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CASE REPORT

Radiological Zebra Lines Correspond to Bisphosphonate Administration in Children with Osteogenesis Imperfecta

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ABSTRACT

Bisphosphonates are widely used in the treatment of osteogenesis imperfecta due to their action of limiting bone resorption by inhibiting osteoclast activity. Sclerotic bands, which are known as metaphyseal lines, are observed in the metaphysis of the long bones in paediatric patients treated with bisphosphonates for osteogenesis imperfecta before closure of the growth plate, and the number of metaphyseal lines corresponds to the number of treatment cycles. Metaphyseal lines are sometimes called 'radiological zebra lines'. This report of two paediatric patients with osteogenesis imperfecta receiving cyclic bisphosphonates describes the pattern of radiological zebra lines corresponding to bisphosphonate administration. The distances between the lines show an increasing interval towards the diaphysis in growing bones.

Key Words: *Bone density conservation agents; Child; Diphosphonates; Osteogenesis imperfecta*

中文摘要

兒童成骨不全症患者雙磷酸鹽類藥物治療相應的放射性斑馬線現象

王馨藝、T Nozaki、M Matsusako、I Kusakawa

雙膦酸鹽能抑制破骨細胞的活性從而限制骨吸收，所以被廣泛用於治療成骨不全症。硬化帶又稱為幹骺端線，可在接受雙膦酸鹽治療的成骨不全症兒童患者的長骨骺板閉合前觀察到；其數目與療程數目相對應。幹骺端線有時也被稱為「放射性斑馬線」。本文報告兩名接受週期性雙膦酸鹽治療的兒童成骨不全症患者，描述相應放射性斑馬線的形態。對於生長期的骨幹，斑馬線之間的間距會越來越大。

INTRODUCTION

The first bisphosphonate was introduced for skeletal disorders more than 30 years ago. Bisphosphonates have been used as the mainstay of treatment for osteogenesis imperfecta (OI) for the past decades, and their use is increasing because of the proven clinical benefits. OI is a heritable skeletal disorder caused by mutation in the gene encoded for type I collagen. The condition is characterised by repeated fractures, skeletal deformities, and osteopenia. Bisphosphonates inhibit osteoclast activity and limit osteocyte apoptosis, interfering with bone remodelling by suppressing bone resorption.[1] At

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the St Luke's International Hospital in Tokyo, Japan, pamidronate — a second-generation bisphosphonate — is given to patients with OI in cyclic doses of 0.5 mg/kg/day by intravenous infusion over 6 hours; each cycle involves 3 consecutive days of treatment at 3- or 4-monthly intervals. Multiple thin sclerotic metaphyseal lines parallel to the growth plates are observed in OI patients receiving bisphosphonate treatment. They are sometimes called 'radiological zebra lines'. This report presents two patients with this finding and describes the pattern of radiological zebra lines corresponding to bisphosphonate administration.

CASE REPORTS

Patient 1

A 4-year-old boy, who had a family history of OI from his mother and maternal grandmother, has been treated for 4 years from his first onset at 3 months old. He was found to have blue sclera at birth, which is a feature of OI. At the age of 3 months, he fractured his left humerus and was diagnosed with OI. He started treatment with pamidronate at the age of 8 months and had completed 12 cycles of treatment at the time of writing. Radiographs of the patient's lower limbs showed the characteristic radiological zebra lines in the metaphysis of the long bones, which corresponded to the cycles of bisphosphonate administration, with each sclerotic line representing 1 cycle (Figure 1). The distances between the radiological zebra lines were similar during the first few cycles in his early life, and the lines moved towards the diaphysis with skeletal growth and bone lengthening. The distances between the lines due to earlier bisphosphonate treatment gradually appeared wider than those due to more recent treatment (Figure 1b). The patient's clinical course and treatment cycles are shown in the timeline in Figure 2.

Patient 2

A 9-year-old boy with unprovoked fracture in the left femur at birth was diagnosed with OI at the age of 1 month and has been treated for 9 years. He received the first dose of pamidronate at the age of 5 years and has now had 10 treatment cycles. Anteroposterior radiographs of the pelvis and both femurs taken after the 6th cycle of pamidronate showed six radiological zebra lines parallel to the growth plates in the bilateral distal femurs, and also in the apophysis, the equivalent of the growth plate, in the bilateral iliac crests (Figure 3). After 9 cycles of bisphosphonate treatment, there were nine radiological zebra lines in the distal metaphysis of the femur. Skeletal deformities and multiple fractures were detected in the long bones, all relating to OI (Figure 3c). The medication profile and its relationship with the radiological findings are shown in Figure 4.

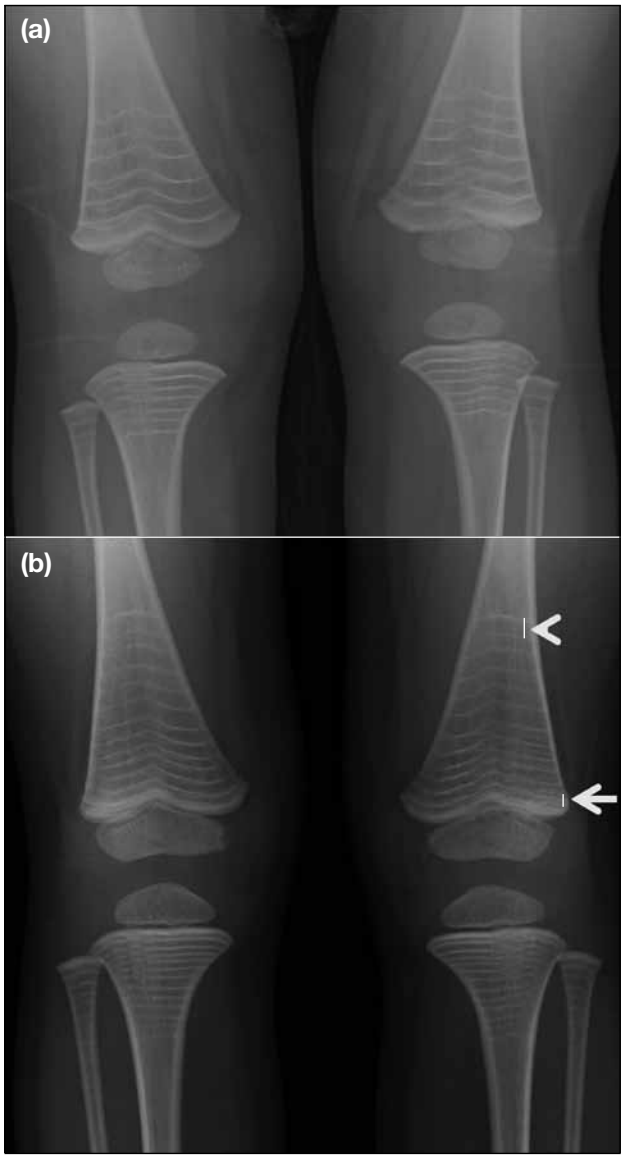

Figure 1. Anteroposterior radiographs of both knees of patient 1 after multiple cycles of bisphosphonate administration for osteogenesis imperfecta. (a) At the age of 1 year and 11 months, after 6 cycles of intravenous pamidronate, it shows symmetrical dense lines at the metaphysis of the bilateral femur, tibia, and fibula. The lines run parallel to the configuration of the growth plates and the distance between the lines appears similar and measures about 4 mm. The number of lines corresponds to the number of treatment cycles. (b) At the age of 3 years and 6 months, after 12 cycles of pamidronate, it shows dense transverse lines in the metaphysis of the bilateral distal femur, proximal tibia, and fibula. The distance between the lines varies with skeletal maturation. The spacing of the lines closest to the growth plate measures about 1.6 mm (arrow) and the spacing of the lines away from growth plate in the distal femur measures about 5 mm (arrowhead). The number of lines corresponds to the number of treatment cycles.

DISCUSSION

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphonate that binds hydroxyapatite. Bisphosphonates inhibit osteoclast activity and limit osteocyte apoptosis, thereby suppressing bone resorption. In the setting of abnormal collagen matrix such as OI, these functions allow bone-forming osteoblasts more time to promote bone formation.[2] Bisphosphonates are mainly used to increase bone density in adult patients with osteoporosis or bony metastasis, where they have a demonstrated effect of preserving bone structure. In the past decade, studies have shown that bisphosphonates can also decrease the incidence of fracture in paediatric patients with OI.[3] Therefore, bisphosphonates are given as treatment for OI. Since more treatment centres have started to prescribe this class of drugs, there has been an increased incidence of the characteristic radiological zebra lines

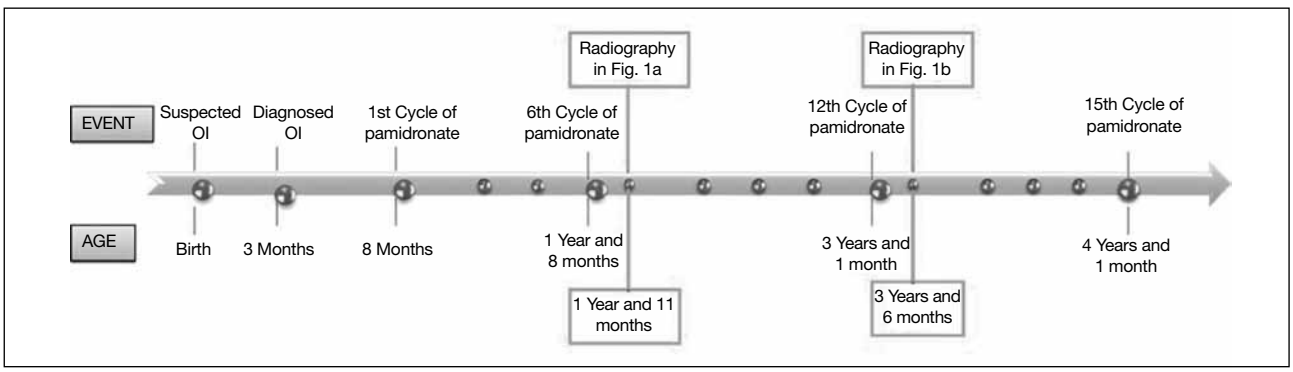

Figure 2. Timeline showing the clinical course of patient 1 and the relationship between radiological findings and treatment cycles. The small circles without labelling correspond to clinical follow-ups and injections between the significant treatment cycles. Abbreviation: OI = osteogenesis imperfecta.

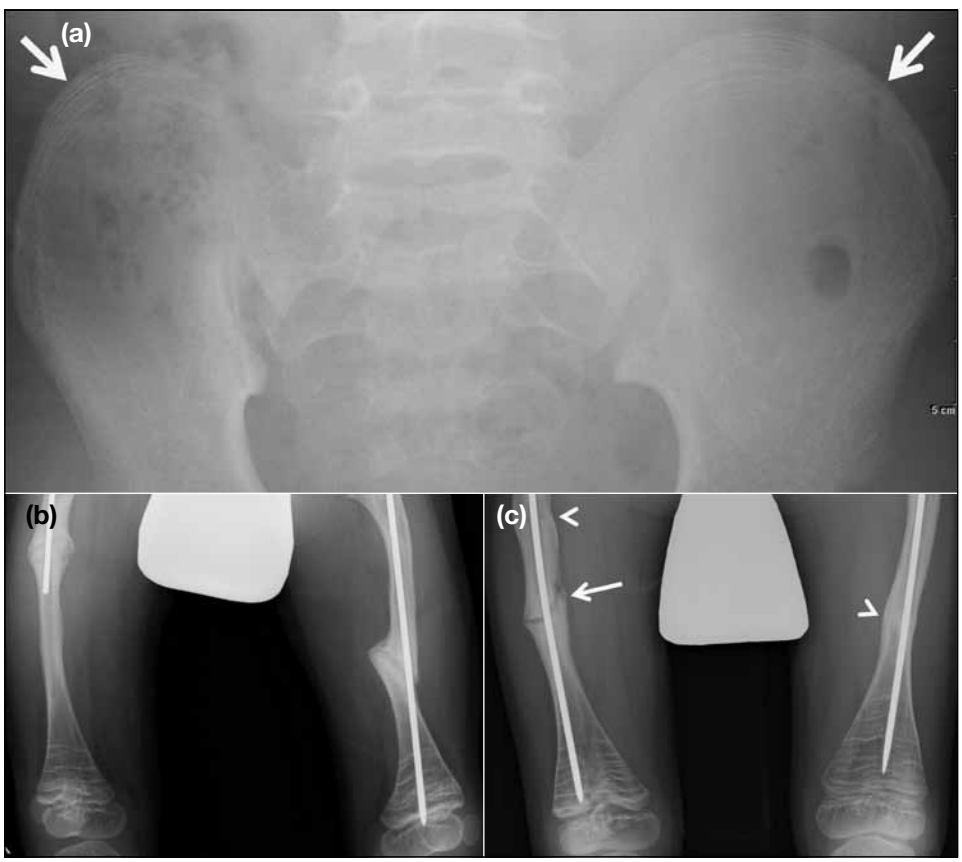

Figure 3. Anteroposterior radiographs of patient 2 after multiple cycles of bisphosphonate administration for osteogenesis imperfecta. (a) The pelvis after 6 cycles of pamidronate shows 6 parallel sclerotic lines in the bilateral iliac crest (arrows) along the apophysis. (b) Both femurs after 6 cycles of pamidronate show zebra lines parallel to the growth plates of the bilateral distal femurs. There are metallic pins for previous fractures in both femoral shafts. The long bones show bowing deformity and generalised osteopenia, which are features of osteogenesis imperfecta. (c) Both femurs after 9 cycles of pamidronate show that the number of zebra lines in the distal metaphysis of the femurs also increased to 9. The previous fractures in the femoral shafts have healed (arrowhead), but there is a new fracture in the right femoral shaft (arrow).

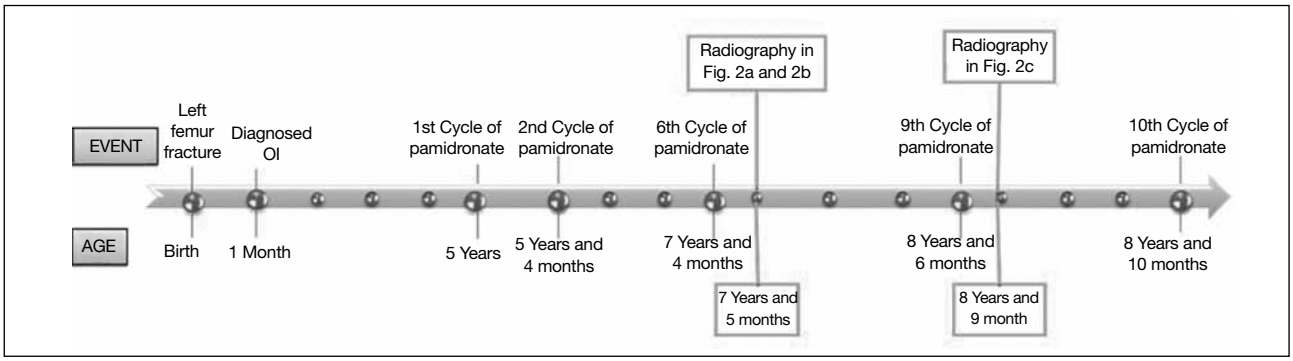

Figure 4. Timeline showing the clinical course of patient 2 and the relationship between radiological findings and treatment cycles. The small circles without labelling correspond to clinical follow-ups and injections between the significant treatment cycles. Abbreviation: OI = osteogenesis imperfecta.

relating to bisphosphonate use. The net benefit-risk of long-term bisphosphonate use remains unclear as recent studies have reported various complications in patients receiving long-term bisphosphonate therapy.[4] Rosenberg et al[5] reported atypical femoral fractures with features of lateral cortical thickening, transverse orientation, or lack of comminution in a group of patients treated with bisphosphonates. However, a population-based nationwide analysis from Sweden concluded that the absolute risk of atypical fractures associated with bisphosphonates for patients at high risk for osteoporotic fracture was small compared with the benefits of treatment.[6]

Approximately 70% of bone strength is due to bone mineral density, and the remaining 30% to bone quality. Bisphosphonates increase bone mineral density, but decrease bone quality. A side-effect of bisphosphonate therapy is oversuppression of bone turnover. Prolonged inhibition of osteoclasts leads to 'frozen bone', characterised by enhanced bone density and increased skeletal fragility due to suppressed bone remodelling.[2] Long-term accumulation of bisphosphonates causes defects in osteoclast activity and produces secondary osteopetrosis, resulting in gradual sclerotic change and fraying in the metaphysis.[7] In these two patients, before commencement of treatment, the characteristic radiographical findings were osteopenia, fractures with deformity, and bowing of the long bones. After treatment with intravenous bisphosphonates, the most prominent findings were multiple thin sclerotic metaphyseal lines in all of the long bones, and in metaphyseal-equivalent sites such as the iliac crest apophysis. The sclerotic lines were parallel to the growth plates and corresponded to the number of treatment cycles. The spacing between the lines varied. The separation depends on the growth rate of the bone and the age of the patient at the time of drug administration. The metaphyseal lines are manifestations of cyclic bisphosphonate therapy,[8] with the number of lines corresponding to the number of treatment cycles and time of administration. The lines become more obvious over time as growth separates them from the zone of provisional calcification.[9] The sclerotic lines reflect decreased osteoclastic activity in response to the drug's effects,[10] and each line corresponds to unresorbed cartilage owing to the inhibition of osteoclasts.[11] The sclerotic lines become denser over time, and the older lines appear more sclerotic than the younger lines. The distances between the lines vary depending on the rate of growth, for example, younger children who grow more rapidly may have wider line spacing than older patients. In a single patient, a period of rapid growth makes the line distance wider than that for a period of slow growth. The spacing between the lines indicates resumption of osteoclast activity and linear growth of the bones between treatments.[9]

In conclusion, the characteristic radiological findings in children receiving cyclic bisphosphonate therapy include sclerotic zebra lines in the metaphysis parallel to the growth plate, and the number of lines corresponds to the number of treatment cycles. With an increasing number of paediatric patients receiving bisphosphonates for OI or other indications, radiologists need to become familiar with the characteristic features of bisphosphonate treatment.

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