Acta Medica Mediterranea, 2008, 24: 131

BISPHOSPHONATE-ASSOCIATED FEMORAL FRACTURE: IMPLICATIONS FOR MANAGEMENT

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[Fratture di femore in pazienti in trattamento a lungo termime con bifosfonati: implicazioni per il management]

SUMMARY

Studies carried out on individuals being treated long term with bisphosphonates have provoked considerable interest and perplexity about the effect that these drugs have on bone turnover in the long run.

In fact the experiences reported by numerous researchers tend to highlight how treatment with high doses of bisphosphonates over many years, of individuals with osteoporosis complicated by or secondary to neoplastic pathologies, causes a suppression of bone turnover that over time predisposes the bone to the accumulation of micro damage that can then result in complicated fractures, as in the case described here.

Key words: Femoral fractures, bisphonates, bone turnover

RIASSUNTO

Studi condotti su soggetti in trattamento a lungo termine con bifosfonati, hanno scatenato notevole interesse e perplessità sull'azione che questi farmaci a lungo andare esplicano sul turnover osseo.

Infatti le esperienze segnalate da più studiosi tendono ad evidenziare come le terapie con bifosfonati ad alti dosaggi e protratte per diversi anni, in soggetti con osteoporosi complicate o secondarie a patologie neoplastiche, determinino una soppressione del turnover osseo, predisponendo l'osso stesso nel tempo, ad accumulare eventuali microdanni che possono poi scaturire in fratture complicate, come nel caso qui di seguito descritto.

***Parole chiave**: Fratture di femore, bifosfonati, turnover osseo*

Recent reports of femoral shaft fractures in patients being treated long-term with bisphosphonates (BPs), whose biopsies showed evidence of severely suppressed bone turnover, raised important concerns about the safety of this class of drugs. Patients with malignant skeletal conditions, such as multiple myeloma are potentially at high risk of suffering from this complication, considering the duration of the treatment and the doses of BPs that these patients are subjected to. In this report we describe the case of a 56 year-old woman who was referred for evaluation to the Bone Clinic of Washington University because of a recent left femoral shaft fracture.

Her history revealed that she had had a stem cell transplant in November. 1999 for multiple myeloma. After the transplant, she was put on a high dose of steroids and pamidronate infusions at 30 mg monthly for 2 years followed by zoledronate infusions at 4 mg monthly for 4 years. This was discontinued when high levels of serum creatinine were detected and because of concerns about osteonecrosis of the jaw. One and a half years later, she developed a left femoral shaft fracture (Figure 1A) while trying to get up from a squatting position.

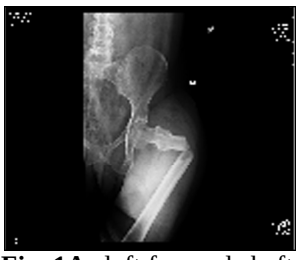

Fig. 1A: left femoral shaft fracture.

She underwent an intramedullary fixation of the left femur but the insertion of the rod resulted in the "splitting" of the fractured bone (Figure 1B).

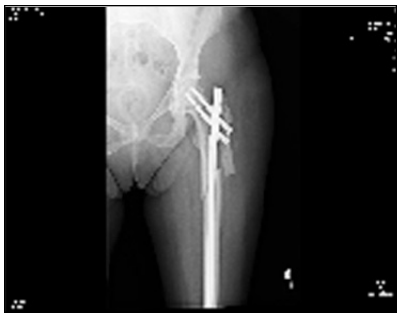

Fig. 1B: Splitting of the fractured bone after the intramedullary fixation of the left femur.

Follow-up x-rays showed poor healing and non-union of the fractured bones even 6 months after surgery.

The levels of serum calcium, alkaline phosphatase, 25-hydroxyvitamin D, parathormone (PTH) and thyroid stimulating hormone were normal., but the level of serum creatinine was elevated at 1.9 ng/ml. Bone mineral density was normal in the femur and mildly low in the lumbar spine. An attempt to do a bone biopsy was unsuccessful because the biopsy needle was unable to penetrate the "rock-hard" iliac crest.

BPs play an important role in preventing and reducing the risk of spinal and non-spinal fractures. However, numerous studies seem to support the theory that prolonged exposure to this type of drug may, over time, lead to the suppression of bone turnover and an accumulation of micro-damage which can eventually cause fractures. Normally, the position of the bones in which these occur are not the normal ones, like for example the femoral metaphases that are mostly made up of cortical bone.

This data has been confirmed by biochemical studies on bioptic sections taken from the bones of individuals who have been on BPs for years, and it can be seen how the bone turnover is completely suppressed after six years of treatment; this picture seems to be the same both for those who use BPs intravenously and for those who take BPs by mouth.

The above case illustrates a potential problem in the management of patients with skeletal fragility fractures from the prolonged use of BPs. Bone X-rays from these patients may appear normal, our patient's x-rays demonstrate, but in reality these bones bio-mechanically compromised.

Our patient had a non traumatic fracture of the left femur, which was complicated by the complete shattering of the fractured bones during surgical repair. In fact, the bones of our patient were hard on the outside, and could not be penetrated by the needle used for the bone biopsy, but on the inside the structure of the bone was more "brittle", and therefore did not allow optimal fusion after the operation.

This suggests the likelihood of a hyper-mineralized bone matrix superimposed on an inactive bone turnover as a possible aetiology of this complication. Recognized trials of IV therapy with BPs do not exist.

The treatment, carried out on an outpatient basis, has a strong impact on the suppression of bone turnover, and resembles osteoporosis in the way that it increases fragility inside the bone itself.

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