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Case Report

Bilateral femoral osteolytic lesions in a patient with type 3 Gaucher disease

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ABSTRACT

Type 3 Gaucher disease (GD) manifests with hematologic, neurological and skeletal involvement including Erlenmeyer flask bone deformities, osteopenia, painful bone crises and fractures. We describe bilateral symmetric osteolytic lesions in a 23 year old with type 3 GD, chronically treated with enzyme replacement therapy. These atypical bone findings, previously reported in two similar patients with type 3 GD, expand our understanding of the evolving natural history of GD in the post-treatment era.

1. Introduction

GD is an autosomal recessive lysosomal storage disorder resulting from deficient glucocerebrosidase activity. The disease is clinically heterogeneous and is classified into three types based on the presence and severity of neurological symptoms. Type 1 is non-neuronopathic, while types 2 and 3 are acute and chronic neuronopathic, respectively [1]. Type 3 is typified by slowing and looping of the horizontal saccadic eye movements, organomegaly and bony involvement. Skeletal features include the classic "Erlenmeyer flask" bone deformities of the distal femurs, pathologic fractures, osteopenia and painful bone crises. Osteolytic lesions are rare and often characterized by large progressive intermedullary lesions with cortical thinning that may become necrotic [2–4]. Previously, two adolescent patients with GD were reported to have bilateral symmetrical osteolytic lesions of the humerii and tibias, with cortical scalloping and indolent growth [5]. Here we present a third patient with GD who has similar symmetrical bilateral osteolytic lesions, this time of the femurs. All three patients are young adults diagnosed with type 3 GD at an early age, with the same genotype, L444P/L444P, and each had a favorable response to enzyme replacement therapy (ERT) administered since childhood. These atypical skeletal findings in unrelated type 3 GD probands sharing the same genotype further illuminate our understanding of the phenotypic spectrum in this single gene disorder in the post-treatment era.

1.1. Case report

The patient is a 23 year old female followed at the National Institutes of Health under an Institutional Review Board approved clinical protocol since her diagnosis of type 3 GD at age 7 months. Two years prior to her birth, her brother, also diagnosed with GD, died from a ruptured spleen at age 2 years.

Her perinatal course was unremarkable, but an enlarged liver and spleen were noted at age 6 months, prompting DNA testing for GD. Her genotype was determined to be L444P/L444P. She was noted to have characteristic horizontal gaze abnormalities at age 9 months. The patient was started on ERT with recombinant glucocerebrosidase at age 7 months at a dose of 60 IU/kg every two weeks. The dose was subsequently doubled to 120 IU/kg every two weeks when she reported hip pain at age 10 years. While she is currently asymptomatic, diffuse moderate reticular lung densities scattered bilaterally are noted on radiographs and computed tomographs of her chest, and pulmonary function tests show a mild restrictive ventilatory defect and a moderate diffusion abnormality. Mild scoliosis is also noted.

At age 22 years, the patient reported two episodes of bone pain that were sudden and severe occurring several months apart. The first, occurring in her left anterior thigh, resolved within a few days after self-treatment with acetaminophen. This was followed by a much more painful episode 7 months later in her right anterior thigh that lasted several weeks, was treated with tramadol, and ultimately resolved. On evaluation at age 23 years, radiographs of her femurs showed bilateral symmetrical lucent cortical lesions, centered in the medial cortices of the mid-diaphysis (Fig. 1A). These had a benign appearance, resembling non-ossifying fibromas. On magnetic resonance imaging (MRI), the femoral lesions had T2 signal hyperintensity, with marginal enhancement

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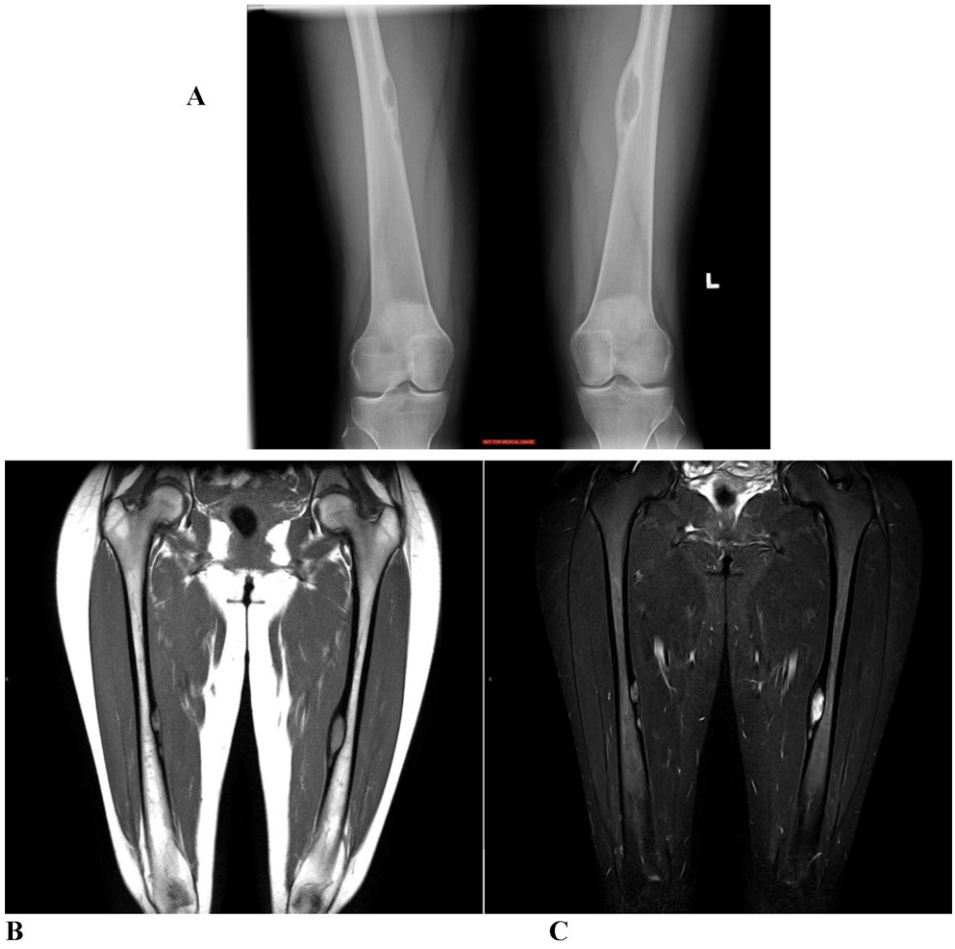

Fig. 1. A) Xray of the femurs demonstrating bilateral lucent cortical lesions. B,C).Corresponding MRI images showing signal hyperintensity and marginal enhancement within the cortex. Multiplanar multisequence MRI images were obtained before and after intravenous injection of 10 ml of Magnevist contrast. B) T1 weighted image showing bilateral cortical lesions with isointense T1 weighting. C) STIR image, demonstrating increased STIR signal intensity in the lesions.

within the cortex of the midshaft diaphysis (Fig. 1B.C). The diameters of the right femur lesion were measured at 1.9 cm-craniocaudad, 1 cm-transverse and 1 cm-anterior-posterior, while the left femur lesion was 3.6 cm-craniocaudad, 1.3 cm-transverse and 1.8 cm-anterior-posterior. The patient had normal bone densitometry for her age and no Erlenmeyer flask deformities were noted on her radiographs.

2. Discussion

This is the third patient with type 3 GD with the unique features of symmetrical bilateral cortical bone lesions [5]. Aside from the bone involvement, this patient shares other similarities with the previously reported cases including abnormal saccadic eye movements, gender, approximate age of disease onset and genotype. All three patients were free from the more common bony symptoms of GD that manifest as larger, progressively expanding lesions occupying corticomedullary regions of bone. Additionally, each patient was started on ERT at an early age and responded favorably, with reduced organomegaly and improved hematologic parameters including hematocrit, hemoglobin and platelet counts. ERT with recombinant glucocerebrosidase, first introduced in the early 1990s, is the standard of care for patients with types 1 and 3 GD and has remarkably altered the extent of visceral, hematologic and bony manifestations, especially in children [6–8].

A bone biopsy was not performed on this patient as her symptoms had resolved. Her future treatment plan includes conservative monitoring. The symmetric appearance, and similarity to the other two patients who did have pathologic confirmation of a GD-related process, aided in this decision. Regular radiographic and orthopedic monitoring for progression of the bone lesions will be performed.

Bone disease is common in patients with type 1 and 3 GD, but the pathophysiology is still not well understood. It is believed that one cause of GD-associated bone pathology in marrow tissue is glucocerebroside accumulation which alters marrow vascularity and may lead to bone infarction, necrosis and fractures [3]. Additionally, in GD, activation of macrophages may induce bone pathology by promoting inflammatory processes, arising from altered expression of cytokines and inflammatory mediators such as IL-1, IL-6 and tumor necrosis factor-alpha [9]. An overall decrease in T-lymphocyte levels has also been reported in patients with GD who have bone involvement [10]. Focal osteolytic lesions resembling those presented here have been associated with increased Cathepsin K by activated osteoclasts [3,11]. More reliable, candidate biomarkers involved in the dynamic bone processes of osteo-immunology and remodeling are needed to better understand the GD-associated bone metabolism changes.

The bilateral symmetrical osteolytic lesions seen in these three cases are atypical findings in patients with type 3 GD. A unique feature shared by the three patients was early diagnosis and treatment with ERT, associated with a relatively benign clinical course. In previous generations, children with type 3 GD often did not survive to their second or third decade and thus, such findings may not had time to manifest and be recognized. Alternately, the findings might be related to the chronic, long-term treatment. Such cases not only serve to catalog the phenotypic diversity of GD-associated bone disease, but also expand our understanding of the evolving natural history of treated GD.

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