CHAPTER 25

Less Common Arthropathies
A. Hematologic and Malignant Disorders

ADEL G. FAM, MD, FRCP(C), FACP

- Recurrent hemarthrosis is the primary clinical manifestation of hemophilia.
- Hemophilia A (classic hemophilia) is a heritable, X-linked recessive disorder of blood coagulation, occurring almost exclusively in males. The disorder is associated with a deficiency of factor VIII.
- Hemophilia B (Christmas disease), somewhat rarer but essentially indistinguishable clinically from hemophilia A, is caused by factor IX deficiency.
- Sickle-cell hemoglobinopathies associated with chronic hemolytic anemia and rheumatic manifestations include both homozygous sickle-cell anemia (Hb SS) and the heterozygous states: sickle-beta thalassemia, sickle-C (S-C) disease, and sickle-D (S-D) disease.
- Sickle-cell disease results from a single nucleotide substitution of valine for glutamic acid in the beta globin gene.
- In SS disease, the painful crises, osteonecrosis, and dactylitis are the result of small blood vessel occlusion in the bone marrow by sickled red cells.
- Osteomyelitis in patients with Hb SS disease is due to a combination of ischemic bone infarction and impaired host immunity. *Salmonella* is the most common organism.
- Thalassemia is a group of inherited hemoglobin disorders characterized by defects in the synthesis of one or more of the alpha or beta subunits of Hb.
- In beta-thalassemia, the reduced or absent production of beta chains leads to the production of an imbalance between the numbers of alpha and beta chains. This leads, in turn, to unstable Hb molecules, precipitation of the unaffected chains during erythropoiesis, and hemolysis.
- Mechanisms by which cancer can cause musculoskeletal symptoms include direct tumor invasion of bones and joints, hemorrhage into the joint, secondary gout, and paraneoplastic syndromes.

Musculoskeletal manifestions of hematologic and malignant disorders are reviewed in this chapter. A list of these conditions is shown in Table 25A-1.

NONMALIGNANT HEMATOLOGIC DISORDERS

Hemophilia

Hemophilia A is a heritable, X-linked recessive disorder of blood coagulation, occurring almost exclusively in males (1 in 5000–10,000 male births). **Hemophilia A** (classic hemophilia) is due to factor VIII deficiency, whereas **hemophilia B** (Christmas disease) is caused by factor IX deficiency. Tissue factor–factor VIIa complex is important in initiating coagulation by activating small amounts of both factors X and IX in the environment of tissue factor–bearing cells. Factor Xa and factor IXa, formed in the initial reaction, then play a role in factor VIII activation, generation of thrombin on platelet surfaces, and blood clotting. Factor VIII is a 340,000 Da coagulant protein that activates factor X in the intrinsic coagulation pathway (1). In hemophilia, the extrinsic tissue-dependent pathway remains intact, and is probably the major hemostatic regulatory system. Gene deletions, insertions, or rearrangements have been implicated in the chromosomal abnormalities leading to hemophilia. These various genetic abnormalities lead to a range of disease severities in hemophilia. Identification of the gene for factor VIII, located on the X chromosome, facilitates both prenatal diagnosis of hemophilia and carrier detection for genetic counseling.

In mild hemophilia, the levels of factor VIII are 6% to 36% of normal, and bleeding generally occurs in response to minor trauma. In a moderately severe

TABLE 25A-1. LESS COMMON ARTHROPATHIES. HEMATOLOGIC AND MALIGNANT DISORDERS.

Nonmalignant hematologic disorders
Hemophilic arthropathy
Hemoglobinopathy-associated arthropathies
Sickle-cell disease
Thalassemia
Malignant disorders
Metastatic (tumor invasion of joints)
Metastatic carcinomatous arthritis
Leukemic arthritis
Lymphomatous arthritis
Angioimmunoblastic T-cell lymphoma–associated arthritis
Myelomatous arthritis
Waldenstrom's macroglobulinemia
Nonmetastatic (paraneoplastic)
Hypertrophic osteoarthropathy (see Chapter 25F)
Carcinoma polyarthritis
Amyloid arthritis
Secondary gout
Miscellaneous: dermatomyositis, paraneoplastic vasculitis

hemophilia, the level ranges from 2% to 5% of normal. In severe hemophilia—two thirds of all patients—the level is 1% or less. Plasma levels of factor VIII of <5% of normal are associated with spontaneous hemarthrosis. The diagnosis of hemophilia can be confirmed by a coagulation screen, including bleeding time, platelet count, prothrombin time, plasma thromboplastin time, and determinations of the levels of factors VIIl and IX.

Christmas disease (hemophilia B), due to factor IX deficiency, is less common than hemophilia A. The gene for factor IX is also located on the X chromosome. Hemophilia B, which occurs in approximately 1 in 30,000 to 100,000 male births, produces a clinical picture that is largely indistinguishable from that of hemophilia A. Factor IX is a 60,000 Da proenzyme that is converted to an active protease (factor IXa) by the tissue factor–VIIa complex. Factor IXa, in combination with activated factor VIII, subsequently activates factor X (2). In rare circumstances, deficiency of factors XI, VII, V, X, or II may be associated with hemarthrosis.

Recurrent hemarthrosis is the most common bleeding manifestation of hemophilia A, occurring in up to two thirds of patients (3). This may occur spontaneously or following minor trauma. The onset is rapid with pain, swelling, local tenderness, and limitation of joint movements. The rising intra-articular pressure eventually terminates bleeding, but resolution of the clot occurs slowly. The knee, elbow, and ankle are the most frequently affected joints. Bleeding into the hip joint can lead to osteonecrosis of the femoral head. Patients with factor VIII levels <5% of normal, who are inadequately treated, may develop a chronic arthritis with intermittent pain, stiffness, persistent synovial swelling, deformity, instability, and secondary osteoarthritis. Chronic arthritis is less frequent and less severe in Christmas disease.

Hemophilic arthropathy is thought to be due to repeated intra-articular bleeding and excessive iron deposition in both the synovial membrane and articular cartilage. Because prothrombin and fibrinogen are absent in normal synovial fluid, the blood remains as a liquid. Plasma gradually resorbs while the remaining red cells are phagocytosed by synovial lining macrophages. Hemosiderin deposition in both synovial lining cells and subsynovial supporting tissue is associated with chronic proliferative synovitis and pannus formation. The synovitis results in the production of lysosomal enzymes, collagenase, catabolic cytokines [interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha)], superoxide anions, and hydroxyl radicals that can lead to cartilage breakdown and osteoarthritis.

Radiographs often show increased periarticular soft tissue swelling due to extensive iron deposition in the synovium. Widening or premature fusion of the epiphyses, enlargement of the femoral and humeral intercondylar notches (Figure 25A-1), "squaring" of the inferior patella, expansion of the radial head at the elbow, and secondary osteoarthritis may occur in later stages. Computed tomography (CT) scans are helpful in delineating the bone and soft tissue lesions. Magnetic resonance imagaing (MRI) is useful in demonstrating intra-articular hemorrhage, subsynovial or muscle hematomata, and chronic synovial hypertrophy.

Bleeding into muscles occurs less frequently and can lead to large bloody collections or "hemophilic pseudotumors" associated with muscle necrosis, cyst formation, and, sometimes, compartment syndromes. Compression femoral neuropathy may result from a retroperitoneal or psoas hematoma. Subperiosteal hemorrhage can result in a bone pseudotumor.

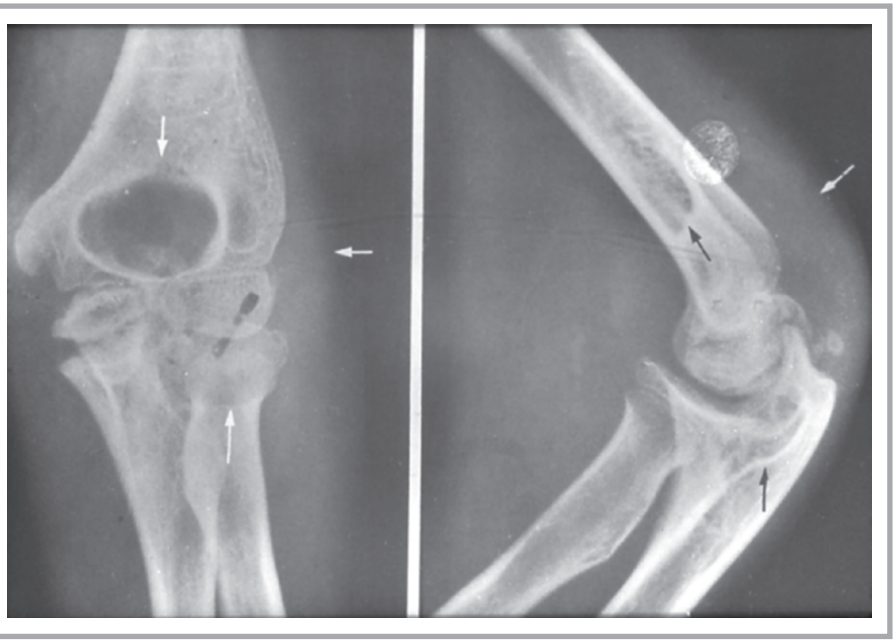
Septic arthritis is a rare complication of hemophilic arthropathy. *Staphylococcus aureus* is the most common organism; coincidental human immunodeficiency virus (HIV) infection appears to be an important contributing factor in this complication. Septic arthritis is suspected when an episode of hemarthrosis fails to respond promptly to treatment with factor VIII and joint immobilization, particularly in the presence of fever or leukocytosis.

Treatment

Since the 1960s, the widespread use of human donor plasma products, concentrated with factor VIII, including cryoprecipitate, has improved the care of patients with hemophilia by reducing the severity and frequency of the bleeding episodes and by permitting surgical procedures. Between 1980 and 1985, however, these products also led to the spread of HIV and viral hepatitis

FIGURE 25A-1

Elbow radiograph in a patient with chronic hemophilia A showing widening of the intercondylar notch and secondary osteoarthritis with joint space narrowing, marginal osteophytes, and intra-articular osseous bodies. Note increased periarticular swelling and density due to iron deposition in the synovium (*arrows*).



(hepatitis B and C) among hemophiliacs. Donor screening and purification of factor VIII concentrates with monoclonal anti–factor VIII antibody and heat lyophilization markedly reduced these infectious complications. The advent of recombinant factor VIII has completely eliminated the risk of infection. Replacement recombinant factor VIII therapy is administered prophylactically to children with severe hemophilia 1 to 3 years of age in order to maintain plasma factor levels >1% (3). This serves to reduce the frequency of spontaneous bleeding and prevent joint damage. Desmopressin (DDAVP), a synthetic analog of vasopressin, stimulates a transient increase in factor VIII levels, and can provide an alternative therapy for patients with mild or moderate hemophilia A (3). Inhibitor IgG antibodies to factor VIII develop in 5% to 10% of young patients with hemophilia A, but are less common in Christmas disease. Therapeutic options in these patients include plasmapheresis and treatment with oral glucocorticoids, azathioprine, cyclophosphamide, or porcine factor VIII concentrate. Factor IX is not present in cryoprecipitate or in factor VIII concentrates. Fresh frozen plasma is an effective therapy, but carries with it some risk of blood-borne infections. Virally inactivated factor IX concentrate and recombinant factor IX are preferred.

Acute hemarthrosis is treated with immobilization, ice packs, and prompt administration of factor VIII concentrate or recombinant factor VIII for approximately 48 hours. If the joint effusion is unusually tense or if infection is suspected, joint aspiration is recommended, preferably following factor VIII replacement. Short-term use of intra-articular or oral glucocorticoids may confer some additional benefit, but repeated use can lead to side effects. For subacute and chronic arthritis, nonsteroidal anti-inflammatory drugs (NSAIDs)—not including aspirin—are relatively safe and beneficial. Physical therapy is useful in preventing joint contractures and deformities (3).

Surgical synovectomy reduces the chronic synovitis and subsequent joint damage, but is associated with significant morbidity. Arthroscopic synovectomy, also effective, has fewer complications. Both chemical synovectomy (by injecting intra-articular osmic acid, rifampicine, or other sclerosing agent) and radiation synovectomy (using intra-articular radioisotope injections such as colloidal P 32 chromic-phosphate, 90-yttrium, or 186-rhenium) may be effective in the short term. The long-term efficacies of both chemical and radiation synovectomy, however, are less favorable (3). Total joint replacement is indicated for advanced osteoarthritis of the hip, shoulder, elbow, or ankle. Promising preliminary results with gene therapy have been reported in a small number of patients with severe hemophilia.

Hemoglobinopathy-Associated Musculoskeletal Manifestations

Sickle-Cell Disease

Sickle-cell hemoglobinopathies associated with chronic hemolytic anemia and rheumatic manifestations include both homozygous sickle-cell anemia (Hb SS) and the heterozygous states: sickle-beta thalassemia, sickle-C (S-C) disease, and sickle-D (S-D) disease. SS disease occurs mostly in Africans, but also in southern Italy, Greece, Turkey, Saudi Arabia, and India (4).

Sickle cell disease results from a single nucleotide substitution of valine for glutamic acid in the beta globin gene. The diagnosis can be confirmed by cellulose acetate Hb electrophoresis showing 76% to 100% Hb SS. Deoxygenation (hypoxia) results in polymerization of HbS, forming liquid crystals. This deforms the red cells from biconcave discs into elongated, rigid, crescent-shaped sickle cells, causing occlusion of the microcirculation and breakdown of red cells (hemolysis), leading in turn to further tissue hypoxia and sickling. Polymerization of HbS is influenced by intracellular concentrations of HbS, HbF, and HbC; blood oxygen saturation; and pH and temperature.

Once a sufficient number of rigid sickle cells is formed, microvascular occlusion will result. Hypoxia of tissues causes a secondary inflammatory reaction mediated by histamine, bradykinin, and prostaglandins, resulting in increased intramedullary pressure and bone pain (4). The painful crises, osteonecrosis, and dactylitis are the result of small blood vessel occlusion in the bone marrow by sickled red cells. These manifestations, most frequent in homozygous (SS) sickle-cell disease, may also occur under certain circumstances in the milder heterozygous sickle hemoglobinopathies such as HbS/beta-thalassemia ("sickle-thal disease") and S-C disease. Individuals with sickle-cell trait (HbAS), healthy carriers of the gene mutation, are free from musculoskeletal symptoms. Pure HbC disease, caused by substitution of lysine for glutamic acid in the beta chain, produces hemolysis. In contrast, Hb S-C disease results in features of both sickling and hemolysis (4). Recurrent painful crises mainly affect the juxta-articular areas of long bones, joints, spine, and ribs (5,6). The pain is often associated with local swelling and tenderness. The crises can be triggered by infection, dehydration, acidosis, cold exposure, traveling at high altitudes, and stress. The duration of crises is variable but usually no longer than 2 weeks. The "pain rate" (number of painful episodes per year) correlates with early death in patients with SS anemia. Hydroxyurea, which increases the levels of fetal Hb, reduces the pain rate and may ultimately improve survival (5,6).

Sickle-cell arthropathy, caused by microvascular ischemia and synovial infarctions, often affects large joints. Reaction to juxta-articular bone infarcts may also contribute to joint pain. Small, non-inflammatory synovial effusions are common.

Osteonecrosis (Figure 25A-2) affects the femoral head in approximately 33% of patients and the humeral head in 25%. Multiple joints, including the spine, may be involved (7). In the spine, the bony infarcts result in the characteristic biconcave or "Lincoln log" vertebrae. The risk of osteonecrosis is highest in those with frequent painful crises and in patients with Hb SS-alpha-thalassemia. Total replacement arthroplasty is recommended for those with advanced secondary osteoarthritis, but there is a high rate of perioperative complications and mechanical loosening (7).

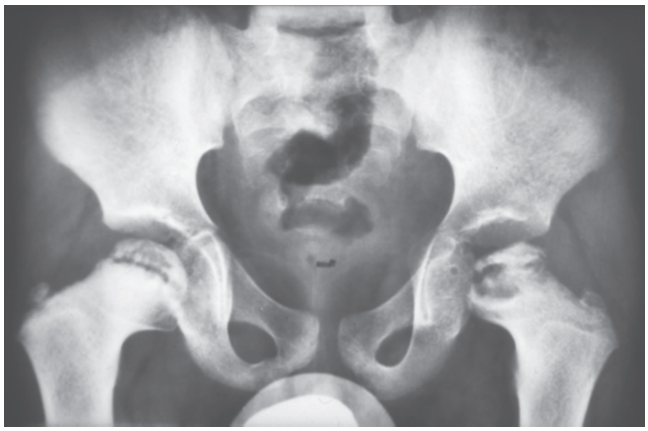


FIGURE 25A-2

Radiograph of the hips, showing bilateral osteonecrosis.

Dactylitis typically occurs in children, and is characterized by acute, painful, nonpitting swelling of the hands and feet ("hand and foot syndrome") (4,6). Fever and leukocytosis, which may be the initial disease manifestations, occur in S-S, S-C, and S-thalassemia disease. Radiographs may show soft tissue swelling, periosteal new bone formation, or intramedullary sclerotic infarcts of the phalanges, metacarpals, and metatarsals. Scintigraphy and MRI are more sensitive in detecting bone infarcts. Symptoms usually resolve within 7 days, but recurrences are frequent. Osteonecrosis of the epiphyses can lead to digital shortening. Osteopenia, stress fractures, vertebral collapse, and growth abnormalities may also occur in sickle-cell disease (6).

Osteomyelitis in patients with Hb SS disease is due to a combination of ischemic bone infarction and impaired host immunity. *Salmonella* is the most common organism, followed by *Staphylococcus aureus* and Gram-negative bacilli. Osteomyelitis usually follows an episode of painful crisis and may affect multiple sites. Chronic sickling of the intestinal microvasculature may predispose the devitalized bowel to invasion by *Salmonella* and other enteric bacteria. Osteomyelitis should be suspected if symptoms of a painful crisis fail to respond after 1 to 2 weeks. The diagnosis is confirmed by radiography, bone scanning, and by cultures from the blood or bone (obtained through a CT-guided aspiration). MRI is more accurate in delineating the lesions. Septic arthritis is caused by the same organisms as osteomyelitis, often occurring in association with osteonecrosis or a painful vaso-occlusive crisis involving the same joint. A high index of suspicion and synovial fluid cultures are essential for early recognition.

Gout is a rare complication of sickle-cell disease. Hyperuricemia results from enhanced erythropoiesis

secondary to chronic hemolysis, increased nucleic acid sythesis, and overproduction of uric acid. In addition, cumulative renal damage occurring by the third decade of life—the result of renal ischemia and microinfarctions—can lead to sustained hyperuricemia and gout.

Severe sickle-cell anemia is treated by blood transfusions and folic acid supplements (1–5 mg folic acid/day) (4). Enhanced erythropoietic activity secondary to chronic hemolysis may lead to folate deficiency through the depletion of folate stores. Measures to prevent painful crises include avoidance of stress, alcohol, overexertion, swimming, and high altitudes. Treatment of the painful crises consists of acetaminophen or NSAIDs for mild episodes, and codeine or oxycodone for more severe attacks (4). Oral controlled-release morphine is as effective as continuous intravenous morphine for the management of painful episodes in children (8). Hydroxyurea enhances the production of HbF, which in turn reduces polymerization of Hb SS (9). Treatment with hydroxyurea has been shown to be both cost-effective and beneficial in reducing the rate of painful crises in adults with SS (9). Favorable results have been reported with bone marrow (stem cell) transplantation in children with SS disease.

Thalassemia

Thalassemia is a group of inherited hemoglobin disorders characterized by defects in the synthesis of one or more of the alpha or beta subunits of Hb. (Normally, alpha-globin proteins are equal to beta-globin proteins.) The reduced or absent production of beta chains in beta-thalassemia, for example, subunit leads to the production of an imbalance between the numbers of alpha and beta chain, unstable Hb molecules, and precipitation of the unaffected chains during erythropoiesis, resulting ultimately in hemolysis and the formation of Heinz bodies. In beta-thalassemia, the precipitated alpha-globin chains are particularly toxic, damaging red cell membranes and causing hemolysis, marrow erythroid hyperplasia, and often hypersplenism. In compensation for the decreased beta subunits, levels of both HbF and HbA2 are often elevated in these patients (10).

Thalassemia is especially common in persons of Mediterranean background. beta-Thalassemia major (also known as Cooley's anemia) is one of the most severe forms of congenital hemolytic anemia. These patients are typically transfusion-dependent and rarely survive into adulthood. Only beta-thalassemia major is associated with musculoskeletal manifestations. These result from expansion of the erythroid marrow, and include osteoporosis with wide medullary spaces, coarse trabeculae, and pathologic fractures. Epiphyseal deformities and leg shortening may also occur, but osteonecrosis is not a feature. Patients with HbS and beta-thalassemia often have HbA2 and features of both SS disease and beta-thalassemia. beta-Thalassemia minor (trait) is a relatively common disorder that is rarely associated with clinical manifestations.

Blood transfusions are the main supportive treatment of beta-thalassemia major, but transfusion hemosiderosis is a common problem and chelation therapy with deferoxamine is often required (10). Splenectomy is indicated if 40% or greater increase in the transfusion requirements occur during a 1-year period. Allogeneic bone marrow (stem cell) transplantation and gene transfer is a promising new treatment in children.

MUSCULOSKELETAL SYMPTOMS AND CANCER

Malignant disease is associated with a number of musculoskeletal manifestations (Table 25A-2) (11). Mechanisms by which cancer can cause musculoskeletal symptoms include: (1) direct tumor invasion of bones and joints (skeletal metastases, metastatic carcinomatous arthritis, leukemic synovitis and lymphomatous arthritis); (2) hemorrhage into the joint (leukemia); (3) secondary gout (leukemia, polycythemia, lymphoma, myeloma, carcinoma); and (4) through remote, non-

TABLE 25A-2. CANCER AND RHEUMATIC DISEASE.

Direct tumor invasion of joints
Metastatic carcinomatous arthritis
Leukemic arthritis
Lymphomatous arthritis
Myelomatous arthritis
Nonmetastatic paraneoplastic rheumatic syndromes
Articular
Hypertrophic osteoarthropathy (Chapter 25F)
Carcinomatous polyarthritis
Amyloid arthritis
Secondary gout
Muscular
Dermatomyositis and polymyositis
Lambert–Eaton myasthenic syndrome
Cutaneous
Palmar fasciitis and arthritis
Panniculitis and arthritis
Eosinophilic fasciitis
Vascular
Paraneoplastic vasculitis
Erythromelalgia
Miscellaneous
Multicentric reticulohistocytosis
Malignancy developing in a preexisting connective tissue disease
Lymphoma developing in Sjögren's syndrome
Malignancy as a complication of therapy for rheumatic disorders
Myelodysplastic syndrome after cyclophosphamide therapy

metastatic effects of the tumor (paraneoplastic syndromes), such as hypertrophic osteoarthropathy. There is an increased incidence of lymphoma in patients with Sjögren's syndrome, rheumatoid arthritis (RA), and systemic lupus erythematosus. Treatment of rheumatic disorders with immunosuppressive drugs may also result in malignancy. Conversely, chemotherapeutic drugs used in the treatment of neoplasms may cause rheumatic syndromes.

Direct Tumor Invasion of Joints

Metastatic Carcinomatous Arthritis

Metastatic carcinomatous arthritis, due to direct invasion of the joint or adjacent bones by metastases, is a rare form of arthritis (11,12). The arthritis may be the initial manifestation of malignant disease. Bronchogenic carcinoma is the most common primary tumor. Other sources include carcinoma of the breast, prostate, thyroid, kidney, and colon. The arthritis is often monoarticular and commonly affects the knee, hip, shoulder, elbow, or ankle. Metastases distal to the elbows and knees are uncommon and involvement of the joints of the hands and feet is rare.

Severe bone and joint pain, worse at night and with movements, is common. Joint effusions are commonly hemorrhagic and often re-accumulate rapidly after aspiration. The fluids are non-inflammatory with low cell counts characterized by mononuclear predominance. Using cytomorphologic techniques, tumor cells may be identified in synovial effusions (Figure 25A-3) (12). Radiographs commonly show juxta-articular osteolytic lesions and bone scanning may reveal metastases at other sites. Carcinomatous invasion of the synovium can be demonstrated by arthroscopic or percutaneous needle synovial biopsy. Treatment with chemotherapy and radiotherapy is often palliative.

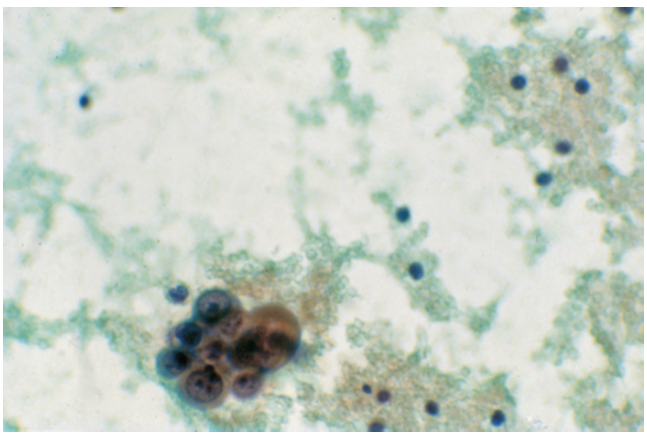


FIGURE 25A-3

Metastatic carcinomatous arthritis of right shoulder: synovial fluid cytology showing malignant cells (carcinoma of lung) with pleomorphic, eccentric, hyperchromatic nuclei and large irregular nucleoli.

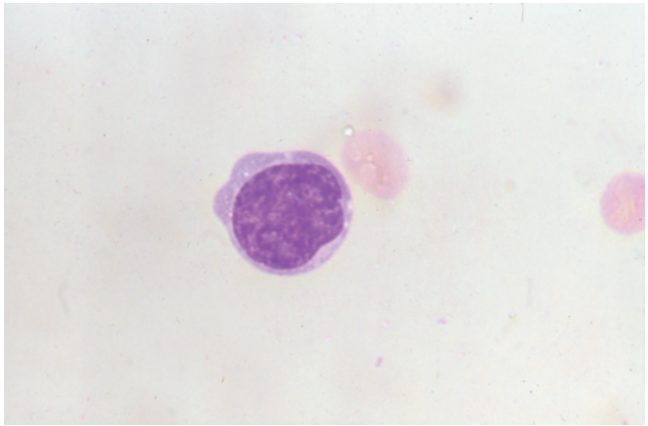


FIGURE 25A-4

Acute lymphoblastic leukemia, leukemic arthritis: cytocentrifuge preparation of synovial fluid from left elbow showing a cALLA-positive lymphoblast by immunocytology (Wright's stain, original magnification ×1000).

Leukemic Arthritis

Joint manifestations occur in about 14% of patients with leukemia (13,14). These are more common in acute leukemia, particularly acute lymphoblastic leukemia in children. Known mechanisms of arthritis in patients with leukemia include leukemic arthritis caused by direct invasion of articular tissues and juxta-articular bones by leukemic cells, joint infection, intra-articular hemorrhage, and gouty arthritis.

Leukemic arthritis is an asymmetric, painful polyarthritis of large joints, such as the knee, shoulder, or ankle. It may precede other manifestations of leukemia. Nocturnal bone pains and severe joint pains, often disproportionate to the apparent degree of arthritis, are characteristic. Hematologic and bone marrow abnormalities are inevitably present in leukemic arthritis. Radiographic findings include metaphyseal rarefaction, osteolytic lesions, and sometimes periosteitis. The diagnosis can be confirmed by demonstration of leukemic cells in synovial fluid and/or synovium (Figure 25A-4) (13,14). Immunocytological techniques employing indirect immunofluorescence and a panel of early B-cell and myeloid antigens (e.g., cALLA or acute lymphoblastic leukemia antigen) have been used to identify leukemic cells in joint effusions and in the synovium (13,14). Leukemic arthritis usually occurs in patients with widespread disease and the response to therapy is generally poor.

Lymphoma and Arthritis

Musculoskeletal symptoms occur in up to 25% of patients with non-Hodgkin's lymphoma. Bone pain is the most common manifestation. Mechanisms of arthritis in patients with lymphoma include lymphomatous arthritis, hypertrophic osteoarthropathy (see Chapter 25F), joint infection, and secondary gout (15). Lymphomatous arthritis, due to invasion of juxta-articular bone or synovial tissue by lymphoma, is rare. Both polyarticular and monoarticular presentations have been described. Lymphoma is suspected in patients in whom severe constitutional symptoms appear out of proportion to the severity of arthritis, and in those with periarticular osteolytic lesions. The diagnosis can be confirmed by bone or synovial biopsy. A symmetric polyarthritis with fever has been described in patients with the rare intravascular lymphoma (intravascular lymphomatosis).

Angioimmunoblastic T-Cell Lymphoma–Associated Arthritis

Angioimmunoblastic T-cell lymphoma (AITL), previously termed *angioimmunoblastic lymphadenopathy*, is a rare type of non-Hodgkin's T-cell lymphoma characterized by fever, weight loss, lymphadenopathy, hepatosplenomegaly, urticaria or other skin eruption, vasculitis, serositis, hemolytic anemia, and polyclonal hypergammaglobulinemia (16).

A nonerosive, nondeforming, symmetric, seronegative polyarthritis may occur as initial manifestation of the disease or concurrent with other features. Joints of the hands are commonly affected. Synovial biopsies may show typical features of AITL. Synovial fluid leukocytosis with decreased number of CD8 lymphocytes may occur. The diagnosis is confirmed by lymph node biopsy showing proliferation of small blood vessels and replacement of normal lymph node architecture by plasma cells, immunoblasts, and eosinophils. Response to chemotherapy is often poor and only 30% of individuals survive 2 years (16).

Multiple Myeloma and Arthritis

Myeloma is a malignant bone marrow plasma cell tumor, occurring most commonly in the fifth and sixth decades. It is often associated with bone pains (particularly in the back and ribs), pathologic fractures, monoclonal serum protein abnormalities, and Bence–Jones proteinuria. Generalized osteopenia due to myeloma-secreted cytokines (IL-1 beta, TNF-beta, and IL-8) occurs in about a third of patients. Myelomatous arthritis, caused by invasion of the articular and juxta-articular bones by myeloma cells, is rare (17). More commonly, about 15% of patients with myeloma develop monoclonal light chain (AL amyloid) amyloidosis, associated with **amyloid arthropathy**. The arthritis typically affects the shoulder, wrists, and knees. It is often symmetrical and relatively painless, but may mimic RA. Amyloid infiltration of the synovium of the shoulders produces the characteristic "shoulder-pad sign." Synovial effusions are non-inflammatory with low total leukocyte counts ($<2000 \times 10^6$/L). Spun synovial fluid sediments often contain "amyloid bodies." These are synovial villi, laden with amyloid. Using Congo red stains, amyloid deposits in both the synovium and synovial fluid sediment demonstrate apple-green birefringence under polarized light. Other manifestations of AL amyloid in patients with myeloma include peripheral neuropathy, carpal tunnel syndrome, subcutaneous amyloid deposits, macroglossia, cardiomyopathy, nephropathy, and hepatosplenomegaly. The diagnosis of amyloid arthritis can be confirmed by bone marrow examination, serum and urine protein immunoelectrophoresis showing an M-protein, and by biopsy of the synovium, abdominal subcutaneous fat, or rectum. Management consists of therapy for the underlying myeloma, and symptomatic treatment of the arthritis with NSAIDs.

Osteosclerotic myeloma is a rare form of myeloma characterized by osteosclerotic rather than osteolytic solitary or multiple bone lesions (18). Other features include an indolent chronic course, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS syndrome). Skin thickening, abnormal pigmentation, and, sometimes, a sclerodermatous appearance are common. Weight loss, fever, thrombocytosis, and arthritis may also occur.

Waldenstrom's Macroglobulinemia

Waldenstrom's macroglobulinemia is a neoplastic lymphoproliferative disorder associated with serum monoclonal IgM, lymphadenopathy, hepatosplenomegaly, purpuric skin lesions, and symptoms of hyperviscosity (headaches, visual changes). Direct tumor invasion of juxta-articular bone and joints is rare, but light chain amyloidosis and amyloid arthritis may occur (17).

Paraneoplastic Rheumatic Syndromes

Paraneoplastic symptoms, often bearing an only indirect relationship to tumor mass, are present at diagnosis in about 10% of patients with cancer. Up to 50% of patients with cancer develop paraneoplastic syndromes at some time during the course of their illness. One third of these are endocrine in nature; the remainder usually comprise hematological, rheumatic, and neuromuscular disorders. Among the paraneoplastic rheumatic syndromes, hypertrophic osteoarthropathy, carcinoma polyarthritis, myositis, and vasculitis are the most frequent (Table 25A-2). These disorders may coincide or

follow the diagnosis of primary malignancy, but may precede the onset of cancer by as long as 2 years (11).

The clinical course of a paraneoplastic musculoskeletal syndrome generally parallels that of the primary tumor. Thus, radical treatment of the primary neoplasm usually, but not invariably, results in regression of the paraneoplastic syndrome. Conversely, recurrence of the tumor can lead to re-appearance of the musculoskeletal symptoms. Paraneoplastic manifestations may be mistaken for metastatic disease, leading to inappropriate therapies. On the other hand, symptoms of true metastases may be attributed to a paraneoplastic syndrome, thereby delaying therapy.

Carcinomatous Polyarthritis

Carcinomatous polyarthritis is an inflammatory, seronegative arthritis that may herald the presence of malignancy (11). Although its clinical presentation is variable, certain features suggest the possibility of an underlying malignancy and serve to distinguish this form of polyarthritis from RA. These include a late age of onset; an explosive onset of asymmetric oligoarthritis or polyarthritis; predominant involvement of the joints of the lower extremities; frequent sparing of the wrists and joints of the hands; and the absence of erosions, deformities, rheumatoid factor, nodules, or family history of RA. On rare occasions, the arthritis is symmetrical and may mimic RA.

The temporal relationship between the onset of carcinomatous polyarthritis and diagnosis of the tumor is usually a close one—typically less than 1 year. Exclusion of hypertrophic osteoarthropathy or metastatic invasion of the synovium or periarticular bone is critical for establishing the appropriate therapeutic approach. The arthritis typically occurs in women with carcinoma of the breast, and in men with carcinoma of the lung. Synovial effusions are mildly inflammatory and the erythrocyte sedimentation rate (ESR) is often elevated. There are no distinctive pathologic or radiographic abnormalities (11).

The pathogenesis of carcinoma polyarthritis is poorly understood. Broad possible mechanisms include: (1) an immune complex–mediated synovitis; (2) cross-reactivity of antigenic determinants on the synovium and neoplastic tissue; and (3) an abnormality of cell-mediated immunity, leading to the expression of both neoplasia and connective tissue disease. The most convincing evidence that carcinoma polyarthritis is a true paraneoplastic disorder is the frequent resolution of the arthritis following resection of the underlying neoplasm, and its reappearance with recurrence of the cancer. The arthritis may respond to NSAIDs and intra-articular glucocorticoids.

"Postchemotherapy rheumatism" is a rare, self-limited syndrome of unknown etiology, characterized by myalgias and migratory arthralgias of hands, feet, knees, and ankles, occurring in some patients with carcinoma of the breast, ovary, or non-Hodgkin's lymphoma, 1 to 3 months after treatment with cyclophosphamide, 5-fluorouracil, or methotrexate.

Gout is rare in patients with solid tumors until the tumor metastasizes widely. Clinically, secondary gout differs from idiopathic gout in that women are more commonly affected and a family history of gout is less frequent. In hematologic malignancies, gout may occur secondary to massive tumor lysis following the institution of chemotherapy. In many protocols, allopurinol is used routinely to prevent this complication of cancer therapy.

Erythromelalgia is an intense pain and erythema afflicting the palms and soles (palms > soles), typically in patients with either polycythemia vera or essential thrombocythemia. Erythromelalgia is exquisitely sensitive to aspirin, usually in doses not exceeding 325 mg/day. Miscellaneous paraneoplastic conditions include dermatomyositis (see Chapter 18A), paraneoplastic vasculitis, and panniculitis (11).

REFERENCES

1. Peake I. The molecular basis of haemophilia A. Haemophilia 1998;4:346–349.
2. Lillicup D. The molecular basis of haemophilia B. Haemophilia 1998;4:350–357.
3. Hilgartner MW. Current treatment of hemophilic arthropathy. Curr Opin Pediatr 2002;14:46–49.
4. Ballas SK. Sickle cell disease: clinical management. Baillieres Clin Hematol 1998;11:185–214.
5. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. N Engl J Med 1991;325:11–16.
6. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol 2005;129:482–490.
7. Vichinsky EP, Neumayr LD, Haberkern C, et al. The perioperative complication rate of orthopedic surgery in sickle cell disease: report of the national sickle cell surgery study group. Am J Hematol 1999;62:129–138.
8. Jacobson SJ, Kopecky EA, Joshi P, Babul N. Randomized trial of oral morphine for painful episodes of sickle-cell disease in children. Lancet 1997;350:1358–1361.
9. Moore RD, Charache S, Terrin ML, et al. Cost-effectiveness of hydroxyurea in sickle cell anemia. Am J Hematol 2000;64:26–31.
10. Perrine SP, Boosalis V. Thalassemia. In: Rakel RE, Bope ET, eds. Conn's current therapy. Philadelphia: Saunders (Elsevier); 2006:488–492.
11. Fam AG. Paraneoplastic rheumatic syndromes. Baillieres Clin Rheumatol 2000;14:515–533.
12. Fam AG, Kolin A, Lewis AJ. Metastatic carcinomatous arthritis and carcinoma of the lung. A report of two cases diagnosed by synovial fluid cytology. J Rheumatol 1980;7:98–104.

13. Evans TL, Nercessian BM, Sanders KM. Leukemic arthritis. Semin Arthritis Rheum 1994;24:48–56.
14. Fam AG, Voorneveld C, Robinson JB, Sheridan BL. Synovial fluid immunocytology in the diagnosis of leukemic synovitis. J Rheumatol 1991;18:293–296.
15. Dorfman HD, Siegeel HL, Perry MC, Oxenhandler R. Non-Hodgkin's lymphoma of the synovium simulating rheumatoid arthritis. Arthritis Rheum 1987;30:155–161.
16. Tsochatzis A, Vassilopoulos D, Deutsch M, et al. Angiommunoblastic T-cell lymphoma-associated arthritis. Case report and literature review. J Clin Rheumatol 2005; 11:326–328.
17. Roux S, Fermand J-P, Brechignac S, et al. Tumoral joint involvement in multiple myeloma and Waldenstrom's macroglobulinemia – report of 4 cases. J Rheumatol 1996;23:1175–1178.
18. Fam AG, Rubenstein JD, Cowan DH. POEMS syndrome. Study of a patient with proteinuria, microangiopathic glomerulopathy and renal enlargement. Arthritis Rheum 1986;29:233–241.

CHAPTER 25

Less Common Arthropathies
B. Rheumatic Disease and Endocrinopathies

PETER A. MERKEL, MD, MPH

- Musculoskeletal signs and symptoms frequently occur in endocrinopathies.
- A number of syndromes of limited joint mobility occur in people with diabetes mellitus, including diabetic hand syndrome (diabetic cheiroarthropathy), adhesive capsulitis (frozen shoulder, periarthritis), Dupuytren's contractures, trigger finger (flexor tenosynovitis), diffuse idiopathic skeletal hyperostosis (DISH syndrome), neuropathic arthritis (Charcot joints, diabetic osteoarthropathy), and diabetic muscle infarction.
- Hyperthyroidism may be associated with proximal myopathy, usually without serum creatine kinase (CK) elevation; thyroid acropachy; and drug-induced vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), usually caused by propylthiouracil.
- Hypothyroidism may be associated with polyarthralgias, carpal tunnel syndrome, and proximal myopathy, with serum CK elevation.
- Hyperparathyroidism may cause osteoporosis, osteitis fibrosa cystica, chondrocalcinosis, and pseudogout.
- Other endocrinopathies that may lead to musculoskeletal complaints are hypoparathyroidism, acromegaly, and glucocorticoid-induced Cushing's syndrome.

Most endocrine disorders are associated with systemic manifestations caused by changes in the quantity or activity of various hormones. Musculoskeletal signs and symptoms are among the more frequent clinical sequelae of endocrinopathies. In some cases, the first clinical signs or symptoms of endocrine disease are rheumatic. Some rheumatic symptoms, such as myalgias, can be seen in a variety of different endocrinopathies; other rheumatic manifestations, such as Raynaud's phenomenon, are indicative of only one or two certain diseases. Various endocrinopathies also may be associated with specific rheumatic diseases.

Understanding the associations between endocrine and rheumatic diseases is important for several reasons. First, appreciating these clinical connections will help clinicians avoid misdiagnoses of primary rheumatic disease and can lead to prompt treatment of a primary endocrine disorder. Second, many of these rheumatic syndromes respond, in full or in part, to treatment of the underlying endocrinopathy. Third, some of the associations are sufficiently common or striking to justify screening for specific endocrine diseases when patients manifest certain rheumatic symptoms or signs. Finally, endocrine disorders may affect the disease activity of established autoimmune diseases. Such findings have led to the investigation of pathophysiologic links between autoimmune and endocrine diseases.

RHEUMATIC SEQUELAE OF SPECIFIC ENDOCRINE DISEASES

Diabetes Mellitus

Diabetes mellitus is associated with a wide variety of musculoskeletal problems, some of which are unique to the disease (1,2). The spectrum of rheumatologic syndromes seen in people with diabetes is outlined in Table 25B-1. The nomenclature of these conditions can be confusing, with some having more than one name in the medical literature. Some of these manifestations are secondary to the microvascular disease, neuropathic complications, or proliferation of connective tissue seen in diabetes. These rheumatic syndromes affect people with either type I or type II diabetes, especially those with evidence of organ damage.

A number of syndromes of limited joint mobility occur in people with diabetes (3). Diabetic hand syn-

TABLE 25B-1. RHEUMATOLOGIC MANIFESTATIONS OF DIABETES MELLITUS.

Syndromes of limited joint mobility
Diabetic hand syndrome (diabetic cheiroarthropathy)
Adhesive capsulitis (frozen shoulder, periarthritis)
Trigger finger (flexor tenosynovitis)
Dupuytren's contractures
Osteoporosis
Diffuse idiopathic skeletal hyperostosis (DISH)
Neuropathies
Neuropathic arthritis (Charcot joints, diabetic osteoarthripathy)
Carpal tunnel syndrome
Diabetic amyotrophy
Reflex sympathetic dystrophy (multiple synonyms)
Various other neuropathies
Diabetic muscle infarction

drome (diabetic cheiroarthropathy) is a condition stemming from alterations in the soft tissue of the hands and fingers, resulting in stiff, waxy skin and joint contractures. This condition can be confused with arthritis and the sclerodactyly seen in systemic sclerosis. Cheiroarthropathy is demonstrated when patients are asked to oppose the palmar surfaces of their hands and fingers (the prayer sign), and they are unable to fully touch these surfaces. Adhesive capsulitis (frozen shoulder, periarthritis) is a similar condition that leads to shoulder joint contractures, which often are severe. This condition frequently is bilateral and sometimes is accompanied by calcific deposits in the surrounding soft tissues (4). Physical therapy appears to be helpful, and spontaneous resolution may occur over months to years. Dupuytren's contractures and trigger finger (flexor tenosynovitis) are frequent, annoying, and potentially disabling conditions that are more common among people with diabetes. These finger problems may respond to glucocorticoid injection or surgical correction.

Two other common musculoskeletal diseases with an increased prevalence and generally younger age of presentation in people with diabetes are osteoporosis and diffuse idiopathic skeletal hyperostosis (DISH syndrome). Insulin-like growth factors are thought to play a pathogenic role in these diseases. Although the association between diabetes and osteoporosis has been questioned, the link between hyperostosis and diabetes is established more firmly. DISH is accompanied by ossification and calcification of spinal ligaments, but does not necessarily cause significant clinical problems.

Patients with diabetes mellitus may encounter several types of neuropathies that result in musculoskeletal symptoms or that may mimic rheumatic diseases. Neuropathic arthritis (Charcot joints, diabetic osteoarthropathy; see Chapter 25D), a destructive bone and joint condition that is the consequence of peripheral neuropathy, most commonly affects the foot (5). Despite the resulting joint obliteration, ankylosis, and deformities, patients usually have little or no pain, and the diagnosis is based on radiographic appearance. Plain radiography, bone scintigraphy, and magnetic resonance imaging are useful imaging modalities for diagnosing diabetic osteoarthropathy and documenting the extent of disease. Similarly, the peripheral neuropathy of diabetes increases the incidence of foot infections and foreign body reactions, in which patients may be unaware of injury due to anesthetic feet; both of these conditions may lead to septic arthritis.

The incidence of carpal tunnel syndrome, a median nerve neuropathy, is increased in people with diabetes and may occur bilaterally. Similarly, reflex sympathetic dystrophy (causalgia) is more common among people with diabetes. Diabetic amyotrophy is characterized by painful, often bilateral, muscle weakness resulting from a mononeuropathy with non-inflammatory atrophy of type II muscle fibers (6). Spontaneous improvement may occur. Other neuropathies that can occur among people with diabetes may be central or peripheral, and include such conditions as mononeuritis multiplex and radiculopathies that mimic other musculoskeletal conditions.

Diabetic muscle infarction is a rare but increasingly recognized syndrome of acute infarction of multiple muscle areas in people with diabetes and organ damage (7). This condition usually occurs with severe pain in one extremity. Diabetic muscle infarction can be confused with pyomyositis or venous thrombosis. Magnetic resonance imaging (MRI) can be diagnostic, although biopsy may be needed in some cases. Although self-limited, this condition can recur. The etiology of diabetic muscle infarction is unclear but may be related to microvasculopathy and microthrombosis.

Improved glycemic control may not reverse the conditions outlined in Table 25B-l, but may help prevent future episodes. When these syndromes are present without an obvious explanation, it is appropriate to consider screening patients for undiagnosed diabetes mellitus by testing fasting glucose and glycosylated hemoglobin levels.

Thyroid Disease

Thyroid disease frequently is accompanied by various musculoskeletal problems (Table 25B-2) (8,9). Hyperthyroidism, hypothyroidism, and thyroxine replacement therapy, in particular, are associated with rheumatic disease. Some studies report that thyroid abnormalities are more common among people with various autoimmune syndromes, including rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. However, these associations have been questioned, and

TABLE 25B-2. RHEUMATOLOGIC MANIFESTATIONS OF THYROID DISEASE.

Hyperthyroidism
Osteoporosis
Myopathy
Periarthritis
Acropachy
Hypothyroidism
Arthralgias
Symmetrical polyarthritis
Joint laxity
Carpal tunnel syndrome
Chondrocalcinosis and pseudogout
Hyeruricemia and gout
Myopathy

the perceived increased prevalence of thyroid disorders among patients with these autoimmune diseases may be confounded by the fact that thyroid diseases are common among women, and women account for 75% to 90% of people with these autoimmune diseases. Musculoskeletal problems may be the first, and sometimes only, clinical sign of thyroid disease.

Because thyroid diseases are easily diagnosed and highly responsive to treatment, screening for thyroid dysfunction among people with various rheumatic symptoms is essential. Achieving a euthyroid status improves many, but not all, of these conditions.

Hyperthyroidism

Hyperthyroidism is an important, reversible, and easily detected cause of osteoporosis. Administration of levothyroxine as replacement therapy or for suppression of thyroid nodules may lead to osteoporosis (10).

Thyrotoxicosis often causes a proximal myopathy that may be severe. Most patients with this myopathy do not have elevated creatinine kinase levels but do have electromyographic abnormalities. This myopathy almost always is reversible upon attainment of a euthyroid state. All patients presenting with weakness must be screened for thyrotoxicosis.

A shoulder periarthritis (often bilateral) may be seen in people with hyperthyroidism.

Thyroid acropachy, an unusual late manifestation of Graves' disease, involves painful soft tissue swelling of hands, fingers, and toes, with clubbing and periostitis. Although similar to hypertrophic osteoarthropathy, most patients with acropachy already have established exophthalmos, pretibial myxedema, and measurable levels of long-acting thyroid stimulator in the serum. Acropachy usually presents after treatment of hyperthyroidism and is thought to have an immunologic basis.

Although many drugs have been associated with vasculitis, some of these associations are poorly supported by the literature. However, the evidence is compelling that propylthiouracil and related thionamides used in the treatment of hyperthyroidism can cause vasculitis syndromes associated with antineutrophil cytoplasmic antibodies (11).

Hypothyroidism

Hypothyroidism in children or fetuses results in multiple skeletal abnormalities, as well as severe developmental problems. In adults, hypothyroidism can cause a series of musculoskeletal problems. Given the high prevalence of hypothyroidism in adults, this diagnosis must be considered in all patients presenting with the syndromes described in this section. The discovery of previously undiagnosed thyroid deficiency among people presenting with rheumatic symptoms is common.

Joint symptoms are extremely common among patients with hypothyroidism, and range from vague arthralgias to a symmetric polyarthritis that may be confused with rheumatoid arthritis. The joint effusions seen in hypothyroidism are non-inflammatory. Additionally, an increased incidence of joint laxity has been noted among people with myxedema. Carpal tunnel syndrome is associated with hypothyroidism and may be bilateral. When a euthyroid state is attained, these rheumatologic symptoms often remit fully.

There is an increased incidence of hypothyroidism among patients with crystal-induced arthritis. In particular, asymptomatic chondrocalcinosis and clinical pseudogout are associated with hypothyroidism. Similarly, there are reports linking hypothyroidism to asymptomatic hyperuricemia and gout.

Myopathy is a common feature of hypothyroidism and can include myalgias and weakness (especially proximally). The weakness usually is mild to moderate in severity and is accompanied by abnormal findings on electromyography. In contrast to the myopathy seen in hyperthyroidism, serum creatinine kinase levels are elevated in most patients with muscle disease associated with hypothyroidism. Muscle bulk is not changed appreciably, and biopsy specimens may demonstrate evidence of degeneration and regeneration of muscle fibers without inflammation. The myopathy reverses with treatment of the underlying thyroid disorder.

Parathyroid Disease

Table 25B-3 outlines the rheumatologic manifestations of parathyroid disease.

Hyperparathyroidism

A wide variety of bone and joint abnormalities have been associated with hyperparathyroidism. Some of these conditions have become less common due to the

TABLE 25B-3. RHEUMATOLOGIC MANIFESTATIONS OF PARATHYROID DISEASE.

Hyperparathyroidism
Osteoporosis
Osteitis fibrosa cystica
Erosive arthritis
Joint laxity
Chondrocalcinosis and pseudogout
Hyperuricemia and gout
Myopathy
Hypoparathyroidism
Ectopic calcification
Myopathy

earlier detection and treatment of hyperparathyroidism. Nevertheless, rheumatologic manifestations of hyperparathyroidism commonly are the presenting features of disease. This section outlines the rheumatologic problems encountered in primary hyperparathyroidism. A series of similar disorders can result from secondary hyperparathyroidism associated with renal failure or malabsorption.

Osteoporosis is a direct consequence of excess parathormone and can cause severe, irreversible bone loss. Bone loss associated with hyperparathyroidism is greater in cortical than in cancellous regions.

Osteitis fibrosa cystica is a syndrome of multiple bony abnormalities associated with severe hyperparathyroidism. Due to earlier detection, this disorder is rarely seen in areas with comprehensive medical care. Osteitis fibrosis cystica involves unique radiographic findings, including bone cysts and subperiosteal erosions. Diffuse bone pain can be present, and an erosive, noneffusive arthritis has been reported. Increased joint laxity, tendon laxity and ruptures, and ectopic calcifications also are associated with hyperparathyroidism.

Chondrocalcinosis and pseudogout commonly occur in people with hyperparathyroidism and may be presenting features of disease (12). A non-inflammatory polyarthritis also has been reported. An increased prevalence of hyperuricemia and gout is seen among people with hyperparathyroidism secondary to nephrocalcinosis. These crystal-induced diseases persist even after correction of excess parathormone production.

Although people with hyperparathyroidism commonly report vague myalgias and malaise, a reversible proximal myopathy is unusual and is associated only with severe disease. Ectopic calcifications, including intravascular lesions, occasionally may result in various neuropathies.

Hypoparathyroidism

Hypoparathyroidism and the related disorders of pseudohypoparathyroidism and pseudopseudohypoparathyroidism are associated with unusual bony abnormalities and ectopic calcification of subcutaneous tissue and paraspinal ligaments.

Myopathies also have been reported.

Acromegaly

Acromegaly, a rare disorder of pituitary hypersecretion of growth hormone, usually is caused by an adenoma and is associated with a large variety of musculoskeletal abnormalities. The syndrome illustrates the protean effects of growth hormone on human physiology (13). In children whose epiphyses have not yet closed, growth hormone excess causes gigantism and presents a set of problems different from those seen in adults with acromegaly. Growth hormone exerts many of its actions via the production of insulin-like growth factors (IGF or somatomedins). In particular, IGF-I and growth hormone itself promote proliferation of soft tissues and bone. Tissues affected by acromegaly include synovium, cartilage, bursae, and muscle.

Table 25B-4 outlines the rheumatic manifestations of acromegaly and categorizes them as articular, bone, neuromuscular, or miscellaneous problems.

The musculoskeletal manifestations of acromegaly usually are present long before the underlying endocrinopathy is diagnosed. Treatment, through a combination of surgical resection of the adenoma and administration of octreotide, can prevent worsening of some aspects of the disease and a few of its complications. In view of the potential for this disease to cause significant deformities, morbidity, and mortality, early detection is a key factor to improving the lives of people with acromegaly.

TABLE 25B-4. RHEUMATOLOGIC MANIFESTATIONS OF ACROMEGALY.

Articular
Arthralgias
Bursal enlargement
Osteoarthritis
Joint laxity
Cartilage hypertrophy and degeneration
Pseudogout (possibly)
Tendinous and capsular calcification
Bone
Back pain
Osteoporosis
Bone hypertrophy and resorption
Neuromuscular
Myopathy and muscle hypertrophy
Compression neuropathy, especially carpal tunnel syndrome
Ischemic neuropathy
Miscellaneous
Raynaud's phenomenon

Articular problems that occur in acromegaly are due to a combination of cartilage hypertrophy, synovial proliferation, and osteophytosis. Vague arthralgias, joint space widening, joint laxity, and non-inflammatory effusions may be followed by degenerative joint disease and clinical osteoarthritis. Whether chondrocalcinosis and pseudogout are associated with acromegaly remains a controversial issue.

Back pain is quite common and may be due to hypertrophy of the vertebral bodies and discs. Patients often exhibit spinal hypermobility. Osteoporosis may develop secondary to the hypogonadism that often occurs. Because increased bone thickness can occur, bone density measurements can be difficult to interpret.

Many of the articular, soft tissue, and bone abnormalities in acromegaly result in characteristic radiographic features, including joint space widening, heel pad hypertrophy, and terminal phalanx enlargement. Once bone and joint problems occur, treatment of acromegaly does not appear to reverse musculoskeletal manifestations and may not prevent damage progression.

The neuromuscular problems seen in acromegaly also are secondary to tissue hypertrophy, including compression and ischemic neuropathies. Carpal tunnel syndrome is especially common and often is bilateral. This complication of acromegaly usually remits with proper treatment of the endocrinopathy. Although muscle hypertrophy can occur, some patients develop proximal muscle weakness and fatigue. The myopathy may not remit with treatment of the growth hormone excess.

Octreotide, a somatostatin analog used to treat acromegaly, occasionally causes neuromuscular weakness. Octreotide also may cause hypothyroidism, leading to the rheumatic problems discussed previously.

Miscellaneous Endocrine Disorders

Glucocorticoid excess (Cushing's syndrome) from primary adrenal hyperproduction, pituitary stimulation (Cushing's disease), or exogenous administration can cause a variety of musculoskeletal problems. Osteoporosis is a particular problem with these disorders and can lead to pathologic fractures. Osteonecrosis can occur in Cushing's disease but is associated more commonly with exogenous corticosteroid administration (14). The so-called steroid myopathy can occur with any form of glucocorticoid excess. This proximal muscle weakness is non-inflammatory, not associated with elevated serum creatinine kinase levels, and resolves with correction of the hormone imbalance.

Glucocorticoid deficiency (Addison's disease) can cause myalgias, arthralgias, and flexion contractures. These problems are responsive to glucocorticoid replacement therapy. Reported rheumatologic manifestations of the carcinoid syndrome include arthralgias, muscle wasting, bony erosions, and retroperitoneal fibrosis (15).

REFERENCES

1. Pastan RS, Cohen AS. The rheumatologic manifestations of diabetes mellitus. Med Clin North Am 1978;62: 829–839.
2. Crisp AJ, Heathcote JG. Connective tissue abnormalities in diabetes mellitus. J R Coll Phys Lond 1984;18:132–141.
3. Schulte L, Roberts MS, Zimmerman C, Ketler J, Simon LS. A quantitative assessment of limited joint mobility in patients with diabetes. Goniometric analysis of upper extremity passive range of motion. Arthritis Rheum 1993; 36:1429–1443.
4. Mavrikakis ME, Drimis S, Kontoyannis DA, Rasidakis A, Moulopoulou ES, Kontoyannis S. Calcific shoulder periarthritis (tendinitis) in adult onset diabetes mellitus: a controlled study. Ann Rheum Dis 1989;48:211–214.
5. Sinha S, Munichoodappa CS, Kozak GP. Neuro-arthropathy (Charcot joints) in diabetes mellitus (clinical study of 101 cases). Medicine (Baltimore) 1972;51:191–210.
6. Krendel DA. Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus [see comments]. Arch Neurol 1995;52:1053–1061.
7. Grigoriadis E, Fam AG, Starok M, Ang LC. Skeletal muscle infarction in diabetes mellitus. J Rheumatol 2000; 27:1063–1068.
8. Bland JH, Frymoyer JW. Rheumatic syndromes of myxedema. N Engl J Med 1970;282:1171–1174.
9. Bland JH, Frymoyer JW, Newberg AH, Revers R, Norman R. Rheumatic syndromes in endocrine disease. Semin Arthritis Rheum 1979;9:23–65.
10. Wartofsky L. Levothyroxine therapy and osteoporosis. An end to the controversy? Arch Intern Med 1995;155: 1130–1131.
11. Merkel P. Drugs associated with vasculitis. Curr Opin Rheumatol 1998;10:45–50.
12. Alexander GM, Dieppe PA, Doherty M, Scott DG. Pyrophosphate arthropathy: a study of metabolic associations and laboratory data. Ann Rheum Dis 1982;41:377–381.
13. Bluestone R, Bywaters EG, Hartog M, Holt PJ, Hyde S. Acromegalic arthropathy. Ann Rheum Dis 1971;30:243–258.
14. Phillips KA, Nance EP Jr, Rodriguez RM, Kaye JF. Avascular necrosis of bone: a manifestation of Cushing's disease. South Med J 1986;79:825–829.
15. Plonk JW, Feldman JM. Carcinoid arthropathy. Arch Intern Med 1974;134:651–654.

CHAPTER 25

Less Common Arthropathies
C. Hyperlipoproteinemia and Arthritis

ROBERT F. SPIERA, MD

- Several recognized heritable disorders of lipid metabolism result in a variety of clinical phenotypes, each of which may be associated with distinct musculoskeletal manifestations.
- Tendinous xanthomas are associated most often with the type II and type III hyperlipoproteinemias, known respectively as familial hypercholesterolemia and familial dysbetalipoproteinemia.
- Tendinous xanthomas characteristically occur on the dorsum of the hands over the digit extensor tendons, or on the heels at the Achilles tendon insertions.
- Osseous xanthomas, observed occasionally in type III hyperlipoproteinemia, can predispose patients to pathologic fractures, particularly in long bones.
- An episodic, acute, migratory inflammatory arthritis occurs in up to 50% of homozygotes with type II hyperlipoproteinemia. The joints are erythematous, warm, and swollen, and acute-phase reactants are elevated.
- Gout can be associated with hypertriglyceridemia in types I, IV, and V hyperlipoproteinemia.

Musculoskeletal problems can occur in association with hyperlipoproteinemia, a condition in which underlying genetic defects lead to overproduction or impaired removal of lipoproteins. The abnormalities, related either to the lipoprotein or its receptor, results in elevated levels of lipoprotein that contribute to the development of premature atherosclerosis. Recognition of these syndromes facilitates both the proper diagnosis and management of the musculoskeletal problem, and the appropriate treatment of a condition that poses significant long-term cardiovascular threats.

Several recognized heritable disorders of lipid metabolism result in a variety of clinical phenotypes (Table 25C-l) (1), each of which may be associated with distinct musculoskeletal manifestations. Hyperlipidemia also can occur secondary to other clinical contexts (e.g., the nephrotic syndrome, primary biliary cirrhosis, cigarette smoking). Arthritis and hyperlipidemia also may be linked because of a common risk factor (e.g., obesity as a risk factor for both osteoarthritis and hyperlipidemia). In this section, we will focus on musculoskeletal syndromes believed to be related directly to hyperlipidemia.

XANTHOMAS

Xanthomas can occur in any of the inherited hyperlipoproteinemias. Tendinous xanthomas are associated most often with the type II and type III hyperlipoproteinemias, known respectively as familial hypercholesterolemia and familial dysbetalipoproteinemia (1). Tendinous xanthomas characteristically occur on the dorsum of the hands over the digit extensor tendons, or on the heels at the Achilles tendon insertions (2). They have been described at other extensor surfaces as well, including the triceps, olecranon, or quadriceps insertions. Achilles tendon xanthomas are more strongly associated with type III hyperlipoproteinemia (1). Although patients with polygenic hypercholesterolemia can have similar lipid profiles, xanthomata are not seen in these patients.

Tendinous xanthomas often are noticeable but not necessarily symptomatic. Tendinitis or tenosynovitis can occur, however, particularly in the Achilles tendon, where the mass effect of the xanthoma contributes to local irritation by overlying footwear. Radiographic findings can include calcifications within the xanthomas, or

TABLE 25C-1. CLASSIFICATION OF HYPERLIPIDEMIA.

PHENOTYPE	LIPOPROTEIN ABNORMALITY	LIPID ABNORMALITY	MUSCULOSKELETAL MANIFESTATION
Type I	Chylomicrons increased	Markedly increased triglycerides	Eruptive xanthomas
Type IIa	LDL increased	Increased cholesterol	Tendinous, tuberous xanthomas; migratory, episodic polyarthritis; Achilles tendonitis
Type IIb	LDL and VLDL increased	Increased cholesterol and triglycerides	Tendinous, tuberous xanthomas, migratory, episodic polyarthritis; Achilles tendonitis
Type III	Chylomicrons and VLDL remnants increased	Increased cholesterol; increased to markedly increased triglycerides	Tendinous, tuberous, and plane xanthomas
Type IV	VLDL increased	Increased triglycerides	Eruptive tendinous and tuberous xanthomas; arthralgias
Type V	Chylomicrons and VLDL increased	Increased cholesterol, markedly increased triglycerides	Eruptive xanthomas

SOURCE: Modified from Fredrickson DS, Levy RI, Lees RS. N Engl J Med 1967;276:34–42, ff., by permission of *New England Journal of Medicine*.
ABBREVIATIONS: LDL, low-density lipoprotein, VLDL, very low-density lipoprotein.

even periarticular cortical erosions, presumably secondary to pressure effects of the enlarged tendons (3). Tendinitis preceding xanthoma formation or even spontaneous tendon ruptures are rare, but have been described in type IIa hyperlipoproteinemia (4,5). The tendinous xanthomas reside within the tendon fibers and move in conjunction with the tendon. Pathologic examination of such xanthomas reveals infiltrates of foam cells that seem to be macrophages congested with remnants of ingested (endocytosed) circulating lipoproteins.

Osseous xanthomas, observed occasionally in type III hyperlipoproteinemia, can predispose patients to pathologic fractures, particularly in long bones. Other locations include the small bones of the hands, skull, spine, and pelvis. Such xanthomas have the radiological appearance of well-defined, round, or oval lucencies (6). In a patient with type V hyperlipidemia, pathologic evaluation of a cystic femoral lesion revealed foamy histiocytes with granulomatous reaction around cholesterol clefts (7).

Tuberous xanthomas are subcutaneous masses generally found over extensor surfaces, including the elbows, knees, hands, or buttocks. They can be observed in types II, III, and IV hyperlipoproteinemias. Xanthomas on the palmar surfaces (xanthoma striata palmaris) occur in type III hyperlipoproteinemia (1).

Although xanthomas generally are associated with heritable disorders of lipid metabolism, other, rarer causes are recognized. Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder in which accumulation of cholestanol or dihydrocholesterol in neural tissue or tendons results in clinical manifestations of disease, including ataxia, paresis, dementia, and tendon xanthomas (8). These manifestations can appear as early as the second decade. Another disorder associated with tendinous xanthomas is beta-sitosterolemia, an autosomal recessive disorder in which there is hyperabsorption of cholesterol and plant sterols from the intestine (9). These disorders should be considered when a patient presents with tendinous xanthomas, particularly at a young age, in the absence of marked elevation of serum cholesterol. Xanthomata also can be seen in the secondary hypercholesterolemia associated with cholestatic liver disease, such as primary biliary cirrhosis.

ARTICULAR DISEASE

There is some controversy about the association of articular disease with familial hyperlipoproteinemias. Some arthropathies purported to be linked with hyperlipidemia based on descriptive case series (5,10,11) have not been borne out in all controlled studies (12,13), although some associations do appear to have been confirmed (14,15). Certain musculoskeletal presentations, however, are well-recognized. An episodic, acute, migratory inflammatory arthritis occurs in up to 50% of homozygotes with type II hyperlipoproteinemia (16,17). This condition primarily affects large peripheral joints, such as knees and ankles, but the small joints of the hands and feet can be involved. The joints are erythematous, warm, and swollen, and acute-phase reactants, such as sedimentation rate and plasma fibrinogen, are elevated. Distinction of this entity from acute rheumatic fever can be difficult, particularly because some of those patients may have valvular disease as a downstream effect of atherosclerosis. The presence of tendinous xanthomas, a markedly elevated cholesterol, and

the absence of antecedent Streptococcal infection helps distinguish the entities. Generally, episodes are self-limited and resolve within 2 weeks. This pattern of arthritis is seen much less commonly (approximately 4%) in heterozygotes.

Self-limited episodes of acute mono- or oligoarthritis, often of the knee or ankle, can be seen in familiar hypercholesterolemia. In type IV hyperlipoproteinemia, a more chronic arthritis can occur. Patients complain of morning stiffness and a bland, often asymmetric, polyarticular arthritis. Both large and small joints may be involved, including proximal interphalangeal joints, metacarpophalangeal joints, wrists, knees, shoulders, and tarsophalangeal and metatarsophalangeal joints (18). Synovial fluid analysis reveals minimally inflammatory or non-inflammatory fluid, without crystals. Synovial biopsy has been described as revealing moderate synovial hyperplasia, with a modest infiltrate of mononuclear cells and foam cells. There may be a relationship between serum triglyceride level and joint complaints.

Even xanthomata, the hallmark physical finding in hyperlipoproteinemias, can be mistaken for other entities, such as gouty tophi in a person with oligoarthritis, or rheumatoid nodules in a person with polyarthritis. Clinicians caring for people with musculoskeletal complaints must therefore be aware of these hyperlipoproteinemia-related musculoskeletal syndromes and distinguish them from more common arthropathies.

CRYSTAL DISEASE

Gout, an eminently treatable form of arthritis related to hyperuricemia, can be associated with hypertriglyceridemia in types I, IV, and V hyperlipoproteinemia. When the clinical scenario is compatible with a microcrystalline disease, examination of the synovial fluid for crystals is essential. The presence of cholesterol crystals has been associated with a worse outcome for a joint affected by degenerative or inflammatory arthritis, and has been shown to maintain the inflammatory reaction in experimental animals (19). In people with primary hyperlipoproteinemia, however, cholesterol crystals have not been specifically implicated in acute or chronic arthrititis. Crystals were found in a retrocalcaneal bursa adjacent to a xanthoma in a patient with type II hyperlipoproteinemia, but the significance of these crystals has not been determined (20).

MANAGEMENT

The acute migratory polyarthritis or oligoarthritis associated with type II hyperlipoproteinemia tends to be self-limited. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful, but recent concerns regarding the potential cardiovascular consequences of long-term NSAID use, particular with selective cyclooxygenase 2 inhibitors, must be considered in this high-risk group of patients (21). Treating the underlying dyslipidemia can lead to regression of tendinous xanthomas. Surgical excision also can be beneficial, particularly in the Achilles tendon, where mechanical irritation by footwear can cause pain and debility. Recurrences can occur. The arthropathy associated with type IV hyperlipidemia seems to wane with improved control of serum lipid levels.

REFERENCES

1. Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins: an integrated approach to mechanisms and disorders. N Engl J Med 1967;276:34–42, 94–103, 148–156, 215–225, 273–281.
2. Fahey JJ, Stark HH, Donovan WE, Drennan DB. Xanthoma of the Achilles tendon. J Bone Joint Surg Am 1973;55A:1197–1211.
3. Yaghami I. Intra- and extraosseous xanthomata associated with hyperlipidemia. Radiology 1978;128:49–54.
4. Shapiro R, Fallat RW, Tsang RC, Glueck CJ. Achilles tendinitis and tenosynovitis. Am J Dis Child 1974;128:486–490.
5. Glueck CJ, Levy R, Fredrickson DS. Acute tendinitis and arthritis. A presenting symptom of familial type II hyperlipoproteinemia. JAMA 1968;206:2895–2897.
6. Bardin T, Kuntz D. Primary hyperlipidemias and xanthomatosis. In: Klippel JH, Dieppe P (eds). Rheumatology. London: Times Mirror International Publishers Limited; 1994;27.1–27.4.
7. Siegelman SS, Schlossberg I, Becker NH, Sachs BA. Hyperlipoproteinemia with skeletal lesions. Clin Orthop 1972;87:228–232.
8. Truswell AS, Pfister PJ. Cerebrotendinous xanthomatosis. Br Med J 1972;1:353–354.
9. Shulman RS, Bhattacharyya AK, Connor WE, Fredrickson DS. Beta-sitosterolemia and xanthomatosis. N Engl J Med 1976;294:482–483.
10. Rooney PJ, Third J, Madkour MM, Spencer D, Dick WC. Transient polyarthritis associated with familial hyperbetal lipoproteinemia. Q J Med 1978;47:249–259.
11. Mathon G, Gagne C, Brun D, Lupien PJ, Moorjani S. Articular manifestations of familial hypercholesterolemia. Ann Rheum Vis 1985;44:599–602.
12. Welin L, Larsson B, Svardsudd K, Tibblin G. Serum lipids, lipoproteins and musculoskeletal disorders among 50- and 60-year-old men. Scand J Rheumatol 1977;1:7–12.
13. Struthers GR, Scott DL, Bacon PA, Walton KW. Musculoskeletal disorders in patients with hyperlipidemia. Ann Rheum Dis 1983;42:519–523.
14. Wysenbeek AJ, Shani E, Beigel Y. Musculoskeletal manifestations in patients with hypercholesterolemia. J Rheumatol 1989;16:643–645.

15. Klemp P, Halland AM, Majoos FL, Steyn K. Musculoskeletal manifestations in hyperlipidemia: a controlled study. Ann Rheum Dis 1993;52:44–48.

16. Khachadurian AK. Migratory polyarthritis in familial hypercholesterolemia (type II hyperlipoproteinemia). Arthritis Rheum 1968;11:385–393.

17. Rimon D, Cohen L. Hypercholesterolemic (type II hyperlipoproteinemic) arthritis. Rheumatology 1989;16:703–705.

18. Buckingham RB, Bole GG, Bassett DR. Polyarthritis associated with type IV hyperlipoproteinemia. Arch Intern Med 1975;135:286–290.

19. Lazarevic MB, Skosey JL, Vitic J, et al. Cholesterol crystals in synovial and bursal fluid. Semin Arthritis Rheum 1993;23:99–103.

20. Schumacher HR, Michaels R. Recurrent tendinits and Achilles tendon nodule with positively birefringent crystals in a patient with hyperlipoprotenemia. J Rheumatol 1989;16:1387–1389.

21. Solomon DH, Avorn J, Stürmer T, Glynn RJ, Mogun H, Schneeweiss S. Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs. Arthritis Rheum 2006;54:1378–1389.

CHAPTER 25

Less Common Arthropathies
D. Neuropathic Arthropathy

ANN K. ROSENTHAL, MD

- Neuropathic arthropathy, also known as a Charcot joint, is a destructive arthritis characterized by fracture, subluxation, and dislocation of the articular structures in the setting of neurologic damage to the involved joint or limb.
- Both central (upper motor neuron) and peripheral (lower motor neuron) lesions may lead to the development of neuropathic arthropathy.
- Diabetic neuropathy is now the most common cause of neuropathic arthropathy. Neuropathic arthropathy occurs in 7.5% of diabetic patients.
- The pathologic features of Charcot arthropathy include cartilage destruction, bone eburnation, osteophytosis, and loose body formation.
- Two major theories have been proposed to explain the development of neuropathic arthropathy: the neurovascular theory and the neurotraumatic theory.
- Neuropathic arthropathy typically presents as an acute or subacute monoarthritis with swelling, erythema, and variable amounts of pain in the affected joint.
- Two consistent clinical features of neuropathic arthropathy are the presence of a significant sensory deficit and a degree of pain that is less than would be expected considering the amount of joint destruction evident on radiographs.
- The differential diagnosis of neuropathic arthropathy includes osteomyelitis and other deep tissue infections, fracture, gout, calcium pyrophosphate dihydrate deposition disease, Milwaukee shoulder/knee syndrome, osteonecrosis, and osteoarthritis.
- Plain radiographs are extremely helpful in making the diagnosis of neuropathic arthropathy.
- Categorizing the disease into three clinical stages—acute, subacute, and remodeling—is a useful way to organize approaches to therapy.

Neuropathic arthropathy is a destructive arthritis characterized by fracture, subluxation, and dislocation of the articular structures in the setting of neurologic damage to the involved joint or limb. The concept of an association between sensory neurologic lesions and arthritis was described elegantly by Jean-Martin Charcot in 1868 (1). Consequently, the terms *Charcot arthropathy*, *neurotrophic arthropathy*, and *neuroarthropathy* are used synonymously with neuropathic arthropathy.

EPIDEMIOLOGY

Accurate figures on the incidence and prevalence of neuropathic arthropathy in the general population are difficult to ascertain. The presence of sensory neuropathy is the only established risk factor for neuropathic arthropathy. Both central (upper motor neuron) and peripheral (lower motor neuron) lesions may lead to the development of neuropathic arthropathy.

The neurologic diseases associated with neuropathic arthropathy have radically changed with time (Table 25D-1). In the pre-penicillin era, neuropathic arthropathy was most commonly seen in the setting of tabes dorsalis from tertiary syphilis. Diabetic neuropathy is now the most common cause of neuropathic arthropathy. Neuropathic arthropathy occurs in 7.5% of diabetic patients, with prevalence rates rising to 29% among diabetic patients with neuropathy (2). Syringomyelia, spina bifida, and spinal cord injuries may also result in neuropathic arthropathy. Less commonly encountered causes of neuropathic arthropathy include inflammatory or neoplastic lesions of the spinal cord or peripheral nerves, congenital neurologic abnormalities, and alcoholic neuropathies. Rarely, cases occur in which no neurologic abnormality is identifiable (3).

PATHOLOGY

The pathologic changes of neuropathic arthropathy are similar to those of advanced osteoarthritis: cartilage destruction, bone eburnation, osteophytosis, and loose body formation. The presence of *detritic synovium*,

TABLE 25D-1. NEUROLOGIC CONDITIONS ASSOCIATED WITH NEUROPATHIC ARTHROPATHY.

Diabetes mellitus
Syringomyelia
Spina bifida
Brain or spinal cord trauma
Peripheral nerve trauma
Syphilis
Multiple sclerosis
Charcot–Marie–Tooth disease
Riley–Day syndrome
Pernicious anemia
Congenital insensitivity to pain
Alcoholism
Amyloidosis
Thalidomide exposure
Polyneuropathy of Dejerine–Sottas
Leprosy
Yaws
Neurofibromatosis

defined as fragments of cartilage and bone embedded in the synovium, is characteristic of neuropathic arthropathy, but is also seen in severe osteoarthritis (3). As reflected radiographically, neuropathic arthropathy can cause exuberant bone and cartilage overgrowth as well as joint destruction. Usually both processes are seen, but one process often predominates.

PATHOPHYSIOLOGY

Two major theories have been proposed to explain the development of neuropathic arthropathy. The *neurovascular theory* postulates that joint denervation produces physiologic changes, such as increased blood flow from loss of sympathetic regulation, and upsets the balance between bone resorption and formation. The *neurotraumatic theory* proposes that repeated episodes of minor trauma to joints unprotected by the usual response to pain cause damage through further trauma and inadequate repair. The neurovascular hypothesis is supported clinically by reports of neuropathic arthropathy in patients at bedrest who could not have sustained trauma and the finding that demineralization of the affected limb may precede the development of neuropathic arthropathy (4). In contrast, the observation that injury often accelerates or initiates neuropathic arthropathy supports the neurotraumatic hypothesis (5). Elements of both theories are probably correct.

CLINICAL FEATURES

Neuropathic arthropathy typically presents as an acute or subacute monoarthritis with swelling, erythema, and variable amounts of pain in the affected joint. The two most consistent clinical features of neuropathic arthropathy are the presence of a significant sensory deficit and a degree of pain that is less than would be expected considering the amount of joint destruction evident on radiographs. Abnormal sensation can be accurately detected with the Semmes–Weinstein monofilament test. When slowly progressive, neuropathic arthropathy often resembles osteoarthritis. When rapidly progressive and acute in onset, it mimics osteomyelitis. Initial examinations show swelling, erythema, effusions, and variable amounts of tenderness. With time, the neuropathic joint becomes deformed with large effusions, palpable osteophytes, and loss of range of motion. Categorizing the disease into three clinical stages—acute, subacute, and remodeling—is a useful way to organize approaches to therapy (see Management section, below) (6).

The pattern of joint involvement in neuropathic arthropathy depends on the location of the neurologic impairment and may involve small as well as large joints. In diabetes, the foot is most commonly involved. In spina bifida, the knee, hip, ankle, and lumbar spine are affected. Patients with syringomyelia typically demonstrate upper extremity involvement.

Neuropathic Arthropathy in the Diabetic Foot

Neuropathic arthropathy of the diabetic foot deserves special consideration. It typically occurs after the fifth decade of life in patients with longstanding diabetes, and may follow minor trauma or surgery. It is unilateral in 80% of patients. Five anatomic patterns have been described, including involvement of the toe joints, the tarsometatarsal joints, the midfoot, ankle, and calcaneus. Midfoot involvement is particularly common (Figure 25D-1) (2). During the acute stage, patients present with a swollen foot or ankle. Concurrent skin ulcers are common. The onset of symptoms and rate of destruction may be acute and dramatic with radiographic evidence of joint dissolution occurring within weeks (7). Involvement of the midfoot may result in

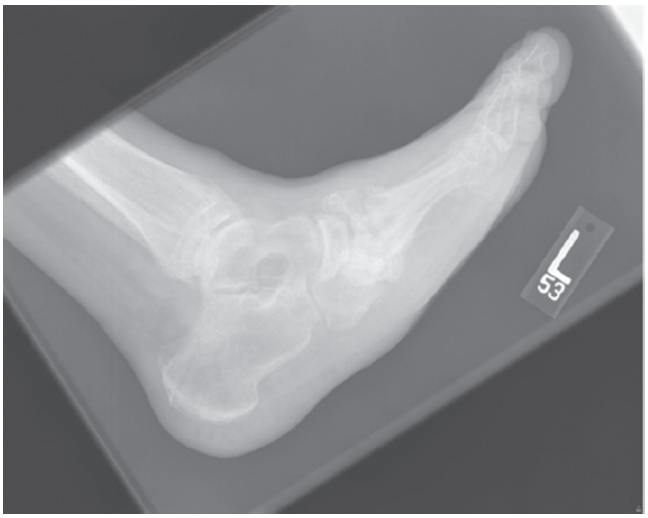


FIGURE 25D-1

Neuropathic arthropathy of the foot in a patient with diabetes. Note the midfoot collapse resulting in a "rocker bottom" deformity. (Courtesy of Dr. Daniel Toutant.)

reversal of the curve of the metatarsal arch and "rocker bottom" deformity. The possibility of osteomyelitis or soft tissue infection in the feet must always be considered in diabetic patients.

DIAGNOSIS

The diagnosis of neuropathic arthropathy can be made clinically. Helpful diagnostic tests include plain radiographs, bone scans, and indium-111–labeled white blood cell (WBC) scans. The differential diagnosis of neuropathic arthropathy includes osteomyelitis and other deep tissue infections, fracture, gout, calcium pyrophosphate dihydrate deposition (CPPD) disease, Milwaukee shoulder/knee syndrome, osteonecrosis, and osteoarthritis. The differentiation between osteomyelitis and acute neuropathic arthropathy in the diabetic foot is particularly challenging.

Plain radiographs are extremely helpful in making the diagnosis of neuropathic arthropathy (3). Early features include demineralization, joint space narrowing, and osteophyte formation. In established disease, bone fragmentation, periarticular debris formation, and joint subluxation occur (Figures 25D-1, 25D-2). Bone absorption, bone shattering, sclerosis and massive soft tissue swelling are seen in some patients. Neuropathic joints are often described radiographically as "disorganized," with chaotic bone destruction and repair. The presence of sharply defined articular surfaces in neuropathic arthropathy is helpful in differentiating radiographic changes of neuropathic arthropathy from those of infection, where involved bone surfaces are indistinct. In neuropathic arthropathy of the diabetic foot, destruction with prominent fragmentation and loose body formation typically occurs in the tarsal bones, while absorptive changes may predominate in the metatarsals and forefoot (Figure 25D-2). In the spine, multilevel thoracic and lumbar involvement is common.

Bone scintigraphy with technetium 99m-MDP and indium-111–labeled WBC scans (8) demonstrate increased uptake of radiolabeled technetium in neuropathic arthropathy; unfortunately, uncomplicated neuropathy as well as infection both can produce similar findings (9). Magnetic resonance imaging should be interpreted with caution as bony changes in osteomyelitis can be difficult to differentiate from those of neuropathic arthropathy. A combined approach using multiple imaging techniques with or without bone cultures is often necessary to differentiate infection from neuropathic arthropathy.

Synovial fluid is typically non-inflammatory in neuropathic arthropathy. Fifty percent of synovial fluids from affected joints are hemorrhagic or xanthochromic. Effusions may be very large. CPPD crystals and basic calcium phosphate crystals have been identified in these joint effusions and may contribute to joint damage.

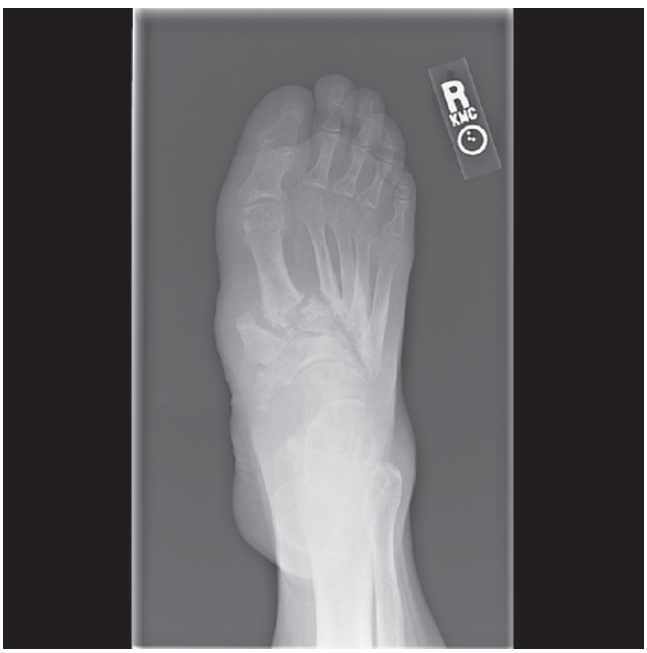


FIGURE 25D-2

Neuropathic arthropathy of the foot in a patient with diabetes. There is involvement of the forefoot and the midfoot. The typical combination of both resorptive and reparative processes results in a disorganized appearance of the involved bones. (Courtesy of Dr. Daniel Toutant.)

MANAGEMENT

There are no specific therapies for neuropathic arthropathy. The prognosis of affected patients is variable and depends on the severity of the condition and the response to treatment.

Standard management strategies for the acute phase (6) of neuropathic arthropathy include joint immobilization, usually achieved by casts, braces, orthotics, and restricted weight bearing. With immobilization, the average time to healing in neuropathic arthropathy of the diabetic foot is approximately 6 months (4). With early diagnosis and bracing, risks for amputation are 2.3%, but 23% will require bracing for 18 months, and 50% will have recurrent ulcers (10). There is some preliminary evidence for the efficacy of bisphosphonates in the early destructive phase of the disease (2).

Surgical treatments, another mainstay of therapy, are generally recommended in the remodeling phase of the disease (2). Goals are to improve pain, joint stability, and alignment, and to prevent or treat overlying skin ulceration. Arthrodesis is useful in the spine, foot, ankle, and knee. Removal of exostoses may restore some motion and decrease joint pain in patients with severe rocker bottom deformities of the foot. With current techniques, joint replacement may also be effective for selected patients.

Prevention is perhaps the best therapy. Prompt attention to any minor trauma to the diabetic foot or ankle may prevent the development of neuropathic arthropathy. Good control of blood glucose levels in diabetics decreases the incidence of neuropathy and thereby reduces the risk of neuropathic arthropathy.

References

1. Gupta A. A short history of neuropathic arthropathy. Clin Orthop 1993;296:43–49.
2. Lee L, Blume P, Sumpio B. Charcot joint disease in diabetes mellitus. Ann Vasc Surg 2003;17:571–580.
3. Resnick D. Neuropathic osteoarthropathy. In: Resnick D, ed. Diagnosis of bone and joint disorders. 3rd ed. Philadelphia: Saunders; 1995:3413–3442.
4. Sinacore D, Withrington N. Recognition and management of acute neuropathic (Charcot) arthropathies of the foot and ankle. J Orthop Sports Phys Ther 1999;29:736–746.
5. Fishco W. Surgically induced Charcot's foot. J Am Podiatr Med Assoc 2001;91:288–293.
6. Eichenholtz S. Charcot joints. Springfield: Thomas; 1966.
7. Sloman-Kovacs S, Braunstein E, Brandt K. Rapidly progressive Charcot arthropathy following minor joint trauma in patients with diabetic neuropathy. Arthritis Rheum 1990;33:412–417.
8. Lipman B, Collier B, Carrera G, et al. Detection of osteomyelitis in the neuropathic foot: nuclear medicine, MRI, and conventional radiography. Clin Nucl Med 1998;23:77–82.
9. Palestro C, Mehta H, Patel M, et al. Marrow versus infection in the Charcot joint: indium-111 leukocyte and technetium-99m sulfur colloid scintigraphy. J Nucl Med 1998;39:346–350.
10. Saltzman C, Hagy M, Zimmerman B, Estin M, Cooper R. How effective is intensive nonoperative intial treatment of patients with diabetes and Charcot arthropathy of the feet? Clin Orthop 2005;435:185–190.

CHAPTER 25

Less Common Arthropathies
E. Dermatologic Disorders

JEFFREY P. CALLEN, MD

- Many rheumatologic diseases have prominent cutaneous findings.
- Careful examination of the skin may lead to prompt diagnoses, relatively noninvasive means of defining systemic disorders, and possibly better outcomes.
- Entities discussed in this chapter include the neutrophilic dermatoses (Sweet's syndrome, pyoderma gangrenosum), panniculitis (e.g., erythema nodosum), the sclerosing/fibrosing diseases (e.g., morphea and scleromyxedema), pustular conditions, and a variety of cutaneous conditions with possible implications for rheumatic disease.

The skin often reflects the presence of disease involving internal organs. Consequently, careful examination of the skin may lead to prompt diagnoses, relatively noninvasive means of defining systemic disorders, and possibly better outcomes. Many rheumatologic diseases have prominent cutaneous findings. This chapter provides an overview of a group of conditions in which skin findings are a major component of systemic disease.

NEUTROPHILIC DERMATOSES

The neutrophilic dermatoses are noninfectious disorders characterized by infiltration of the skin by polymorphonuclear leukocytes (Table 25E-1) (1). Some of these disorders may be angiocentric, but typically they are not associated with the type of vessel wall destruction observed in vasculitis. The neutrophilic dermatoses include Sweet's syndrome, pyoderma gangrenosum, neutrophilic dermatosis of the dorsal hands, rheumatoid neutrophilic dermatosis, and the bowel-associated dermatosis–arthritis syndrome.

Sweet's syndrome (2), originally termed *acute febrile neutrophilic dermatosis*, is characterized by painful, erythematous plaques on almost any body surface (Figure 25E-1). The surface of the lesions, frequently tender, may be so edematous that the lesions appear vesicular. Subcutaneous nodules and dermal nodules are unusual manifestations of Sweet's syndrome. The characteristic histopathological findings of Sweet's syndrome are shown in Figure 25E-2. The patients are usually febrile, have a leukocytosis, and frequently have arthralgias or arthritis. The process is more common in women. The disease may be classified further based upon its potential associations with malignancy, inflammatory disorders, infections, drugs, or a group of miscellaneous conditions. In approximately 15% to 20% of patients with Sweet's syndrome, myeloid malignancy or preleukemia occurs. Solid tumors are very rare in these patients. The diagnosis is confirmed by excluding other diseases, particularly cellulitis. Patients with Sweet's syndrome demonstrate pathergy—the occurrence of the characteristic skin lesions following minor trauma.

Patients with Sweet's syndrome often have antineutrophil cytoplasmic antibodies (ANCA) by immunofluorescence testing, but the ANCA specificity is not directed against either myeloperoxidase or proteinase-3 (the specificity observed in microscopic polyangiitis, Wegener's granulomatosis, and related vasculitides). No laboratory findings are pathognomonic of Sweet's syndrome. Patients with Sweet's syndrome secondary to myelodysplasia or leukemia, however, are frequently anemic or thrombocytopenic. Although generally confined to the skin, extracutaneous neutrophilic infiltration occurs in a small percentage of Sweet's syndrome patients, potentially affecting any organ (most commonly the lungs). Osteolytic bone lesions have also been reported. The entity known as *multifocal sterile recurrent osteomyelitis* might represent an orthopedic variant of Sweet's syndrome.

Therapy for Sweet's syndrome is directed toward any identified underlying condition, including cessation of drugs with the potential to trigger this condition.

TABLE 25E-1. ASSOCIATIONS WITH NEUTROPHILIC DERMATOSES.

DERMATOSIS	SWEET'S SYNDROME	PYODERMA GANGRENOSUM (PG)	RHEUMATOID NEUTROPHILIC DERMATOSIS	BOWEL-ASSOCIATED DERMATOSIS ARTHRITIS SYNDROME	NEUTROPHILIC DERMATOSIS OF THE DORSAL HANDS
Inflammatory bowel disease—Crohn's disease and ulcerative colitis	Some	20%–25%	No	Yes	Occasional
Rheumatoid arthritis	Occasional	10% for superficial forms, less for classical PG	Yes, occasionally seronegative	No, but joint disease may simulate RA	Occasional
Hematologic malignancies	25%–30%	15% for the superficial forms	No	No	15%
Solid tumors	Rare	Rare	No	No	Rare
Sjögren's syndrome	Possible	No	Possible	No	Possible
Drug-induced	Occasionally	No	No	No	Possible
Pregnancy	Occasionally	No	No	No	No

Medications known to be associated with Sweet's syndrome include granulocyte-monocyte colony-stimulating factor (GMCSF), granulocyte colony stimulating factor (GCSF), bortezomib, imatinib, minocycline, hydralazine, and oral contraceptives. For acute disease, a short course of oral prednisone tapered over 2 weeks is often sufficient. For recurrent disease without an associated condition, glucocorticoid-sparing agents such as dapsone, thalidomide, immunosuppressive agents, and tumor necrosis factor alpha (TNF-alpha) antagonists are often used. In patients with acute, idiopathic disease, the prognosis is generally good; many have only episode. However, the course of patients with underlying leukemia or myelodysplasia follows that of the associated disease. Absent disease remission or a cure, recurrences are common.

Pyoderma gangrenosum (PG) is a form of ulcerative skin disease. There are at least four clinical variants of PG: classical, atypical, peristomal, and mucosal (3). The classical lesion is a rapidly progressing, painful ulcer, most often on the leg, with a violaceous, undermined (overhanging) border (Figure 25E-3). Atypical PG occurs as a more superficial lesion, often on the dorsal hands (Figure 25E-4), extensor forearms, or face. The border of atypical PG may appear bullous, leading to clinical confusion with Sweet's syndrome. Peristomal PG occurs as a deep ulcer near the site of a stoma, usually created after gastrointestinal or genitourinary surgery. Finally, mucosal PG is associated with ulcerations that can resemble simple aphthae or vegetative lesions. Mucosal PG must be differentiated from Behçet's disease.

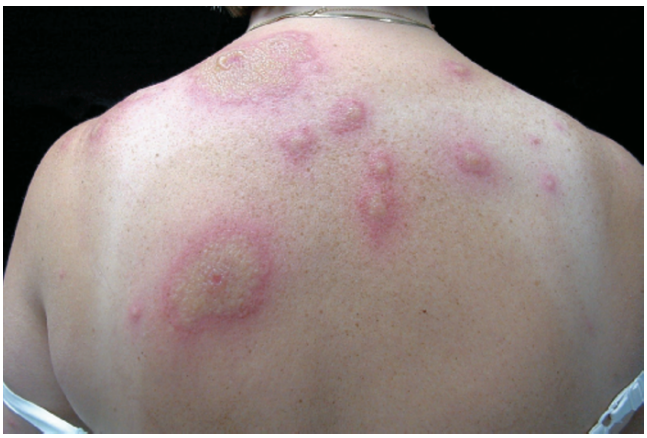


FIGURE 25E-1

Sweet's syndrome.

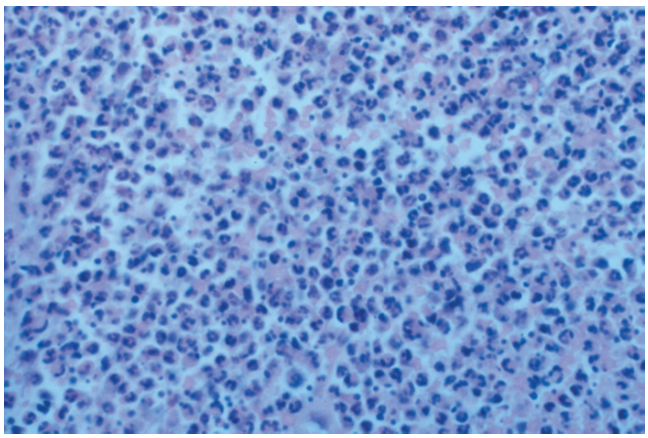


FIGURE 25E-2

Histopathological findings in Sweet's syndrome.

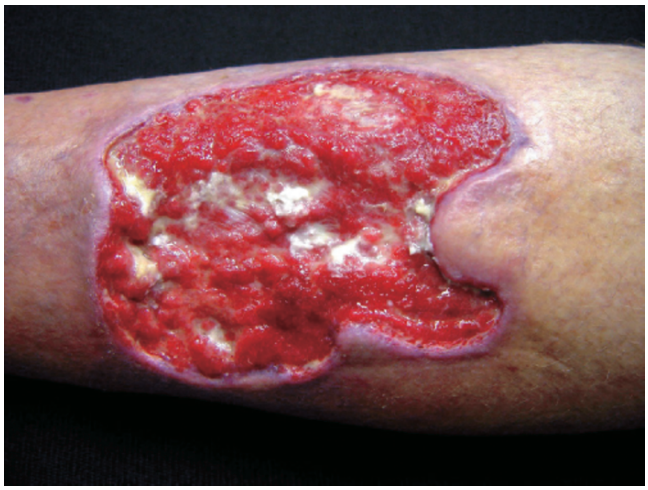


FIGURE 25E-3

Pyoderma gangrenosum in a patient without an associated disease.

Patients with PG also demonstrate pathergy. Thus, this condition has been reported following a variety of surgical procedures, for example, thoracotomy or fasciotomy. The systemic associations vary depending on the type of PG. Classical disease and peristomal PG are associated more frequently with inflammatory bowel disease and/or arthritis. Careful evaluation for inflammatory bowel disease is warranted in cases of peristomal PG, even when the stoma was created for other reasons (e.g., following cancer surgery). In contrast, atypical pyoderma gangrenosum is found more frequently in the setting of myelocytic leukemia or preleukemic conditions.

The diagnosis of PG is one of exclusion. Although biopsies should be performed to exclude other conditions, PG does not have a distinctive histopathology. Because of the importance of excluding disease mimickers—particularly infections—biopsy is almost always performed as part of the evaluation, despite the possibility that the ulcer will extend through pathergy. Culture of the lesions following skin biopsy is essential. Infectious mimickers are not common but include deep fungal infections; for example, blastomycosis, sporotrichosis, histoplasmosis, and coccidioidomycosis; as well as nocardiosis, tuberculosis, atypical mycobacteria; and herpes simplex virus. Following diagnosis, appropriate studies should be undertaken to exclude inflammatory bowel disease, rheumatoid arthritis (RA), systemic vasculitis, paraproteinemia, and other hematologic disorders. As with Sweet's syndrome, neutrophilic infiltration of organs other than the skin may sometimes occur in PG.

For cases of PG associated with an underlying disease (e.g., inflammatory bowel disease or RA), treatment of the primary condition often leads to improvement in PG. Prednisone (1 mg/kg/day) is generally the first line of therapy for idiopathic PG. Infliximab (3–5 mg/kg every 6 weeks following two initial doses 2 weeks apart) is also an effective therapy for PG, even in the absence of inflammatory bowel disease. Other therapies employed in PG include dapsone [100–200 mg/day (assuming normal levels of glucose-6-phosphate dehydrogenase; G6-PD)], thalidomide (100 mg/day), cyclosporine (5 mg/kg/day), azathioprine [2 mg/kg/day, assuming normal levels of thiopurine methyltransferase; (TPMT)], and mycophenolate mofetil (1.0–.5 g b.i.d.).

Neutrophilic dermatosis of the dorsal hands (NDDH) (4), considered by some to be a separate disease entity, is regarded more commonly as a variant of either Sweet's syndrome or atypical PG. NDDH is associated with the same underlying conditions as Sweet's syndrome and atypical PG, and the management considerations are identical.

Rheumatoid neutrophilic dermatosis, an unusual complication of RA, is characterized by symmetrical erythematous papules and plaques on the dorsal hands, elbows, and extensor surfaces of the forearms (5). Patients generally have active and often severe RA, but the condition has been reported in at least two patients with seronegative RA. In terms of histopathology, rheumatoid neutrophilic dermatosis resembles Sweet's syndrome. Treatments that have been suggested include glucocorticoids, dapsone (100–200 mg/day), and colchicine (0.6 mg b.i.d.); however, spontaneous resolution has been reported to occur.

Bowel-associated dermatosis–arthritis syndrome was first recognized in the 1970s following gastric bypass surgery for morbid obesity. Fortunately, because of major alterations in surgical technique, this syndrome is

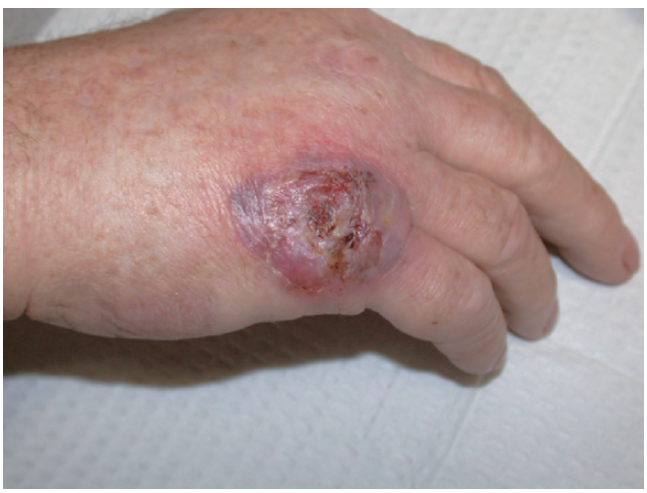


FIGURE 25E-4

Atypical pyoderma gangrenosum, also known as neutrophilic dermatosis of the dorsal hands.

rarely observed today. The former procedure involved the creation of a blind intestinal loop that frequently led to bacterial overgrowth, presumed responsible for the clinical manifestations. The bowel-associated dermatosis–arthritis syndrome was initially called *bowel bypass syndrome* until recognition of the fact that similar changes occurred in patients with ulcer surgery that created a blind loop.

The skin lesions of the bowel-associated dermatosis–arthritis syndrome are characterized by pustular lesions or erythematous papules and/or plaques. Lesions that simulate NDDH (see above) have also been reported. The joint manifestations consist of a symmetrical, nondeforming arthropathy, most often involving the small joints of the hands and feet. These patients often respond to antibiotic therapy, including tetracycline or metronidazole.

PANNICULITIDES

Panniculitis refers to inflammation of the subcutaneous fat (6,7). The process probably evolves from neutrophilic infiltration through lymphocytic and histiocytic infiltration to fibrosis. The classification of panniculitides is controversial, but several clear-cut entities are defined here.

Erythema nodosum, perhaps the most common form of panniculitis, is characterized histologically by septal inflammation (8). Erythema nodosum is most often characterized by red, tender subcutaneous nodules on the anterior leg (Figure 25E-5). The disorder is believed to be a reactive process commonly triggered by infections in the upper respiratory tract and/or lungs. The most common association is streptococcal pharyngitis, but tuberculosis, coccidioidomycosis, and psittacosis are other common infectious causes. Pregnancy, oral contraceptive use, inflammatory bowel disease, and sarcoidosis are other common causes of erythema nodosum. In sarcoidosis, erythema nodosum typically occurs in the setting of arthritis and hilar adenopathy, a syndrome known as Löfgren's syndrome. Löfgren's syndrome, self-limited in two thirds of cases, usually requires symptomatic treatment only.

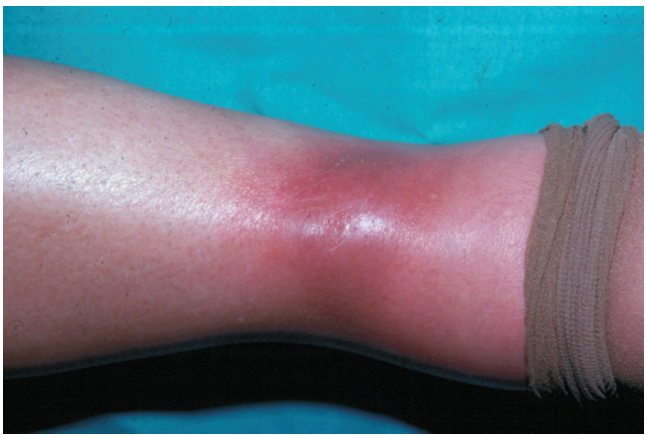


FIGURE 25E-5

Erythema nodosum.

Joint inflammation may accompany erythema nodosum, but at times the inflammatory reaction on the legs surrounds the joints, creating a "periarthritis" but not a true synovitis. Patients with erythema nodosum should be evaluated with a careful history and physical examination. Skin biopsies are required only for atypical presentations or persistent disease. Additional evaluation should include throat cultures, a streptozyme titer, and a chest radiograph. Treatment is often supportive, including gradient support stockings, elevation of the legs, and nonsteroidal anti-inflammatory agents. Other therapies that have been reported to be effective in single cases or small case series include potassium iodide, dapsone, antimalarial agents, colchicine, glucocorticoids, immunosuppressive agents, and TNF-alpha antagonists.

The existence of **Weber–Christian disease** as a distinct entity is controversial. The condition is characterized by recurrent, often multiple, tender subcutaneous nodules accompanied by fever. In contrast to erythema nodosum (a septal panniculitis), Weber–Christian disease is a lobular panniculitis. With regard to nomenclature, the issue is whether the lobular panniculitis associated with Weber–Christian disease occurs as a primary disorder or as a complication of another underlying illness. For example, a lobular panniculitis is known to occur in alpha-1-antitrypsin deficiency, pancreatic disease-associated panniculitis, and a wide array of other inflammatory disorders. Systemic involvement due to inflammation of fatty tissues other than the subcutis has also been reported in cases labeled Weber–Christian disease. There is no specific therapy for this entity, but suggested therapies include those for chronic erythema nodosum (see above).

Lupus panniculitis (also known as lupus profundus), a rare manifestation of systemic lupus erythematosus (SLE), is a form of chronic cutaneous lupus erythematosus. The histopathology of lupus profundus reveals both lobular and septal inflammation, sometimes demonstrating an interface dermatitis (deposition of immunoreactants such as immunoglobulins and complement proteins at the dermal/epidermal junction) that is characteristic of cutaneous lupus. Hydroxychloroquine [6.5 mg/kg (ideal body weight)/day in single or divided doses] is usually an effective first approach to therapy.

Lipodermatosclerosis, also known as sclerosing panniculitis, is characterized by tender, subcutaneous nodules most often over the medial malleolus, accompanied by hyperpigmentation, telangiectases, tortuous

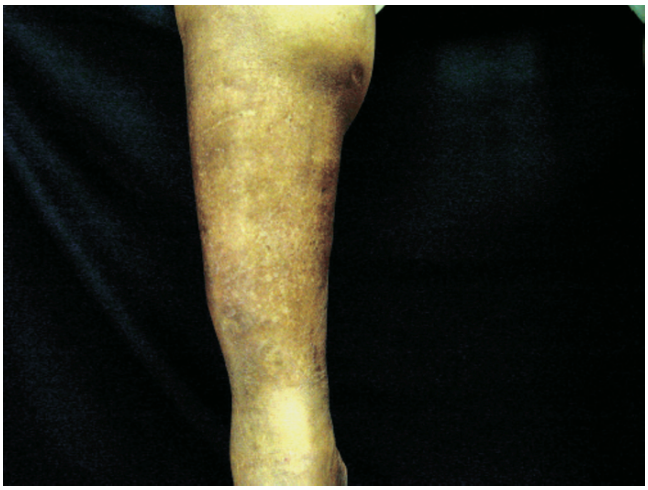


FIGURE 25E-6

Lipodermatosclerosis.

veins, edema, and a woody induration (Figure 25E-6) (9). Women older than 40 years of age are affected most commonly by this condition. The histopathology includes inflammation of the panniculus in addition to dermal sclerosis. This process, occasionally diagnosed incorrectly as localized scleroderma or as an inflammatory type of panniculitis, is in fact simply a long-term complication of venous insufficiency. The most effective therapy is the application of support stockings with a 30 to 40 mm Hg gradient.

Calcifying panniculitis is a variant of calciphylaxis (more properly termed *calcific uremic arteriolopathy*). This process most often occurs in people with renal failure, frequently on dialysis. The management of these patients involves a control of their serum calcium and phosphate levels and, when present, treatment of secondary hyperparathyroidism.

Cytophagic histiocytic panniculitis, an entity associated with tender subcutaneous nodules, fever, hepatosplenomegaly, pancytopenia, and serositis (10), is believed now to be a manifestation of subcutaneous panniculitislike T-cell lymphoma. The disorder frequently masquerades as an undefined connective tissue disease until its progression allows the proper diagnosis. Treatment of this condition is directed at the underlying lymphoma.

SCLEROSING/FIBROSING DISEASES

Several skin conditions are associated with cutaneous thickening and varying levels of systemic disease (Table 25E-2). These disorders are not necessarily related to each other aside from the finding of skin induration that may be localized or generalized.

Localized scleroderma, one subtype of which is morphea, is more common in children and women (11). Localized scleroderma is differentiated from systemic sclerosis by the lack of Raynaud's phenomenon, sclerodactyly, and the absence of internal organ involvement. The term *morphea* is synonymous with localized scleroderma, of which there are at least five subtypes: (1) guttate morphea refers to patients with small "drop-like" lesions; (2) morphea profundus refers to deep lesions that involve the panniculus along with the dermis; (3) bullous morphea; (4) generalized morphea (Figure 25E-7) encases the body in hard skin with—in contrast to systemic sclerosis—sparing of the acral areas, face, and nipples; and (5) linear scleroderma (Figure 25E-8). When linear scleroderma occurs on the face and/or scalp, the term *en coup de sabre* (blow of the saber) is used. The Parry–Romberg syndrome, associated with facial hemiatrophy, is usually accompanied by linear scleroderma. In the Parry–Romberg syndrome, however, there is atrophy of the underlying bony structures, muscles and, in some instances, even the contiguous nervous system.

Most patients with any form of morphea improve over time, with softening of the sclerotic skin lesions. However, there may be residual dyspigmentation, limb atrophy or deformity, or joint contracture. Therapy includes topical glucocorticoids or calcipotriene for localized disease. Methotrexate with or without pulse methylprednisolone has been used for widespread disease. Phototherapy with ultraviolet (UV)A-1 light has also been reported to be successful in patients with localized scleroderma.

Lichen sclerosus is a superficial dermatosis that has recently been linked to circulating autoantibodies directed against extracellular matrix protein 1 (12). The disease is manifested by induration and superficial, atrophic, hypopigmented patches or plaques that resemble cigarette paper (Figure 25E-9). These same changes are observed in some patients with morphea and may also occur in patients with chronic graft-versus-host disease (Figure 25E-10). In some cases the disease affects only the genitalia and in women may be associated with a risk of malignant transformation. Potent topical glucocorticoids are the treatment of choice for lichen sclerosus.

Scleromyxedema is characterized by a generalized papular and sclerodermatous eruption often described as "waxy papules." The distribution of the skin lesions in scleromyxedema is over the head, neck, arms, and upper trunk. Papular lesions are often situated on thickened, indurated skin. On biopsy, these lesions demonstrate mucin deposition, fibrosis, and fibroblast proliferation on biopsy. Patients are often misdiagnosed as having systemic sclerosis (scleroderma). Thyroid

TABLE 25E-2. DERMATOLOGICAL CONDITIONS ASSOCIATED WITH SCLERODERMOID AND/OR FIBROSING ALTERATIONS.

DISEASE	CUTANEOUS MANIFESTATIONS	SYSTEMIC MANIFESTATIONS	EVALUATION	MANAGEMENT	COMMENTS
Morphea (and guttate morphea)	Indurated plaques. Sometimes the borders are violaceous. Surface changes of lichen sclerosus may coexist.	Rare involvement, but esophageal dysfunction, pulmonary fibrosis have been reported.	ANA, Anti-ssDNA, antihistone antibodies, PFTs.	Topical glucocorticoids, topical calcipotriene, UVA-1, methotrexate.	Positive serology is predictive of a more prolonged course.
Linear scleroderma	Indurated linear lesions on the arms, legs or face [en coup de sabre (Figure 25E-7)]. Facial lesions may be accompanied by atrophy of underlying bone, soft tissues and nervous system. Surface changes of lichen sclerosus may coexist.	Same as morphea	Same as morphea	Same as morphea	
Generalized morphea	Generalized indurated plaques, often with sparing of the nipples (Figure25E-8). Surface changes of lichen sclerosus may coexist.	Same as morphea	Same as morphea	Topical therapy is adjunctive to systemic therapies or phototherapy.	
Lichen sclerosus	Cigarette paper–like changes on the surface (Figure 25E-9). May be present on trunk or extremities. Genital lesions, particularly in girls, may be mistaken for abuse because bleeding into the lesion is common.	None	Antibodies to extracellular matrix 1 protein have been recently observed in patients with lichen sclerosus, suggesting that it is an autoimmune disorder.	Superpotent topical glucocorticoids for localized disease. Methotrexate or UV phototherapy for extensive disease.	Elevated risk of cancer in patients with genital lesions.
Scleredema	Indurated, erythematous plaque usually on the upper back.	Often complicates diabetes mellitus. May occur post–streptococcal infection.	Biopsy reveals deposition of amorphous material that stains positive with mucin stains. SPEP should be done.	There is no known effective therapy.	Occassional monoclonal gammopathy is present.

(*continued*)

TABLE 25E-2. *Continued*

DISEASE	CUTANEOUS MANIFESTATIONS	SYSTEMIC MANIFESTATIONS	EVALUATION	MANAGEMENT	COMMENTS
Scleromyxedema	Linear flesh-colored papules are an early change, but eventually induration occurs.	Monoclonal gammopathy and plasma cell dyscrasia is common.	Biopsy reveals increase in mucin in the dermis. SPEP, IEP, bone marrow aspiration or biopsy.	Stem-cell transplant has resulted in complete responses in patients with plasma cell dyscrasia. Systemic glucocorticoids or cytotoxic agents are used in patients without plasma cell dyscrasia.	
Nephrogenic fibrosing dermopathy/ nephrogenic systemic fibrosis	Acute onset of induration often follows anasarca. Usually affects the arms [Figure 25E-11(B)] and forearms, or the legs. Decrease in the range of motion of the hands [Figure 25E-11(A)] and feet lead to limitations of the patient's ability to function.	Renal disease of some sort is almost always present. Pulmonary fibrosis may occur. Calcifications may also compromise the process.	Tests of renal function. Monoclonal protein is absent. Biopsy looks identical to scleromyxedema.	Renal transplantation may improve process. Other therapies that have been reported to be effective include thalidomide, photopheresis, plasmapheresis, methotrexate, phototherapy, IVIG.	The process may be preceded by a surgical procedure, particularly vascular revision of hemodialysis shunt, or by a thrombotic event.
Graft-versus-host disease (GVHD)	Acute disease is associated with a morbilliform eruption. As the process becomes more chronic, lichen planus–like lesions may develop. Eventually sclerotic lesions, often with superficial features of lichen sclerosus occur. (Figure 25E-10).	Hepatic dysfunction and/or bowel dysfunction.	There is no test to determine whether a patient has GVHD. Biopsy in the late stages simulates morphea or lichen sclerosus, but there is often an interface dermatitis as well.	Topical superpotent glucocorticoids and/or calcineurin inhibitors for localized disease. Phototherapy, thalidomide, immunosuppressive agents for widespread or systemic disease.	

ABBREVIATIONS: ANA, antinuclear antibodies; Anti-ssDNA, anti–single-stranded DNA; IEP, immunoelectrophoresis; IVIG, intravenous immune globulin; PFT, pulmonary function tests; SPEP, serum protein electrophoresis; UV, ultraviolet.

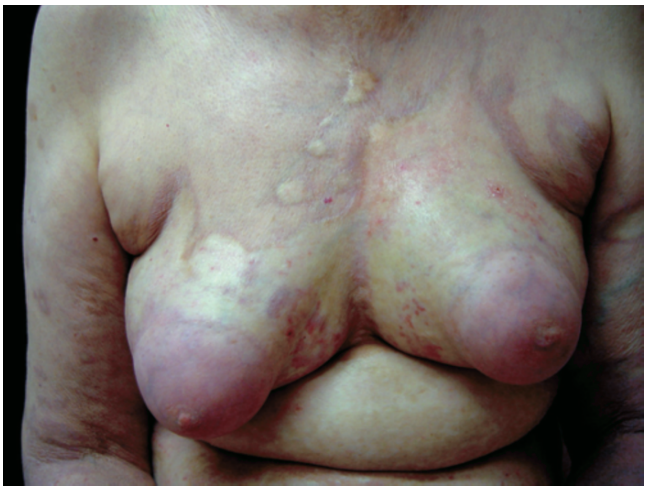


FIGURE 25E-7

Generalized morphea—this patient has widespread disease on her trunk and proximal extremities. Note the sparing of scleroderma on the nipples, which is a common feature of generalized morphea.

disease must also be excluded. Monoclonal gammopathies, particularly IgG lambda, are common in scleromyxedema, which may also be associated with multiple myeloma and amyloidosis. Treatment of patients with scleromyxedema is often difficult. Therapies that have been used include cytotoxic agents, including melphalan, thalidomide, and, most recently, autologous stem cell transplantation (13).

Nephrogenic systemic fibrosis (NSF; also termed **nephrogenic fibrosing dermopathy** or **nephrogenic fibrosing systemic disorder**) is a recently described process characterized by a rapid onset of skin thickening [14; Figure 25E-11(A,B)]. The process is accompanied by limited range of motion, particularly of the feet and hands. The biopsy is identical to the changes observed

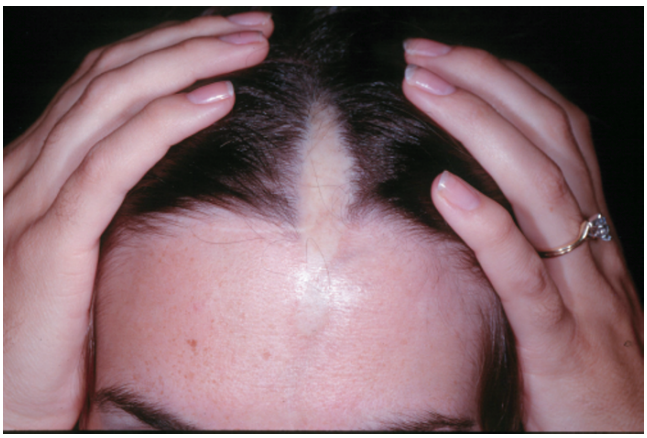


FIGURE 25E-8

Linear scleroderma.

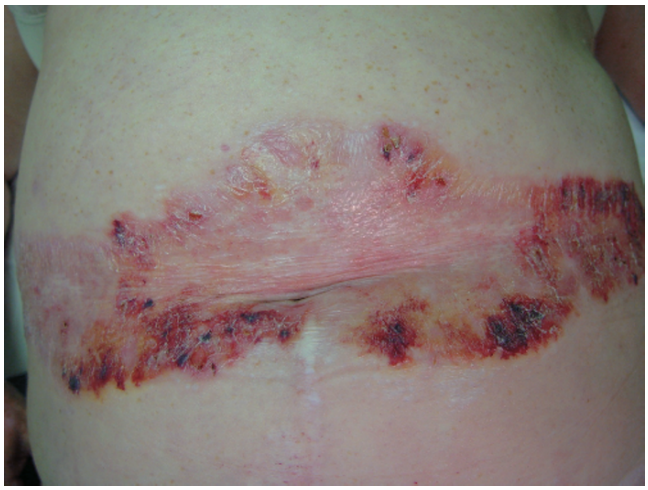


FIGURE 25E-9

Lichen sclerosus. Note the cigarette paper–like changes on the surface. Hemorrhage within the lesions is quite characteristic.

in scleromyxedema. Features that separate this entity from scleromyxedema are the lack of a monoclonal gammopathy and the presence of renal disease. Since its initial description, systemic fibrosis (particularly affecting the lungs) has been described in many patients, leading to debate over the appropriate name of the condition. Many patients improve with renal transplantation, while others have been treated with thalidomide, methotrexate, TNF antagonists, plasmapheresis, and photopheresis with variable success. NSF is now known to be associated strongly with the administration of gadolinium, a contrast agent used in magnetic resonance imaging, to patients with renel insufficiency.

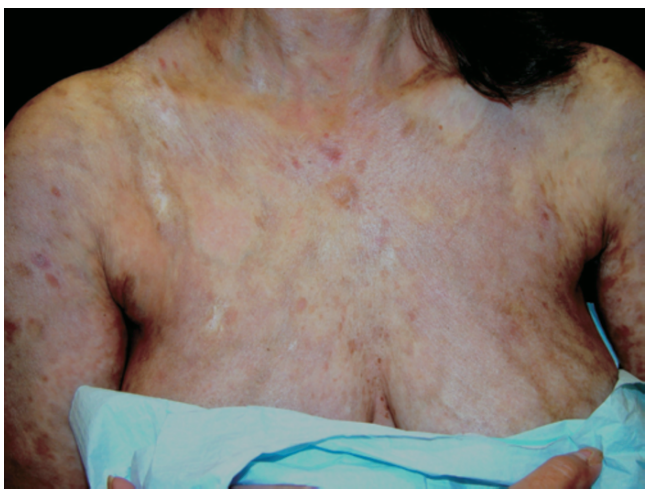


FIGURE 25E-10

Graft-versus-host disease (GVHD). Patients with chronic GVHD often have cutaneous manifestations. This patient demonstrates the widespread nature of the disease which simulates both morphea and lichen sclerosus.

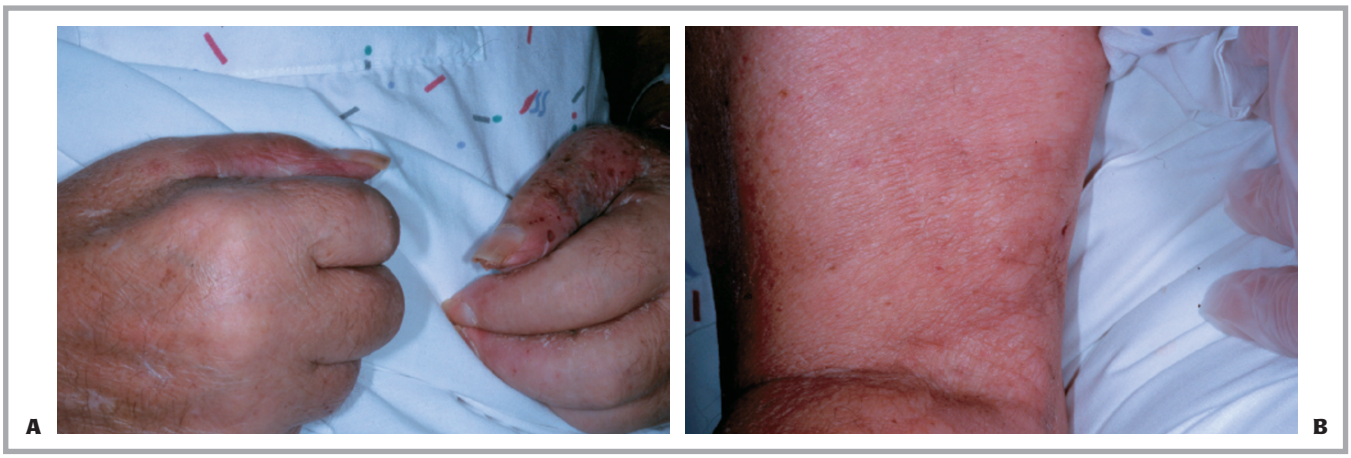


FIGURE 25E-11

(A, B) Nephrogenic systemic fibrosis in a patient with acute renal failure who underwent a magnetic resonance imaging study with gadolinium dialysis.

PUSTULAR CONDITIONS

The following disease entities, characterized by pustular lesions, demonstrate substantial overlap.

Generalized pustular psoriasis is a rare phenomenon, but pustular psoriasis localized to the palms and soles (Figure 25E-12) is relatively common. These diseases may be induced by various medications, including the withdrawal of systemic glucocorticoids in the case of generalized pustular psoriasis and the use of TNF antagonists in the case of palmoplantar pustular psoriasis (15). Generalized pustular psoriasis, a highly labile form of psoriasis, can be accompanied by systemic symptoms. Control with oral retinoids, methotrexate, or possibly infliximab is useful. Pustular lesions of the palms and soles are difficult to treat and can cause disability.

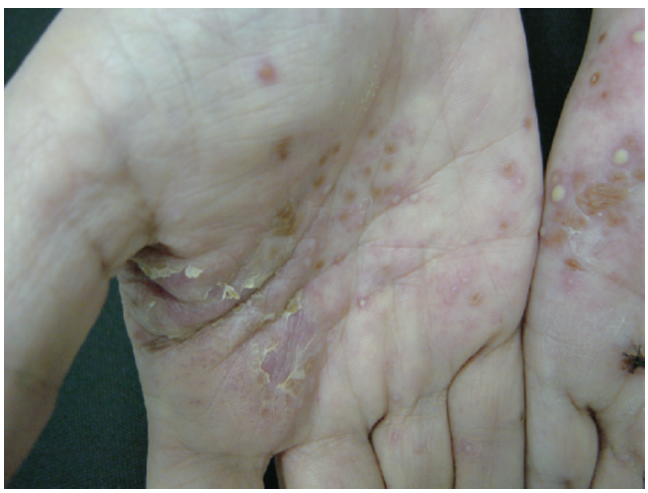


FIGURE 25E-12

Palmoplantar pustulosis—note the crusts accompanied by both large and small pustules on the palms of this patient.

SAPHO syndrome is a rare disorder characterized by synovitis, acne, pustulosis of the palms and soles, hyperostosis of one of the bones of the chest wall, and sterile osteitis (16). These patients may also have psoriasis vulgaris or accompanying inflammatory bowel disease. The synovitis may involve either peripheral or axial joints. The osteitis is similar to chronic recurrent sterile osteomyelitis. The prevalence of human leukocyte antigen (HLA)-B27 is increased among patients with the SAPHO syndrome, leading some authorities to classify this entity as a spondyloarthropathy. SAPHO syndrome has considerable overlap with the other pustular conditions discussed in this section, however, as well as with the neutrophilic dermatoses discussed above. The pathogenetic mechanisms of all of these conditions remain incompletely defined. Treatment of SAPHO is often difficult. Drugs that have been reported to be effective in individual cases or small case series include nonsteriodal anti-inflammatory drugs (NSAIDs), colchicine, glucocorticoids, sulfasalazine, methotrexate, infliximab, and second generation bisphosphonates.

The **PAPA syndrome** is the occurrence of sterile pyogenic arthritis, pyoderma gangrenosum, and acne. Usually the acne is nodulocystic. The differentiation of this syndrome from SAPHO may be difficult.

Hidradenitis suppurativa is a disorder of apocrine glands. Patients present with pustules and draining sinus tracts in the axilla, under the breasts, within inguinal folds, and on the buttocks. Women appear to be affected more frequently than men. Hidradenitis may be associated with Crohn's disease in some patients. Oral antibiotics are frequently prescribed but often not fully effective. Oral isotretinoin is often suggested, but in this

author's opinion, it is rarely effective. Recent case reports and case series have documented responses to infliximab. Definitive therapy with surgical exenteration of the involved areas is curative.

Acne fulminans is a severe form of acne that is accompanied by systemic symptoms (17). It is explosive in its onset and most often occurs in adolescent boys. The face, chest, and upper back are the most common sites. The lesions may begin as mild typical acne, but they rapidly become markedly inflamed and coalesce into painful and oozing friable plaques with hemorrhagic crusts. Systemic involvement includes fever, arthralgia, myalgia, hepatosplenomegaly, and severe prostration. Erythema nodosum may occur in some patients with acne fulminans. Osteolytic bone lesions have also been reported. There is no specific laboratory abnormality associated with this process, but elevation of the erythrocyte sedimentation rate, leukocytosis, and anemia may occur. Therapy with oral glucocorticoids and isotretinoin is helpful. Oral dapsone has also been utilized as an adjunctive therapy. Residual scarring is common.

MISCELLANEOUS DERMATOLOGICAL CONDITIONS WITH POSSIBLE RHEUMATOLOGIC CONSEQUENCES

Scurvy, caused by vitamin C deficiency, frequently presents with purpura or ecchymoses and bone pain. It is more common in alcoholics. The purpuric lesions tend to be perifollicular (Figure 25E-13). Careful examination reveals corkscrew hairs that are also characteristic.

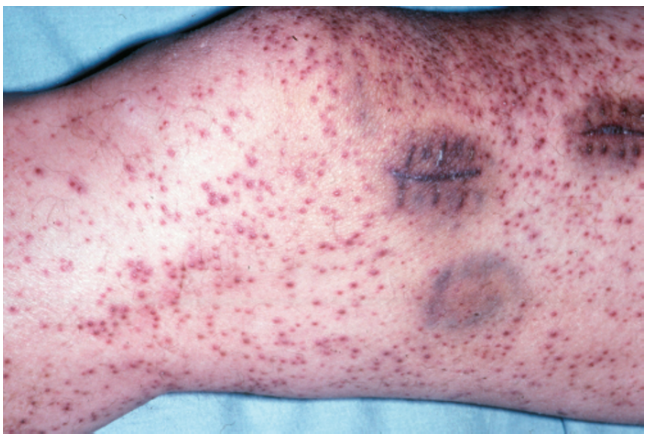


FIGURE 25E-13

Scurvy. Perifollicular purpura with corkscrew hairs. (Courtesy of Kenneth E. Greer, MD, Charlottesville, VA.)

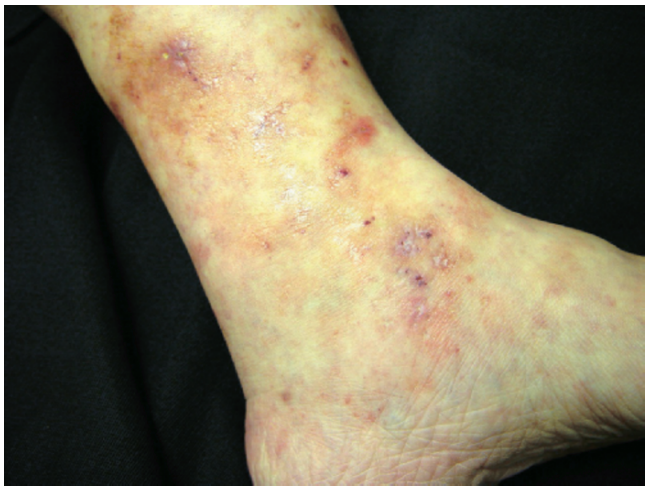


FIGURE 25E-14

Livedoid vasculopathy (also known as atrophie blanche).

Occasionally scurvy may masquerade as small vessel vasculitis. Reintroduction of vitamin C into the diet leads to resolution of the process.

Livedoid vasculopathy, also known as segmental hyalinizing vasculopathy, livedoid vasculitis, atrophie blanche, and livedo reticularis with summer ulcerations, is a clinical entity manifested by painful ulcerations of the distal legs, more commonly over the medial malleolus (Figure 25E-14). This process is not an inflammatory disease. On biopsy, the characteristic change is fibrin deposition within the vessel lumina. The process may represent an end result of a number of coagulation disorders, including cryofibrinogenemia, Factor V Leiden mutation, and other inherited thrombophilic conditions, and the antiphospholipid syndrome (18). Livedoid vasculopathy may mimic vasculitis or stasis dermatitis clinically. Therefore, a biopsy is helpful in directing the evaluation. Therapy should include smoking cessation and prevention of trauma, in addition to addressing any underlying coagulation disorder. Various platelet inhibitors and anticoagulants have been reported to be effective in individual cases or small case series.

Granuloma annulare is a relatively common cutaneous disease not generally associated with systemic conditions. The findings of granuloma annulare are flesh-colored or erythematous lesions that are annular (Figure 25E-15) and may occur on any surface of the body. The histopathology of granuloma annulare is a necrobiotic granuloma—essentially the same histopathological finding that occurs in necrobiosis lipoidica and rheumatoid nodules. Biopsies are frequently read as rheumatoid nodules by general pathologists; patients are then referred inappropriately for rheumatologic evaluations. Treatment of granuloma annulare with intralesional injections of triamcinolone acetonide in

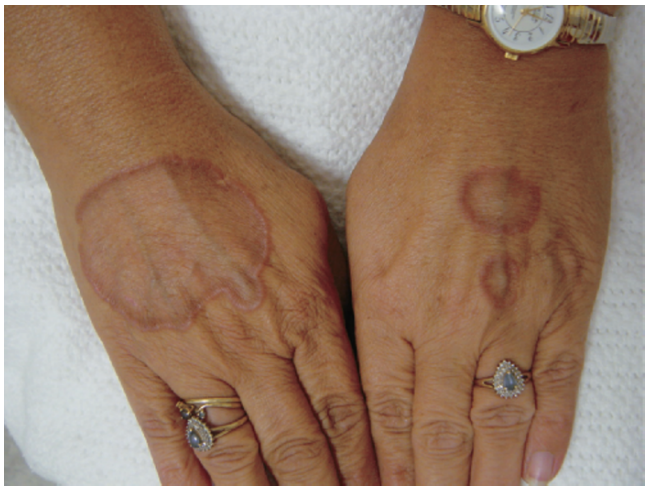


FIGURE 25E-15

Granuloma annulare on the dorsal hands.

dilute concentrations usually leads to resolution of the disorder.

Two variants of granuloma annulare are worth mentioning: the subcutaneous variant (19) and a recently described acute acral variant (20). Subcutaneous granuloma annulare often presents on the feet or hands and may be slightly tender (Figure 25E-16). Acute acral granuloma annulare is a process associated with the sudden onset of tender acral erythematous lesions, usually on the hands and fingers (Figure 25E-17). The acral variant, which often occurs in patients with a history of various forms of arthritis, is managed with topical glucocorticoids, oral antimalarial agents, oral dapsone, or (rarely) oral glucocorticoids.

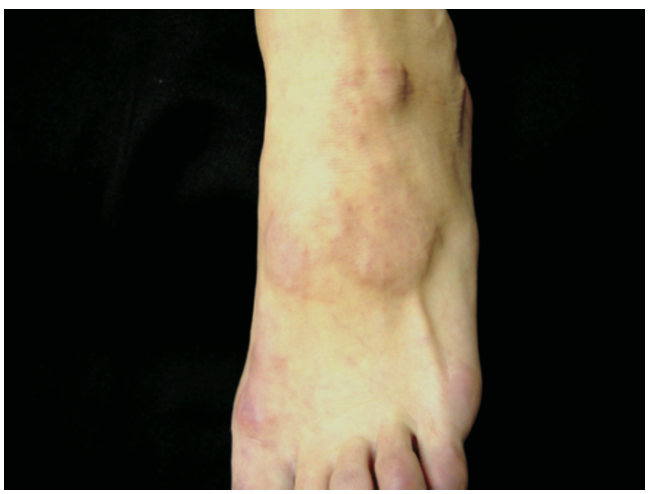


FIGURE 25E-16

Subcutaneous granuloma annulare. This patient was misdiagnosed as having rheumatoid arthritis after her initial biopsy was interpreted as a rheumatoid nodule.

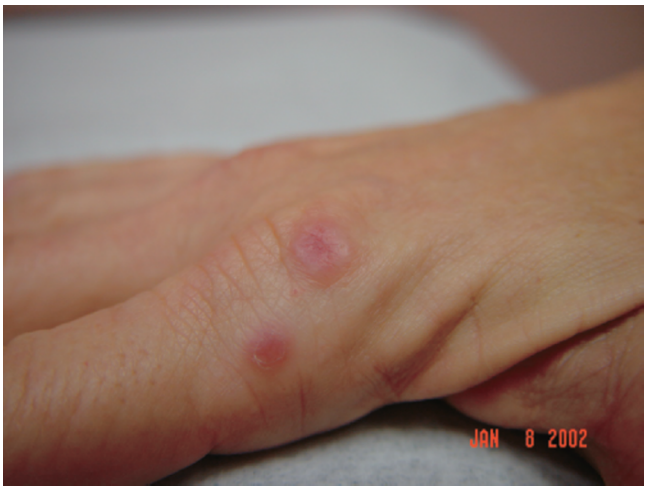


FIGURE 25E-17

Acute, acral granuloma annulare. This patient had disease which clinically mimicked Sweet's syndrome, but the histopathology demonstrated a necrobiotic granuloma.

Cutaneous extravascular necrotizing granulomas are known as the Churg–Strauss granulomas. The term *palisaded neutrophilic and granulomatous dermatitis with arthritis*, rheumatoid papules, superficial ulcerating rheumatoid necrobiosis, and interstitial granulomatous dermatitis with arthritis have also been used to describe this entity (21). Whether this is a distinct entity is controversial and the exact relationship to arthritis has been questioned. Patients present with symmetrical, annular, erythematous lesions, often favoring intertriginous sites. Recently multiple drugs have been linked to the development of interstitial granulomatous dermatitis, but even when a drug has appeared to trigger the cutaneous disease, it is likely that the patient has an underlying rheumatologic disease, particularly SLE, RA, Wegener's granulomatosis, or the Churg-Strauss syndrome. Treatment involves discontinuation of a drug in an appropriate setting and treatment of the associated condition.

Lichen planus is a common cutaneous disease characterized by pruritic, purple, polygonal papules and plaques (Figure 25E-18). The surface scale, when examined closely demonstrates a reticulated pattern known as "Wickham striae." Common areas of involvement include the wrists and mouth but any surface may be involved. Erosive oral and/or genital disease may lead to malignancy. Lichen planus is frequently associated with hepatitis C. A variant of lichen planus is caused by drugs and has occurred more commonly in patients treated with gold or penicillamine. Lichen planus–like lesions may be a manifestation of acute graft-versus-host disease. The disease is self-limited but may be treated with topical or systemic glucocorticoids.

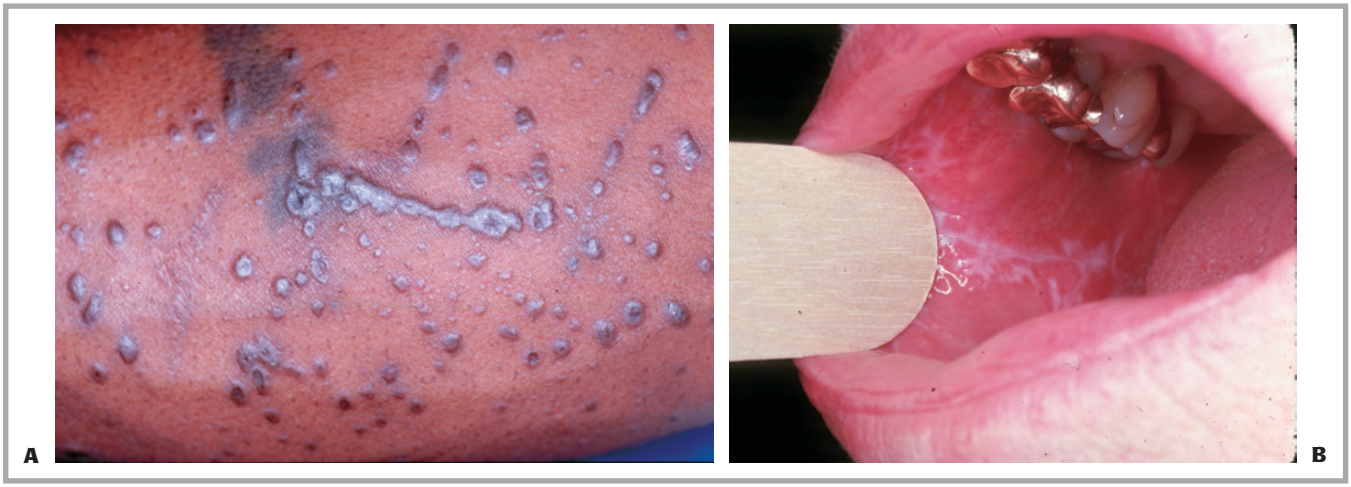


FIGURE 25E-18

Lichen planus lesions on the wrist (A) and in the mouth (B).

REFERENCES

1. Callen JP. Miscellaneous disorders that commonly affect both skin and joints. In: Sontheimer RD, Provost TT, eds. Cutaneous manifestations of rheumatic diseases. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2004:221–241.
2. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. Int J Dermatol 2003;42:761–778.
3. Jackson JM, Callen JP. Pyoderma gangrenosum. An expert commentary. Int J Dermatol 2006;41:916–918.
4. Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis of the dorsal hands and sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. Arch Dermatol 2006;142:57–63.
5. Brown TB, Fearneyhough PF, Burruss JB, Callen JP. Rheumatoid neutrophilic dermatitis in a woman with seronegative rheumatoid arthritis. J Am Acad Dermatol 2001;45:596–600.
6. Requena L, Yus ES. Panniculitis. Part I. Mostly septal panniculitis. J Am Acad Dermatol 2001;45:163–183.
7. Requena L, Sanchez Yus E. Panniculitis. Part II. Mostly lobular panniculitis. J Am Acad Dermatol 2001;45:325–361.
8. Requena L, Requena C. Erythema nodosum. Dermatol Online J 2002;8:4.
9. Bruce AJ, Bennett DD, Lohse CM, Rooke TW, Davis MD. Lipodermatosclerosis: review of cases evaluated at Mayo Clinic. J Am Acad Dermatol 2002;46:187–192.
10. Ma L, Bandarchi B, Glusac EJ. Fatal subcutaneous panniculitis-like T-cell lymphoma with interface change and dermal mucin, a dead ringer for lupus erythematosus. J Cutan Pathol 2005;32:360–365.
11. Zulian F, Vallongo C, Woo P, et al. Localized scleroderma in childhood is not just a skin disease. Arthritis Rheum 2005;52:2873–2881.
12. Oyama N, Chan I, Neill SM, et al. Development of antigen-specific ELISA for circulating autoantibodies to extracellular matrix protein 1 in lichen sclerosus. J Clin Invest 2004;113:1550–1559.
13. Donato ML, Feasel AM, Weber DM, et al. Scleromyxedema: role of high-dose melphalan with autologous stem cell transplantation. Blood 2006;107:463–466.
14. Cowper SE, Boyer PJ. Nephrogenic systemic fibrosis: an update. Curr Rheumatol Rep 2006;8:151–157.
15. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum 2005;52:2513–2518.
16. Suei Y, Taguchi A, Tanimoto K. Diagnostic points and possible origin of osteomyelitis in synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome: a radiographic study of 77 mandibular osteomyelitis cases. Rheumatology (Oxford) 2003;42:1398–1403.
17. Mehrany K, Kist JM, Weenig RH, Witman PM. Acne fulminans. Int J Dermatol 2005;44:132–133.
18. Hairston BR, Davis MDP, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. Arch Dermatol 2006;142:1413–1418.
19. McDermott MB, Lind AC, Marley EF, Dehner LP. Deep granuloma annulare (pseudorheumatoid nodule) in children: clinicopathologic study of 35 cases. Pediatr Dev Pathol 1998;1:300–308.
20. Brey NV, Malone J, Callen JP. Acute-onset, painful acral granuloma annulare: a report of 4 cases and a discussion of the clinical and histologic spectrum of the disease. Arch Dermatol 2006;142:49–54.
21. Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. Arch Dermatol 1994;130:1278–1283.

CHAPTER 25

Less Common Arthropathies
F. Hypertrophic Osteoarthropathy

MANUEL MARTINEZ-LAVIN, MD

- Hypertrophic osteoarthropathy is characterized by abnormal proliferation of skin and bone at the distal parts of the extremities.
- Clinical features include bulbous deformity of the tips of the digits (conventionally known as clubbing) and periostosis of the tubular bones.
- The development of hypertrophic osteoarthropathy may indicate the presence of a significant internal illness, often a pulmonary malignancy or inflammatory disease of the lung.
- Abnormal vascular endothelial growth factor expression may play a central role in the pathogenesis of this condition.

Hypertrophic osteoarthropathy (HOA) or *acropachy* is a syndrome characterized by excessive proliferation of skin and bone at the distal parts of the extremities. Its most conspicuous feature is a unique bulbous deformity of the tips of the digits, conventionally known as clubbing (Figure 25F-1). In advanced stages, periosteal proliferation of the tubular bones and synovial effusions become evident. The classification of HOA is shown in Table 25F-1 (1). In most instances, HOA appears as a consequence of an internal illness, often localized to the chest. Nevertheless, there are cases of primary HOA. This subgroup affects mostly males and demonstrates a familial predisposition.

PATHOLOGY AND PATHOGENESIS

Clubbing develops as a result of edema and excessive collagen deposition. In addition, endothelial cell activation and vascular hyperplasia are prominent features. At the tubular bone level, there is vascular hyperplasia with proliferation of the periosteal layers (2).

Any proposed scheme for the pathogenesis of HOA must explain how a group of diseases as diverse as those listed in Table 25F-1 could induce the unique connective tissue abnormalities of HOA. Cyanotic heart diseases are excellent models for studying the pathogenesis of this syndrome, because practically all patients with such conditions develop clubbing, and more than one third display fully developed HOA. Patients with cardiogenic HOA frequently have circulating macrothrombocytes with distorted volume distribution curves. Such abnormalities concur with the notion that normally megakaryocytes rupture in the highly dichotomized pulmonary vascular bed. It has been proposed that in patients with right-to-left shunts, large platelet fragments gain direct access to the systemic circulation and reach its most distal sites on axial streams. In the distal microcirculation abnormally large platelets interact with endothelial cells, leading to the release of growth factor(s) and the induction of acropachy (Figure 25F-2) (3). The finding of elevated levels of von Willebrand factor antigen in HOA further supports the notion of enhanced platelet/endothelial cell activation.

Vascular endothelial growth factor (VEGF) may be involved in the pathogenesis of HOA. This growth factor, a potent angiogenic stimulus and osteoblast-differentiation agent, is derived from platelets and induced by hypoxia. A variety of malignant tumors also produce VEGF, fostering their uncontrolled growth. People with primary HOA and HOA associated with lung cancer have elevated levels of VEGF in their plasma (2,4). Immunohistochemistry studies show increased VEGF deposition in the stroma of clubbed digits (5). Overproduction of VEGF may explain how diverse hypoxic or neoplastic pathologies induce HOA, and may also explain how diseases with prominent endothelial cell involvement, such as infective endocarditis, Graves' disease, or mesothelioma, lead to acropachy. More studies are needed to elucidate the pathogenesis of HOA.

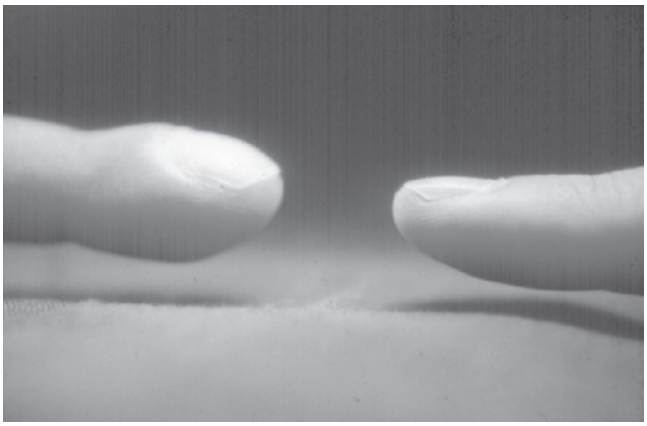


FIGURE 25F-1

A clubbed finger (left) is compared with a normal finger.

CLINICAL FEATURES

Many people with HOA are asymptomatic and unaware of the deformity of their digits (Figure 25F-1). However, other patients, particularly those with pulmonary malignancies, suffer incapacitating bone pain (4). Characteristically, this pain is deep-seated and often more prominent in the legs.

The diagnosis of HOA is based primarily on physical examination and the finding of characteristic radiologic features. The increased volume of soft tissue molds the fingernail into a "watch-crystal" convexity. The nailbed rocks when palpated. Toes are also affected, but early changes are more difficult to discern due to the normal splaying of the toes. The digital index is a practical bedside method to measure clubbing. With a string, the circumference of each finger is measured at the nailbed (NB) and at the distal interphalangeal joint (DIP). If the sum of the 10 NB/DIP ratios is more than 10, clubbing is most likely present (6).

When the complete features of HOA are evident, bone thickening may be appreciated in areas of the extremities not covered by muscles, such as ankles and wrists. These areas can be tender to palpation. Effusions in large joints may be present but do not produce detectable synovial hypertrophy on examination. Range of motion of the affected joint may be slightly decreased. Arthrocentesis yields a clear, viscous fluid with few inflammatory cells; the leukocyte count is typically less than 1000 cells/mm^3. These findings indicate that HOA does not cause inflammatory or proliferative synovial disease, but rather the effusions are most likely a reaction to the adjacent periostosis (7).

Particular types of HOA are associated with peculiar clinical findings. Thyroid acropachy (see Chapter 25B) is distinguished by an exuberant periosteal proliferation that principally involves the small tubular bones of the hands and feet. In thyroid acropachy, clubbing usually coexists with exophthalmos and pretibial myxedema. Other forms of HOA are localized to

TABLE 25F-1. CLASSIFICATION OF HYPERTROPHIC OSTEOARTHROPATHY.

DIGITAL CLUBBING					
HYPERTROPHIC OSTEOARTHROPATHY					
	Secondary				
		Localized			
Primary	**Generalized**	**Hemiplegia**	**Aneurysm**	**Infective arteritis**	**Patent ductus arteriosus**
Pulmonary	Cardiac	Hepatic	Intestinal	Mediastinal	Miscellaneous
Cystic fibrosis	Congenital cyanotic diseases	Cirrhosis	Crohn's disease	Esophageal carcinoma	Graves disease
Pulmonary fibrosis	Infective endocarditis	Carcinoma	Ulcerative colitis	Thymoma	Thalassemia
Chronic infections			Chronic infections	Achalasia	Diverse malignancies
Cancer: primary or metastatic			Laxative abuse		POEMS syndrome
Arterio-venous fistulae			Polyposis		Others
Mesothelioma			Malignant tumors		

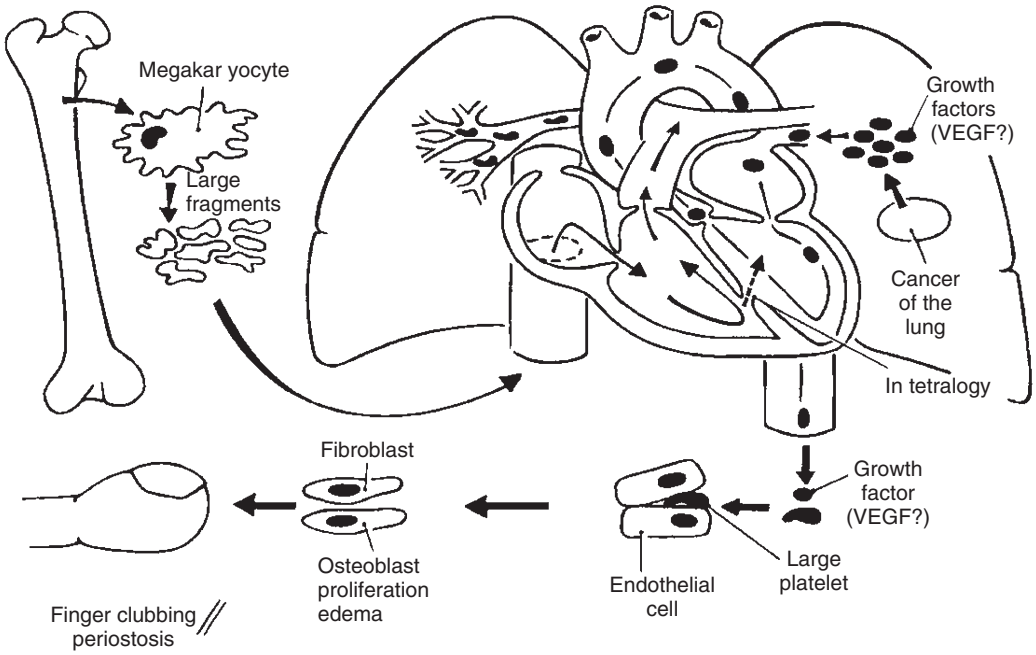


FIGURE 25F-2

The theoretical pathogenesis of hypertrophic osteoarthropathy.

one or two extremities. Such cases usually occur as a response to prominent endothelial injury to the involved limb, for example, damage caused by aneurysms or infective endarteritis. Alternatively, they may be associated with patent ductus arteriosus and reversal of the physiologic direction of blood flow. People with primary HOA may display a generalized skin hypertrophy called *pachyderma* (Figure 25F-3). This skin overgrowth roughens the facial features and can reach the extreme of *cutis verticis gyrata*, which is the most advanced stage of cutaneous hypertrophy. In addition, these patients often demonstrate glandular dysfunction of the skin that is manifested as hyperhidrosis, seborrhea, or acne (7).

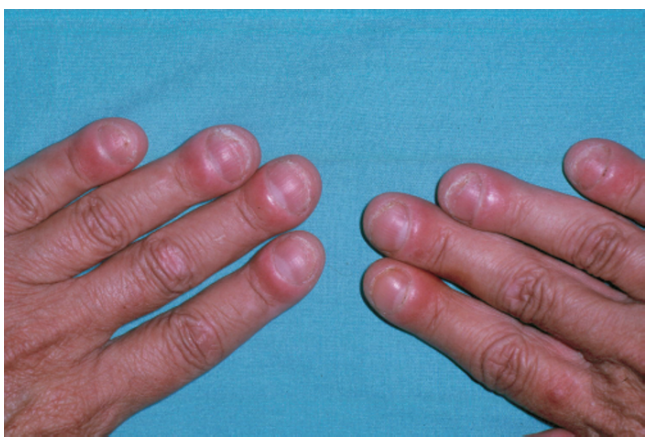


FIGURE 25F-3

Generalized skin hypertrophy in hypertrophic osteoarthropathy, known as pachyderma. Note also the clubbed fingers.

LABORATORY FEATURES AND IMAGING

There are no distinctive clinical laboratory test abnormalities associated with HOA. However, an array of biochemical alterations that reflect the underlying illness may be found. Longstanding clubbing produces a prominent bone remodeling of the distal phalanges.

Periostosis evolves in an orderly manner, with symmetrical bone changes. Initially, periostosis affects the distal parts of the lower extremities and then evolves in a centripetal fashion (8). When mild it involves only few selected bones (usually the tibia and fibula). Moreover, periosteal apposition is limited to the diaphysis in mild cases, and has a monolayer configuration [Figure 25F-4(A)]. In contrast, severe periostosis affects all tubular bones, spreads to the metaphyses and epiphyses, and generates irregular configurations [Figure 25F-4(B)]. Typically, the joint space is preserved, and there are no erosions or periarticular osteopenia. Radionuclide bone scanning is a sensitive method for demonstrating periosteal involvement.

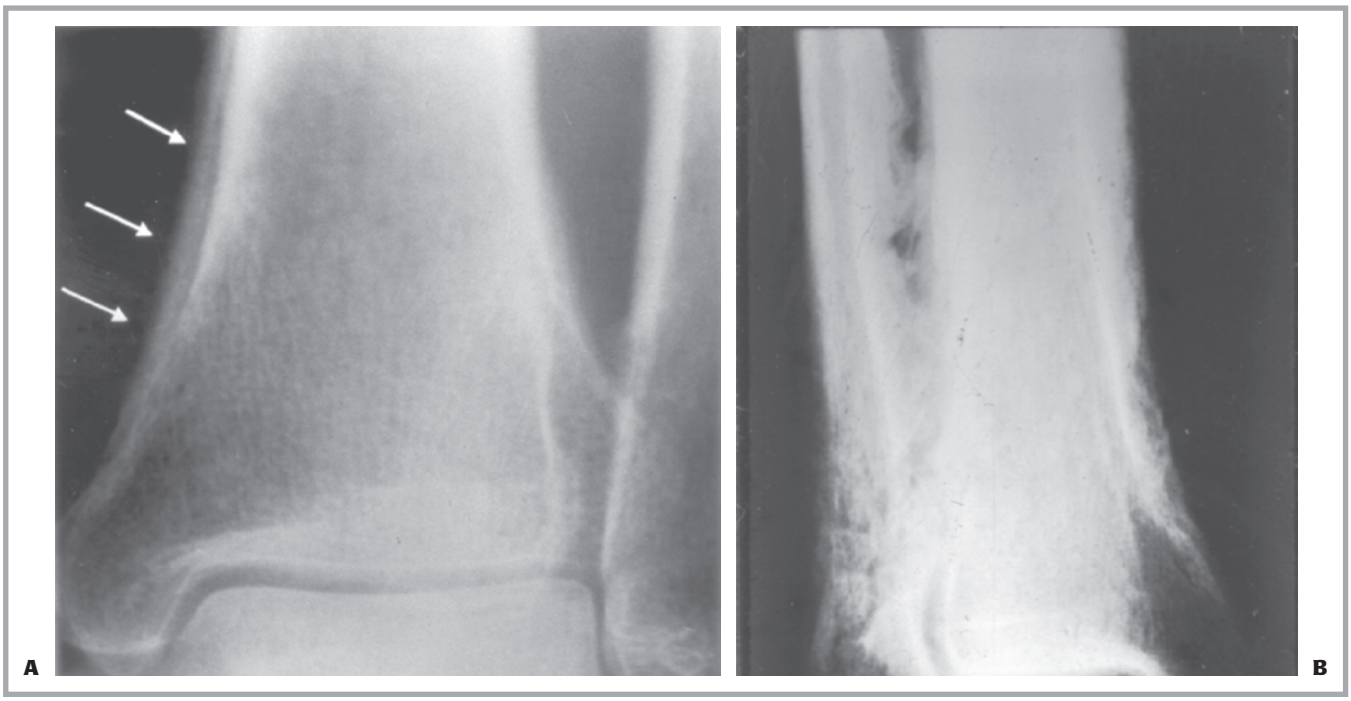


FIGURE 25F-4

Radiograph of the bones of the distal lower extremities in hypertrophic osteoarthropathy in mild (A) and severe (B) cases.

DIAGNOSIS

When HOA is fully expressed, the "drumstick" fingers are so unique that recognition poses no dilemma. The symptoms of HOA can be subtle. Nevertheless, in some patients with lung cancer, painful arthropathy may be the initial manifestation, occurring before clubbing is detectable. Such patients are sometimes misclassified as having an inflammatory arthritis. Patients with the exuberant skin hypertrophy of HOA may be misdiagnosed as having acromegaly.

The diagnosis of HOA requires the combined presence of clubbing and periostosis of the tubular bones (1). Synovial effusion is not essential for the diagnosis. An important feature that distinguishes HOA from inflammatory types of arthritis is that in HOA the pain involves not only the joint, but also the adjacent bones.

If a previously healthy individual develops any of the manifestations of HOA, a thorough search for underlying illness should be undertaken. Primary HOA should be diagnosed only after careful clinical scrutiny fails to disclose any of the internal illnesses listed in Table 25F-1. In an individual with a previous diagnosis of pulmonary fibrosis, cystic fibrosis, liver cirrhosis, or inflammatory bowel disease, the development of clubbing is usually a poor prognostic sign. Clubbing in a person with known rheumatic heart disease may indicate infective endocarditis. Similarly, clubbing in a patient with polyneuropathy of recent onset should lead to the suspicion of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome (see Chapter 25B) (9).

TREATMENT

Apart from the disfigurement, clubbing is usually asymptomatic and does not require therapy. Painful osteoarthropathy generally responds to analgesics or nonsteroidal anti-inflammatory drugs. Several uncontrolled case reports have described that pamidronate, an inhibitor of osteoclastic bone resorption, relieves the pain in cases of resistant painful osteoarthropathy (10). Interestingly, pamidronate and other biphosphonate compounds are potent VEGF inhibitors. Correction of a heart defect, removal of a lung tumor, or successful treatment of endocarditis produce rapid regression of the syndrome.

REFERENCES

1. Martínez-Lavín M, Matucci-Cerinic M, Pineda C, et al. Hypertrophic osteoarthropathy: consensus on its definition, classification, assessment and diagnostic criteria. J Rheumatol 1993;20:1386–1387.

2. Silveira L, Martínez-Lavín M, Pineda C, Navarro C, Fonseca MC, Nava A. Vascular endothelial growth factor in hypertrophic osteoarthropathy. Clin Exp Rheumatol 2000;18:57–62.
3. Vazquez-Abad D, Martínez-Lavín M. Macrothrombocytes in the peripheral circulation of patients with cardiogenic hypertrophic osteoarthropathy. Clin Exp Rheumatol 1991;9:59–62.
4. Olan F, Portela M, Navarro C, Gaxiola M, Silveira V, Martinez-Lavin M. Circulating vascular endothelial growth factor concentrations in a case of pulmonary hypertrophic osteoarthropathy. Correlation with disease activity. J Rheumatol 2004;31:614–616.
5. Atkinson S, Fox SB. Vascular endothelial growth factor (VEGF)-A and platelet-derived growth factor (PDGF) play a central role in the pathogenesis of digital clubbing. J Pathol 2004;203:721–728.
6. Vazquez-Abad D, Martínez-Lavín M. Digital clubbing: a numerical assessment of the deformity. J Rheumatol 1989; 16:518–520.
7. Martínez-Lavín M, Pineda C, Valdéz T, et al. Primary hypertrophic osteoarthropathy. Semin Arthritis Rheum 1988;17:156–162.
8. Pineda C, Fonseca C, Martínez-Lavín M. The spectrum of soft tissue and skeletal abnormalities in hypertrophic osteoarthropathy. J Rheumatol 1990;17:773–778.
9. Martínez-Lavín M, Vargas AS, Cabré J, et al. Features of hypertrophic osteoarthropathy in patients with POEMS syndrome. A metaanalysis. J Rheumatol 1997;24:2267–2268.
10. Guyot-Drouot MH, Solau-Grvais E, Cortet B, et al. Rheumatologic manifestations of pachydermoperiostosis and preliminary experience with bisphosphonates. J Rheumatol 2000;27:2418–2423.