

Pathologic Femur Fracture in a Young Patient with Suspected Gaucher Disease: A Multidisciplinary Approach in the Diagnosis and Management of a Rare Condition

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ABSTRACT

We present the case of an 18-year-old female patient with a history of pathologic right femur fracture in 2022, who was admitted to the emergency department for a diaphyseal fracture of the left femur secondary to a low-energy fall. Clinical, radiological and laboratory evaluation revealed findings suggestive of underlying systemic disease, including pancytopenia, splenomegaly and abnormal cellular features on bone marrow aspirate, compatible with a lysosomal deposition disease, specifically Gaucher disease. Management included open reduction and internal fixation of the left femur, along with multiple blood product transfusions due to refractory anemia. Despite surgical treatment, the patient presented postoperative complications, including persistent anemia and poor bone quality, suggesting a poor functional prognosis. This case highlights the importance of a multidisciplinary approach in the diagnosis and management of pathologic fractures in young patients, especially when underlying systemic disease is suspected. Diagnostic confirmation by measuring glucocerebrosidase enzyme activity is essential to establish specific treatment and improve long-term prognosis.

KEYWORDS: pathologic fracture, Gaucher disease, pancytopenia, splenomegaly, bone marrow aspirate, open reduction and internal fixation, refractory anemia.

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INTRODUCTION:

Pathologic fractures represent a diagnostic and therapeutic challenge in clinical practice, especially when they occur in young patients without significant traumatic history. These fractures are usually associated with underlying conditions that compromise bone integrity, such as neoplasms, infections or metabolic diseases. Among the latter, lysosomal deposition diseases, such as Gaucher disease, are a rare but important cause of pathological fractures, characterized by abnormal accumulation of glucocerebrosides in various tissues, including bone, liver and spleen.^{1,2}

Gaucher disease is an autosomal recessive disorder caused by mutations in the GBA gene, which codes for the enzyme glucocerebrosidase. Deficiency of this enzyme leads to the accumulation of glucocerebrosides in macrophages, forming typical Gaucher cells, which can infiltrate the bone marrow, liver and spleen, causing clinical manifestations such as hepatomegaly, splenomegaly, pancytopenia and bone

disease. Bone complications include osteopenia, osteonecrosis, pathological fractures and painful bone crises, which can significantly affect patients' quality of life.^{3,4}

In this context, we present the case of a young patient with a pathologic fracture of the left femur, in whom clinical and laboratory evaluation strongly suggested the presence of Gaucher disease. This case illustrates the importance of a multidisciplinary approach in the management of pathologic fractures, especially when an underlying systemic disease is suspected. Furthermore, it highlights the need for specific diagnostic studies, such as measurement of glucocerebrosidase enzyme activity, to confirm the diagnosis and establish appropriate treatment. Finally, we discuss the prognostic and therapeutic implications of this condition, as well as the challenges in the management of patients with rare diseases who present with severe orthopedic complications.^{5,6}

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CLINICAL CASE PRESENTATION

We present the case of an 18-year-old female patient who was admitted to the emergency department on May 31, 2024 after suffering a fall from her own height, resulting in a fracture of the left femur. The patient had a history of a previous fracture of the right femur in February 2022, which was treated with open reduction and internal fixation, and at that time an aneurysmal bone cyst was reported on biopsy. During her current hospitalization, clinical, radiological and laboratory findings were identified that suggest an underlying systemic disease, possibly Gaucher's Disease.

The patient had no history of chronic degenerative diseases, allergies, neoplasms or congenital diseases. However, in February 2022, she suffered a fracture of the right femur, which was surgically treated with the placement of an anterograde centromedullary nail.(Figure 1).



Figure 1. Femur treated with medullary center nail.

During that procedure, a biopsy was performed which reported an aneurysmal bone cyst. In addition, the patient received two globular packet transfusions at that time.

The patient came to the emergency department after a fall from her own height, reporting severe pain and deformity in the left pelvic limb. On physical examination, increased volume was observed in the affected limb, with pain on palpation and functional limitation. Initial radiograph of the left femur showed a diaphyseal fracture in a bone of pathologic appearance, with decreased cortical thickness and an aneurysmal cystic appearance. CT confirmed a multifragmented fracture with poor bone quality, suggesting a pathologic fracture.

The patient was conscious and oriented, with a Glasgow scale of 15 points. She had generalized skin pallor and palpable splenomegaly on abdominal examination. The left lower extremity showed mild shortening, internal rotation and pain on palpation, with distal pulses present and capillary filling

less than 2 seconds. No evidence of peritoneal irritation or acute neurovascular compromise was noted.

Laboratory studies revealed pancytopenia, with a hemoglobin of 6.9 g/dL, platelets of 75,000/ μ L and leukocytes of $2.8 \times 10^3/\mu$ L. Ferritin was elevated (2678 ng/mL), and the bone marrow aspirate (Figure 2) showed increased cellularity with the presence of large cells with extensive cytoplasm and round nuclei, findings compatible with a lysosomal deposition disease, such as Gaucher's disease.

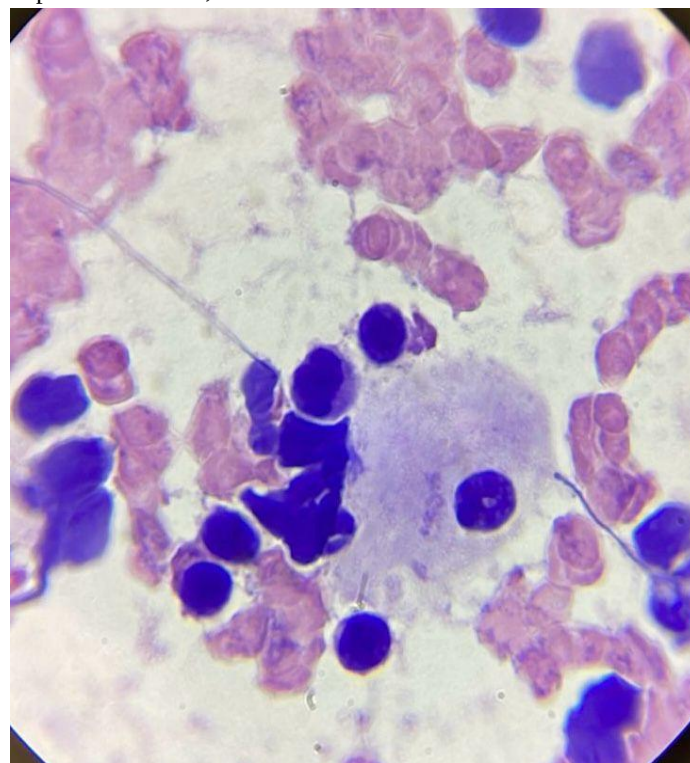


Figure 2. Bone marrow aspirate.

The results of the Abnormal GBA sequence analysis yielded the following:

Exon/intron: Exon 8

Nucleotide change: c.847T>C

Amino acid change: p.Tyr283His

Zygosity: Homozygous

Type: Pathogenic

The interpretation of the study was that this patient has Gaucher disease. Parental studies or deletion/duplication analysis may be suggested, as the presence of an extensive deletion in one copy of the GBA gene cannot be ruled out by this sequencing analysis. Genetic counseling is recommended to ensure the best possible care for the patient and family members.

The histologic study commentary suggests "that this patient has Gaucher disease. Parental studies or deletion/duplication analysis may be suggested, as the presence of an extensive deletion in one copy of the GBA gene cannot be ruled out by this sequencing analysis. Genetic counseling is recommended to ensure the best possible care for the patient and family members."

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Beta-glucosidase levels were measured and 0.41 nmol/mL was obtained. Beta-glucosidase activity is low and within the range previously observed in patients with Gaucher disease (0-0.831 nmol/mL blood/h).

METHOD:

A 3.2 mm sample from a dried blood sample card is incubated with a solution containing enzyme-specific substrate and an internal standard for the standards. The standards are analyzed by ultra high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Enzyme activity is calculated by comparing the peak area of each product with the peak area of its corresponding internal standard, which has a known concentration and normal tolerance ranges for each enzyme, as described in our laboratory.

Radiography and CT of the left femur confirmed the pathologic fracture, with poor quality bone and cystic appearance. Abdominal ultrasound showed splenomegaly (143x63x144 mm) and diffuse hepatic steatosis.

On July 19, 2024, an open reduction with internal fixation of the left femur was performed, using a 320 mm anterograde centromedullary nail and the application of 20 cc of bone chips. During surgery, poor bone quality, multifragmented fracture and abundant fibrosis were observed. The patient received 4 globular packs, platelet apheresis and fresh frozen plasma during the procedure.

Despite surgical management and transfusions, the patient presented persistent anemia, with hemoglobin not exceeding 4.2 g/dL despite transfusion of 7 globular packs. In addition, tachycardia and volume increase in the left thigh were observed, with no evidence of active bleeding in the surgical wound. The functional prognosis was considered reserved, with high risk of complications such as refracture, pseudoarthrosis and functional sequelae.

Clinical, radiological and laboratory findings, including pancytopenia, splenomegaly and cellular features in the bone marrow aspirate, strongly suggested Gaucher disease. Measurement of glucocerebrosidase enzyme activity was requested to confirm the diagnosis, the results of which were pending at the time of discharge.

The patient was discharged on July 31, 2024 with recommendations of relative rest, avoiding support of the left leg, and performing hip and knee flexion-extension exercises. Follow-up appointments were scheduled in the outpatient clinic of Hematology and Traumatology, with control X-rays and removal of stitches in 15 days. She was instructed to be attentive to alarm signs such as bleeding, fever or respiratory difficulty.

ANALYSIS

The case presented offers an invaluable opportunity to discuss the diagnostic, therapeutic and prognostic challenges associated with pathologic fractures in young patients, particularly when these are linked to underlying systemic

diseases, such as Gaucher disease. The patient, an 18-year-old female with a history of pathological fracture of the right femur, developed a new diaphyseal fracture of the left femur following low-energy trauma, which set off alarms about the presence of an underlying bone condition. This clinical scenario not only highlights the importance of considering metabolic and depositional diseases in the differential diagnosis of atypical fractures, but also illustrates the complexities of multidisciplinary management in these cases. Diagnostically, the presence of pancytopenia, splenomegaly and abnormal findings in the bone marrow aspirate (large cells with large cytoplasm and round nucleus) pointed to a lysosomal deposition disease, specifically Gaucher disease. The histologic study commentary suggests "that this patient has Gaucher disease. Parental studies or deletion/duplication analysis may be suggested, as the presence of an extensive deletion in one copy of the GBA gene cannot be ruled out by this sequencing analysis. Genetic counseling is recommended to ensure the best possible care for the patient and family members."

Beta-glucosidase levels were measured and 0.41 nmol/mL was obtained. Beta-glucosidase activity is low and within the range previously observed in patients with Gaucher disease (0-0.831 nmol/mL blood/h).

This condition, although rare, should be considered in young patients with pathologic fractures, especially when accompanied by hematologic and visceral manifestations. Gaucher disease is caused by mutations in the GBA gene, which codes for the enzyme glucocerebrosidase, resulting in the accumulation of glucocerebrosides in macrophages and their infiltration into organs such as the liver, spleen and bone marrow. Bone involvement in this disease can manifest as osteopenia, osteonecrosis, pathological fractures and painful bone crises, which explains the bone fragility observed in this patient.^{5,6,7}

Management of this patient required a comprehensive approach that combined immediate orthopedic stabilization with evaluation and treatment of possible underlying systemic disease. Open reduction and internal fixation of the left femur was necessary to correct the fracture and restore limb function. However, the poor bone quality observed during surgery, characterized by fragile and multifragmented bone, suggests that the underlying disease had significantly compromised the structural integrity of the bone. This finding highlights the limitations of conventional surgical management in patients with metabolic or depositional disease, where bone fragility not only increases the risk of fractures, but also hinders internal fixation and bone healing. From the hematologic point of view, pancytopenia and refractory anemia despite multiple transfusions of globular packets were worrisome findings. Bone marrow infiltration by Gaucher cells may suppress normal hematopoiesis, which explains the pancytopenia observed in this patient.^{8,9}

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In addition, massive splenomegaly may contribute to anemia and thrombocytopenia through splenic sequestration, further aggravating the clinical picture. These findings underscore the importance of addressing not only orthopedic complications, but also the systemic manifestations of the disease, which requires coordinated management between traumatologists, hematologists and internal medicine specialists.^{10,11}

The prognosis of this patient is considered guarded due to the high probability of long-term complications, such as refracture, pseudarthrosis, osteonecrosis and functional disability. In addition, persistent anemia and poor bone quality suggest that the underlying disease is uncontrolled, increasing the risk of new fractures and systemic complications. Diagnostic confirmation of Gaucher disease by measuring glucocerebrosidase enzyme activity is essential to establish specific treatment, such as enzyme replacement therapy (ERT) or substrate reduction therapy (SRT), which have been shown to significantly improve bone, hematological and visceral symptoms in these patients.^{10,11} This case also highlights the importance of early clinical suspicion and the use of advanced diagnostic tools in the management of rare diseases. Delayed diagnosis and treatment of Gaucher disease can lead to irreversible complications, such as bone deformities, functional disability and progressive organ damage. Therefore, it is crucial that physicians consider this condition in the differential diagnosis of pathologic fractures in young patients, especially when accompanied by hematologic and visceral manifestations.¹² In summary, this clinical case illustrates the complexity of pathologic fracture management in the context of rare systemic diseases, such as Gaucher disease. A multidisciplinary approach, early clinical suspicion, and the use of targeted therapies are critical to improving clinical outcomes and preventing long-term complications. This case serves as a reminder of the importance of maintaining a high index of suspicion for rare conditions that may initially manifest as orthopedic complications, and underscores the need for comprehensive management that addresses both local and systemic manifestations of the disease.

CONCLUSION

The present case report highlights the diagnostic and therapeutic complexity of pathologic fractures in young patients, especially when associated with underlying systemic diseases such as Gaucher disease. The patient, an 18-year-old female with a history of pathologic right femur fracture, presented with a new diaphyseal fracture of the left femur following low-energy trauma, which alerted to the possibility of an underlying bone condition. Clinical, radiological and laboratory findings, including pancytopenia, splenomegaly and the presence of abnormal cells in the bone marrow aspirate, pointed to a lysosomal deposition disease, with high suspicion of Gaucher disease.

The management of this patient required a multidisciplinary approach, integrating traumatology, hematology and internal medicine, to address both the acute orthopedic complication and the possible underlying systemic disease. Open reduction and internal fixation of the left femur, along with transfusion support for refractory anemia, were mainstays of initial treatment. However, the persistence of anemia and poor bone quality observed during surgery highlight the limitations of conventional surgical management in patients with metabolic or depositional diseases affecting bone integrity.

This case also emphasizes the importance of making an accurate etiologic diagnosis in patients with pathologic fractures, particularly in the absence of traditional risk factors such as neoplasms or infections. The suspicion of Gaucher disease in this patient was based on clinical and laboratory findings, but definitive confirmation requires measurement of glucocerebrosidase enzyme activity, which would allow initiation of specific treatment, such as enzyme replacement therapy, which has been shown to significantly improve prognosis and quality of life in these patients.

In addition, this case illustrates the challenges in the management of rare diseases with severe orthopedic complications. Lack of early diagnosis and delay in initiating specific treatment can lead to complications such as recurrent fractures, bone deformities and functional disability. Therefore, it is crucial that physicians consider systemic diseases, such as Gaucher disease, in the differential diagnosis of pathologic fractures in young patients, especially when accompanied by hematologic and visceral manifestations.

In conclusion, this clinical case highlights the need for a comprehensive and multidisciplinary approach in the management of pathologic fractures, with emphasis on the identification and treatment of underlying diseases that may compromise the patient's bone and systemic health. Early clinical suspicion, the use of specific diagnostic tools and the implementation of targeted therapies are critical to improving clinical outcomes and preventing long-term complications in patients with rare diseases such as Gaucher disease. This case serves as a reminder of the importance of maintaining a high index of suspicion for rare conditions that may initially manifest as orthopedic complications.

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