Gaucher Disease

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Abstract

Gaucher disease is an autosomal recessive inherited disorder of glycolipid metabolism in which the failure to metabolize a glucocerebroside results in its storage in the macrophages of the reticuloendothelial system with secondary end-organ effects. Three clinical types exist based upon the severity of CNS involvement. Severity of the bone disease does not necessarily correlate with that of other viscera. Bone modeling deformities, osteopenia, and avascular necrosis of bone may occur. Histologic hallmark is the presence of large macrophages containing pale eosinophilic, cytoplasm having the appearance of crinkled tissue paper. Gaucher cells are PAS positive, diastase resistant, and stain weakly with Sudan black. Prognosis depends on disease type. Enzyme replacement therapy improves life quality for patients with type I disease.

Definition

- An inherited disorder of glycolipid metabolism in which the failure to metabolize glucosylceramide (glucocerebroside) results in the storage of this glycolipid in the macrophages of the reticuloendothelial system with attendant secondary end-organ effects.

Synonyms

- Glucocerebroside storage disorder
- Glucosylceramidase deficiency
- Acid beta-glucosidase deficiency

Etiology

- When the lysosomal enzyme activity of glucocerebrosidase is defective, glucocerebroside accumulates in tissue macrophages. Occasionally, glucocerebrosidase activity is normal but there is deficiency of saposin C, a cofactor for glucocerebroside. The accumulation results in secondary complications of those organs containing histiocytes.
- The liver, spleen, and bone marrow are usually affected, resulting in hepatomegaly, splenomegaly, and bone modeling deformities in addition to an increased propensity for bone infarcts and aseptic necrosis of bone ends. In some types, the central nervous system is involved, and life span is significantly shortened.
- While the accumulation of glucosylceramide alone is not responsible for the clinical severity of the disease, the primary enzyme defect underlies its pathogenesis.

Clinical Features

Epidemiology

- Inherited in an autosomal recessive manner

Sex

- Sex incidence is equal.

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Age

- The three clinical types based upon the severity of CNS involvement are as follows:
  - Type I, without CNS involvement, may present from childhood to late adulthood and is compatible with a normal life span.
  - Type II, with severe CNS involvement, presents in infancy, and patients usually die in infancy.
  - Type III, with less severe CNS involvement, presents in childhood, and the patient's life span is usually two to four decades.

Sites of Involvement

- Since it is a systemic disorder, any bone with a marrow compartment can be affected.
- While there is histological evidence of the process anywhere there is marrow, the bones may show modeling deformities, particularly in those bones having the most active growth when the disease is manifested. Consequently, the distal femur and proximal tibia are often clinically affected.
- Convex ends of bone having end-arterial circulations are prone to secondary avascular necrosis.
- Bone infarcts usually affect the medullary cavities of the long bones and spare the overlying cortices.
- Tumorlike accumulations of Gaucher histiocytes ("Gaucheromas") as isolated or multiple lesions within the bones.

Clinical Symptoms and Signs

- Hepatosplenomegaly with anemia and thrombocytopenia in type I disease. Bone involvement is also seen in type III disease.
- Severity of the bone disease does not necessarily correlate with that of other viscera and bone marrow.
- Bone modeling deformities during skeletal growth.
- Osteopenia as a result of expansion of the marrow compartment with increased incidence of secondary fractures, especially compression vertebral fractures.
- Bone crises, or acute pain similar to that seen in sickle cell disease, may simulate infections.
- Avascular necrosis of bone ends may result in decreased mobility and joint collapse.

Image Diagnosis

Radiographic Features

- Cortical atrophy and scalloping with generalized radiolucency sparing bone ends
- Modeling deformities of long bones with diaphyseal expansion with diminished concavity of metaphyses (Erlenmeyer flask deformity)
- Areas of irregular radiodensity and radiolucency of bone shafts secondary to infarcts
- Reactive periostitis with ossification leading to a "bone within bone" form
- Vertebra plana secondary to collapse, with secondary spinal deformities
- Epiphyseal osteonecrosis with radiodensity and subsequent collapse of femoral and humeral heads, distal femur, and tibial plateau

MRI Features

- May demonstrate fluid collections beneath periosteum.
- May reveal the extent of marrow replacement.
- Can indicate the amount of infarction and the presence of fibrosis.
- Signal changes can be used to demonstrate responses to therapy.

Image Differential Diagnosis

Niemann-Pick Disease

- Erlenmeyer flask deformities may be present.
- Usually severe mental retardation.
- Avascular necrosis less common.

Thalassemia

- The skull often has hair-on-end appearance.
- Hepatosplenomegaly from extramedullary hematopoiesis.
- Avascular necrosis is less common.
- Modeling deformities less common.

Legg-Calvé-Perthes Disease

- Avascular necrosis of femoral heads in children.
- Usually unilateral, and the epiphyses have different sizes on affected and unaffected sides.

- Sclerosis with or without collapse of epiphysis.
- Other bone signs of Gaucher not present.

Hurler Syndrome

- Bones of the extremities are short.
- Anterior inferior "beak" of vertebral bodies.
- Pelvis may be hypoplastic.
- Hepatosplenomegaly.
- Mental retardation.

Morquio Syndrome

- Vertebra plana.
- Vertebral bodies are ovoid and have a central anterior "beak."
- "Wineglass"-shaped pelvis.

Myeloma

- Generalized osteopenia.
- Bone destruction may have adjacent soft tissue mass.
- If there is no associated fracture, often silent on radionuclide scans.
- Older age presentation than Gaucher patients.

Pathology

Gross Features

- In large specimens, the compact bone is thin, and the medullary space is expanded.
- Bone infarcts appear as other bone infarcts; there is no hemorrhagic stage. The specific appearance reflects their age rather than their etiology.
- Osteonecrosis of bone ends appears grossly similar to osteonecrosis of other etiology. Secondary changes including partial or total collapse with degenerative joint disease are dependent upon the stage of the necrosis.

Histological Features

- The hallmark is the presence of large storage macrophages, up to 80 μ in diameter containing pale eosinophilic, striate cytoplasm having the appearance of crinkled tissue paper.
- Macrophages may be present singly, in groups, or in sheets; they are often mixed with hematopoietic elements.
- Cytoplasm of Gaucher cells is PAS positive, diastase resistant, and stains weakly with Sudan black.
- There may be associated infarction of the marrow.
- The cortex is usually thin and atrophic.
- In avascular necrosis of the bone ends, the necrotic area appears the same as with other causes of osteonecrosis, but often Gaucher cells may be seen in the marrow spaces that are still viable.

Pathologic Differential Diagnosis

Other Storage Disorders

- Niemann-Pick disease and mucopolysaccharidoses have large macrophages, but the cytoplasm is vacuolated or foamy rather than striate and crinkled.
- Erdheim-Chester disease and xanthomatosis contain multivacuolated histiocytes containing lipid; the PAS stains are negative.
- Certain hematopoietic diseases with high cell turnover may contain cells identical to Gaucher histiocytes. These are probably derived from destruction of cells with increased quantities of cell membranes released that may temporarily overwhelm normal levels of glucocerebrosidase.

Ancillary Techniques

Genetics

- The gene encoding glucocerebrosidase has been located on chromosome 1q21; approximately 100 mutations have been documented.
- The correlation of genotype with phenotypic severity is inconstant, even in identical twins.

Prognosis

- Type I Gaucher disease is compatible with a normal life span. However, the skeletal manifestations may be disabling, resulting in a diminished quality of life. Patients may have growth impairment, and there is a significantly increased risk of multiple myeloma, leukemia, and lymphoma.
- Type II Gaucher disease eventuates in death, usually in the first 2 years of life.
- Type III Gaucher disease is more slowly progressive, with death usually in the third decade of life.

Treatment

- Enzyme replacement therapy improves life quality and has reduced complications for patients with type I disease. Unfortunately, because the enzyme does not traverse the blood-brain barrier, it is not effective in the other types.
- Supportive therapy is a mainstay of care, particularly for pain and Gaucher crises.
- Splenectomy has fallen into disfavor because it is thought to accelerate the progress of lesions elsewhere.

Images

See Figs. 67.1, 67.2, 67.3, 67.4, 67.5, 67.6, 67.7, and 67.8 for images of Gaucher disease.

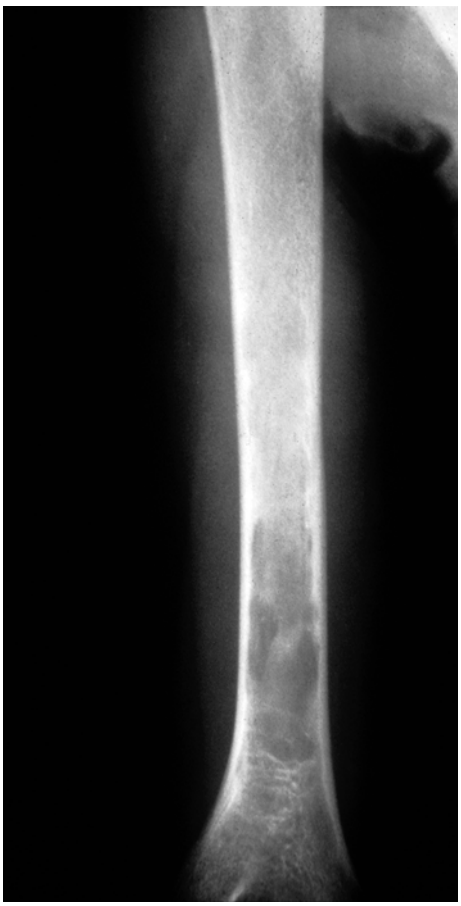

Fig. 67.1 Gaucher disease involving the humerus. Note the radiolucency with cortical scalloping involving the distal diaphysis; the trabecular pattern of the distal end is spared

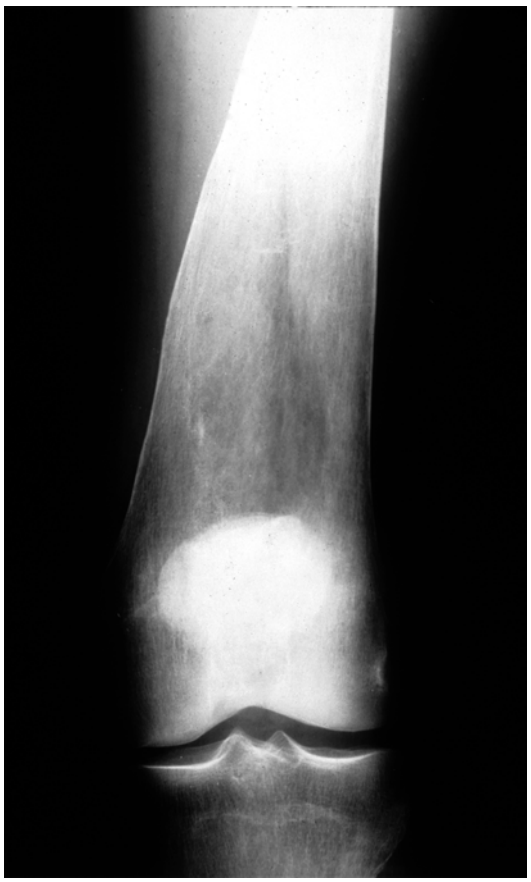

Fig. 67.2 Gaucher disease causing modeling deformity and cortical thinning of the femur. There is overall radiolucency of the femur, and the normal tapering cortical flare is widened, giving rise to the so-called Erlenmeyer flask deformity

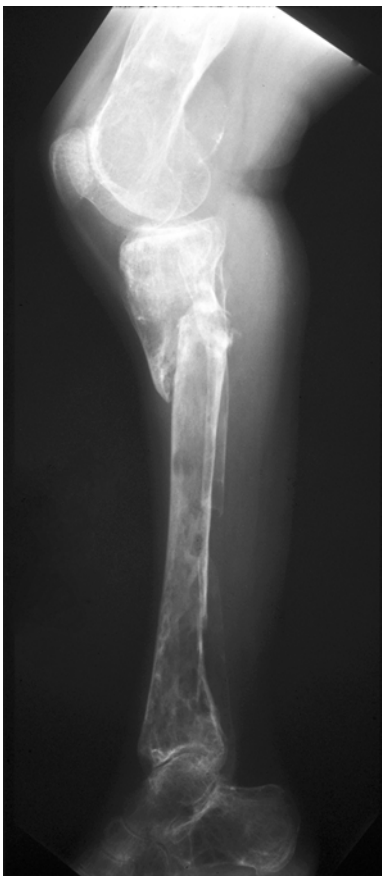

Fig. 67.3 Gaucher disease, leg. There are areas of radiodensity and space-occupying radiolucency secondary to deposits of Gaucher histiocytes with extreme attenuation of the tibial and fibular cortex leading to pathologic fracture. The distal femur demonstrates "bone within a bone" configuration suggesting old reactive periostitis

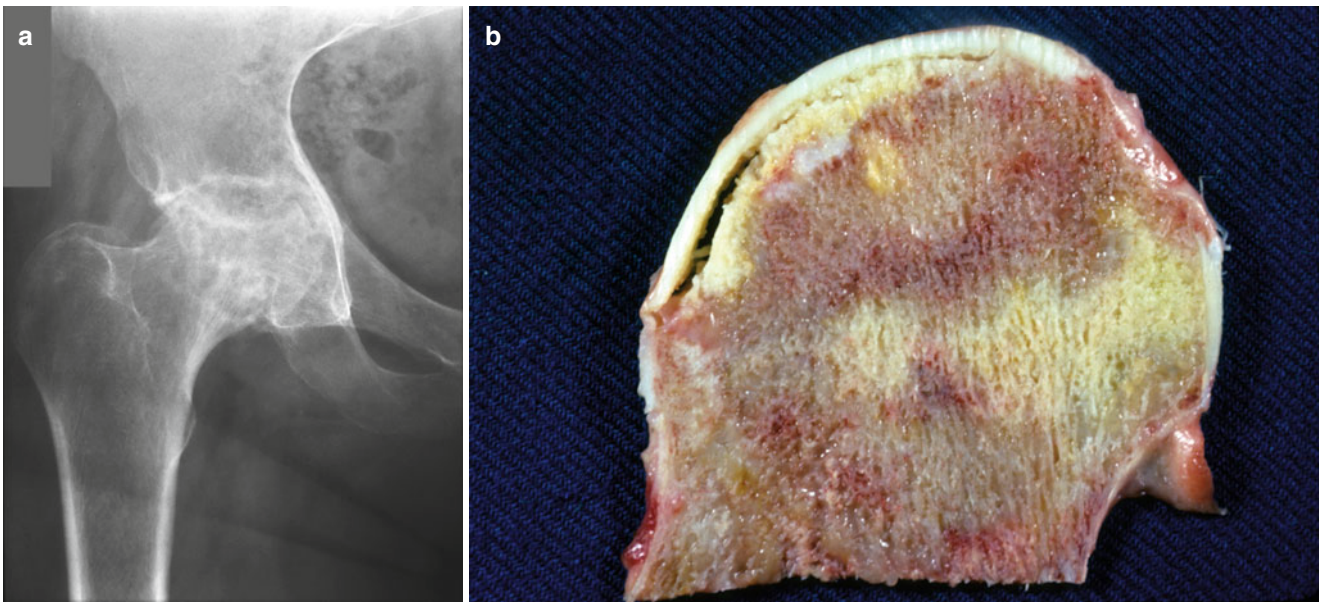

Fig. 67.4 (**a**) Gaucher disease with avascular necrosis. AP conventional radiograph of the right hip demonstrates a mixture of sclerosis and lysis of the superior femoral head with joint narrowing and deformity but without secondary osteophytes. This is consistent with stage 2 avascular necrosis with superficial collapse of the articular plate. (**b**) Gaucher disease with avascular necrosis. The resected gross specimen seen in (**a**) demonstrating irregular areas of necrosis and viable bone with separation of the subarticular bone plate and overlying articular cartilage, giving rise to the so-called crescent sign observed when this separation can be seen with routine radiographs

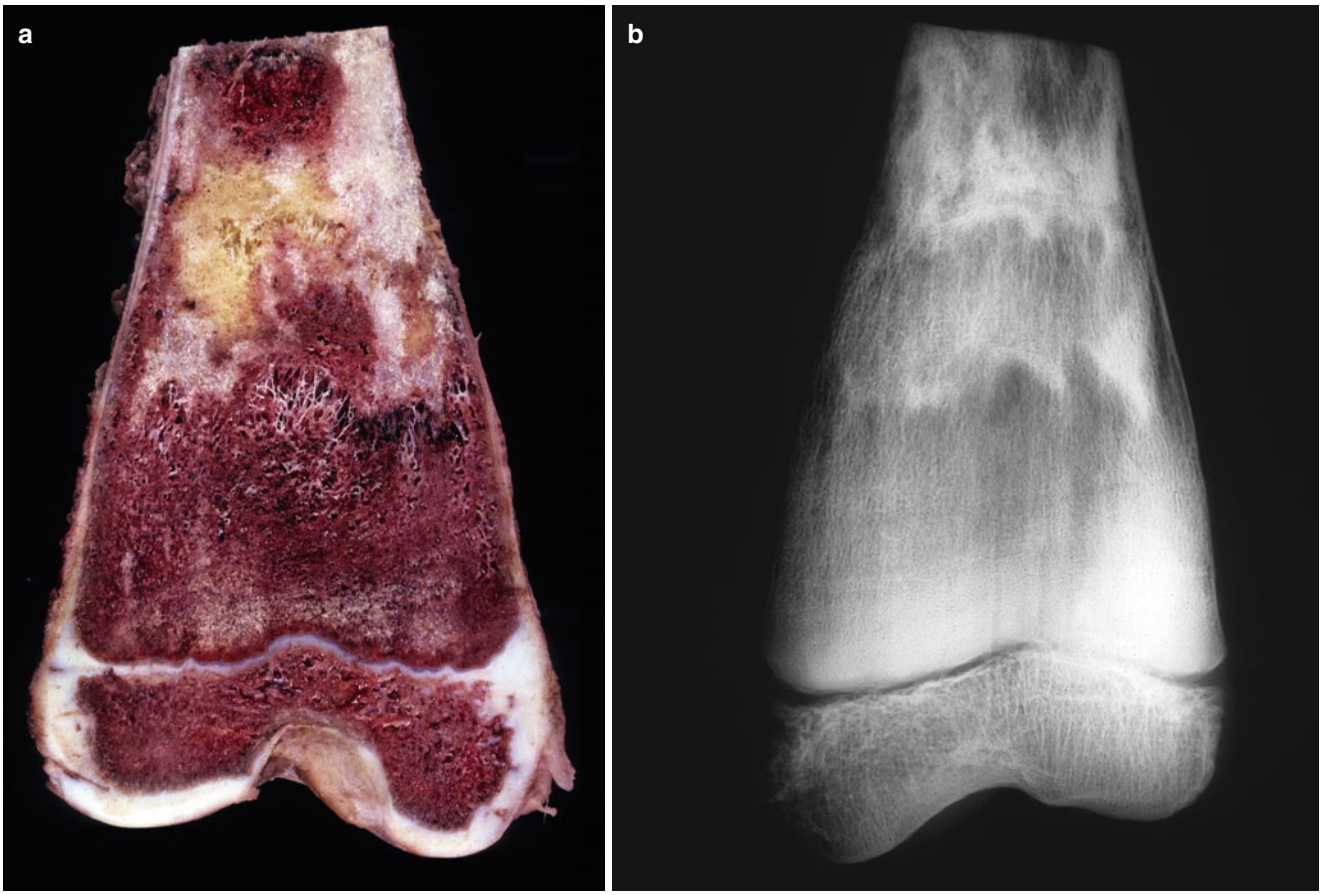

Fig. 67.5 (**a**) Gaucher disease, autopsy specimen of distal femur in a child unsuccessfully treated with enzyme therapy. The metaphyseal flare is convex rather than concave, accounting for the typical Erlenmeyer flask deformity, and the cortex is attenuated to almost paper thinness. The marrow, which is usually yellow at this site at this age, is *red* because of replacement of the more proximal marrow with Gaucher histiocyte storage. Note irregular *whitish* and *yellow* areas representing medullary infarctions. (**b**) Specimen radiograph of the femur seen in (**a**) demonstrates that the cortex is thinned almost to invisibility and the irregular radiodensities are secondary to dead bone and calcification of marrow fat in medullary fat necrosis (From Klein et al.; with permission)

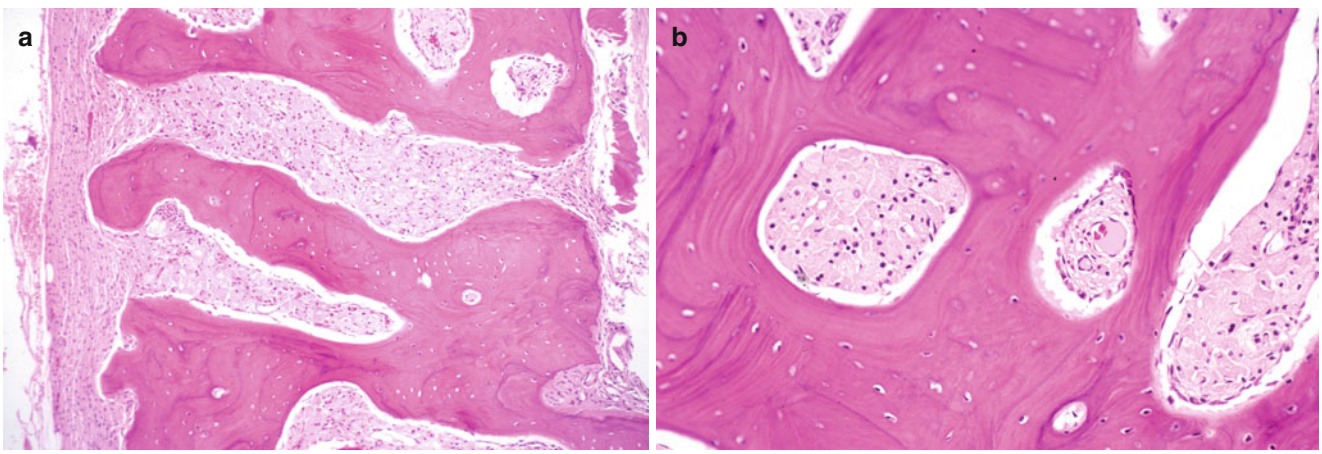

Fig. 67.6 (**a**) Cortex of specimen seen in Fig. 67.5a demonstrates delicate striate organizing periosteal reaction comprising most of the extant cortex. The subperiosteal connective tissue, Volkmann canals, and Haversian canals are filled with storage histiocytes (Gaucher cells) containing glucocerebrosides (hematoxylin-eosin 63×). (**b**) Higher power of reaction seen in (**a**) demonstrates large *pink* storage histiocytes (Gaucher cells) filling Haversian systems (hematoxylin-eosin 157×)

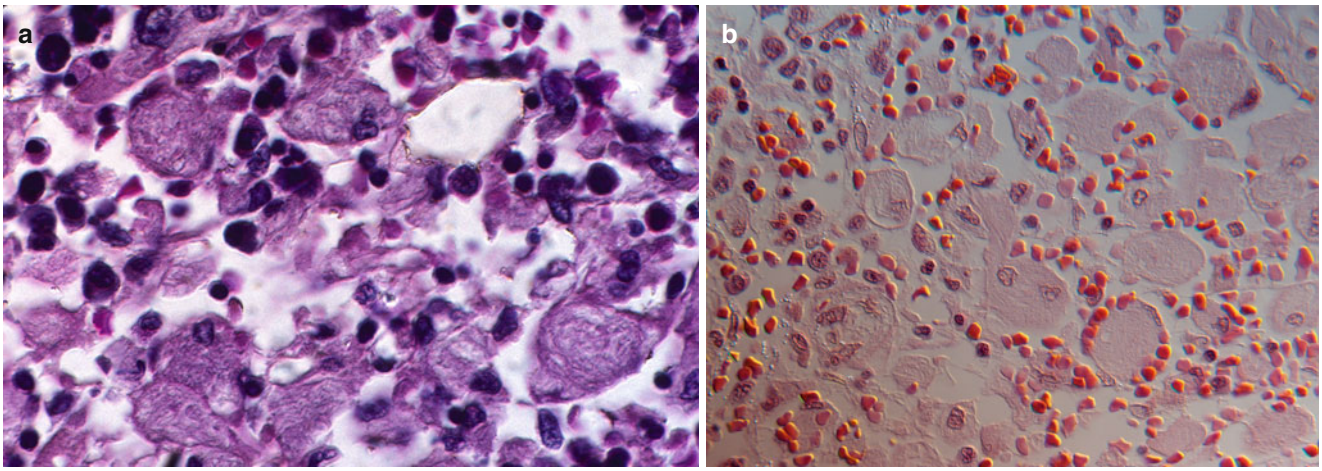

Fig. 67.7 (**a**) Gaucher cells admixed with a few normal marrow elements, emphasizing the "crumpled paper" appearance of the cytoplasm (700×, hematoxylin-eosin). (**b**) Gaucher cells admixed with a few erythrocytes; the crumpled appearance of the cytoplasm of the storage histiocytes is emphasized (polarization contrast microscopy, hematoxylin-eosin, 787×)

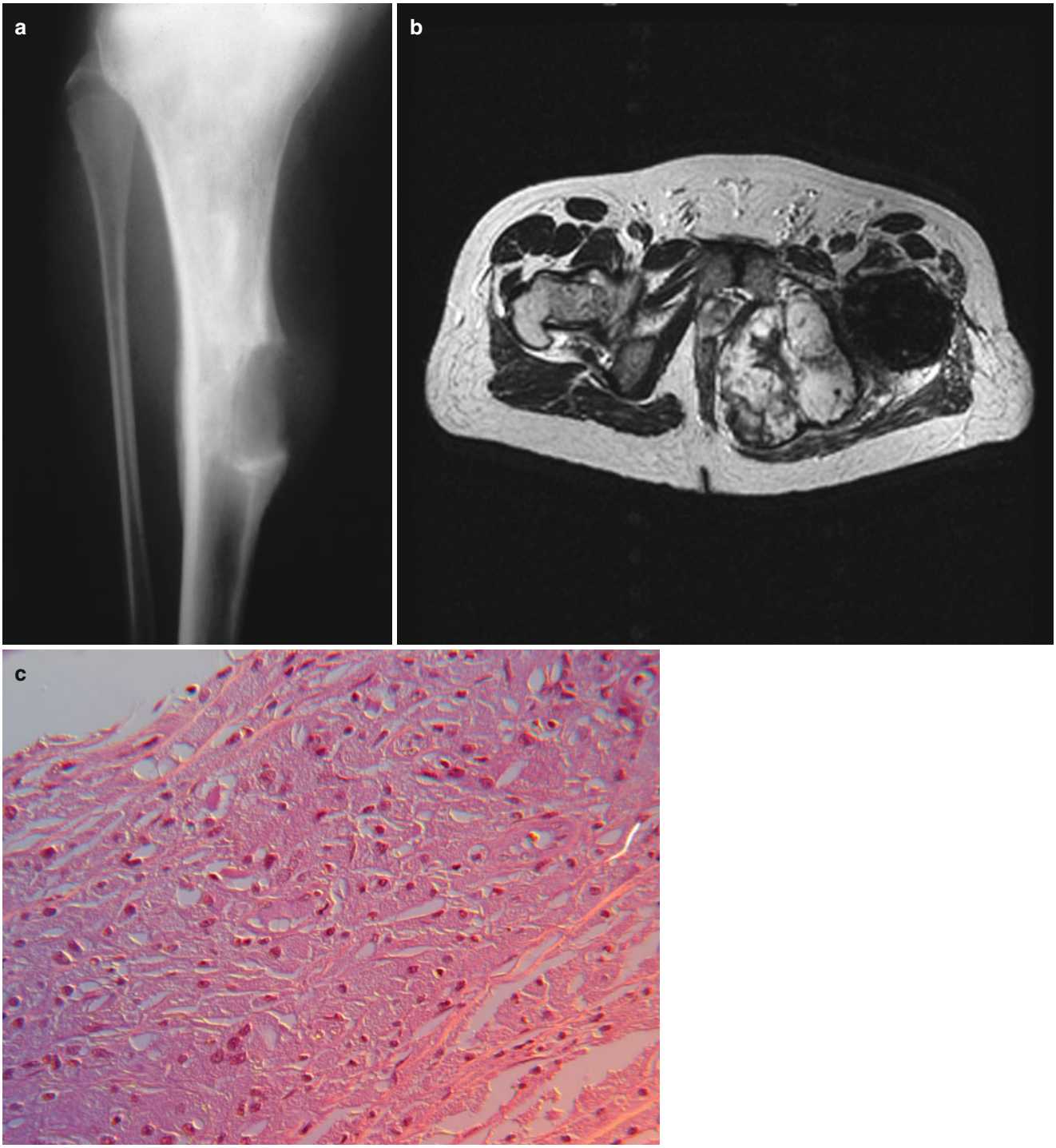

Fig. 67.8 (**a**) Aggregations of Gaucher cells within a bone resembling a space-occupying primary bone tumor (so-called Gaucheroma) with organized but incomplete periosteal reaction. (**b**) T_2-weighted axial MRI demonstrating bright signal in Gaucher pseudotumor adjacent to the femur in another patient (Courtesy of George Hermann, MD). (**c**) Core biopsy of soft tissue mass in (**b**) Gaucher cells, showing indistinct cell borders, *pink*, somewhat crinkled cytoplasm enhanced by microscopic technique (interference contrast, hematoxylin-eosin, 250×)

Recommended Reading

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