Case report

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

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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 detailed 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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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 posterolateral 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
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.
Consent for publication information was disclosed in any form.

We have obtained written consent to publish from the patient to publish including clinical and genetics information. No identifiable

### Table 1

| 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                          | None                 |
| 5  | Ashby [11] | 70 | F   | Infected nonunion  | Cemented                      | N/A           | None           | None                          | None                 |
| 6  | Ashby [11] | 52 | F   | Nonunion           | Cemented                      | N/A           | None           | 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                          | 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           | None           | Sciatic palsy                  | None                 |
| 16 | Ramiah [18] | 38 | M   | Nonunion           | Cemented                      | N/A           | None           | 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           | None           | Fracture of greater trochanter | None                 |
| 20 | Jones [13] | 45 | F   | Osteoarthritis     | Cementless                    | N/A           | None           | None                          | None                 |
| 21 | Jones [13] | 45 | F   | Osteoarthritis     | Cementless                    | N/A           | None           | 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           | None           | Femoral canal perforation     | None                 |
| 25 | Hashimoto [23] | 45 | M   | Osteoarthritis     | Cemented                      | N/A           | None           | Femoral canal perforation     | None                 |
| 26 | Hashimoto [23] | 44 | M   | Osteoarthritis     | Cemented                      | N/A           | None           | Femoral calcar fracture       | None                 |
| 27 | Hashimoto [23] | 45 | M   | Osteoarthritis     | Cemented                      | N/A           | None           | None                          | None                 |
| 28 | Benum [24] | 32 | F   | Osteoarthritis     | Reverse hybrid                | N/A           | None           | None                          | Femoral fracture     |
| 29 | Benum [24] | 32 | F   | Osteoarthritis     | Reverse hybrid                | N/A           | None           | None                          | None                 |
| 30 | Siljander [16] | 45 | F   | Nonunion           | Hybrid                        | 217           | None           | Acetabular fracture           | None                 |
| 31 | Siljander [16] | 56 | F   | Femoral neck fracture | Hybrid | 387 | None | Femoral fracture  | Sciatic palsy |
| 32 | Siljander [16] | 41 | F   | Nonunion           | Cemented                      | 402           | None           | Nerve palsy                   | None                 |
| 33 | Siljander [16] | 47 | M   | Osteoarthritis     | Hybrid                        | 294           | None           | Multiple fracture             | None                 |
| 34 | Siljander [16] | 24 | F   | Nonunion           | Hybrid                        | 189           | None           | Acetabular fracture           | Femoral Fracture     |
| 35 | Siljander [16] | 34 | F   | Proximal femoral fracture | Hybrid | 91 | None | Acetabular fracture | Femoral Fracture |
| 36 | Siljander [16] | 73 | M   | Osteoarthritis     | Hybrid                        | 134           | None           | None                          | None                 |
| 37 | Siljander [16] | 57 | F   | Femoral neck fracture | Cemented | 197 | None | Acetabular fracture | None |
| 38 | Siljander [16] | 55 | F   | Osteoarthritis     | Cementless                    | 268           | None           | Acetabular & femoral fracture | Femoral Fracture     |
Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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None declared.

Ethical approval
The study 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

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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.

References
[1] C.J. Wilson, A. Vellodi, Autosomal recessive osteopetrosis: diagnosis, management, and outcome, Arch. Dis. Child. 83 (5) (2000) 449–452.
[2] S. Penna, A. Villa, V. Capo, Autosomal recessive osteopetrosis: mechanisms and treatments, Dir Model Mech. 14 (5) (2021), dmm048940.
[3] A. Frattini, P.J. Orchard, C. Sobacchi, S. Gilliani, M. Abinun, J.P. Mattsson, et al., Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis, Nat. Genet. 25 (5) (2000 Jul) 343–346.
[4] C.C. Wu, M.J. Econs, L.A. DiMeglio, K.L. Insogna, M.A. Levine, P.J. Orchard, et al., Diagnosis and management of osteopetrosis: consensus guidelines from the osteopetrosis working group, J. Clin. Endocrinol. Metab. 102 (9) (2017 Sep 1) 3111–3123.
[5] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, A. Kerwan, SCARE Group, The SCARE 2020 guideline: updating consensus Surgical Care And Risk demon (SCARE) guidelines, Int. J. Surg. Lond. Engl. 84 (2020) 226–230.
[6] C. Sobacchi, A. Pangrazio, A.G.M. Lopez, D.P.V. Gomez, M.E. Caldana, L. Susami, et al., As little as needed: the extraordinary case of a mild recessive osteopetrosis owing to a novel splicing hypomorphic mutation in the TCIRG1 gene, J. Bone Miner. Res. 29 (7) (2014) 1646–1652.
[7] Zhang J, Yang, W. Li, J. Wei, W. Zhen, C. Wang, Zhang Z, Lin, Novel mutations of TCIRG1 cause a malignant and mild phenotype of autosomal recessive osteopetrosis (ARO) in four Chinese families, Acta Pharmacol Sin. 38 (11) (2017) 1456–1465.
[8] R.A. Zirngibl, A. Wang, Y. Yao, M.F. Manoloff, J. Kuegener, L. Dupuis, et al., Novel c.6630A TCIRG1 mutation causes aberrant splicing resulting in an unusually mild form of autosomal recessive osteopetrosis, J. Cell. Biochem. 120 (10) (2019 Oct) 17180–17193.
[9] C.J. Janecki, C.L. Nelson, Osteoarthrosis associated with osteopetrosis treated by total hip replacement arthroplasty. Report of a case, Cleve Clin. Q. 38 (4) (1971) 169–177.
[10] H.U. Cameron, F.P. Dewar, Degenerative osteoarthrosis associated with osteopetrosis, Clin. Orthop. 127 (1977) 148–149.
[11] M.E. Ashby, Total hip arthroplasty in osteopetrosis. A report of two cases, Clin. Orthop. 276 (1992) 214–221.
[12] H. Egawa, S. Nakano, D. Hamada, R. Sato, N. Yasui, Total hip arthroplasty in osteopetrosis using computer-assisted fluoroscopic navigation, J. Arthroplasty 20 (8) (2005) 1074–1077.
[13] D.P. Gweynne Jones, B.F. Hodgson, N.A. Hung, Bilateral, un cemented total hip arthroplasty in osteopetrosis, J. Bone Joint Surg. Br. 86 (2) (2004) 276–278.
[14] T. Matsuno, N. Katayama, Osteopetrosis and total hip arthroplasty. Report of two cases, Int. Orthop. 21 (6) (1997) 409–411.
[15] C.T. Wang, H.C. Amsitz, Bilateral metal-on-metal hybrid hip resurfacing in a patient with osteopetrosis: a case report, J. Bone Joint Surg.Am. 91 (12) (2009) 2941–2944.
[16] M.P. Stijlender, R.T. Trousdale, K.I. Perry, T.M. Mahry, D.J. Berry, M.P. Abdel, Total hip arthroplasty in patients with osteopetrosis, J. Arthroplast. 36 (4) (2021) 1367–1372.
[17] J.P. Strickland, D.J. Berry, Total joint arthroplasty in patients with osteopetrosis: a report of 5 cases and review of the literature, J. Arthroplasty 20 (6) (2005) 815–820.
[18] R.D. Ramiah, R.P. Baker, G.C. Bannister, Conversion of failed proximal femoral internal fixation to total hip arthroplasty in osteoporotic bone, J. Arthroplast. 21 (8) (2006) 1200–1202.
[19] G. Manzi, D. Romano, L. Moneghini, C.L. Romano, Successful staged hip replacement in septic hip osteoarthritis in osteopetrosis: a case report, BMC Musculoskelet. Disord. 2 (13) (2012) 50.
[20] L. Xie, F. Ding, J. Jiao, W. Kan, J. Wang, Total hip and knee arthroplasty in a patient with osteopetrosis: a case report and review of the literature, BMC Musculoskelet. Disord. 21 (16) (2015) 259.
[21] Z.F. Zhang, D. Wang, L.D. Wu, X.S. Dai, Case report: A 10 years follow-up of periprosthetic femoral fracture after total hip arthroplasty in osteopetrosis, Chin. J. Traumatol. Zhonghua Chuang Shang Za Zhi 20 (3) (2017) 173–176.
[22] X. Gao, Q. Cheng, X. Zhang, G. Zhao, Successful total hip arthroplasty for autosomal dominant osteopetrosis complicated by hip osteoarthritis: a case report and review of the literature, Exp. Ther. Med. 19 (4) (2020) 2702–2706.
[23] A. Hashimoto, M. Sonohata, M. Kitajima, S. Kawano, S. Eto, M. Mawatari, Complications of total hip arthroplasty for patients with osteopetrosis: a report of four hips in two patients, J. Orthop. Sci. 27 (2) (2022) 500–503.
[24] P. Benum, A. Aannoot, L. Nordsetten, Customised femoral stems in osteopetrosis and the development of a guiding system for the preparation of an intramedullary cavity: a report of two cases, J Bone Joint Surg Br. 92 (9) (2010 Sep) 1303–1305.