# Osteonecrosis in a Patient with Gaucher's Disease Treated with Enzyme Replacement

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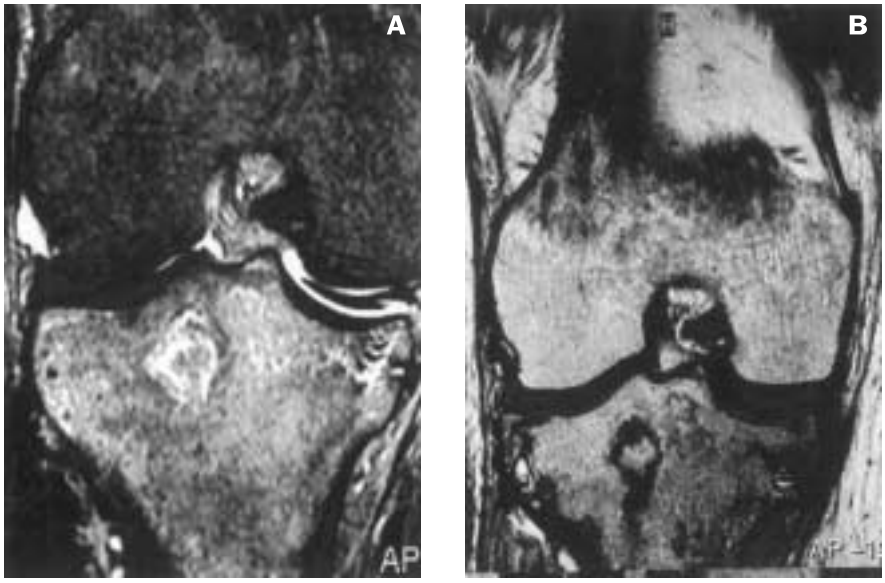
Gaucher disease, the most prevalent lysosomal storage disorder, is caused by an inherited enzymatic defect with consequent accumulation of undegraded glucocerebroside in monocyte-macrophage cells, known as the "Gaucher cells" [1]. The most debilitating, albeit most variable symptom, is bone involvement: pathologic fractures after slight trauma, destruction of heads of the femur or humerus in the hip or shoulder joints (avascular necrosis), and compression fractures of the spine, as well as "bone crises" of pain, which although self-limiting and diminishing after puberty may require pain relief. It was hoped that the introduction of enzyme replacement therapy for Gaucher disease [2] would eliminate this devastating involvement of bones. We present the case of a patient with an osteolytic lesion of the proximal tibia that developed under enzyme therapy. The use of various imaging techniques for differential diagnosis is discussed.

## Patient Description

A 69 year old patient with type I Gaucher disease was admitted to the emergency room with acute right knee pain. Pain was aggravated by weight-bearing and relieved by rest. Gaucher disease was diagnosed at age 47 years, secondary to severe knee pain. Skeletal evaluation revealed old infarcts of the left distal femur and right femoral head. Visceral involvement was minimal with very mild hepatosplenomegaly, low-normal hemoglobin, and normal platelet counts. Enzyme replacement therapy was begun in 1999 with the low dose regimen of 30 u/kg per month.

On physical examination of the right knee, local medial joint-line tenderness was found with vague tenderness of the proximal tibia. No joint effusion was noted and there was no limitation in movement. Varus stress was severely painful, but other stability tests were negative. Laboratory tests revealed: white blood cells 5,400/mm$^3$ (66% polymorphonuclears), hemoglobin 14.0 g/dl, and platelets 145,000/mm$^3$; sedimentation rate was 13 and C-reactive protein 0.2; all other tests were normal. Plain knee radiographs were normal; a computed tomography scan that was ordered to rule out an occult fracture showed a low density region of the medial tibial metaphysis without fracture or collapse of the articular surface. A positron emission tomography scan of bone showed "hot" regions in the medial tibial metaphysis and "cold" region under the tibial eminence. Bone mineral density evaluation revealed only very mild osteoporosis: z-score for the lumbar spine was -0.5 (in the low-normal range for age and gender).

All imaging results supported the diagnosis of osteonecrosis of the proximal tibia rather than infection or a neoplastic process. The patient was treated symptomatically with oral opioids and given




Coronal images of the knee (MRI). **[A]** T1-weighted and **[B]** T2-weighted images. **[B]** shows a region of low signal intensity in the proximal tibia, reflecting bone sclerosis and edema characteristic of bone necrosis.

crutches to prevent weight-bearing on the right leg.

Magnetic resonance imaging performed a week later showed a large area of marrow edema of the tibial epiphysis with central cystic lesion compatible with osteonecrosis [Figure]. Eight months after the event, he reports mild exertional knee pain but has returned to his regular routine except for dancing. Radiographs show resolution and sclerosis of the necrotic region without collapse.

## Comment

This case raises two clinically relevant issues: the process of diagnosing a lytic lesion in an unusual site, and development of a new bone infarct despite more than 2 years of enzyme therapy in a patient with Gaucher disease.

The differential diagnosis of cystic lesions of bone includes multiple myeloma [3] and osteomyelitis [4], both reported to evince increased prevalence in Gaucher disease. But in this case both were excluded by imaging radiographs. CT and PET were performed when plain X-rays were negative; follow-up MRI proved to be diagnostic. Thus, in patients at risk for bone involvement, but also in patients with credible bone pain, the imaging workup should include MRI if osteonecrosis is suspected.

The development of osteonecrosis during treatment is relatively rare. One may question whether the dosage regimen was too low in our patient; although a similar case has been reported on the high dose regimen [5]. It may also be that enzyme therapy was initiated after bone deterioration had begun.

In prioritizing treatment regimens for patients with Gaucher disease, clinicians should note that considerable benefit may be derived from symptomatic pain relief and from surgical intervention, as seen in other patients with comparable signs. Enzyme replacement is not the only or the best clinical solution. Yet in a case such as this, where there is MRI evidence of hip and knee involvement, enzyme therapy may prevent the development of necrosis at other sites. Thus, the recommendation to start enzyme therapy early for children with symptomatic disease should not be disregarded, since, along with a decrease in the need for splenectomy – which in itself may also be a risk factor for increased bone involvement in Gaucher disease – early normalization of enzyme levels may preclude the secondary processes of Gaucher disease that damage bone.

PET = positron emission tomography

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