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Harrison's Internal Medicine  >  Chapter 330. Arthritis Associated with Systemic Disease and Other Arthritides  >

ARTHRI TIS ASSOCI ATED W ITH SYSTEMI C DI SEASE

Arthropathy of Acromegaly

Acromegaly is the result of excessive production of growth hormone by an adenoma in the anterior pituitary gland (Chap. 333). Middle-aged persons are most often affected. The excessive secretion of growth hormone along with insulin-like growth factor I stimulates proliferation of cartilage, periarticular connective tissue, and bone, resulting in several musculoskeletal abnormalities, including osteoarthritis, back pain, muscle weakness, and carpal tunnel syndrome.

An arthropathy resembling osteoarthritis is a common feature, affecting most often the knees, shoulders, hips, and hands. Single or multiple joints may be affected. The overgrowth of cartilage initially produces widening of the joint space. The newly synthesized cartilage is not developed in an organized manner, making it susceptible to fissuring, ulceration, and destruction. Ligamental laxity of the joint resulting from the growth of connective tissue also contributes to the development of osteoarthritis. With breakdown and loss of cartilage, the joint space narrows, and subchondral sclerosis and osteophytes appear on radiographs. Joint examination reveals marked crepitus and hypermobility. Joint fluid is noninflammatory. Calcium pyrophosphate dihydrate crystals are found in the cartilage in some cases of acromegaly arthropathy and, when shed into the joint, can produce attacks of pseudogout. Chondrocalcinosis may also be observed radiographically. Approximately half of the patients with acromegaly experience back pain, which is predominantly lumbosacral. Hypermobility of the spine may be a contributing factor in back pain. Radiograph of the spine shows normal or increased intervertebral disk spaces, hypertrophic anterior osteophytes, and ligamental calcification. These changes are similar to those observed in patients with diffuse idiopathic skeletal hyperostosis. Dorsal kyphosis in conjunction with elongation of the ribs contributes to the development of the barrel chest seen in acromegalic patients. The hands and feet become enlarged owing to soft tissue proliferation. The fingers are thickened and have spadelike distal tufts. One-third of patients have a thickened heel pad. Approximately 25% of patients have Raynaud's phenomenon.

Carpal tunnel syndrome occurs in about half of patients. The median nerve is compressed by the excessive growth of connective tissue in the carpal tunnel. The median nerve also becomes enlarged. Patients with acromegaly also develop proximal muscle weakness, which is thought to be caused by the effect of growth hormone on muscle. Results of muscle enzyme assays and electromyography are normal. Muscle biopsy specimens show muscle fibers of varying size and no inflammatory changes.

Arthropathy of Hemochromatosis

Hemochromatosis is a disorder of iron storage. Excessive amounts of iron are absorbed from the intestine, leading to iron deposition in parenchymal cells, which results in tissue damage and impairment of organ function (Chap. 351). Symptoms of hemochromatosis usually begin between the ages of 40 and 60 but can occur earlier. Arthritis, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. The arthropathy is an osteoarthritis-like disorder affecting the small joints of the hands, followed later by larger joints such as knees, ankles, shoulders, and hips. The second and third metacarpophalangeal joints of both hands are...
often the first joints affected; they can provide an important clue to the possibility of hemochromatosis. Patients experience stiffness and pain. Morning stiffness usually lasts less than half an hour. The affected joints are enlarged and mildly tender. Synovial tissue is not appreciably increased. Radiographs show irregular narrowing of the joint space, subchondral sclerosis, and subchondral cysts. There is juxtaarticular proliferation of bone, with frequent hooklike osteophytes. The synovial fluid is noninflammatory. The synovium shows mild to moderate proliferation of lining cells, fibrosis, and a low number of inflammatory cells, which are mononuclear. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease (CPPD), and patients may experience episodes of pseudogout. Iron can be demonstrated in the lining cells of the synovium and also in chondrocytes.

Iron may damage the articular cartilage in several ways. Iron catalyzes superoxide-dependent lipid peroxidation, which may play a role in joint damage. In animal models, ferric iron has been shown to interfere with collagen formation. Iron has also been shown to increase the release of lysosomal enzymes from cells in the synovial membrane. Iron may also play a role in the development of chondrocalcinosis. Iron inhibits synovial tissue pyrophosphatase in vitro and, therefore, may inhibit pyrophosphatase in vivo, resulting in chondrocalcinosis. Iron in synovial cells may also inhibit the clearance of calcium pyrophosphate from the joint.

**ARTHROPATHY OF HEMOCROMATOSIS: TREATMENT**

The treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little effect on the arthritis, which, along with chondrocalcinosis, usually continues to progress. Treatment of the arthritis consists of administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Acute pseudogout attacks are treated with higher doses of an NSAID or a short course of glucocorticoids. Placement of a hip or knee prosthesis has been successful in advanced disease.

**Hemophilic Arthropathy**

Hemophilia is a sex-linked recessive genetic disorder characterized by the absence or deficiency of factor VIII (hemophilia A, or classic hemophilia) or factor IX (hemophilia B, or Christmas disease) (Chap. 110). Hemophilia A is by far the more common type, constituting 85% of cases. Spontaneous hemarthrosis is a common problem with both types of hemophilia and can lead to a chronic deforming arthritis. The frequency and severity of hemarthrosis are related to the degree of clotting factor deficiency. Hemarthrosis is not common in other inherited disorders of coagulation, such as von Willebrand disease or factor V deficiency.

Hemarthrosis becomes evident after 1 year of age, when the child begins to walk and run. In order of frequency, the joints most commonly affected are the knees, ankles, elbows, shoulders, and hips. Small joints of the hands and feet are occasionally involved.

In the initial stage of arthropathy, hemarthrosis produces a warm, tensely swollen, and painful joint. The patient holds the affected joint in flexion and guards against any movement. Blood in the joint remains liquid because of the absence of intrinsic clotting factors and the absence of tissue thromboplastin in the synovium. The blood in the joint space is resorbed over a period of a week or longer, depending on the size of the hemarthrosis. Joint function usually returns to normal or baseline in about 2 weeks.

Recurrent hemarthrosis leads to the development of a chronic arthritis. The involved joints remain swollen, and flexion deformities develop. In the later stages of arthropathy, joint motion is restricted and function is severely limited. Joint ankylosis, subluxation, and laxity are features of end-stage disease.
Bleeding into muscle and soft tissue also causes musculoskeletal disorders. When bleeding into the iliopsoas muscle occurs, the hip is held in flexion because of the pain, resulting in a hip flexion contracture. Rotation of the hip is preserved, which distinguishes this problem from intraarticular hemorrhage. Expansion of the hematoma may place pressure on the femoral nerve, resulting in a femoral neuropathy. Another problem is shortening of the heel cord secondary to bleeding into the gastrocnemius. Hemorrhage into a closed compartment space, such as the volar compartment in the forearm, can result in muscle necrosis, neuropathy, and flexion deformities of the wrist and fingers. When bleeding involves periosteum or bone, a pseudotumor forms. These occur distal to the elbows or knees in children and improve with treatment of the hemophilia. Surgical removal is indicated if the pseudotumor continues to enlarge. In adults, they occur in the femur and pelvis and are usually refractory to treatment. When bleeding occurs in muscle, cysts may develop within the muscle. Needle aspiration of a cyst is contraindicated because it can induce bleeding.

Septic arthritis can occur in hemophilia and is difficult at times to distinguish from acute hemarthrosis on physical examination. Whenever there is suspicion of an infected joint, the joint should be aspirated immediately, the fluid cultured, and the patient started on antibiotics that provide broad coverage until the results of the culture are known. The patient should be infused with the deficient clotting factor before the joint is tapped to decrease the risk of further bleeding.

Radiographs of joints reflect the stage of disease. In early stages there is only capsule distention; later, juxtaarticular osteopenia, marginal erosions, and subchondral cysts develop. In late disease, the joint space is narrowed and there is bony overgrowth. The changes are similar to those observed in osteoarthritis. Unique features of hemophilic arthropathy are widening of the femoral intercondylar notch, enlargement of the proximal radius, and squaring of the distal end of the patella.

Recurrent hemarthrosis produces synovial hyperplasia and hypertrophy. A pannus covers the cartilage. Cartilage is damaged by collagenase and other degradative enzymes released by mononuclear cells in the overlying synovium. Hemosiderin is found in synovial lining cells, the subsynovium, and chondrocytes and may also play a role in cartilage destruction.

HEMARTHROSI S: TREATMENT

The treatment of hemarthrosis is initiated with the immediate infusion of factor VIII or IX at the first sign of joint or muscle hemorrhage. The patient is placed at bed rest, with the involved joint in as much extension as the patient can tolerate. Analgesic doses of an NSAID and local icing may help with the pain. NSAIDs can be given safely for short periods even though they have a stabilizing effect on platelets. Studies have shown no significant abnormalities in platelet function or bleeding time in hemophiliacs receiving ibuprofen. The cyclooxygenase-2 inhibitors do not interfere with platelet function and can be safely given for pain where their use is felt to be safe and indicated based upon the risks versus benefits. Synovectomy, open or arthroscopic, may be indicated in patients with chronic synovial proliferation and recurrent hemarthrosis. Hypertrophied synovium is very vascular and subject to bleeding. Both types of synovectomy reduce the number of hemarthroses and slow the roentgenographic progression of hemophilic arthropathy. Open surgical synovectomy, however, is associated with some loss of range of motion. Radiosynovectomy with either yttrium 90 silicate or phosphorus 31 colloid also has been effective and may be a useful alternative when surgical synovectomy is not practical. Total joint replacement is indicated for severe joint destruction and incapacitating pain. Because of the young age of hemophilic patients, total-joint prostheses may need to be replaced more than once during their lives.

Arthropathies Associated with Hemoglobinopathies
Sickle cell disease (Chap. 99) is associated with several musculoskeletal abnormalities (Table 330-1). Children under the age of 5 may develop diffuse swelling, tenderness, and warmth of the hands and feet lasting from 1 to 3 weeks. The condition, referred to as sickle cell dactylitis or hand-foot syndrome, has also been observed in sickle cell disease and sickle cell thalassemia. Dactylitis is believed to result from infarction of the bone marrow and cortical bone leading to periostitis and soft tissue swelling. Radiographs show periosteal elevation, subperiosteal new bone formation, and areas of radiolucency and increased density involving the metacarpals, metatarsals, and proximal phalanges. These bone changes disappear after several months. The syndrome leaves little or no residual damage. Because hematopoiesis ceases in the small bones of hands and feet with age, the syndrome is rarely seen after age 4 or 5 and does not occur in adults.

**Table 330-1 Musculoskeletal Abnormalities in Sickle Cell Disease**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell dactylitis</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Joint effusions in sickle cell crises</td>
<td>Bone changes secondary to marrow hyperplasia</td>
</tr>
<tr>
<td>Infarction of bone</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Infarction of bone marrow</td>
<td>Gouty arthritis</td>
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</table>

Sickle cell crisis is often associated with periarticular pain and joint effusions. The joint and periarticular area are warm and tender. Knees and elbows are most often affected, but other joints can be involved. Joint effusions are noninflammatory, with white cell counts < 1000/µL; mononuclear cells predominate. There have been a few reports of sterile inflammatory effusion with high cell counts consisting of mostly polymorphonuclear white cells. Synovial biopsies have shown mild lining cell proliferation and microvascular thrombosis. Scintigraphic studies have shown decreased marrow uptake adjacent to the involved joint. The joint effusion and periarticular pain are considered to be the result of ischemia and infarction of the synovium and adjacent bone and bone marrow. The treatment is that for sickle cell crisis (Chap. 99).

Patients with sickle cell disease may also develop osteomyelitis, which commonly involves the long tubular bones (Chap. 120). These patients are particularly susceptible to bacterial infections, especially *Salmonella* infections, which are found in more than half of cases. The most common isolate is *S. typhimurium* (Chap. 146). Radiographs of the involved site show periosteal elevation initially, followed by disruption of the cortex. Treatment of the infection results in healing of the bone lesion. Sickle cell disease is also associated with bone infarction resulting from thrombosis secondary to the sickling of red cells. Bone infarction also occurs in hemoglobin sickle cell disease and sickle cell thalassemia (Chap. 99). The bone pain in sickle cell crisis is due to bone and bone marrow infarction. In children, infarction of the epiphyseal growth plate interferes with normal growth of the affected extremity.

Radiographically, infarction of the bone cortex results in periosteal elevation and irregular thickening of the bone cortex. Infarction in the bone marrow leads to lysis, fibrosis, and new bone formation.

Avascular necrosis of the head of the femur is seen in ~5% of patients. It also occurs in the humeral head and less commonly in the distal femur, tibial condyles, distal radius, vertebral bodies, and other juxtaarticular sites. The mechanism for avascular necrosis is most likely the same as for bone infarction. Subchondral hemorrhage may play a role in the deterioration of articular cartilage. Irregularity of the femoral head or of other bone surfaces affected by avascular necrosis eventually results in degenerative joint disease. Radiograph of the affected joint may show patchy radiolucency and density followed by flattening of the bone. MRI is a sensitive technique for detecting early avascular necrosis as well as
bone infarction elsewhere. Total hip replacement and placement of prostheses in other joints may improve function and relieve pain in those patients with severe joint destruction.

Septic arthritis is occasionally encountered in sickle cell disease (Chap. 328). Multiple joints may be infected. Joint infection may result from hematogenous spread or from spread of contiguous osteomyelitis. Microorganisms identified include *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli*, and *Salmonella*. The latter is not seen as frequently in septic arthritis as it is in osteomyelitis. Acute gouty arthritis is uncommon in sickle cell disease, even though 40% of patients are hyperuricemic. Hyperuricemia is due to overproduction of uric acid secondary to increased red cell turnover. Attacks may be polyarticular.

The bone marrow hyperplasia in sickle cell disease results in widening of the medullary cavities, thinning of the cortices, and coarse trabeculations and central cupping of the vertebral bodies. These changes are also seen to a lesser degree in hemoglobin sickle cell disease and sickle cell thalassemia. In normal individuals, red marrow is located mostly in the axial skeletal, but in sickle cell disease, red marrow is found in the bones of the extremities and even in the tarsal and carpal bones. Vertebral compression may lead to dorsal kyphosis, and softening of the bone in the acetabulum may result in protrusio acetabuli.

**THALASSEMIA**

β-Thalassemia is a congenital disorder of hemoglobin synthesis characterized by impaired production of β chains (Chap. 99). Bone and joint abnormalities occur in β-thalassemia, being most common in the major and intermedia groups. In one study, ~50% of patients with β-thalassemia had evidence of symmetric ankle arthropathy, characterized by a dull aching pain aggravated by weight bearing. The onset was most often in the second or third decade of life. The degree of ankle pain in these patients varied. Some patients experienced self-limited ankle pain, which occurred only after strenuous physical activity and lasted several days to weeks. Other patients had chronic ankle pain, which became worse with walking. Symptoms eventually abated in a few patients. Compression of the ankle, calcaneus, or forefoot was painful in some patients. Synovial fluid from two patients was noninflammatory. Radiographs of ankle showed osteopenia, widened medullary spaces, thin cortices, and coarse trabeculations. These findings were largely the result of bone marrow expansion. The joint space was preserved. Specimens of bone from three patients revealed osteomalacia, osteopenia, and microfractures. Increased osteoblasts as well as increased foci of bone resorption were present on the bone surface. Iron staining was found in the bone trabeculae, in osteoid, and in the cement line. Synovium showed hyperplasia of lining cells, which contained deposits of hemosiderin. This arthropathy was considered to be related to the underlying bone pathology. The role of iron overload or abnormal bone metabolism in the pathogenesis of this arthropathy is not known. The arthropathy was treated with analgesics and splints. Patients were also transfused to decrease hematopoiesis and bone marrow expansion.

Patients with β-thalassemia major and intermedia also have involvement of other joints, including the knees, hips, and shoulders. Acquired hemochromatosis with arthropathy has been described in a patient with thalassemia. Gouty arthritis and septic arthritis can occur. Avascular necrosis is not a feature of thalassemia because there is no sickling of red cells leading to thrombosis and infarction.

β-Thalassemia minor (trait) is also associated with joint manifestations. Chronic seronegative oligoarthritis affecting predominantly ankles, wrists, and elbows has been described. These patients had mild persistent synovitis without large effusions. Joint erosions were not seen. Recurrent episodes of an acute asymmetric arthritis have also been reported; episodes last less than a week and may affect knees, ankles, shoulders, elbows, wrists, and metacarpal phalangeal joints. The mechanism for this
arthropathy is unknown. Treatment with nonsteroidal drugs was not particularly effective.

**Musculoskeletal Disorders Associated with Hyperlipidemia**

(See also Chap. 350) Musculoskeletal manifestations may be the first indication of a hereditary disorder of lipoprotein metabolism. Patients with familial hypercholesterolemia (previously referred to as type II hyperlipoproteinemia) may have recurrent migratory polyarthritis involving knees and other large peripheral joints and, to a lesser degree, peripheral small joints. In a few patients, the arthritis is monarticular. Fever may accompany the arthritis. Pain ranges from moderate to very severe to incapacitating. The involved joints can be warm, erythematous, swollen, and tender. Arthritis usually has a sudden onset, lasts from a few days to 2 weeks, and does not cause joint damage. Episodes may suggest acute gout attacks. Several attacks occur per year. Synovial fluid from involved joints is not inflammatory and contains few white cells and no crystals. Joint involvement may actually represent inflammatory periartitis or peritendinitis and not intraarticular disease. The recurrent, transient nature of the arthritis may suggest rheumatic fever, especially since patients with hyperlipoproteinemia have an elevated erythrocyte sedimentation rate and a falsely elevated antistreptolysin O titer. Patients may also experience Achilles tendinitis, which can be very painful. Attacks of tendinitis come on gradually and last only a few days. Fever is not present. Patients may be asymptomatic between attacks. During an attack the Achilles tendon is warm, erythematous, swollen, and tender to palpation. Achilles tendinitis and other joint manifestations often precede the appearance of xanthomas and may be the first clinical indication of hyperlipoproteinemia. Attacks of tendinitis may occur following treatment with a lipid-lowering drug. Patients can also have tendinous xanthomas in the Achilles, patellar, and extensor tendons of the hands and feet. Xanthomas have also been reported in the peroneal tendon, the plantar aponeurosis, and the periosteam overlying the distal tibia. These xanthomas are located within tendon fibers. Tuberous xanthomas are soft subcutaneous masses located over the extensor surfaces of the elbows, knees, and hands, as well as on the buttocks. They appear in childhood in homozygous patients and after the age of 30 in heterozygous patients. Patients with elevated plasma levels of very low-density lipoprotein (VLDL) and triglyceride (previously referred to as type IV hyperlipoproteinemia) may also have a mild inflammatory arthritis affecting large and small peripheral joints, usually in an asymmetric pattern with only a few joints involved at a time. The onset of arthritis is usually in middle age. Arthritis may be persistent or recurrent, with episodes lasting a few days to weeks. Joint pain is severe in some patients. Patients may experience morning stiffness. Joint tenderness and periarticular hyperesthesia may also be present, as may synovial thickening. Joint fluid is usually noninflammatory and without crystals but may have increased white blood cell counts with predominantly mononuclear cells. The fluid is occasionally lactescent. Radiographs may show juxtaarticular osteopenia and cystic lesions. Large bone cysts have been noted in a few patients. Xanthoma and bone cysts are also observed in other lipoprotein disorders. The pathogenesis of arthritis in patients with familial hypercholesterolemia or with elevated levels of VLDL and triglyceride is not well understood. Salicylates, other NSAIDs, or analgesics usually provide relief of symptoms. Clinical improvement may also occur in patients treated with lipid-lowering agents; however, patients treated with an HMG-CoA reductase inhibitor may experience myalgias, and a few patients may develop polymyositis or even rhabdomyolysis. Myositis has also been reported with the use of niacin (Chap. 384).

Deceased. A contributor to HPIM since the 11th edition, Dr. Gilliland passed away on February 17, 2007.

**OTHER ARTHRITIDIES**

**Neuropathic Joint Disease**
Neuropathic joint disease (Charcot's joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. In addition, normal muscular reflexes that modulate joint movement are decreased. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Neuropathic arthropathy was first described by Jean-Martin Charcot in 1868 in patients with tabes dorsalis. The term Charcot joint is commonly used interchangeably with neuropathic joint. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease (Fig. 330-1). A variety of other disorders are associated with neuropathic arthritis including leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease is seen in patients who have received frequent intraarticular glucocorticoid injections into a weight-bearing joint and in patients with CPPD. The distribution of joint involvement depends on the underlying neurologic disorder (Table 330-2). In tabes dorsalis, knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints.

**Figure 330-1**


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**Charcot arthropathy associated with diabetes mellitus.** Lateral foot radiograph demonstrating complete loss of the arch due to bony fragmentation and dislocation in the midfoot. (*Courtesy of Andrew Neckers, MD, and Jean Schils, MD.*)

<table>
<thead>
<tr>
<th>Table 330-2 Disorders Associated with Neuropathic Joint Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Tabes dorsalis</td>
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<tr>
<td>Meningomyelocele</td>
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<tr>
<td>Syringomyelia</td>
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**PATHOLOGY AND PATHOPHYSIOLOGY**
The pathologic changes in the neuropathic joint are similar to those found in the severe osteoarthritic joint. There is fragmentation and eventual loss of articular cartilage with eburnation of the underlying bone. Osteophytes are found at the joint margins. With more advanced disease, erosions are present on the joint surface. Fractures, devitalized bone, and intraarticular loose bodies may be present. Microscopic fragments of cartilage and bone are seen in the synovial tissue.

At least two underlying mechanisms are believed to be involved in the pathogenesis of neuropathic arthritis. An abnormal autonomic nervous system is thought to be responsible for the increased blood flow to the joint and subsequent resorption of bone. Loss of bone, particularly in the diabetic foot, may be the initial manifestation. With the loss of deep pain, proprioception, and protective neuromuscular reflexes, the joint is subjected to repeated injuries including ligamental tears and bone fractures. The mechanism of injury that occurs following frequent intraarticular glucocorticoid injections is thought to be due to the analgesic effect of glucocorticoids leading to overuse of an already damaged joint, which results in accelerated cartilage damage. It is not understood why only a few patients with neuropathies develop neuropathic arthritis.

CLINICAL MANIFESTATIONS

Neuropathic joint disease usually begins in a single joint and then progresses to involve other joints, depending on the underlying neurologic disorder. The involved joint progressively becomes enlarged from bony overgrowth and synovial effusion. Loose bodies may be palpated in the joint cavity. Joint instability, subluxation, and crepitus occur as the disease progresses. Neuropathic joints may develop rapidly, and a totally disorganized joint with multiple bony fragments may evolve in a patient within weeks or months. The amount of pain experienced by the patient is less than would be anticipated based on the degree of joint involvement. Patients may experience sudden joint pain from intraarticular fractures of osteophytes or condyles.

Neuropathic arthritis is encountered most often in patients with diabetes mellitus, with the incidence estimated in the range of 0.5%. The usual age of onset is 50 years following several years of diabetes, but exceptions occur. The tarsal and tarsometatarsal joints are most often affected, followed by the metatarsophalangeal and talotibial joints. The knees and spine are occasionally involved. In about 20%, neuropathic arthritis may be present in both feet. Patients often attribute the onset of foot pain to antecedent trauma such as twisting their foot. Neuropathic changes may develop rapidly following a foot fracture or dislocation. Swelling of the foot and ankle are often present. Downward collapse of the tarsal bones leads to convexity of the sole, referred to as a "rocker foot." Large osteophytes may protrude from the top of the foot. Calluses frequently form over the metatarsal heads and may lead to infected ulcers and osteomyelitis. Radiographs may show resorption and tapering of the distal metatarsal bones. The term Lisfranc fracture-dislocation is sometimes used to describe the destructive changes at the tarsometatarsal joints.

DIAGNOSIS

The diagnosis of neuropathic arthritis is based on the clinical features and characteristic radiographic findings in a patient with an underlying sensory neuropathy. The differential diagnosis of neuropathic arthritis includes osteomyelitis, osteonecrosis, advanced osteoarthritis, stress fractures, and CPPD. Radiographs in neuropathic arthritis initially show changes of osteoarthritis with joint space narrowing, subchondral bone sclerosis, osteophytes, and joint effusions followed later by marked destructive and hypertrophic changes. Soft tissue swelling, bone resorption, fractures, large osteophytes, extraarticular bone fragments, and subluxation are present with advanced arthropathy. The radiographic findings of neuropathic arthritis may be difficult to differentiate from those of osteomyelitis, especially in the
diabetic foot. The joint margins in a neuropathic joint tend to be distinct, while in osteomyelitis, they are blurred. Imaging studies and cultures of fluid and tissue from the joint are often required to exclude osteomyelitis. MRI is helpful in differentiating these disorders. Another useful study is a bone scan using indium 111–labeled white blood cells or indium 111–labeled immunoglobulin G, which will show an increased uptake in osteomyelitis but not in a neuropathic joint. A technetium bone scan will not distinguish osteomyelitis from neuropathic arthritis, as increased uptake is observed in both. The joint fluid in neuropathic arthritis is noninflammatory; may be xanthochromic or even bloody; and may contain fragments of synovium, cartilage, and bone. The finding of calcium pyrophosphate dihydrate crystals suggests the diagnosis of a crystal-associated neuropathic-like arthropathy. In the absence of such crystals, the presence of increased number of leukocytes may indicate osteomyelitis.

**NEUROPATHIC JOINT DISEASE: TREATMENT**

The primary focus of treatment is to provide stabilization of the joint. Treatment of the underlying disorder, even if successful, does not usually alter the joint disease. Braces and splints are helpful. Their use requires close surveillance, since patients may be unable to appreciate pressure from a poorly adjusted brace. In the diabetic patient, early recognition and treatment of a Charcot's foot by prohibiting weight-bearing of the foot for at least 8 weeks may possibly prevent severe disease from developing. Fusion of a very unstable joint may improve function, but nonunion is frequent, especially when immobilization of the joint is inadequate.

**Hypertrophic Osteoarthropathy and Clubbing**

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of digits and, in more advanced stages, by periosteal new bone formation and synovial effusions. HOA occurs in primary or familial form and usually begins in childhood. The secondary form of HOA is associated with intrathoracic malignancies, suppurative lung disease, congenital heart disease, and a variety of other disorders and is more common in adults. Clubbing is almost always a feature of HOA but can occur as an isolated manifestation (Fig. 330-2). The presence of clubbing in isolation is generally considered to represent either an early stage or an element in the spectrum of HOA. The presence of only clubbing in a patient usually has the same clinical significance as HOA.

**Figure 330-2**
In HOA, the bone changes in the distal extremities begin as periostitis followed by new bone formation. At this stage, a radiolucent area may be observed between the new periosteal bone and subjacent cortex. As the process progresses, multiple layers of new bone are deposited, which become contiguous with the cortex and result in cortical thickening. The outer portion of bone is laminated in appearance, with an irregular surface. Initially, the process of periosteal new bone formation involves the proximal and distal diaphyses of the tibia, fibula, radius, and ulna and, less frequently, the femur, humerus, metacarpals, metatarsals, and phalanges. Occasionally, scapulae, clavicles, ribs, and pelvic bones are also affected. In long-standing disease, these changes extend to involve metaphyses and musculotendinous insertions. The adjacent interosseous membranes may become ossified. The distribution of the bone manifestations is usually bilateral and symmetric. The soft tissue overlying the distal third of the arms and legs may be thickened. Mononuclear cell infiltration may be present in the adjacent soft tissue. Proliferation of connective tissue occurs in the nail bed and volar pad of digits, giving the distal phalanges a clubbed appearance. Small blood vessels in the clubbed digits are dilated and have thickened walls. In addition, the number of arteriovenous anastomoses is increased. The synovia of involved joints show edema, varying degrees of synovial cell proliferation, thickening of the subsynovium, vascular congestion, vascular obliteration with thrombi, and small numbers of lymphocyte infiltrates.

Several theories have been suggested for the pathogenesis of HOA. Most have been disproved or have not explained the development in all clinical disorders associated with HOA. Previously proposed neurogenic and humoral theories are no longer considered likely explanations for HOA. The neurogenic theory was based on the observation that vagotomy resulted in symptomatic improvement in a small number of patients with lung tumors and HOA. It was postulated that vagal stimuli from the tumor site led via a neural reflex to efferent nerve impulses to the distal extremities, resulting in HOA. This theory, however, did not explain HOA in conditions where vagal stimulation did not occur, as in cyanotic congenital heart disease or arterial aneurysms. The humoral theory postulated that soluble substances...
that are normally inactivated or removed during passage through the lung reached the systemic circulation in an active form and stimulated the changes of HOA. Substances proposed included prostaglandins, ferritin, bradykinin, estrogen, and growth hormone. These substances seemed unlikely candidates, since their blood levels in HOA patients overlapped those in individuals without HOA. Furthermore, these substances did not explain the development of localized HOA associated with arterial aneurysms or infected arterial grafts.

Recent studies have suggested a role for platelets in the development of HOA. It has been observed that megakaryocytes and large platelet particles, present in venous circulation, were fragmented in their passage through normal lung. In patients with cyanotic congenital heart disease and in other disorders associated with right-to-left shunts, these large platelet particles bypass the lung and reach the distal extremities, where they can interact with endothelial cells. Platelet clumps have been demonstrated to form on an infected heart valve in bacterial endocarditis, in the wall of arterial aneurysms, and on infected arterial grafts. These platelet particles may also reach the distal extremities and interact with endothelial cells. Platelet-endothelial activation in the distal portion of extremities would then result in the release of platelet-derived growth factor (PDGF) and other factors leading to the proliferation of connective tissue and periostea. Stimulation of fibroblasts by PDGF and transforming growth factor \( B \) results in cell growth and collagen synthesis. Elevated plasma levels of von Willebrand factor antigen have been found in patients with both primary and secondary forms of HOA, indicating endothelial activation or damage. Abnormalities of collagen synthesis have been demonstrated in the involved skin of patients with primary HOA. Fibroblasts from affected skin were shown to have increased collagen synthesis, increased \( \alpha 1(I) \) procollagen mRNA, and evidence for upregulation of collagen transcription. Other factors are undoubtedly involved in the pathogenesis of HOA, and further studies are needed to better understand this disorder.

**CLINICAL MANIFESTATIONS**

Primary or familial HOA, also referred to as *pachydermoperiostitis* or *Touraine-Solente-Golé syndrome*, usually begins insidiously at puberty. In a smaller number of patients, the onset is in the first year of life. The disorder is inherited as an autosomal dominant trait with variable expression and is nine times more common in boys than in girls. Approximately one-third of patients have a family history of primary HOA.

Primary HOA is characterized by clubbing, periostitis, and unusual skin features. A small number of patients with this syndrome do not express clubbing. The skin changes and periostitis are prominent features of this syndrome. The skin becomes thickened and coarse. Deep nasolabial folds develop, and the forehead may become furrowed. Patients may have heavy-appearing eyelids and ptosis. The skin is often greasy, and there may be excessive sweating of the hands and feet. Patients may also experience acne vulgaris, seborrhea, and folliculitis. In a few patients, the skin over the scalp becomes very thick and corrugated, a feature that has been descriptively termed *cutis verticis gyrata*. The distal extremities, particularly the legs, become thickened owing to proliferation of new bone and soft tissue; when the process is extensive, the distal lower extremities resemble those of an elephant. The periostitis is usually not painful, as it may be in secondary HOA. Clubbing of the fingers may be extensive, producing large, bulbous deformities and clumsiness. Clubbing also affects the toes. Patients may experience articular and periarticular pain, especially in the ankles and knees, and joint motion may be mildly restricted owing to periarticular bone overgrowth. Noninflammatory effusions occur in the wrists, knees, and ankles. Synovial hypertrophy is not found. Associated abnormalities observed in patients with primary HOA include hypertrophic gastropathy, bone marrow failure, female escutcheon, gynecomastia, and cranial suture defects. In patients with primary HOA, the symptoms disappear when
adulthood is reached.

HOA secondary to an underlying disease occurs more frequently than primary HOA. It accompanies a variety of disorders and may precede clinical features of the associated disorder by months. Clubbing is more frequent than the full syndrome of HOA in patients with associated illnesses. Because clubbing evolves over months and is usually asymptomatic, it is often recognized first by the physician and not the patient. Patients may experience a burning sensation in their fingertips. Clubbing is characterized by widening of the fingertips, enlargement of the distal volar pad, convexity of the nail contour, and the loss of the normal 15° angle between the proximal nail and cuticle. The thickness of the digit at the base of the nail is greater than the thickness at the distal interphalangeal joint. An objective measurement of finger clubbing can be made by determining the diameter at the base of the nail and at the distal interphalangeal joint of all 10 digits. Clubbing is present when the sum of the individual digit ratios is > 10. At the bedside, clubbing can be appreciated by having the patient place the dorsal surface of the distal phalanges of the fourth fingers together with the nails of the fourth fingers opposing each other. Normally, an open area is visible between the bases of the opposing fingernails; when clubbing is present, this open space is no longer visible. The base of the nail feels spongy when compressed, and the nail can be easily rocked on its bed. Marked periungual erythema is usually present. When clubbing is advanced, the finger may have a drumstick appearance, and the distal interphalangeal joint can be hyperextended. Periosteal involvement in the distal extremities may produce a burning or deep-seated aching pain. The pain can be quite incapacitating and is aggravated by dependency and relieved by elevation of the affected limbs. The overlying soft tissue may be swollen, and the skin slightly erythematous. Pressure applied over the distal forearms and legs may be quite painful.

Patients may also experience joint pain, most often in the ankles, wrists, and knees. Joint effusions may be present; usually they are small and noninflammatory. The small joints of the hands are rarely affected. Severe joint or bone pain may be the presenting symptom of an underlying lung malignancy and may precede the appearance of clubbing. In addition, the progression of HOA tends to be more rapid when associated with malignancies, most notably bronchogenic carcinoma. Unlike primary HOA, excessive sweating and oiliness of the skin and thickening of the facial skin are uncommon in secondary HOA.

HOA occurs in 5–10% of patients with intrathoracic malignancies, the most common being bronchogenic carcinoma and pleural tumors (Table 330-3). Lung metastases infrequently cause HOA. HOA is also seen in patients with intrathoracic infections, including lung abscesses, empyema, bronchiectasis, chronic obstructive lung disease, and, uncommonly, pulmonary tuberculosis. HOA may also accompany chronic interstitial pneumonitis, sarcoidosis, and cystic fibrosis. In the latter, clubbing is more common than the full syndrome of HOA. Other causes of clubbing include congenital heart disease with right-to-left shunts, bacterial endocarditis, Crohn’s disease, ulcerative colitis, sprue, and neoplasms of the esophagus, liver, and small and large bowel. In patients with congenital heart disease with right-to-left shunts, clubbing alone occurs more often than the full syndrome of HOA.

<table>
<thead>
<tr>
<th>Table 330-3 Disorders Associated with Hypertrophic Osteoarthropathy</th>
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<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
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<tr>
<td>Bronchogenic carcinoma and other neoplasms</td>
</tr>
<tr>
<td>Lung abscesses, empyema, bronchiectasis</td>
</tr>
<tr>
<td>Chronic interstitial pneumonitis</td>
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</tbody>
</table>
Cystic fibrosis
Chronic obstructive lung disease
Sarcoidosis
Gastrointestinal
  Inflammatory bowel disease
  Sprue
  Neoplasms: esophagus, liver, bowel
Cardiovascular
  Cyanotic congenital heart disease
  Subacute bacterial endocarditis
  Infected arterial grafts
  Aortic aneurysm
  Aneurysm of major extremity artery
  Patent ductus arteriosus
  Arteriovenous fistula of major extremity vessel
  Thyroid (thyroid acropathy)
  Hyperthyroidism (Graves' disease)

A Unilateral involvement.
B Bilateral lower extremity involvement.

Unilateral clubbing has been found in association with aneurysms of major extremity arteries, with infected arterial grafts, and with arteriovenous fistulas of brachial vessels. Clubbing of the toes but not fingers has been associated with an infected abdominal aortic aneurysm and patent ductus arteriosus. Clubbing of a single digit may follow trauma and has been reported in tophaceous gout and sarcoidosis. While clubbing occurs more commonly than the full syndrome in most diseases, periostitis in the absence of clubbing has been observed in the affected limb of patients with infected arterial grafts.

Hyperthyroidism (Graves' disease), treated or untreated, is occasionally associated with clubbing and periostitis of the bones of the hands and feet. This condition is referred to as thyroid acropathy. Periostitis is asymptomatic and occurs in the midshaft and diaphyseal portion of the metacarpal and phalangeal bones. The long bones of the extremities are seldom affected. Elevated levels of long-acting thyroid stimulator are found in the serum of these patients.

LABORATORY FINDINGS

The laboratory abnormalities reflect the underlying disorder. The synovial fluid of involved joints has < 500 white cells per microliter, and the cells are predominantly mononuclear. Radiographs show a faint radiolucent line beneath the new periosteal bone along the shaft of long bones at their distal end. These changes are observed most frequently at the ankles, wrists, and knees. The ends of the distal phalanges may show osseous resorption. Radionuclide studies show pericortical linear uptake along the cortical margins of long bones that may be present before any radiographic changes.

HYPERTROPHIC OSTEOARTHRPATHY: TREATMENT
The treatment of HOA is to identify the associated disorder and treat it appropriately. The symptoms and signs of HOA may disappear completely with removal or effective chemotherapy of a tumor or with antibiotic therapy and drainage of a chronic pulmonary infection. Vagotomy or percutaneous block of the vagus nerve leads to symptomatic relief in some patients. Aspirin, NSAIDs, or analgesics may help control symptoms of HOA.

**Reflex Sympathetic Dystrophy Syndrome**

The reflex sympathetic dystrophy syndrome is now referred to as complex regional pain syndrome, type 1, by the new Classification of the International Association for the Study of Pain. It is characterized by pain and swelling, usually of a distal extremity, accompanied by vasomotor instability, trophic skin changes, and the rapid development of bony demineralization. Reflex sympathetic dystrophy syndrome, including its treatment, is covered in greater detail in Chap. 371.

**Tietze Syndrome and Costochondritis**

Tietze syndrome is manifested by painful swelling of one or more costochondral articulations. The age of onset is usually before 40, and both sexes are affected equally. In most patients only one joint is involved, usually the second or third costochondral joint. The onset of anterior chest pain may be sudden or gradual. The pain may radiate to the arms or shoulders and is aggravated by sneezing, coughing, deep inspirations, or twisting motions of the chest. The term costochondritis is often used interchangeably with Tietze syndrome, but some workers restrict the former term to pain of the costochondral articulations without swelling. Costochondritis is observed in patients over age 40; tends to affect the third, fourth, and fifth costochondral joints; and occurs more often in women. Both syndromes may mimic cardiac or upper abdominal causes of pain. Rheumatoid arthritis, ankylosing spondylitis, and Reiter’s syndrome may involve costochondral joints but are distinguished easily by their other clinical features. Other skeletal causes of anterior chest wall pain are xiphoidalgia and the slipping rib syndrome, which usually involves the tenth rib. Malignancies such as breast cancer, prostate cancer, plasma cell cytoma, and sarcoma can invade the ribs, thoracic spine, or chest wall and produce symptoms suggesting Tietze syndrome. They should be easily distinguishable by radiographs and biopsy. Analgesics, anti-inflammatory drugs, and local glucocorticoid injections usually relieve symptoms.

**MYOFASCIAL PAIN SYNDROME**

Myofascial pain syndrome is characterized by localized musculoskeletal pain and tenderness in association with trigger points. The pain is deep and aching and may be accompanied by a burning sensation. Myofascial pain may follow trauma, overuse, or prolonged static contraction of a muscle or muscle group, which may occur when reading or writing at a desk or working at a computer. In addition, this syndrome may be associated with underlying osteoarthritis of the neck or low back. Trigger points are a diagnostic feature of this syndrome. Pain is referred from trigger points to defined areas distant from the original tender points. Palpation of the trigger point reproduces or accentuates the pain. The trigger points are usually located in the center of a muscle belly, but they can occur at other sites, such as costosternal junctions, the xiphoid process, ligamentous and tendinous insertions, fascia, and fatty areas. Trigger point sites in muscle have been described as feeling indurated and taut, and palpation may cause the muscle to twitch. These findings, however, have been shown not to be unique for myofascial pain syndrome, since in a controlled study they were also present in fibromyalgia patients and normal subjects. Myofascial pain most often involves the posterior neck, low back, shoulders, and chest. Chronic pain in the muscles of the posterior neck may involve referral of pain from the trigger point in the erector neck muscle or upper trapezius to the head, leading to persistent
headaches, which may last for days. Trigger points in the paraspinal muscles of the low back may refer
pain to the buttock. Pain may be referred down the leg from a trigger point in the gluteus medius and
can mimic sciatica. A trigger point in the infraspinatus muscle may produce local and referred pain over
the lateral deltoid and down the outside of the arm into the hand. Injection of a local anesthetic such as
1% lidocaine into the trigger point site often results in pain relief. Another useful technique is first to
spray from the trigger point toward the area of referred pain with an agent such as ethyl chloride and
then to stretch the muscle. This maneuver may need to be repeated several times. Massage and
application of ultrasound to the affected area also may be beneficial. Patients should be instructed in
methods to prevent muscle stresses related to work and recreation. Posture and resting positions are
important in preventing muscle tension. The prognosis in most patients is good. In some patients,
myofascial pain syndrome may evolve into fibromyalgia (Chap. 329). Patients at risk for developing
fibromyalgia are thought to be those with anxiety, depression, nonrestorative sleep, and fatigue.

**TUMORS OF JOINTS**

Primary tumors and tumor-like disorders of synovium are uncommon but should be considered in the
differential diagnosis of monarticular joint disease. In addition, metastases to bone and primary bone
tumors adjacent to a joint may produce joint symptoms. For further discussion, see Chap. 94.

*Pigmented villonodular synovitis* is characterized by the slowly progressive, exuberant, benign
proliferation of synovial tissue, usually involving a single joint. The most common age of onset is in the
third decade, and women are affected slightly more often than men. The cause of this disorder is
unknown.

The synovium has a brownish color and numerous large, finger-like villi that fuse to form pedunculated
nodules. There is marked hyperplasia of synovial cells in the stroma of the villi. Hemosiderin granules
and lipids are found in the cytoplasm of macrophages and in the interstitial tissue. Multinucleated giant
cells may be present. The proliferative synovium grows into the subsynovial tissue and invades adjacent
cartilage and bone.

The clinical picture of pigmented villonodular synovitis is characterized by the insidious onset of swelling
and pain in one joint, most commonly the knee. Other joints affected include the hips, ankles,
calcaneocuboid joints, elbows, and small joints of the fingers or toes. The disease may also involve the
common flexor sheath of the hands or fingers. Less commonly, tendon sheaths in the wrist, ankle, or
foot may be involved. Symptoms may be mild and intermittent and may be present for years before the
patient seeks medical attention. Radiographs may show joint space narrowing, erosions, and
subchondral cysts. The joint fluid contains blood and is dark red or almost black in color. Lipid-
containing macrophages may be present in the fluid. The joint fluid may be clear if hemorrhages have
not occurred.

The treatment of pigmented villonodular synovitis is complete synovectomy. With incomplete
synovectomy, the villonodular synovitis recurs, and the rate of tissue growth may be faster than it was
originally. Irradiation of the involved joint has been successful in some patients.

*Synovial chondromatosis* is a disorder characterized by multiple focal metaplastic growths of normal-
appearing cartilage in the synovium or tendon sheath. Segments of cartilage break loose and continue
to grow as loose bodies. When calcification and ossification of loose bodies occur, the disorder is
referred to as *synovial osteochondromatosis*. The disorder is usually monarticular and affects young to
middle-aged individuals. The knee is most often involved, followed by hip, elbow, and shoulder.
Symptoms are pain, swelling, and decreased motion of the joint. Radiographs may show several
rounded calcifications within the joint cavity. Treatment is synovectomy; however, the tumor may
Hemangiomas occur in synovium and in tendon sheaths. The knee is affected most commonly. Recurrent episodes of joint swelling and pain usually begin in childhood. The joint fluid is bloody. Treatment is excision of the lesion. Lipomas occur most often in the knee, originating in the subsynovial fat on either side of the patellar tendon. Lipomas also appear in tendon sheaths of the hands, wrists, feet, and ankles. In some instances, surgical removal is necessary.

Synovial sarcoma is a malignant neoplasm often found near a large joint of both upper and lower extremities, being more common in the lower extremity. It seldom arises within the joint itself. Synovial sarcomas constitute 10% of soft tissue sarcomas. The tumor is believed to arise from primitive mesenchymal tissue that differentiates into epithelial cells and/or spindle cells. Small foci of calcification may be present in the tumor mass. It occurs most often in young adults and is more common in men. The tumor presents as a slowly growing deep seated mass near a joint, without much pain. The area of the knee is the most common site, followed by the foot, ankle, elbow, and shoulder. Other primary sites include the buttocks, abdominal wall, retroperitoneum, and mediastinum. The tumor spreads along tissue planes. The most common site of visceral metastasis is lung. The diagnosis is made by biopsy. Treatment is wide resection of the tumor including adjacent muscle and regional lymph nodes, followed by chemotherapy and radiation therapy. Currently used chemotherapeutic agents are doxorubicin, ifosfamid, and cisplatin. Amputation of the involved distal extremity may be required. Chemotherapy may be beneficial in some patients with metastatic disease. Isolated pulmonary metastasis can be surgically removed. The 5-year survival with treatment is variable depending on the staging of the tumor, ranging from approximately 25% to 60% or higher. Synovial sarcomas tend to recur locally and eventually metastasize to regional lymph nodes, lungs, and skeleton.

FURTHER READINGS


BIBLIOGRAPHY


