CHAPTER 28

Storage and Deposition Diseases

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- Some unusual arthropathies are caused by deposition of normal material, such as metal ions, or storage of abnormal material, such as lipids.
- Hemochromatosis, ochronosis, and Wilson's disease are characterized by cellular deposition of the normal metal ions: iron, calcium, and copper, respectively.
- In Gaucher's disease, Fabry's disease, Farber's disease, and multicentric reticulohistiocytosis, rheumatic manifestations result from cellular storage of abnormal lipids.

This chapter covers a number of unusual arthropathies that are caused by deposition of normal material, such as metal ions, *or* storage of abnormal material, such as lipids (1). Hemochromatosis, ochronosis, and Wilson's disease are characterized by cellular deposition of the normal metal ions: iron, calcium, and copper, respectively. In the case of Gaucher's disease, Fabry's disease, Farber's disease, and multicentric reticulohistiocytosis, rheumatic manifestations result from cellular storage of abnormal lipids. In hemochromatosis, arthralgias may be the first indication of a systemic disorder, but arthritis evolves as a predominant feature in ochronosis, Gauchers's disease, and multicentric reticulohistiocytosis.

HEMOCHROMATOSIS

Hemochromatosis is a common inherited autosomal recessive disorder affecting as many as 5 per 1000 white persons of European extraction. It is characterized by excessive body iron stores and the deposition of hemosiderin, which cause tissue damage and organ dysfunction (2). The disorder rarely appears before age 40 unless there is a family history, and men are affected 10 times more frequently than women, who are protected by menstruation. Increased intestinal iron absorption and visceral deposition can lead to the phenotypic features of hepatic cirrhosis, cardiomyopathy, diabetes mellitus, pituitary dysfunction (including hyogonadism), sicca syndrome, and skin pigmentation mostly of melanin (2). In a survey of 2851 patients with hemochromatosis, symptoms had been present for an average of 10 years before the diagnosis was made. Arthralgia (44%) was among the most common and most troublesome complaints (3).

The gene for hemochromatosis (HFE, *HLA-H*) was discovered in 1996 by positional cloning methods near the human leukocyte antigen (HLA)-A locus on chromosome 6 (4). More than 90% of typical patients possess the C282Y mutation of the *HFE* gene. Homozygous and heterozygous genotypes correlate with major or minor disease expression, respectively. The association of hemochromatosis with arthritis is most common in homozygotes with the heaviest iron overload. The C282Y mutation is most common in whites, and most C282Y homozygotes have elevations in serum ferritin levels and transferrin saturation. However, the absence of C282Y mutation does not account for high mean serum ferritin levels and transferrin values in nonwhites (5).

Prolonged excessive iron ingestion and repeated blood transfusion in chronic hypoproliferative anemia and thalassemia may also result in iron deposition. If iron overload occurs without tissue damage, the disorder is known as *hemosiderosis*. With tissue damage, it is called *secondary hemochromatosis*. The iron deposition in macrophages in secondary hemochromatosis is associated with less tissue damage and end-organ dysfunction compared with the idiopathic form.

Yersinia septic arthritis or septicemia is an unusual complication that may occur in people with hemochromatosis because of a microbial requirement for an iron-rich environment. Hepatitis B and C viral infection may accelerate liver damage in people with hemochromatosis (6).

Clinical Features

Chronic progressive arthritis, predominantly affecting the second and third metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, is the presenting

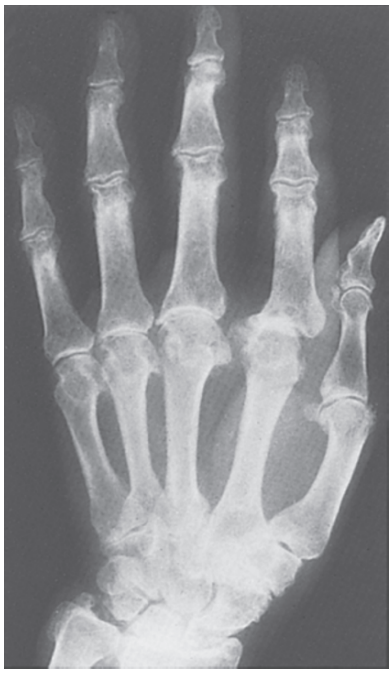

FIGURE 28-1

Radiograph of hand with hemochromatosis. Note the joint space narrowing, cystic subchondral lesions, joint space irregularity, mild subluxation, bony sclerosis, and small osteophytes in the metacarpophalangeal joints. Chondrocalcinosis is present in the ulnar carpal joint, and soft tissue has calcified around the interphalangeal joint of the thumb. (Courtesy of Dr. H.R. Schumacher, Jr.)

feature in about one half of cases (Figure 28-1). Involvement of the MCP joints is typically the most common rheumatologic feature at the time of diagnosis (7). The dominant hand may be solely or more severely affected. The finger joints and wrists are mildly tender with limited motion. Larger joints, such as the shoulders, hips, and knees, may also be affected. Hemochromatotic arthropathy of the hips or shoulders may, at times, be rapidly progressive. True morning stiffness is not a feature of hemochromatosis.

Individuals heterozygous for the C282Y *HFE* mutation may be at increased risk for hand osteoarthritis (8). Therefore the detection of an osteoarthritislike disease that involves MCP and wrist joints, particularly in men during the fifth and sixth decade of life, should signal the possibility of underlying hemochromatosis. Arthropathy may also be seen in juveniles and may affect individuals as young as 26 before any other manifestations of the disease develop.

Radiographic Features

The radiologic changes of hemochromatosis resemble osteoarthritis, except that in hemochromatosis there is less osteophytosis. Ulnar styloid erosion may suggest rheumatoid diseases, but the irregular joint narrowing and sclerotic cyst formation are more indicative of a degenerative process. Although the distal interphalangeal joints may be affected, the carpometacarpal joint changes of generalized osteoarthritis are not a feature. Somewhat similar MCP changes can occur in calcium pyrophosphate dehydrate crystal deposition without hemochromatosis. Some degree of diffuse osteoporosis may be present, presumably due to hypogonadism, but a direct effect of iron on bone is also possible. Chondrocalcinosis is characteristic of the arthropathy and is a late complication in about 50% of patients; it may be the sole abnormality (7). The hyaline cartilage of the shoulder, wrist, hip, and knee, and the fibrocartilage of the triangular ligament of the wrist and symphysis pubis may be affected. Superimposed attacks of calcium pyrophosphate dihydrate crystal synovitis occur in these cases. The finding of chondrocalcinosis should always suggest the possibility of hemochromatosis.

Laboratory Features

Synovial fluid has good viscosity, with leukocyte counts below 1000 cells/mm^3. During acute episodes of pseudogout, synovial fluid leukocytosis with calcium pyrophosphate crystals can be found. Except for such episodes, the erythrocyte sedimentation rate is usually normal. In patients with chronic liver disease, rheumatoid factor tests may be positive.

The diagnosis may be suspected by a raised serum iron and high ferritin concentration with increased saturation of the plasma iron-binding protein transferrin (2). The latter, however, is more specific and should be regarded as the cornerstone test for diagnosis (2). For population screening, the simpler unbound *iron* binding capacity (UIBC) showed higher sensitivity and fewer false positives. Needle biopsy of the liver provides definitive evidence of iron overload in hemochromatosis, but nowadays it is usually reserved for cases in diagnostic doubt, or more often to assess the severity of liver damage associated with fibrosis, cirrhosis, or hepatoma.

In idiopathic hemochromatosis, iron deposits affect parenchymal hepatic cells, whereas reticuloendothelial cells are most affected in secondary forms. In hemochromatosis, synovial biopsy shows iron deposition in the type B synthetic lining cells of synovium. In rheumatoid arthritis, traumatic hemarthrosis, hemophilia, and villonodular synovitis, deposits are in the deeper layers or in the phagocyte type A lining cells. Hemosiderin deposits may also be found in the chondrocytes. Further evidence of iron may be found in biopsies of skin and intestinal mucosa, or in bone marrow, buffy coat, or urine sediment. The amount of iron excreted in

the urine after administration of the iron-chelating agent deferoxamine correlates with the presence of parenchymal hepatic iron in hemochromatosis. Where available, direct noninvasive magnetic measurements of hepatic iron stores provide a quantitative method for early detection of iron overload or rapid evaluation of treatment.

The pathogenesis of the arthritis is unknown, as degenerative joint changes do not necessarily develop in relation to synovial iron. The low frequency of chondrocalcinosis in people with hemophilia and rheumatoid arthritis weighs against synovial hemosiderin as a cause of chondrocalcinosis. It is speculated that ionic iron might inhibit pyrophosphatase activity and lead to a local concentration of calcium pyrophosphate in the joint. The deposition of calcium in cartilage appears to predispose to inflammatory and degenerative joint disease (2).

Treatment

Following the diagnosis of hemochromatosis in any patient, it is imperative to obtain biochemical screening of at least first-degree relatives for medical preventive reasons. Screening may be done by measuring serum iron-binding transferrin or the UIBC test. Genotyping for the C282Y mutation of the *HFE* gene is a useful diagnostic aid and helpful in counseling and predicting the risk of disease in healthy relatives (2). However, it gives no indication of iron stores or prognosis.

Aggressive phlebotomy therapy promotes longevity and can prevent or reverse much organ damage. Weekly phlebotomies are generally needed until iron is depleted and mild anemia is present. Venesection may not prevent the progression of arthritis in hemochromatosis, but in some cases arthritis may improve after this therapy. It has been suggested that prophylactic phlebotomy should be considered on the basis of genetic predisposition. Iron-chelating therapy with intravenous deferoxamine is generally effective but impractical because of the expense and the need for intravenous administration. Arthritis symptoms may be difficult to control even with nonsteroidal anti-inflammatory drugs (NSAIDs). Agents requiring hepatic metabolism, such as diclofenac or nabumetone, should be avoided. Prosthetic hip, knee, and shoulder arthroplasties can be performed when required.

ALKAPTONURIA (OCHRONOSIS)

Alkaptonuria (AKU), a rare autosomal recessive inherited disorder, results from a complete deficiency of the enzyme homogentisic acid oxidase (HGO) (9). In six reported pedigrees it was mapped to chromosome 3q2. Since then a Spanish group has reported the cloning of the human HGO gene and established that it is the gene responsible for AKU (10). This *HGO* gene harbors misuse mutation(s) that represent a loss of function. This defect causes accumulation of homogentisic acid, a normal intermediate in the metabolism of phenylalanine and tyrosine, which is excreted in the urine. Alkalization and oxidation of this acid cause the urine to turn black. The homogentisic acid retained in the body is deposited as a pigmented polymer in the cartilage and, to a lesser degree, in skin and sclerae. The darkening of tissues parts by this pigment is designated *ochronosis*.

The pigment, which is found in the deeper layers of the articulator cartilage, is bound to collagen fibers, causing this tissue to lose its normal resiliency and become brittle and fibrillated. The erosion of this abnormal cartilage leads to denuding of subchondral bone and the penetration of tiny shards of pigmented cartilage into the bone, synovium, and joint cavity (11). It is likely that these pigmented cartilage fragments become a nidus for the formation of osteochondral bodies.

Clinical Features

A progressive degenerative arthropathy develops, with symptoms usually beginning in the fourth decade of life (9). Features include arthritis of the spine (ochronotic spondylosis) and larger peripheral joints, with chondrocalcinosis, formation of osteochondral bodies, and synovial effusions (ochrontonotic peripheral arthropathy). Initially, the spinal column is affected with pigment found in the annulus fibrosus and nucleus pulposus of the intervertebral discs (Figure 28-2). Later, the knees, shoulders, and hips deteriorate; the small peripheral joints are spared. In adults, the first sign of spondylosis may be an acute disc syndrome. Eventually, it clinically resembles ankylosing spondylitis, with progressive lumbar rigidity and loss of stature.

Disability is common and severe, with stiffness and loss of joint mobility predominant and pain less prominent (9). Knee effusions, crepitus, and flexion contractures are common, but other signs of articular inflammation are ordinarily lacking. Fragments of darkly pigmented cartilage can occasionally be found floating in the joint fluid. Osteochondral bodies, which form in response to the deposition of cartilaginous fragments in the synovium, are often palpable in and around the knee joint and may reach several centimeters in diameter.

Nonarticular features of ochronosis include bluish discoloration and calcification of the ear pinnae, triangular pigmentation of the sclera, and pigmentation over the nose, axillae, and groin. Prostatic calculi are common in men, and cardiac murmurs may develop from valvular pigment deposits.

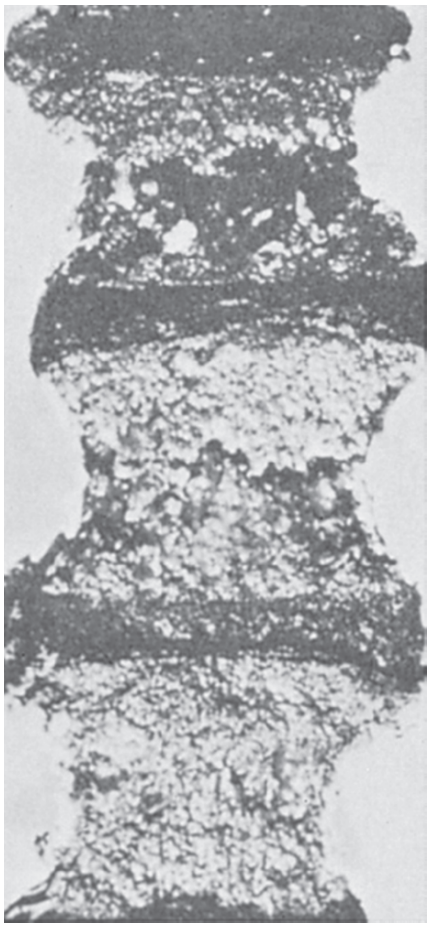

FIGURE 28-2

Part of a lumbar vertebral column of a 49-year-old woman with alkaptonuria who died of real failure (ochronotic nephrosis). Blackened intervertebral discs are thin and focally calcified. This patient had incapacitationg pain since age 36, with progressive limitation of back motion. Microscopic examination of the discs, which splintered easily, revealed nonrefractile granular pigment. (Reprinted from Cooper J, Moran TJ. Studies on ochronosis. I. Report of case with death from ochronotic nephrosis. Arch Pathol 1957;61:46–53.)

Radiographic Features

The earliest features visible on roentgenograms are multiple vacuum discs of the spine. Eventually, the entire spine shows ossification of the discs with narrowing, collapse, and fusion. Chondrocalcinosis may affect the symphysis pubis, costal cartilage, and ear helix. In contrast to ankylosing spondylitis, the sacroiliac and apophyseal joints are not affected. The roentgenographic appearance of the peripheral joints resembles that in primary osteoarthritis, with loss of cartilage space, marginal osteophytes, and eburnation of the subchondral bone. Unlike primary osteoarthritis, however, degeneration of the shoulders and hips is more severe, and osteochondral bodies are seen.

Laboratory Features

The diagnosis of AKU is suspected when the patient gives a history of passing dark urine, or when fresh urine turns black on standing or on alkalinization. In individuals lacking this history, the diagnosis is made only after the detection of a false-positive test for diabetes mellitus or the onset of arthritis. Dark pigmented synovium may be seen on arthroscopy. A specific enzymatic method permits quantitation of homogentisic acid in urine and blood and molecular cloning of the HGO gene makes detection of heterozygotic carriers possible (10).

Synovial fluid is usually clear, yellow, and viscous and does not darken with alkalinization. At times the fluid may be speckled with many particles of debris resembling ground pepper (Figure 28-3). Leukocyte counts of a few hundred cells are predominantly mononuclear. Occasionally, the cytoplasm of mononuclear and polymorphonuclear cells contains dark inclusions of phagocytosed ochronotic pigment.

Centrifugation and microscopic examination of synovial fluid sediment may show fragments of pigmented cartilage. Effusions may contain calcium pyrophosphate dihydrate crystals and show no inflammation. Pigmented cartilage fragments are embedded in synovium and are often surrounded by giant cells (11).

No effective treatment is available for the underlying metabolic disorder, but the herbicide nitisinone, an enzyme inhibitor, can deplete and markedly reduce urinary excretion of homogentisic acid in persons with

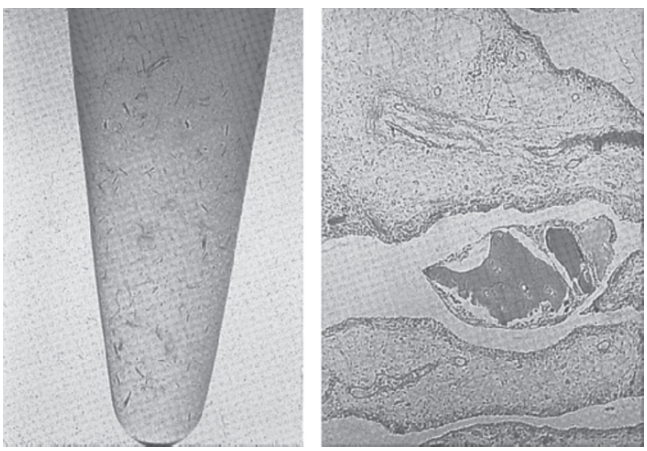

FIGURE 28-3

Ochronosis: synovial fluid and synovium (gross and microscopic). On the left, the synovial fluid reveals numerous dark particles and shards having the appearance of ground pepper. On the right, a low-power microscopic view of the synovium shows fragments of darkly pigmented cartilage (hemotoxylin and eosin stain). (Reprinted with permission from Hunter T, Gordon DA, Ogryzlo MA. The ground pepper sign of synovial fluid: a new diagnostic feature of ochronosis. J Rheumatol 1974;1:45–53.)

AKU. Limited trials with low doses of it suggest the possibility of preventing joint destruction and providing relief of pain. However, side effects may preclude its long-term use (12). Surgical removal of osteochondral loose bodies from the knee joint is warranted when these interfere with motion. Prosthetic joint replacement may be helpful.

WILSON'S DISEASE

Wilson's disease (hepatolenticular degeneration) is a rare metabolic disorder in which deposition of copper leads to dysfunction of the liver, brain, and kidneys. It is inherited as an autosomal recessive trait affecting about 1 in 30,000 persons in most populations. It becomes symptomatic for individuals aged 6 to 40 years. A defective gene and related mutations mapped to chromosome 13 provide some explanation for the wide phenotypic variation seen in Wilson's disease (13).

Clinical Features

Total body copper is increased. The accumulation of copper in the liver leads to cirrhosis; in the cornea, to characteristic Kayser–Fleischer rings; in the basal ganglia, to lentricular degeneration and movement disorders; in the kidneys, renal tubular damage (13). An arthropathy may develop in as many as 50% of affected adults, but arthritis is rare in children (14). Patients usually develop hepatic or neurologic symptoms in childhood or adolescence. Liver disease is the most common presentation between ages 8 and 16, with symptoms of jaundice, nausea, vomiting, and malaise. Acute hepatic failure may rarely develop. Neurologic symptoms are rare before age 12. Dysarthria and decreased coordination of voluntary movements are the most common complaints. Other presenting symptoms include acute hemolytic anemia, arthralgias, renal stones, and renal tubular acidosis. The arthropathy is characterized by mild premature osteoarthritis of the wrists, MCP joints, knees, or spine. Occasionally, joint hypermobility also may be found (14). Ossified bodies of the wrists may be associated with subchondral cysts. Chondromalacia patellae, osteochondritis dissecans, or chondrocalcinosis of the knee may be associated with mild knee effusions. Arthropathy tends to be mild in patients treated early in life, but it may be more severe in patients with untreated disease of longer duration. A few patients show acute or subacute polyarthritis that resembles rheumatoid arthritis and may be associated with a positive rheumatoid factor. These seropositive cases are possibly a result of penicillamine therapy.

The pathogenesis of the arthropathy is unclear, and its presence does not correlate with neurologic, hepatic, or renal disease. Although chondrocalcinosis has been observed in patients with Wilson's disease, light and transmission electron microscopy have failed to detect crystals containing calcium in synovial fluids or in cartilage and synovial biopsies. Copper has been found in the articular cartilage by elemental analysis of a few patients with Wilson's disease and could theoretically cause tissue damage mediated by oxygen-derived free radicals (14). Although the arthropathy is generally milder than that seen in hemochromatosis, its cause may be similar and it may involve deposition of calcium pyrophosphate dehydrate and the development of chronic arthritis.

Radiographic Features

Radiologic features may include subchondral cysts, joint space narrowing, sclerosis, marked ostophyte formation, and multiple calcified loose bodies, especially at the wrist. Unlike hemochromatosis, involvement of the hip and MCP joints is uncommon.

Periostitis at the femoral trochanters and other tendinous insertions, periarticular calcifications, and chondrocalcinosis have been reported. Changes in the spine are seen mainly in the mid-thoracic to lumbar areas and include squaring of the vertebral bodies, intervertebral joint space narrowing, osteophytes, and osteochondritis.

Skeletal manifestations of Wilson's disease include generalized osteoporosis in as many as 50% of patients. The osteoporosis is usually asymptomatic, unless spontaneous fractures occur (14). Osteomalacia, Milkman pseudofractures, and renal rickets have been reported. Some cases are from areas where nutritional deficiencies may also affect skeletal abnormalities.

Laboratory Features

Although Kayser–Fleischer corneal rings are pathognomonic of Wilson's disease, the diagnosis is established by laboratory investigations. Low serum copper and decreased serum ceruloplasmin levels occur in most cases, and in symptomatic patients urinary copper excretion is increased. Biliary excretion of copper is also markedly decreased. Microchemical evidence of copper deposition may be obtained from needle biopsy of the liver, but histochemical methods are unreliable. In doubtful cases, specialized studies with radioactive copper may be necessary.

Synovial biopsies show hyperplasia of synovial lining cells with mild inflammation. Neither calcium pyrophosphate nor copper are seen by standard methods. Limited data are available concerning morphologic changes in joints. Microvilli formation, initial cell hyperplasia, chronic inflammatory infiltrates, and vascular changes have been reported in synovium. Joint fluids have had low leukocyte counts.

Treatment

Copper chelation with penicillamine along with dietary copper restriction is the treatment of choice. Whether penicillamine can control the arthropathy is unclear, but contemporary series suggest that the arthropathy is milder because of earlier diagnosis with more intensive chelation therapy. Side effects from penicilamine reported in people with Wilson's disease rarely include acute polyarthritis, polymyositis, or a syndrome resembling systemic lupus erythematosus. Trientine or tetrathiomolybate are chelating agents available for patients intolerant of penicillamine. Liver transplantation is the only treatment option available for acute hepatic failure or longstanding cirrhosis where penicillamine or trientine are not options. Otherwise, symptomatic measures suffice to control arthritis symptoms.

GAUCHER'S DISEASE

Gaucher's disease is a *lysosomal glycolipid* storage disease in which glucocerebroside accumulates in the reticuloendothelial cells of the spleen, liver, and bone marrow (15). It is an autosomal recessive disorder caused by subnormal activity of the hydrolytic enzyme glucocerebrosidase. The gene for Gaucher's disease is located on chromosome 1 in the q21 region. Modern DNA technology has led to the cloning of the glucocerebroside genes and identification of their mutations. All the cells of the body are deficient in glucocerebroside activity in Gaucher's disease, but it is the glycolipid-engorged macrophages that account for all the non-neurologic features of the disease.

Fortunately, the most severe forms of Gaucher's disease are extremely rare, whereas milder forms are encountered frequently, particularly in the Jewish population. Gaucher's disease has been classified into clinical subdivisions. Type I, the most common form, is the adult or chronic type that accounts for more than 99% of cases. It is a common familial disorder in Ashkenzi Jews while other types occur in all ethnic groups. It is defined by the lack of neurologic involvement, and affected adults present with accumulation of glucocerebroside in the reticuloendothelial system causing organomegaly, hypersplenism, conjunctival pingueculae, skin pigmentation, and osteoarticular disease. It has the best prognosis, but may be mistaken for juvenile rheumatoid arthritis.

Clinical Features

Some patients with type I disease have few or no clinical manifestations. In these cases the condition may be discovered only when bone marrow is examined for some other reason, or if mild thrombocytopenia is investigated.

Type 2, infantile, is a fulminating disorder with severe brain involvement and death within the first 18 months of life. Type 3, the intermediate or juvenile form, begins in early childhood and shows many features of the chronic form, with or without central nervous system dysfunction.

Skeletal involvement is characteristic of type 1 and to a lesser extent type 3, but not type 2 disease. Musculoskeletal involvement occurs in the adult and juvenile forms, but it is rarely the first symptom. Patients usually present with lymphadenopathy, hepatosplenomegaly, or signs and symptoms of hypersplenism. Nevertheless, rheumatic complaints may appear early in the disease course. Pain in the hip, knee, or shoulder is caused by disease of adjacent bone. In young individuals, the most common complaint is chronic aching around the hip or proximal tibia. This may last a few days but is usually recurrent. Another complaint is excruciating pain (bone crisis) involving the femur and tibia with tenderness, swelling, and erythema. Monoarticular hip or knee degeneration is typical, and unexplained migratory polyarthritis sometimes occurs. Bony pain tends to lessen with age. Other skeletal features include pathologic long bone fractures, vertebral compression, and osteonecrosis of the femoral or humeral heads or proximal tibia. The osteonecrosis can develop slowly, or can appear rapidly with bone crisis. These crises usually affect only one bone area at a time. Because acute-phase reactants and bone scans are usually positive, the clinical picture of acute osteomyelitis is mimicked (pseudo-osteomyelitis). Surgical drainage in these cases commonly leads to infection and chronic osteomyelitis. Due to this increased susceptibility to infection, conservative management of bony lesions is recommended.

Radiographic Features

Asymptomatic radiologic areas of rarefaction, patchy sclerosis, and cortical thickening are common. Osteonecrosis of bone, particularly of the hips, and pathologic fractures of the femur and vertebrae are the most serious and deforming features of Gaucher's disease. Involvement of the femur is thought to be a "barometer" of bone symptoms. Widening of the distal femur with the radiologic appearance of an Erlenmeyer flask is a frequent finding, but flaring of the bones can occur in the tibia and humerus as well.

Laboratory Features

When bone pain or other articular symptoms appear, the serum acid phosphatase and the angiotensin-converting enzymes are usually elevated. However, the most reliable method for diagnosing Gaucher's disease is the determination of leukocyte beta-glucosidase. Diagnosis has been confirmed by examination of bone

marrow aspirate for the Gaucher cell, a large lipid storage histiocyte. This cell should be differentiated from globoid cells of another lysosomal storage disorder, Krabbe's disease (galactocerebrosidosis). However, histologic diagnosis of Gaucher's disease is unnecessary and can be misleading. Moreover, bone biopsy is not recommended because of the risk of secondary infection. Needle biopsy of the liver for assay of glucocerebroside may be performed, but washed leukocytes and extracts of cultured skin fibroblasts are easily obtained for glucocerebrosidase testing. These assays may also be used to detect heterozygous carriers. Amniocentesis has been used for the prenatal detection of diseased fetuses. When the diagnosis is established, genetic counseling for family members or prospective parents is recommended. Although enzyme assays are useful for genetic screening, DNA analysis using the polymerase chain reaction is much more precise (15).

Treatment

Until recently, therapy of Gaucher's disease was mostly symptomatic, based on control of pain and infection. In adults, splenectomy may control hypersplenism, but bone disease may then accelerate. Bisphosphonates have been effective in treating bone disease in Gaucher's disease. Intermittent intravenous pamidronate with oral calcium has been effective in the treatment of a few patients with type I Gaucher's disease with severe bone involvement. Partial splenectomy has been recommended as protection against postsplenectomy infection, and for its hepatic and bone-sparing effect. Arthroplasty and complete joint replacement is often necessary, but loosening of prostheses occurs more often than in other disorders. Bleeding can be an operative problem.

With the commercial availability of replacement enzyme, the modified glucocerebroside (Ceredase), effective but costly treatment of Gaucher's disease has become a reality, but not without its limitations (16). Periodic intravenous infusions of the enzyme over many months commonly results in regression of the features of Gaucher's disease (15). However, alternatives to enzyme replacement therapy include substrate reduction, active site-specific chaperone therapy, and gene therapy (17). The latter involves using retroviral vector constructs for coding the gene for glucocerebrosidase into hematopoietic progenitors.

FABRY'S DISEASE

Fabry's disease is a lysosomal lipid storage disease in which glycosphingolipids accumulate widely in nerves, viscera, skin, and osteoarticular tissues. It is a sex-linked inherited disease caused by a deficiency of the enzyme alpha-galactosidase A. The gene and its mutations responsible for expression of this enzyme have been localized to the middle of the long arm of the X chromosome.

Clinical Features

As a slowly progressive disorder predominately affecting males, clinical features are widespread and nonspecific; thus, diagnosis is often missed or delayed. In childhood, the deposition is particularly marked in and around blood vessels, giving rise to the characteristic rash of dark blue or red angiokeratomas or angiectases around the buttocks, thighs, and lower abdomen. When diffuse, it is referred to as *angiokeratoma corgoris diffusum* and is almost always associated with hypohydrosis.

The kidneys are the main target organ and proteinuria gradually develops in childhood or adolescence, with abnormal urinary sediments including birefringent lipid crystals (Maltese crosses). Progressive renal disease leads to renal failure. Cardiovascular and cerebrovascular deposition of the sphingolipid parallels the renal disease, with vascular insufficiencies such as cryptogenic stroke or death in young persons. Ocular changes are severe. A characteristic corneal opacity seen by slit-lamp examination occurs early and can be helpful in diagnosis even in heterozygous women.

Some patients experience the insidious development of polyarthritis with degenerative changes and flexion contractures of the fingers, particularly of the distal interphalageal joints. Foam cells have been described in the synovial vessels and connective tissues. Radiographs may show infarctlike opacities of bone and osteoporosis of the spine. Osteonecrosis of the hip and talus have been described. Eighty percent of children or young adults undergo painful crises of burning paresthesias of the hands and feet and later of whole extremities. These attacks are associated with fever and elevations of the erythrocyte sedimentation rate.

Genetic counseling should be offered to affected families. Measurement of alpha-galactosidase to alpha-galactosidase activity ratios in leukocytes and fibroblasts provide reasonable discrimination between carriers and noncarriers. Identification by DNA studies is reserved for subjects showing equivocal results.

Treatment

Treatment has not been satisfactory. However, the prospect of effective gene therapy using recombinant adenovirus AxCAG alpha-gal to provide enzyme replacement has been reported in a randomized, controlled trial (18). Antiplatelet medication may suppress vascular damage. Burning paresthesias may benefit from phenytoin or carbamazepine. Without dialysis or

transplantation most affected males succumb to renal failure before age 50.

FARBER'S DISEASE

Farber's disease is a lysosomal lipid storage disease in which a glycolipid ceramide accumulates widely in many tissues, including the skin and musculoskeletal system (19). It is an autosomal recessive disorder caused by a deficiency of the enzyme acid ceramidase. Affected children show disease manifestations by the age of 4 months and die before the age of 4 years.

A hoarse cry from thickened vocal cords or swollen painful joints may be the first feature. The appearance of tender, subcutaneous nodules follows and the early occurrence of nodules correlates with shortened survival. All the extremities may be swollen and tender, but this gives way to more localized joint swelling with nodules around the fingers, wrists, elbows, and knees. Joint contractures, especially affecting the fingers and wrists, develop later. The gastrointestinal, cardiovascular, and nervous systems gradually become involved, and death results from respiratory disease. Diagnosis can be confirmed by demonstrating a deficiency of ceramidase both in leukocytes and fibroblasts.

LIPOCHROME HISTIOCYTOSIS

Lipochrome histiocytosis is an extremely rare lysosomal storage disease associated with pulmonary infiltrates, splenomegaly, hypergammaglobulinemia, polyarthritis, and increased susceptibility to infection (20). The disorder is familial. Histiocytes show lipochrome pigment granulation and peripheral blood leukocytes exhibit impaired activity.

MULTICENTRIC RETICULOHISTIOCYTOSIS

Multicentric reticulohistiocytosis is a rare dermatoarthritis of unknown cause or familial association. It is characterized by the cellular accumulation of glycolipid-laden histocytes and multinucleated giant cells in skin and joints (21). The most common presentation is a painful destructive polyarthritis resembling rheumatoid arthritis, for which affected persons may be mistakenly treated. The joint manifestations precede the appearance of skin lesions in most patients, but the appearance and location of the skin nodules are not entirely characteristic of rheumatoid arthritis (Figure 28-4). Although a self-limited form may be seen in childhood, adult multicentric reticulohistiocytosis predominantly affects middle-aged women.

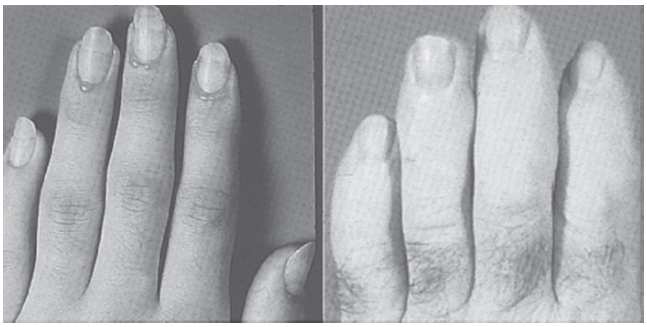

FIGURE 28-4

The fingers of a 16-year-old girl (left) with multicentric reticulohistiocytosis reveal multiple, reddish-brown, tender papulonodules that are periungual in distribution. On the right is another patient with multiple nodules in the fingers. These nodules are firm, can fluctuate in size, and may disappear spontaneously. (Reprinted from Revised Clinical Slide Collection on the Rheumatic Diseases, with permission of the American College of Rheumatology.)

Clinical Features

Disease onset is insidious and is characterized by polyarthritis, skin nodules, and, in many cases, xanthelasma. Small papules and beadlike clusters around the nailfolds are characteristic, with skin nodulation of the face and hands. Varying sizes of skin nodules are yellowish, purple, and occur over the hands (Figure 28-5), elbows, face, and ears. Oral, nasal, and pharyngeal mucosa

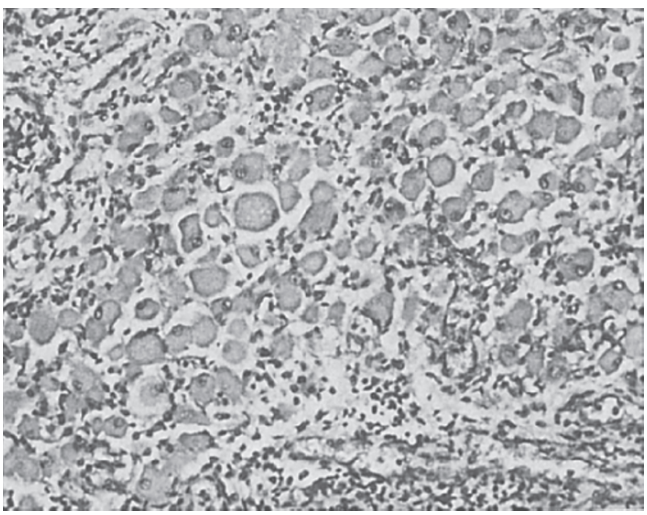

FIGURE 28-5

Photomicrograph of synovium (knee) from a 54-year-old woman with multicentric reticulohistiocytosis shows numerous histiocytes and multinucleated giant cells that contain large amounts of periodic acid-Schiff (PAS)-positive material. (Reprinted from McCarthy DJ, Koopman WJ. Arthritis and allied conditions. Philadelphia: Lea & Febiger; 1993.)

involvement sometimes with ulceration is seen in one fourth of patients. Various visceral sites may also be affected.

Symmetric polyarthritis resembles rheumatoid disease when PIP joints are affected, and psoriatic arthritis when involvement of distal interphalangeal joints predominates. Tenosynovial involvement may also occur. Remission of polyarthritis may be seen after many years of progressive disease.

Early radiographs early on show "punched out" bony lesions resembling gouty tophi. Severe joint destruction will be seen in later radiographs. Spinal involvement with erosions and subluxations including atlanto-axial damage may occur.

Laboratory Features

No specific laboratory abnormality has yet been demonstrated, and the diagnosis is established by examination of biopsies of affected tissues. Both the skin and synovium (Figure 28-5) are infiltrated by large, multinucleated giant cells. The cytoplasm has a "ground glass" appearance and stains positively for lipids and glycoproteins with periodic acid-Schiff stain (PAS positive). Definitive analysis of these cell contents has not been made, but it is probably a glycolipid. Triglycerides, cholesterol, and phosphate esters appear to be present in the lesion, suggesting either that histiocytes are stimulated to produce these substances or that this is a form of lipid storage disease. A lymphocytic origin for the giant cells has been proposed because of the presence of T-cell markers, but multicentric reticulocytosis cells also stain for macrophage markers (21). A monocyte/macrophage origin for these cells has also been suggested because of the detection of macrophage-activated cytokines of IL-1 beta, IL-12, and tumor necrosis factor alpha (TNF-alpha). The distribution of TNF-alpha appears similar to that for rheumatoid synovial cell proliferation. Synovial fluid leukocyte counts range from 220 to 79,000 cells/mm^3, with mononuclear cells predominating. Scanning the synovial fluid Wright-stained smear or wet preparation may reveal giant cells or large, bizarre macrophages.

The foregoing specific histologic picture of multicentric reticulohistiocytosis is quite different from the myofibroblast cells in a collagen matrix characteristic of the cutaneous nodules and polyarthritis of fibroblastic rheumatism (22).

Although the pathogenesis is unknown, hidden malignancy and tuberculosis have been implicated. Rheumatoid factor does not occur. Some patients develop positive reactions to tuberculin (PPD positive). There are case descriptions with associated Sjögren's syndrome and polymyositis. Multicentric reticulohistiocytosis has also been implicated with a variety of malignancies (21). Death due to the disease itself has not been reported, but patients may be left with severe joint disability.

Treatment

Spontaneous remission of skin and arthritis occurs in some cases, especially in childhood. In the remainder, corticosteroids or topical nitrogen mustard may improve the skin lesions. In cases with severe skin and joint disease combinations of corticosteroid, methotrexate (MTX) plus cyclophosphamide or cyclosporine, and bisphosphonates have been effective. Low-dose MTX alone has shown prolonged effect, and MTX plus hydroxychloroquine has also been beneficial. The presence of synovial TNF-alpha in the disease indicates that, in addition to MTX, dramatic clinical and serologic improvement may occur with TNF-alpha inhibition (23).

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