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DIFFUSE "VERTEBRA-WITHIN-VERTEBRA" APPEARANCE AT THE ADULT AGE DUE TO BIPHOSPHONATE (PAMIDRONATE) ADMINISTRATION DURING EARLY ADOLESCENCE

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We report a rare case of diffuse alteration of the vertebral bony structure fortuitously found in a 20-year-old patient and essentially characterized by an impressive "vertebra-within-vertebra" appearance. This aspect was found being the result of an unusual use of intravenous perfusions of biphosphonate (Pamidronate) during early adolescence for reflex sympathetic dystrophy after tibial fracture. The clinical applications of biphosphonates are briefly reminded and the physiopathology of the induced bone changes is explained.

Key-words: Biphosphonates – Bones, growth and development – Children, skeletal system.

Biphosphonates are not commonly used in childhood and adolescence youth except for very specific entities like osteogenesis imperfecta, recurrent multifocal osteomyelitis and juvenile osteoporosis. We report a very rare case of diffuse alteration of the vertebral bony structure fortuitously found in a 20-year-old patient and essentially characterized by an impressive "vertebra-within-vertebra" appearance. This aspect was found being the result of an unusual use of intravenous perfusions of biphosphonate (Pamidronate) during early adolescence (at the age of eleven) for – probably overestimated – reflex sympathetic dystrophy after tibial fracture. The clinical applications of biphosphonates are briefly remembered and the physiopathology of the induced bone changes is explained.

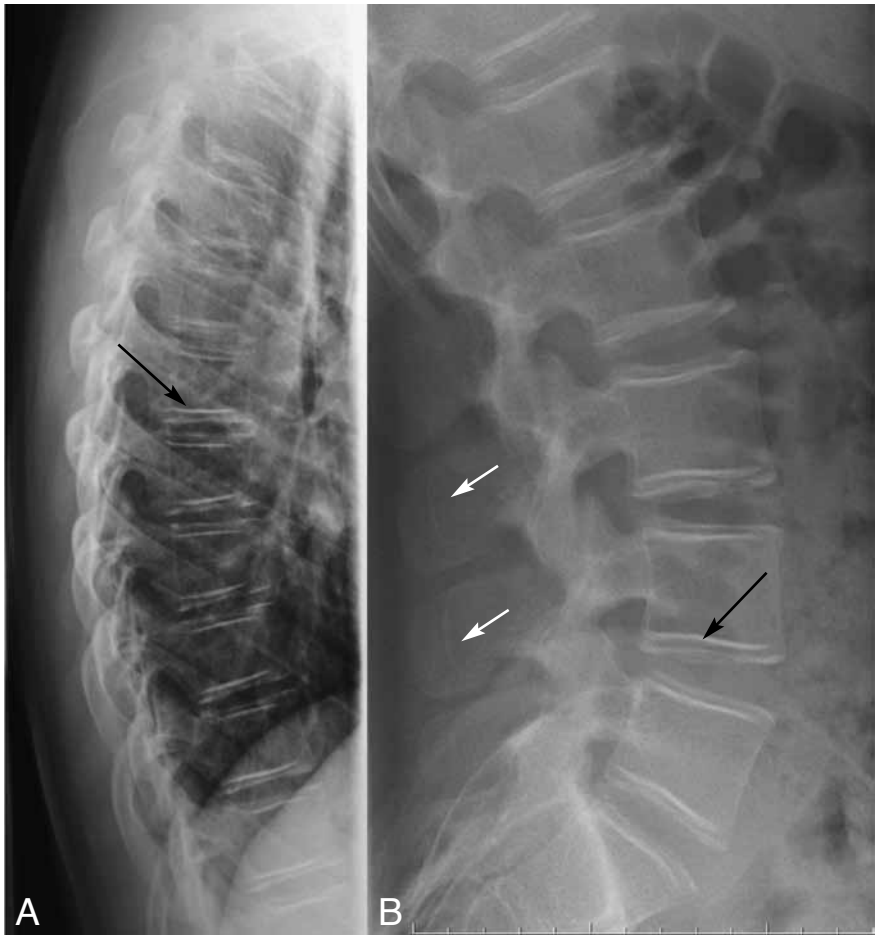

Fig. 1. — Lateral plains films of the thoracic (A) and lumbar (B) spine. Vertebral bodies are all delineated by a double bony cortex creating an impressing "bone-within-bone" or "vertebra-within-vertebra" configuration (black arrows). Duplication of the bony cortex is also visible at the level the vertebral spinous processes (white arrows).

Case report

A 20-year-old patient was referred for X-ray evaluation of spine after a car accident. He presented with complaints of moderate low back pain. Plain films failed to reveal any vertebral fracture but demonstrated atypical uniform diffuse alterations of the vertebral structure. All vertebral bodies were delineated by a double bony cortex creating an impressing "bone-within-bone" or "vertebra-within-vertebra" appearance. Duplication of the bony cortex was also found at the level of the iliac crests, acetabular roofs, sacroiliac joints and vertebral spinous processes (Fig. 1, 2). The patient was unsuccessfully questioned about the occurrence of serious medical events during childhood or early adolescence. Fortunately a revue of his medical records revealed a history of tibiofibular fracture (not illustrated) at the age of eleven. Two months after trauma a diagnosis of – probably overestimated – reflex sympathetic dystrophy (RSD) was evocated on the basis of clinical signs, plain films and bone scintigraphy (not illustrated). The patient received intravenous perfusions of biphosphonate (pamidronate).

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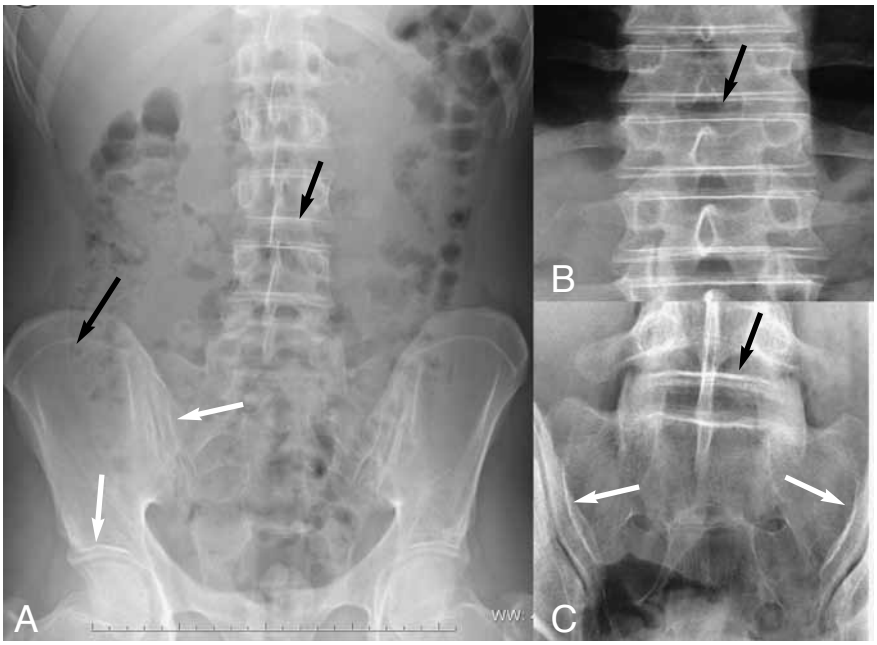

Fig. 2. — A to C: Postero anterior plains films of the lumbar spine (B). Vertebral bodies express the typical "vertebra-within-vertebra" configuration (small black arrows). Duplication of the bony cortex is also found at the level of the iliac crests (black arrow), acetabular roofs (white arrow) and sacroiliac joints (small white arrows).

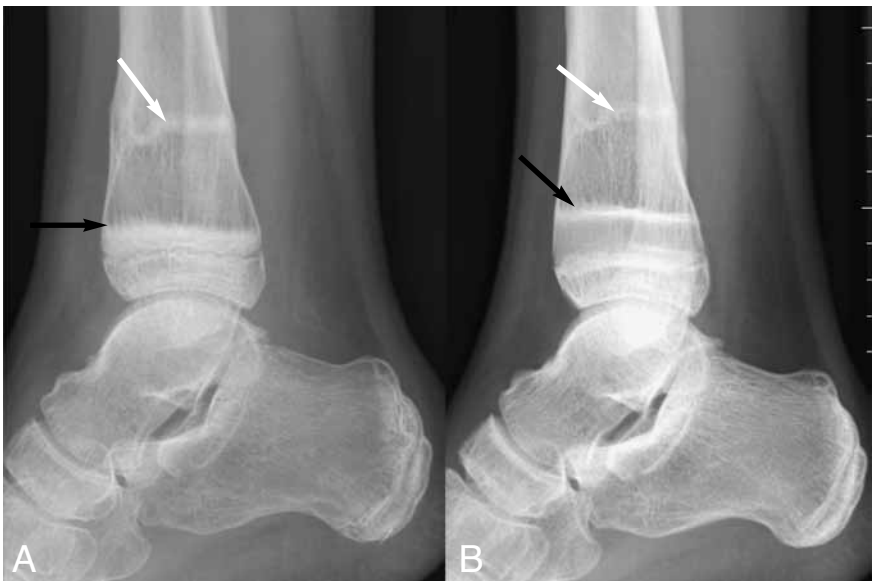

Fig. 3. — Digital plain films of the ankle obtained two (A) and twenty months (B) after the administration of biphosphonate. A typical metaphyseal bandlike sclerosis (black arrow) or "zebra line" has developed near the cartilaginous grow plate after two months and this band typically migrated and significantly decreased after 20 months. White arrow = healed fracture.

Digital plain films of the ankle obtained two (Fig. 3A) and twenty months (Fig. 3B) after the administration of biphosphonate were retrieved from our picture archiving system. A typical metaphyseal bandlike sclerosis or "zebra line" had developed near the cartilaginous grow plate after two months and this band had typically migrated and significantly decreased after 20 months.

Discussion

Bisphosphonates are structural analogues of inorganic pyrophosphate. They are resistant to enzymatic and chemical breakdown and inhibit bone resorption by selective adsorption to mineral surfaces and subsequent incorporation within bone-resorbing osteoclasts where they interfere with various biochemical processes. After it was shown that they inhibited experimentally induced calcification and bone resorption, their potential application to clinical disorders was obvious, but it took about 30 years for them to become well established (1).

Biphosphonates were first clinically used to inhibit calcification in myositis ossificans, to prevent subsequent heterotopic ossification and improve mobility in patients who had undergone total hip replacement surgery and finally as agents for bone imaging for which they still remain outstandingly useful for detecting bone metastases and other bone lesions (1).

Their most impressive clinical application has been as inhibitors of bone resorption. They so became the treatment of choice for a variety of bone diseases in which excessive osteoclast activity is an important pathologic feature (1, 2). For example, they are the most important drugs used in the treatment of Paget disease (2).

Bisphosphonates are also remarkably effective in malignancies where they significantly reduce the incidence of pathologic fracture, spinal cord compression and hypercalcemia in myeloma or in patients presenting with metastasis of breast, prostate and lung cancer, renal cell carcinoma and other solid tumors (1, 2).

Bisphosphonates have also emerged in the past few years as the leading effective treatments for postmenopausal and other forms of osteoporosis (1, 2). They can increase bone mass and reduce fracture rates at the spine by 30% to 50% and at other sites in postmenopausal women. They also prevent bone loss associated with glucocorticosteroid administration.

In pediatrics, pamidronate has proved remarkably effective in increasing bone in children with the inherited osteogenesis imperfecta (1). Good results have also been reported in patients presenting with juvenile osteoporis (2) and chronic recurrent multifocal osteomyelitis (3).

Reflex sympathetic dystrophy (RSD) is characterized by spontaneous pain, swelling, dysaethesia, and allodynia (4). Other features relate to the autonomic nervous system and include cyanosis, mottling,

sweating and reduction in temperature. In some cases more permanent and serious features may develop including muscle atrophy, demineralization of bone, and contractures of soft tissue around the affected joint. There is currently great controversy over the pathogenesis of RSD (5). Some authors believe that the disease is the result of a post-traumatic reflexive neuronal mechanism which leads to abnormal pain perception and exacerbated efferent sympathetic activity (5).

Innumerable conditions are associated with the development of RSD but in more than 60% of cases described in adults there is a history of trauma.

Among pediatrics RSD is considered as being a rare and under-diagnosed event. The history of trauma is less common and, when present, usually of lesser intensity. RSD usually involves children in late childhood or early adolescence, with a mean age of onset of 12-13 years and a higher frequency in girls than boys (5).

Bisphosphonates were proposed in the treatment of RSD due to their action as potent osteoclast-blocking agents (6). Pamidronate appeared to be effective and well tolerated in the treatment of refractory RSD (6-8). Use of pamidronate as the first-intention treatment for RSD can also be proposed (2). However, there are two limiting factors: the cost of amidronate and the need for intravenous administration. Osteonecrosis of the jaw (ONJ) has been described as a complication of bisphosphonate therapy in adults but not among paediatric patients up to now (9).

The occurrence of metaphyseal bandlike sclerosis (and in minder proportion of metaphyseal undertubulation) induced by biphosphonates is probably the result of the establishment of a new equilibrium between osteoblastic and osteoclastic activity within the bone after an initial phase of inhibition of osteoclastic activity without equal decrease in the osteoblastic activity (10). The relative resultant increase in bone formation in addition to the already high level of osteoblastic activity near the growth plates result in the development of sclerosis in the growing child. Multiple linear bands of increased bone density have also been described at the metaphysic of long bones in children receiving cyclical pamidronate infusions. The same phenomenon in areas of concentric bone growth (epi- and apophyses and vertebral bodies) causes ringlike sclerosis resulting in bone-within-bone or vertebra-within-vertebra appearance (11-14).

A gradual decrease in the degree of sclerosis has been observed after discontinuation of medication before the closure of the growth plates and in patients receiving medication after closure. This observation is probably due to a return to a normal level of bone turnover with a gradual replacement of the sclerotic bone by bone with normal density. The disappearance of metaphyseal sclerosis in follow-up studies in individual subjects has suggested that sclerosis was a completely reversible phenomenon.

A bone-within-bone appearance is a rare finding. In children, this appearance can occur after bone infarction in sickle cell anemia and Gaucher disease. In these disorders, however, this abnormality is most commonly seen in the diaphyses of the long tubular bones and is rarely generalized. It can also accompany heavy metal intoxication and can be a normal finding in the spine of neonates (10).

Sclerosing bone dysplasias must also be mentioned. These diseases are classified into three groups: dysplasias of endochondral bone formation (essentially affecting the spongiosa), dysplasias of intramembranous bone formation (essentially affecting the diaphysis) and mixed sclerosing dysplasia. Among dysplasias of endochondral bone formation type II autosomal-dominant (adult type) osteopetrosis and osteopathia striata can commonly show the bone-within-bone appearance and/or dense striations (15).

The persistence of bone-within-bone in the axial skeleton of the reported case appears rather remarkable and has, to our knowledge only exceptionally been reported (10, 14). The reason probably resides in the fact that biphosphonates are not currently used as first line treatment of reflex sympathetic dystrophy during early adolescence. Moreover the opportunity to fortuitously obtain plain films of the spine in a young adult who has received this atypical treatment during grow is extremely uncommon.

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