Healing of subtrochanteric atypical fractures after strontium ranelate treatment

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Summary
Oral bisphosphonates comprise the most widely prescribed
class of antosteoporotic drugs. Recent reports, however,
suggest a link between prolonged bisphosphonate use and
atypical low-energy, subtrochanteric fractures. We descri-
be the clinical course of two patient treated for a long term
with different bisphosphonates who developed subtro-
chanteric atypical fractures. They were treated initially with
intramedullary rodding without pain disappearance or hea-
lung of the fracture. Strontium ranelate, a new orally admi-
istered agent for the treatment of osteoporosis, was given
to these patients with complete closure of the fracture and
pain disappearance after a few months. We conclude that
based on the chronology of fracture healing and pain dis-
sappearance of our patients and published evidence that
strontium ranelate can accelerate fracture healing in a rat
model, that strontium ranelate had a positive anabolic ef-
fect that contributed to fracture healing that produced the
secondary disappearance of pain.

KEY WORDS: bisphosphonate; atypical fractures; delayed healing; strontium
ranelate.

Introduction
Bisphosphonates are the primary therapy for postmenopausal and
glucocorticoid-induced osteoporosis worldwide. Several large, ran-
domized controlled trials have shown that bisphosphonates are
effective in improving bone mineral density and reducing osteo-
porotic fractures in postmenopausal women (1, 2). However, re-
cent studies report a possible link between prolonged bisphos-
phonate therapy and atypical, subtrochanteric low-energy frac-
tures of the femoral shaft (3-7). A task force from the American
Society for Bone and Mineral Research has defined major and mi-
nor features for atypical femoral fractures. They recommend that
all major features, including their location in the subtrochanteric
region and femoral shaft, transverse or short oblique orientation,
minimal or no associated trauma, a medial spike within the frac-
ture is complete, and absence of comminution, be present to de-
signate a femoral fracture as atypical. The incidence of these aty-
pical subtrochanteric femoral fractures in bisphosphonate users
is unknown, but considering the large number of patients taking
this class of medication, it appears to be low (8).

There have been reports of treatment of atypical subtrochan-
teric femoral fractures related to long-term bisphosphonate therapy
that healed after treatment with a bone forming agent as teripa-
ratide (9, 10). Recently Carvalho et al. have shown a similar fin-
ding with short term strontium ranelate treatment (10). Although
these beneficial effects are consistent with the efficacy of anabolic
therapy in the healing of these types of fractures, more eviden-
ce is needed.

In this report we describe the cases of two postmenopausal wo-
men that suffered from subtrochanteric atypical low-energy frac-
tures after prolonged bisphosphonate therapy that failed to heal
after intramedullary nailing that healed after few months of stron-
tium ranelate oral therapy.

Case 1
A 79 year old white woman was diagnosed osteoporosis in 1998.
She had had the menopause at age 49. She was treated with cal-
cium salts, vitamin D and alendronate 70 mg/week for 8 years and
afterward with ibandronate 150 mg/month for another four more
years. In January 2010, she began with acute pain at the mid left
thigh. Few weeks later she suffered a spontaneous fracture of the
same femur. Intramedullary nailing of the femur was performed
and bisphosphonate therapy was stopped. After several months
the fracture had not healed. She was sent for consultation at our
institution. A diagnosis of atypical subtrochanteric femoral fracture
after prolonged bisphosphonate therapy was made and ibandronate
was stopped. Laboratory data showed: total calcium: 9.9 mg/dl,
serum phosphorus: 3.8 mg/dl, iPTHi: 26 pg/ml, serum ALP: 231
IU, serum crosslaps: 183 pg/ml. She was given strontium rane-
late 2 gr/day plus calcium and vitamin D. Closure of the fracture
line was seen after five months treatment with strontium ranelate-
ate (Figures 1 and 2) with complete resolution of thigh pain.

Case 2
A 68 year old white woman was diagnosed osteoporosis in 1993.
She had had surgical menopause (hysterectomy) at age 48. She
was treated initially with pamidronate 200 mg/day and calcium salts
for 1 year after which her gynecologist changed her treatment to
transdermal estrogen. She continued with that treatment until May
1995 when she was changed to alendronate 10 mg/day plus cal-
cium salts returning to transdermal estrogen in October 1996. In
July 2003, her medication was changed back to alendronate 70
mg once a week and then to risedronate which she took until July
2005. During 2006 she stopped taking medications for osteopo-
rosis. In May 2007 she began taking ibandronate 150 mg once
a month. In September 2009, she began with acute pain at the
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While walking in the beach, she had a spontaneous fracture of the right femur. She had x-rays of both femurs that revealed cortical thickening in the midshafts of both femurs with an oblique complete loss of continuity of the right femoral cortex with a unicortical beak at the fracture site. She was operated and a Kun-cher nail was introduced as fixation in her right femur. Ibandronate was stopped. In September 2010, despite the intramedullary nail, she continued with pain and failure of the fracture to heal. Laboratory data at that moment showed: total calcium: 9.8 mg/dl, serum phosphorus: 4.2 mg/dl, serum crosslaps 191, 25 OH D: 41.6 ng/ml, serum osteocalcin 13.8, serum ALP: 175 IU. She was given Strontium ranelate 2 g/day. By March 2010 her pain had completely resolved and the fracture showed complete healing (Figures 3 and 4).

Discussion

In this report we present two patients who had atypical subtrochanteric femoral fractures after long-term bisphosphonate therapy. Despite intramedullary rodding in both cases, healing of the fractures and pain disappearance did not occur until the introduction of several months of strontium ranelate treatment. Spontaneous healing related to time cannot be assumed in these cases, as several months had elapsed after fracture with adequate juxtaposition of fracture ends with the nailing. Thus we suggest that anabolic treatment with strontium ranelate has been the cure for these atypical fractures.

Recent evidence indicates suppression of the bone turnover and increased risk of bone fragility after long term bisphosphonate therapy (11). The delayed recovery from fracture and evidences of severe suppression of bone metabolism were first reported by Odvina (12). Between 2006 and 2007 several case reports about atypical insufficiency fractures after long term exposure to bisphosphonates were published (4, 13-15). These case reports and conflicting findings from small observational studies (7, 16, 17) have left clinicians and patients uncertain about whether bisphosphonates increase the risk of subtrochanteric or femoral shaft fractures. A recent population-based study have confirmed the as-

Figure 1 - Case 1: Postoperative non-comminuted fracture of the femur diaphysis, before strontium ranelate treatment.

Figure 2 - Case 1: After five months of strontium ranelate treatment.

Figure 3 - Case 2: Postoperative oblique fracture of the femur diaphysis before strontium ranelate treatment.
studies suggest that strontium ranelate potentially increases cement of bone and tissue volume within the callus and from promoted fracture healing in OVX rats. This effect resulted from enhanced bone formation activity of osteoblasts and decreases the bone resorption activity of osteoclasts, thus leading to the prevention of bone loss and an increase in bone mass and strength. No defect of mineralization due to strontium ranelate was observed in studies on animals (25) and humans (26). Recently strontium ranelate has been shown to increase bone repair and favor callus formation. In a model of screw fixation in ovariectomized rats, treatment with strontium enhanced the process after 4 and 8 weeks of treatment (27). Two recent studies also revealed that 4 and 8 weeks of treatment with strontium ranelate promoted fracture healing in OVX rats. This effect resulted from enhancement of bone and tissue volume within the callus and from formation of a more mature and tightly arranged bone after 8 weeks (28). Our results suggest potential benefits of strontium ranelate on bone formation in vivo, with the cure of atypical fractures, albeit more clinical studies are required to confirm this effect.

References


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