

BRIEF REPORT

Bisphosphonate-Induced Osteopetrosis

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BISPHOSPHONATES, SYNTHETIC ANALOGUES OF INORGANIC PYROPHOSPHATE, potentially inhibit skeletal resorption by suppressing the recruitment and activity of osteoclasts and shortening their life span.¹ Consequently, several bisphosphonates were developed to treat hypercalcemia (associated with cancer), osteoporosis, and Paget's disease of bone and are used for additional disorders in adults.¹ Increasingly, bisphosphonates are being administered to children²⁻⁴ and have been reported to improve clinical outcomes and augment bone mass in conditions such as osteogenesis imperfecta,⁵ juvenile osteoporosis,² and fibrous dysplasia,⁶ although controlled studies of these compounds in children are lacking.^{3,4,7} Genetic defects that abrogate the action of osteoclasts cause osteopetrosis, which is characterized by dense, poorly formed, and brittle skeletal tissue.⁸ Acquired osteopetrosis, or marble bone disease, could therefore result from treatment with bisphosphonates during growth. Here, we document a case of drug-induced osteopetrosis.

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CASE REPORT

A 12-year-old white boy, referred to us for unexplained skeletal pains and markedly elevated serum alkaline phosphatase activity, first began to limp as a result of left-hip discomfort after unobserved playground trauma at the age of 5 years. The symptoms subsequently became intermittent but intensified and included pain deep in the left thigh and leg. A finding of hyperphosphatasemia (alkaline phosphatase level, approximately 1400 U per liter; normal level, <350), reflecting bone alkaline phosphatase, prompted a biochemical assessment of mineral homeostasis, skeletal radiography and scintigraphy, and magnetic resonance imaging. Only possible synovitis of the left hip was identified. Nevertheless, the child's condition improved little with analgesics and nonsteroidal antiinflammatory drugs.

At six years of age, his right distal radius healed uneventfully after substantial trauma; however, his fingertips also reportedly broke after a minor injury. At 7½ years of age, the results of dual-energy x-ray absorptiometry were interpreted as showing low density of the lumbar spine, although the z score was -1.0. Extensive investigations included tests for osteogenesis imperfecta, lysosomal storage diseases, rheumatologic diseases, mitochondrial-gene defects, and aminoaciduria, all of which were negative. The results of karyotyping and electromyography with nerve-conduction velocity were normal. Bone antiresorptive therapy was begun with intranasal salmon calcitonin daily for one month to treat "idiopathic hyperphosphatasia," yet urinary excretion of total hydroxyproline was 58 mg per day (442 μmol per day; normal level, 23 to 77 mg [175 to 587 μmol] per day), and the serum osteocalcin level was 12 ng per milliliter (normal level, 18 to 24), reflecting no acceleration of skeletal turnover. The boy's pain diminished, but serum alkaline phosphatase activity did not decrease. Soon after, discomfort provoked by exercise intensified and included his right lower limb.

At 7¾ years of age, his antiresorptive treatment was changed to pamidronate (Aredia, Novartis). Initially, a dose of 10 mg (0.37 mg per kilogram of body weight) infused intravenously on three consecutive days seemed to diminish the intensity, duration, and

frequency of his pain. However, worsening symptoms prompted a second course involving a total of 60 mg. A calcium supplement was also prescribed because “food allergies” compromised his diet.

By eight years of age, he was receiving a 60-mg dose of pamidronate intravenously over a three-hour period approximately every three weeks. This treatment failed to abolish his episodic pains, although the serum alkaline phosphatase level decreased to approximately 800 U per liter. The dose of pamidronate was increased to 80 mg and then to 100 mg (2.8 and 3.4 mg per kilogram, respectively), infused over a period of four to five hours, but it was reportedly administered somewhat less regularly.

Mild, idiopathic thrombocytopenia (80,000 to 150,000 platelets per cubic millimeter) with large circulating platelets had been documented since early childhood. Tests for antiplatelet antibodies were negative. Bone marrow biopsy at 8½ years of age revealed normocellular marrow with increased megakaryocytes.

At 10 years of age, a wedge biopsy of the iliac crest revealed “rock-hard” bone. The histopathology report described some peritrabecular fibrosis consistent with the presence of hyperparathyroidism, without impaired mineralization of the skeletal matrix (osteomalacia). At 10½ years of age, pamidronate treatment was stopped because the boy’s bones appeared radiographically dense and “saturated.” The nadir serum alkaline phosphatase level was 525 U per liter. Mildly elevated serum parathyroid hormone levels were noted, reflecting secondary hyperparathyroidism. The results of screening for fluorosis and exposure to heavy metals were negative. At 11 years of age, during a smooth automobile ride, the boy suddenly began to have intense, low back pain, which persisted for several days. Radiographs showed bilateral pars defects (spondylolysis) at L4. Subsequently, he took oral analgesics or a cyclooxygenase-2 inhibitor occasionally. A few salmon calcitonin injections were given when he was 11½ years of age and seemed helpful, but side effects limited the dose. We first saw the boy 18 months after his last dose of pamidronate, after all medications and supplements had been stopped for at least 2 weeks.

METHODS

Analyses included laboratory measurements, agarose-gel electrophoresis of alkaline phosphatase, a review of radiologic examinations and biopsy spec-

imens, and dual-energy x-ray absorptiometry (model QDR-4500A, Hologic). To rule out an unlikely forme fruste of progressive diaphyseal dysplasia or juvenile Paget’s disease (idiopathic hyperphosphatasia)^{9,10} — disorders involving hyperphosphatasemia, bone thickening, and skeletal pain — or autosomal dominant (“benign”) osteopetrosis, we used the polymerase chain reaction to amplify and sequence exons and splice junctions of the genes encoding transforming growth factor β 1, osteoprotegerin, and chloride channel 7.¹¹⁻¹³ To investigate our patient’s hyperphosphatasemia, we analyzed the gene encoding the tissue-nonspecific (bone) isoenzyme of alkaline phosphatase (TNSALP) and its promoter.¹⁴

RESULTS

Physical examination when the patient was 12 years of age showed an engaging, nondysmorphic, prepubertal boy (75th percentile for height and head circumference and 60th percentile for weight) who appeared well and was without pain. His wrists flared slightly. Skeletal percussion and compression elicited no discomfort. Some low back aching followed spinal flexion.

Agarose-gel electrophoresis (Quest Diagnostics) of serum alkaline phosphatase measuring 1493 U per liter (normal range, 133 to 347) revealed 90 percent bone isoform and 10 percent liver isoform. Other biochemical indicators of mineral and skeletal homeostasis were essentially unremarkable while the boy consumed a gelatin-free diet with average ad libitum calcium levels of approximately 1100 mg daily (recommended daily allowance, 1500) (Table 1). Urinary osmolality, creatinine clearance, and protein excretion were normal. Notably, as in heritable forms of osteopetrosis,⁸ serum acid phosphatase activity was considerably elevated at 25 U per liter (normal value, <6) (Table 1), and the brain isoenzyme of creatine kinase (BB-CK), also expressed in osteoclasts, was detectable (constituting 39 percent of normal serum total creatine kinase activity).¹⁵

A review of skeletal radiographs obtained before the start of antiresorptive therapy showed no deformities or evidence of disease (Fig. 1A). Sequential bone scans obtained between the ages of six and nine years were also unrevealing. During prolonged pamidronate therapy, however, remarkable changes occurred, especially in the long bones. When the boy was 12 years old, the metaphyses were dense

with club-shaped deformities indicating osteopetrosis (Fig. 1B and 1C). The base of the skull had also become sclerotic. The height of vertebral bodies seemed diminished, and end-plate thickening appeared without any “bone-in-bone” (“endobone”) configuration to indicate congenital osteopetrosis (Fig. 1D).⁸ Our radiographic studies showed that there was no resolution of osteosclerosis subadjacent to epiphyses, despite the fact that pamidronate treatment had been discontinued 18 months earlier and despite the occurrence of recent linear growth averaging 7 cm (2¾ in.) yearly. Scintigraphy with technetium-99m–labeled methylenediphosphonate showed symmetric, enhanced uptake in the metaphyses, but no evidence of an acute fracture at L4 or elsewhere (Fig. 1E). Abdominal sonography revealed no renal, hepatic, or splenic abnormality.

Dual-energy x-ray absorptiometry demonstrated bone mineral density values of 0.861 g per square centimeter at L1 through L4, 1.041 g per square centimeter for the total hip, and 1.048 g per square centimeter for the whole body, reflecting age-matched z scores for boys of +0.67, +2.3, and +2.5, respectively.¹⁷ Review of the bone marrow–biopsy specimen obtained after nine months of exposure to pamidronate disclosed an “osteopetrotic process” characterized by delayed removal of calcified primary spongiosa by osteoclasts (Fig. 2A). The iliac-crest sections, obtained after 2¼ years of bisphosphonate treatment, contained these cartilage “bars” throughout — the hallmark of osteopetrosis (Fig. 2B and 2C).⁸ Osteoclasts were not on the bone surfaces, were abnormally rounded, and had nonpolarized nuclei (Fig. 2C, inset). Both biopsy specimens comprised only lamellar bone.

A review of the child’s pharmacy records, which were available only from the age of nine years onward, showed that 2800 mg of pamidronate had been dispensed. There was no family history of skeletal disease or consanguinity. Neither his parents nor his sister had hyperphosphatasemia. His mother’s serum acid phosphatase activity and findings on dual-energy x-ray absorptiometry were unremarkable. Genetic studies revealed no mutation in the genes for transforming growth factor β 1, osteoprotegerin, chloride channel 7, or the tissue-nonspecific isoenzyme of alkaline phosphatase or its promoter.

DISCUSSION

Although we cannot unequivocally explain our patient’s symptoms and persistent hyperphosphata-

Table 1. Results of Studies of Mineral and Skeletal Homeostasis.*

Measurement	Patient's Value	Reference Range
Fasting serum		
Calcium (mg/dl)	9.1	9.4–10.6
Ionized calcium (mg/dl)	4.9	4.9–5.4
Phosphate (mg/dl)	4.4	4.3–5.7
Intact parathyroid hormone (pg/ml)	92	7–53
Alkaline phosphatase (U/liter)	1493	133–347
Bone-specific alkaline phosphatase (U/liter)†	746	47–181
Osteocalcin (ng/ml)	124	15–103
Acid phosphatase (U/liter)	25	<6‡
Creatine kinase (U/liter)	106	0–200‡
Collagen cross-linked N-telopeptide (nmol of bone collagen equivalents/liter)	50	11–23‡
24-Hour urine		
Total hydroxyproline (mg/day)	92	68–169§
Calcium (mg/g of creatinine)	104¶	30–662
Collagen cross-linked N-telopeptide (nmol of bone collagen equivalents/mmol of creatinine)	197	91–1115§**
Free deoxyypyridinoline (nmol/mmol of creatinine)	17	2–58§

* Studies were conducted 18 months after the last infusion of pamidronate. To convert values for serum calcium to millimoles per liter, multiply by 0.250. To convert values for phosphate to millimoles per liter, multiply by 0.3229. To convert values for hydroxyproline to micromoles per day, multiply by 7.626. Unless otherwise stated, normal ranges for fasting blood and 24-hour urine collections are the mean (\pm 2 SD) values for 20 healthy children (age, 4.6 to 12.9 years) and 33 healthy children (age, 0.5 to 14.5 years), respectively, receiving ad libitum diets in St. Louis.

† The Metra Biosystems assay was used.

‡ The reference range is that of Quest Diagnostics and refers to adults.

§ The reference range is that of Quest Diagnostics and refers to children.

¶ The value is the average of three collections.

|| Values are log-transformed.

** Values were obtained from a random sample.

tasemia, clinical, biochemical, radiologic, and densitometric studies predating antiresorptive therapy showed no evidence of skeletal disease. In fact, two markers of bone remodeling (turnover) — urinary hydroxyproline and serum osteocalcin levels — which are often elevated in the presence of skeletal pain and hyperphosphatasemia, were not increased for his age. In addition, genetic studies for candidate heritable diseases, including juvenile Paget’s disease (osteoprotegerin deficiency),^{9,12} were negative. Familial idiopathic bone pain,¹⁸ as well as familial or sporadic unexplained elevations in

serum alkaline phosphatase activity,⁹ has been described, and the findings in our patient could represent “isolated hyperphosphatasemia,” characterized by Kruse in 1985.¹⁹

Nevertheless, unquestionable evidence of osteopetrosis developed in this boy over a period of 2 $\frac{3}{4}$ years, coinciding with the administration of pamidronate. First, his long bones failed to model properly. Normally shaped metaphyses became characteristically club-like owing to defective osteoclast action, which impairs tubulation. However, widened medullary cavities indicated some resorption on endosteal bone surfaces. Second, bone densitometry showed a supranormal whole-body value. Third, BB-CK (the creatine kinase isoenzyme of osteoclasts) was present in serum — a hallmark of osteopetrosis among sclerosing bone disorders.¹⁵ Furthermore, serum acid phosphatase (which is rich in osteoclasts) was substantially elevated — another feature of osteopetrosis.⁸ Fourth, skeletal histopathological analysis revealed that primary spongiosa, the cartilage scaffolding for osseous tissue produced during endochondral-bone formation, did not disappear during pamidronate therapy, but instead became encased and persisted within trabecular bone.⁸

We uncovered no evidence that our patient had a forme fruste of heritable osteopetrosis unmasked by pamidronate therapy. There are at least eight human phenotypes of osteopetrosis.⁸ Three molecular defects have been identified that compromise the genes encoding carbonic anhydrase II, chloride channel 7, and a proton-pump subunit; together these proteins enable osteoclasts to secrete acid.^{8,13} Albers-Schönberg disease,⁸ which is a relatively mild autosomal dominant form of osteopetrosis that is due to a mutation in the gene for chloride channel 7, occasionally skips generations.²⁰ However, this form of osteopetrosis was ruled out by genetic testing in our patient.¹³ Finally, his intermittent skeletal pain and marked hyperphosphatasemia are not features of osteopetrosis,⁸ and his family was unaffected.

Our patient, who had acquired osteopetrosis, has not had any of the principal manifestations of congenital types of osteopetrosis, such as short stature, ankylosed teeth, cranial-nerve palsy, and skeletal deformity.⁸ Nor has there been compromised hematopoiesis with myelophthisis leading to extramedullary hematopoiesis and hepatosplenomegaly.⁸ Perhaps such complications did not occur because osteopetrosis developed between 7 $\frac{3}{4}$ and

Figure 1 (facing page). Radiologic Studies Obtained When the Patient Was 8 Years Old (Panel A), 9 Years Old (Panel B), 12 Years Old (Panels C, D, and E), and 12 $\frac{1}{2}$ Years Old (Panel F).

In Panel A, the patient's left distal femur is unremarkable at eight years of age. There is no metaphyseal clubbing or splaying to indicate congenital osteopetrosis⁸ or diaphyseal thickening or widening to indicate juvenile Paget's disease.¹⁶ In Panel B, at nine years of age, there is an area of dense horizontal banding in the metaphysis (brackets) extending from the growth plate, reflecting 1 $\frac{1}{4}$ years of exposure to pamidronate. The margins of the epiphyses are sclerotic. There is early failure of modeling (shaping) in the metaphyses. In Panel C, at 12 years of age, there is a severe modeling defect characterized by club-shaped metaphyses and marked osteosclerosis, including sclerotic bands, 18 months after the last infusion of pamidronate (total duration of therapy, 2 $\frac{3}{4}$ years). The epiphyses have wide, peripheral, sclerotic bands and have become square. The growth plates remain open, but the osteopetrotic process is not regressing. In Panel D, the lateral lumbar spine shows dense vertebrae of reduced height, with end-plate sclerosis, and a lucent defect (arrow) of L4, causing slippage anteriorly (grade I spondylolisthesis). No “bone-in-bone” (“endobone”) changes are present. In Panel E, a bone scan shows symmetrically increased uptake of radioisotope in the metaphyses, but not in the L4 pars defect, and there is no evidence of other fractures. In Panel F, a lateral radiograph obtained at the age of 12 $\frac{1}{2}$ years shows a Salter II (buckle) fracture (arrow) at the dorsum of the distal right radius through bone that remains sclerotic and poorly modeled two years after the last dose of pamidronate. The epiphysis is slightly displaced dorsally (arrowhead).

10 $\frac{1}{2}$ years of age. His idiopathic thrombocytopenia, which predated antiresorptive treatment, was not affected by the pamidronate infusions. Nevertheless, our patient now seems predisposed to one clinically significant manifestation of marble bone disease: fractures.⁸ The L4 pars defects, leading to spondylolisthesis, may be sentinel. Defective skeletal remodeling in patients with osteopetrosis compromises bone quality, because the removal of primary spongiosa and the interconnection of osteons are impaired.⁸ Consequently, spondylolysis (leading to spondylolisthesis) seems more prevalent in such patients,²¹ and other fractures are established complications of the disease.⁸ In fact, despite taking precautions during play after his return home, he sustained a distal break of his right radius when catching a basketball. The formation of metaphyseal bone, two years after pamidronate therapy was stopped, does not appear to be recovering (Fig. 1F). Bisphosphonates are long-acting.¹ Metaphyseal



sclerotic “banding” is a well-recognized effect of periodic intravenous bisphosphonate treatment in growing children,^{2,5,22} yet epiphyseal and metaphyseal sclerosis and subtle metaphyseal undertubulation reportedly resolve in children after therapy with potent aminobisphosphonates is terminated.⁷ Our patient’s nascent metaphyseal bone remains radiodense. Although markers of skeletal

turnover suggest that the rates of bone formation and resorption are normal, they emanate from supranormal skeletal mass. BB-CK is detectable and acid phosphatase activity is elevated in his serum. Hence, we are unsure whether his bones will model properly and whether the cartilage bars will resorb.

Pamidronate-induced nephrotoxicity has occurred in a few adults with various disorders,²³ but

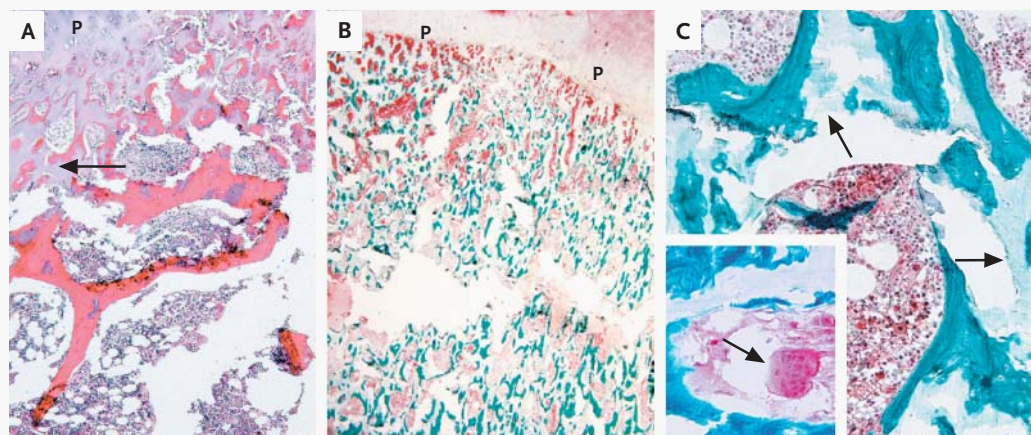


Figure 2. A Bone Marrow–Biopsy Specimen Obtained at the Age of 8½ Years (Panel A) and an Iliac-Crest–Biopsy Specimen Obtained at the Age of 10 Years (Panels B and C).

In Panel A, primary spongiosa (arrow) derived from the growth plate (P) is removed slowly but is not encased more deeply in the red-staining trabecular bone (hematoxylin and eosin, $\times 40$). In Panel B, pale areas of cartilage (“bars”) are within green-staining trabecular bone throughout the specimen (Goldner’s trichrome, $\times 20$). In Panel C, a high-power view ($\times 100$) reveals that these areas are cartilage “islands” (arrows) entrapped in trabecular bone — the hallmark of osteopetrosis — reflecting the failure of osteoclasts to resorb primary spongiosa. The inset shows a representative osteoclast with an abnormally rounded appearance, nonpolarized nuclei, and localization in the marrow space off the bone surface ($\times 400$).

it was not found in our patient. To date, untoward suppression of bone resorption has not been reported in children treated with bisphosphonates.^{3,4,7} However, in a mouse model of osteogenesis imperfecta, metaphyses retained primary spongiosa after high-dose exposure to alendronate.²⁴ Furthermore, increased numbers of cartilage bars were found in iliac-crest specimens from children with osteogenesis imperfecta who were treated intermittently (for, on average, 2.4 years) with pamidronate.²⁵

The amount of pamidronate our patient received is more than four times the amount that is typically administered during this time frame to children with osteogenesis imperfecta²⁵ and other disorders.²⁻⁷ Had the cumulative dose been given over a longer period, the changes would most likely have been less pronounced. However, bisphosphonate treatment is often administered for years to children.²⁻⁴ To date, the therapeutic end points seem unclear for most pediatric conditions.²⁶ Accordingly, more cases of bisphosphonate-induced toxicity

may emerge. One hopes that monitoring of biochemical markers of skeletal turnover will help guide clinicians so that skeletal resorption is not excessively suppressed in these patients. Perhaps elevated serum acid phosphatase activity and the appearance of circulating CK-BB can be used to indicate osteoclast failure.¹⁵ In addition, studies of bone modeling may be important for children who are treated with bisphosphonates. On the basis of our finding of drug-induced osteopetrosis in a child, we caution that excessive doses of bisphosphonates may compromise skeletal quality in growing patients despite concomitant increases in bone density.

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