

BISPHOSPHONATE-INDUCED OSTEOPETROSIS (Abstract)

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Bisphosphonates potently inhibit the recruitment, activity, and lifespan of osteoclasts and, in so doing, increase bone mineral density in children as well as adults. However, genetic disorders that impair osteoclast activity cause osteopetrosis manifesting as a dense, but brittle and poorly formed skeleton. Marble bone disease is therefore a potential complication of bisphosphonate toxicity in children.

A 12-year old Caucasian boy was referred with radiographic features of osteopetrosis 18 months after cessation of pamidronate therapy prescribed for unexplained skeletal pain, markedly elevated serum alkaline phosphatase activity, and incidental fingertip fractures. He had received 2.5 years of intermittent i.v. pamidronate starting at 7^{1/4} years-of-age, including at least 2800 mg by age 10^{1/2}. Dosing was in response to limb pain (60-100 mg infusions ~ q 3 weeks).

Skeletal x-rays predating antiresorptive therapy were normal. By age 12, metaphyses appeared dense and exhibited club-shaped deformities. The skull base was also dense. Vertebral body height was subnormal with end-plate sclerosis. Serologic evidence of osteopetrosis included elevated acid phosphatase activity (25 U/L: 6 normal) and the presence of the brain isoform of creatine kinase, 39% of serum CK activity (normal: undetected). Bone marrow biopsy, 9 months into his pamidronate treatment, showed an early osteopetrotic process featuring a delay in removal of calcified primary spongiosa produced by endochondral bone formation. Wedge biopsy of an iliac crest, after 2^{1/4} years into pamidronate treatment, showed pathognomonic calcified cartilage throughout the specimen. Molecular studies for a possible *forme fruste* of osteopetrosis or Engelmann's disease were normal. Juvenile Paget disease (osteoprotegerin deficiency) was also excluded. The bone alkaline phosphatase gene was intact. Thus we present osteopetrosis in a 12-year old patient secondary to high and frequent doses of i.v. pamidronate. This is the first report of drug-induced osteopetrosis.