International Journal of Surgery Case Reports 95 (2022) 107262

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Successful total hip arthroplasty for patient with TCIRG1-associated autosomal recessive osteopetrosis

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ARTICLE INFO

Keywords:
Osteopetrosis
Hip osteoarthritis
Total hip replacement
TCIRG1

ABSTRACT

Introduction and importance: Autosomal recessive osteopetrosis (ARO) is a group of disease characterized by osteoclast dysfunction inhibiting bone resorption and bone turnover, with TCIRG1-associated ARO leading to autosomal recessive infantile malignant osteopetrosis (OPTB1, MIM entry number # 259700). While most patients with TCIRG1-associated osteopetrosis present a malignant clinical course and shortened lifespan, a few cases of mild osteopetrosis associated with TCIRG1 have been reported recently. In this study we report a rare case of non-malignant TCIRG1-associated osteopetrosis, with detail clinical characterization, genetic analysis and underwent successful total hip replacement surgery.

Case presentation: 24-year-old female patient came to us with limp gait, hip pain in both sides, severe stiffness. She suffered multiple fractures, bilateral hip osteoarthritis, right leg was 2 cm shorter compared with left leg. The patient had a limp gait due to severe pain and leg length discrepancy.

Clinical discussion: Whole Exome Sequencing, result of genetic analysis shown the patient had a compound heterozygous genotype at *TCIRG1* (c.1194dup, p.Gly399ArgTer and c.334G > A, p.Gly112Arg). Total hip replacement was performed. The joint exposure and femoral canal reaming was difficult due to complete deformity of femoral head, loss of canal and high bone density. Post-operation period was uneventful; the patient rehabilitated as planned without further complication.

Conclusion: This is the first case of TCIRG1-associated osteopetrosis reported in Vietnam and one of the few cases of non-malignant TCIRG1-associated osteopetrosis. This case report suggests that total hip replacement is a viable option for the treatment of hip osteoarthritis in patients with mild form osteopetrosis.

1. Introduction

Autosomal recessive osteopetrosis (ARO) is a group of disease characterized by osteoclast dysfunction inhibiting bone resorption and bone turnover, with an incident of 1 in 250,000 births [1]. Due to the decrease in bone marrow cavity and nerve compression, patients are subjected to secondary hematological complication and a range of neurological disorders (deafness or blindness) [2]. While most patient with TCIRG1-associated osteopetrosis present a malignant clinical course and have been reported to die within the first or second decade of life, in recent years, cases of the mild form of TCIRG1-associated osteopetrosis were reported [3]. The mild form of osteopetrosis, while patient typically expect a full life expectancy, still suffer from frequent fractures and other musculoskeletal disorders such as osteoarthritis. Total hip replacement surgery to manage hip osteoarthritis in patients with osteopetrosis is an effective option despite facing many difficulties in surgery [4].

In this study we report a rare case of non-malignant TCIRG1-associated osteopetrosis, with detail clinical characterization, genetic analysis and underwent successful total hip replacement surgery. So far this is the first case of TCIRG1-associated osteopetrosis reported in Vietnam and one of the few cases of non-malignant TCIRG1-associated osteopetrosis.

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https://doi.org/10.1016/j.ijscr.2022.107262
Received 8 April 2022; Received in revised form 23 May 2022; Accepted 28 May 2022
Available online 1 June 2022

2. Case presentation

A 24-year-old female patient came to our attention with limp gait, hip pain in both sides with right hip pain worse than left, severe stiffness. She was diagnosed with osteopetrosis when she was 4 years old; her parents were normal, she had 2 sisters with similar phenotype, suffering from early onset osteopetrosis and multiple fractures, though they had not been indicated genetic testing previously. Genetic testing shown the patient had a compound heterozygous genotype at *TCIRG1* (c.1194dup/c.334G > A).

She had 5 fractures over the last 20 years. Her maximum walking time was only about 10 min, and she had difficulty putting on shoes and socks. The patient's height and weight were 149 cm and 43 kg, her BMI was 19.4, clinical inspection shown no apparent disfigurement or facial abnormalities. Range of motion of the right hip joint: flexion of 70°, extension of 3°, abduction of 5°, adduction of 10°, internal rotation of 10° and external rotation of 0°. Right leg was 2 cm shorter than left leg. The patient's Harris score when she was admitted was 37.55.

The patient was given necessary imaging tests such as chest, pelvic, spine, both thighs and knees x-rays; CT scan and MRI of the pelvic. The diagnosis was confirmed by typical images such as increased bone density, narrowing and loss of femoral canals, bilateral femoral neck and head deformities (Fig. 1A), sandwich-like spine images (Fig. 1B–C). The MRI image shows calcification of the hip capsule, the labrum and the transverse acetabular ligament. The parameters of the right hip were measured on CT scan and MRI images. Blood tests revealed normal blood cell count, normal liver and kidney functions, serum calcium level of 2.42 mmol/L, alkaline phosphatase of 44.6 U/L, vitamin D 25OH of 13.54 ng/mL.

The patient underwent continuous femoral condyle skeletal traction of the right lower limb for 3 weeks in order to gradually stretch the soft tissue to reduce the risk of post-operative sciatic nerve palsy. The patient then underwent total hip replacement surgery. Due to the patient high bone density and brittleness, the surgeons had prepared for remedial situation such as internal fixation, fluorescent image system, bio-cement, etc. The prosthetic hip joint used in this patient had a 48 mm acetabular socket (porocoat acetabular shell sector II-Depuy Synthes). We used Corail dysplasia no. 6 stem (Depuy Synthes-USA) which is the smallest stem specially used for cases of dysplastic or hypoplastic hip with small femoral canal. The patient was under endotracheal anesthesia. A postero-lateral approach of right hip was used. The joint exposure was difficult because of the complete deformity of the femoral head (Fig. 2). In addition, the soft tissues around the joint were sclerotic, the capsule, the labrum and the transverse acetabular ligament were covered by osteophytes. Histopathological study of the femoral head was conducted (Fig. 3).

The femoral canal reaming was very difficult due to the loss of the canal and the thickening of the bone. We performed femoral canal reaming with chisels and guided drill under C-arm control. This process encountered a complication of perforating the bone wall of proximal third of the femur, which was then secured with a titanium belt. The surgery lasted 3.5 h. During surgery, the patient received a blood transfusion of 700 ml of red blood cells and 250 ml of fresh frozen plasma.

Post-operation period was uneventful; the patient rehabilitated as planned without sciatic nerve palsy. The length of the right leg was 1 cm longer than the left leg. The patient was able to stand on the 7th day after surgery, with partial weight bearing. At 2 weeks after surgery, the range of motion of right hip was improved compared to before surgery: flexion of 70°, extension of 5°, abduction of 10°, adduction of 10°, internal rotation of 10° and external rotation of 10°. On the post-operative x-ray image, the artificial hip was in the correct position; the perforation of the proximal third of the femur was well fixed.

The patient was given prophylactic antibiotics with a combination of beta-lactam and second-generation quinolone. Rehabilitation exercises were mainly aimed at increasing range of motion of the hip, full weight bearing was achieved 4 weeks after surgery. On the post-operative x-ray image, the artificial hip was in the correct position; the perforation of the proximal third of the femur was well fixed. The patient quality of life improved significantly, with near normal walking gait and daily life activity. She expressed satisfaction with the outcome of the procedure and rehabilitation period during subsequent follow-ups.

This work has been reported in line with the SCARE 2020 criteria [5].

3. Discussions

Mild phenotype of TCIRG1-accosicated osteopetrosis is very rare, with the first ever patient reported by Cristina in 2014; an 8-years-old patient with compound heterozygous TCIRG1 mutation that suffer no growth abnormalities, hematological or neurological defects [6]. Subsequently, another two case of mild TCIRG1-accosicated osteopetrosis was reported [7] [8]. The mechanism in which these rare instances occur is still unknown. Cristina et al. suggested that the small amount of

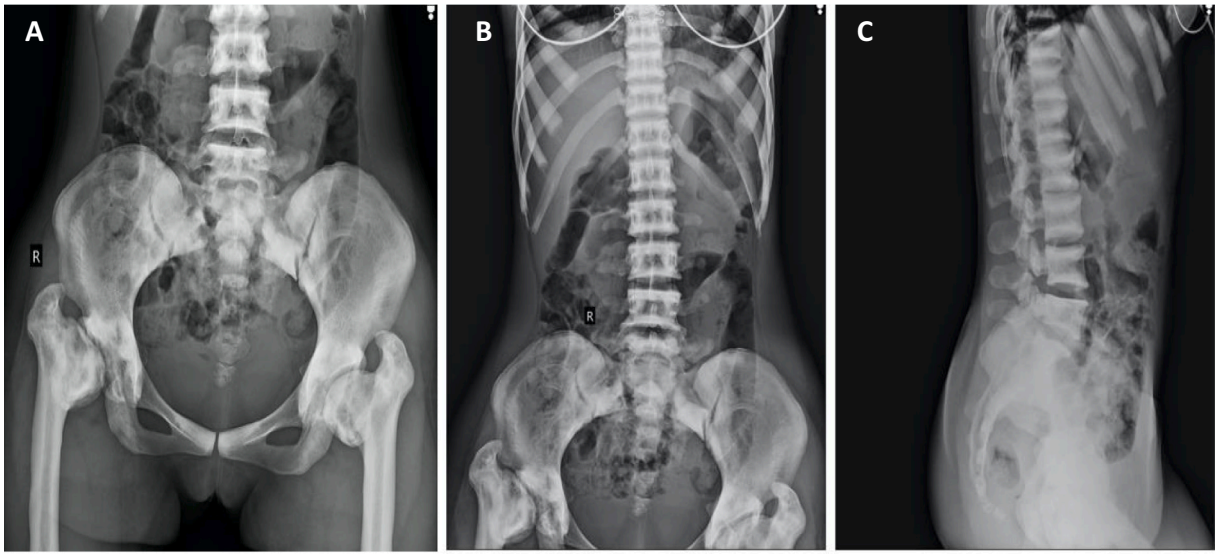

Fig. 1. The anteroposterior (A – B) and lateral (C) pelvic x-ray image of the patient revealed high bone density and hip osteoarthritis on both sides; Sandwich vertebral body (densely sclerotic endplates) was observed on both lateral and anteroposterior view.

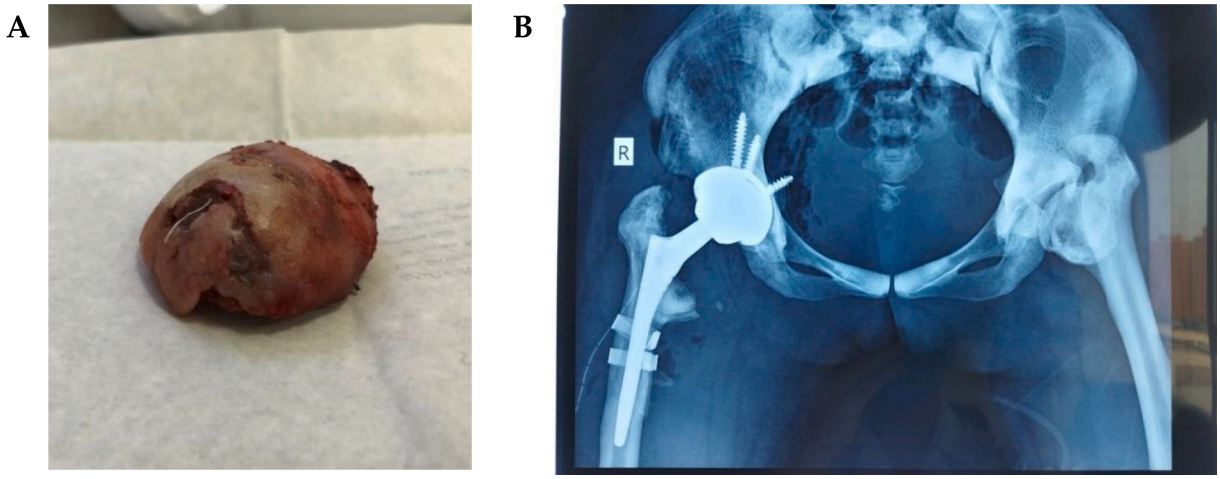

Fig. 2. (A)The patient's deformed femoral head (B) Post-operative pelvic X-ray image of the patient.

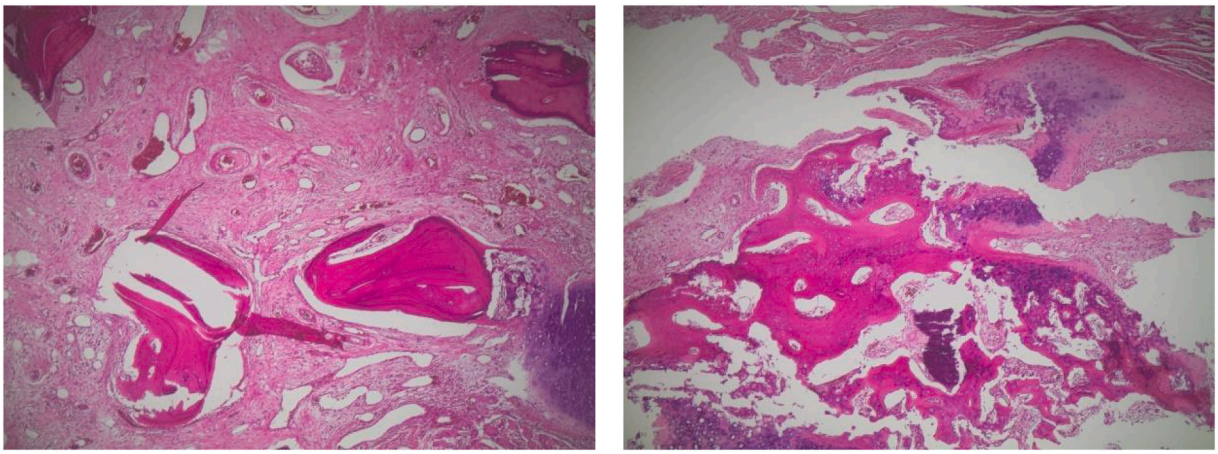

Fig. 3. Histopathological image of the patient's femoral head with large trabecular, reduction and disappearance of inter-trabecular space, absent of osteoclast.

residual enzymatic activity is enough to dampen the otherwise fatal clinical outcome of the disease [6]; however Zirngibl et al. finding on their patient shown that there was no residual protein expression, citing other reason for the mild clinical form [8]. In this study we reported three patients with definitive diagnosis of osteopetrosis but otherwise no dysmorphic feature, nor any hematological/neurological deficit. We suggest that in these patients, other than the deleterious p.Gly399ArgTer variant, the missense p.Gly112Arg variant would leave a residual enzymatic activity enough to avoid a malignant disease course.

The surgical team consist of four physician with Dr. N.D.Hieu as the chief surgeon. He graduated from Hanoi Medical University in 2012. He graduated from the Specialized Medical Training Diploma (DFMS) program at Paris Diderot University, France in 2019. He underwent a 2-year period training at the Department of orthopedic, hospital Kremlin Bicetre, Paris, France. He specialized in arthroplasty surgery, with over 400 successful cases performed. The operation was conducted at E hospital, a tertiary hospital in Hanoi with fully equipped, sterile surgical room.

According to the literature, the first case of total hip replacement in osteopetrosis patient was performed in 1971 by Janecki [9]. The first osteopetrosis patient who received a bilateral hip replacement was in 1977 by Cameron [10]. The main treatment of this disease is still symptomatic treatment and control of complications [2]. Osteoarthritis is a common condition in these patients, leading to difficulties in daily activities and reduced quality of life. Joint replacement surgery is also a good treatment option for degenerative joints, especially hip and knee joints [1] [2]. Up to now, there are only 7 patients with osteopetrosis have had both hip replacements [10] [11–16]. Our patient also had a left hip replacement scheduled after the right hip was stabilized. According to the literature review, total hip arthroplasty is a feasible option for the treatment of hip osteoarthritis in patients with osteopetrosis. Surgery may face many difficulties such as high bone density, deformed acetabulum, narrow or sealed femoral canal, fragile bones, etc., which make the surgery time longer. Table 1 is the summarization of the literature on total hip replacement in patients with osteopetrosis. It is necessary to carefully prepare plans and anticipate possible complications that may occur during and after surgery to have a plan to overcome. The goals of surgery are to relieve hip pain, improve the range of motion, and thereby improve the patient's quality of life.

4. Conclusions

This is the first case of TCIRG1-associated osteopetrosis reported in Vietnam and one of the few cases of non-malignant TCIRG1-associated osteopetrosis. Total hip arthroplasty is a feasible option for the treatment of hip osteoarthritis in patients with mild form of osteopetrosis. Surgery may face many difficulties such as high bone density, deformed acetabulum, narrow or sealed femoral canal, fragile bones, etc., which make the surgery time longer. It is necessary to carefully prepare plans and anticipate possible complications that may occur during and after surgery.

Table 1
Literature review on total hip replacement in patients with osteopetrosis.

No	Author	Age	Sex	Reason for surgery	Surgery (arthroplasty procedure)	Time (minutes) Blood loss (ml)	Intra-operative complications	Post-op complications
1	Our case	24	F	Osteoarthritis	Cementless	310	Femoral canal perforation	None
2	Janecki [9]	44	M	Osteoarthritis	Cemented	N/A	Fracture of lesser trochanter	None
3	Cameron [10]	41	F	Osteoarthritis	Cemented	N/A	None	None
4	Cameron [10]	42	F	Osteoarthritis	Cemented	N/A	None	None
5	Ashby [11]	70	F	Infected nonunion	Cemented	N/A	None	None
6	Ashby [11]	52	F	Nonunion	Cemented	N/A	None	Hip dislocation
7	Ashby [11]	52	F	Osteoarthritis& femoral neck fracture	Cemented	N/A	Femoral canal perforation	None
8	Matsuno [14]	16	F	Osteoarthritis	Hybrid	N/A	None	None
9	Matsuno [14]	16	F	Osteoarthritis	Hybrid	N/A	None	None
10	Matsuno [14]	59	M	Osteoarthritis	Hybrid	N/A	None	None
11	Egawa [12]	48	M	Osteoarthritis	Hybrid	N/A	None	None
12	Egawa [12]	48	M	Osteoarthritis	Hybrid	N/A	None	None
13	Strickland [17]	45	F	Nonunion	Hybrid	387 3200	None	None
14	Strickland [17]	47	M	Osteoarthritis	Hybrid	294 800	None	None
15	Strickland [17]	41	F	Nonunion	Hybrid	217 1500	None	Sciatic palsy
16	Ramiah [18]	38	M	Nonunion	Cemented	N/A	None	Femoral fracture
17	Wang [15]	22	F	Nonunion	Metal-on-metal hybrid hip resurfacing	150 500	Acetabular fracture	None
18	Manzi [19]	36	F	Septic arthritis	Cementless	300	None	None
19	Xie [20]	59	F	Osteoarthritis	Hybrid	180	Fracture of greater trochanter	None
20	Jones [13]	45	F	Osteoarthritis	Cementless	N/A	None	None
21	Jones [13]	45	F	Osteoarthritis	Cementless	N/A	None	None
22	Zhang [21]	44	M	Osteoarthritis	Cementless	210 1000	None	Femoral fracture
23	Gao [22]	52	F	Osteoarthritis	Cementless	N/A 300	Femoral fracture	Sciatic palsy
24	Hashimoto [23]	44	M	Osteoarthritis	Cemented	N/A	Femoral canal perforation	None
25	Hashimoto [23]	45	M	Osteoarthritis	Cemented	N/A	Femoral canal perforation	None
26	Hashimoto [23]	44	M	Osteoarthritis	Cemented	N/A	Femoral calcar fracture	None
27	Hashimoto [23]	45	M	Osteoarthritis	Cemented	N/A	None	None
28	Benum [24]	32	F	Osteoarthritis	Reverse hybrid	N/A	None	Femoral fracture
29	Benum [24]	32	F	Osteoarthritis	Reverse hybrid	N/A	None	None
30	Siljander [16]	45	F	Nonunion	Hybrid	217	None	None
31	Siljander [16]	56	F	Femoral neck fracture	Hybrid	387	Acetabular fracture	Hematoma after surgery
32	Siljander [16]	41	F	Nonunion	Cemented	402	None	Nerve palsy
33	Siljander [16]	47	M	Osteoarthritis	Hybrid	294	None	Multiple fracture
34	Siljander [16]	24	F	Nonunion	Hybrid	189	Acetabular fracture	Femoral fracture
35	Siljander [16]	34	F	Proximal femoral fracture	Hybrid	91	Acetabular fracture	Femoral fracture
36	Siljander [16]	73	M	Osteoarthritis	Hybrid	134	None	None
37	Siljander [16]	57	F	Femoral neck fracture	Cementless	197	Acetabular fracture	None
38	Siljander [16]	55	F	Osteoarthritis	Cementless	268	Acetabular & femoral fracture	Femoral fracture

Consent for publication

We have obtained written consent to publish from the patient to publish including clinical and genetics information. No identifiable information was disclosed in any form.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Sources of funding

None declared.

Ethical approval

The study design was reviewed and approved by the E Hospital Institutional Ethical Review Board. The study complies with the Declaration of Helsinki regarding the use of human samples and identifiable information.

Consent

Informed consent was obtained from the patients' parents regarding the use of information including clinical and genetics results for research purpose. No identifiable information was disclosed in any form.

Research registration

N/A.

Guarantor

Tran Thuy Nguyen MD, PhD

Provenance and peer review

Not commissioned, externally peer-reviewed.

CRediT authorship contribution statement

HND, LHL, TTN coordinated the study. TMTM, HDN, TNT involved in clinical diagnosis, surgical procedure and collected patient data. LHL, TNT performed genetic analysis. HND, LHL, HND, TTN interpreted the results and wrote the manuscript. All authors have read the manuscript and approved of the final version for publication.

Declaration of competing interest

The authors declare no conflict of interest.

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