CASE REPORT

Polyostotic Fibrous Dysplasia: Response to Zoledronic Acid

Jia Cheng Ong[1,2,4], Ahmad Hadif Zaidin Samsudin[3], Suhaimi Hussain[1,2]

[1] Department of Pediatrics, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bahru, Kelantan, Malaysia
[2] Hospital Universiti Sains Malaysia (HUSM), Health Campus, Kubang Kerian, 16150 Kota Bahru, Kelantan, Malaysia
[3] Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bahru, Kelantan, Malaysia
[4] Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, 20400 Kuala Terengganu, Terengganu, Malaysia

ABSTRACT

Fibrous Dysplasia (FD) is a rare developmental bone disorder in which fibro-osseous tissue replaces normal bone tissue. FD can manifest as either monostotic or polyostotic. Polyostotic FD is often associated with McCune-Albright syndrome (MAS). Treatment of FD varies due to its diverse clinical manifestations. Bisphosphonate therapy, with its antiresorptive properties, is commonly used as part of the treatment. Two commonly used bisphosphonates are pamidronate and alendronate. However, literature on the use of intravenous zoledronate is limited. In this report, we share our experience using zoledronate to treat polyostotic fibrous dysplasia in a 10-year-old girl.
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Corresponding Author:
Suhaimi Hussain, MD
Email: hsuhaimi@usm.my
Tel: +6097676536

INTRODUCTION

Fibrous Dysplasia primarily manifests as monostotic, while polyostotic FD is commonly associated with McCune-Albright Syndrome (MAS). MAS is diagnosed by the presence of polyostotic fibrous dysplasia, autonomous endocrine hyperfunction, and cafй-au-lait skin pigmentation. FD typically presents in the first decade of life, with an equal risk for both males and females.

FD results from a missense mutation in the gene encoding the alpha-subunit of the stimulatory G protein (Gsα) within the GNAS complex on chromosome 20q13. This mutation causes abnormal proliferation and differentiation of bone marrow stromal cells, along with increased osteoclastic activity.

Clinical features of FD include limping, pathological fractures, or discomfort affecting various bones, including long bones, craniofacial bones, and ribs. Diagnosis of FD is based on clinical and radiological examination. Treatment varies due to its diverse presentation. Fractures associated with FD can be managed through conservative measures, surgical intervention, and medical treatments such as vitamin D supplementation, bisphosphonate therapy, and analgesics.

CASE REPORT

A 10-year-old girl with an underlying right hip deformity and limping gait suffered a fracture in the midshaft of her right femur following a trivial fall. Further history revealed that she began menstruating at age 3, appeared taller than her peers, and developed breasts by age 5. Apart from these findings, her developmental history was appropriate for her age. She was the eldest of four siblings, with no similar illnesses in her family history.

On examination, prominent scoliosis was observed in the lumbar region, along with hyperpigmented patches with irregular borders on her back resembling the "Coast of Maine" appearance. Her Tanner staging indicated A2 for axillary hair, B3 for breast development, and P3 for pubic hair. Her height was 149 cm (97th centile) and her weight was 33 kg (25th centile). A comprehensive workup was conducted as she showed signs of precocious puberty, bony abnormalities, and café-au-lait skin lesions suggestive of McCune-Albright syndrome.

A skeletal survey revealed multiple patchy areas of lucency with irregular margins in the skull, pelvic bones, and bilateral radius/ulna, as well as a right midshaft femoral fracture. An MRI of the spine showed multiple bony lesions within the pelvic bones and the presence

of a left adnexal cystic lesion suggestive of an ovarian cyst. Initial blood parameters revealed normal calcium and phosphate levels but low serum vitamin D which was 21 nmol/L. Alkaline phosphatase (ALP) and intact Parathyroid Hormone (iPTH) were high. Her first Bone Mineral Density (BMD) assessment was low, indicating osteoporosis. She was diagnosed with a right femur fracture secondary to polyostotic fibrous dysplasia.

Her right midshaft femoral fracture was managed with a proximal femoral nail and valgus osteotomy of the proximal third of the right femur. She was treated with oral calcium carbonate 500 mg four times daily and oral cholecalciferol 2,000 units daily for three months. After this period, calcium carbonate was discontinued. Following three months of high dose oral cholecalciferol D at 2,000 units daily, her serum vitamin D level raised to 50 nmol/L. To maintain normal serum vitamin D level, oral cholecalciferol was continued at 1,000 units daily. Intravenous Zoledronate was initiated three months after fracture. She was given a total of five doses of intravenous zoledronate (0.0125 mg/kg) every three months, starting six months after the fracture. She tolerated the zoledronate well, with no reported side effects such as hypocalcemia, flu-like symptoms, or gastrointestinal issues. Subsequently, her zoledronate dose was increased to 0.025 mg/kg every six months. Her fracture healed, and both the fibrous dysplasia findings on radiograph (Figure 1a, 1b & 1c). Her bone parameters before and after zoledronate therapy were recorded (Figures 2a, 2b & 2c). Her BMD showed marked improvement where it increased from 0.688 g/cm^2 (T score: -3.9) to 0.887 g/cm^2 (T score: 1.2). Her responses were consistent with the findings reported by Tripathy et al. (1).

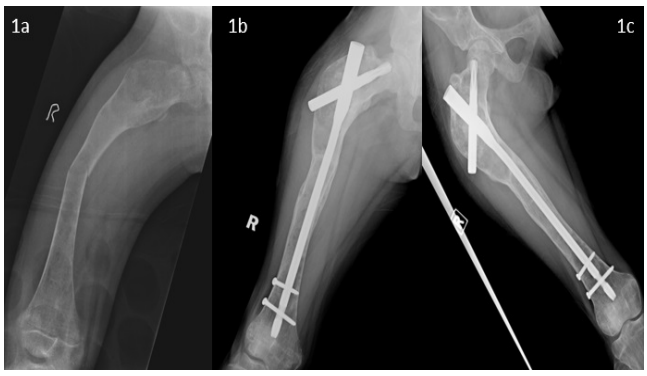


Figure 1: Initial plain radiograph (1a) shows expansile lytic lesion of the proximal right femur with ground glass opacities and present of mid femoral fracture. On subsequent follow-up (1b & 1c), the lytic lesion appears to be reducing in size and increased in the bone density as well as appear to be more homogenous. The fracture line had disappeared on the latest radiograph.

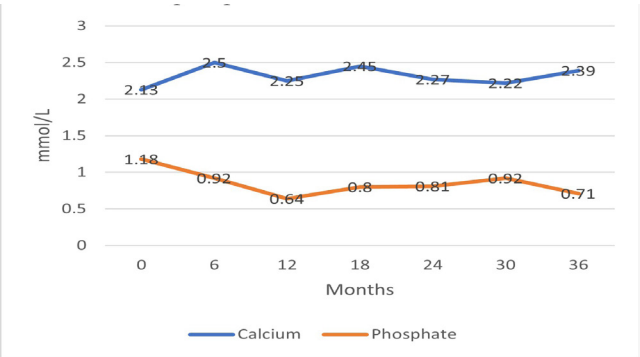


Figure 2a: Changes of serum calcium and phosphate after zoledronate

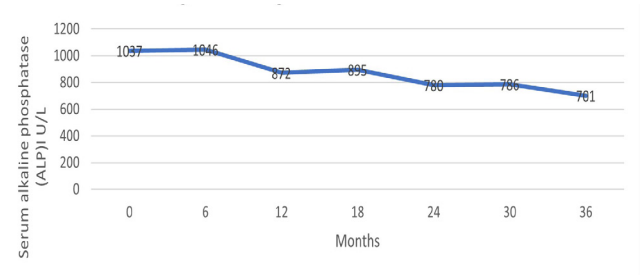
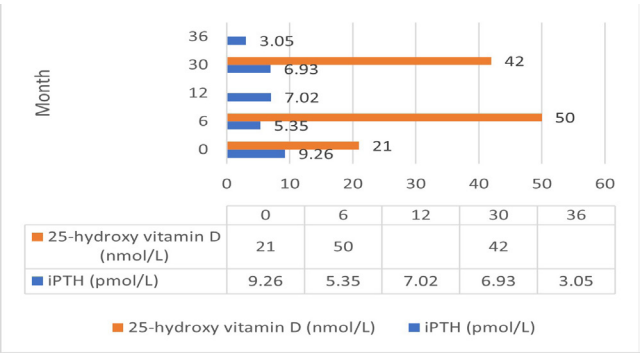


Figure 2b: Changes of ALP after zoledronate



	0	6	12	30	36
25-hydroxy vitamin D (nmol/L)	21	50		42	
iPTH (pmol/L)	9.26	5.35	7.02	6.93	3.05

Figure 2c: Changes of vitamin D and iPTH after zoledronate

DISCUSSION

Bisphosphonates increase bone mineralization by inhibiting bone resorption. Although bisphosphonates have been used to treat fibrous dysplasia in multiple studies, literature on the use of intravenous zoledronic acid in children is limited. Zoledronate is a potent third-generation bisphosphonate that can be administered every 6 months, whereas pamidronate requires monthly or tri-monthly administrations. Oral administration of alendronate can impact compliance. Both pamidronate and zoledronate have shown similar effects on bone turnover rates, with no disruption to children's linear growth. Oral alendronate is considered inferior to

intravenous bisphosphonates, as it suppresses bone resorption markers more slowly and carries a higher risk of gastrointestinal side effects such as nausea, constipation, and diarrhea (1).

Several studies have discussed the efficacy of intravenous zoledronic acid in treating fibrous dysplasia. Lala et al. treated nine children with moderate to severe fibrous dysplasia using intravenous pamidronate and observed promising results, including resolution of bone pain, absence of new fractures, reduction in alkaline phosphatase levels, and increased bone mineral density (2). We observed a similar response in our patient with zoledronate therapy. Pamidronate can serve as a suitable alternative to zoledronate if the latter is unavailable. However, Plotkin et al. reported no observable difference in histomorphometric findings in fibrous dysplasia tissue between patients receiving pamidronate and untreated patients (1).

Wu et al. treated a case of polyostotic fibrous dysplasia with intravenous zoledronate (5 mg per year) (4). The patient showed improvements in bone pain and filling of bone defects, with decreased bone resorption markers such as serum collagen type 1 cross-linked C-telopeptide and type 1 procollagen N-terminal (P1NP). Unfortunately, these markers are not available for measurement at our center. Ganda et al. used zoledronate to treat fibrous dysplasia in two patients, aged 44 and 48 years, respectively (3). However, the desired responses such as a decrease in bone resorption markers and improvement in clinical condition were not observed, likely due to the severity of fibrous dysplasia in these older patients (3).

The decision to discontinue bisphosphonate infusion remains challenging due to limited evidence regarding the long-term use of zoledronate. Corsi et al. reported the presence of "zebra lines" in radiographs of bones affected by fibrous dysplasia after pamidronate infusion, reflecting the progressive substitution of normal bone with fibrous dysplasia-affected bone (5). Improvement in bone mineral density and bone markers can also serve as parameters for determining the continuation of bisphosphonate therapy. A collective decision should be based on both biochemical and radiological changes. Further follow-up is necessary, as fibrous dysplasia is known to cause lifelong disease.

CONCLUSION

The administration of intravenous zoledronate enhances bone mineral density and demonstrates improvements in bone biomarkers. It was well tolerated and should be considered for use in McCune-Albright syndrome with fibrous dysplasia of the bone.

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