ATYPICAL FEMORAL FRACTURES AFTER LONG-TERM BISPHOSPHONATES THERAPY: CASE REPORT

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ATYPICAL FEMORAL FRACTURES AFTER LONG-TERM BISPHOSPHONATES THERAPY: CASE REPORT. (Abstract). We present a 77 years-old woman with no history of trauma, or associated with low-energy trauma, admitted to our clinic after three weeks of a left femoral fracture treated in Orthopedic Clinic. The patient was in treatment with bisphosphonates over 10 years for osteoporosis. Discussion and conclusions: The causal relationship between prolonged bisphosphonate use and the occurrence of atypical femoral fractures (AFF) has not yet been established. For the patient at high risk of fracture, it may be beneficial to continue bisphosphonate treatment beyond five years. The absolute risk of atypical femoral fractures is low (about 100 cases per 100,000 person-years among long-term users). For most people with osteoporosis, the proven fragility-fracture risk-reduction benefits of bisphosphonates outweigh the risks of AFF. Keywords: ATYPICAL FEMORAL FRACTURE; BISPHOSPHONATES; OSTEOPOROSIS.

Bisphosphonates are a class of widely prescribed drugs that are proven to be effective in reducing common bone fractures in people with osteoporosis and those at a high risk of fractures. Concern among doctors and patients has arisen following recent media reports that cite a possible association between unusual and unexpected (atypical) fractures of the upper thigh bone and bisphosphonate use. Recent published studies (1) examining this potential association are conflicting regarding the existence and strength of this association. Bisphosphonate-related proximal femoral fractures are an example of insufficiency fractures, although the direct causative link remains somewhat controversial (1). According to a task force report from the American Society for Bone and Mineral Research (ASBMR), this relationship has not yet been shown to be causal. All current evidence indicates that atypical femoral fractures (AFF) represent a rare subset of subtrochanteric and femoral shaft fractures (2). Femoral shaft fractures had an incidence of 2.5 to 9.9 per 100,000 person-years, but 75% occurred with high-energy trauma and the majority were comminuted and had a spiral configuration (3). A review of radiographs by
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Schilcher et al. (4) found an incidence of 55 atypical fractures per 100,000 person-years among bisphosphonate users compared with 0.9 per 100,000 person-years among those with no bisphosphonate use. Characteristics of AFF are: a transverse, noncomminuted fracture at the subtrochanteric or femoral shaft region with a medial cortical spike at the fracture area. Other features include prodromal pain and generalized thickening of the femoral cortices on radiographs. For the clear criteria to define atypical femoral fractures, the ASBMR task force established major and minor features for both complete and incomplete atypical fractures of the femur (2). All of the major features should be present to designate a fracture as atypical: No history of trauma, or associated with low-energy trauma; Fracture located anywhere from distal to the lesser trochanter to proximal to the supracondylar area; Transverse or short oblique fracture configuration; Noncomminuted fracture; Medial spike in complete fractures, incomplete fractures involve only the lateral cortex. The minor features have also been described in association with atypical femoral fractures, but they are not required for diagnosis. Localized periosteal thickening of the lateral cortex; Generalized thickening of the femoral cortices; Prodromal symptoms; May be associated with bilateral fractures or symptoms; Evidence of delayed fracture-healing; Comorbid conditions or the use of some medications.

CASE REPORT

A 77 years-old woman, weight 62 kg and height 1.58 was admitted to Endocrinology clinic after three weeks of a left femur fracture in mid-thigh, threatened in Orthopedic Clinic (fig. 1).

Orthopedic Surgery underwent the closed reduction and internal fixation with intra medullary hip screw (fig.2 b). The patient was in our clinical observation since 1983 for hypothyroidism after thyroidectomy in treatment with 100 mcg LT4. In 2002 the patient was diagnosed with osteoporosis following the DXA examination. The bone mineral density (BMD), measured by dual-energy X-ray absorptiometry (DXA) showed T-score at total lumbar spine: -4.0, total hip: -2.1, and left femur neck: -3.0. 25-OHD3 level varied between 17.69 ng/mL and 5.54 ng/mL (normal>30 ng/mL). Thyroid Stimulating Hormone, thyroxin and triiodothyronine level was normal. Has been established treatment with risedronicum acidum 35 mg/week (Actonel), Alfacalcidol 1 mcg/day and calcium 1000 mg/day. Annual DXA-BMD shows a slight increase the density of the bone; patient medical treatment has been changed in zoledronicum acidum and then on alendronicum acidum.
In 2013 there is a decrease of BMD DXA, but our patient require the continuation of the therapy with a drug with large intervals administration. Ibandronicum acidum has been recommended. After surgical orthopedic treatment were discussed with the patient, the risks and benefits of each option. The new antosteoporotic treatment was strontium ranelate in association with Alfacalcidol and calcium. An association between bisphosphonate long-term use and the occurrence of AFF has been suggested. This diagnostic has been supported and by the x-ray. The radiographic features of an atypical femoral fracture: femoral shaft region (fig. 2a), transverse fracture configurations, absence of commination, a medial spike, localized peristomial thickening of the lateral cortex, and generalized thickening of the femoral cortices.

**DISCUSSION**

AFF have been associated with various factors, including: bilateral fractures, prodromal pain, the use of glucocorticoids and proton pump inhibitors, delayed fracture-healing, presence of rheumatoid arthritis or diabetes mellitus as well as vitamin-D3 deficiencies (5, 6). A post hoc analysis of data from three randomized trials of bisphosphonates for postmenopausal osteoporosis identified twelve subtrochanteric or diaphyseal femoral fractures in ten of the 14,195 study participants, yielding a rate of 23 per 100,000 person-years. Reanalysis of the data in three major randomized controlled trials showed no statistically significant increase in the risk of subtrochanteric femoral fracture in patients treated with bisphosphonates for as long as ten years (2). Given the mixture of results and the different methodologies used in these studies, it is difficult to demonstrate consisten-
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cy of this association. Studies (7) have shown an increased risk of atypical femoral fractures in patients taking bisphosphonates for five or more years, suggesting a dose-response relationship. The ASBMR task force reported an incidence of 2 per 100,000 cases per year after two years of bisphosphonate use, increasing to 78 per 100,000 cases per year after eight years of use. Management of patients with AFF: Stop bisphosphonates. Consider an anabolic agent such as teriparatide. Calcium and vitamin-D supplementation (6). Identify any underlying metabolic bone diseases by laboratory investigations such as serum calcium, phosphate, 25-hydroxyvitamin D, intact parathyroid hormone, thyroid-stimulating hormone, bone turnover markers, and 24-hour urine calcium. Intramedullary nailing is the preferred method of fixation. Assess the contralateral femur. If the patient has an incomplete fracture, a period of conservative therapy may be considered. Five of six patients had progression of the lesion to complete fracture at a mean of ten months. Management of patients with prolonged bisphosphonate therapy: If a patient sustains an atypical femoral fracture, bisphosphonates must be stopped. Once administered, bisphosphonates accumulate in the bone and continue to be released for months or years after treatment is discontinued. Regarding over suppression of bone turnover with prolonged bisphosphonate therapy, it is recommended that osteoporosis treatment with bisphosphonates be stopped after a period of five years to provide patients a so-called “drug holiday”. Park-Wyllie et al. performed a nested case-control study to explore the association between bisphosphonate use and femoral fractures, and they reported that bisphosphonates treatment of more than five years was associated with an increased risk of atypical subtrochanteric or femoral shaft fractures (7). Therefore, it may be appropriate to consider a drug holiday in patients with a cumulative duration of bisphosphonate treatment of more than five years. The absolute risk of atypical femoral fractures is low (3.2 to 50 cases per 100,000 person-years among short-term bisphosphonate users and about 100 cases per 100,000 person-years among long-term users). Consequently, for most people with osteoporosis, the proven fragility-fracture risk-reduction benefits of bisphosphonates outweigh the risks of AFF (8).

CONCLUSIONS
Patient confirms the risk of atypical femoral fractures in prolonged bisphosphonate therapy, but let us not forgets benefits of bisphosphonates.

REFERENCES

**SHED - BASIC STRUCTURE FOR STEM CELL RESEARCH**

Stem cells are defined as clonogenic cells capable of both self-renewal and multi lineage differentiation. Stem cells have been differentiated from variety of body parts and have shown great promise in the management of variety of diseases in medicine. Recently, stem cells have been isolated and grown from: Human permanent dental pulp tissue stem cells (DPSCs), Stem cells from human exfoliated deciduous teeth (SHEDs), and Periodontal ligament apical papilla of immature teeth (PDLSCs). If we have in hand population of stem cells that reproducibly reform bone, cementum, dentin, and perhaps even periodontal ligament; it is possible to envision complete restoration of the hard tissues in the oral cavity using the patient’s own cells, thereby avoiding issues of histocompatibility. This would be a more biological approach rather mere mechanical one. It has been reported that the stem cells obtained from the above said sources can generate dentin like tissue both in vitro and in vivo studies in animals. In addition transplanted skeletal or dental stem cells have the potential to “rephrase” repair craniofacial defects and repair/regenerate teeth. This review study showed that stem cells from human exfoliated deciduous teeth are distinct from dental pulp stem cells by virtue of their proliferation rate, increased cell population doublings and osteoinductive capacity in vivo. It also demonstrated that human exfoliated deciduous teeth stem cells may not be a single-cell type, may well be a heterogenous population of cells from the pulp (Kashyap R. SHED - Basic Structure for Stem Cell Research. *Journal of Clinical and Diagnostic Research*. 2015 Mar, Vol-9(3): 7-9).

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