate flares of active inflammation alternating with periods of little or no inflammation. Proper treatment in most patients results in minimal or no disability and in a full, productive life despite back stiffness. Occasionally, the course is severe and progressive, resulting in pronounced incapacitating deformities.

Treatment

• NSAIDs

• Sulfasalazine, methotrexate, or tumor necrosis factor (TNF) antagonists

• Exercises and supportive measures

The goals of treatment are relieving pain, maintaining joint range of motion, and preventing end-organ damage. Because the condition may cause lung fibrosis, cigarette smoking is discouraged.

NSAIDs reduce pain and suppress joint inflammation and muscle spasm, thereby increasing range of motion, which facilitates exercise and prevents contractures. Most NSAIDs work in AS, and tolerance and toxicity dictate drug choice. The daily dose of NSAIDs should be as low as possible, but maximum doses may be needed with active disease. Drug withdrawal should be attempted only slowly, after systemic and joint signs of active disease have been suppressed for several months.

Sulfasalazine may help reduce peripheral joint symptoms and laboratory markers of inflammation. Dosage should be started at 500 mg/day and increased by 500 mg/day at 1-wk intervals to 1 to 1.5 g bid maintenance. Peripheral joint symptoms may also abate with methotrexate (see p. 337). Systemic corticosteroids, immunosuppressants, and most disease-modifying antirheumatic drugs have no proven benefit and should generally not be used. TNF-α antagonists (eg, etanercept, infliximab, adalimumab) are effective treatments for inflammatory back pain.

For proper posture and joint motion, daily exercise and other supportive measures (eg, postural training, therapeutic exercise) are vital to strengthen muscle groups that oppose the direction of potential deformities (ie, the extensor rather than flexor muscles). Reading while lying prone and pushing up on the elbows or pillows and thus extending the back may help keep the back flexible. Because chest wall motion can be restricted, which impairs lung function, cigarette smoking, which also impairs lung function, is strongly discouraged.

Intra-articular depot corticosteroids may be beneficial, particularly when one or two peripheral joints are more severely inflamed than others, thereby compromising exercise and rehabilitation. They may also help if systemic drugs are ineffective. Corticosteroids injected into the sacroiliac joints may occasionally help severe sacroiliitis.

For acute uveitis, topical corticosteroids and mydriatics are usually adequate. If severe hip arthritis

develops, total hip arthroplasty may lessen pain and improve flexibility dramatically.

Reactive Arthritis

Reactive arthritis is an acute spondyloarthropathy that often seems precipitated by an infection, usually GU or GI. Common manifestations include asymmetric arthritis of variable severity that tends to affect the lower extremities, sausage-shaped deformities of fingers or toes or both, constitutional symptoms, enthesitis, tendinitis, and mucocutaneous ulcers, including hyperkeratotic or crusted vesicular lesions (keratoderma blennorrhagicum). Diagnosis is clinical. Treatment involves NSAIDs and sometimes sulfasalazine or immunosuppressants.

Spondyloarthropathy associated with urethritis or cervicitis, conjunctivitis, and mucocutaneous lesions (previously called Reiter's syndrome) is one type of reactive arthritis.

Etiology

Two forms of reactive arthritis are common: sexually transmitted and dysenteric. The sexually transmitted form occurs primarily in men aged 20 to 40. Genital infections with *Chlamydia trachomatis* are most often implicated. Men or women can acquire the dysenteric form after enteric infections, primarily *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*. Reactive arthritis probably results from joint infection or postinfectious inflammation. Although there is evidence of microbial antigens in the synovium, organisms cannot be cultured from joint fluid.

Epidemiology: The prevalence of the HLA-B27 allele in patients is 63 to 96% vs 6 to 15% in healthy white controls, thus supporting a genetic predisposition.

Symptoms and Signs

Reactive arthritis can range from transient monarticular arthritis to a severe, multisystem disorder. Constitutional symptoms may include fever, fatigue, and weight loss. Arthritis may be mild or severe. Joint involvement is generally asymmetric and oligoarticular or polyarticular, occurring predominantly in the large joints of the lower extremities and in the toes. Back pain may occur, usually with severe disease. Enthesopathy (inflammation at tendinous insertion into bone—eg, plantar fasciitis, digital periostitis, Achilles tendinitis) is common and characteristic. Mucocutaneous lesions—small, transient, relatively painless, superficial ulcers—commonly occur on the oral mucosa, tongue, and glans penis (balanitis circinata). Particularly characteristic are vesicles (sometimes identical to pustular psoriasis) of the palms and soles and around the nails that become hyperkeratotic and form crusts (keratoderma blennorrhagicum). Rarely, cardiovascular complications (eg, aortitis, aortic insufficiency, cardiac conduction defects), pleuritis, and CNS or peripheral nervous system symptoms develop.

Urethritis may develop 7 to 14 days after sexual contact (or occasionally after dysentery); low-grade fever, conjunctivitis, and arthritis develop over the next few weeks. Not all features may occur, so incomplete forms need to be considered. In men, the urethritis is less painful and productive of purulent discharge than acute gonococcal urethritis and may be associated with hemorrhagic cystitis or prostatitis. In women, urethritis and cervicitis may be mild (with dysuria or slight vaginal discharge) or asymptomatic. Conjunctivitis is the most common eye lesion. It usually causes eye redness and grittiness, but keratitis and anterior uveitis can develop also, causing eye pain, photophobia, and tearing.

Diagnosis

• Typical arthritis

• Symptoms of GI or GU infection

• One other extra-articular feature

Reactive arthritis should be suspected in patients with acute, asymmetric arthritis affecting the large joints of the lower extremities or toes, particularly if there is tendinitis or a history of an antecedent diarrhea or

dysuria. Diagnosis is ultimately clinical and requires the typical peripheral arthritis with symptoms of GU or GI infection or one of the other extra-articular features. Because these features may manifest at different times, definitive diagnosis may require several months. Serum and synovial fluid complement levels are high, but these findings are not usually diagnostic and need not be measured.

Disseminated gonococcal infection can closely simulate reactive arthritis (see p. 1472). Arthrocentesis may fail to differentiate them, owing to inflammatory characteristics of synovial fluid in both disorders and the difficulty of culturing gonococci from this fluid. Clinical characteristics may help; disseminated gonococcal infection tends to involve upper and lower extremities equally, be more migratory, and not produce back pain, and vesicles tend not to be hyperkeratotic. A positive gonococcal culture from blood or skin lesions helps differentiate the two disorders, but a positive culture from the urethra or cervix does not. If differentiation is still difficult, ceftriaxone may be required for simultaneous diagnosis and treatment.

Psoriatic arthritis can simulate reactive arthritis, causing similar skin lesions, uveitis, and asymmetric arthritis. However, psoriatic arthritis often affects mostly the upper extremities and especially the distal interphalangeal joints, may be abrupt in onset but may also develop gradually, causes less enthesopathy, and tends not to cause mouth ulcers or symptoms of GU or GI infection.

Prognosis

Reactive arthritis often resolves in 3 to 4 mo, but up to 50% of patients experience recurrent or prolonged symptoms over several years. Joint, spinal, or sacroiliac inflammation or deformity may occur with chronic or recurrent disease. Some patients are disabled.

Treatment

• NSAIDs

• Sometimes sulfasalazine, doxycycline, azathioprine or methotrexate, or a combination

• Supportive measures

NSAIDs (eg, indomethacin 25 to 50 mg po tid) usually help relieve symptoms. If induced by infection with *C. trachomatis*, doxycycline 100 mg po bid for up to 3 mo may accelerate recovery, but this is controversial. Sulfasalazine as used to treat RA may also be helpful (see p. 337). If symptoms are severe despite NSAIDs and sulfasalazine, azathioprine or methotrexate may be considered. Systemic corticosteroids have no proven value.

Local injection of depot corticosteroids for enthesopathy or resistant oligoarthritis may relieve symptoms. Physical therapy aimed at maintaining joint mobility is helpful during the recovery phase. Anterior uveitis is treated as usual, with corticosteroid and mydriatic eye drops to prevent scarring. Conjunctivitis and mucocutaneous lesions require only symptomatic treatment.

Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritis that occurs in people with psoriasis of the skin or nails. The arthritis is often asymmetric, and some forms involve the distal interphalangeal joints. Diagnosis is clinical. Treatment is usually similar to that of RA but can also involve phototherapy.

Psoriatic arthritis develops in 5 to 40% of patients with psoriasis. Prevalence is increased in patients with AIDS. Risk of some involvement is increased in patients with HLA-B27 or some other specific alleles and in family members. Etiology and pathophysiology are unknown.

Symptoms and Signs

Psoriasis of the skin or nails may precede or follow joint involvement. Skin lesions may be hidden in the scalp, gluteal folds, or umbilicus and go unrecognized by the patient.

The distal interphalangeal (DIP) joints of fingers and toes are especially affected. Asymmetric involvement of large and small joints, including the sacroiliacs and spine, is common. Joint and skin symptoms may lessen or worsen simultaneously. Inflammation of the fingers, toes, or both may lead to sausage-shaped deformities. Rheumatoid nodules are absent. Arthritic remissions tend to be more frequent, rapid, and complete than in RA, but progression to chronic arthritis and crippling may occur. There may be arthritis mutilans (destruction of multiple hand joints with telescoping of the digits).

Back pain may be present. It is often accompanied by asymmetric syndesmophytes of the spine.

Diagnosis

• Clinical evaluation

• RF

Psoriatic arthritis should be suspected in patients with both psoriasis and arthritis. Because psoriasis may be overlooked or hidden or develop only after arthritis occurs, psoriatic arthritis should be considered in any patient with seronegative inflammatory arthritis; these patients should be examined for psoriasis and nail pitting and should be questioned about a family history of psoriasis. Patients suspected of having psoriatic arthritis should be tested for rheumatoid factor, which can coexist. Psoriatic arthritis is diagnosed clinically and by excluding other disorders that can cause such similar manifestations. X-ray findings common in psoriatic arthritis include DIP involvement; resorption of terminal phalanges; arthritis mutilans; and extensive destruction, proliferative bone reaction, and dislocation of large and small joints.

Treatment

• Arthritis treated generally similarly to RA

• Phototherapy

Treatment is directed at control of skin lesions (see p. 677) and at joint inflammation. Drug therapy is similar to that for RA, particularly methotrexate. Hydroxychloroquine is inconsistently of benefit and may cause exfoliative dermatitis or aggravate underlying psoriasis. Benefit may be gained from NSAIDs, cyclosporine, and TNF antagonists (see p. 335 under Drugs for RA); TNF antagonists have been particularly effective.

Phototherapy using long-wave psoralen plus ultraviolet A (PUVA) combined with oral methoxsalen 600 µg/kg po 2 h before PUVA twice/wk seems to be highly effective for psoriatic lesions and somewhat effective for peripheral arthritis, but not for spine involvement.

Other Spondyloarthropathies

Spondyloarthropathy can develop in association with GI conditions (sometimes called enteropathic arthritis) such as inflammatory bowel disease, intestinal bypass surgery, or Whipple's disease.

Juvenile-onset spondyloarthropathy is an asymmetric, mostly lower extremity spondyloarthropathy that begins most commonly in boys aged 7 to 16.

Spondyloarthropathy can also develop in people without characteristics of other specific spondyloarthropathy (undifferentiated spondyloarthropathy). Treatment of the arthritis of these other spondyloarthropathies is similar to that of treatment of reactive arthritis (see p. 344).

Osteoarthritis

(Degenerative Joint Disease; Osteoarthrosis; Hypertrophic Osteoarthritis)

Osteoarthritis (OA) is a chronic arthropathy characterized by disruption and potential loss of

joint cartilage along with other joint changes, including bone hypertrophy (osteophyte formation). Symptoms include gradually developing pain aggravated or triggered by activity, stiffness lasting < 30 min on awakening and after inactivity, and occasional joint swelling. Diagnosis is confirmed by x-rays. Treatment includes physical measures (including rehabilitation), patient education, and drugs.

OA, the most common joint disorder, often becomes symptomatic in the 40s and 50s and is nearly universal (although not always symptomatic) by age 80. Only half of patients with pathologic changes of OA have symptoms. Below age 40, most OA is in men and results from trauma. Women predominate from age 40 to 70, after which men and women are equally affected.

Classification

OA is classified as primary (idiopathic) or secondary to some known cause.

Primary OA may be localized to certain joints (eg, chondromalacia patellae is a mild OA that occurs in young people). Primary OA is usually subdivided by the site of involvement (eg, hands and feet, knee, hip). If primary OA involves multiple joints, it is classified as primary generalized OA.

Secondary OA results from conditions that change the microenvironment of the cartilage. These conditions include significant trauma, congenital joint abnormalities, metabolic defects (eg, hemochromatosis, Wilson's disease), infections (causing postinfectious arthritis), endocrine and neuropathic diseases, and disorders that alter the normal structure and function of hyaline cartilage (eg, RA, gout, chondrocalcinosis).

Pathophysiology

Normal joints have little friction with movement and do not wear out with typical use, overuse, or trauma. Hyaline cartilage is avascular, aneural, and alymphatic. It is 95% water and extracellular cartilage matrix and only 5% chondrocytes. Chondrocytes have the longest cell cycle in the body (similar to CNS and muscle cells). Cartilage health and function depend on compression and release of weight bearing and use (ie, compression pumps fluid from the cartilage into the joint space and into capillaries and venules, whereas release allows the cartilage to reexpand, hyperhydrate, and absorb necessary electrolytes and nutrients).

OA begins with tissue damage from mechanical injury (eg, torn meniscus), transmission of inflammatory mediators from the synovium into cartilage, or defects in cartilage metabolism. The tissue damage stimulates chondrocytes to attempt repair, which increases production of proteoglycans and collagen. However, efforts at repair also stimulate the enzymes that degrade cartilage, as well as inflammatory cytokines, which are normally present in small amounts. Inflammatory mediators trigger an inflammatory cycle that further stimulates the chondrocytes and synovial lining cells, eventually breaking down the cartilage. Chondrocytes undergo programmed cell death (apoptosis). Once cartilage is destroyed, exposed bone becomes eburnated and sclerotic.

All articular and some periarticular tissues become involved in OA. Subchondral bone stiffens, then undergoes infarction, and develops subchondral cysts. Attempts at bony repair cause subchondral sclerosis and osteophytes at the joint margins. The osteophytes seem to develop in an attempt to stabilize the joint. The synovium becomes inflamed and thickened and produces synovial fluid with less viscosity and greater volume. Periarticular tendons and ligaments become stressed, resulting in tendinitis and contractures. As the joint becomes less mobile, surrounding muscles thin and become less supportive. Menisci fissure and may fragment.

OA of the spine can, at the disk level, cause marked thickening and proliferation of the posterior longitudinal ligaments, which are posterior to the vertebral body but anterior to the spinal cord. The result can be transverse bars that encroach on the anterior spinal cord. Hypertrophy and hyperplasia of the ligamenta flava, which are posterior to the spinal cord, often compress the posterior canal, causing lumbar spinal stenosis. In contrast, the anterior and posterior nerve roots, ganglia, and common spinal nerve are relatively well protected in the intervertebral foramina, where they occupy only 25% of the

available and well-cushioned space.

Symptoms and Signs

Onset is most often gradual, usually beginning with one or a few joints. Pain is the earliest symptom, sometimes described as a deep ache. Pain is usually worsened by weight bearing and relieved by rest but can eventually become constant. Stiffness follows awakening or inactivity but lasts < 30 min and lessens with movement. As OA progresses, joint motion becomes restricted, and tenderness and crepitus or grating sensations develop. Proliferation of cartilage, bone, ligament, tendon, capsules, and synovium, along with varying amounts of joint effusion, ultimately cause the joint enlargement characteristic of OA. Flexion contractures may eventually develop. Acute and severe synovitis is uncommon.

Tenderness on palpation and pain on passive motion are relatively late signs. Muscle spasm and contracture add to the pain. Mechanical block by intra-articular loose bodies or abnormally placed menisci can occur and cause locking or catching. Deformity and subluxations can also develop.

The joints most often affected in generalized OA include the following:

- Distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints (causing Heberden's and Bouchard's nodes)
- Thumb carpometacarpal joint
- Intervertebral disks and zygapophyseal joints in the cervical and lumbar vertebrae
- First metatarsophalangeal joint
- Hip
- Knee

Cervical and lumbar spinal OA may lead to myelopathy or radiculopathy. However, the clinical signs of myelopathy are usually mild. Lumbar spinal stenosis may cause lower back or leg pain that is worsened by walking or back extension. Radiculopathy can be prominent but is less common because the nerve roots and ganglia are well protected. Insufficiency of the vertebral arteries, infarction of the spinal cord, and dysphagia due to esophageal impingement by osteophytes occasionally occur. Symptoms and signs from OA in general may also derive from subchondral bone, ligamentous structures, synovium, periarticular bursae, capsules, muscles, tendons, disks, and periosteum, all of which are pain sensitive. Venous pressure may increase within the subchondral bone marrow and cause pain (sometimes called bone angina).

Hip OA causes gradual loss of range of motion. Pain may be felt in the inguinal area or greater trochanter or referred to the knee.

Knee OA causes cartilage to be lost (medial loss occurs in 70% of cases). The ligaments become lax and the joint becomes less stable, with local pain arising from the ligaments and tendons.

Erosive OA causes synovitis and cysts in the hand. It primarily affects the DIP or PIP joints. The thumb carpometacarpal joints are involved in 20% of hand OA, but the metacarpophalangeal joints and wrists are usually spared. At this time, it is uncertain whether erosive interphalangeal OA is a variant of hand OA or whether it represents a separate entity.

OA is usually sporadically progressive but occasionally, with no predictability, stops or reverses.

Diagnosis

- X-rays

OA should be suspected in patients with gradual onset of symptoms and signs, particularly in older adults. If OA is suspected, plain x-rays should be taken of the most symptomatic joints. X-rays generally reveal marginal osteophytes, narrowing of the joint space, increased density of the subchondral bone, subchondral cyst formation, bony remodeling, and joint effusions. Standing x-rays of knees are more sensitive in detecting joint space narrowing.

Laboratory studies are normal in OA but may be required to rule out other disorders (eg, RA) or to diagnose an underlying disorder causing secondary OA. If OA causes joint effusions, synovial fluid analysis can help differentiate it from inflammatory arthritides; in OA, synovial fluid is usually clear, viscous, and has ≤ 2000 WBC/μL.

OA involvement outside the usual joints suggests secondary OA; further evaluation may be required to determine the underlying primary disorder (eg, endocrine, metabolic, neoplastic, biomechanical disorders).

Treatment

• Rehabilitative and supportive measures

• Adjunctive drug therapy

Treatment goals are relieving pain, maintaining joint flexibility, and optimizing joint and overall function. Primary treatments include physical measures that involve rehabilitation; support devices; exercise for strength, flexibility, and endurance; patient education; and modifications in activities of daily living. Adjunctive therapies include drug treatment and surgery.

Physical measures: Rehabilitation techniques are best begun before disability develops. Exercises (range of motion, isometric, isotonic, isokinetic, postural, strengthening—see p. 3453) maintain range of motion and increase the capacity for tendons and muscles to absorb stress during joint motion. Exercise can sometimes arrest or even reverse hip and knee OA. Stretching exercises should be done daily. Immobilization for any prolonged period of time can promote contractures and worsen the clinical course. However, a few minutes of rest (every 4 to 6 h in the daytime) can help if balanced with exercise and use.

Modifying activities of daily living can help. For example, a patient with lumbar spine, hip, or knee OA should avoid soft deep chairs and recliners in which posture is poor and from which rising is difficult. The regular use of pillows under the knees while reclining encourages contractures and should also be avoided. Patients should sit in straight-back chairs without slumping, sleep on a firm bed, perhaps with a bed board, use a car seat shifted forward and designed for comfort, do postural exercises, wear well-supported shoes or athletic shoes, and continue employment and physical activity.

In OA of the spine, knee, or thumb carpometacarpal joint, various supports can relieve pain and increase function, but to preserve flexibility, they should be accompanied by specific exercise programs. In erosive OA, range-of-motion exercises done in warm water can help prevent contractures.

Drugs: Drug therapy is an adjunct to the physical program. Acetaminophen in doses of up to 1 g po qid may relieve pain and is safe. More potent analgesia may be required.

NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors or coxibs, may be considered if patients have refractory pain or signs of inflammation (eg, redness, warmth). NSAIDs may be used simultaneously with other analgesics (eg, tramadol, opioids) to provide better relief of symptoms.

Muscle relaxants (usually in low doses) occasionally relieve pain that arises from muscles strained by attempting to support OA joints. In the elderly, however, they may cause more adverse effects than relief.

Oral corticosteroids have no role. However, intra-articular depot corticosteroids help relieve pain and increase joint flexibility.

Synthetic hyaluronans (similar to hyaluronic acid, a normal component of the joint) can be injected into

the knee, with pain relief for prolonged periods of time (up to a year). However, the effect seems to be small. The treatment is a series of 3 to 5 weekly injections.

Glucosamine sulfate 1500 mg po once/day has been suggested to relieve pain and slow joint deterioration; chondroitin sulfate 1200 mg once/day has also been suggested for pain relief. Studies to date have shown mixed results in terms of pain relief.

Other adjunctive and experimental therapies: Other adjunctive measures can relieve pain, including massage, heating pads, weight loss, acupuncture, transcutaneous electrical nerve stimulation, and local rubs (eg, with capsaicin). Laminectomy, osteotomy, and total joint replacement should be considered if all nonsurgical approaches fail. (See also the Agency for Healthcare Research and Quality's Evidence-Based Practice Program's evidence report.)

Experimental therapies that may preserve cartilage or allow chondrocyte grafting are being studied. It is not clear whether using a lidocaine 5% patch relieves pain. Flavocoxid, a new drug, can be tried.

Neurogenic Arthropathy

(Neuropathic Arthropathy; Charcot's Joints)

Neurogenic arthropathy is a rapidly destructive arthropathy due to impaired pain perception and position sense, which can result from various underlying disorders, most commonly diabetes and stroke. Common manifestations include joint swelling, effusion, deformity, and instability. Pain may be disproportionately mild due to the underlying neuropathy. Diagnosis requires x-ray confirmation. Treatment consists of joint immobilization, which slows disease progression, and sometimes surgery if the disease is advanced.

Pathophysiology

Many conditions predispose to neurogenic arthropathy (see Table 35-4). Impaired deep pain sensation or proprioception affects the joint's normal protective reflexes, often allowing trauma (especially repeated minor episodes) and small periarticular fractures to go unrecognized. Increased blood flow to bone from reflex vasodilation, resulting in active bone resorption, contributes to bone and joint damage. Each new injury sustained by the joint causes more distortion as it heals. Hemorrhagic joint effusions and multiple small fractures can occur, accelerating disease progression. Ligamentous laxity, muscular hypotonia, and rapid destruction of joint cartilage are common, predisposing to joint dislocations, which also accelerate disease progression. Advanced neurogenic arthropathy can cause hypertrophic changes, destructive changes, or both.

[**Table 35-4.** Conditions Underlying Neurogenic Arthropathy]

Symptoms and Signs

Arthropathy does not usually develop until years after onset of the neurologic condition but can then progress rapidly and lead to complete joint disorganization in a few months. Pain is a common early symptom. However, because the ability to sense pain is commonly impaired, the degree of pain is often unexpectedly mild for the degree of joint damage. A prominent, often hemorrhagic, effusion and subluxation and instability of the joint are usually present during early stages. Acute joint dislocation sometimes occurs also.

During later stages, pain may be more severe if the disease has caused rapid joint destruction (eg, periarticular fractures or tense hematomas). During advanced stages, the joint is swollen from bony overgrowth and massive synovial effusion. Deformity results from dislocations and displaced fractures. Fractures and bony healing may produce many loose pieces of cartilage or bone that can slough into the joint, causing a coarse, grating, often audible crepitus usually more unpleasant for the observer than for the patient. The joint may feel like a "bag of bones."

Although many joints can be involved, the knee and the ankle are most often affected. Distribution

depends largely on the underlying disease. Thus, tabes dorsalis affects the knee and hip, and diabetes mellitus affects the foot and ankle. Syringomyelia commonly affects the spine and upper limb joints, especially the elbow and shoulder. Frequently, only one joint is affected and usually no more than two or three (except for the small joints of the feet), in an asymmetric distribution.

Infectious arthritis may develop with or without systemic symptoms (eg, fever, malaise), particularly with diabetes. Structures such as blood vessels, nerves, and the spinal cord can become compressed due to the tissue overgrowth.

Diagnosis

• X-rays

The diagnosis should be considered in a patient with a predisposing neurologic disorder who develops a destructive but unexpectedly painless arthropathy, usually several years after the onset of the underlying neurologic condition. If neurogenic arthropathy is suspected, x-rays should be taken. Diagnosis is established by characteristic x-ray abnormalities in a patient with a predisposing condition and typical symptoms and signs.

X-ray abnormalities in early neurogenic arthropathy are often similar to those in osteoarthritis (OA). The cardinal signs are bone fragmentation, bone destruction, new bone growth, and loss of joint space. There may also be synovial effusion and joint subluxation. Later, the bones are deformed, and new bone forms adjacent to the cortex, starting within the joint capsule and often extending up the shaft, particularly in long bones. Rarely, calcification and ossification occur in the soft tissues. Large, bizarrely shaped osteophytes may be present at the joint margins or within joints. Large curved (parrot's beak) osteophytes frequently develop in the spine in the absence of clinical spinal disease.

In its early stages, neurogenic arthropathy can simulate OA. However, neurogenic arthropathy progresses more rapidly than OA and frequently causes proportionately less pain.

Treatment

• Treatment of cause

• Sometimes surgery

Early diagnosis of asymptomatic or minimally symptomatic fractures facilitates early treatment; immobilization (with splints, special boots, or calipers) protects the joint from further injury, possibly stopping disease evolution. Prevention of neurogenic arthropathy may even be possible in a patient at risk.

Treatment of the underlying neurologic condition may slow progression of the arthropathy and, if joint destruction is still in the early stages, partially reverse the process. For a grossly disorganized joint, arthrodesis using internal fixation, compression, and an adequate bone graft may be successful. For grossly disorganized hip and knee joints, if neurogenic arthropathy is not expected to be progressive, good results can be obtained with total hip and knee replacements. However, loosening and dislocation of the prosthesis are major hazards.

Chapter 36. Crystal-Induced Arthritides

Introduction

Arthritis can result from intra-articular deposition of crystals: monosodium urate, Ca pyrophosphate dihydrate, basic Ca phosphate (apatite), and, rarely, others such as Ca oxalate crystals. Diagnosis requires synovial fluid analysis (see p. 287). Polarized light microscopy is used to specifically identify most crystals; basic Ca phosphate crystals are of ultramicroscopic size and require other methods. Crystals may be engulfed in WBCs or may be extracellular. The presence of crystals does not exclude the possibility of simultaneous infectious or other inflammatory forms of arthritis.

Gout

Gout is precipitation of monosodium urate crystals into tissue, usually in and around joints, most often causing recurrent acute or chronic arthritis. Acute arthritis is initially monarticular and often involves the 1st metatarsophalangeal joint. Symptoms include acute pain, tenderness, warmth, redness, and swelling. Diagnosis requires identification of crystals in synovial fluid. Treatment of acute attacks is with anti-inflammatory drugs. The frequency of attacks can be reduced by regular use of NSAIDs, colchicine, or both and by treating hyperuricemia with allopurinol or uricosuric drugs.

Gout is more common among men than women. Usually, gout develops during middle age in men and after menopause in women. Gout is rare in younger people but is often more severe in people who develop the disorder before age 30. Gout often runs in families.

Pathophysiology

The greater the degree and duration of hyperuricemia, the greater is the likelihood of gout and the more severe are the symptoms. Urate levels can be elevated because of

• Decreased excretion

• Increased production

• Increased purine intake

Why only some people with elevated serum uric acid (urate) levels develop gout is not known.

Decreased renal excretion is by far the most common cause of hyperuricemia. It may be hereditary and also occurs in patients receiving diuretics and in those with diseases that decrease GFR. Ethanol increases purine catabolism in the liver and increases the formation of lactic acid, which blocks urate secretion by the renal tubules. Lead poisoning and cyclosporine, usually given to transplant patients, irreversibly damage renal tubules, leading to urate retention.

Increased production of urate may be caused by increased nucleoprotein turnover in hematologic conditions (eg, lymphoma, leukemia, hemolytic anemia) and in conditions with increased rates of cellular proliferation and cell death (eg, psoriasis, cytotoxic cancer therapy, radiation therapy). Increased urate production may also occur as a primary hereditary abnormality and in obesity, because urate production correlates with body surface area. In most cases, the cause is unknown, but a few cases are attributable to enzyme abnormalities; deficiency of hypoxanthine-guanine phosphoribosyltransferase (complete deficiency is Lesch-Nyhan syndrome) is a possible cause, as is overactivity of phosphoribosylpyrophosphate synthetase.

Increased intake of purine-rich foods (eg, liver, kidney, anchovies, asparagus, consomme, herring, meat gravies and broths, mushrooms, mussels, sardines, sweetbreads) can contribute to hyperuricemia. However, a strict low-purine diet lowers serum urate by only about 1 mg/dL.

Urate precipitates as needle-shaped monosodium urate (MSU) crystals, which are deposited

extracellularly in avascular tissues (eg, cartilage) or in relatively avascular tissues (eg, tendons, tendon sheaths, ligaments, walls of bursae) and skin around cooler distal joints and tissues (eg, ears). In severe, longstanding hyperuricemia, MSU crystals may be deposited in larger central joints and in the parenchyma of organs such as the kidney. At the acid pH of urine, urate precipitates readily as small platelike or irregular crystals that may aggregate to form gravel or stones, which may cause obstruction. Tophi are MSU crystal aggregates that most often develop in joint and cutaneous tissue.

Acute gouty arthritis may be triggered by trauma, medical stress (eg, pneumonia or other infection), and especially vascular occlusions (eg, stroke or MI), or by surgery, use of thiazide diuretics or drugs with uricosuric activity (eg, allopurinol), or indulgence in purine-rich food or alcohol. Attacks are often precipitated by a sudden increase or, more commonly, a sudden decrease in serum urate levels. Why acute attacks follow some of these precipitating conditions is unknown. Tophi in and around joints can limit motion and cause deformities, called chronic tophaceous gouty arthritis.

Symptoms and Signs

Acute gouty arthritis usually begins with sudden onset of pain (often nocturnal). The metatarsophalangeal joint of a great toe is most often involved (podagra), but the instep, ankle, knee, wrist, and elbow are also common sites. Rarely, the hip, shoulder, sacroiliac, sternoclavicular, or cervical spine joints are involved. The pain becomes progressively more severe, usually over a few hours, and is often excruciating. Swelling, warmth, redness, and exquisite tenderness may suggest infection. The overlying skin may become tense, warm, shiny, and red or purplish. Fever, tachycardia, chills, and malaise sometimes occur. Coexisting hypertension, hyperlipidemia, and obesity are common.

Course: The first few attacks usually affect only a single joint and last only a few days. Later attacks may affect several joints simultaneously or sequentially and persist up to 3 wk if untreated. Subsequent attacks develop after progressively shorter symptom-free intervals. Eventually, several attacks may occur each year.

Tophi: Tophi develop most often in patients with chronic gout, but they can occur in patients who have never had acute gouty arthritis. They are usually firm yellow or white papules or nodules, single or multiple. They can develop in various locations, commonly the fingers, hands, feet, and around the olecranon or Achilles tendon. Tophi can also develop in the kidneys and other organs and under the skin on the ears. Patients with osteoarthritic Heberden's nodes may develop tophi in the nodes. This development occurs most often in elderly women taking diuretics. Normally painless, tophi, especially in the olecranon bursae, can become acutely inflamed and painful. Tophi may even erupt through the skin, discharging chalky masses of urate crystals. Tophi may eventually cause deformities.

Chronic gout: Chronic gouty arthritis can cause pain, deformity, and limited joint motion. Inflammation can be flaring in some joints while subsiding in others. About 20% of patients with gout develop urolithiasis with uric acid stones or Ca oxalate stones. Complications include obstruction and infection, with secondary tubulointerstitial disease. Untreated progressive renal dysfunction, most often related to coexisting hypertension or, less often, some other cause of nephropathy, further impairs excretion of urate, accelerating crystal deposition in tissues.

Cardiovascular disease and the metabolic syndrome are common among patients with gout.

Diagnosis

• Clinical criteria

• Synovial fluid analysis

Gout should be suspected in patients with acute monarticular or oligoarthritis, particularly older adults or those with other risk factors. Podagra and recurrent instep inflammation are particularly suggestive. Similar symptoms can result from

• Ca pyrophosphate dihydrate (CPPD) crystal deposition disease (see p. 354) (however, CPPD generally

attacks larger joints and its clinical course is usually milder)

- Acute rheumatic fever with joint involvement and juvenile RA (however, these disorders occur mostly in young people, who rarely get gout)

- RA (however, in RA, all affected joints flare and subside together, whereas in gout, inflammation is usually flaring in some joints while subsiding in others)

- Acute fracture in patients unable to provide a history of injury

- Infectious arthritis (see pp. 365 and 369; differentiation may require synovial fluid analysis)

- Palindromic rheumatism

Palindromic rheumatism is characterized by acute, recurrent attacks of inflammation in or near one or occasionally several joints with spontaneous resolution; pain and erythema can be as severe as in gout. Attacks subside spontaneously and completely in 1 to 3 days. Such attacks may herald the onset of RA, and rheumatoid factor tests can help in differentiation; they are positive in about 50% of patients (these tests are positive in 10% of gouty patients also).

Synovial fluid analysis: If acute gouty arthritis is suspected, arthrocentesis and synovial fluid analysis should be done at the initial presentation. A typical recurrence in a patient with known gout does not mandate arthrocentesis, but it should be done if there is any question of the diagnosis or if the patient's risk factors or any clinical characteristics suggest infectious arthritis. Synovial fluid analysis can confirm the diagnosis by identifying needle-shaped, strongly negatively birefringent urate crystals that are free in the fluid or engulfed by phagocytes. Synovial fluid during attacks has inflammatory characteristics (see Table 36-1), usually 2,000 to 100,000 WBCs/μL, with > 80% polymorphonuclear WBCs. These findings overlap considerably with infectious arthritis, which must be excluded by Gram stain and culture.

Serum urate level: An elevated serum urate level supports the diagnosis of gout but is neither specific nor sensitive; at least 30% of patients have a normal serum urate level during an acute attack. However, the serum urate level reflects the size of the extracellular miscible urate pool. The level should be measured on 2 or 3 occasions in patients with newly proven gout to establish a baseline; if elevated (> 7 mg/dL [> 0.41 mmol/L]), 24-h urinary urate excretion can also be measured. Normal 24-h excretion in people eating a regular diet is about 600 to 900 mg. Quantification of urinary uric acid can indicate whether hyperuricemia results from impaired excretion or increased production and help guide any serum urate-lowering therapy. Patients with elevated urine excretion of urate are at increased risk of urolithiasis.

X-rays: X-rays of the affected joint may be taken to look for bony tophi but are probably unnecessary if the diagnosis has been established by synovial fluid analysis. In CPPD, radiopaque deposits are present in fibrocartilage, hyaline articular cartilage (particularly the knee), or both.

Diagnosis of chronic gouty arthritis: Chronic gouty arthritis should be suspected in patients with persistent joint disease or subcutaneous

[**Table 36-1.** Microscopic Examination of Crystals in Joints]

or bony tophi. Plain x-rays of the 1st metatarsophalangeal joint or other affected joint may be useful. These x-rays may show punched-out lesions of subchondral bone with overhanging bony margins, most commonly in the 1st metatarsophalangeal joint; lesions must be ≥ 5 mm in diameter to be visible on x-ray.

Bone lesions are not specific or diagnostic but nearly always precede the appearance of subcutaneous tophi.

Prognosis

With early diagnosis, therapy enables most patients to live a normal life. For many patients with advanced disease, aggressive lowering of the serum urate level can resolve tophi and improve joint function. Gout

is generally more severe in patients whose initial symptoms appear before age 30. The metabolic syndrome and cardiovascular disease probably increase mortality in patients with gout.

Some patients do not improve sufficiently with treatment. The usual reasons include nonadherence, alcoholism, and undertreatment by physicians.

Treatment

• Termination of an acute attack with NSAIDs or corticosteroids

• Prevention of recurrent acute attacks with daily colchicine or an NSAID

• Prevention of further deposition of MSU crystals and resolution of existing tophi by lowering the serum urate level

• Treatment of coexisting hypertension, hyperlipidemia, and obesity

Treatment of acute attacks: NSAIDs are effective in treating acute attacks and are generally well tolerated. However, they can still cause adverse effects, including GI upset, hyperkalemia, increases in creatinine, and fluid retention. Elderly and dehydrated patients are at particular risk, especially if there is a history of renal disease. Virtually any NSAID used in anti-inflammatory (high) doses is effective and is likely to exert an analgesic effect in a few hours (see Table 35-2 on p. 336). Treatment should be continued for several days after the pain and signs of inflammation have resolved to prevent relapse.

Oral colchicine, a traditional therapy, often produces a dramatic response if begun soon after the onset of symptoms. Joint pain generally begins to subside after 12 to 24 h of treatment and ceases within 3 to 7 days. One regimen is colchicine 0.6 mg po q 1 h until symptoms abate to a maximum total dose of 4 to 5 mg or until diarrhea or vomiting occurs. However, diarrhea, sometimes severe, develops in up to 80% of patients given this regimen of oral colchicine for an acute attack. If treatment is started very early, regimens such as 0.6 to 1.2 mg bid to tid for 1 to 2 days are better tolerated and may be effective. If colchicine is tolerated, 0.6 to 1.2 mg once/day can be continued as the attack subsides.

IV colchicine is much less likely to cause GI symptoms and provides an alternative, particularly for postoperative patients. Colchicine 1 mg is diluted with 0.9% saline to 20 mL and injected slowly (over 2 to 5 min); a second 1-mg dose can be given in 12 h if needed; no more than 2 mg is given in 24 h (and no more than 4 mg over 7 days). *IV colchicine should not be given to patients with renal or liver disease or those receiving prophylactic oral colchicine, because severe bone marrow suppression, shock, and death may occur.* IV colchicine is also locally irritating, particularly if extravasated. Although effective and perhaps the option of choice in certain specific situations, IV colchicine should only be used with careful adherence to prescribing indications and contraindications.

Corticosteroids are sometimes used to treat acute attacks; however, this use is controversial because inflammation may continue while symptoms are masked. Aspiration of affected joints, followed by instillation of corticosteroid ester crystal suspension, is very effective, particularly for monarticular symptoms; prednisolone tebutate 4 to 40 mg or prednisolone acetate 5 to 25 mg can be used, with dose depending on the size of the affected joint. Oral prednisone (about 40 mg once/day), IM or IV corticosteroids, or single-dose ACTH 80 U IM is also very effective, particularly if multiple joints are involved. As with NSAID therapy, corticosteroids should be continued until after the attack fully resolves to prevent relapse.

In addition to NSAIDs or corticosteroids, supplementary analgesics, rest, ice application, and splinting of the inflamed joint may be helpful. Because lowering the serum urate level during an attack prolongs the attack or predisposes to recurrence, drugs that lower the serum urate level should not be initiated until acute symptoms have been completely controlled.

Prevention of recurrent attacks: The frequency of acute attacks is reduced by taking one to two 0.6-mg tablets of colchicine daily (depending on tolerance and severity). An extra two or three 0.6-mg tablets

of colchicine taken at the first suggestion of an attack may abort flares. A (reversible) neuropathy or myopathy can develop during chronic colchicine ingestion. This condition may occur in patients with renal insufficiency, in patients also receiving a statin or macrolide, or in patients with none of these risk factors. Attack frequency can also be decreased with daily low-dose NSAIDs.

Lowering the serum urate level: Colchicine, NSAIDs, and corticosteroids do not retard the progressive joint damage caused by tophi. Such damage can be prevented and, if present, reversed with urate-lowering drugs. Tophaceous deposits are resorbed by lowering serum urate. Lowering serum urate may also decrease the frequency of acute arthritic attacks. This decrease is accomplished by

- Blocking urate production with allopurinol
- Increasing urate excretion with a uricosuric drug
- Using both types of drugs together in severe tophaceous gout

Uricase can also be given but is not yet routinely used. Uricase is an enzyme that converts urate to allantoin, which is more soluble. IV uricase transiently lowers serum urate by a large amount.

Hypouricemic therapy is indicated for patients with

- Tophaceous deposits
- Frequent or disabling attacks of gouty arthritis (eg, more than 2 attacks/yr or very severe attacks) despite prophylactic colchicine, an NSAID, or both
- Gout with persistent serum urate ≥ 9 mg/dL
- Urolithiasis
- Multiple comorbidities (eg, peptic ulcer disease, chronic kidney disease) that are relative contraindications to the drugs used to treat acute attacks (NSAIDs or corticosteroids)

Hyperuricemia is not usually treated in the absence of gout.

If the goal of hypouricemic therapy is to dissolve tophi, the serum urate level should be lowered to 4.5 mg/dL (0.26 mmol/L), the saturation level at the normal temperature (31° C) of the bunion joint, or even lower. If tophi do not need to be dissolved, a level of 5 to 6 mg/dL (0.30 to 0.36 mmol/L), which is below the level of saturation (> 7.0 mg/dL [> 0.41 mmol/L] at normal core body temperature and pH), is acceptable. These target levels should be maintained indefinitely. Low levels are often difficult to maintain.

Drugs are effective in lowering serum urate; dietary restriction of purines is less effective, but high intake of high-purine food and alcohol (beer in particular) should be avoided. Carbohydrate restriction and weight loss can lower serum urate in patients with insulin resistance because high insulin levels suppress urate excretion. Because acute attacks tend to develop during the first months of hypouricemic therapy, such therapy should be started in conjunction with once or twice daily colchicine or NSAIDs and during a symptom-free period. Resolution of tophi may take many months even with maintenance of serum urate at low levels. Serum urate should be measured periodically, usually monthly while determining required drug dosage and then yearly to confirm the effectiveness of therapy.

Allopurinol, which inhibits urate synthesis, is the most commonly prescribed hypouricemic therapy. It is especially helpful in treating patients who repeatedly pass uric acid or Ca oxalate stones or who have severe renal dysfunction. Uric acid stones or gravel may dissolve during allopurinol treatment. Treatment begins with 100 mg po once/day and can be increased up to 800 mg po once/day, or even higher, to achieve target urate levels; however, the dose must be decreased in patients with renal insufficiency. The most common daily dose is 300 mg. Adverse effects include mild GI distress and skin rash, which can be a harbinger of Stevens-Johnson syndrome, life-threatening hepatitis, vasculitis, or leukopenia. Adverse

effects are more common among patients with renal dysfunction.

Uricosuric therapy is preferred to allopurinol as initial therapy for patients ≤ 60 yr with normal renal function, no history of urolithiasis, and decreased renal urate excretion. Probenecid or sulfinpyrazone can be used. Probenecid treatment begins with 250 mg po bid, with doses increased as needed, to a maximum of 1 g po tid. Sulfinpyrazone treatment begins with 50 to 100 mg po bid, with doses increased as needed, to a maximum of 100 mg po qid. Sulfinpyrazone is more potent than probenecid but is more toxic. Salicylates at low doses antagonize both drugs and can increase urate levels. Low doses may worsen hyperuricemia, but a therapeutic trial of a cardioprotective dose while monitoring urate levels may be indicated for patients at high risk of cardiovascular disease. Acetaminophen provides comparable analgesia without interfering with drug efficacy.

Other treatments: Fluid intake ≥ 3 L/day is desirable for all patients, especially those who chronically pass urate gravel or stones. Alkalinization of urine (with K citrate 20 to 40 mEq po bid or acetazolamide 500 mg po at bedtime) is also occasionally effective for patients with persistent uric acid urolithiasis despite hypouricemic therapy and adequate hydration. However, excessive urine alkalinization may cause deposition of Ca oxalate crystals. Extracorporeal shock wave lithotripsy may be needed to disintegrate renal stones. Large tophi in areas with healthy skin may be removed surgically; all others should slowly resolve under adequate hypouricemic therapy. Losartan, which has uricosuric effects, can be considered as an alternative to thiazide diuretics.

Asymptomatic Hyperuricemia

Asymptomatic hyperuricemia is elevation of serum urate > 7 mg/dL (> 0.42 mmol/L) in the absence of clinical gout. Generally, treatment is not required. However, patients with overexcretion of urate who are at risk of urolithiasis may receive allopurinol.

Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

(Pseudogout)

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease involves intra-articular and/or extra-articular deposition of CPPD crystals. Manifestations are protean and may be minimal or include intermittent attacks of acute arthritis and a degenerative arthropathy that is often severe. Diagnosis requires identification of CPPD crystals in synovial fluid. Treatment is with intra-articular corticosteroids or oral NSAIDs or colchicine.

CPPD crystal deposition (chondrocalcinosis), whether symptomatic and asymptomatic, becomes more common with age.

The incidence of radiologic (usually asymptomatic) chondrocalcinosis in patients aged 70 is about 3%, reaching nearly 50% in patients aged 90. Asymptomatic chondrocalcinosis is common in the knee, hip, anulus fibrosus, and symphysis pubis. Men and women are affected equally.

Etiology

The cause is unknown. Frequent association with other conditions, such as trauma (including surgery), amyloidosis, myxedema, hypomagnesemia, hyperparathyroidism, gout, hemochromatosis, and old age, suggests that CPPD crystal deposits are secondary to degenerative or metabolic changes in the affected tissues. Some cases are familial, usually transmitted in an autosomal dominant pattern, with complete penetration by age 40.

Symptoms and Signs

Acute, subacute, or chronic arthritis can occur, usually in the knee or other large peripheral joints, which can mimic many other forms of arthritis. Attacks are sometimes similar to gout but are usually less severe. There may be no symptoms between attacks or continuous low-grade symptoms in multiple joints, similar to RA or osteoarthritis. These patterns tend to persist for life.

Diagnosis

• Synovial fluid analysis

• Identification of crystals microscopically

CPPD crystal deposition disease should be suspected in older patients with arthritis, particularly inflammatory arthritis. Diagnosis is established by identifying rhomboid or rod-shaped, weakly positively birefringent crystals on polarized light microscopy of synovial fluid (see Table 36-1). Coincident infectious arthritis must be ruled out by Gram stain and culture. X-rays are indicated if synovial fluid cannot be obtained for analysis; findings of multiple linear or punctate calcification in articular cartilage, especially fibrocartilages, support the diagnosis but do not exclude gout or infection.

Prognosis

The prognosis for individual attacks is usually excellent. However, chronic arthritis can occur, and severe destructive arthropathy resembling neuropathic (Charcot's) joints occasionally occurs.

Treatment

• Intra-articular corticosteroids

• NSAIDs

• Colchicine maintenance

Symptoms of acute synovial effusion abate with synovial fluid drainage and instillation of a microcrystalline corticosteroid ester suspension into the joint space (eg, 40 mg prednisolone acetate or prednisolone tertiary butylacetate into a knee). Indomethacin, naproxen, or another NSAID given at anti-inflammatory doses (see Table 35-2 on p. 336) often stops acute attacks promptly. Colchicine 0.6 mg po once/day or bid may decrease the number of acute attacks.

Basic Calcium Phosphate and Calcium Oxalate Crystal Deposition Diseases

Basic Ca phosphate (apatite) and Ca oxalate crystal disorders tend to cause clinical manifestations similar to other crystal-induced arthritides.

Basic Ca phosphate crystal deposition disease: Most pathologic calcifications throughout the body contain mixtures of carbonate-substituted hydroxyapatite and octacalcium phosphate. Because these ultramicroscopic crystals are nonacidic Ca phosphates, the term basic Ca phosphate (BCP) is much more precise than apatite. These ultramicroscopic crystals occur in snowball-like clumps in rheumatic conditions (eg, calcific tendinitis, calcific periarthritis, some cases of progressive systemic sclerosis and dermatomyositis). They also occur in joint fluids of patients with all degenerative arthropathies sufficiently advanced to cause joint space narrowing on x-ray.

BCP crystals can destroy joints and can cause severe intra-articular or periarticular inflammation. Milwaukee shoulder syndrome is one example, a profoundly destructive arthropathy affecting predominantly elderly women that usually develops in the shoulders and (often) knees.

Acute podagra due to periarticular BCP deposition can mimic gout; it occurs as a discrete syndrome in young women (less often in young men) and is treated the same as acute gout.

Besides synovial fluid analysis, x-rays should be taken of symptomatic joints. On x-ray, BCP crystals may be visible as periarticular cloudlike opacities. Definitive assay for BCP crystals in synovial fluid is not readily available. Clumped crystals can be identified only with transmission electron microscopy. The clumps are not birefringent under polarized light.

Treatment with oral or IV colchicine, an NSAID, or, if a large joint is involved, intra-articular corticosteroid ester crystal suspension is helpful. Treatment is the same as that for acute gout (see p. 352).

Ca oxalate crystal deposition disease: Ca oxalate crystal deposition is rare. It occurs most often in azotemic patients receiving hemodialysis or peritoneal dialysis, particularly those treated with ascorbic acid (vitamin C), which is metabolized to oxalate. Crystals may deposit in blood vessel walls and skin, as well as joints. The crystals appear as birefringent bipyramidal structures (see Table 36-1). Synovial fluid may have > 2000 WBC/µL. On x-ray, Ca oxalate crystals are indistinguishable from BCP periarticular calcifications or Ca pyrophosphate dihydrate (CPPD) crystal deposits in cartilage. Treatment is the same as that for CPPD crystals (see above).

Chapter 37. Osteoporosis

Introduction

Osteoporosis is a progressive metabolic bone disease that decreases bone density (bone mass per unit volume), with deterioration of bone structure. Skeletal weakness leads to fractures with minor or inapparent trauma, particularly in the thoracic and lumbar spine, wrist, and hip. Acute or chronic back pain is common. Diagnosis is by dual-energy x-ray absorptiometry. Prevention and treatment involve Ca and vitamin D supplements, exercises to maximize bone and muscle strength and minimize the risk of falls, and drug therapy to preserve bone mass or stimulate new bone formation.

Pathophysiology

Normally, bone formation and resorption are closely coupled. Osteoblasts (cells that make the organic matrix of bone and then mineralize bone) and osteoclasts (cells that resorb bone) are regulated by parathyroid hormone (PTH), calcitonin, estrogen, vitamin D, various cytokines, and other local factors such as prostaglandins.

Peak bone mass in men and women occurs by the mid 20s. Blacks reach higher bone mass than whites and Asians, whereas Hispanics have intermediate values. Men have higher bone mass than women. Bone mass plateaus for about 10 yr, during which time bone formation approximately equals bone resorption. After this, bone loss occurs at a rate of about 0.3 to 0.5%/yr. Beginning with menopause, bone loss accelerates in women to about 3 to 5%/yr for about 5 to 7 yr.

Osteoporotic bone loss affects cortical and trabecular (cancellous) bone. Cortical thickness and the number and size of trabeculae decrease, resulting in increased porosity. Trabeculae may be disrupted or entirely absent.

Classification

Osteoporosis can develop as a primary disorder or secondarily due to some other factor.

Primary osteoporosis: More than 95% of osteoporosis in women and probably about 80% in men is primary. Most cases occur in postmenopausal women and older men. The terms postmenopausal, involutional, senile, and age-related osteoporosis have been used to describe primary osteoporosis in elderly patients. Estrogen deficiency is an important factor in men as well as women. Other contributing factors may include decreased Ca intake, low vitamin D levels, and secondary hyperparathyroidism.

The major mechanism is increased bone resorption, which results in decreased bone mass and microarchitectural deterioration, but other mechanisms also contribute not only in primary osteoporosis but also in the various secondary forms of osteoporosis. The mechanisms of bone loss may involve the following:

- Local changes in the production of bone-resorbing cytokines, such as increases in cytokines that stimulate bone resorption

- Impaired formation response during bone remodeling (probably caused by age-related decline in the number and activity of osteoblasts)

- Other factors such as a decline in local and systemic growth factors

Trabecular bone loss occurs more rapidly than cortical bone loss because trabecular bone is more porous and bone turnover is high. However, loss of both types contributes to skeletal fragility.

The most common sites for fragility fractures are the distal radius (dorsally displaced fractures), spine (vertebral compression fractures), femoral neck, and greater trochanter. Other sites include the proximal humerus and pelvis. Fragility fractures rarely occur in children or young adults with normal gonadal

function and no detectable secondary cause. This condition is called idiopathic osteoporosis.

Secondary osteoporosis: Secondary osteoporosis accounts for < 5% of osteoporosis cases in women but probably more in men. The causes (see Table 37-1) may also aggravate bone loss and increase fracture risk in patients with primary osteoporosis.

Risk Factors

Because stress, including weight bearing, is necessary for bone growth, immobilization or extended sedentary periods result in bone loss. Being thin predisposes to decreased bone mass. Insufficient dietary intake of Ca, P, and vitamin D predisposes to bone loss, as does endogenous acidosis (eg, high-protein diets). Cigarette smoking and excessive caffeine or alcohol use also adversely affect bone mass. Whites and Asians are at higher risk. A family history of osteoporosis also increases risk. Other risk factors (eg, decreasing

[**Table 37-1.** Causes of Secondary Osteoporosis]

amounts of sex hormones) predispose to specific types of osteoporosis. Patients who have had one fragility fracture are at increased risk of having other clinical (symptomatic) fractures as well as clinically asymptomatic vertebral compression fractures.

Symptoms and Signs

Most of the chronic pain typical of osteoporosis results from fractures, which may develop after minimal, inapparent, or no trauma. Patients may be asymptomatic for years, until fractures begin to occur. Eventually, patients often develop pain in the bones or muscles, particularly of the back. Vertebral compression fractures are common, usually in weight-bearing vertebrae (T6 and below). The pain begins acutely, usually does not radiate, is aggravated by weight bearing, may cause local tenderness, and generally begins to subside in 1 wk. However, residual pain may last for months or be constant.

Multiple thoracic compression fractures eventually cause dorsal kyphosis, with exaggerated cervical lordosis (dowager's hump). Abnormal stress on the spinal muscles and ligaments may cause chronic, dull, aching pain, particularly in the lower back. Fractures can develop at other sites, commonly the hip or wrist, usually from falls.

Diagnosis

• Dual-energy x-ray absorptiometry (DEXA)

Osteoporosis should be suspected in patients who sustain fractures after only mild or trivial trauma; older adults, particularly those with risk factors and unexplained back pain; patients with decreased bone density that is incidentally noted on imaging studies; and patients at risk of secondary osteoporosis. If imaging studies have been done or are necessary to evaluate symptoms (eg, back pain), osteoporosis may be obvious. However, imaging studies are often equivocal, and the diagnosis should be established by bone density measurement.

Plain x-rays: Bones show decreased radiodensity and loss of trabecular structure, but not until about 30% of bone has been lost. A loss of horizontally oriented trabeculae increases the prominence of the cortical end plates and of vertically oriented, weight-bearing trabeculae. Loss of height and increased biconcavity characterize vertebral compression fractures. Thoracic vertebral fractures may cause anterior wedging. In long bones, although the cortices may be thin, the periosteal surface remains smooth. Vertebral fractures at T4 or above suggest cancer rather than osteoporosis.

Corticosteroid-induced osteoporosis is likely to cause rib fractures and exuberant callus formation at sites of healing fractures. Osteomalacia may cause abnormalities on imaging tests similar to those of osteoporosis (see Sidebar 37-1). Hyperparathyroidism can be differentiated when it causes subperiosteal resorption or cystic bone lesions, but these are uncommon.

Bone density measurement: DEXA is used to measure bone density. DEXA is diagnostic for osteoporosis, predicts the risk of fracture, and can be used to follow treatment response. Bone density of the lumbar spine, hip, distal radius or ulna, or the entire body can be measured. (Quantitative CT scanning can produce similar measurements in the spine or hip.) Usually, the lumbar spine, total proximal femur, or femoral neck is measured. DEXA results are reported as T scores. A T score corresponds to the number of standard deviations by which bone density differs from a healthy, young person of the same sex and race. A DEXA result of > 1 is defined as osteopenia and suggests an increased risk of osteoporosis; > 2.5 is diagnostic for osteoporosis.

If DEXA scanning of the central skeleton is unavailable, portable, less expensive systems such as peripheral DEXA or quantitative ultrasonography of the heel can be used. However, monitoring the response to treatment with serial measurements of bone density should be done only with central DEXA scanning.

Sidebar 37-1 Osteopenia: Differentiating Osteoporosis and Osteomalacia

Osteopenia is decreased bone mass. Two metabolic bone diseases decrease bone mass: osteoporosis and osteomalacia. In osteoporosis, bone mass decreases, but the ratio of bone mineral to bone matrix is normal. In osteomalacia, the ratio of bone mineral to bone matrix is low.

Osteoporosis results from a combination of low peak bone mass, increased bone resorption, and impaired bone formation. Osteomalacia is due to impaired mineralization, usually because of severe vitamin D deficiency or abnormal vitamin D metabolism (see p. 41). Osteoporosis is much more common than osteomalacia in the US. The 2 disorders may coexist, and their clinical expression is similar; moreover, mild to moderate vitamin D deficiency can occur in osteoporosis.

Current central DEXA systems can also assess vertebral deformities in the lower thoracic and lumbar spine, a procedure termed vertebral fracture analysis (VFA). Vertebral deformities, even those clinically silent, may indicate increased risk of future fractures. VFA is more likely to be useful in patients with loss of ≥ 3 cm in height.

Other testing: Once osteoporosis is diagnosed, patients should be checked for causes of secondary osteoporosis. Serum Ca should be measured to rule out asymptomatic hyperparathyroidism. PTH levels may be increased in patients with decreased Ca absorption or hypercalciuria. Other tests such as thyroid-stimulating hormone or free thyroxine to check for hyperthyroidism, vitamin D levels, measurements of urinary free cortisol, and blood counts and other tests to rule out cancer, especially myeloma (eg, serum protein electrophoresis), should be considered depending on the clinical findings. Serum alkaline phosphatase is usually normal but may be elevated by recent fracture.

Patients with weight loss should be screened for GI disorders as well as cancer. Bone biopsy is reserved for unusual cases (eg, young patients with pathologic fractures and no apparent cause). Levels of serum or urine N-telopeptide crosslinks (NTX) or free deoxypyridinoline (DPYR) may reflect increased breakdown of collagen. These tests are not sufficiently accurate for routine clinical use but may be used to assess the effectiveness of therapy.

Screening

DEXA screening is recommended for all women > 65. Bone density should also be measured in women between 50 and 65 who have risk factors, including a family history of osteoporosis, a history of fragility fractures, and low body weight. Screening is also recommended for both men and women who have had fragility fractures, even at younger ages.

Treatment

• Risk factor modification

• Ca and vitamin D supplements

• Bisphosphonates or sometimes other antiresorptive drugs

The goals of treatment are to preserve bone mass, prevent fractures, decrease pain, and maintain function.

Preserving bone mass: The rate of bone loss can be slowed with drugs and, when possible, modification of risk factors. Ca and vitamin D intake and physical activity must be adequate for drug treatment to be effective.

Risk factor modification can include maintaining adequate body weight, increasing weight-bearing exercise, minimizing caffeine and alcohol intake, and stopping smoking. The optimal amount of weight-bearing exercise is not established, but an average of 30 min/day is recommended. A physical therapist can develop a safe exercise program.

All men and women should consume at least 1000 mg of elemental Ca daily. An intake of 1200 to 1500 mg/day is recommended for postmenopausal women and older men and for periods of increased requirements, such as pubertal growth, pregnancy, and lactation. Diet alone is rarely adequate; Ca supplements are needed, most commonly as Ca carbonate or Ca citrate. Supplements differ in their elemental Ca concentration. Ca citrate is better absorbed in patients with achlorhydria, but both are well absorbed when taken with meals. Ca should be taken in divided doses of 500 to 600 mg bid or tid.

Vitamin D in doses of 800 U once/day is generally recommended, but up to 2000 U/day is safe and may be helpful in osteoporotic patients. Patients with vitamin D deficiency may need even higher doses. Supplemental vitamin D is usually given as cholecalciferol, the natural form of vitamin D, although ergocalciferol, the synthetic plant derived form, is probably also acceptable.

Bisphosphonates are first-line drug therapy. By inhibiting bone resorption, bisphosphonates preserve bone mass and can decrease vertebral and hip fractures by 50%. To treat osteoporosis, bisphosphonates can be given orally. Alendronate can be given at doses of 10 mg po once/day or 70 mg po once/wk, ibandronate 2.5 mg po once/day or 150 mg once/mo, or risedronate at 5 mg po once/day or 35 mg once/wk. All increase bone mineral density and decrease risk of at least vertebral fractures. Oral bisphosphonates must be taken on an empty stomach with a full glass of water, and the patient must remain upright for ≥ 30 min. They can cause esophageal irritation. Esophageal disorders that delay transit time and symptoms of upper GI disorders are relative contraindications to oral bisphosphonates. Weekly or monthly therapy is generally preferred for its greater convenience and probably fewer adverse effects.

Parenteral zolendronate is an alternative to oral bisphosphonates. Doses of 5 mg IV once/year increase bone mass and decrease risk of vertebral and nonvertebral fractures. Pamidronate can also be given IV but has not yet been shown to prevent fractures.

Osteonecrosis of the jaw has been associated with use of bisphosphonates; however, this condition is rare in patients taking oral bisphosphonates. Risk factors include IV bisphosphonate use and cancer. Bisphosphonates may also be associated with atrial fibrillation, but the mechanism is not clear and there has been no association with increased cardiovascular mortality.

Salmon calcitonin is less effective than bisphosphonates for treating osteoporosis. The subcutaneous dose is 100 IU/day or every other day; the nasal spray dose is 200 U/day in alternating nostrils (1 spray). Salmon calcitonin may provide short-term analgesia after an acute fracture.

Estrogen can preserve bone density and prevent fractures. Most effective if started within 4 to 6 yr of menopause, estrogen may slow bone loss and possibly reduce fractures even when started much later. It is usually given as conjugated estrogen 0.625 to 1.25 mg po once/day. However, 0.3 mg po once/day may be as effective. Use of estrogen increases the risk of thromboembolism and endometrial cancer and may increase the risk of breast cancer. The risk of endometrial cancer can be reduced in women with an intact uterus by taking a progestin with estrogen (see p. 2519). However, taking a combination of a progestin

and estrogen increases the risk of breast cancer, coronary artery disease, stroke, and biliary disease.

Raloxifene is a selective estrogen receptor modulator (SERM) that may be appropriate for treatment of osteoporosis in women who cannot take bisphosphonates. It reduces vertebral fractures by about 50% but has not been shown to reduce nonvertebral fractures. Raloxifene does not stimulate the uterus and antagonizes estrogen effects in the breast, probably reducing the risk of breast cancer.

PTH, which stimulates new bone formation, is generally reserved for patients who have the following characteristics:

- Cannot tolerate antiresorptive drugs or have contraindications to their use
- Fail to respond to antiresorptive drugs, as well as Ca, vitamin D, and exercise, developing new fractures and loss of bone mineral density
- Possibly have severe osteoporosis (eg, T score < 3.5)

When given daily by injection for an average of 20 mo, synthetic PTH (PTH 1-34; teriparatide) increases bone mass and reduces risk of fractures.

Preventing fractures: Many elderly patients are at risk of falls because of poor coordination, poor vision, muscle weakness, confusion, and use of drugs that cause postural hypotension or alter the sensorium. Educating patients about the risks of falls and fractures and developing individualized programs to increase physical stability and attenuate risk can help. Strengthening exercises may increase stability. Hip pads can reduce the incidence of hip fracture despite continued falls.

Treating pain and maintaining function: Acute back pain from a vertebral compression fracture should be treated with orthopedic support, analgesics, and (when muscle spasm is prominent) heat and massage (see p. 3459). Chronic backache may be relieved by an orthopedic garment and exercises to strengthen paravertebral muscles. Avoiding heavy lifting can help. Bed rest should be minimized, and consistent, carefully designed weight-bearing exercise should be encouraged.

In some cases, vertebroplasty, sometimes preceded by kyphoplasty, can relieve severe pain. In vertebroplasty, methyl methacrylate is injected into the vertebral body. In kyphoplasty, the vertebral body is expanded with a balloon. These procedures may reduce deformity in the injected vertebrae but do not reduce and may even increase the risk of fractures in adjacent vertebrae. Other risks may include rib fractures, cement leakage, and pulmonary edema or MI.

Prevention

The goals of prevention are to preserve bone mass and prevent fractures. Preventive measures are indicated in postmenopausal women and older men, patients taking long-term systemic corticosteroids, and patients at high risk (eg, osteopenia with multiple risk factors or secondary causes).

Preventive measures are similar to treatment measures, including those aimed at preserving bone mass. Bisphosphonates and other drugs can be given as for treatment of osteoporosis, but alendronate is given at a reduced dose (5 mg po once/day or 35 mg once/wk). Measures to prevent fractures are also indicated.

Chapter 38. Paget's Disease of Bone

Introduction

(Osteitis Deformans)

Paget's disease of bone is a chronic disorder of the adult skeleton in which bone turnover is accelerated in localized areas. Normal matrix is replaced with softened and enlarged bone. The disease may be asymptomatic or cause gradual onset of bone pain or deformity. Diagnosis is by x-ray. Treatment includes symptomatic measures and often drugs, usually bisphosphonates.

About 1% of adults in the US > 40 have Paget's disease, with a 3:2 male predominance. Prevalence increases with aging. However, overall prevalence seems to be decreasing. The disease is most common in Europe (except Scandinavia), Australia, and New Zealand. It is particularly common in England.

Etiology

Several genetic abnormalities, many affecting osteoclast generation and activity, have been identified. Mutations of the *Sequestrum 1* gene from chromosome 6 are commonly related to Paget's disease. Appearance of involved bone on electron microscopy suggests a viral infection, but a viral cause has not been established.

Pathophysiology

Any bone can be involved. The bones most commonly affected are, in decreasing order, the pelvis, femur, skull, tibia, vertebrae, clavicle, and humerus.

Bone turnover is accelerated at involved sites. Pagetic lesions are metabolically active and highly vascular. Excessively active osteoclasts are often large and contain many nuclei. Osteoblastic repair is also hyperactive, causing coarsely woven, thickened lamellae and trabeculae. This abnormal structure weakens the bone, despite bone enlargement and heavy calcification.

Complications: Overgrown bone may compress nerves and other structures passing through small foramina. Spinal stenosis or spinal cord compression may develop. Osteoarthritis may develop in joints adjacent to involved bone.

In about 10 to 15% of patients, increased bone formation and Ca requirement leads to secondary hyperparathyroidism; if this need is not matched by an increase in Ca intake, hypocalcemia may occur. Hypercalcemia (see p. 843) occasionally develops in patients who are immobile. It also occurs in patients with Paget's disease who develop secondary hyperparathyroidism.

Large or numerous lesions may lead to high-output heart failure.

Symptoms and Signs

There are usually no symptoms for a prolonged period. If symptoms occur, they develop insidiously, with pain, stiffness, fatigue, and bone deformity. Bone pain is aching, deep, and occasionally severe, sometimes worse at night. Pain also may arise from compression neuropathy or osteoarthritis. If the skull is involved, there may be headaches and hearing impairment.

Signs may include skull enlargement bitemporally and frontally (frontal bossing); dilated scalp veins; nerve deafness in one or both ears; angioid streaks in the fundus of the eye; a short kyphotic trunk with simian appearance; hobbling gait; and anterolateral angulation (bowing) of the thigh or leg, often with warmth and tenderness. Deformities may develop from bowing of the long bones or osteoarthritis. Pathologic fractures may be the presenting manifestation. Sarcomatous degeneration develops in < 1% and is often suggested by increasingly severe pain.

Diagnosis

• Plain x-rays

• Serum alkaline phosphatase, Ca, and PO_4

• Bone scan after the diagnosis is established

Paget's disease should be suspected in patients with the following:

• Unexplained bone pain or deformity

• Suggestive findings on x-ray

• Unexplained elevation of serum alkaline phosphatase on laboratory tests done for other reasons, particularly if γ-glutamyl-transpeptidase (GGT) is normal

• Hypercalcemia that develops during bed rest, particularly among elderly patients

• Bone sarcoma in elderly patients

If Paget's disease is suspected, plain x-rays and serum alkaline phosphatase, Ca, and PO_4 levels should be obtained. Confirmation on x-ray is required to establish the diagnosis. Characteristic x-ray findings include the following:

• Increased bone sclerosis

• Abnormal architecture with coarse cortical trabeculation or cortical thickening

• Bowing

• Bone enlargement

There may be stress microfractures of the tibia or femur.

Characteristic laboratory findings include elevated serum alkaline phosphatase (increased anabolic activity of bone) but usually normal GGT and serum PO_4 levels. Serum Ca is usually normal but can increase because of immobilization or hyperparathyroidism or decrease (often transiently) because of increased bone synthesis. If alkaline phosphatase is not elevated or it is unclear whether the increased serum alkaline phosphatase is of bony origin (ie, if GGT is increased in proportion to alkaline phosphatase), a bone-specific fraction can be measured.

Occasionally, increased catabolic activity of bone, as demonstrated by elevated urine markers of bone collagen turnover (eg, pyridinoline crosslinks), supplements the findings.

Radionuclide bone scan using technetium-labeled phosphonates should be done at baseline to determine the extent of bone involvement.

Treatment

• Supportive care for symptoms and complications

• Bisphosphonates

Localized, asymptomatic disease requires no treatment. Symptomatic treatment includes

[
Table 38-1. Drug Therapy for Paget's Disease]

analgesics or NSAIDs for pain. Orthotics help correct abnormal gait caused by bowed lower extremities. Some patients require orthopedic surgery (eg, hip or knee replacement, decompression of the spinal cord). Weight bearing should be encouraged, and bed rest should be avoided.

Drug therapy: Drug therapy suppresses osteoclast activity. It is indicated for the following:

- To prevent or reduce bleeding during orthopedic surgery
- To prevent or retard progression of complications (eg, hearing loss, deformity, osteoarthritis, paraparesis or paraplegia related to vertebral Paget's disease, or other neurologic deficits, particularly in a poor surgical candidate)
- To treat pain clearly related to the pagetic process and not to another source (eg, osteoarthritis)
- When serum alkaline phosphatase (of bony origin) is > 2 times the normal level, even in the absence of symptoms

Although disease progression can be retarded, existing deficits (eg, deformity, osteoarthritis, hearing loss, neural impingement) are not reversed.

Several bisphosphonates are available and are the drugs of choice (see Table 38-1 on p. 361). Synthetic salmon calcitonin is an alternative to bisphosphonates for patients intolerant of or resistant to them. The newer bisphosphonates (amino-containing bisphosphonates, eg, zolendronate) seem to provide more prolonged response.

Chapter 39. Osteonecrosis

Introduction

(Avascular Necrosis; Aseptic Necrosis; Ischemic Necrosis of Bone)

Osteonecrosis (ON) is a focal infarct of bone that may be caused by specific etiologic factors or may be idiopathic. It can cause pain, limitation of motion, joint collapse, and osteoarthritis. Diagnosis is by x-rays and MRI. In early stages, surgical procedures may slow or prevent progression. In later stages, joint replacement may be required for relief of pain and maintenance of function.

In the US, ON affects about 20,000 new patients annually. The hip (femoral head) is most commonly affected, followed by the knee and shoulder (humeral head). The wrist and ankle are less often involved. It is unusual for ON to involve the shoulder or other less commonly affected sites without the hip also being involved.

Etiology

The most common cause of ON is trauma. Nontraumatic ON affects men more often than women, is bilateral in > 60% of cases, and occurs primarily in patients between ages 30 and 50.

Traumatic ON: The most common cause of traumatic ON is a displaced subcapital fracture of the hip (see p. 3211); ON is uncommon after intertrochanteric fractures. The incidence of ON after hip dislocation is high without prompt reduction; the sooner reduction occurs, the lower the incidence. Fracture or dislocation may cause ON by grossly disrupting or compressing nearby blood vessels.

Spontaneous ON of the knee (SPONK) is localized ON of the femoral condyle or tibial plateau in elderly women (occasionally men). SPONK is thought to be caused by an insufficiency fracture (a type of fragility fracture caused by normal wear and tear on osteoporotic bone that occurs without direct trauma).

Nontraumatic ON: Factors causing or contributing to nontraumatic ON are listed in Table 39-1. The most common factors are the following:

• Chronic corticosteroid use

• Excessive alcohol consumption

The risk of ON is increased when the dose of prednisone or an equivalent corticosteroid is > 25 mg/day for several weeks or months, resulting in a cumulative dose usually > 3000 mg. The risk of ON also is increased when > 3 drinks/day (> 500 mL ethanol/wk) are consumed for several years. Some genetic factors increase susceptibility to ON. Subtle clotting abnormalities due to deficiencies in protein C, protein S, or antithrombin III or to anticardiolipin antibodies (see Ch. 110) can be detected in a high percentage of patients with ON. Some disorders that are themselves associated with ON are treated with corticosteroids (eg, SLE), so it is not clear whether risk is increased because of corticosteroid use or the disorder. About 20% of cases are idiopathic.

[**Table 39-1.** Nontraumatic Risk Factors for Osteonecrosis]

ON of the jaw has recently been reported in several patients who have received high-dose IV bisphosphonate therapy (see Sidebar 39-1). Nontraumatic ON of the hip is bilateral in 60% of patients.

Pathophysiology

ON involves the death of osteocytes and bone marrow. Mechanisms of nontraumatic ON may include embolization by blood clots or lipid droplets, intravascular thrombosis, and extravascular compression. After the vascular insult, the repair processes attempt to remove necrotic bone and marrow and replace them with viable tissue. If the infarct is small, particularly if it is not subject to major weight bearing, this

process may succeed. However, in about 80% of patients, the process is not successful and the infarct gradually collapses. The overlying articular surface becomes flattened and irregular, causing increased pain and eventually leading to osteoarthritis.

Symptoms and Signs

General symptoms: Affected areas may remain asymptomatic for weeks to months after the vascular insult. Usually pain then develops gradually, although it may be acute. With progressive collapse of the joint, pain increases and is exacerbated by motion and weight bearing and is relieved by rest.

Joint-specific symptoms: ON of the hip causes groin pain that may radiate down the thigh or into the buttock. Motion becomes limited, and a limp usually develops. SPONK usually causes sudden knee pain without preceding trauma. This pain is most often on the medial side of the femoral condyle or tibial plateau and manifests with tenderness, joint effusion, painful motion, and a limp. ON of the humeral head often causes less pain and disability than hip and knee involvement. With advanced disease, patients have pain and decreased motion, although passive range of motion is less affected than active range of motion.

Sidebar 39-1 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has no unanimously accepted definition but is generally held to be an oral lesion involving bare mandibular or maxillary bone, which usually manifests with pain and purulent discharge, although it may be asymptomatic. ONJ may occur spontaneously or after dental extraction or trauma, radiation therapy to the head and neck (osteoradionecrosis), or high-dose IV bisphosphonate therapy (eg, for cancer treatment). It is not clear whether routine use of oral bisphosphonates for treatment or prevention of osteoporosis increases risk of ONJ. Currently, otherwise appropriate bisphosphonate use should not be discouraged. However, it seems reasonable to do any necessary oral surgery before beginning bisphosphonate therapy and to encourage good oral hygiene while patients are taking bisphosphonates.

Once established, ONJ is challenging to treat and should be managed by an oral surgeon with experience treating ONJ. Treatment typically involves limited debridement, antibiotics, and oral rinses. Surgical resection of the affected area may worsen the condition and should not be the initial treatment.

Diagnosis

• X-rays

• MRI

ON should be suspected in patients with the following:

• Fractures associated with an increased incidence of ON, particularly if pain persists or worsens

• Persistent spontaneous hip, knee, or shoulder pain, particularly if risk factors for ON are present

Plain x-rays should be done initially. They may show no abnormalities for months. The earliest findings are localized areas of sclerosis and lucency. Later, a subchondral crescent sign may appear. Then, gross collapse and flattening of the articular surface is seen, followed by advanced degenerative changes.

When x-rays are normal or nondiagnostic, an MRI, which is much more sensitive and more specific, should be done. Both hips should be imaged. Bone scans are less sensitive and less specific than MRI. CT is rarely needed, although it may occasionally be of value to detect joint collapse, which does not appear on plain x-rays.

Laboratory studies are usually normal and of little value in detecting ON. However, they might help detect

an underlying disorder (eg, coagulation defects, hemoglobinopathies, lipid abnormalities).

Treatment

• Symptomatic measures (eg, rest, physical therapy, NSAIDs)

• Surgical decompression or other procedures to stimulate healing

• Hip replacement

Nonsurgical treatments: Small, asymptomatic lesions may heal spontaneously and may not need treatment.

Larger lesions, both symptomatic and asymptomatic, have a poor prognosis if untreated, especially when in the femoral head. Therefore, early treatment to slow or prevent progression and save the joint is desirable. No completely effective treatment is yet available. Nonsurgical treatments include drugs (eg, bisphosphonates) and physical modalities (eg, electromagnetic fields and acoustic waves). Drug therapy and physical modalities have shown promise in limited studies but are not currently in general use.

Surgical treatments: Surgical treatments are most effective when done before joint collapse. They have been used most often in treating ON of the hip when the prognosis without treatment is worse than that for other regions. Core decompression is the procedure most frequently done; one or more cores of bone are removed from the necrotic region or multiple small tracks or perforations are made in an attempt to decrease intraosseous pressure and stimulate repair. Core decompression is technically simple, and the complication rate is very low if the procedure is done correctly. Protected weight bearing is needed for about 6 wk. Most reports indicate satisfactory or good results in 65% of patients, including those whose hips have some degree of collapse, and in 80% of patients whose hips have small, early lesions. Other established procedures include various proximal femoral osteotomies and bone grafting, both vascularized and nonvascularized. These procedures are technically demanding, require protected weight bearing for up to 6 mo, and have not been done often in the US. Reports vary as to their indications and effectiveness. They should be done primarily at selected centers that have the surgical experience and facilities to achieve optimal results. An approach currently being evaluated is injection of autologous marrow into the necrotic lesion.

If extensive collapse of the femoral head and degenerative changes in the acetabulum cause sufficient pain and disability, an arthroplasty usually is the only way to effectively relieve pain and increase range of motion. The conventional approach is total hip replacement. Good to excellent results are achieved in 95% of total hip and total knee replacements, complication rates are low, and patients resume most activities of daily living within 3 mo. Most prosthetic hips and knees last > 15 to 20 yr.

Two alternatives under investigation include surface replacement arthroplasty (SRA) and hemi-SRA. SRA, which can be done instead of total hip replacement, involves the insertion of 2 metal caps, one into the acetabulum and one onto the femoral head, producing a metal-on-metal articulation. Hemi-SRA involves placement of a metal cap onto only the femoral head. It is done only if disease is limited to the femoral head and is considered a temporizing procedure.

ON of the knee and shoulder can be managed nonsurgically more often than ON of the hip. Limited experience with core decompression has been promising. In advanced stages, partial or total joint replacement may be indicated.

Prevention

Risk of ON caused by corticosteroids can be minimized by using them only when essential and by giving them in as low a dose as needed and for as short a duration as possible. To prevent ON caused by decompression sickness, people should follow accepted rules for decompression when diving and when working in pressurized environments. Excessive alcohol use and smoking should be discouraged. Various drugs (eg, anticoagulants, vasodilators, lipid-lowering drugs) are being evaluated for prevention of ON in patients at high risk.

Chapter 40. Infections of Joints and Bones

Acute Infectious Arthritis

Acute infectious arthritis is a joint infection that evolves over hours or days. The infection resides in synovial or periarticular tissues and is usually bacterial—in younger adults, frequently *Neisseria gonorrhoeae*. However, nongonococcal bacterial infections can also occur and can rapidly destroy joint structures. Symptoms include rapid onset of pain, effusion, and restriction of both active and passive range of motion, usually within a single joint. Diagnosis requires synovial fluid analysis and culture. Treatment is IV antibiotics and drainage of pus from joints.

Acute infectious arthritis may occur in children. About 50% of children with joint infection are < 3 yr. However, routine childhood vaccination for *Haemophilus influenzae* and *Streptococcus pneumoniae* is decreasing the incidence in this age group.

Risk factors are listed in Table 40-1. Risk is substantially increased in patients with RA and other disorders causing chronic joint damage, a past history of joint infection, IV drug abuse, or a prosthetic joint (see p. 370). RA patients are at particular risk of bacterial arthritis (prevalence 0.3 to 3.0%; annual incidence 0.5%). Most children who develop infectious arthritis do not have identified risk factors.

Etiology

Infectious organisms reach joints by direct penetration (eg, trauma, surgery, arthrocentesis, bites), extension from an adjacent infection (eg, osteomyelitis, a soft-tissue abscess, an infected wound), or hematogenous spread from a remote site of infection.

[**Table 40-1.** Risk Factors for Infectious Arthritis]

Common organisms are listed in Table 40-2. In adults, most cases result from bacteria and are classified as gonococcal or nongonococcal. In adults overall, *Staphylococcus aureus* tends to be the most frequent cause of infectious arthritis. Methicillin resistance has become more common among community isolates of *S. aureus*. In young adults and adolescents, *Neisseria gonorrhoeae* is the most common cause and results when *N. gonorrhoeae*

[**Table 40-2.** Organisms that Commonly Cause Acute Infectious Arthritis]

spreads from infected mucosal surfaces (cervix, urethra, rectum, pharynx) via the bloodstream. Affected patients often have simultaneous genital infections with *Chlamydia trachomatis* (see p. 1468). *Streptococcus* species are also frequent causes, particularly in patients with polyarticular infections.

Pathophysiology

Infecting organisms multiply in the synovial fluid and synovial lining. Some bacteria (eg, *S. aureus*) produce virulence factors (adhesins), which allow bacteria to penetrate, remain within, and infect joint tissues. Other bacterial products (eg, endotoxin from gram-negative organisms, cell wall fragments, exotoxins from gram-positive organisms, immune complexes formed by bacterial antigens and host antibodies) augment the inflammatory reaction.

PMNs migrate into the joint and phagocytose the infecting organisms. Phagocytosis of bacteria also results in PMN autolysis with release of lysosomal enzymes into the joint, which damage synovia, ligaments, and cartilage. Therefore, PMNs are both the major host defense system and the cause of joint damage. Articular cartilage can be destroyed within hours or days. Inflammatory synovitis may occasionally persist even after the infection has been eradicated by antibiotics. Particularly in gonococcal cases, persistent antigen debris from bacteria or infection may alter cartilage, causing it to become antigenic, and—together with the adjuvant effects of bacterial components—immune-mediated, "sterile"

chronic inflammatory synovitis results.

Symptoms and Signs

Over a few hours to a few days, patients develop moderate to severe joint pain, warmth, tenderness, effusion, restricted active and passive motion, and sometimes redness. Systemic symptoms may be minimal or absent. Infants and children may present with limited spontaneous movement of a limb (pseudoparalysis), irritability, feeding disturbances, and a high, low-grade, or no fever.

Gonococcal arthritis: Gonococcal arthritis can cause a distinctive dermatitis-polyarthritistenosynovitis syndrome. Classic manifestations are fever (for 5 to 7 days); shaking chills; multiple skin lesions (petechiae, papules, pustules, hemorrhagic vesicles or bullae, necrotic lesions) on mucosal surfaces and on the skin of the trunk, hands, or lower extremities; and migratory arthralgias, arthritis, and tenosynovitis, which evolves into persistent inflammatory arthritis in one or more joints, most often the small joints of the hands, wrists, elbows, knees, and ankles, and rarely the axial skeletal joints. Symptoms of the original mucosal infection (eg, urethritis, cervicitis) may not be present.

Nongonococcal bacterial arthritis: Nongonococcal bacterial arthritis causes progressive moderate to severe joint pain that is markedly worsened by movement or palpation. Most infected joints are swollen, red, and warm. Fever is absent or low grade in up to 50% of patients; 20% of patients report a shaking chill. Virulent organisms (eg, *S. aureus, Pseudomonas aeruginosa*) generally cause a more fulminant arthritis, whereas less virulent organisms (eg, coagulase-negative staphylococci, *Propionibacterium acnes*) cause a less fulminant arthritis. In 80% of adults, nongonococcal bacterial arthritis is monarticular and usually occurs in a peripheral joint: knee, hip, shoulder, wrist, ankle, or elbow. In children, ≥ 90% is monarticular: knee (39%), hip (26%), and ankle (13%). Polyarticular involvement is somewhat more common among patients who are immunosuppressed or have an underlying chronic arthritis (eg, RA, osteoarthritis). In IV drug users and patients with indwelling vascular catheters, axial joints (eg, sternoclavicular, costochondral, hip, shoulder, vertebral, symphysis pubis, sacroiliac) are often involved.

Infectious arthritis secondary to bite wounds: Infection due to human, dog, or cat bites usually develops within 48 h. Rat bites cause systemic symptoms such as fever, rash, and joint pain or true arthritis with regional adenopathy within about 2 to 10 days.

Viral infectious arthritis: Viral infectious arthritis sometimes causes symptoms similar to acute nongonococcal bacterial arthritis and is more likely to be polyarticular than bacterial arthritis.

***Borrelia burgdorferi* arthritis:** Patients with *B. burgdorferi* arthritis may have other symptoms of Lyme disease (see p. 1269) or present only with acute monarthritis or oligoarthritis.

Diagnosis

• Arthrocentesis with synovial fluid examination and culture

• Blood culture

• Sometimes imaging studies

• Often CBC and ESR (or C-reactive protein)

Infectious arthritis is suspected in patients with acute monarticular arthritis and in patients with other combinations of symptoms characteristic of particular infectious arthritis syndromes (eg, migratory polyarthritis, tenosynovitis and skin lesions typical of disseminated gonococcal infection; erythema migrans or other symptoms and signs of Lyme disease—see p. 1269). Even mild monarticular joint symptoms should arouse suspicion in patients with risk factors (eg, RA), a prosthetic joint, or an extra-articular infection capable of spreading to a joint (eg, genital gonococcal infection, bacteremia, any anaerobic infection).

General arthritis: Synovial fluid examination is the cornerstone of diagnosis. Fluid is examined

grossly and sent for cell count and differential, Gram stain, aerobic and anaerobic culture, and crystals. Foul-smelling synovial fluid suggests anaerobic infection. Fluid from an acutely infected joint usually reveals a WBC count > 20,000/µL (often > 100,000/µL) consisting of > 95% PMNs. WBC counts tend to be higher in nongonococcal bacterial than in gonococcal infectious arthritis. WBC counts may also be lower in early or partially treated infections. Gram stain reveals organisms in only 50 to 75% of joints with acute bacterial arthritis, most often with staphylococci. If positive, Gram stain is usually relatively specific, but cultures are definitive. The presence of crystals does not exclude infectious arthritis. Sometimes synovial fluid analysis cannot differentiate between infectious and other inflammatory synovial fluid. If differentiation is impossible by clinical means or synovial fluid examination, infectious arthritis is assumed, pending culture results.

Blood tests, such as blood cultures, CBC, and ESR (or C-reactive protein), are usually obtained. However, normal results do not exclude infection. Likewise, WBC count, ESR, or C-reactive protein may be increased in noninfectious as well as infectious joint inflammation.

Plain x-rays of the involved joint are not diagnostic of acute infection but can exclude other conditions under consideration (eg, fractures). Abnormalities in early acute bacterial arthritis are limited to soft-tissue swelling and signs of synovial effusions. After 10 to 14 days of untreated bacterial infection, destructive changes of joint space narrowing (reflecting cartilage destruction) and erosions or foci of subchondral osteomyelitis may appear. Gas visible within the joints suggests infection with *Escherichia coli* or anaerobes.

MRI is considered if the joint is not easily accessible for examination and aspiration (eg, an axial joint). MRI or ultrasonography can identify sites of effusion or abscess that can be aspirated or drained for both diagnosis and therapy. MRI can provide early suggestion of associated osteomyelitis. Bone scans using technetium-99m can be falsely negative in infectious arthritis. Also, because they show increased uptake with increased blood flow in inflamed synovial membranes and in metabolically active bone, they can be falsely positive in noninfectious inflammatory arthritis. Nuclear imaging and MRI do not distinguish infection from crystal-induced arthritis.

Gonococcal arthritis: If gonococcal arthritis is suspected, blood and synovial fluid samples should be *immediately* plated on nonselective chocolate agar, and specimens from the urethra, endocervix, rectum, and pharynx should be plated on selective Thayer-Martin medium. Genital chlamydial cultures are also done. Blood cultures are positive in 60 to 75% of cases during the first week and may be the only method by which to identify the organism; cultures from joints with early tenosynovitis or arthritis are often negative. Synovial fluid cultures from joints with frank purulent arthritis are usually positive, and fluid from skin lesions may be positive. If disseminated gonococcal infection is suspected based on clinical criteria, it is assumed to be present even if all gonococcal cultures are negative. Clinical response to antibiotics (anticipated within 5 to 7 days) can help confirm the diagnosis.

Prognosis

Acute nongonococcal bacterial arthritis can destroy articular cartilage, permanently damaging the joint within hours or days. Gonococcal arthritis does not usually damage joints permanently. Factors that increase susceptibility to infectious arthritis may also increase disease severity. In patients with RA, functional outcome is particularly poor, and the mortality rate is increased.

Treatment

- IV antibiotics

- Drainage of pus from infected joints (for acute nongonococcal bacterial arthritis or any septic arthritis with persistent effusion

Antibiotic therapy: Initial antibiotic selection is directed at the most likely pathogens. The regimen is adjusted based on the results of culture and susceptibility testing.

Gonococcal arthritis is treated with ceftriaxone 1 g IV once/day until at least 24 h after symptoms and

signs resolve, followed by cefixime 400 mg po bid for 7 days. Joint drainage and debridement may be unnecessary. Coexisting genital infection with *C. trachomatis* is also treated, often with doxycycline 100 mg po bid for 7 days, and sexual contacts of the patient are treated as necessary (see p. 1470).

If nongonococcal gram-positive infection is suspected by Gram stain in an adult, the empiric choice is one of the following: a semisynthetic penicillin (eg, nafcillin 2 g IV q 4 h), a cephalosporin (eg, cefazolin 2 g IV q 8 h), or vancomycin 1 g IV q 12 h (if methicillin resistance is common among local community isolates of *S. aureus*). If gram-negative infection is suspected, empiric treatment includes a parenteral 3rd-generation cephalosporin with antipseudomonal activity (eg, ceftazidime 2 g IV q 8 h) and, if infection is severe, an aminoglycoside.

Parenteral antibiotics are continued until clinical improvement is clear (usually 2 to 4 wk), and oral antibiotics should be given at high doses for another 2 to 6 wk according to the clinical response. Infections caused by streptococci and *Haemophilus* are usually eradicated after 2 wk of oral antibiotics after IV treatment. Staphylococcal infections require at least 3 wk and often 6 wk or longer, especially in patients with prior arthritis.

Other therapies: In addition to antibiotics, acute nongonococcal bacterial arthritis requires large-bore needle aspiration of intra-articular pus at least once/day, or tidal irrigation lavage, arthroscopic lavage, or arthrotomy for debridement. Infected RA joints should generally undergo even earlier and more aggressive surgical debridement and drainage. For gonococcal arthritis with persistent effusion, pus is aspirated and drainage may need to be repeated as necessary. Acute bacterial arthritis requires joint splinting for the first few days to reduce pain, followed by passive and active range-of-motion exercises to limit contractures, with muscle strengthening as soon as tolerated. NSAIDs can help decrease pain and inflammation.

Viral arthritis and arthritis secondary to bite wounds: Viral arthritis is treated supportively. Bite wounds are treated with antibiotics and surgical drainage as necessary (see p. 3307).

Chronic Infectious Arthritis

Chronic infectious arthritis develops over weeks and is usually caused by mycobacteria, fungi, or bacteria with low pathogenicity.

Chronic infectious arthritis accounts for 5% of infectious arthritis. It can develop in healthy people, but patients at increased risk include those with

- RA
- HIV infection
- Immunosuppression (eg, hematologic or other cancers, immunosuppressive drug use)
- Prosthetic joints (see p. 370)

Examples of possible causes are *Mycobacterium tuberculosis, M. marinum, M. kansasii, Candida* sp, *Coccidioides immitis, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Sporothrix schenckii, Aspergillus fumigatus, Actinomyces israelii*, and *Brucella* sp. The arthritis of Lyme disease is usually acute but may be chronic and recurrent. Unusual opportunistic organisms are possible in patients with hematologic cancers or HIV infection or who are taking immunosuppressive drugs. In chronic infectious arthritis, the synovial membrane can proliferate and can erode articular cartilage and subchondral bone.

Onset is often indolent, with gradual swelling, mild warmth, minimal or no redness of the joint area, and aching pain that may be mild. Usually a single joint is involved. A prolonged duration and lack of response to conventional antibiotics suggest a mycobacterial or fungal cause.

Patients should have fungal and mycobacterial cultures taken of synovial fluid or synovial tissue, as well

as routine studies. Plain x-ray findings may differ from those of acute infectious arthritis in that joint space is preserved longer, and marginal erosions and bony sclerosis may occur. Mycobacterial and fungal joint infections require prolonged treatment. Mycobacterial infections are often treated with multiple antibiotics, guided by sensitivity testing results.

Prosthetic Joint Infectious Arthritis

Prosthetic joints are at risk of acute and chronic infection, which can cause sepsis, morbidity, or mortality.

Etiology

Infections are more common in prosthetic joints. They are frequently caused by perioperative inoculations of bacteria into the joint or by postoperative bacteremia resulting from skin infection, pneumonia, dental procedures, invasive instrumentation, UTI, or possibly falls. They develop within 1 yr of surgery in two thirds of cases. During the first few months after surgery, the causes are *Staphylococcus aureus* in 50% of cases, mixed flora in 35%, gram-negative organisms in 10%, and anaerobes in 5%.

Symptoms and Signs

There is a history of a fall within 2 wk of symptom onset in about 25% of patients and of prior surgical revisions in about 20%. Some patients have had a postoperative wound infection that appeared to resolve, satisfactory postoperative recovery for many months, and then development of persistent joint pain at rest and during weight bearing. Symptoms and signs may include pain, swelling, and limited motion; temperature may be normal.

Diagnosis

• Clinical, microbiologic, pathologic, and radiographic criteria

The diagnosis often uses a combination of clinical, microbiologic, pathologic, and radiographic criteria. Communication between a sinus tract and the prosthesis may also be considered diagnostic of infection. Synovial fluid should be sampled for cell count and culture. X-rays may show loosening of the prosthesis or periosteal reaction but are not diagnostic. Technetium-99m bone scanning and indium-labeled WBC scanning are more sensitive than plain x-rays but may lack specificity in the immediate postoperative period. Ultimately, periprosthetic tissue collected at the time of surgery may be sent for culture and histologic analysis.

Treatment

• Arthrotomy with debridement

• Long-term systemic antibiotic therapy

Treatment must be prolonged and usually involves arthrotomy for prosthesis removal with meticulous debridement of all cement, abscesses, and devitalized tissues. Debridement is followed by immediate prosthesis revision or placement of an antibiotic-impregnated spacer and then delayed (2 to 4 mo) implantation of a new prosthesis using antibiotic-impregnated cement. Long-term systemic antibiotic therapy is used in either case; empiric therapy is initiated after intraoperative culture is done and usually combines coverage for methicillin-resistant gram-positive organisms (eg, vancomycin 1 g IV q 12 h) and aerobic gram-negative organisms (eg, piperacillin/tazobactam 3.375 g IV q 6 h or ceftazidime 2 g IV q 8 h) and is revised based on results of culture and sensitivity testing. Infection develops in 38% of new implants, whether replaced immediately or after delay.

If patients cannot tolerate surgery, long-term antibiotic therapy alone can be tried. Excision arthroplasty with or without fusion usually is reserved for patients with uncontrolled infection and insufficient bone stock.

Prevention

In the absence of other indications (eg, valvular heart disease), patients with prosthetic joints do not need prophylactic antibiotics before procedures such as dental work and urologic instrumentation. Detailed recommendations are available at www.aaos.org.

Osteomyelitis

Osteomyelitis is inflammation and destruction of bone caused by bacteria, mycobacteria, or fungi. Common symptoms are localized bone pain and tenderness with constitutional symptoms (in acute osteomyelitis) or without constitutional symptoms (in chronic osteomyelitis). Diagnosis is by imaging studies and cultures. Treatment is with antibiotics and sometimes surgery.

Etiology

Osteomyelitis is caused by

• Contiguous spread (from infected tissue or an infected prosthetic joint)

• Bloodborne organisms (hematogenous osteomyelitis)

• Open wounds (from contaminated open fractures or bone surgery)

Trauma, ischemia, and foreign bodies predispose to osteomyelitis. Osteomyelitis may form under deep decubitus ulcers.

About 80% of osteomyelitis results from contiguous spread or from open wounds; it is often polymicrobial. *Staphylococcus aureus* (including both methicillin-sensitive and methicillin-resistant strains) is present in ≥ 50%; other common bacteria include streptococci, gram-negative enteric organisms, and anaerobic bacteria. Osteomyelitis that results from contiguous spread is common in the feet (in patients with diabetes or peripheral vascular disease), at sites where bone was penetrated during trauma or surgery, at sites damaged by radiation therapy, and in bones contiguous to decubitus ulcers, such as the hips and sacrum. A sinus, gum, or tooth infection may spread to the skull.

Hematogenously spread osteomyelitis usually results from a single organism. In children, gram-positive bacteria are most common, usually affecting the metaphyses of the tibia, femur, or humerus. Hematogenously spread osteomyelitis in adults usually affects the vertebrae. Risk factors in adults are older age, debilitation, hemodialysis, sickle cell disease, and IV drug use. Common infecting organisms include *S. aureus* (methicillin-resistant *S. aureus* [MRSA] is common) and enteric gram-negative bacteria (in adults who are older, debilitated, or receiving hemodialysis); *S. aureus*, *Pseudomonas aeruginosa*, and *Serratia* sp (in IV drug users); and *Salmonella* sp (in patients with sickle cell disease). Fungi and mycobacteria can cause hematogenous osteomyelitis, usually in immunocompromised patients or in areas of endemic infection with histoplasmosis, blastomycosis, or coccidioidomycosis. The vertebrae are often involved.

Pathophysiology

Osteomyelitis tends to occlude local blood vessels, which causes bone necrosis and local spread of infection. Infection may expand through the bone cortex and spread under the periosteum, with formation of subcutaneous abscesses that may drain spontaneously through the skin. In vertebral osteomyelitis, paravertebral or epidural abscess can develop.

If treatment of acute osteomyelitis is only partially successful, low-grade chronic osteomyelitis develops.

Symptoms and Signs

Patients with acute osteomyelitis of peripheral bones usually experience weight loss, fatigue, fever, and

localized warmth, swelling, erythema, and tenderness.

Vertebral osteomyelitis causes localized back pain and tenderness with paravertebral muscle spasm that is unresponsive to conservative treatment. Patients are usually afebrile.

Chronic osteomyelitis causes intermittent (months to many years) bone pain, tenderness, and draining sinuses.

Diagnosis

• ESR or C-reactive protein

• X-rays, MRI, or radioisotopic bone scanning

• Culture of bone, abscess, or both

Acute osteomyelitis is suspected in patients with localized peripheral bone pain, fever, and malaise or with localized refractory vertebral pain, particularly in patients with recent risk factors for bacteremia. Chronic osteomyelitis is suspected in patients with persistent localized bone pain, particularly if they have risk factors.

If osteomyelitis is suspected, CBC and ESR or C-reactive protein, as well as plain x-rays of the affected bone, are obtained. The WBC count may not be elevated, but the ESR and C-reactive protein usually are. X-rays become abnormal after 2 to 4 wk, showing periosteal elevation, bone destruction, soft-tissue swelling, and, in the vertebrae, loss of vertebral body height or narrowing of the adjacent infected intervertebral disk space and destruction of the end plates above and below the disk.

If x-rays are equivocal or symptoms are acute, CT and MRI are the current imaging techniques of choice to define abnormalities and reveal abscesses (eg, paravertebral or epidural abscesses). Alternatively, a radioisotope bone scan with technetium-99m can be done. The bone scan shows abnormalities earlier than plain x-rays but does not distinguish among infection, fractures, and tumors. A white blood cell scan using indium-111-labeled cells may help to better identify areas of infection seen on bone scan. Bacteriologic diagnosis is necessary for optimal therapy of osteomyelitis; bone biopsy with a needle or surgical excision and aspiration or debridement of abscesses provides tissue for culture and antibiotic sensitivity testing. Culture of sinus drainage does not necessarily reveal the bone pathogen. Biopsy and culture should precede antibiotic therapy unless the patient is in shock or has neurologic dysfunction.

Treatment

• Antibiotics

• Surgery for abscess, constitutional symptoms, potential spinal instability, or much necrotic bone

Antibiotics effective against both gram-positive and gram-negative organisms are given until culture results and sensitivities are available. Initial antibiotic treatment for acute hematogenous osteomyelitis should include a penicillinase-resistant semisynthetic penicillin (eg, nafcillin or oxacillin 2 g IV q 4 h) or vancomycin 1 g IV q 12 h (when MRSA is prevalent in a community) and a 3rd- or 4th-generation cephalosporin (such as ceftazidime 2 g IV q 8 h or cefepime 2 g IV q 12 h). Empiric treatment of chronic osteomyelitis arising from a contiguous soft-tissue focus, particularly in patients with diabetes, must be effective against anaerobic organisms in addition to gram-positive and gram-negative aerobes. Ampicillin/sulbactam 3 g IV q 6 h or piperacillin/tazobactam 3.375 g IV q 6 h is commonly used; vancomycin 1 g IV q 12 h is added when infection is severe or MRSA is prevalent. Antibiotics must be given parenterally for 4 to 8 wk and tailored to results of appropriate cultures. If any constitutional findings (eg, fever, malaise, weight loss) persist or if large areas of bone are destroyed, necrotic tissue is debrided surgically. Surgery may also be needed to drain coexisting paravertebral or epidural abscesses or to stabilize the spine to prevent injury. Skin or pedicle grafts may be needed to close large surgical defects. Broad-spectrum antibiotics should be continued for > 3 wk after surgery. In chronic osteomyelitis, long-term antibiotic therapy may be needed.

Chapter 41. Bursa, Muscle, and Tendon Disorders

Introduction

Often, muscles, bursae, and tendons are injured during sports activities. Injury, overuse, infection, and occasionally disease can temporarily or permanently damage these structures. Damage can cause pain, limit control of movement, and reduce range of motion.

Bursitis

Bursitis is acute or chronic inflammation of a bursa. The cause is usually unknown, but trauma, repetitive or acute, may contribute, as may infection and crystal-induced disease. Symptoms include pain (particularly with motion or pressure), swelling, and tenderness. Diagnosis is usually clinical; however, ultrasonography may be needed to evaluate deep bursae. Diagnosis of infection and crystal-induced disease requires analysis of bursal fluid. Treatment includes splinting, NSAIDs, sometimes corticosteroid injections, and treatment of the cause.

Bursae are fluid-filled sac-like cavities or potential cavities that are located where friction occurs (eg, where tendons or muscles pass over bony prominences). Bursae minimize friction between moving parts and facilitate movement. Some communicate with joints.

Bursitis may occur in the shoulder (subacromial or subdeltoid bursitis), particularly in patients with rotator cuff tendinitis, which is usually the primary lesion in the shoulder. Other commonly affected bursae include olecranon (miners' or barfly's elbow), prepatellar (housemaid's knee), suprapatellar, retrocalcaneal, iliopectineal (iliopsoas), ischial (tailor's or weaver's bottom), greater trochanteric, pes anserine, and first metatarsal head (bunion) bursae. Occasionally, bursitis causes inflammation in a communicating joint.

Etiology

Bursitis may be caused by the following:

• Injury

• Chronic overuse

• Inflammatory arthritis (eg, gout, RA)

• Acute or chronic infection (eg, pyogenic organisms, particularly *Staphylococcus aureus*)

Idiopathic and traumatic causes are by far the most common. Acute bursitis may follow unusual exercise or strain and usually causes bursal effusion. Infection most often affects olecranon and prepatellar bursae.

Chronic bursitis may develop after previous attacks of bursitis or repeated trauma. The bursal wall is thickened, with proliferation of its synovial lining; bursal adhesions, villus formation, tags, and chalky deposits may develop.

Symptoms and Signs

Acute bursitis causes pain, particularly when the bursa is compressed or stretched during motion. Swelling, sometimes with other signs of inflammation, is common if the bursa is superficial (eg, prepatellar, olecranon). Swelling may be more prominent than pain in olecranon bursitis. Crystal- or bacterial-induced bursitis is usually accompanied by erythema, pitting edema, pain, and warmth in the area over the bursa.

Chronic bursitis may last for several months and may recur frequently. Bouts may last a few days to several weeks. If inflammation persists near a joint, the joint's range of motion may be limited. Limited

motion may lead to muscle atrophy.

Diagnosis

• Clinical evaluation

• Ultrasonography or MRI for deep bursitis

• Aspiration for suspected infection or crystal-induced bursitis

Superficial bursitis should be suspected in patients with swelling or signs of inflammation over bursae. Deep bursitis is suspected in patients with unexplained pain worsened by motion in a location compatible with bursitis. Usually, bursitis can be diagnosed clinically. Ultrasonography or MRI can help confirm the diagnosis when deep bursae are not readily accessible for inspection, palpation, or aspiration. These tests are done to confirm or exclude a suspected diagnosis. These imaging techniques increase the accuracy of identifying the involved structures.

If bursal swelling is particularly painful, red, or warm or if the olecranon or prepatellar bursa is affected, infection and crystal-induced disease should be excluded by bursal aspiration. After a local anesthetic is injected, fluid is withdrawn from the bursa using sterile techniques; analysis includes cell count, Gram stain and culture, and microscopic search for crystals. Gram stain, although helpful, may not be specific, and WBC counts in infected bursae are usually lower than those in septic joints. Urate crystals are easily seen with polarized light, but the apatite crystals typical of calcific tendinitis appear only as shiny chunks that are not birefringent. X-rays should be taken if bursitis is persistent or if calcification is suspected.

Acute bursitis should be distinguished from hemorrhage into a bursa, which can cause similar manifestations because blood is inflammatory. Fluid in traumatic bursitis is serosanguineous. Cellulitis can cause signs of inflammation but does not normally cause bursal effusion; cellulitis overlying the bursa is a relative contraindication to bursal puncture through the cellulitis, but if septic bursitis is strongly suspected, aspiration must occasionally be done.

Treatment

• Rest

• High-dose NSAIDs

• Treatment of crystal-induced disease or infection

Crystal-induced disease (see p. 349) or infection should be treated if present. For infection, choice of antibiotic is determined by results of Gram stain and culture. Empiric antibiotics effective against *S. aureus* should be given. Infectious bursitis requires drainage or excision in addition to antibiotics.

Acute nonseptic bursitis is treated with temporary rest or immobilization and high-dose NSAIDs and sometimes with other analgesics. Voluntary movement should be increased as pain subsides. Pendulum exercises are helpful for the shoulder joint.

If oral drugs and rest are inadequate, aspiration and intrabursal injection of depot corticosteroids 0.5 to 1 mL (eg, triamcinolone acetonide 40 mg/mL) are the treatment of choice. About 1 mL of local anesthetic (eg, 2% lidocaine) can be injected before the corticosteroid injection. The same needle is used; it is kept in place and the syringes are changed. Dose and volume of the corticosteroid may vary according to the size of the bursa. Infrequently, a flare-up occurs within several hours of injection of a depot corticosteroid; the flare-up is probably a form of crystal-induced synovitis. It usually lasts ≤ 24 h and responds to cold compresses plus analgesics. Oral corticosteroids (eg, prednisone) can be used if a local injection is not feasible.

Chronic bursitis is treated the same as acute bursitis, except that splinting and rest are less likely to help and range-of-motion exercises are especially important. Rarely, the bursa needs to be excised.

Tendinitis and Tenosynovitis

Tendinitis is inflammation of a tendon, often developing after degeneration (tendinopathy); tenosynovitis is tendinitis with inflammation of the tendon sheath lining. Symptoms usually include pain with motion and tenderness with palpation. Chronic deterioration or inflammation can cause scars that restrict motion. Diagnosis is clinical, sometimes supplemented with imaging. Treatment includes rest, NSAIDs, and sometimes corticosteroid injections.

Tendinopathy usually results from repeated small tears or degenerative changes (sometimes with Ca deposit) that occur over years in the tendon.

Tendinitis and tenosynovitis most commonly affect tendons associated with the shoulder (rotator cuff), the tendon of the long head of the biceps muscle (bicipital tendon), flexor carpi radialis or ulnaris, flexor digitorum (for infectious flexor tenosynovitis, see p. 390), popliteus tendon, Achilles tendon (see p. 3304), and the abductor pollicis longus and extensor pollicis brevis, which share a common fibrous sheath (the resulting disorder is de Quervain's syndrome—see p. 393).

Etiology

The cause of tendinitis is often unknown. It usually occurs in people who are middle-aged or older as the vascularity of tendons decreases; repetitive microtrauma may contribute. Repeated or extreme trauma (short of rupture), strain, and excessive or unaccustomed exercise probably also contribute. Some quinolone antibiotics may increase the risk of tendinopathy and tendon rupture.

Risk of tendinitis may be increased by certain systemic disorders—most commonly RA, systemic sclerosis, gout, reactive arthritis, and diabetes or, very rarely, amyloidosis or markedly elevated blood cholesterol levels. In younger adults, particularly women, disseminated gonococcal infection may cause acute migratory tenosynovitis.

Symptoms and Signs

Affected tendons are usually painful when moved. Occasionally, tendon sheaths become swollen and fluid accumulates, usually when patients have infection, RA, or gout. Swelling may be visible or only palpable. Along the tendon, palpation elicits localized tenderness of varying severity.

In systemic sclerosis, the tendon sheath may remain dry, but movement of the tendon in its sheath causes friction, which can be felt, or heard with a stethoscope.

Diagnosis

• Clinical evaluation

• Sometimes imaging

Usually, the diagnosis can be based on symptoms and physical examination, including palpation or specific maneuvers to assess pain. MRI or ultrasonography may be done to confirm the diagnosis or rule out other disorders. MRI can detect tendon tears and inflammation (as can ultrasonography).

• **Rotator cuff tendinitis:** This disorder is the most common cause of shoulder pain. Active abduction in an arc of 40 to 120° and internal rotation cause pain (see p. 3298). Passive abduction causes less pain. Ca deposits in the tendon just below the acromion are sometimes visible on x-ray. Ultrasonography or MRI may help with further evaluation and with treatment decisions.

• **Bicipital tendinitis:** Pain in the biceps tendon is aggravated by shoulder flexion or resisted supination of the forearm. Examiners can elicit tenderness proximally over the bicipital groove of the humerus by rolling (flipping) the bicipital tendon under their thumb.

- **Volar flexor tenosynovitis** (digital tendinitis): This common musculoskeletal disorder is often overlooked (see p. 393). Pain occurs in the palm on the volar aspect of the thumb or other digits and may radiate distally. Palpation of the tendon and sheath elicits tenderness; swelling and sometimes a nodule are present. In later stages, the digit may lock when it is flexed, then extend suddenly with a snap (trigger finger).

- **Gluteus medius tendinitis:** Patients with trochanteric bursitis almost always have gluteus medius tendinitis. In patients with trochanteric bursitis, palpation over the lateral prominence of the greater trochanter elicits tenderness. Patients often have a history of chronic pressure on the joint, trauma, a change in gait (eg, due to osteoarthritis, stroke, or leg-length discrepancy), or inflammation at this site (eg, in RA).

Treatment

- Rest or immobilization, heat or cold, followed by exercise

- High-dose NSAIDs

- Sometimes corticosteroid injection

Symptoms are relieved by rest or immobilization (splint or sling) of the tendon, application of heat (usually for chronic inflammation) or cold (usually for acute inflammation), and high-dose NSAIDs (see Table 35-2 on p. 336) for 7 to 10 days. Indomethacin or colchicine may be helpful if gout is the cause (see p. 349). After inflammation is controlled, exercises that gradually increase range of motion should be done several times a day, especially for the shoulder, which can develop contractures rapidly.

Injecting a sustained-release corticosteroid (eg, betamethasone 6 mg/mL, triamcinolone 40 mg/mL, methylprednisolone 20 to 40 mg/mL) in the tendon sheath may help; injection is usually indicated if pain is severe or if the problem has been chronic. Injection volume may range from 0.3 mL to 1 mL, depending on the site. An injection through the same needle of an equal or double volume of local anesthetic (eg, 1 to 2% lidocaine) confirms the diagnosis if pain is relieved immediately. Clinicians should be careful not to inject the tendon (which can be recognized by marked resistance to injection); doing so may weaken it, increasing risk of rupture. Patients are advised to rest the injected joint to reduce the slight risk of rupture. Infrequently, symptoms can worsen for up to 24 h after the injection.

Repeat injections and symptomatic treatment may be required. Rarely, for persistent cases, particularly rotator cuff tendinitis, surgical exploration with removal of Ca deposits or tendon repair, followed by graded physical therapy, is needed. Occasionally, patients require surgery to release scars that limit function or tenosynovectomy to relieve chronic inflammation.

Fibromyalgia

(Myofascial Pain Syndrome; Fibrositis; Fibromyositis)

Fibromyalgia is a common nonarticular disorder of unknown cause characterized by generalized aching (sometimes severe); widespread tenderness of muscles, areas around tendon insertions, and adjacent soft tissues; muscle stiffness; fatigue; and poor sleep. Diagnosis is clinical. Treatment includes exercise, local heat, stress management, drugs to improve sleep, and analgesics.

In fibromyalgia, any fibromuscular tissues may be involved, especially those of the occiput, neck, shoulders, thorax, low back, and thighs. There is no specific histologic abnormality. Symptoms and signs are generalized, in contrast to localized soft-tissue pain and tenderness (myofascial pain syndrome—see also p. 533), which is often related to overuse or microtrauma.

Fibromyalgia is common; it is about 7 times more common among women, usually young or middle-aged women, but can occur in men, children, and adolescents. Because of the sex difference, it is sometimes overlooked in men. It sometimes occurs in patients with systemic rheumatic disorders.

The cause is unknown, but disruption of stage 4 sleep may contribute, as can emotional stress. Patients may tend to be perfectionists. Fibromyalgia may be precipitated by a viral or other systemic infection (eg, Lyme disease) or a traumatic event.

Symptoms and Signs

Stiffness and pain frequently begin gradually and diffusely and have an achy quality. Symptoms can be exacerbated by environmental or emotional stress, poor sleep, trauma, or exposure to dampness or cold or by a physician who implies that the disorder is "all in the head."

Patients tend to be stressed, tense, anxious, fatigued, ambitious, and sometimes depressed. Many patients also have irritable bowel syndrome symptoms or migraine or tension headaches. Pain may worsen with fatigue, muscle strain, or overuse. Specific, discrete areas of muscle (tender points) may be tender when palpated.

Diagnosis

• Clinical criteria

Fibromyalgia is suspected in patients with the following:

• Generalized pain and tenderness, especially if disproportionate to physical findings

• Negative laboratory results despite widespread symptoms

• Fatigue as the predominant symptom

Tests should include ESR or C-reactive protein, CK, and probably tests for hypothyroidism and hepatitis C (which can cause fatigue and generalized myalgias). The diagnosis is based on clinical criteria, including tenderness at some of the 18 specified tender points (see Fig. 41-1). Most experts no longer require a specific number of tender points to make the diagnosis, as originally proposed (≥ 11 of 18). Patients with only some of the specified features may still have fibromyalgia.

[**Fig. 41-1.** Diagnosing fibromyalgia.]

To avoid potential pitfalls, clinicians should consider the following:

• Fibromyalgia is often overlooked in men, children, and adolescents.

• Chronic fatigue syndrome (see p. 3442) can cause similar generalized myalgias and fatigue and typically produces normal laboratory test results.

• Polymyalgia rheumatica (see p. 325) can cause generalized myalgias, particularly in older adults; it can be distinguished because it tends to affect proximal muscles selectively and ESR is high.

• In patients with systemic rheumatic disorders, diagnosing fibromyalgia may be difficult. For example, fibromyalgia may be misinterpreted as an exacerbation of RA or SLE.

Prognosis

Fibromyalgia tends to be chronic but may remit spontaneously if stress decreases. It can also recur at frequent intervals. Functional prognosis is usually favorable for patients being treated with a comprehensive, supportive program, although symptoms tend to persist to some degree.

Treatment

• Stretching and aerobic exercise, local heat, and massage

• Stress management

• Tricyclic antidepressants or cyclobenzaprine to improve sleep

• Analgesics

Stretching exercises, aerobic exercises, sufficient sound sleep, local applications of heat, and gentle massage may provide relief. Overall stress management (eg, deep breathing exercises, meditation, psychologic support, counseling if necessary) is important.

Exercises to gently stretch the affected muscles should be done daily; stretches should be held for about 30 sec and repeated about 5 times. Aerobic exercise (eg, fast walking, swimming, exercise bicycle) can lessen symptoms.

Improving sleep is critical. Low-dose oral tricyclic antidepressants at bedtime (eg, amitriptyline 10 to 50 mg, trazodone 50 to 150 mg, doxepin 10 to 25 mg) or the pharmacologically similar cyclobenzaprine 10 to 40 mg may promote deeper sleep and decrease muscle pain. The lowest effective dose should be used. Drowsiness, dry mouth, and other adverse effects may make some or all of these drugs intolerable, particularly for the elderly.

Nonopioid analgesics (eg, tramadol, propoxyphene, acetaminophen, NSAIDs) may help some patients but on average are not effective. Opioids should be avoided. Pregabalin, used as an adjunct to exercise, measures to improve sleep, and stress management, may help reduce pain.

Rarely, injections of 0.5% bupivacaine or 1% lidocaine 1 to 5 mL are used to treat incapacitating areas of focal tenderness, but such injections should not be relied on as primary treatment.

Drugs taken by the patient should be reviewed to identify those that may aggravate sleep problems. Such drugs should be stopped, and future use should be avoided. Anxiety or depression, if present, may require treatment.

Muscle Cramps

A muscle cramp is a sudden, brief, painful contraction of a muscle or group of muscles.

Cramps (charley horses) can occur in healthy people (usually middle-aged and elderly people), sometimes during rest, but particularly during or after exercise. Leg cramps can occur during sleep, causing pain and plantar flexion of the foot and toes.

Tight calf muscles (eg, from lack of stretching, inactivity, or sometimes chronic lower leg edema) are a common cause of leg cramps. Cramps may also be caused by electrolyte abnormalities (eg, hypokalemia). Exertional muscle pain from ischemia due to peripheral arterial disease (claudication) may cause similar calf pain, but this pain is due to inadequate blood flow to muscles and not to a muscle contraction as with a cramp.

Treatment

• Stretching

If a cramp occurs, stretching the affected muscle often relieves the cramp. For example, for a calf cramp, the person could use a hand to pull the foot and toes upward (dorsiflexion) or do the runner's stretch.

Prevention

Measures to prevent cramps include the following:

- Not exercising immediately after eating
- Gently stretching the muscles before exercising or going to bed
- Drinking plenty of fluids (particularly beverages that contain potassium) after exercise
- Not consuming stimulants (eg, caffeine, nicotine, ephedrine, pseudoephedrine)

The runner's stretch is most useful. A person stands with one leg forward and bent at the knee and the other leg behind and the knee straight—a lunge position. The hands can be placed on the wall for balance. Both heels remain on the floor. The knee of the front leg is bent further until a stretch is felt along the back of the other leg. The greater the distance between the two feet and the more the front knee is bent, the greater the stretch. The stretch is held for 30 sec and repeated 5 times. The set of stretches is repeated on the other side.

Most of the drugs prescribed to prevent cramps (eg, quinine, magnesium, benzodiazepines) have no demonstrated efficacy and are not recommended. Mexiletine sometimes helps, but whether using it is worth the risk of adverse effects is unclear. These adverse effects include nausea, vomiting, heartburn, dizziness, and tremor. Ca supplements are safe and have few adverse effects but have not proved effective.

Chapter 42. Neck and Back Pain

Introduction

Neck pain and back pain are among the most common reasons for physician visits. This discussion covers neck pain involving the posterior neck (not pain limited to the anterior neck) and does not cover most major traumatic injuries (eg, fractures, dislocations, subluxations).

Pathophysiology

Depending on the cause, neck or back pain may be accompanied by neurologic symptoms.

If a nerve root is affected, pain may radiate distally along the distribution of that root (called radicular pain or, in the low back, sciatica). Strength, sensation, and reflexes of the area innervated by that root may be impaired.

If the spinal cord is affected, strength, sensation, and reflexes may be impaired at the affected spinal cord level and all levels below (called segmental neurologic deficits).

If the cauda equina is affected, segmental deficits develop in the lumbosacral region, typically with loss of bowel and bladder function, loss of perianal sensation, erectile dysfunction, urinary retention, and loss of rectal tone and sphincter (eg, bulbocavernosus, anal wink) reflexes.

Any painful disorder of the spine may also cause reflex tightening (spasm) of paraspinal muscles, which can be excruciating.

Etiology

Most neck and back pain is caused by disorders of the spine. Fibromyalgia is also a common cause. Occasionally, pain is referred from extraspinal disorders (particularly vascular, GI, or GU disorders). Some uncommon causes—spinal and extraspinal—are serious.

Most spinal disorders are mechanical. Only a few involve infection, inflammation, or cancer (considered nonmechanical).

Common causes: Most mechanical spine disorders that cause neck or back pain involve a nonspecific mechanical derangement:

• Muscle strain, ligament sprain, spasm, or a combination

Only about 15% involve specific structural lesions that clearly cause the symptoms, primarily the following:

• Disk herniation

• Compression fracture

• Lumbar spinal stenosis

• Osteoarthritis

• Spondylolisthesis

In the other mechanical disorders, there are no specific lesions, or the findings (eg, disk bulging or degeneration, osteophytes, spondylolysis, congenital facet abnormalities) are common among people without neck or back pain, and thus are questionable as the etiology of pain. However, etiology of back pain, particularly if mechanical, is often multifactorial, with an underlying disorder exacerbated by fatigue, physical deconditioning, and sometimes psychosocial stress or psychiatric abnormality. Thus, identifying

a single cause is often difficult or impossible.

Serious uncommon causes: Serious causes may require timely treatment to prevent disability or death.

Serious **extraspinal** disorders include the following:

• Abdominal aortic aneurysm

• Aortic dissection

• Carotid or vertebral artery dissection

• Acute meningitis

• Angina or MI

• Certain GI disorders (eg, cholecystitis, diverticulitis, diverticular abscess, pancreatitis, penetrating peptic ulcer, retrocecal appendicitis)

• Certain pelvic disorders (eg, ectopic pregnancy, ovarian cancer, salpingitis)

• Certain pulmonary disorders (eg, pleuritis, pneumonia)

• Certain urinary tract disorders (eg, prostatitis, pyelonephritis)

Serious **spinal** disorders include the following:

• Infections (eg, diskitis, epidural abscess, osteomyelitis)

• Primary tumors (of spinal cord or vertebrae)

• Metastatic vertebral tumors (most often from breasts, lungs, or prostate)

Mechanical spine disorders can be serious if they compress the spinal nerve roots or, particularly, the spinal cord. Spinal cord compression may result from disorders such as tumors and spinal epidural abscess or hematoma.

Other uncommon causes: Neck or back pain can result from many other disorders, such as Paget's disease of bone, torticollis, thoracic outlet syndrome, temporomandibular joint syndrome, herpes zoster, and spondyloarthropathies (ankylosing spondylitis most often, but also enteropathic arthritis, psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy).

Evaluation

General: Because the cause is often multifactorial, a definitive diagnosis cannot be established in many patients. However, clinicians should determine the following if possible:

• Whether pain has a spinal or extraspinal cause

• Whether the cause is a serious disorder

History: History of present illness should include quality, onset, duration, severity, location, radiation, and time course of pain, as well as modifying factors such as rest, activity, changes in position, weight bearing, and time of day (eg, at night, when awakening). Accompanying symptoms to note include stiffness, numbness, paresthesias, weakness, urinary retention, and incontinence.

Review of systems should note symptoms suggesting a cause, including fever and chills (infection); weight loss and poor appetite (infection or cancer); fatigue, depressive symptoms, and headaches

(multifactorial mechanical back pain); worsening of neck pain during swallowing (esophageal disorders); anorexia, nausea, vomiting, and change in bowel function or stool (GI disorders); urinary symptoms and flank pain (urinary tract disorders); cough, dyspnea, and worsening during inspiration (pulmonary disorders); vaginal bleeding or discharge and pain related to menstrual cycle phase (pelvic disorders).

Past medical history includes known neck or back disorders (including osteoporosis, osteoarthritis, disk disorders, recent or remote injury) and surgery, risk factors for back disorders (eg, cancer, osteoporosis), risk factors for aneurysm (eg, smoking, hypertension), and risk factors for infection (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection).

Physical examination: Temperature and general appearance are noted. When possible, patients should be unobtrusively observed as they move into the examination room, undress, and climb onto the table. If symptoms are exacerbated by psychologic issues, true functional level can be assessed more accurately when patients are not aware they are being evaluated.

The examination focuses on the spine and the neurologic examination. If no mechanical spinal source of pain is obvious, patients are checked for sources of referred pain.

In the spinal examination, the back and neck are inspected for any visible deformity, area of erythema, or vesicular rash. The spine and paravertebral muscles are palpated for tenderness and muscle spasm. Gross range of motion is tested.

In the neurologic examination, strength and deep tendon reflexes are tested. In patients with neurologic symptoms, sensation and sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex) are tested. These tests are among the most reliable physical tests for confirming normal spinal cord function. Corticospinal tract dysfunction is indicated by the extensor plantar response and Hoffman's sign. To test for Hoffman's sign, clinicians tap the nail or flick the volar surface of the 3rd finger; if the distal phalanx of the thumb flexes, the test is positive, usually indicating corticospinal tract dysfunction caused by stenosis of the cervical cord. Sensory findings are subjective and may be unreliable.

The straight leg raise test helps confirm sciatica. The patient is supine with both knees extended and the ankles dorsiflexed. The clinician raises the affected leg, keeping the knee extended. If sciatica is present, 10 to 60° of elevation typically causes symptoms. For the crossed straight leg raise test, the unaffected leg is raised; the test is positive if sciatica occurs in the affected leg. A positive straight leg test is sensitive but not specific for herniated disk; the crossed straight leg raise test is less sensitive but 90% specific. The seated straight leg raise test is done while patients are seated with the hip joint flexed at 90°; the lower leg is slowly raised until the knee is fully extended. If sciatica is present, the pain occurs as the leg is extended.

In the general examination, the lungs are auscultated. The abdomen is checked for tenderness, masses, and, particularly in patients > 55, a pulsatile mass (which suggests abdominal aortic aneurysm). With a fist, clinicians percuss the costovertebral angle for tenderness, suggesting pyelonephritis.

Rectal examination, including stool testing for occult blood and, in men, prostate examination, is done. In women with symptoms suggesting a pelvic disorder or with unexplained fever, pelvic examination is done.

Lower-extremity pulses are checked.

Red flags: The following findings are of particular concern:

• Abdominal aorta that is > 5 cm (particularly if tender) or lower-extremity pulse deficits

• Acute, tearing mid-back pain

• Cancer, diagnosed or suspected

• Duration of pain > 6 wk

- Neurologic deficit
- Fever
- GI findings such as localized abdominal tenderness, peritonitis, melena, or hematochezia
- Infection risk factors (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection)
- Meningismus
- Severe nocturnal or disabling pain
- Unexplained pain after age 55
- Unexplained weight loss

Interpretation of findings: Although serious extraspinal disorders (eg, cancers, aortic aneurysms, epidural abscesses, osteomyelitis) are uncommon causes of back pain, they are not rare, particularly in high-risk groups.

A spinal cause is more likely (but not definitive) than referred pain from an extraspinal cause when

- Pain is worsened by movement or weight bearing and is relieved by rest or recumbency
- Vertebral or paravertebral tenderness is present

Red flag findings should heighten suspicion of a serious cause (see Table 42-1).

Other findings are also helpful. Erythema and tenderness over the spine suggests infection, particularly in patients with risk factors. Worsening of pain with flexion is consistent with intervertebral disk disease; worsening with extension suggests spinal stenosis, arthritis affecting the facet joints, or retroperitoneal inflammation or infiltration (eg, pancreatic or kidney inflammation or tumor). Tenderness over certain specific trigger points suggests fibromyalgia. Deformities of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) finger joints and stiffness that lessens within 30 min after awakening suggest osteoarthritis. Neck pain that is unrelated to swallowing and is exertional may indicate angina.

Testing: Usually, if duration of pain is short (< 4 to 6 wk), no testing is required unless red flag findings are present, patients have had a serious injury (eg, vehicular crash, fall from a height, penetrating trauma), or evaluation suggests a specific nonmechanical cause (eg, pyelonephritis).

Plain x-rays can identify most osteoporotic fractures and osteoarthritis. However, they do not identify abnormalities in soft tissue (the most common cause of back and neck pain) or nerve tissue (as occurs in many serious disorders). Thus, x-rays are usually unnecessary and do not change management. Sometimes

[**Table 42-1.** Interpretation of Red Flag Findings in Patients with Back Pain]

x-rays are done to identify obvious bone abnormalities (eg, those due to infection or tumors) and to avoid MRI and CT, which are harder to obtain but which are much more accurate and usually necessary.

Testing is guided by findings and suspected cause:

- Neurologic deficits, particularly those consistent with spinal cord compression: MRI or CT myelography, done as soon as possible
- Possible infection: WBC count, ESR, imaging (usually MRI or CT), and culture of infected tissue

- Possible cancer: CT or MRI and possibly biopsy
- Possible aneurysm: CT, angiography, or sometimes ultrasonography
- Possible aortic dissection: Angiography, CT, or MRI
- Symptoms that are disabling or that persist > 6 wk: Imaging (usually MRI or CT) and, if infection is suspected, WBC count and ESR
- Other extraspinal disorders: Testing as appropriate (eg, chest x-ray for pulmonary disorders, urinalysis for urinary tract disorders)

Treatment

Underlying disorders are treated.

Acute musculoskeletal pain (with or without radiculopathy) is treated with

- Analgesics
- Heat and cold
- Early mobilization followed by stabilization exercises

Acetaminophen or NSAIDs are the initial choice of analgesics, but opioids may be necessary for severe pain. Adequate analgesia is important immediately after acute injury to help limit the cycle of pain and spasm.

Acute muscle spasms may also be relieved by cold or heat. Cold is usually preferred to heat during the first 2 days after an injury. Ice and cold packs should not be applied directly to the skin. They should be enclosed (eg, in plastic) and placed over a towel or cloth. The ice is removed after 20 min, then later reapplied for 20 min over a period of 60 to 90 min. This process can be repeated several times during the first 24 h. Heat, using a heating pad, can be applied for the same periods of time. Because the skin on the back may be insensitive to heat, heating pads must be used cautiously to prevent burns. Patients are advised not to use a heating pad at bedtime to avoid prolonged exposure due to falling asleep with the pad still on their back. Diathermy may help reduce muscle spasm and pain after the acute stage.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial. Benefits of these drugs should be weighed against their CNS and other adverse effects, particularly in elderly patients, who may have more severe adverse effects.

Although a brief initial period (eg, 1 to 2 days) of decreased activity is sometimes needed for comfort, prolonged bed rest, spinal traction, and corsets are not beneficial. Patients with severe torticollis may benefit from a cervical collar and contour pillow until pain is relieved and they can participate in a stabilization program.

Spinal manipulation may help relieve pain caused by muscle spasm or an acute neck or back injury; however, some forms of manipulation may have risks for patients with disk disorders or osteoporosis.

When acute pain decreases enough that motion is possible, a lumbar stabilization program is begun. This program includes exercises that strengthen abdominal and low back muscles plus instruction in work posture; the aim is to strengthen the supporting structures of the back and reduce the likelihood of the condition becoming chronic or recurrent.

Clinicians should reassure patients with acute nonspecific musculoskeletal back pain that the prognosis is good and that activity and exercise are safe even when they cause some discomfort. Clinicians should be thorough, kind, firm, and nonjudgmental. If depression or secondary gain persists for several months,

psychologic evaluation should be considered.

Geriatrics Essentials

Low back pain affects 50% of adults > 60.

Abdominal aortic aneurysm (and CT or ultrasonography to detect it) should be considered in elderly patients with atraumatic low back pain, even if no physical findings suggest this diagnosis.

Imaging of the spine may be appropriate for elderly patients (eg, to rule out cancer) even when the cause appears to be uncomplicated musculoskeletal back pain.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial; anticholinergic, CNS, and other adverse effects may outweigh potential benefits in elderly patients.

Key Points

- Most neck and back pain is caused by mechanical spinal disorders, usually nonspecific, self-limited musculoskeletal derangements.
- Most mechanical disorders are treated with analgesics, early mobilization, and exercises; prolonged bed rest and immobilization are avoided.
- Back pain is often multifactorial, making diagnosis difficult.
- Serious spinal or extraspinal disorders are unusual causes.
- Red flag findings often indicate a serious disorder and the need for testing.
- Patients with segmental neurologic deficits suggesting spinal cord compression require MRI or CT myelography as soon as possible.
- Normal spinal cord function during physical examination is best confirmed by tests of sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex).
- Pain not worsened by movement is often extraspinal, particularly if no vertebral or paravertebral tenderness is detected.
- Abdominal aortic aneurysm should be considered in any elderly patient with low back pain, even if no physical findings suggest this diagnosis.

Spasmodic Torticollis

Spasmodic torticollis is characterized by involuntary tonic contractions or intermittent spasms of neck muscles. The cause is unknown. Diagnosis is clinical. Treatment can include physical therapy, drugs, and selective denervation of neck muscles with surgery or locally injected botulinum toxin.

In torticollis, contraction of the neck muscles causes the neck to turn from its usual position. It is the most common dystonia (see p. 1760).

Spasmodic (or adult-onset) torticollis is usually idiopathic. About 5% of patients with spasmodic torticollis have a family history. One third of these patients have other dystonias (eg, eyelids, face, jaw, hand). Torticollis can also be congenital or secondary to other conditions such as lesions of the brain stem and basal ganglia.

Symptoms and Signs

Symptoms may begin at any age but usually begin between age 20 and 60, with a peak between age 30 and 50.

Symptoms usually begin gradually but may begin suddenly. Painful tonic contractions or intermittent spasms of the sternocleidomastoid, trapezius, and other neck muscles occur, usually unilaterally, and result in abnormal head position. Sternocleidomastoid muscle contraction causes the head to rotate to the opposite side and the neck to flex laterally to the same side. Rotation may involve any plane but almost always has a horizontal component. Besides rotational tilting (torticollis), the head can tilt laterally (laterocollis), forward (anterocollis), or backward (retrocollis). During sleep, muscle spasms disappear.

Spasmodic torticollis ranges from mild to severe. Usually, it progresses slowly for 1 to 5 yr, then plateaus. About 10 to 20% of patients recover spontaneously within 5 yr of onset (usually in milder cases with younger age onset). However, it may persist for life and can result in restricted movement and postural deformity.

Diagnosis

• Clinical evaluation

The diagnosis is based on characteristic symptoms and signs and exclusion of alternative diagnoses, such as the following:

• Tardive dyskinesia can cause torticollis but can usually be distinguished by a history of chronic antipsychotic use and involuntary movements in muscles outside of the neck.

• Basal ganglia disease and occasionally CNS infections can cause movement disorders but usually also involve other muscles. Also, CNS infections are usually acute and cause other symptoms.

• Neck infections or tumors are usually differentiated by features of the primary process.

• Antipsychotics and other drugs can cause acute torticollis, but the symptoms usually develop in hours and resolve within days.

Treatment

• Physical measures

• Sometimes botulinum toxin or oral drugs

Spasms can sometimes be temporarily inhibited by physical therapy and massage, including sensory biofeedback techniques (slight tactile pressure to the jaw on the same side as head rotation) and any light touch.

Injections of botulinum toxin type A into the dystonic muscles can reduce painful spasms for 1 to 3 mo in about 70% of patients, restoring a more neutral position of the head. However, this treatment can lose effectiveness with repeated injections because antibodies develop against the toxin. Drugs can usually relieve pain, but they suppress dystonic movements in only about 25 to 33% of patients. Anticholinergics such as trihexyphenidyl 10 to 25 mg po once/day or bid may help, but adverse effects may limit their use; benzodiazepines (particularly clonazepam 0.5 mg po bid) and baclofen and carbamazepine may help. All drugs should be started in low doses. Doses should be increased until symptoms are controlled or intolerable adverse effects (particularly likely in the elderly) develop.

Surgery is controversial. The most successful surgical approach selectively severs nerves to affected neck muscles, permanently weakening or paralyzing them. Results are favorable when the procedure is done at centers with extensive experience.

Rarely, an emotional problem contributes to spasmodic torticollis; psychiatric treatment is indicated.

Psychiatric prognosis is best if symptom onset coincided with exogenous stress.

Sciatica

Sciatica is pain along the sciatic nerve. It usually results from compression of nerve roots in the lower back. Common causes include intervertebral disk herniation, osteophytes, and narrowing of the spinal canal (spinal stenosis). Symptoms include pain radiating from the buttocks down the leg. Diagnosis sometimes involves MRI or CT. Electromyography and nerve conduction studies can identify the affected level. Treatment includes symptomatic measures and sometimes surgery, particularly if there is a neurologic deficit.

Etiology

Sciatica is typically caused by nerve root compression, usually due to intervertebral disk herniation (see p. 1810), bony irregularities (eg, osteoarthritic osteophytes, spondylolisthesis), or, much less often, intraspinal tumor or abscess. Compression may occur within the spinal canal or intervertebral foramen. The nerves can also be compressed outside the vertebral column, in the pelvis or buttocks. L5-S1, L4-L5, and L3-L4 nerve roots are most often affected (see Table 186-1 on p. 1805).

Symptoms and Signs

Pain radiates along the course of the sciatic nerve, most often down the buttocks and posterior aspect of the leg to below the knee. The pain is typically burning, lancinating, or stabbing. It may occur with or without low back pain. The Valsalva maneuver or coughing may worsen pain due to disk herniation. Patients may complain of numbness and sometimes weakness in the affected leg.

Nerve root compression can cause sensory, motor, or, the most objective finding, reflex deficits see p. 1810). L5-S1 disk herniation may affect the ankle jerk reflex; L3-L4 herniation may affect the knee jerk. Straight leg raising may cause pain that radiates down the leg when the leg is raised above 60° and sometimes less. This finding is sensitive for sciatica; pain radiating down the affected leg when the contralateral leg is lifted (crossed straight leg raising) is more specific for sciatica.

Diagnosis

• Clinical evaluation

• Sometimes MRI, electrodiagnostic studies, or both

Sciatica is suspected based on the characteristic pain. If it is suspected, strength, reflexes, and sensation should be tested. If there are neurologic deficits or if symptoms persist for > 6 wk, imaging and electrodiagnostic studies should be done. Structural abnormalities causing sciatica (including spinal stenosis) are most accurately diagnosed by MRI or CT. Electrodiagnostic studies can confirm the presence and degree of nerve root compression and can exclude conditions that may mimic sciatica, such as polyneuropathy. These studies may help determine whether the lesion involves single or multiple nerve levels and whether the clinical findings correlate with MRI abnormalities (especially valuable before surgery). However, abnormalities may not be evident on electrodiagnostic studies for up to a few weeks after symptoms begin.

Treatment

• Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain

• Surgery for severe cases

Acute pain relief can come from 24 to 48 h of bed rest in a recumbent position with the head of the bed elevated about 30° (semi-Fowler's position). Measures used to treat low back pain, including nonopioid analgesics (eg, NSAIDs, acetaminophen), can be tried for up to 6 wk. Drugs that decrease neuropathic

pain (see p. 1633), such as gabapentin or other anticonvulsants or low-dose tricyclic antidepressants (no tricyclic is superior to another), may relieve symptoms. Gabapentin 100 to 300 mg po at bedtime is used initially, but doses typically have to be much higher, up to 3600 mg/day. As with all sedating drugs, care should be taken in the elderly, patients at risk of falls, and those with arrhythmias.

Muscle spasm may be relieved with therapeutic heat or cold (see p. 3459), and physical therapy may be useful. Whether corticosteroids should be used to treat acute radicular pain is controversial. Given epidurally, corticosteroids may accelerate pain relief, but they probably should not be used unless pain is severe or persistent.

Surgery is indicated only for unequivocal disk herniation plus one of the following:

- Muscular weakness
- Progressive neurologic deficit
- Intolerable, intractable pain that interferes with job or personal functions in an emotionally stable patient and that has not lessened after 6 wk of conservative treatment

Some of these patients benefit from epidural corticosteroids instead of surgery.

Classic diskectomy with limited laminotomy for intervertebral disk herniation is the standard procedure. If herniation is localized, microdiskectomy may be done; with it, the skin incision and laminotomy can be smaller. Chemonucleolysis, using intradiskal injection of chymopapain, is no longer used.

Predictors of poor surgical outcome include

- Prominent psychiatric factors
- Persistence of symptoms for > 6 mo
- Heavy manual labor
- Prominence of back pain (nonradicular)
- Secondary gain (ie, litigation and compensability)

Lumbar Spinal Stenosis

Lumbar spinal stenosis (LSS) is narrowing of the lumbar spinal canal, which puts pressure on the sciatic nerve roots (or sometimes the cord) before their exit from the foramina. It causes positional back pain, symptoms of nerve root compression, and lower-extremity pain during walking or weight bearing.

Spinal stenosis can be congenital or acquired. It may involve the cervical or lumbar spine. Acquired LSS is a common cause of sciatica in middle-aged or elderly patients. The most common causes of LSS are osteoarthritis, degenerative disk disorders, and spondylolisthesis with compression of the cauda equina. Other causes include Paget's disease of bone, RA, and ankylosing spondylitis.

Symptoms and Signs

Pain occurs in the buttocks, thighs, or calves during walking, running, climbing stairs, or even standing. The pain is not relieved by standing still but by flexing the back or by sitting (although paresthesias may continue). Walking up hills is less painful than walking down because the back is slightly flexed. Patients may have pain, paresthesias, weakness, and diminished reflexes in the affected nerve root distribution. Rarely, spinal cord compression may cause cauda equina syndrome (see p. 1806).

Diagnosis

• Clinical evaluation

• Sometimes MRI, electrodiagnostic studies, or both

Spinal stenosis is suspected based on characteristic symptoms. Diagnostic tests are the same as for sciatica (see p. 383). Calf symptoms may simulate those of intermittent claudication. Claudication can be differentiated by relief with rest (not position change), skin atrophy, and abnormalities in pulses, capillary refill, and vascular tests.

Treatment

• Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain

• Surgery for severe cases

Conservative treatments and indications for surgery are similar to those for sciatica. For advanced spinal stenosis, surgery involves decompression of nerve root entrapment by vertebral canal and foraminal encroachments, which sometimes requires laminectomy at 2 or 3 levels plus foraminotomies.

Spinal stability must be preserved. Spinal fusion is indicated if there is instability or severe, well-localized arthritic changes in 1 or 2 vertebral interspaces.

Nontraumatic Subluxation

Spinal dislocation and subluxation (partial dislocation) are usually due to trauma. For example, atlantoaxial subluxation and spondylolisthesis can result from obvious major trauma, such as a high-speed deceleration injury. However, these disorders can occur with minimal, unrecognized, or no trauma. Rarely, cervical disk disorders can cause nontraumatic spinal subluxation.

Atlantoaxial Subluxation

(C1-C2 Subluxation)

Atlantoaxial subluxation is misalignment of the 1st and 2nd cervical vertebrae, which may occur only with neck flexion.

Atlantoaxial subluxation can result from major trauma or can occur without trauma in patients with RA, juvenile RA, or ankylosing spondylitis.

Atlantoaxial subluxation is usually asymptomatic but may cause vague neck pain, occipital headache, or occasionally intermittent (and potentially fatal) cervical spinal cord compression.

Diagnosis

• Plain x-rays

• MRI if cord compression suspected

It is usually diagnosed with plain cervical x-rays; however, flexion views may be required to show intermittent subluxation. Views during flexion, done by the patient, show dynamic instability of the entire cervical spine. If x-rays are normal and subluxation is still suspected, MRI, which is more sensitive, should be done. MRI also provides the most sensitive evaluation of spinal cord compression and is done immediately if cord compression is suspected.

Treatment

Indications for treatment include pain, neurologic deficits, and potential spinal instability. Treatment includes symptomatic measures and cervical immobilization, usually beginning with a rigid cervical collar. Surgery may be needed to stabilize the spine.

Spondylolisthesis

Spondylolisthesis is subluxation of lumbar vertebrae, usually occurring during adolescence. It usually results from a congenital defect in the pars interarticularis (spondylolysis).

Spondylolisthesis is usually fixed. It usually involves the L3-L4, L4-L5, or L5-S1 vertebrae. Spondylolisthesis often occurs in adolescents or young adults who are athletes and who have had only minimal trauma; the cause is a lumbar vertebra weakened by a congenital defect in the pars interarticularis. This defect is easily fractured; separation of the fracture fragments causes the subluxation. Spondylolisthesis can also occur with minimal trauma in patients who are > 60 and have osteoarthritis. If mild to moderate (subluxation of ≤ 50%), spondylolisthesis, particularly in the young, may cause little or no pain. Spondylolisthesis can predispose to later development of spinal stenosis. If due to major trauma, spondylolisthesis can cause spinal cord compression or other neurologic deficits (see p. 1810); these deficits rarely occur.

Spondylolisthesis is staged according to the degree of subluxation of adjacent vertebral bodies:

- Stage I: 0 to 25%
- Stage II: 25 to 50%
- Stage III: 50 to 75%
- Stage IV: 75 to 100%

Spondylolisthesis is evident on plain lumbar x-rays. The lateral view is usually used for staging.

Treatment is usually symptomatic.

Chapter 43. Hand Disorders

Introduction

Common hand disorders include a variety of deformities, ganglia, infections, Kienbock's disease, nerve compression syndromes, noninfectious tenosynovitis, and osteoarthritis. Complex regional pain syndrome (reflex sympathetic dystrophy) is discussed on p. 1633, and hand injuries are discussed in Ch. 323.

Evaluation

History and physical examination findings are often diagnostic in hand disorders.

History: The history should include information about the trauma or other events that may be associated with symptoms. The presence and duration of deformity and difficulty with motion are noted. The presence, duration, severity, and factors that exacerbate or relieve pain are elicited. Associated symptoms, such as fever, swelling, rashes, Raynaud's syndrome (see p. 2221), paresthesias, and weakness, are also recorded.

Physical examination: Examination should include inspection for redness, swelling, or deformity and palpation for tenderness. Active range of motion should be tested for any possible tendon injury. Passive range of motion can assess whether specific motions aggravate pain. Sensation is tested most accurately by 2-point discrimination, using 2 ends of a paper clip. Motor function testing involves muscles innervated by the radial, median, and ulnar nerves. Vascular examination should include evaluation of capillary refill, radial and ulnar pulses, and Allen's test (see p. 1856). Stress testing is helpful when specific ligament injuries are suspected (eg, ulnar collateral ligament in gamekeeper's thumb—see p. 3216). Provocative testing can aid in the diagnosis of tenosynovitis and nerve compression syndromes.

Laboratory testing: Laboratory testing has a limited role. Plain x-rays and MRI are helpful for injuries, arthritis, and Kienbock's disease or to rule out hidden foreign bodies that could be sources of infections. Nerve conduction testing can help diagnose nerve compression syndromes. Bone scans may assist in diagnosing occult fractures and reflex sympathetic dystrophy.

Deformities

Deformities can result from generalized disorders (eg, arthritis) or dislocations, fractures, and other localized disorders. Most nontraumatic localized disorders can be diagnosed by physical examination. Once a hand deformity becomes firmly established, it cannot be significantly altered by splinting, exercise, or other nonsurgical treatment.

Mallet Finger

Mallet finger is a flexion deformity of the distal interphalangeal joint preventing extension (see Fig. 43-1).

This deformity results from an extensor tendon rupture or an avulsion fracture of the distal phalanx. The deformity may not be obvious immediately after injury, but on examination, patients cannot fully extend the distal interphalangeal (DIP) joint. Closed injuries may be treated with splinting that holds the DIP joint in extension and leaves the proximal interphalangeal (PIP) joint free. Avulsion fractures are usually united after 6 wk, but pure tendon injuries require an additional 2 to 4 wk of nighttime splinting. Surgery may be required if there is a fracture that involves a large proportion of the articular surface or if the joint is subluxated.

Swan-Neck Deformity

A swan-neck deformity consists of hyperextension of the PIP joint, flexion of the DIP joint, and sometimes flexion of the metacarpophalangeal joint (see Fig. 43-2).

Although characteristic in RA, swan-neck deformity has several causes, including untreated mallet finger, laxity of the ligaments of the volar aspect of the PIP joint, spasticity of intrinsic hand muscles, rupture of the flexor tendon of the PIP joint, and malunion of a fracture of the middle or proximal phalanx. The inability to correct or compensate for hyperextension of the PIP joint makes finger closure impossible and can cause severe disability. Treatment is aimed at correcting the underlying disorder when possible (eg, correcting the mallet finger or any bony malalignment, releasing spastic intrinsic muscles). Mild deformities in patients with RA may be treated with a functional ring splint.

True swan-neck deformity does not affect the thumb, which has only one interphalangeal

[Fig. 43-1. Mallet finger.]

[Fig. 43-2. Boutonniere and swan-neck deformities.]

joint. However, severe hyperextension of the interphalangeal joint of the thumb with flexion of the metacarpophalangeal (MCP) joint can occur; this is called a duck bill, Z (zigzag) type, or 90°-angle deformity. With simultaneous thumb instability, pinch is greatly impaired. This deformity can usually be corrected by interphalangeal arthrodesis along with tendon reconstruction at the MCP joint.

Boutonniere Deformity

(Buttonhole Deformity)

A boutonniere deformity consists of flexion of the PIP joint accompanied by hyperextension of the DIP joint (see Fig. 43-2).

This deformity can result from tendon laceration, dislocation, fracture, osteoarthritis, or RA. Classically, the deformity is caused by disruption of the central slip attachment of the extensor tendon to the base of the middle phalanx, allowing the proximal phalanx to protrude ("buttonhole") between the lateral bands of the extensor tendon. Initial treatment consists of splinting, but it must occur before scarring and fixed deformities develop. Surgical reconstruction often cannot restore normal motion but may decrease the deformity and improve hand function.

Dupuytren's Contracture

(Palmar Fibromatosis)

Dupuytren's contracture is progressive contracture of the palmar fascial bands, causing flexion deformities of the fingers.

Dupuytren's contracture is one of the more common hand deformities; the incidence is higher among men and increases after age 45. This autosomal dominant condition with variable penetrance may occur more commonly among patients with diabetes, alcoholism, or epilepsy. However, the specific factor that causes the palmar fascia to thicken and contract is unknown.

Symptoms and Signs

The earliest manifestation is usually a tender nodule in the palm, most often near the middle or ring finger; it gradually becomes painless. Next, a superficial cord forms and contracts the MCP joints and interphalangeal joints of the fingers. The hand eventually becomes arched. The disease is occasionally associated with fibrous thickening of the dorsum of the PIP joints (Garrod's pads), Peyronie's disease (penile fibromatosis) in about 7 to 10% of patients, and rarely nodules on the plantar surface of the feet (plantar fibromatosis). Other types of flexion deformities of the fingers can also occur in diabetes, systemic sclerosis, and chronic reflex sympathetic dystrophy, which need to be differentiated.

Treatment

• Corticosteroid injection (before contractures develop)

• Surgery for disabling contractures

Injection of a corticosteroid suspension into the nodule can relieve local tenderness if begun before contractures develop. If the hand cannot be placed flat on a table or, especially, when significant contracture develops at the PIP joints, surgery is usually indicated. Excision of the diseased fascia must be meticulous because it surrounds neurovascular bundles and tendons. Incomplete excision or new disease results in recurrent contracture, especially in patients who are young at disease onset or who have a family history, Garrod's pads, Peyronie's disease, or plantar foot involvement. Injectable collagenase may reverse some contractures, although this treatment is not yet in widespread clinical use.

Ganglia

(Ganglion Cysts)

Ganglia are cystic swellings occurring usually on the hands, especially on the dorsal aspect of the wrists. Aspiration or excision is indicated for symptomatic ganglia.

Ganglia constitute about 60% of chronic soft-tissue swellings affecting the hand and wrist. They usually develop spontaneously in adults aged 20 to 50, with a female:male preponderance of 3:1.

Etiology

The cause of most ganglia is unknown. The cystic structures are near or attached (often by a pedicle) to tendon sheaths and joint capsules. The wall of the ganglion is smooth, fibrous, and of variable thickness. The cyst is filled with clear gelatinous, sticky, or mucoid fluid of high viscosity. The fluid in the cyst is sometimes almost pure hyaluronic acid.

Most ganglia are isolated abnormalities. The dorsal wrist ganglion arises from the scapholunate joint and constitutes about 65% of ganglia of the wrist and hand. The volar wrist ganglion arises over the distal aspect of the radius and constitutes about 20 to 25% of ganglia. Flexor tendon sheath ganglia and mucous cysts (arising from dorsal distal interphalangeal joint) make up the remaining 10 to 15%. Ganglia may spontaneously regress.

Diagnosis

• Examination

Ganglia are evident on examination. Another type of ganglion on the dorsal wrist occurs in patients with RA; it is easily differentiated by its soft irregular appearance and association with proliferative rheumatoid extensor tenosynovitis.

Treatment

• Aspiration or excision if troublesome

Most ganglia do not require treatment. However, if the patient is disturbed by its appearance or if the ganglion is painful or tender, a single aspiration with a large-bore needle is effective in about 50% of patients. Attempting to rupture the ganglion by hitting it with a hard object risks local injury without likely benefit. Nonsurgical treatment fails in about 40 to 70% of patients, necessitating surgical excision. Recurrence rates after surgical removal are about 5 to 15%.

Infections

Common bacterial hand infections include paronychia (see p. 735), infected bite wounds, felon, palm abscess, and infectious flexor tenosynovitis. Herpetic whitlow is a viral hand infection. Infections often begin with constant, intense, throbbing pain and are usually diagnosed by physical examination. X-rays are taken in some infections (eg, bite wounds, infectious flexor tenosynovitis) to detect occult foreign

bodies but may not detect small or radiolucent objects.

Treatment

• Surgical measures and antibiotics

The increased incidence of community-acquired and nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) should be taken into consideration. Uncomplicated MRSA infections are best treated with incision and drainage. If there is a high incidence of MRSA and the infection is severe, hospitalization and vancomycin or daptomycin (for IV therapy) are recommended, as is consultation with an infectious disease specialist. For outpatients, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid (for oral therapy) can be given. Once culture and sensitivity results rule out MRSA, nafcillin, cloxacillin, dicloxacillin, or a 1st- or 2nd-generation cephalosporin can be given.

Infected Bite Wounds

A small puncture wound, particularly from a human or cat bite, may involve significant injury to the tendon, joint capsule, or articular cartilage. The most common cause of human bites is a tooth-induced injury to the metacar-pophalangeal

[
Fig. 43-3. Splint in the functional position (20° wrist extension, 60° metacarpophalangeal joint flexion, slight interphalangeal joint flexion).]

joint as a result of a punch to the mouth (clenched fist injury). The oral flora of humans includes *Eikenella corrodens*, staphylococci, streptococci, and anaerobes. Patients with clenched fist injuries tend to wait hours or days after the wound occurs before seeking medical attention, which increases the severity of the infection. Animal bites usually contain multiple potential pathogens, including *Pasteurella multocida* (particularly in cat bites), staphylococci, streptococci, and anaerobes. Serious complications include infectious arthritis and osteomyelitis.

Diagnosis

• Clinical evaluation

• X-rays

Erythema and pain localized to the bite suggest infection. Tenderness along the course of a tendon suggests spread to the tendon sheath. Pain worsening significantly with motion suggests infection of a joint or tendon sheath.

The diagnosis is clinical, but if the skin is broken, x-rays should be taken to detect fracture or teeth or other foreign bodies that could be a nidus of continuing infection.

Treatment

• Debridement

• Antibiotics

Treatment includes surgical debridement, with the wound left open, and antibiotics. For outpatient treatment, empiric antibiotics usually include monotherapy with amoxicillin/clavulanate 500 mg po tid or combined therapy with a penicillin 500 mg po qid (for *E. corrodens*, *P. multocida*, streptococci, and anaerobes) plus a cephalosporin (eg, cephalexin 500 mg po qid) or semisynthetic penicillin (eg, dicloxacillin 500 mg po qid) for staphylococci. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin. If the patient is allergic to penicillin, clindamycin 300 mg po q 6 h can be used. The hand should be splinted in the functional position and elevated (see Fig. 43-3).

Noninfected bites may require surgical debridement and prophylaxis with 50% of the dose of antibiotic used to treat infected wounds.

Felon

A felon is an infection of the pulp space of the fingertip, usually with staphylococci and streptococci.

The most common site is the distal pulp, which may be involved centrally, laterally, or apically. The septa between pulp spaces ordinarily limit the spread of infection, resulting in an abscess, which creates pressure and necrosis of adjacent tissues. The underlying bone, joint, or flexor tendons may become infected. There is intense throbbing pain and a swollen, warm, extremely tender pulp. Treatment involves prompt incision and drainage (using a mid-lateral incision that adequately divides the fibrous septa) and oral antibiotic therapy. Empiric treatment with a cephalosporin is adequate. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Palm Abscess

A palm abscess is a purulent infection of deep spaces in the palm, typically with staphylococci or streptococci.

Palm abscesses can include collar-button abscesses, thenar space abscesses, and midpalmar space abscesses. An abscess can occur in any of the deep palmar compartments and spread between the metacarpals, from the midpalmar space to the dorsum, manifesting as an infection on the dorsum of the hand. Intense throbbing pain occurs with swelling and severe tenderness on palpation. X-rays should be taken to detect occult foreign bodies. Incision and drainage in the operating room (with cultures), with care to avoid the many important anatomic structures, and antibiotics (eg, a cephalosporin) are required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Infectious Flexor Tenosynovitis

Infectious flexor tenosynovitis is an acute infection within the flexor tendon sheath.

The usual cause is a penetration and bacterial inoculation of the sheath.

Diagnosis

• Kanavel's signs

• X-rays

Infectious flexor tenosynovitis causes Kanavel's signs:

• Flexed resting position of the digit

• Fusiform swelling

• Tenderness along the flexor tendon sheath

• Pain with passive extension of the digit

X-rays should be taken to detect occult foreign bodies. Acute calcific tendinitis and RA can restrict motion and cause pain in the tendon sheath but can usually be differentiated from infectious flexor tenosynovitis by a more gradual onset and the absence of some of Kanavel's signs. Disseminated gonococcal infection can cause tenosynovitis but often involves multiple joints (particularly those of the wrists, fingers, ankles,

and toes), and patients often have recent fever, rash, polyarthralgias, and often risk factors for an STD. Infection of the tendon sheath may involve atypical mycobacteria, but these infections are usually indolent and chronic.

Treatment

• Surgical drainage and antibiotics

Treatment is surgical drainage (eg, irrigation of the tendon sheath by inserting a cannula into one end and allowing the irrigating fluid to pass along the tendon sheath to the other end). Antibiotic therapy (beginning empirically with a cephalosporin) and cultures are also required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Herpetic Whitlow

Herpetic whitlow is a cutaneous infection of the distal aspect of the finger caused by herpes simplex virus.

Herpetic whitlow may cause intense pain. The digital pulp is not very tense. Vesicles develop on the volar or dorsal distal phalanx but often not until 2 to 3 days after pain begins. The intense pain can simulate a felon, but herpetic whitlow can usually be differentiated by the absence of tenseness in the pulp or the presence of vesicles. The condition is self-limited but may recur. Incision and drainage are contraindicated. Topical acyclovir 5% can shorten the duration of a first episode. Oral acyclovir (800 mg po bid) may prevent recurrences if given immediately after onset of recurrent symptoms. Open or draining vesicles should be covered to prevent transmission.

Kienbock's Disease

Kienbock's disease is avascular necrosis of the lunate bone.

Kienbock's disease occurs most commonly in the dominant hand of men aged 20 to 45, usually in workers doing heavy manual labor. Overall, Kienbock's disease is relatively rare. Its cause is unknown. The lunate can eventually collapse and cause fixed rotation of the scaphoid and subsequent degeneration of the carpal joints.

Symptoms and Signs

Symptoms generally start with insidious onset of wrist pain, localized to the region of the lunate carpal bone; patients have no recollection of trauma. Kienbock's disease is bilateral in 10% of cases. There is localized tenderness in the lunate bone.

Diagnosis

• Imaging

MRI and CT are the most sensitive; plain x-rays show abnormalities later, usually beginning with a sclerotic lunate, then later cystic changes, fragmentation, and collapse.

Treatment

• Surgical procedures

Treatment is aimed at relieving pressure on the lunate by surgically shortening the radius or lengthening the ulna. Alternative treatments attempt to revascularize the lunate (eg, implanting a blood vessel or bone graft on a vascular pedicle). Salvage procedures (eg, proximal row carpectomy or intercarpal fusions) may help preserve some wrist function if the carpal joints have degenerated. Total wrist arthrodesis can be done as a last resort to relieve pain. Nonsurgical treatments are not effective.

Nerve Compression Syndromes

Common nerve compression syndromes include carpal tunnel syndrome, cubital tunnel syndrome, and radial tunnel syndrome. Compression of nerves often causes paresthesias; these paresthesias can often be reproduced by tapping the compressed nerve, usually with the examiner's fingertip (Tinel's sign). Suspected nerve compression can be confirmed by testing nerve conduction velocity and distal latencies, which accurately measure motor and sensory nerve conduction. Initial treatment is usually conservative, but surgical decompression may be necessary if conservative measures fail or if there are significant motor or sensory deficits.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is compression of the median nerve as it passes through the carpal tunnel in the wrist. Symptoms include pain and paresthesias in the median nerve distribution. Diagnosis is suggested by symptoms and signs and is confirmed by nerve conduction velocity testing. Treatments include ergonomic improvements, analgesia, splinting, and sometimes corticosteroid injection or surgery.

Carpal tunnel syndrome is very common and most often occurs in women aged 30 to 50. Risk factors include RA or other wrist arthritis (sometimes the presenting manifestation), diabetes mellitus, hypothyroidism, acromegaly, amyloidosis, hemodialysis, and pregnancy-induced edema in the carpal tunnel. Activities or jobs that require repetitive flexion and extension of the wrist may contribute, but rarely. Most cases are idiopathic.

Symptoms and Signs

Symptoms include pain of the hand and wrist associated with tingling and numbness, classically distributed along the median nerve (the palmar side of the thumb, the index and middle fingers, and the radial half of the ring finger) but possibly involving the entire hand. Typically, the patient wakes at night with burning or aching pain and with numbness and tingling and shakes the hand to obtain relief and restore sensation. Thenar atrophy and weakness of thumb opposition and abduction may develop late.

Diagnosis

• Clinical evaluation

• Nerve conduction testing

The diagnosis is strongly suggested by Tinel's sign, in which median nerve paresthesias are reproduced by tapping at the volar surface of the wrist over the site of the median nerve in the carpal tunnel. Reproduction of tingling with wrist flexion (Phalen's sign) is also suggestive. However, clinical differentiation from other types of peripheral neuropathy may sometimes be difficult. If symptoms are severe or the diagnosis is uncertain, nerve conduction testing should be done on the affected arm for diagnosis and to exclude a more proximal neuropathy.

Treatment

• Splinting

• Sometimes corticosteroid/anesthetic injection

• Sometimes surgical decompression

Changing the position of computer keyboards and making other ergonomic corrections may occasionally provide relief. Otherwise, treatment includes wearing a lightweight neutral wrist splint (see Fig. 43-4), especially at night, and taking mild analgesics (eg, acetaminophen, NSAIDs). If these measures do not control symptoms, a mixture of a corticosteroid and an anesthetic (eg, 1.5 mL of a 4-

mg/mL dexamethasone solution mixed with 1.5 mL of 1% lidocaine) should be injected into the carpal tunnel at a site just ulnar to the palmaris longus tendon and proximal to the distal crease at the wrist. If bothersome symptoms persist or recur or if hand weakness and thenar wasting develop, the carpal tunnel can be surgically decompressed by using an open or endoscopic technique.

[Fig. 43-4. Neutral wrist splint.]

Cubital Tunnel Syndrome

(Ulnar Neuropathy)

Cubital tunnel syndrome is compression or traction of the ulnar nerve at the elbow.

The ulnar nerve is commonly irritated at the elbow or, rarely, the wrist. Cubital tunnel syndrome is most often caused by leaning on the elbow or by prolonged and excessive elbow flexion. It is less common than carpal tunnel syndrome. Baseball pitching (particularly sliders), which can injure the medial elbow ligaments, confers risk.

Symptoms and Signs

Symptoms include numbness and paresthesia along the ulnar nerve distribution (in the ring and little fingers and the ulnar aspect of the hand) and elbow pain. In advanced stages, weakness of the intrinsic muscles of the hand and the flexors of the ring and little fingers may develop. Weakness interferes with pinch between the thumb and index finger and with hand grip.

Diagnosis

• Clinical evaluation

• Sometimes nerve conduction studies

Diagnosis is often possible clinically. However, if clinical diagnosis is equivocal and when surgery is being considered, nerve conduction studies are done. Cubital tunnel syndrome is differentiated from ulnar nerve entrapment at the wrist (in Guyon's canal) by the presence of sensory deficits (on sensory testing or with Tinel's sign) over the ulnar dorsal hand and by the presence of ulnar nerve deficits proximal to the wrist on muscle testing or nerve conduction velocity testing.

Treatment

Treatment involves splinting at night, with the elbow extended at 45°, and use of an elbow pad during the day. Surgical decompression can help if conservative treatment fails.

Radial Tunnel Syndrome

(Posterior Interosseous Nerve Syndrome)

Radial tunnel syndrome is compression of the radial nerve in the proximal forearm.

Compression at the elbow can result from trauma, ganglia, lipomas, bone tumors, or radiocapitellar (elbow) synovitis.

Symptoms and Signs

Symptoms include lancinating pain in the dorsum of the forearm and lateral elbow. Pain is precipitated by attempted extension of the wrist and fingers and forearm supination. Sensory loss is rare because the radial nerve is principally a motor nerve at this level. This disorder is sometimes confused with backhand tennis elbow (lateral epicondylitis). When weakness of the extensor muscles is the primary finding, the condition is referred to as posterior interosseus nerve palsy.

Diagnosis

• Clinical evaluation

Lateral epicondylitis can cause similar tenderness around the lateral epicondyle but does not cause Tinel's sign or tenderness along the course of the radial nerve.

Treatment

• Splinting

Splinting allows avoidance of the forceful or repeated motion of supination or wrist dorsiflexion, reducing pressure on the nerve. If wristdrop or weakened digital extension develops, or conservative treatment fails to provide relief after 3 mo, surgical decompression may be needed.

Noninfectious Tenosynovitis

(See also p. 374.)

Although the digital flexor tendons and extensor pollicis brevis are commonly affected, tenosynovitis may involve any of the tendons in or around the hand.

Digital Flexor Tendinitis and Tenosynovitis

(Trigger Finger)

Digital flexor tendinitis and tenosynovitis are inflammation, sometimes with subsequent fibrosis, of tendons and tendon sheaths of the digits.

These conditions are idiopathic but are common among patients with RA or diabetes mellitus. Repetitive use of the hands (as may occur when using heavy gardening shears) may contribute. In diabetes, they often coexist with carpal tunnel syndrome and occasionally with fibrosis of the palmar fascia. Pathologic changes begin with a thickening or nodule within the tendon; when located at the site of the tight first annular pulley, the thickening or nodule blocks smooth extension or flexion of the finger. The finger may lock in flexion, or "trigger," suddenly extending with a snap.

Treatment

• Conservative measures

• Sometimes corticosteroid injection

Treatment of acute inflammation and pain includes splinting, moist heat, and anti-inflammatory doses of NSAIDs (see p. 335). If these measures fail, injection of a corticosteroid suspension into the flexor tendon sheath, along with splinting, may provide safe, rapid relief of pain and triggering. Operative release can be done if corticosteroid therapy fails.

De Quervain's Syndrome

(Washerwoman's Sprain)

De Quervain's syndrome is stenosing tenosynovitis of the short extensor (extensor pollicis brevis) and long abductor tendon (abductor pollicis longus) of the thumb within the first extensor compartment.

De Quervain's syndrome usually occurs after repetitive use (especially wringing) of the wrist, although it occasionally occurs in association with RA. The major symptom is aching pain at the wrist and thumb,

aggravated by motion. Tenderness can be elicited just proximal to the radial styloid process over the site of the involved tendon sheaths. Diagnosis is highly suggested by the Finkelstein test. The patient adducts the involved thumb into the palm and wraps the fingers over the thumb. The test is positive if gentle passive ulnar deviation of the wrist provokes severe pain at the affected tendon sheaths.

Treatment

• Corticosteroid injection

• Thumb spica splint

Rest, warm soaks, and NSAIDs may help in very mild cases. Local corticosteroid injections and a thumb spica splint help 70 to 80% of cases. Tendon rupture is a rare complication of injection and can be prevented by confining infiltration to the tendon sheath and avoiding injection of the corticosteroid into the tendon. Intratendinous location of the needle is likely if injection is met with moderate or severe resistance. Surgical release of the first extensor compartment is very effective when conservative therapy fails.

Osteoarthritis of the Hand

Hand involvement is extremely common in osteoarthritis.

Osteoarthritis affecting the hand may be asymptomatic enlargement of nodules at the proximal interphalangeal joint (Bouchard's nodules) or distal interphalangeal joint (Heberden's nodes) or angulation at these joints. Pain and stiffness of these joints and the base of the thumb are also common. The wrist usually is spared, and there is usually minimal or no metacarpophalangeal joint involvement unless the patient also has a metabolic disorder (eg, hemochromatosis). Differentiation of hand changes in osteoarthritis from those in RA is discussed in
Table 32-7 on p. 296.

Treatment

• Conservative measures

• Occasionally corticosteroid injection or surgery

Treatment is symptomatic with analgesics, appropriate rest, splinting, and occasionally corticosteroid injection as needed. Surgical procedures can help relieve pain and correct deformity for severe changes at the base of the thumb and, less commonly, for advanced degeneration of the interphalangeal joints.

Chapter 44. Foot and Ankle Disorders

Introduction

Most foot problems result from anatomic disorders or abnormal function of articular or extra-articular structures (see Fig. 44-1). Less commonly, foot problems reflect a systemic disorder (see Table 44-1).

In people with diabetes and people with peripheral vascular disease, careful examination of the feet, with evaluation of vascular sufficiency and neurologic integrity, should be done at least twice/yr. People with these diseases should examine their own feet at least once/day.

The feet are also common sites for corns and calluses (see p. 660) and infections by fungus (see Tinea Pedis on p. 708), bacteria (see p. 694), and viruses (see Warts on p. 715).

Table 44-2 lists foot and ankle disorders according to anatomic site.
Table 44-3 lists common causes of heel pain according to location.

Tibialis Posterior Tendinosis

Tibialis posterior tendinosis, degeneration of the tibialis posterior tendon, is the most common cause of pain behind the medial malleolus.

The posterior tibial tendon lies immediately behind the medial malleolus. Degeneration results from long-standing biomechanical problems, such as excessive pronation often in obese people. The tendon can also be involved by primary inflammatory disorders, such as RA or gout.

Symptoms and Signs

Early on, patients experience occasional pain behind the medial malleolus. Over time, the pain becomes severe, with painful swelling behind the medial malleolus. Normal standing, walking, and standing on the toes become difficult.

[**Fig. 44-1.** Bones of the foot.]

[**Table 44-1.** Foot Manifestations of Systemic Disorders]

Diagnosis

• MRI

Clinical findings suggest the diagnosis. Palpation of the tendon in an inverted-plantar flexed position usually elicits pain. Standing on the toes is usually painful and may not be possible if the tendon is ruptured. Pain and swelling behind the medial malleolus, especially with tibialis posterior tendon pain on

[**Table 44-2.** Common Foot and Ankle Disorders by Anatomic Site]

palpation, are highly suggestive. MRI or ultrasonography can confirm injury to the tendon and its extent.

Treatment

• Orthotics and braces or surgery

Complete rupture requires surgery if normal function is the goal. Surgery is especially important in young active patients with acute tears. Conservative therapy consists of mechanically off-loading the tendon by using orthotics and ankle braces. Corticosteroid injections exacerbate the degenerative process (see Sidebar 44-1). If the tendon is inflamed, rest and aggressive anti-inflammatory therapy are warranted.

Tarsal Tunnel Syndrome

(Posterior Tibial Nerve Neuralgia)

Tarsal tunnel syndrome is pain along the course of the posterior tibial nerve, usually resulting from nerve compression within the tarsal tunnel.

At the level of the ankle, the posterior tibial nerve passes through a fibro-osseous canal and divides into the medial and lateral plantar nerves. Tarsal tunnel syndrome refers to compression of the nerve within this canal, but the term has been loosely applied to neuralgia of the posterior tibial nerve resulting from any cause. Synovitis of the flexor tendons of the ankle caused by abnormal foot function, inflammatory arthritis (eg, RA), fracture, and ankle venous stasis edema are contributing factors. Patients with hypothyroidism may develop tarsal tunnel-like symptoms as a result of perineural mucin deposition.

Symptoms and Signs

Pain (occasionally burning and tingling) is usually retromalleolar and sometimes in the plantar medial heel and may extend along the plantar surface as far as the toes. Although the pain is worse during standing and walking, pain at rest may occur as the disorder progresses.

Diagnosis

• Examination and electrodiagnostic testing

Tapping or palpating the posterior tibial nerve below the medial malleolus at a site of compression or injury often causes distal tingling (Tinel's sign). While false-negative results on electrodiagnostic tests are somewhat common, a positive history combined with supportive physical findings and positive electrodiagnostic results makes the diagnosis of tarsal tunnel syndrome highly likely. The cause of any swelling near the nerve should be determined.

Treatment

• Foot inversion, injection, surgery, or a combination

Strapping the foot in a neutral or slightly inverted position or wearing an orthotic that keeps the foot inverted reduces nerve tension. Local infiltration of a mixture of an insoluble corticosteroid and an anesthetic may be effective if the cause is inflammation or fibrosis. Surgical decompression may be necessary to relieve suspected fibro-osseus compression with recalcitrant symptoms.

[Table 44-3. Disorders Associated with Heel Pain According to Location]

Metatarsalgia

Metatarsalgia is a general term for pain in the area of the metatarsophalangeal joints (ball of the foot). Most common causes include Freiberg's disease, interdigital nerve pain (Morton's neuroma), metatarsophalangeal joint pain, and sesamoiditis.

Freiberg's Disease

Freiberg's disease is avascular necrosis of the metatarsal head.

Freiberg's disease is caused by microtrauma at the metaphysis and growth plate. Avascular necrosis flattens the metatarsal head. The 2nd metatarsal head is most often affected. Freiberg's disease occurs more frequently among pubertal females and among people who have a short 1st metatarsal bone, which increases stress on the 2nd metatarsal head and joint.

Symptoms and Signs

The pain is most pronounced in the forefoot at the metatarsal head with weight bearing, particularly when pushing off or when wearing high-heeled footwear. The metatarsophalangeal joint may also be swollen and have limited and painful passive range of motion.

Diagnosis

• X-rays

The diagnosis is confirmed with x-rays. Typically, the head of the 2nd metatarsal is widened and flattened, and the metatarsal joint is sclerotic and irregular.

Sidebar 44-1 Considerations for Using Corticosteroid Injections

Corticosteroid injections should be used judiciously to avoid adverse effects. Injectable corticosteroids should be reserved for inflammation, which is not present in most foot disorders. Because the tarsus, ankle, retrocalcaneal space, and dorsum of the toes have little connective tissue between the skin and underlying bone, injection of insoluble corticosteroids into these structures may cause depigmentation, atrophy, or ulceration, especially in elderly patients with peripheral arterial disease.

Insoluble corticosteroids can be given deeply rather than superficially with greater safety (eg, in the heel pad, tarsal canal, or metatarsal interspaces). The foot should be immobilized for a few days after tendon sheaths are injected. Unusual resistance to injection suggests injection into a tendon. Repeated injection into a tendon should be avoided because the tendon may weaken (partially tear), predisposing to subsequent rupture.

Treatment

• Immobilization and weight unloading if acute, then modification of footwear

Corticosteroid injections and immobilization may help to alleviate acutely painful flare-ups. Long-term management may require orthoses with metatarsal bars and low-heeled footwear to reduce stress on the 2nd metatarsal head and joint. Corticosteroid injections can be tried, and, rarely, surgical excision of the metatarsal head may be necessary to relieve recalcitrant pain.

Interdigital Nerve Pain

(Morton's Neuroma/Neuralgia)

Interdigital nerve irritation (neuralgia) or persistent benign enlargement of the perineurium (neuroma) can cause pain, which may be nonspecific, burning, or lancinating, or a foreign body sensation. Diagnosis is usually clinical. Treatment may involve correction of footwear, local injection, or sometimes surgical excision.

The interdigital nerves of the foot travel beneath and between the metatarsals, extending distally to innervate the toes. Neuralgia of the interdigital nerve along its distal innervation near the ball of the foot develops primarily as a result of improper or constrictive footwear or, less commonly, nerve traction resulting from abnormal foot structure. As a result of chronic repetitive trauma, a benign thickening of the nerve develops (Morton's neuroma).

Symptoms and Signs

Interdigital neuralgia is characterized by pain around the metatarsal heads or the toes. Early interdigital neuralgia often causes an occasional mild ache or discomfort in the ball of the foot, usually when wearing a specific shoe, such as those that are too narrow at the front. Neuralgia is usually unilateral. As the condition progresses, the nerve thickens. The pain becomes worse, often with a burning or lancinating

quality or paresthesias. In time, patients are unable to wear most shoes. While walking, patients often falsely sense a pebble in their shoes, which they take off for relief. Neuroma most frequently affects the 3rd interspace. Only slightly less common is involvement of the 2nd interspace. Sometimes both interspaces or feet are involved simultaneously.

Diagnosis

• Clinical evaluation

The symptoms are often specific, and the diagnosis is confirmed by tenderness on plantar palpation of the interdigital space and reproduction of the radiating burning pain by squeezing the space. Although MRI does not usually confirm neuroma, it may be useful to rule out other interspace lesions or arthritis causing similar symptoms.

Treatment

• Modification of footwear and injection

Neuralgia of recent onset usually resolves quickly with properly fitting shoes and insoles or with local anesthetic injection. In contrast, neuromas may require one or more perineural infiltrations of long-acting corticosteroids with a local anesthetic. Injection is at a 45° angle to the foot, into the interspace at the level of the dorsal aspect of the metatarsophalangeal joints. An appropriate orthotic often relieves symptoms. If conservative therapy is ineffective, excision often brings complete relief. However, another neuroma occasionally develops at the site of nerve excision (amputation or stump neuroma).

Metatarsophalangeal Joint Pain

Metatarsophalangeal joint pain usually results from tissue changes due to aberrant foot biomechanics. Symptoms and signs include pain with walking and tenderness. Diagnosis is clinical; however, infection or systemic rheumatic diseases (eg, RA) may need to be excluded by testing. Treatment includes orthotics, sometimes local injection, and occasionally surgery.

Metatarsophalangeal joint pain most commonly results from misalignment of the joint surfaces with altered foot biomechanics, causing joint subluxations, capsular impingement, and joint cartilage destruction (osteoarthrosis). Misaligned joints may cause synovial impingement, with minimal if any heat and swelling (osteoarthritic synovitis).

Metatarsophalangeal joint subluxations also occur as a result of inflammatory arthropathy, particularly RA. Inflammatory synovitis and interosseous muscle atrophy in RA lead to subluxations of the lesser metatarsophalangeal joints as well, resulting in hammer toe deformities. Consequently, the metatarsal fat pad, which usually cushions the stress between the metatarsals and interdigital nerves during walking, moves distally under the toes; interdigital neuralgia or Morton's neuroma may result. To compensate for the loss of cushioning, adventitial calluses and bursae may develop.

Metatarsophalangeal joint pain may also result from functional hallux limitus, which limits passive and active joint motion and usually occurs at the 1st metatarsophalangeal joint. Patients usually have foot pronation disorders that result in elevation of the 1st ray with lowering of the medial longitudinal arch during weight bearing. As a result of the 1st ray elevation, the proximal phalanx of the great toe cannot freely extend on the 1st metatarsal head; the result is jamming at the dorsal joint leading to osteoarthritic changes and loss of joint motion. Over time, pain may develop, and the joint may become less mobile with an arthrosis (hallux rigidus), which can be debilitating.

Symptoms and Signs

Symptoms include pain on walking. Dorsal and plantar joint tenderness is usually present on palpation and during passive range of motion. Mild swelling with minimal heat occurs in osteoarthritic synovitis. Significant warmth, swelling, or redness suggests inflammatory arthropathies or infection.

Diagnosis

• Mainly clinical evaluation

• Exclusion of infection or arthropathy if signs of inflammation

Metatarsophalangeal joint pain can usually be differentiated from neuralgia or neuroma of the interdigital nerves by the absence of burning, numbness, and tingling and interspace pain, although these symptoms may develop from joint inflammation; if so, palpation can help with differentiation.

Monarticular heat, redness, and swelling indicate infection until proven otherwise, although gout is more likely. When warmth, redness, and swelling involve multiple joints, evaluation for a systemic cause of joint inflammation (eg, gout, RA, viral-associated arthritis, enteropathic arthritis) with a rheumatic disease assessment (eg, antinuclear antibodies, rheumatoid factor, ESR) is indicated.

Treatment

• Orthoses

Foot orthoses may help to redistribute and relieve pressure from the noninflamed joints. With excess subtalar eversion or when the feet are highly arched, an orthotic that corrects these abnormal motions should be prescribed. For functional hallux limitus, orthosis modifications may further help to plantarflex the 1st ray to improve metatarsophalangeal joint motion and reduce pain. For more severe limitation of 1st metatarsophalangeal motion or pain, the use of rigid orthoses, carbon fiber plates, or external shoe bars or rocker soles may be necessary to reduce motion at the joint. Surgery may be needed if conservative therapies are ineffective. If inflammation (synovitis) is present, injection of a local corticosteroid/anesthetic mixture may be useful.

Sesamoiditis

Sesamoiditis is pain at the sesamoid bones beneath the head of the 1st metatarsal, with or without inflammation or fracture. Diagnosis is usually clinical. Treatment is usually modification of footwear.

The 2 semilunar-shaped sesamoid bones aid the foot in locomotion. The medial bone is the tibial sesamoid, and the lateral bone is the fibular sesamoid. Direct trauma or positional change of the sesamoids due to alterations in foot structure (eg, lateral displacement of a sesamoid due to lateral deviation of the great toe) can make the sesamoids painful. Sesamoiditis is particularly common among dancers, joggers, and those who have high-arched feet or wear high heels. Many people with sesamoiditis have bunions.

Symptoms and Signs

The pain of sesamoiditis is beneath the head of the 1st metatarsal; the pain is usually made worse by walking and may be worse when wearing certain shoes. Occasionally, inflammation occurs, causing mild warmth and swelling or occasionally redness that may extend medially and appear to involve the 1st metatarsophalangeal joint. Sesamoid fracture can also cause pain, moderate swelling, and possibly inflammation.

Diagnosis

• Clinical evaluation

• Imaging if fracture, infection, or gout is suspected

With the foot and 1st (big) toe dorsiflexed, the examiner inspects the metatarsal head and palpates each sesamoid. Tenderness is localized to a sesamoid, usually the tibial sesamoid. Hyperkeratotic tissue may indicate that a wart or corn is causing pain. If inflammation causes swelling around the 1st

metatarsophalangeal joint, arthrocentesis is usually indicated to exclude gout and infectious arthritis. If fracture, osteoarthritis, or displacement is suspected, x-rays are taken. Sesamoids separated by cartilage or fibrous tissue (bipartite sesamoids) may appear fractured on x-rays. If plain x-rays are equivocal, MRI may be ordered.

Treatment

• New shoes, orthotics, or both

Simply not wearing the shoes that cause pain may be sufficient. If symptoms persist, shoes with a thick sole and orthotics are prescribed and help by reducing sesamoid pressure. If fracture without displacement is present, conservative therapy may be sufficient and may also involve immobilization of the joint with the use of a flat, rigid, surgical shoe. NSAIDs and injections of a corticosteroid/local anesthetic solution can be helpful. Although surgery may help in recalcitrant cases, it is controversial because of the potential for disturbing biomechanics and locomotion of the foot. If inflammation is present, treatment includes conservative measures plus local infiltration of a corticosteroid/anesthetic solution to help reduce symptoms.

Plantar Fasciosis

(Plantar Fasciitis)

Plantar fasciosis is pain at the site of the attachment of the plantar fascia and the calcaneus, with or without accompanying pain along the medial band of the plantar fascia. Diagnosis is mainly clinical. Treatment involves calf muscle and plantar soft-tissue foot-stretching exercises, night splints, and orthotics.

Syndromes of pain in the plantar fascia have been called plantar fasciitis; however, because there is usually no inflammation, plantar fasciosis is more correct. Other terms used include calcaneal enthesopathy pain or calcaneal spur syndrome; however, there may be no bone spurs on the calcaneus. Plantar fasciosis may involve acute or chronic stretching, tearing, and degeneration of the fascia at its attachment site.

Etiology

Recognized causes include shortening or contracture of the calf muscles and plantar fascia. Risk factors for such shortening include a sedentary lifestyle, occupations requiring sitting, very high or low arches in the feet, and wearing high-heel shoes. The disorder is also common among runners and dancers and may occur in people whose occupations involve standing or walking on hard surfaces for prolonged periods. Disorders that may be associated with plantar fasciosis are obesity, RA, reactive arthritis, and psoriatic arthritis. Multiple injections of corticosteroids may contribute by causing degenerative changes of the fascia and possible loss of the cushioning subcalcaneal fat pad.

Symptoms and Signs

Plantar fasciosis is characterized by pain at the bottom of the heel on weight bearing, particularly when first arising in the morning; pain usually improves within 5 to 10 min, only to return later in the day. It is often worse when pushing off of the heel (the propulsive phase of gait). Acute severe heel pain, especially with mild local puffiness, may indicate an acute tear. Some patients describe burning or sticking pain along the plantar medial border of the foot when walking.

Diagnosis

• Pain reproduced by calcaneal pressure during dorsiflexion

Other disorders causing heel pain can mimic plantar fasciosis:

• Throbbing heel pain, particularly when the shoes are removed or when mild heat and puffiness are

present, is more suggestive of calcaneal bursitis (see p. 401).

- Acute severe retrocalcaneal pain, with redness and heat, may indicate gout.
- Pain that radiates from the low back to the heel may be an S1 radiculopathy due to an L5 disk herniation.

Plantar fasciosis is confirmed if firm thumb pressure applied to the calcaneus when the foot is dorsiflexed elicits pain. Fascial pain along the plantar medial border of the fascia may also be present. If findings are equivocal, demonstration of a heel spur on x-ray may support the diagnosis; however, absence does not rule out the diagnosis, and visible spurs are not generally the cause of symptoms. Also, infrequently, calcaneal spurs appear ill defined on x-ray, exhibiting fluffy new bone formation, suggesting spondyloarthropathy (eg, ankylosing spondylitis, reactive arthritis). If an acute fascial tear is suspected, MRI is done.

Treatment

- Splinting, stretching, and cushioning or orthotics

To alleviate the stress and pain on the fascia, the person can take shorter steps and avoid walking barefoot. Activities that involve foot impact, such as jogging, should be avoided. The most effective treatments include the use of in-shoe heel and arch cushioning with calf-stretching exercises and night splinting devices that stretch the calf and plantar fascia while the patient sleeps. Prefabricated or custom-made foot orthotics may also alleviate fascial tension and symptoms. Other treatments may include activity modifications, NSAIDs, weight loss in obese patients, cold and ice massage therapy, and occasional corticosteroid injections. However, because corticosteroid injections can predispose to plantar fasciosis, many clinicians limit these injections. For recalcitrant cases, physical medicine, oral corticosteroids, and cast immobilization should be used before surgical intervention is considered.

Inferior Calcaneal Bursitis

Bursitis can develop at the inferior calcaneus, near the insertion of the plantar fascia. Symptoms and signs include throbbing heel pain, particularly when the shoes are removed; mild warmth; and swelling. The pain is most pronounced when the heel first contacts the ground during walking or running activity. Treatment is injection of a local anesthetic/corticosteroid mixture and soft-soled shoes with added protective heel cushion padding.

Achilles Tendon Enthesopathy

Achilles tendon enthesopathy is pain at the insertion of the Achilles tendon at the posterosuperior aspect of the calcaneus.

The cause is chronic traction of the Achilles tendon on the calcaneus. Contracted or shortened calf muscles (resulting from a sedentary lifestyle and obesity) and athletic overuse are factors. Enthesopathy may be caused by a spondyloarthropathy.

Pain at the posterior heel below the top of the shoe counter during ambulation is characteristic. Pain on palpation of the tendon at its insertion is diagnostic. Manual dorsiflexion of the ankle during palpation usually exacerbates the pain. Recurrent and especially multifocal enthesitis should prompt evaluation (history and examination) for a spondyloarthropathy.

Treatment

- Stretching, splinting, and heel lifts

Physical therapy aimed at calf muscle stretching should be done 10 min three times/day. The patient can exert pressure posteriorly to stretch the calf muscle while facing a wall at arms' length, with knees extended and foot dorsiflexed. To minimize stress to the Achilles tendon with weight bearing, the patient

should move the foot and ankle actively through their range of motion for about 1 min when rising after extended periods of rest. Night splints may also be prescribed to provide passive stretch during sleep and help prevent contractures. Heel lifts should be used temporarily to decrease tendon stress during weight bearing and relieve pain. Heel lifts should be used bilaterally to prevent gait disturbance even if pain is only in one heel.

Anterior Achilles Tendon Bursitis

(Albert's Disease; Retromalleolar Bursitis)

Anterior Achilles tendon bursitis is inflammation of the retromalleolar (retrocalcaneal) bursa, located anterior (deep) to the attachment of the Achilles tendon to the calcaneus.

Bursitis is due to trauma (eg, from rigid or poorly fitting shoes) or inflammatory arthritis (eg, RA, gout). On occasion, small calcaneal erosions may develop from severe inflammation.

Symptoms and Signs

Symptoms and signs caused by trauma or gout develop rapidly; those caused by another systemic disorder develop gradually. Pain, swelling, and warmth around the heel are common, as are difficulty walking and wearing shoes. The bursa is tender. Initially, the swelling is localized anterior to the Achilles tendon but in time extends medially and laterally.

Using the thumb and index finger, side-to-side compression anterior to the Achilles tendon causes pain.

Diagnosis

• Clinical evaluation and x-rays

Fracture of the posterolateral talar tubercle also causes tenderness anterior to the insertion of the Achilles tendon. Bursitis is often differentiated from the fracture by the localization of warmth and swelling contiguous to the tendon and pain localized primarily in the soft tissue. Also, x-rays are taken to rule out fracture as well as erosive calcaneal changes characteristic of chronic RA or other rheumatic disorders.

Treatment

• Intrabursal injection of a soluble corticosteroid/anesthetic solution

A corticosteroid/anesthetic injection, NSAIDs, and warm or cold compresses may be effective. Care must be taken to inject only the bursal sac and not the tendon proper because tendon injection may lead to tendon weakening or tearing, predisposing to subsequent rupture.

Posterior Achilles Tendon Bursitis

Posterior Achilles tendon bursitis is inflammation of a bursa that forms in response to shoe pressure and is located at the top edge of the posterior shoe counter between the skin and Achilles tendon.

This disorder occurs mainly in young women. Wearing high-heeled shoes is a risk factor. Many patients have a bony prominence (Haglund's deformity) on the calcaneus.

Symptoms and Signs

Symptoms and signs develop at the top edge of the posterior shoe counter. Early symptoms may be limited to redness, pain, and warmth. Later, superficial skin erosion may occur. After months or longer, a fluctuant, tender, cystic nodule 1- to 3-cm in diameter develops. It is red or flesh-colored. In chronic cases, the bursa becomes fibrotic.

Diagnosis

• Symptoms and a small, tender, flesh-colored or red nodule

The presence of the small, tender, flesh-colored or red nodule in a patient with compatible symptoms is diagnostic. Rarely, an Achilles tendon xanthoma develops at the top edge of the posterior shoe counter but tends to be pink and asymptomatic. Achilles tendon enthesopathy causes pain mainly at the tendon's insertion but may also cause pain at the top edge of the posterior shoe counter. Enthesopathy is differentiated by the absence of a soft-tissue lesion.

Treatment

• Modification of footwear

Properly fitting shoes with low heels are essential. A foam rubber or felt heel pad may be needed to lift the heel high enough so that the bursa does not hit the shoe counter. Padding around the bursa or the wearing of a backless shoe until inflammation subsides is indicated. Foot orthotics may enhance rear foot stability and help reduce irritating motion on the posterior calcaneus while walking. Warm or cool compresses, NSAIDs, and intrabursal injection of a local anesthetic/corticosteroid solution offer temporary relief; the Achilles tendon itself must not be injected. Surgical removal of a portion of the underlying bone may rarely be necessary to reduce soft-tissue impingement.

Epiphysitis of the Calcaneus

(Sever's Disease)

Epiphysitis of the calcaneus is painful disruption between the calcaneal apophysis and the body of the heel that occurs before calcaneal ossification is complete.

The calcaneus develops from two centers of ossification: one begins at birth, the other usually after age 8. Ossification is usually complete by age 15. The cartilaginous disruption in calcaneal epiphysitis may result from an excessive pull on the apophysis by contracted or shortened calf muscles. Bone growth spurts without adaptive calf muscle lengthening may play a role.

Pain develops in a patient (usually aged 9 to 14) with a history of athletic activity; it affects the sides or margins of the heel and is aggravated by standing on tip toes or running. Warmth and swelling are occasionally present.

The diagnosis is clinical. X-rays are not helpful.

Treatment

• Heel pads and splinting or casting

Heel pads relieve symptoms by reducing the pull of the Achilles tendon on the heel. Night splints may be used to passively stretch the calf muscles, helping maintain flexibility. In more severe or recalcitrant cases, cast immobilization may be used to relieve pain and stretch the calf muscles. Reassurance is important because symptoms may last several months.

Medial Plantar Nerve Entrapment

Medial plantar nerve entrapment is symptomatic compression of the medial branch of the posterior tibial nerve at the medial heel.

Symptoms include almost constant pain, with and without weight bearing. Simple standing is often difficult. Burning, numbness, and paresthesias are usually absent.

Diagnosis

• Clinical evaluation

Medial plantar nerve entrapment may be confused with plantar fasciosis and heel spur pain as well as tarsal tunnel syndrome. In medial plantar nerve entrapment, the following are present:

• Tenderness is at the medial heel.

• Other signs of tarsal tunnel syndrome are absent.

• Symptoms can be reproduced by palpation over the proximal aspect of the abductor hal-lucis, the origin of the plantar fascia, or both at the medial tubercle of the calcaneus.

Treatment

• Orthoses, immobilization, and physical therapy

Immobilization and foot orthoses to prevent irritating motion and pressure may be helpful, as may physical therapy and cryotherapy. If these treatments are ineffective, injection with a sclerosing agent that contains alcohol or careful surgical decompression of the nerve may help relieve pain.

Plantar Fibromatosis

Plantar fibromatosis is a benign proliferative neoplasia of the plantar fascia.

In plantar fibromatosis, nodules are displayed most easily when the foot is dorsiflexed against the leg. Most patients also have palmar nodules, usually located at the 4th metacarpophalangeal joint. Reported associations with diabetes, epilepsy, and alcoholism may be anecdotal. Treatment is usually not indicated unless the nodules become large enough to cause pressure-related pain with weight bearing. If so, orthoses can help redistribute pressure away from the fibrotic nodular lesions. Surgery usually results in recurrence and may also result in unintentional instability of the foot when fascial removal is excessive.

Hammer Toe Deformity

Hammer toe is a C-shaped deformity caused by dorsal subluxation at the metatarsophalangeal joint.

[
Fig. 44-2. Hammer toe.]

The usual cause is misalignment of the joint surfaces due to a genetic predisposition toward aberrant foot biomechanics and tendon contractures. RA and neurologic disorders such as Charcot-Marie-Tooth disease are other causes. The 2nd toe is the most common digit to develop a hammer toe deformity (see Fig. 44-2). Second toe hammer toes commonly result from an elongated 2nd metatarsal and from pressure due to an excessively abducted great toe (hallux valgus deformity) causing a bunion (see below). Painful corns (see p. 660) often develop in hammer toe deformity, particularly of the 5th toe. Reactive adventitial bursas often develop beneath corns, which may become inflamed.

Symptoms include pain while wearing shoes, especially shoes with low and narrow toe boxes, and sometimes metatarsalgia. Diagnosis is clinical. Joints are examined for coexistent arthritis (eg, RA).

Treatment

• Wide toe box, toe pads, orthotics, or a combination

Shoes should have a wide toe box. Toe pads sold in pharmacies also help by shielding the affected toes from the overlying shoe. If these measures are ineffective, surgical correction of the deformity often relieves symptoms. If there is accompanying metatarsalgia, OTC or prescription orthotic devices with

metatarsal pads and cushioning may help alleviate the pain.

Bunion

Bunion is a prominence of the medial portion of the head of the 1st metatarsal bone. The cause is often variations in position of the 1st metatarsal bone or great toe, such as lateral angulation of the great toe (hallux valgus). Secondary osteoarthritis and spur formation are common. Symptoms may include pain and redness, bursitis medial to the joint, and mild synovitis. Diagnosis is usually clinical. Treatment is usually a shoe with a wide toe box, protective pads, and orthotics. For bursitis or synovitis, corticosteroid injection may be helpful.

Contributing factors may include excessive turning in (pronation) of the ankles, wearing tight and pointed-toe shoes, and occasionally trauma. Joint misalignment causes osteoarthritis with cartilage erosion and exostosis formation, resulting in joint motion being limited (hallux limitus) or eliminated (hallux rigidus). In late stages, synovitis occurs, causing joint swelling. In reaction to pressure from tight shoes, an adventitious bursa can develop medial to the joint prominence, which can become painful, swollen, and inflamed (see
Fig. 44-3).

Symptoms and Signs

The initial symptom may be pain at the joint prominence when wearing certain shoes. The joint capsule may be tender at any stage. Later symptoms may include a painful, warm, red, cystic, movable, fluctuant swelling located medially (adventitial bursitis) and swellings and mild inflammation affecting the entire joint (osteoarthritic synovitis), which is more circumferential. With hallux limitus or rigidus, there is restriction of passive joint motion, tenderness of the lateral aspect of the joint, and increased dorsiflexion of the distal phalanx.

[**Fig. 44-3.** Bunion.]

Diagnosis

• Clinical evaluation

Clinical findings are usually specific. Acute circumferential intense pain, warmth, swelling, and redness suggest gouty arthritis or infectious arthritis, mandating examination of synovial fluid. If multiple joints are affected, gout or another systemic rheumatic disease should be considered. If clinical diagnosis of osteoarthritic synovitis is equivocal, x-rays are taken. Suggestive findings include joint space narrowing and bony spurs extending from the metatarsal head or sometimes from the base of the proximal phalanx. Periarticular erosions (Martel's sign) seen on imaging studies suggest gout.

Treatment

• Wide toe box, bunion pads, orthotics, or a combination

• Treatment of complications

Mild discomfort may lessen by wearing a shoe with a wide toe box. If not, bunion pads purchased in most pharmacies can shield the painful area. Orthotics can also be prescribed to redistribute and relieve pressure from the affected articulation. If conservative therapy fails or if the patient is unwilling to wear large, wide shoes and orthotics because they are unattractive, surgery aimed at correcting abnormal bony alignments and restoring joint mobility should be strongly considered. For bursitis, bursal aspiration and injection of a corticosteroid are indicated. For osteoarthritic synovitis, oral NSAIDs or an intra-articular injection of a corticosteroid/anesthetic solution reduces symptoms. For hallux limitus or hallux rigidus, treatment aims to preserve joint mobility by using passive stretching exercises, which occasionally require injection of a local anesthetic to relieve muscle spasm. Sometimes surgical release of contractures is necessary.

Chapter 45. Tumors of Bones and Joints

Introduction

Bone tumors may be primary or metastatic and benign or malignant.

In children, most bone tumors are primary and benign; some are malignant primary tumors (eg, osteosarcoma, Ewing's sarcoma). Very few are metastatic tumors (eg, neuroblastoma, Wilms' tumor). Bone also can be affected by childhood leukemia and lymphomas.

In adults, especially those over age 40, metastatic tumors are about 100 times more common than primary malignant tumors. Excluding marrow cell tumors (eg, multiple myeloma), there are only about 2500 cases of primary malignant bone tumors in the US each year among children and adults.

Synovial tumors are extremely rare in both children and adults. Pigmented villonodular synovitis is a benign but at times destructive tumor of synovial cells. Synovial sarcoma (often with both spindle cell and glandular-like components) is a malignant soft-tissue tumor not of synovial origin, which seldom occurs inside of a joint.

Symptoms and Signs

Bone tumors typically cause unexplained, progressive pain and swelling. Pain can occur without weight bearing or bone stress and can occur at rest and at night.

Diagnosis

• Plain x-rays

• MRI usually and sometimes CT

• Bone scan if multicentric or metastatic tumors are suspected

• Biopsy unless imaging studies clearly show benign characteristics

The most common reason that diagnosis of bone tumors is delayed is that physicians fail to suspect the tumor and order appropriate imaging studies. Persistent or progressive unexplained pain of the trunk or extremities, particularly if associated with a mass, is suggestive. Plain x-rays are the first test. Tumors should also be suspected if a radiographic study shows an unexplained abnormality consistent with a tumor. Lesions suggestive of tumors usually require further assessment, often with additional imaging studies and a biopsy.

Characteristic findings: Some tumors (eg, Paget's disease, nonossifying fibroma, fibrous dysplasia, enchondromas) may have characteristic radiographic findings and can be diagnosed without biopsy.

Radiographic findings that suggest cancer include the following:

• A lytic, destructive, or permeative appearance

• Irregular tumor borders

• Areas, especially multiple areas, of bone destruction (moth-eaten appearance)

• Cortical destruction

• Soft-tissue extension

• Pathologic fracture

A lytic appearance is characterized by clear areas of bone destruction that are sharply demarcated. A permeative appearance is characterized by a faint, gradual loss of bone or an infiltrating pattern without clear borders. Certain tumors have a characteristic appearance (eg, Ewing's sarcoma typically shows permeative-type bone destruction, including a large soft-tissue mass with periosteal onion-skin reactive bone often before there is an extensive, lytic, destructive appearance; giant cell tumor has a cystic appearance without a sclerotic interface between the tumor and normal bone). The tumor's location may narrow diagnostic possibilities (eg, Ewing's sarcoma commonly appears in the shaft of a long bone; osteosarcoma usually appears in the metaphyseal-diaphyseal region toward the end of a long bone; giant cell tumor usually occurs in the epiphysis).

Some benign conditions, however, can mimic a malignant tumor:

- Heterotopic ossification (myositis ossificans) and exuberant callus formation after fracture can cause mineralization around bony cortices and in adjacent soft tissues, mimicking malignant tumors.

- Langerhans' cell histiocytosis (histiocytosis X, Letterer-Siwe disease, Hand-Schuller-Christian disease, eosinophilic granuloma) can cause solitary or multiple bone lesions that are usually distinguishable on x-ray. In solitary lesions, there may be periosteal new bone formation, suggesting a malignant bone tumor.

- Osteopoikilosis (spotted bones) is an asymptomatic condition of no clinical consequence but can simulate osteoblastic bone metastases of breast cancer. It is characterized by multiple small, round, or oval foci of bony sclerosis, usually in the tarsal, carpal, or pelvic bones or the metaphyseal-epiphyseal regions of tubular bones.

Other testing: CT and MRI may help define the location and extent of a bone tumor and sometimes suggest a specific diagnosis. MRI is usually done if cancer is suspected. If tumors are suspected of being metastatic or involving multiple foci (multicentric), then radioisotopic technetium bone scanning should be done to search for all tumors.

Biopsy is usually essential for diagnosis of malignant tumors, unless the imaging studies have a classically benign appearance. The pathologist should be given pertinent details of the clinical history and should review imaging studies. Histopathologic diagnosis may be difficult and requires sufficient viable tissue from a representative portion of the tumor (usually the soft portion). The best results are obtained in centers with extensive experience in bone biopsies. Immediate, accurate, definitive diagnosis is possible in > 90% of cases. If a malignant diagnosis is suspected on frozen section histology, often the surgeon will wait upon permanent histology before treating definitively. Mistakes occur more frequently in hospitals that infrequently encounter patients with malignant primary tumors.

Benign Bone Tumors

Osteochondroma: Osteochondromas (osteocartilaginous exostoses), the most common benign bone tumors, may arise from any bone but tend to occur near the ends of long bones. These tumors manifest most often in people aged 10 to 20 and may be single or multiple. Multiple osteochondromas tend to run in families. Secondary malignant chondrosarcoma develops in about 10% of patients with multiple osteochondromas and in well < 1% of those with single osteochondromas. Osteochondromas rarely cause the bone to fracture.

On imaging studies, the lesion appears as a bony prominence with a cartilage cap (< 2 cm) off the surface of the bone with no underlying cortex under the prominence.

Excision is needed if the tumor is compressing a large nerve; causes pain (especially when impinging on muscle and creating an inflammatory bursa); disturbs growth; or on imaging study has a destructive appearance, soft-tissue mass, or thickened cartilaginous cap (> 2 cm) suggesting transformation into malignant chondrosarcoma.

Enchondroma: Enchondromas may occur at any age but tend to be recognized in patients aged 10 to 40. They are usually located within the medullary bone metaphyseal-diaphyseal region. These tumors are

usually asymptomatic but may enlarge and become painful. They are often found when x-rays are taken for another reason.

On x-ray, the tumor may appear as a lobulated calcified area within bone; some lesions are less calcified, with areas of stippled calcification either on plain films or CT. If adjacent to the cortex, enchondromas show minor endosteal scalloping. Almost all enchondromas have increased uptake on a bone scan and thus create concern of cancer. X-ray findings, including MRI and CT, may be diagnostic; if they are not, and especially if the tumor (not the associated joint) is painful, the diagnosis should be confirmed by biopsy. To help differentiate bone pain from joint pain, the joint can be injected, usually with a long-lasting anesthetic (eg, bupivacaine); if pain persists, it may be caused by the bone lesion.

An asymptomatic enchondroma does not need biopsy, excision, or other treatment (usually curettage); however, follow-up imaging studies are indicated to rule out disease progression. These are done at 6 mo and again at 1 yr or whenever symptoms develop.

Chondroblastoma: Chondroblastoma is rare and occurs most commonly among people aged 10 to 20. Arising in the epiphysis, this tumor may continue to grow and destroy bone and the joint. It appears on imaging studies as a sclerotic marginated cyst containing spots of punctate calcification. MRI can help diagnostically by showing characteristic changes well away from the lesion.

The tumor must be surgically removed by curettage, and the cavity must be bone grafted. Local recurrence rate is about 10 to 20%, and recurrent lesions often resolve with repeat bone curettage and bone grafting.

Chondromyxofibroma: Chondromyxofibroma is very rare and usually occurs before age 30. The appearance on imaging studies (usually eccentric, sharply circumscribed, lytic, and located near the end of long bones) suggests the diagnosis. Treatment after biopsy is surgical excision or curettage.

Osteoid osteoma: Osteoid osteoma, which tends to affect young people (commonly aged 10 to 35), can occur in any bone but is most common among long bones. It can cause pain (usually worse at night) that is typically relieved by mild analgesics, particularly aspirin or other NSAIDs. In growing children, the inflammatory response and associated hyperemia, if close to the open growth plate, may cause overgrowth and limb length discrepancy. Physical examination may reveal atrophy of regional muscles because the pain causes muscle disuse.

Characteristic appearance on imaging studies is a small radiolucent zone surrounded by a larger sclerotic zone. If a tumor is suspected, a technetium-99m bone scan should be done; an osteoid osteoma appears as an area of increased uptake. CT with fine image sequences is also done and is most helpful in distinguishing the lesion.

Removal of the small radiolucent zone with percutaneous radiofrequency ablation provides permanent relief. Most osteoid osteomas are treated by an interventional musculoskeletal radiologist using percutaneous techniques and anesthesia. Less often, osteoid osteomas are surgically curetted or excised.

Benign giant cell tumor: These tumors, which most commonly affect people in their 20s and 30s, occur in the epiphyses and may eventually erode the rest of the bone and extend into the soft tissues. They may cause pain. Giant cell tumors are notorious for their tendency to recur. Rarely, a giant cell tumor may metastasize to the lung, even though it remains histologically benign.

Benign giant cell tumors appear as expansile lytic lesions on imaging. On imaging studies, there is a margin without a sclerotic rim where the tumor ends and normal trabecular bone begins.

Most benign giant cell tumors are treated by curettage and packing with methyl methacrylate or by bone graft. To reduce recurrence rate, surgeons often prefer using an adjuvant such as thermal heat (provided by the hardening of methyl methacrylate) or chemically by phenol or freezing with liquid nitrogen. If a tumor is very large and destructive to the joint, complete excision with joint reconstruction may be necessary.

Primary Malignant Bone Tumors

(See also Ch. 117.)

Multiple myeloma: Multiple myeloma is the most common primary malignant bone tumor but is often considered a marrow cell tumor within the bone rather than a bone tumor. It is of hematopoietic derivation (see also p. 1029) and occurs mostly in older adults. The neoplastic process is usually multicentric and often involves the bone marrow so diffusely that bone marrow aspiration is diagnostic. Imaging studies usually show sharply circumscribed lytic lesions or diffuse demineralization. Rarely, the lesion can appear as sclerotic or as diffuse osteopenia, especially in a vertebral body. An isolated single myeloma lesion without systemic marrow involvement is called a plasmacytoma.

Osteosarcoma: Osteosarcoma (osteogenic sarcoma) is the 2nd most common primary bone tumor and is highly malignant. It is most common among people aged 10 to 25, although it can occur at any age. Osteosarcoma produces malignant osteoid (immature bone) from tumor bone cells. Osteosarcoma usually develops around the knee (distal femur more often than proximal tibia) or in other long bones, particularly the metaphyseal-diaphyseal area, and may metastasize, usually to lung or other bone. Pain and swelling are the usual symptoms.

Findings on imaging studies vary and may include sclerotic or lytic features. Diagnosis requires biopsy. Patients need a chest x-ray and CT to detect lung metastases and a bone scan to detect bone metastases.

Treatment is a combination of chemotherapy and surgery. Use of adjuvant chemotherapy increases survival from < 20% to > 65% at 5 yr. Chemotherapy usually begins before any surgery. Decreased tumor size on x-ray, decreased pain level, and decreased serum alkaline phosphatase indicate some response, but the desired response is for > 95% tumor necrosis on mapping of the resected specimen. After several courses of chemotherapy (over several months), limb-sparing surgery and limb reconstruction can proceed. In limb-sparing surgery, the tumor is resected en bloc, including all surrounding reactive tissue and a rim of surrounding normal tissue; to avoid microscopic spillage of tumor cells, the tumor is not violated. More than 80% of patients can be treated with limb-sparing surgery without decreasing long-term survival rate. Continuation of chemotherapy after surgery is usually necessary. If there is nearly complete tumor necrosis (about 99%) from preoperative chemotherapy, 5-yr survival rate is > 90%.

Fibrosarcoma: Fibrosarcomas have similar characteristics to osteosarcomas but produce fibrous tumor cells (rather than bone tumor cells), affect the same age group, and pose similar problems.

Malignant fibrous histiocytoma: This tumor is clinically similar to osteosarcoma and fibrosarcoma, although malignant fibrous histiocytomas have been classified as different from the osteosarcoma group because of a different histology (no tumor bone production). Malignant fibrous histiocytomas tend to occur in children and teenagers but can also occur in older adults as secondary lesions in bone infarcts and radiation fields. Treatment is similar to that of osteosarcoma.

Chondrosarcoma: Chondrosarcomas are malignant tumors of cartilage. They differ from osteosarcomas clinically, therapeutically, and prognostically. Of chondrosarcomas, 90% are primary tumors. Chondrosarcomas arise in other pre-existing conditions, particularly multiple osteochondromas and multiple enchondromatosis (eg, in Ollier's disease and Maffucci's syndrome). Chondrosarcomas tend to occur in older adults. They often develop in flat bones (eg, pelvis, scapula) but can develop in any portion of any bone and can implant in surrounding soft tissues.

X-rays often reveal punctate calcifications. Primary chondrosarcomas often also exhibit cortical bone destruction and loss of normal bone trabeculae. Secondary chondrosarcoma may be suggested by the appearance of punctate calcifications or an increase in size of an osteochondroma. Technetium-99m bone scintigraphy is a helpful screening study; all cartilaginous lesions show increased uptake on the scan, although chondrosarcomas exhibit particularly high uptake. Biopsy is required for diagnosis and can also determine the tumor's grade (probability of metastasizing).

Low-grade chondrosarcomas (grade 1/2 or grade 1) are often treated intralesionally (wide curettage) with addition of an adjuvant (often freezing liquid nitrogen; argon beam; heat of methyl methacrylate; radiofrequency; or phenol). Other tumors are treated with total surgical resection. When surgical resection with maintenance of function is impossible, amputation may be necessary. Because of the potential to implant the tumor, meticulous care must be taken to avoid spillage of tumor cells into the soft tissues during biopsy or surgery. Recurrence is inevitable if tumor cells spill. If no spillage occurs, the cure rate depends on the tumor grade. Low-grade tumors are nearly all cured with adequate treatment. Because these tumors have limited vascularity, chemotherapy and radiation therapy have little efficacy.

Ewing's sarcoma of bone: Ewing's sarcoma is a round-cell bone tumor with a peak incidence between 10 and 25 yr. Most develop in the extremities, but any bone may be involved. Ewing's sarcoma tends to be extensive, sometimes involving the entire bone shaft, most often the diaphyseal region. About 15 to 20% occur around the metaphyseal region. Pain and swelling are the most common symptoms.

Lytic destruction, particularly a permeative infiltrating pattern without clear borders, is the most common finding on imaging, but multiple layers of subperiosteal reactive new bone formation may give an onion-skin appearance. X-rays do not usually reveal the full extent of bone involvement, and a large soft-tissue mass usually surrounds the affected bone. MRI better defines disease extent, which can help guide treatment. Many other benign and malignant tumors can appear very similar, so diagnosis is made by biopsy. At times this tumor may be confused with an infection. Accurate histologic diagnosis can be accomplished with molecular markers, including evaluation for a typical clonal chromosomal abnormality.

Treatment includes various combinations of surgery, chemotherapy, and radiation therapy. Currently, > 60% of patients with primary localized Ewing's sarcoma may be cured by this multimodal approach. Cure is sometimes possible even with metastatic disease. Chemotherapy in conjunction with surgical en bloc resection, if applicable, often yields better long-term results.

Lymphoma of bone: Lymphoma of bone (previously known as reticulum cell sarcoma) affects adults, usually in their 40s and 50s. It may arise in any bone. The tumor consists of small round cells, often with a mixture of reticulum cells, lymphoblasts, and lymphocytes. It can develop as an isolated primary bone tumor, in association with similar tumors in other tissues, or as a metastasis from known soft-tissue lymphomatous disease. Pain and swelling are the usual symptoms. Pathologic fracture is common.

Imaging studies reveal bone destruction, which may be in a mottled or patchy or even infiltrating, permeative pattern, often with a clinical and radiographic large soft-tissue mass. In advanced disease, the entire outline of the affected bone may be lost.

In isolated primary bone lymphoma, the 5-yr survival rate is ≥ 50%. Combination radiation therapy and chemotherapy is as curative as amputation or other extensive ablative surgery. Stabilization of long bones is often necessary to prevent pathologic fracture. Amputation is indicated only rarely, when function is lost because of pathologic fracture or extensive soft-tissue involvement that cannot be managed otherwise.

Malignant giant cell tumor: Malignant giant cell tumor, which is rare, is usually located at the extreme end of a long bone. X-ray reveals classic features of malignant destruction (predominantly lytic destruction, cortical destruction, soft-tissue extension, and pathologic fracture). A malignant giant cell tumor that develops in a previously benign giant cell tumor is characteristically radioresistant. Treatment is similar to that of osteosarcoma, but the cure rate is low.

Chordoma: Chordoma, which is rare, develops from the remnants of the primitive notochord. It tends to occur at the ends of the spinal column, usually in the middle of the sacrum or near the base of the skull. A chordoma in the sacrococcygeal region causes nearly constant pain. A chordoma in the base of the skull can cause deficits in a cranial nerve, most commonly in nerves to the eye.

Symptoms may exist for months to several years before diagnosis. A chordoma appears on imaging studies as an expansile, destructive bone lesion that may be associated with a soft-tissue mass. Metastasis is unusual, but local recurrence is not. Chordomas in the sacrococcygeal region may be cured by radical en bloc excision. Chordomas in the base of the skull are usually inaccessible to surgery but may respond to radiation therapy.

Metastatic Bone Tumors

Any cancer may metastasize to bone, but metastases from carcinomas are the most common, particularly those arising in the following areas:

• Breast

• Lung

• Prostate

• Kidney

• Thyroid

• Colon

Prostate cancer in men and breast cancer in women are the most common types of cancers. Lung cancer is the most common cause of cancer death in both sexes. Breast cancer is the most common cancer to metastasize to bone. Any bone may be involved with metastases. Metastatic disease does not commonly spread to bone below the mid forearm or mid calf, but when it occurs in those sites, it results most often from lung or sometimes kidney cancer.

Symptoms and Signs

Metastases manifest as bone pain, although they may remain asymptomatic for some time. Bone metastases may cause symptoms before the primary tumor is suspected or may appear in patients with a known diagnosis of cancer.

Diagnosis

• X-ray

• Radionuclide scanning to identify all metastases

• Clinical evaluation and testing to diagnose the primary tumor (if unknown)

• Often biopsy if the primary tumor is unknown after assessment

Metastatic bone tumors are considered in all patients with unexplained bone pain, but particularly in patients who have

• Known cancer

• Pain at more than one site

• Findings on imaging studies that suggest metastases

Prostate cancer is most often blastic, lung cancer is most often lytic, and breast cancer may be blastic or lytic.

CT and MRI are highly sensitive for specific metastases. However, if metastases are suspected, a radionuclide whole-body scan, which is not quite as sensitive, is usually done. Bone scan is more sensitive for early and asymptomatic metastases than plain x-rays and can be used to scan the entire body. Lesions on the scan are usually presumed to be metastases if the patient has a known primary cancer. Metastases should be suspected in patients who have multiple lesions on bone scan. Although metastases are suspected in patients with known cancer and a single bone lesion, the lesion may not be

a metastasis; thus, a needle biopsy of the lesion is often done to confirm the diagnosis of a metastasis. PET for almost whole-body scanning is now often used for some tumors.

If bone metastases are suspected because multiple lytic lesions are found, assessment for the primary tumor can begin with clinical evaluation for primary cancers (particularly focused on the breast, prostate, and thyroid), chest x-ray, mammography, and measurement of prostate-specific antigen level. Initial CT of the chest, abdomen, and pelvis may also reveal the primary tumor. However, bone biopsy, especially fine-needle or core biopsy, is necessary if metastatic tumor is suspected and the primary tumor has not been otherwise diagnosed. Biopsy with use of immunohistologic stains may give clues to the primary tumor type.

Treatment

• Usually radiation therapy

• Surgery to stabilize bone at risk of pathologic fracture

• Kyphoplasty or vertebraplasty for certain painful vertebral fractures

Treatment depends on the type of tissue involved (which organ tissue type). Radiation therapy, combined with selected chemotherapeutic or hormonal drugs, is the most common treatment modality. Early use of radiation (30 Gy) and bisphosphonates (eg, zoledronate, pamidronate) slows bone destruction. Some tumors are more likely to heal after radiation therapy; for example, blastic lesions of prostate and breast cancer are more likely to heal than lytic destructive lesions of lung cancer and renal cell carcinoma.

If bone destruction is extensive, resulting in imminent or actual pathologic fracture, surgical fixation or resection and reconstruction may be required to provide stabilization and help minimize morbidity. When the primary cancer has been removed and only a single bone metastasis remains (especially if the metastatic lesion appears ≥ 1 yr after the primary tumor), en bloc excision sometimes combined with radiation therapy, chemotherapy, or both rarely may be curative. Insertion of methyl methacrylate into the spine (kyphoplasty or vertebraplasty) relieves pain and expands and stabilizes compression fractures that do not have epidural soft-tissue extension.

Other Bone Lesions

Many nonneoplastic conditions of bone may clinically or radiologically mimic solitary bone tumors.

Unicameral bone cyst: Simple unicameral bone cysts occur in the long bones starting distal to the epiphyseal plate in children. The cyst causes the cortex to thin and predisposes the area to a buckle-like pathologic fracture, which is usually how the cyst is recognized. Cysts < 5 cm may heal and may disappear as the fracture heals. Cysts > 5 cm, particularly in children, may require excision or curettage and bone grafting; however, many respond to injections of corticosteroids, demineralized bone matrix, or synthetic bone substitutes. The response may be variable and may require multiple injections. Regardless of treatment, cysts persist in about 10 to 15% of patients.

Fibrous dysplasia: Fibrous dysplasia involves abnormal bone development during childhood. It may affect one or several bones. Cutaneous pigmentation and endocrine abnormalities may be present (Albright's syndrome). The abnormal bone lesions of fibrous dysplasia commonly stop developing at puberty. They rarely undergo malignant degeneration. On x-ray, the lesions can appear cystic and may be extensive and deforming. Calcitonin may help relieve pain. Progressive deformities, fractures that do not heal with immobilization, or intractable pain may be effectively treated with orthopedic surgery.

Aneurysmal bone cyst: An aneurysmal bone cyst is an idiopathic expansile lesion that usually develops before age 25 yr. This cystic lesion usually occurs in the metaphyseal region of the long bones, but almost any bone may be affected. It tends to grow slowly. A periosteal new bone shell forms around the expansile lesion and is often wider than the original bone. Pain and swelling are common. The lesion may be present for a few weeks to a year before diagnosis. The appearance on x-ray is often characteristic: The rarefied area is usually well circumscribed and eccentric; the periosteum bulges, extending into the

soft tissues, and may be surrounded by new bone formation.

Surgical removal of the entire lesion is the most successful treatment; regression after incomplete removal sometimes occurs. Radiation should be avoided when possible because sarcomas occasionally develop. However, radiation may be the treatment of choice in completely surgically inaccessible vertebral lesions that are compressing the spinal cord.

Joint Tumors

Tumors rarely affect joints, unless by direct extension of an adjacent bone or soft-tissue tumor. However, 2 conditions—synovial chondromatosis and pigmented villonodular synovitis—occur in the lining (synovium) of joints. These conditions are benign but locally aggressive. Both usually affect one joint, most often the knee and second most often the hip, and can cause pain and effusion. Both are treated by synovectomy and removal of any intra-articular bodies.

Synovial chondromatosis: Synovial chondromatosis (previously called synovial osteochondromatosis) is considered metaplastic. It is characterized by numerous calcified cartilaginous bodies in the synovium, which often become loose. Each body may be no larger than a grain of rice, in a swollen, painful joint. Malignant change is very rare. Recurrence is common.

Pigmented villonodular synovitis: Pigmented villonodular synovitis is considered neoplastic. The synovium becomes thickened and contains hemosiderin, which gives the tissue its blood-stained appearance and characteristic appearance on MRI. This tissue tends to invade adjacent bone, causing cystic destruction and damage to the cartilage. Pigmented villonodular synovitis is usually monarticular but may be polyarticular. Late management, especially after recurrence, may require total joint replacement. On rare occasions after several synovectomies, radiation therapy can be used.