Case Report

Osteopetrosis in young women presented with a fragility fracture and very high bone density

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Abstract:

Osteopetrosis is a rare genetic disease characterized by increased bone density due to osteoclast dysfunction, leading to osteosclerosis on radiological findings. Osteopetrosis is broadly divided into autosomal recessive and autosomal dominant forms; the former is more severe with high mortality, while the latter is more common and often presents with fragility fractures in late childhood or adulthood. We report a case of a 29-year-old Burmese woman with right leg pain who was unable to walk or bear weight after minor trauma. She had no history of previous fractures, dental problems, or chronic bone pain. She denied any chronic medical conditions or visual or hearing problems and was not on any medications. Examination showed tenderness of the left thigh with a limited range of motion; otherwise, the findings were unremarkable. Laboratory findings revealed normal serum calcium, phosphate, and parathyroid hormone levels, except for a low vitamin D level. A BMD scan showed high bone density. Genetic testing for skeletal disorders revealed heterogeneous CLCN7 mutations consistent with osteopetrosis. This case highlights the importance of considering osteopetrosis in patients with fragility fractures and high bone density. Early diagnosis and management can help prevent recurrent fractures and improve quality of life.

Keywords: ● *Osteopetrosis* ● *Fracture*

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รายงานผู้ป่วย

โรคกระดูกแข็งในผู้ป่วยหญิงอายุน้อยที่มีอาการกระดูกหักง่ายและมีความหนาแน่นของกระดูกสูงมาก

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บทคัดย่อ

โรคกระดูกแข็งเป็นโรคทางพันธุกรรมที่พบได้ยาก เกิดจากการที่มีความหนาแน่นของกระดูกเพิ่มขึ้น เนื่องจากความผิดปกติของเซลล์สร้างกระดูก ซึ่งนำไปสู่การพบการหนาตัวของกระดูกจากการตรวจทางรังสีวิทยา โรคกระดูกแข็งสามารถถูกแบ่ง เป็นรูปแบบ autosomal recessive และ autosomal dominant โดยแบบแรกมีความรุนแรงมากกว่าและมีอัตราการเสียชีวิตสูง ในขณะที่แบบหลังพบได้บ่อยกว่าและมักมีกระดูกหักเปราะบางในวัยเด็กตอนปลายหรือวัยผู้ใหญ่ ขอนำเสนอรายงานผู้ป่วยหญิงชาวพม่า อายุ 29 ปี มีอาการเจ็บต้นขาซ้าย ไม่สามารถเดินและรับน้ำหนักไม่ได้ หลังจากได้รับการกระแทกเพียงเล็กน้อย ผู้ไม่มีประวัติกระดูกหัก ไม่มีปัญหาทางทันตกรรมหรืออาการปวดกระดูกเรื้อรังมาก่อน ผู้ป่วยไม่มีอาการป่วยเรื้อรัง ปัญหาด้านการมองเห็นหรือการได้ยิน และไม่ได้รับประทานยาใดๆ การตรวจร่างกายพบว่ามีอาการกดเจ็บที่ต้นขาขวาและมีระยะการเคลื่อนไหวที่จำกัด ส่วนการตรวจร่างกายอื่นๆ อยู่ในเกณฑ์ปกติทั้งหมด ผลการตรวจทางห้องปฏิบัติพบว่า ระดับแคลเซียม ฟอสเฟต และฮอร์โมนพาราไธรอยด์ในเลือดอยู่ในเกณฑ์ปกติ แต่มีระดับวิตามินดีต่ำเล็กน้อย การตรวจเพิ่มเติมพบว่ามีความหนาแน่นของกระดูกสูงมาก การส่งตรวจทางพันธุกรรมพบว่ามีการกลายพันธุ์ของยีน CLCN7 ซึ่งสอดคล้องกับโรคกระดูกแข็ง รายงานผู้ป่วยนี้เน้นย้ำถึงความสำคัญในการสงสัยโรคนี้ในผู้ป่วยที่มีกระดูกหักจากอุบัติเหตุเพียงเล็กน้อยและมีความหนาแน่นของกระดูกสูงมาก การวินิจฉัยและการจัดการดูแลรักษาแต่ระยะเริ่มแรก สามารถช่วยป้องกันกระดูกหักซ้ำและปรับปรุงคุณภาพชีวิตผู้ป่วยให้ดีขึ้นได้

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Introduction:

Osteopetrosis, first described in 1904 by German radiologist Dr. Albers-Schönberg, is also known as "stone bone." This rare genetic disease is characterized by increased bone density due to a disorganization between bone production and resorption[1] Osteopetrosis is broadly classified into two types based on the mode of inheritance: autosomal recessive osteopetrosis (ARO) and autosomal dominant osteopetrosis (ADO)[2] ARO is known for its high severity and mortality in early childhood, while ADO is more common and may remain asymptomatic until adulthood[3,4]

Clinical findings of osteopetrosis generally depend on the type of disease. ARO tends to present with neurological symptoms and hematologic manifestations, such as progressive deafness, blindness, or bone marrow failure. Conversely, ADO typically has mild symptoms and may present with pathologic fractures[5,6] Here, we present a case of osteopetrosis in a 29-year-old Burmese woman who experienced left leg pain and an inability to bear weight after minor trauma despite having an unremarkable clinical history.

Case Report:

A 29-year-old Burmese woman presented to the emergency department with a three-hour history of pain in her left thigh after a fall in the bathroom. She was brought to a nearby hospital because she was unable to walk or bear weight. She had no history of previous fractures, dental problems, or bone pain. She denied any changes in her weight, visual problems, or hearing problems. Her menstrual cycle was consistently normal. She had not been on any medications and had no history of surgery. She completed compulsory education and did not drink alcohol, use other substances, or smoke tobacco. There was no family history of metabolic bone diseases or unexplained fractures. A plain film of the left hip revealed a closed fracture of the proximal end of the left femur **(Figure 1A, 1B)**. The lateral spine film showed a dense band at the superior and inferior endplate (Sandwich vertebrae) **(Figure 2A)**. The pelvis film revealed cortical thickening and bands of sclerosis along femoral necks (Bone within Bone) **(Figure 2B)**. She was then referred to our hospital for further evaluation and treatment.

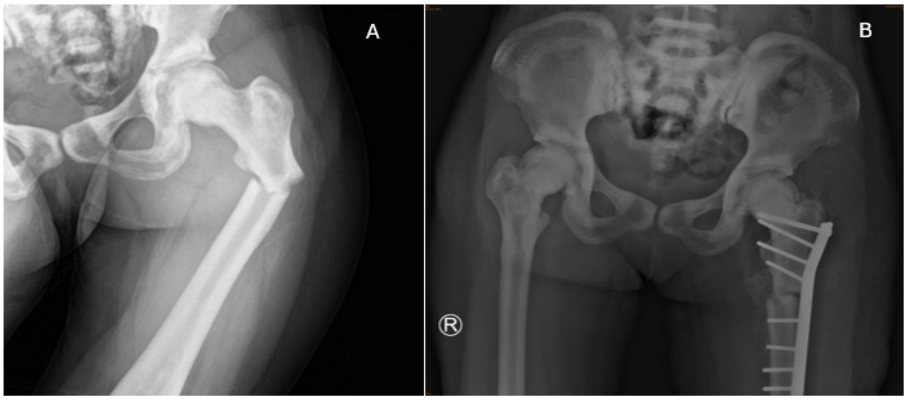

Figure 1 (A) Fracture of the proximal end of the left femur **(B)** After surgical fixation with a proximal femoral nail anti-rotation (PFNA).

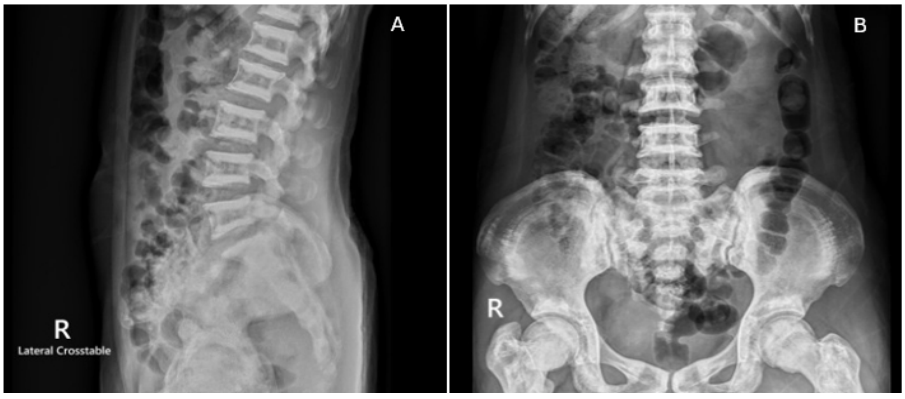

Figure 2 (A) Dense band at superior and inferior endplate (sandwich vertebrae)
(B) Cortical thickening and bands of sclerosis along femoral necks (bone within bone)

Physical examination showed stable vital signs. She was a well-nourished woman with a body weight of 60 kg and a height of 163 cm, giving her a BMI of 23 kg/m². No facial or skull deformities were seen. She did not have icterus or pale conjunctivae. The thyroid examination revealed a normal-sized thyroid without any bruit. The lower extremities appeared normal but were positive for left thigh tenderness and limited range of motion due to pain. There were no varus or valgus deformities. No pitting edema was observed. Heart and lung examinations were normal. Neurological examinations were unremarkable.

Initial laboratory testing showed a normal complete blood count, kidney function tests, and electrolytes. Further blood tests for metabolic bone panels revealed normal serum calcium of 9.43 mg/dL (reference range: 8.5-10.5 mg/dL), normal serum phosphate of 3.99 mg/dL (reference range: 2.7-4.2 mg/dL), decreased 25-hydroxyvitamin D (25-OHD) level of 9.43 ng/mL (reference range: 30-100 ng/mL), and normal parathyroid hormone (PTH) levels of 38.9 pg/mL (reference range: 10-65 pg/mL). A Bone Mineral Density (BMD) scan revealed a Z-score of +4 at the lumbar spine and +3 at the femoral neck. Given the presence of a fragility fracture at the subtrochanteric femur and high bone mass but no clinical suspicions of secondary causes of a pathologic fracture, further genetic testing for skeletal disorders was ordered. This revealed a heterozygous mutation in the CLCN7 gene (c.2073+1G>C), consistent with autosomal dominant osteopetrosis.

The patient underwent surgical fixation with a proximal femoral nail anti-rotation (PFNA). She was discharged from the hospital on day five without post-operative complications. She was prescribed calcium supplementation with oral calcium carbonate 1.5 g daily, a vitamin D supplement with oral vitamin D2 (20,000 IU), one capsule three times per week, and pain medications. She was instructed to follow up with her outpatient physician to monitor bone health and manage complications.

Discussion

Osteopetrosis is a group of rare genetic disorders, previously named "marble bone disease," characterized by increased bone density on radiographs[1] The incidence of osteopetrosis varies with the mode of inheritance. Autosomal recessive osteopetrosis (ARO) has an incidence of 1 in 250,000 births, is severe, and has a poor life expectancy. Autosomal dominant osteopetrosis (ADO) has an incidence of 1 in 20,000 births. However, specific epidemiological data for osteopetrosis in Thailand and other Asian countries are limited. The scarcity of comprehensive studies in these regions makes it challenging to determine precise incidence and prevalence rates. This lack of data underscores the need for further research to better understand the epidemiology of osteopetrosis in Asian populations.[3,7] ADO is associated with inactivating mutations of the chloride channel 7 (CLCN7) gene, contributing to ineffective osteoclast-mediated bone resorption[8] ADO is classified into two types: ADO type I, which tends to have mild clinical manifestations and commonly causes osteosclerotic thickening of the cranial vault, and ADO type II (Albers-Schönberg disease), the most common type of osteopetrosis, which tends to present in adulthood with pathologic fractures, early arthritis, and anemia[9,10]

Diagnosis of osteopetrosis is based on clinical findings and radiographic appearance. Standard radiological features include increased cortical bone thickening (affecting the spine, pelvis, and appendicular bones), a "bone-in-bone" appearance in vertebrae and phalanges, and "sandwich vertebrae" which occurs secondary to excessive sclerosis of the vertebral endplates[1] Laboratory findings, such as increased creatinine kinase BB and tartrate-resistant acid phosphatase, may assist in diagnosis without radiological finding[11] Genetic testing can confirm the diagnosis and differentiate subtypes of osteopetrosis for prognostic prediction.

Patients with osteopetrosis are prone to fractures, even with minimal trauma. Waguespack et al. found that osteopetrosis carries a high risk of fractures despite increased BMD[4] In this case, the patient presented with a fragility fracture of the left femur without clinical clues for possible metabolic bone diseases or other risk factors. Her significantly increased bone density on the BMD scan led us to consider osteopetrosis as the primary differential diagnosis. The patient had normal serum calcium, phosphate, and PTH levels, which did not aid in the diagnosis, as these laboratory findings are typically unremarkable in osteopetrosis.[12] Additionally, her low serum 25-hydroxyvitamin D level could reflect vitamin D deficiency, which is more prevalent in the female sex; younger age was independently associated with lower serum 25(OH)D levels.[13]

There is no definitive treatment for osteopetrosis besides supportive treatment and surveillance. Frequent complications, such as fractures, require surgical management, which can be challenging due to the risks of nonunion, delayed union, and osteomyelitis[14] An ophthalmologic evaluation may be necessary to prevent visual loss in cases of optic nerve compression, although this complication is more common in individuals with childhood-onset[4,15]

Diagnosing osteopetrosis can be challenging, especially in regions where its prevalence is rare and other clinical findings are absent. However, it is essential to consider osteopetrosis in patients with fragility fractures and high bone density. Differential diagnoses include Paget's disease of bone, fluorosis, pycnodysostosis, and other sclerosing bone dysplasias like Camurati-Engelmann disease and melorheostosis. Paget's disease can be differentiated by its typical mosaic pattern of lamellar bone on histology, elevated alkaline phosphatase levels, and deformities like bowed legs. Fluorosis presents with diffuse skeletal sclerosis, a history of high fluoride exposure, and dental mottling. Pycnodysostosis can be identified by its characteristic features such as short stature, open cranial sutures, and acro-osteolysis. Camurati-Engelmann disease primarily affects the diaphyses of long bones, with associated limb pain and muscle weakness. Melorheostosis is characterized by hyperostotic changes resembling "dripping wax" on radiographs, which are often localized to a single limb. Early diagnosis and appropriate management of osteopetrosis can help prevent recurrent fractures and improve quality of life.

Conclusion

Osteopetrosis is a rare genetic disease characterized by increased bone density due to unorganized bone production. The most common type, autosomal dominant osteopetrosis, has a normal life expectancy. Patients with osteopetrosis tend to have pathologic fractures and a significant disease burden, requiring management by a multidisciplinary team of specialists, including orthopedists, endocrinologists, and geneticists. This case highlights the importance of considering osteopetrosis in patients with fragility fractures and high bone density despite the challenges in the absence of other clinical clues. Early diagnosis and management can help prevent recurrent fractures and improve quality of life.

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