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Case Report

Bilateral avascular necrosis: A rare complication of Fabry disease

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ABSTRACT

Fabry disease is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which encodes for the α–galactosidase A enzyme responsible for degrading globotriaosylceramide. Its deficiency leads to the accumulation of GL3 in lysosomes, resulting in progressive multi-organ involvement, with predilection for the heart and kidneys.

Clinical features associated with Fabry disease include acroparesthesia, angiokeratomas, hypohidrosis, corneal whorls, chronic kidney disease, cardiomyopathy, and strokes. Osteopenia and osteoporosis are less known complications, with rare reported cases of avascular necrosis of the hips.

We report bilateral avascular necrosis in a 40-year-old-man diagnosed with Fabry at the age of 25 years. He carriers the familiar p.G328V *GLA* pathogenic variant. His Fabry features includes acroparesthesia, angiokeratomas, hypohidrosis, temperature and exercise intolerance, pain crises, abdominal pain and diarrhea, tinnitus, hearing loss, hypertrophic cardiomyopathy, palpitations, and chest pain. Family history reveals Fabry disease affecting multiple maternal relatives. The patient was recently diagnosed with avascular necrosis of the right hip requiring total arthroplasty due to failure of conservative treatment. Nine months later, he developed left hip pain attributed to avascular necrosis, also treated with total arthroplasty.

This case highlights a rare skeletal complication of Fabry disease, underscoring the need for early diagnosis, optimizing treatment of Fabry disease, managing atypical comorbidities, and vigilant monitoring of bone health.

1. Introduction

Fabry disease is a rare X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene, which results in absent or remarkably low activity of the α-galactosidase A enzyme which leads to accumulation of globotriaosylceramides (GL3 or Gb3) [1,2]. The accumulation of globotriaosylceramides lead to cell and organ dysfunction, affecting many organ systems including the heart, kidneys, skin, central nervous system, and the blood vessels [2].

The multi-organ clinical manifestations of Fabry disease include, but are not limited, to corneal opacities, angiokeratomas, anhidrosis, acroparesthesia, abdominal pain, constipation, and diarrhea. Fabry-related renal complications include proteinuria and progressive kidney damage that may ultimately require dialysis or renal transplantation [1]. Cardiac findings include arrhythmias, left ventricular hypertrophy, and hypertrophic cardiomyopathy. Currently, approved therapies for Fabry disease include α-galactosidase, and pegunigalsidase enzyme replacement therapy (ERT), and migalastat, a chaperone which stabilizes and facilitates trafficking of amenable mutant forms of α-galactosidase A enzyme from the endoplasmic reticulum to lysosomes and increases its lysosomal activity [3].

Fabry disease is associated with an increased risk of early-onset osteoporosis, likely due to the accumulation of GL3 in bone, and other risk factors including renal failure, hyperparathyroidism, treatment for pain management with drugs such as carbamazepine, and medications used to manage organ dysfunction and transplantation [4]. While

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osteonecrosis and pathological fractures of the hip are common and disabling complications of Gaucher disease, it is a rare complication of Fabry. Understanding the mechanism of avascular necrosis in Fabry disease may help prevent hip pain and fractures with early surveillance and treatment [5].

2. Case report

We report a 41-year-old man patient who was diagnosed with Fabry disease at the age of 25 years associated with the familial c., p.G328V *GLA* gene variant. His Fabry features includes proteinuria, lymphedema, angiokeratomas, acroparesthesia, pain crises, hypohidrosis, temperature and exercise intolerance, gastrointestinal features including abdominal pain and diarrhea, tinnitus, and hearing loss. He has been treated with recombinant alpha-galactosidase beta therapy 1 mg/kg alternate week since the age of 25 years. The patient denies recent oral steroid consumption or viral infection. He reports vaping, and has a history of moderate alcohol consumption, about 14 units per week, for the past 5 years, and his BMI is 24.4.

His most recent cardiac magnetic resonance imaging (MRI) performed at age 38 years showed mild left ventricular hypertrophy, measuring 14 mm at the basal septal wall during end diastole, associated with mild left atrial enlargement and trace of mitral regurgitation managed with lisinopril 5 mg daily.

Relevant laboratory values include sodium of 140 mEq/l, potassium 4.4 mEq/l, creatinine of 0.72 mg/dl, low vitamin D of 26 ng/dl (normal range $>$ 30 ng/dl), agalsidase beta IgG Ab 1/100, Lyso-GL-3, plasma 16 ng/ml (normal range $<$ 0.30 ng/ml), and GL-3, plasma 2.25 μg/ml (normal range: 1.37–4.04 μg/ml).

His recent dual-energy X-ray absorptiometry (DXA) bone densitometry performed at 38 years old revealed osteopenia with a bone mineral density of −1.6 standard deviation (SD) below in the femoral head and − 1.5 SD below in the lumbar spine compared to normal age, sex, and ethnicity. He takes vitamin D supplement sporadically.

An X-ray, and MRI without contrast were performed at the age of 39 years due to persistent right hip pain described as dull to sharp in quality, localized over the anterior hip with diffuse radiation. The pain occurred without any history of trauma was rated as 4–5 over 10 in severity, exacerbated by weight-bearing activities, and improved with rest and ice. The pain interfered significantly with activities of daily living, concomitantly with mechanical symptoms, such as popping, clicking, and grinding, which had not improved with conservative treatment. The imaging revealed bilateral avascular necrosis (AVN). The right hip showed mild flattening of the weight-bearing portion. There was associated bone marrow edema extending throughout the femoral head and into the trochanteric region. A large joint effusion was also present. Additionally, moderate partial-thickness chondral loss was noted, along with anterosuperior labral degeneration. The left femoral head also showed signs of AVN without collapse, as well as a moderate left hip joint effusion (Figs. 1a, 1b, 2a, 2b). He underwent a cementless right total hip arthroplasty via direct anterior approach for his AVN (Fig. 3a). By the age of 40 years, his left hip AVN further progressed. There was evidence of a subchondral fracture with a double line sign, along with mild collapse/flattening of the anterosuperior femoral head. The associated bone marrow edema extended through the neck of the left femur, and there was a large joint effusion present. Coexistent osteoarthritic change affecting the left hip (Figs. 3b, 4a, 4b) was noted which was treated with total left hip arthroplasty (Fig. 5). The gross description of the femoral head showed an articular surface tan-yellow and glistening with scant eburnation or erosion. A portion of the cartilage was loosely attached, exposing underlying bone. Sectioning reveled yellow-pink, trabecular cut surfaces with moderate areas of possible necrosis. The microscopic description showed marked necrosis of bone tissue, with loss of osteocytes and trabecular structure. The marrow shows extensive presence of fat droplets. The bone demonstrates areas of hyalinization with empty lacunae, suggesting osteocyte death (Figs. 6, 7, 8).

Relevant family history (Fig. 9) includes Fabry disease in his mother, sister, brother, nephew, maternal aunt, male cousin and two female cousins. His mother has suspected Alzheimer's disease and experienced a stoke at the age of 70 years old. His maternal ethnic background is Mexican, while his paternal ethnic background is a mix of German and Mexican. His mother had eight additional siblings, four of whom died in childhood, and two sisters who died in their 60s from unknown causes.

3. Discussion

A literature review identified only a few case reports of AVN in Fabry disease [7,8]. In one similar case, a 26-year-old male with AVN of both femoral head was subsequently diagnosed with Fabry disease following evaluation of his family history [9]. Further evaluations revealed additional symptoms consistent with Fabry disease, including tinnitus, acroparesthesia, fever pain crises, borderline interventricular conduction delay and left ventricular hypertrophy. The patient began receiving alpha-galactosidase beta at the age of 26 to manage his condition. In a retrospective monocentric study of 40 patients with Fabry disease, avascular osteonecrosis of the lower limbs was reported in two cases, however no further information is available [4].

Although the exact mechanism of the AVN is not fully understood, it is believed that ceramide trihexoside accumulates in the femoral head in Fabry, particularly within the vascular endothelial cells [5,6]. Horiuchi et al. (2002) [6] reported a case of AVN in a setting of FD, including histologic analysis of the femoral head. The analysis revealed lipid-laden foamy macrophages in both the necrotic and viable bone areas. The

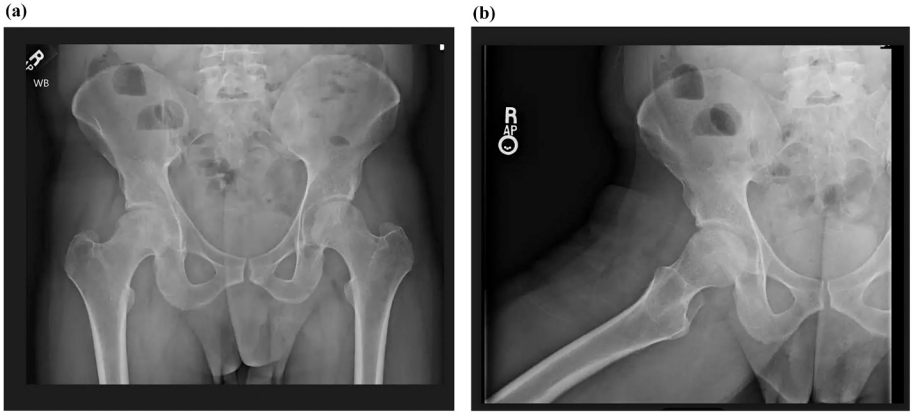

Fig. 1. a: Antero-posterior X-ray of the pelvis showing bilateral hip osteonecrosis. b: X-ray of the right hip frog view showing collapsed femoral head osteonecrosis.

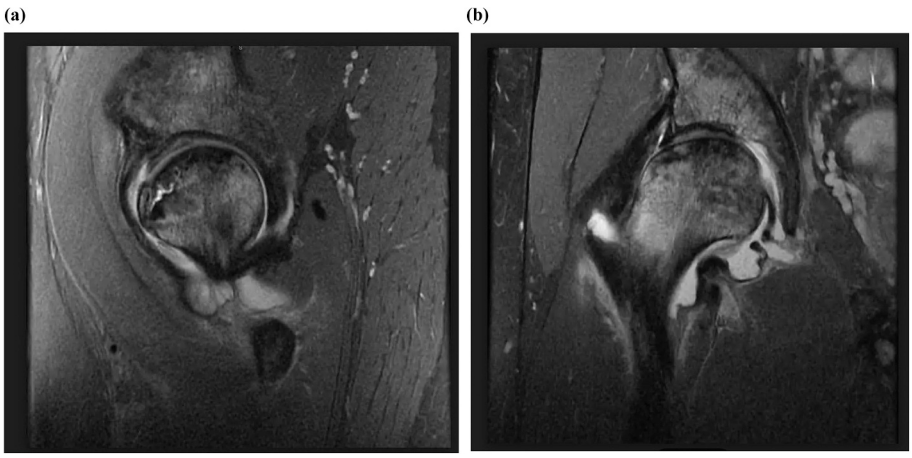

Fig. 2. a: Sagittal MRI of right hip with proton density fat saturation: Femoral head osteonecrosis with collapse is noted.
b: Coronal MRI of the right hip with proton density fat saturation: Femoral head osteonecrosis with collapse is noted.

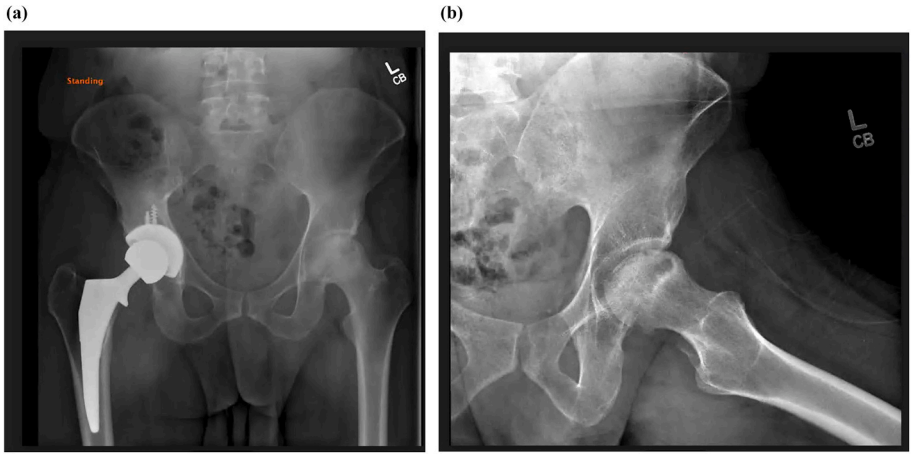

Fig. 3. a: X-ray anterior posterior view of the pelvis post-surgery: Right total right arthroplasty and left hip femoral head osteonecrosis is noted.
b: X-ray of the left hip frog view: Collapsed femoral head osteonecrosis is noted.

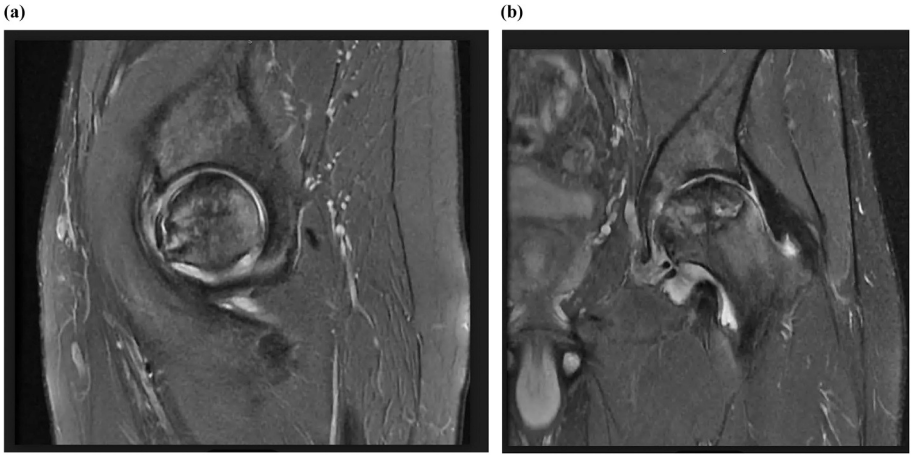

Fig. 4. a: MRI sagittal proton density fat saturation of the left hip: Femoral head osteonecrosis with collapse is noted.
b: MRI left coronal proton density fat saturation: Femoral head osteonecrosis with collapse is noted.

histological analysis of the hip bone in our patient revealed extensive necrosis attributed to avascular necrosis and couldn't exclude the possibility of ceramide contributing to the marked necrosis of bone tissue.

Our patient reports moderate alcohol intake which is a known risk factor for AVN. Alcohol leads to increased generation of lipids leading to vascular occlusion from fat emboli and osteocyte death. Previous studies have shown a significantly higher risk of AVN in consumers of >400 mL of alcohol daily [10,11]. Current alcohol intake was associated with an

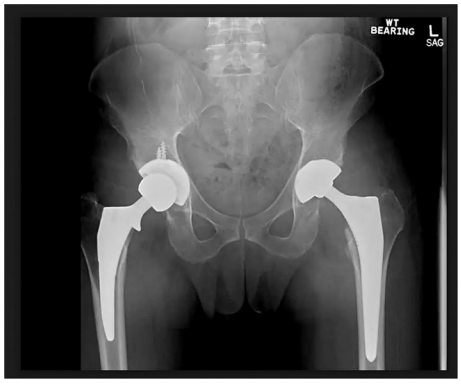

Fig. 5. X-ray anterior-posterior view of the pelvis: Post bilateral total hip arthroplasties noted.

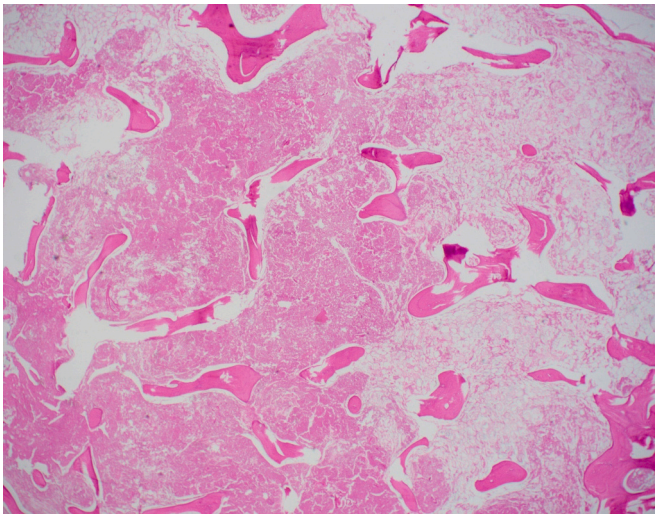

Fig. 6. Low power imaging of the right hip bone. Histology shows the interface between the viable marrow (right) and the wedge-shaped necrosis (left) (2× magnification).

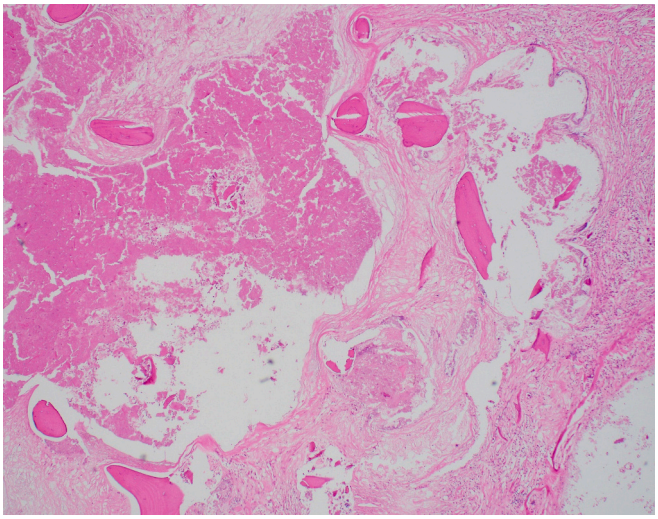

Fig. 7. Intermediate power image of the histology of the right hip bone. Microscopy shows the eosinophilic ischemic necrotic tissue (left) and viable bone marrow and trabeculae (right) with intact nuclei (10× magnification).

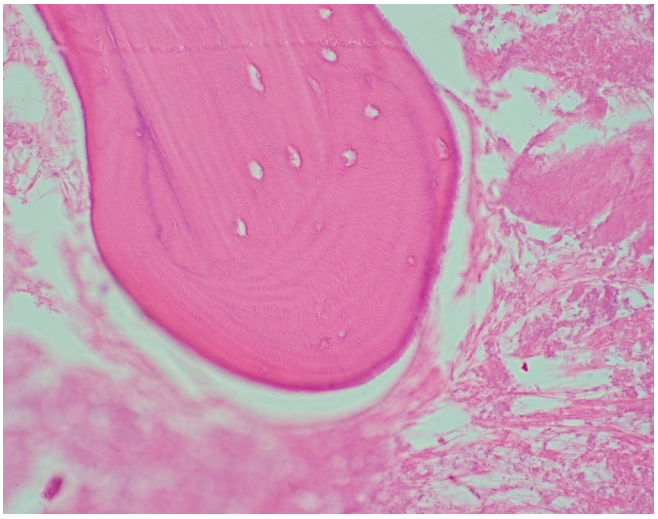

Fig. 8. High power histology image of the right hip bone. Microscopy shows the non-viable bone trabeculae lacking osteocytes within the bone lacunae, with surrounding necrosis (10× magnification).

increased risk of AVN even in occasional drinkers [12].

Additionally, patients with Fabry disease have an increased risk for thrombosis and are recommended to take daily low dose aspirin to prevent strokes. A previous study reported that patients at risk of AVN were able to reduce disease progression with acetylsalicylic acid [13].

In a study of Japanese patients with Fabry disease, decreased bone mineral density (BMD) was reported to be associated with the accumulation of Gb3, a characteristic feature of the disease [14]. The study also found that ERT could help increase BMD in patients with Fabry disease. Osteoporosis is an often underrecognized complication of Fabry disease [15]. Several mechanisms may contribute to its development of reduced BMD, including, renal failure, malabsorption of vitamin D, drugs used for pain management, low body mass index, and reduced physical activities associated with chronic pain common in Fabry disease. Moreover, Fabry disease has been associated with significant impairment of bone, which is shown to be an independent predictor of low lumbar spine trabecular bone score and BMD [16]. Shmara et al. 2025 [17] has recently published their experience with DXA results in 25 patients with Fabry disease, including the patient in this report. Twenty-four percent of all participants had significantly low *Z*-scores below ≤ -2.0. There was a correlation with calcium levels ($p = 0.03$), and a strong negative correlation between T-scores and Lyso-GL3 levels ($p = 0.001$).

AVN has been associated with other lipid storage diseases, in particular with Gaucher disease (GD) [18,19]. Gaucher cells may contribute to occlusion of the intraosseous circulation, either through intravascular coagulation or by increasing intramedullary pressure. Khan et al. (2012) [20] showed that from a total of 5894 patients with Gaucher disease, 544 experienced at least one episode of AVN, and 319 patients suffered fractures. Among them, 49.3 % had a spine lumbar DXA *Z*-scores ≤ -1 compared to 31.0 % in the control group (patients without fracture). Hughes et al. (2019) [21] showed monitoring by MRI and DXA yield useful information on the likelihood of future events such as avascular necrosis. Infarction, and fractures in Gaucher disease.

Given the varied manifestations of Fabry disease it is often not diagnosed or overlooked. Knowledge of the clinical spectrum of disease (cardiac, renal, pain, angiokeratomas, stoke manifestations), a thorough family history and appropriate genetic testing with enzyme and molecular testing are important for accurate diagnosis. Early treatment with ERT and acetylsalicylic acid of Fabry disease are essential to prevent comorbidities. We expand awareness of early AVN as a potential new complication of Fabry disease in a young patient. Early diagnosis,

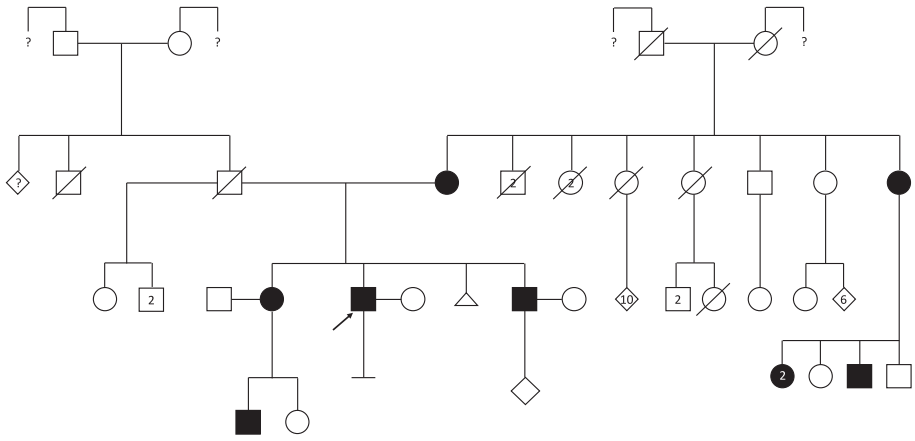

Fig. 9. Family pedigree of the patient with pertinent maternal family history. Males are depicted by squares, females are circles, filled figures depict patients with Fabry disease, and deceased individuals are indicated by a diagonal line. The arrow depicts the patient in this case report.

treatment with ERT, intervention and proactive management of osteoporosis, and thromboprophylaxis with acetylsalicylic acid and avoidance of alcohol are crucial to preventing AVN in this patient population.

CRediT authorship contribution statement

Candela Romano: Writing – review & editing, Writing – original draft, Validation, Conceptualization, Resources, Visualization. **Joel Wells:** Visualization, Supervision. **Nicholas Stanzione:** Writing – review & editing. **Virginia Kimonis:** Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

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Data availability

Data will be made available on request.

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