



Bisphosphonate-Associated Bilateral Atraumatic Ulna Fractures

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Authors' contributions

This work was carried out in collaboration between both authors. Author WBH wrote the first draft of the paper. Both authors contributed equally to the detailed editing of the paper and the acquisition of the references. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: From 2003, low-impact fractures have been reported in association with bisphosphonate (BP) therapy. Most have involved the proximal femur, but over 100 cases involving other anatomic locations have been published. The 2010 American Society for Bone and Mineral Research case definition for subtrochanteric or femoral shaft "atypical" fractures (AFF) included non-comminution, transverse orientation, cortical thickening, beaking, and minimal trauma. Because other anatomic locations were excluded, there has been an unstated assumption since then that these atypical fractures are limited to the femur. We present a case of bilateral fractures of the proximal shaft of ulna after bisphosphonate therapy. The similarity to the AFFs suggests that the anatomic location of atypical fractures is not limited to the femur.

Methodology: Case report.

Results and Discussion: After 15 years of BP use and several months of pain, the patient was diagnosed with a non-displaced transverse fracture of the left proximal ulnar diaphysis. Subsequently she developed a similar insufficiency fracture in her right ulna, and 2 months later the

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left fracture broke spontaneously. It was non-comminuted, transverse, with cortical thickening, and beaking. It was preceded by prodromal pain. This similarity to the AFFs suggests that the anatomic location of atypical fractures is not limited to the femur.

Conclusions: Non-femoral atypical-type fractures have been associated with BP therapy. These atypical fractures suggest a systemic rather than local BP effect, and their exclusion has thus understated the incidence of BP-associated atypical fractures.

Keywords: Bisphosphonates; atypical fractures; ulna; metatarsal; alendronate; zoledronate; teriparatide; denosumab.

1. INTRODUCTION

Beginning with index cases first reported in 2003, there has been a steadily increasing number of fractures reported associated with bisphosphonate (BP) therapy. The varied anatomic locations of the first small group of cases [1] suggested a generalized effect. Recognition of the BP-association was slow in coming but case reports continued to accumulate and concern continued to mount until the leadership of the American Society for Bone and Mineral Research (ASBMR) convened [2] a "Task Force" to address the problem. For reasons that were never clearly defined, the report of this committee was limited to fractures of the femur. The report surveyed the English-language medical literature between January 1990 and April 30, 2010 and tabulated some 37 case series reporting femur fractures meeting a definition derived from commonalities among the clinical descriptions; 97% of the fractures so-defined were in patients who had received BP therapy. These were termed atypical femur fractures (AFFs). The exact number of individual fractures reported was somewhat indeterminate. 153 affected individuals were found in the published works but 35 were acknowledged likely to be duplicates. Thus perhaps 118 affected individuals were found. In 35 of these, the fractures were bilateral, thus making the total number of femur fractures associated with BP therapy reported between 1990 and April 2010 to be ~153. These fractures were severally associated with alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid. Fractures associated with BP-therapy described in the same publications which did not meet the derived AFF definition were not mentioned [examples: 3, 4] in the Task Force report.

The index fractures associated with BP therapy presented by Odvina in 2003 were not all femur fractures. Four individuals were described who suffered one "proximal femur", two pelvic, two sacral, and an undisclosed number of rib,

metatarsal, and metacarpal fractures among them. Thus only 1 out of the original 8 (or more) of the initially reported BP-associated fractures involved the femur. A later publication [3] defined that single "proximal femur" fracture as subtrochanteric. Our survey [5] of the medical literature on BP-associated non-femur atypical-type fractures discovered 13 case series in the same 1990-2010 interval reporting at least 29 individuals suffering more than 50 non-femur breaks. This demonstrates that these fractures associated with BP-therapy were being reported at about 1/3 the rate of the femur reports at the time the ASBMR committee chose to focus on the femur only.

We present here a case of bilateral fractures of the proximal shaft of the ulna associated with long-term BP use in a woman who, because of childhood polio has, for her entire adult life, been able to ambulate only with crutches, transferring her weight to her arms. Except for the anatomical location, the long-term clinical course in this case was similar to that of the AFFs we have previously described [6].

2. PRESENTATION OF CASE

A now 67-year-old Caucasian woman contracted polio at about one year of age. Post-polio syndrome deprived her of the use of her legs and she has never walked unsupported. For most of her life, she has used axillary crutches for ambulation. In her teens she sustained fall-associated fractures of both hands, and compression fractures of the spine, diagnosed later, may have originated at that time as well. She has led an independent, courageous, and productive life, including three successful pregnancies resulting in healthy live births. She maintained long-term professional employment.

For many years, she has been a patient under the care of the same multispecialty clinic. In December 1995, when she was 46, her first bone mineral density scan results met the WHO definition of osteoporosis and she was started on

alendronate 10 mg/day. Seven years later (February 2002) her medication was changed to alendronate 70 mg/week. She confirms that she was very compliant in her use of this treatment.

In November 2008, after 13 years of alendronate use, it was replaced by zoledronic acid 5 mg (Reclast™) infusions. These were continued approximately annually for 3 infusions, the last one in January 2011. In August 2010, about 5 months *prior* to the last infusion, she was diagnosed with a non-displaced transverse fracture of the left proximal ulnar diaphysis [Fig. 1, 1a]. She had been experiencing deep pain in her upper forearm for several months previously.

This fracture was managed conservatively with casting and she continued using axillary crutches. In January 2011, a similar pain developed in her right forearm; an X-ray showed another insufficiency fracture in the right proximal ulnar diaphysis. This was essentially revealed by a mild cortical reaction. In early March, the left

fracture broke spontaneously and required ORIF [Fig. 2]. This non-comminuted transverse break with a cortical reaction, beaking, and prodromal pain parallels the AFF characteristics defined by the ASBMR task force [1]. By the time the operated left side was declared healed 10 months later, the symptoms and radiological evidence of the right ulnar pathology had resolved.

During this healing interval, she ambulated exclusively by motorized wheelchair, thus alleviating the weight-bearing strain on her arms. About 2 months after the completed fracture (and 5 months after the last zoledronic acid infusion) she was started on teriparatide (Forteo™) daily 20 mcg sc. Two months after the completion of 24 months of teriparatide, she was given 60 mg of denosumab (Prolia™) sc. One year later after several months of foot pain, an atraumatic transverse fracture of the proximal one-third of the diaphysis of the 5th right metatarsal bone [Fig. 3] was diagnosed, despite her using only



Fig. 1. Ulnar insufficiency fracture



Fig. 1a. Detail of Fig. 1



Fig. 2. Completed ulnar fracture



Fig. 3. 5th metatarsal fracture

crutches to walk in the interval. This fracture healed with conservative management within seven months. She declined further treatment with denosumab.

During the interval of the treatments described above, the general health of the patient remained stable. She did not suffer a stroke or any other new medical condition. The post-therapy fractures described were not associated with falling.

Because of instability of her right ankle unrelated to the above problems, at age 65 she underwent elective right tibiotalar calcaneal arthrodesis for cavovarus deformity of the foot. [6] This surgery, which requires no fracture healing, was successful and resolved as expected.

3. RESULTS AND DISCUSSION

In this report we present a case of a patient treated with long-term BP therapy who developed atypical ulnar fractures. Among the more than 200 cases which we have collected of individuals who have incurred BP-associated fractures, this case is unique in that this individual never had any stress applied to the femurs before or during that therapy. Her case is presented in support of the hypothesis that the effect of BP-therapy on the skeleton is systemic. She has ambulated her entire life using her arms instead of her legs, thus transferring to her arms the forces normally applied to the legs. Similar fractures have been reported in patients employing crutches but not using BP drugs. [7] Among patients developing femur fractures in association with BP therapy, fractures meeting the AFF definition are in the longest highly stressed portions of the femur, the lateral subtrochanteric region and the lateral shaft (ST/FS). It seems likely that the increased standing stress on these locations is the reason the AFFs occur there [8]. This hypothesis is supported by the finding that populations that have a genetically determined increased bowing of the upper femur also have an increased incidence of AFFs [9]. Support is also found in the high incidence of insufficiency fractures in BP-treated patients in another highly-stressed long bone: the metatarsal. The present case is an example. Her ulna fractures meet many of the diagnostic standards of the AFFs and she developed a subsequent metatarsal fracture.

Among the 81 patients we previously described [5] who experienced BP-related AFFs, 35% also

suffered one or more metatarsal fractures subsequent to their AFF.

There are clinical consequences to the conclusion that bisphosphonate use can result in atypical fractures in bones other than the femur.

Stopping strong anti-resorptive drugs when an associated fracture is suspected or diagnosed has been recommended by the USFDA for many years [10]. Despite a diagnosis of an undisplaced insufficiency fracture of the proximal left ulna, the present patient was continued on zoledronic acid. This was followed by completion of that fracture and diagnosis of a contralateral insufficiency lesion. After anabolic therapy, she was again started on a strong antiresorptive, denosumab, and afterwards incurred the described slow-healing metatarsal fracture. We have reported elsewhere [11] a similar case where a second AFF followed the use of denosumab administered after anabolic therapy which had been used to assist recovery from an initial BP-associated AFF.

In 2011 the United Kingdom Medicines and Healthcare products Regulatory Agency decided that their previously announced caution regarding the BP side effects was at an end and the AFFs were declared [12] a class-effect of the BP drugs. The Committee for Medicinal products for Human Use of the European Medicines Agency announced the same conclusion [13]. The increasing reports of non-femur fractures with the characteristics attributed by the ASBMR to the ST/FS femur suggests that this class effect should be extended all skeletal locations where the anatomic characteristics of the fracture are sufficient to suggest association with the drugs [14-20]. It is difficult to envision this extension happening without a consensus development from a responsible multidisciplinary agency such as the ASBMR. But it is equally difficult to imagine a systemic medication affecting a single bone in the human body to the exclusion of all others.

4. CONCLUSION

This report presents a case of bilateral fractures of the proximal shaft of the ulna associated with long term bisphosphonate use in a woman who has ambulated her whole life using crutches. Except for the location, the anatomic characteristics and course of these fractures was parallel to the atypical femoral fractures associated with bisphosphonate therapy

described by the ASBMR leadership. We conclude that this case contributes evidence that the BP-related atypical fractures are not limited to the mid-femur.

CONSENT

Both authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author WBH has provided expert testimony in civil litigation involving bisphosphonates. Author JPS declares that she has that no competing interests.

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