Case Report

Atypical Fracture of Proximal Ulna Associated with Prolonged Bisphosphonate Therapy Managed with Nonoperative Treatment: A Case Report and Literature Review

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Prolonged bisphosphonate (BP) treatment is associated with some complications, such as atypical femoral fractures (AFFs). Recent studies showed that atypical fractures also occurred in other bones, especially in the atypical fracture of the proximal ulna (AFPU). Although, AFPUs frequently share the same characteristics of atypical fractures as AFFs, such as fracture configuration and high risk of non-union, there is still limited evidence of the role of non-operative treatment in AFPU. The aim of the present study was to present an interesting case involving an 80-year-old female presented with non-displaced AFPU after receiving long-term BP medication and had been treated with a conservative method for 2.5 years, and to review the literature regarding the available AFPU treatment options. To the best of the authors' knowledge, the present case report introduced new insight of the outcome of non-operative treatment for AFPU.

Keywords: Non-displaced fracture; Ulna fracture; Long-term bisphosphonates; Conservative treatment; Nonunion; Osteoporosis

Received 22 February 2021 | Revised 30 July 2021 | Accepted 5 August 2021

J Med Assoc Thai 2021;104(9):1557-62

Website: http://www.jmatonline.com

Bisphosphonates (BPs) are one of the most common anti-resorptive medications prescribed globally due to the increasing worldwide incidence of osteoporosis. Despite the clinical benefits, long-term BP therapy has been found to be associated with a few uncommon complications related to the effect of severe suppression of bone turnover (SSBT), such as atypical femoral fractures (AFFs) and osteonecrosis of the jaw[1,2]. However, recent studies showed that atypical fractures in patients receiving long-term BP treatment could also occur in the upper extremity long bones, such as the forearm[3,4] and humerus[5] but are more common in the proximal ulna area[4,6-15].

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How to cite this article:

Sabsuantang K, Pengrung N, Sirisreetreerux N, Kulachote N, Sa-ngasoongsong P. Atypical Fracture of Proximal Ulna Associated with Prolonged Bisphosphonate Therapy Managed with Nonoperative Treatment: A Case Report and Literature Review. J Med Assoc Thai 2021;104:1557-62.

doi.org/10.35755/jmedassocthai.2021.09.12593

Regarding the atypical fracture of the proximal ulna (AFPU), previous studies revealed this fracture shares the following similar characteristics with AFFs, which is history of prolonged BP use, prodromal pain, no associated trauma or minor trauma, and high risk of delayed union or non-union[6,8]. The AFPU fracture configuration, transverse or short oblique without comminution and localized periosteal thickening, is also similar to that of AFFs[6,8]. Nonetheless, due to the paucity of AFPU, no definitive guideline exists for AFPU management, especially in patients who had incomplete or non-displaced fracture[8,16,17]. The present study aimed to report on the outcome of a female elderly patient who had non-displaced AFPU and received long-term non-operative treatment, and to provide a literature review for both non-operative and operative management of AFPU.

Case Report

A Thai 80-year-old female presented at the outpatient clinic in December 2017 with left forearm pain for seven days, after a minor injury from a light blow on the toilet sink while hand washing. She denied history of prodromal pain, falling, or other significant trauma. Her pre-injury ambulatory

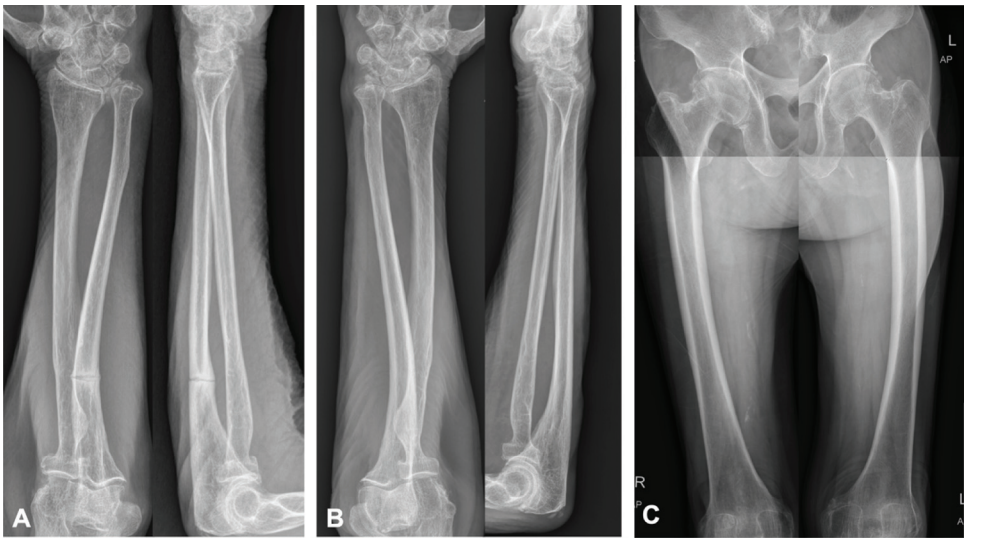

Figure 1. Initial radiographs of left forearm (A) with the screening radiographs of right forearm (B) and both femurs (C) showed incomplete fracture of proximal ulna without any atypical femoral lesion.

status was independent ambulatory with single cane. She had the following underlying diseases, hypertension, dyslipidemia, degenerative scoliosis, and osteoporosis. She had been treated with atenolol, hydrochlorothiazide, amiloride, simvastatin, aspirin, calcium, vitamin D3, and anti-osteoporotic agents. She was diagnosed with osteoporosis in 2011 and received anti-osteoporotic therapy over a 6-year period, ibandronate 150 mg per month for three years, risedronate 35 mg per week for three months, denosumab 60 mg every six months for one year and a half, and alendronate 70 mg per week for one year and a half before this visit. Physical examination revealed minimal swelling and mild tenderness of the proximal ulna without bruises or external wounds. The elbow and wrist range-of-motion were normal, and the distal neurovascular status was intact. The initial radiographs showed a transverse radiolucent line with sclerotic ends on the proximal one-third of the left ulna and thickening of the diaphysis of the ulna (Figure 1A). Due to the uncommon radiographic findings, incomplete proximal ulna fracture and cortical thickening with minor trauma and a history of prolonged bisphosphonates and denosumab treatment, she was diagnosed with AFPU. The screening radiographs of the contralateral forearm and bilateral femurs were sent and revealed neither local periosteal thickening nor any abnormal radiolucent line (Figure 1B, C). The metabolic bone workup showed mild anemia as hemoglobin 10.5 g per dL, with normal levels of calcium, 25-OH vitamin D, glucose, creatinine, alkaline phosphatase, procollagen type 1 amino-terminal propeptide (P1NP), b-crosslaps, parathyroid hormone, and thyroid hormone.

After discussion about the AFPU treatment options, she opted for the conservative treatment of four weeks of long arm slab immobilization and teriparatide injection due to the concern of surgical risk and her low-demand sedentary lifestyle. After treatment, she experienced lesser pain on motion without any significant functional deficit on her daily activities. The follow-up radiographs at five months, fourteen months, and two years and a half showed the fracture was progressively displaced without callus formation (Figure 2). During the follow-up period, surgery was recommended for treating the non-union, but she confirmed her initial decision for conservative treatment. The teriparatide was given for 12 months and then stopped due to the poor bone healing response and the patient's request. A bone mineral density scan was performed and showed the T-scores of the total hip and the lumbar spine as –2.5 and –0.2, respectively. At the final follow-up, at 2.5 years, the patient reported mild pain during daily activities with nearly full range-of-motion, almost identical to the right elbow (Figure 3). She was satisfied with the outcomes of the conservative method.

Patient has given her informed consent for data allowance and publication. The present study has been reviewed and approved by the Institutional Review Board at Mahidol University, based on the Declaration of Helsinki (COA. MURA2021/62).

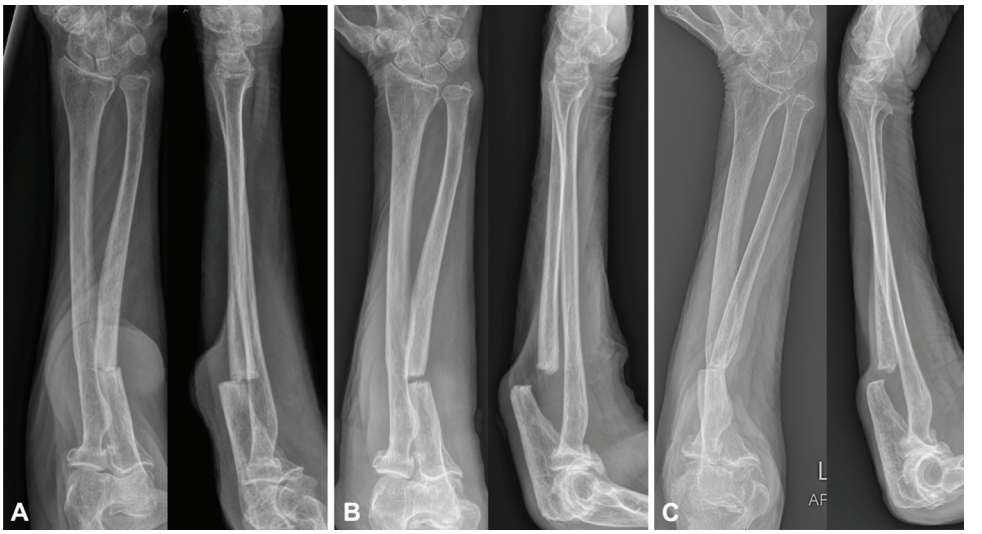

Figure 2. Follow-up radiographs of the atypical fracture of proximal ulna at 5 months (A), 14 months (B), and 2.5 years (C) showed progressive displacement and nonunion without callus formation.

Figure 3. Final clinical outcomes at 2.5 years follow-up. The patient had nearly similar range of motion for both elbows (A), with bony prominence on the proximal ulna fracture site (B).

Discussion

AFPU is a rare complication after long-term BP treatment. Theoretically, this condition is likely to be caused by the combined effect of SSBT and chronic repetitive bone microdamage[7], therefore, resulting in a high rate of non-union. However, to the authors' knowledge, no consensus exists for the treatment of this injury. The present case report aimed to demonstrate the clinical outcomes after the non-operative treatment in AFPU and reviewed the treatment of AFPU in the previous literature.

Regarding the clinical and radiographic features of AFPU in the present case, the findings were comparable with those in the previous systematic review study by Tan et al[6] and the report by Asano et al[8] for cases involving an elderly female, associated with only minor trauma history, located in the proximal third of the ulna, non-comminuted transverse, or short oblique fracture configuration, complete or incomplete fracture, and localized periosteal thickening (Figure 1, Table 1). The present case also supported the findings from the previous study by Cha et al[18] that the predisposing factors for AFPU were a total period of BP used more than 65 months and a prescription by multiple physicians, as shown by the different BP regimens in the present patient. Moreover, these findings also implied that screening for atypical lesion of the forearm in

patients who received long-term BPs, especially with forearm pain, is necessary for the prevention and early management of AFPU. In highly suspected cases, a bone scan and MRI would be recommended, just liked in the management of suspected AFFs[18]. However, the role of prophylactic surgery in AFPU remains controversial, and further studies are required.

The results of the present case were comparable with the previous studies and confirmed that the non-operative treatment in non-displaced or minimally displaced AFPU has a very high risk of late displacement and nonunion, as shown by the 100% nonunion rate in three cases, including the present case (Table 1)[16,17]. However, those cases involved only incomplete lesion, as demonstrated by a focal periosteal or endosteal thickening on the dorsal and lateral cortex of the proximal ulna in two cases with 100% union (Table 1)[8,16], may be appropriate for the conservative treatment of BP discontinuation, adequate calcium and vitamin D, immobilization (slab or cast) and weight-bearing protection, and possible adjunct with teriparatide medication. Regarding the long-term outcome of nonoperative treatment, the present case data also showed that the functional outcomes after AFPU non-union remain acceptable due to the low-demand sedentary lifestyle in the elderly who can avoid weight-bearing on their injured forearms during daily activities. These findings signify the role of non-operative treatment in some geriatric patients who are considered non-active and those who cannot tolerate the risk of surgical related complication.

Regarding the surgical treatment of displaced AFPU, the authors' literature review showed that the operative treatment can reliably achieve bony union as in ten cases with 100% union rate and 10% reoperation rate (Table 2)[4,7-15]. The operative treatment includes excision of the non-union tissue, open reduction, and internal fixation with locking compression plate or dual plates. Due to the risk of delayed union as the average union time was 11.7±8.2 months, bone grafting is usually recommended via autologous bone graft during surgery. Teriparatide should also be given in cases without contraindication. Although little supporting evidence exists, postoperative low-intensity pulsed ultrasonography (LIPUS) is an alternative option for fracture healing augmentation in AFPU.

Notably, the present study also had some limitations. First, the present case report focused on an atypical complication after prolonged BP therapy. The findings and literature review on nonoperative methods, therefore, provided only low-quality evidence for AFPU treatment. However, due to the rarity of AFPU, the results of the present study would be beneficial for the prevention and treatment in patients received long-term BP therapy. Second, the authors' literature review included articles from only an English-based database, which might be inadequate.

In conclusion, AFPU is a rare complication of prolonged BP therapy and requires physicians' awareness for prevention and detection. While atypical incomplete lesion can be successfully treated with the non-operative method, complete fractures of AFPU are most likely to progress as non-union. However, the long-term functional outcome of AFPU non-union is still acceptable in elderly patients with low demand of upper-extremity function during daily activities.

What is already known on this topic?

AFPU is the second most common atypical fracture associated with prolonged BP use. This fracture shared some common characteristics with AFF such as risk factors, fracture configuration, and high risk of non-union. Therefore, similar treatment strategy from AFF treatment guideline including operative treatment is usually applied in AFPU and shows the improvement of bony union rate. However, due to paucity of cases, there are no definitive guideline of AFPU management.

What this study adds?

The authors reported another case of AFPU who denied an operative treatment and, therefore, was treated with conservative methods for 2.5 years. Although, the fracture unsurprisingly progressed as non-union, her functional outcome was acceptable with satisfaction. Therefore, this case report showed the treatment strategy in AFPUs may have some different aspects from those in AFFs. Moreover, the authors have reviewed the literature involving treatment methods of AFPU, especially in conservative treatment, to describe the patient and fracture characteristics influencing the prognosis and summarized the role of conservative treatment in AFPU from available limited data.

Acknowledgement

The authors would like to thank the Department of Orthopedics, Faculty of Medicine Ramathibodi Hospital, Mahidol University for the kind assistance and for permission to conduct the study.

Table 1. Literature review of the nonoperative treatment of atypical fracture of proximal ulna associated with prolonged bisphosphonates therapy compared with current study

First author (year)	Age, sex	Comorbidities	Side	Frx type	Sclerosis	Duration of symptoms	BPs duration (year)	Treatment	Adjuvant	F/U period	Union status
Tang[17] (2011)	76 year, F	HTN, IHD, PUD, GERD, colonic diverticulitis	Lt	D	No	n/a	7	LAC	No	8 month	Nonunoin
Ang[19] (2013)	84 year, F	None	Bilat	ND	Yes	n/a	15	Backslab	No	n/a	n/a
Erdem[3] (2016)	62 year, F	T2DM, RA, HTN	Rt	D	Yes	7 days	7	LAC 4 weeks, SAC 2 weeks	No	6 week	n/a
Yam[16] (2017)	89 year, F	Hypothyroidism, HLP, gout	Bilat	Incomplete (Rt)	No (Rt)	n/a	10	Cast	No	1 year	Union (Rt)
				D (Lt)	Yes (Lt)						Nonunoin (Lt)
This study (2020)	80 year, F	HTN, HLP	Lt	ND	Yes	No	6	Backslab, brace	TPTD 1 year	2.5 year	Nonunoin

Frx=fracture; BPs=bisphosphonates; F/U=follow up; HTN=hypertension; IHD=ischemic heart disese; PUD=peptic ulcer disease; GERD=gastroesophageal reflux disease; T2DM=type 2 diabetes mellitus; RA=rheumatoid arthritis; HLP=hyperlipidemia; Lt=left; Rt=right; Bilat=bilateral, D=displaced, ND=non-displaced; n/a=not available; LAC=long arm cast; SAC=short arm cast; TPTD=teriparatide; mo=month

Table 2. Literature review of the operative treatment of atypical fracture of proximal ulna associated with prolonged bisphosphonates therapy

First author (year)	Age, sex	Comorbidities	Side	Frx type	Sclerosis	Duration of symptoms	BPs duration (year)	Treatment	Adjuvant	F/U period	Union status	Union time
Stathopoulos[15] (2011)	76 years, F	HTN, Sjogren's syndrome, secondary HPTH	Rt	D	No	No	7[a]	ORIF with plating	No	4 month	Union	4 month
Bjørgul[9] (2011)	82 years, F	None	Lt	ND	Yes	n/a	16	Excision, ORIF	BG	n/a	Union	n/a
Moon[4] (2013)	76 years, F	HTN, PD, ischemic stroke	Lt	D	No	No	12	ORIF with plating	No	6 month	Union	6 month
Chiang[10] (2014)	77 years, F	None	Rt	D	Yes	3 mo.	9	ORIF with plating	No	n/a	n/a	n/a
Osada[13] (2015)	85 years, F	None	Lt	D	Yes	No	7	Excision, ORIF	BG	1.5 year	Union	6 month
Shimada[14] (2017)	79 years, F	None	Rt	D	Yes	1 mo.	6	Excision, ORIF	BG, TPTD, LIPUS	1 year	Union	1 year
	89 years, F	None	Lt	ND	Yes	No	9	Excision, ORIF	BG, TPTD, LIPUS	1.5 year	Union	1.5 year
Oh[12] (2018)	72 years, F	None	Lt	ND	No	No	7	ORIF with plating	No	6 month	Union	6 month
Ito[11] (2019)	78 years, F	None	Lt	ND	Yes	6 mo.	10	1. ORIF with plating	No	34 month	Union	2.5 year
								2. Revision surgery with excision and ORIF	BG, TPTD, LIPUS			
Abe[7] (2020)	84 years, F	n/a	Lt	D	Yes	Yes	10	ORIF with dual plating	BG, TPTD, LIPUS	n/a	Union	11 month
Asano[8] (2020)	86 years, F	n/a	Bilat*	D (Lt)	Yes (Lt)	n/a	6	ORIF with plating	BG, LIPUS	2 year	Union	1 year

Frx=fracture; BPs=bisphosphonates; F/U=follow up; HTN=hypertension; HPTH=hyperparathyroidism; PD=Parkinson's disease; Lt=left; Rt=right; Bilat=bilateral; D=displaced; ND=non-displaced; n/a=not available; a=already received 2-year teriparatide treatment; ORIF=open reduction and internal fixation; BG=bone grafting; TPTD=teriparatide; LIPUS=low-intensity pulsed ultrasonography

* Presented data only for the fracture treated operatively

Conflicts of interest

The authors declare no conflict of interest.

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