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# Pamidronate "zebra lines": A treatment timeline

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ABSTRACT

Osteogenesis imperfecta is a hereditary bone dysplasia characterized by bone fragility, deformity, and short stature. Treatment focuses on preventing bone fractures and symptom relief. Pamidronate, a second-generation bisphosphonate drug that minimizes bone loss, is the chosen treatment in osteogenesis imperfecta. Radiologically, each cycle of pamidronate treatment is depicted as a line of sclerosed nondecalcified cartilage at the metaphysis, termed a pamidronate line. In this case report, we demonstrate that a treatment timeline can be visualized on plain radiographs as the number and spacing of pamidronate lines reflects the number and timing of treatment cycles. The educational value of this is to reassure physicians of the benign nature of "zebra lines," to demonstrate that the pamidronate lines migrate and fade with bone growth, and alert physicians that the lack of expected pamidronate lines during treatment may reflect a change in the patient's condition that reduces the effectiveness of bisphosphonate infusions.



## Introduction

Osteogenesis imperfecta (OI) is a skeletal dysplasia characterized by fractures due to bone fragility, with variable features of blue sclera, bone deformity, short stature, ligamentous laxity, and dental abnormalities (dentinogenesis imperfecta) [1]. Mutations in the alpha 1 and alpha 2 chains of Collagen Type 1 (*COL1A1* and *COL1A2*) account for 80%-90% cases but with intriguing heterogeneity. The original 1979 Sillence OI classification system remains useful [2]. Recent nomenclature revision occurred to reflect the complexity of now 19 different genes implicated in OI [3]. Nevertheless, it largely retains categorization according to clinical severity with Type 1 the mildest form, Type 3 severely progressively deforming, and Type 2 lethal. Multidisciplinary team management of patients with OI has significantly developed over recent years, encompassing bone strengthening medical treatments, orthopedic interventions, and comprehensive therapy inputs. Management focuses on reducing fractures, limb

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deformity, and pain, with the aim of improving patient's quality of life.

Bisphosphonates are the main medical treatment in OI, with intravenous pamidronate, a second-generation bisphosphonate, the most widely used approach [4]. Pamidronate is administered as regular infusions over several years to increase bone mineral density and reduce fractures. At a cellular level, pamidronate reduces osteoclast activity which minimizes bone loss. Each pamidronate infusion interrupts the active osteoblast front within the growth plate from decalcifying the growth plate cartilage during cell turnover [5]. These rows of sclerosed nondecalcified cartilage present as lines of cartilage calcification persisting from metaphysis into diaphysis, termed pamidronate lines. In a child's growing skeleton, bone growth takes each pamidronate line up into the diaphysis, and each round of treatment brings a new pamidronate line. These parallel lines progressively result in a "zebra line appearance." The number and spacing of pamidronate lines reflects the number and timing of treatments, much like tree-rings reflect the age of a tree as well as the amount of growth in a year. With time, they disappear as the calcified cartilage moves from the metaphysis into the diaphysis, and they are gradually converted into bone [5,6]. The pamidronate lines are not correlated with worsening pathology in children with OI; they are a radiological finding that reflects the effective administration of the bisphosphonate infusion and should not be the cause of alarm in physicians.

## Case report

This 9.5-year-old Caucasian boy was noted at birth to have positional talipes equinovarus, joint laxity, large anterior fontanelle, and blue sclerae. The patient experienced his first low trauma fracture of right tibial shaft fracture when he was 6 months old, with minimal handling. Family history indicated a large pedigree with many affected members with osteogenesis imperfecta type 1 with an inheritance pattern consistent with the expected autosomal dominant nature of Type 1 OI. By the age of 6-10 months, the patient had 7 fractures due to minimal trauma. The fractures were mainly of the lower limb bones, specifically the tibia, fibula, and metatarsals. Two fractures were found in larger bones such as the femur and pelvis. Physical examination at birth revealed features supportive of a diagnosis of OI. Clinical features during childhood were similarly consistent: hypermobility, pes planus, and mild lumbar scoliosis.

Radiological evidence showed features of OI, such as the presence of Wormian bones on lateral skull radiographs. However, radiographs do not provide an accurate assessment of bone density. Bone densitometry was assessed using dual-energy X-ray absorptiometry. At aged 3.6 years it showed total body bone mineral density z-score +0.7 SDS and lumbar (L1-L4) bone mineral density z-score +1.4 SDS. These values are within the normal range, which can occur in OI. Dual-energy X-ray absorptiometry is a proxy marker for bone strength, although the collagen abnormality present in OI affects bone quality and strength and not always density. Genetic studies indicated that the patient had the same mutation as other affected family members and was heterozygous for c.3584G>A, p.C1195Y mutation within the *COL1A1* gene.

The diagnosis of OI Type 1 is largely made on clinical grounds. The patient's clinical history and examination were indicative of OI. Genetic studies are not a prerequisite for the diagnosis of Type OI, although they are increasingly undertaken in today's practice. Genetic studies cannot predict clinical severity in fracture frequency. There is significant clinical heterogeneity even within individuals affected with the same mutation in 1 kindred, as was the case in this pedigree. Bisphosphonate therapy is not used prophylactically in pediatric OI, but this patient's frequent fragility fractures in infancy crossed the threshold to recommend bisphosphonate therapy which is now a well-accepted form of treatment [7].

The patient commenced a standard course of pamidronate infusions. The patient's radiographs provide a visual story of his pamidronate treatment (Fig. 1). Over 3 years, the patient received 8 cycles (1 mg/kg/day for 3 consecutive days) of pamidronate. Treatment was interrupted for 3 years due to severe procedural anxiety around cannulation, giving "pamidronate-free" bone formation over that period. The patient

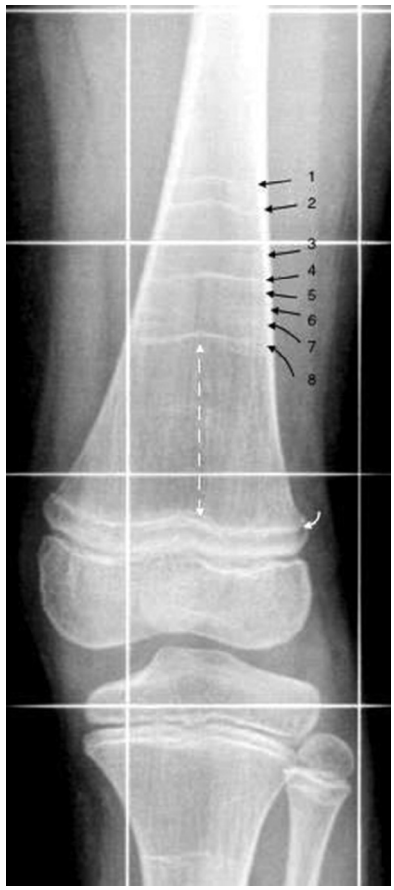


**Fig. 1 – Radiograph of the left knee taken aged 7.25 years. Black arrows indicate 8 dense parallel pamidronate lines in the distal femoral and proximal tibial diaphysis, each corresponding to a treatment cycle (numbered from oldest to most recent). The ensuing 3-year treatment discontinuation corresponds to the lower density bone (broken 2-headed arrow). This radiograph was taken 6 months after recommencing pamidronate infusions and re-institution (white arrow).**