Annals of Clinical and Medical Case Reports

Case Report ISSN 2639-8109 Volume 7

Tamoxifen May Have a Negative Effect on Bone Mineral Density in Fanconi Syndrome-Related Osteomalacia

Hatano M[1*], Kitajima I[1], Nakamura M[1], Isawa K[1], Suwabe T [2,3], Hoshino J [2,3], Sawa N[2,3] Yamamoto S[1]and Ubara Y[2,3*]

[1]Department of Orthopaedic Surgery, Toranomon Hospital, Tokyo, Japan

[2]Department of Nephrology and Rheumtology, Toranomon Hospital, Tokyo, Japan

[3]Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan

[*]Corresponding author:

Masaki Hatano, MD and Yoshifumi Ubara, Department of Orthopaedic Surgery and Department of Nephrology Center, Toranomon Hospital Kajigaya, 1-3-1, Takatsu, Kawasaki, Kanagawa, 212-0015, Japan,
Tel: 81-44-877-5111; Fax: 81-44-877-5333,
E-mail: hm0523jp@yahoo.co.jp; ubara@toranomon.gr.jp

Keywords:

Bisphosphonate, bone histomorphometry, Fanconi syndrome, osteomalacia, tamoxifen, selective estrogen receptor modulator

Received: 03 Sep 2021
Accepted: 18 Sep 2021
Published: 23 Sep 2021

Citation:

Hatano M, Ubara Y, Tamoxifen May Have a Negative Effect on Bone Mineral Density in Fanconi Syndrome-Related Osteomalacia. Ann Clin Med Case Rep. 2021; V7(9): 1-4

Abbreviations:

ALP: Alkaline Phosphatase; SERMs: Selective Estrogen-Receptor Modulators; Tc: Tetracycline

1. Abstract

A 61-year-old Japanese woman was admitted to our hospital for further examination of generalized bone pain. At age 46 years, the patient was diagnosed with Fanconi syndrome associated with benign monoclonal gammopathy of undetermined significance. At age 56 years, alkaline phosphatase (ALP) increased to 448 IU/mL. A bone biopsy was performed, and osteomalacia was diagnosed. The patient began treatment with active vitamin D_3 derivative (alfacalcidol) and sodium bicarbonate; ALP decreased but then it increased again to 742 IU/mL at age 57. Two years later at age 59, the patient developed generalized bone pain. Consequently, we re-examined the pathogenesis of the vitamin D-resistant osteomalacia in this patient. We noticed that tamoxifen was started as postoperative treatment after breast cancer surgery at the age of 58 years. Besides having positive effects in breast cancer, tamoxifen has been reported to have beneficial effects on bone mineral density; however, in our patient osteomalacia began to worsen when treatment with tamoxifen was started. The breast oncologist wanted the patient to continue with tamoxifen for another 2 years, so we started treatment with bisphosphonate preparation in combination with vitamin D therapy. ALP consequently decreased from to 400 IU/L but then remained at this level. Three years after tamoxifen was discontinued, the patient's severe bone pain subsided and ALP gradually returned to within the reference range. This case indicates that tamoxifen may have a negative effect in patients with Fanconi syndrome-related osteomalacia.

2. Introduction

Osteomalacia is caused by decreased bone mineralization, which results in increased osteoid volume. In older individuals, whose epiphyses have closed, osteomalacia can be caused by defective mineralization. Another cause of osteomalacia is Fanconi syndrome, in which proximal-type renal tubular acidosis (type 2) is associated with generalized proximal tubular dysfunction, such as glucosuria, phosphaturia, uricosuria, aminoaciduria, and tubular proteinuria [1]. In adulthood, acquired Fanconi syndrome can be caused by monoclonal gammopathies, including those associated with multiple myeloma and lymphoma [2,3].

Selective estrogen-receptor modulators (SERMs), eg, tamoxifen and raloxifene, are nonsteroidal compounds that act as estrogen agonists in some tissues and as estrogen antagonists in others [4]. Tamoxifen is widely used in the treatment of breast cancer and has beneficial effects on bone mineral density because it is a weak agonist on bone [5]. Raloxifene is the only SERM approved worldwide for the prevention and treatment of postmenopausal osteopo-

rosis and vertebral fractures [6]. However, no publications have reported on the efficacy of these drugs in osteomalacia.

Here, we present a case in which Fanconi syndrome-related osteomalacia worsened with tamoxifen, which was administered for treatment of breast cancer, and subsided after tamoxifen was discontinued. We report on the case findings and discuss the relation between SERMs and osteomalacia.

3. Case Presentation

A 61-year-old Japanese woman was admitted to our hospital for further examination of generalized bone pain. At age 43 years, urinary glucose was noted at a health check, but the patient had no associated symptoms. At age 46 years, the patient was diagnosed with Fanconi syndrome on the basis of the following criteria: hypophosphatemia (2.8 mg/dL), glycosuria (5.1 g/day), aminoaciduria (an increase in urinary excretion of 31 out of 39 amino acids), hyperuricosuria (serum uric acid, 1.4 g/dL), and proximal renal tubular acidosis with non-anion gap. Benign monoclonal gammopathy of undetermined significance was also diagnosed because IgG-kappa type monoclonal protein was detected in the urine and blood and multiple myeloma was excluded. At age 56 years, alkaline phosphatase (ALP) increased to 448 IU/mL (reference range: 117 to 350 IU/mL) (Figure 1), so a bone biopsy was performed. Bone histomorphometry was analyzed at the Ito Bone Science Institute, Niigata, Japan, and the findings are described in detail elsewhere [1,7]. Tetracycline (Tc) double labeling was also performed with doxycycline at a dose of 200 mg/day (with a schedule of 3 days on, 18 days off, 3 days on, and 49 days off).

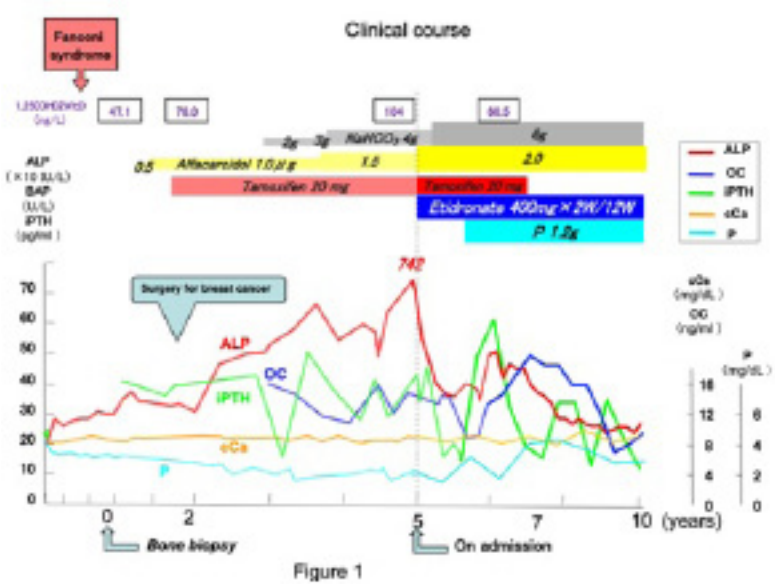


Figure 1: Clinical course. Results of blood tests performed over more than 10 years.
ALP, alkaline phosphatase; OC, osteocalcin; iPTH, intact parathyroid hormone; cCa, corrected calcium; P, phosphate

4. Bone Biopsy

Analysis of the bone biopsy sample led to a diagnosis of osteomalacia. The osteoid volume to bone volume was 16.3% (> 15% required for diagnosis according to the Sherrard et al. classification of renal osteodystrophy), and the fibrous tissue volume to total volume was 0% (< 0.5% required for diagnosis) (Figure 2, Table 1) [8].

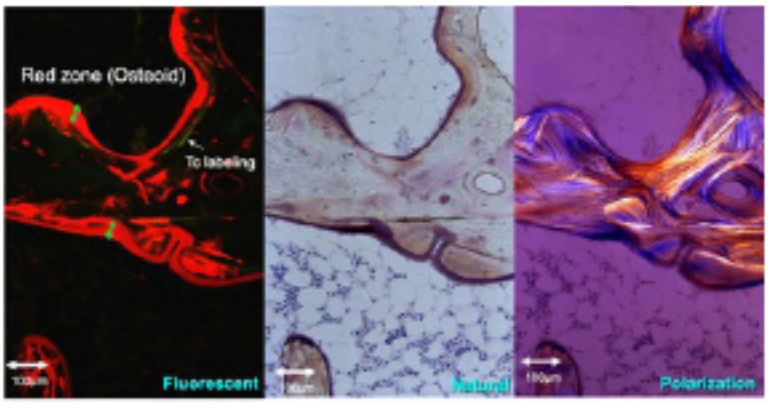


Figure 2: Natural light, polarization, and fluorescent microscopic analysis of the iliac bone section. An increase in osteoid (red zone) was observed on the bone surface. Binding of tetracycline was observed in only a few areas (white arrow).

Table 1: Histomorphometric analysis of the iliac crest

Parameter		Ratio or abbreviation	Unit	Measured value	Normal range
Bone volume	Bone volume	BV/TV	%	35.2	20.8±1.5
	Trabecular thickness	Tb.Th	μm	206.6	133.0±34.4
	Wall thickness	W.Th	μm	NM	30.34±3.45
Osteoid	Osteoid volume	OV/TV	%	5.78	0.44±0.24
	Osteoid volume	OV/BV	%	16.3	2.17±1.14
	Osteoid surface	OS/BS	%	79.1	16.7±6.99
	Osteoid thickness	O.Th	μm	16.9	9.16±2.0
Resorption	Eroded surface	ES/BS	%	15.4	5.6±1.94
	Osteoclast number	N.Oc/BS	N.mm	0.13	
	Fibrous volume	Fb.V/TV	%	0	0
Mineralization	Mineral apposition rate	MAR	mcm/day	0.61	0.526±0.044
	Double labeled surface	dLS/BS	%	16	
	Singlel abeled surface	sLS/BS	%	8.51	
	Bone formation rate	BFR/BS	mm3/mm2/year	0.045	0.015±0.008
	Bone formation rate	BFR/BV	%/year	43.4	22.6±12.5

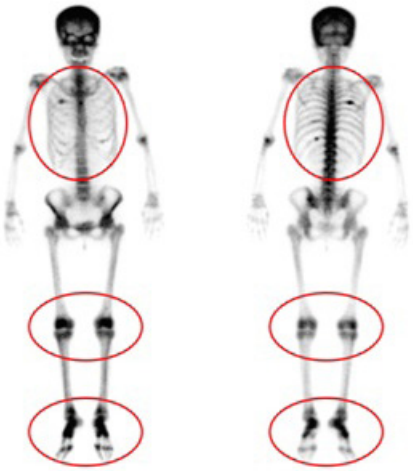
BFR/BV, bone formation rate per unit of bone volume; BV/TV, trabecular bone volume to total volume; ES/BS, eroded surface to bone surface; Fb.V/TV, fibrous tissue volume to total volume; N.Oc/BS, number of osteoclasts to bone surface; Ob.S/BS, osteoblasts surface to bone surface; OS/BS, osteoid surface to bone surface; O.Th, osteoid thickness; OV/BV, osteoid volume to bone volume; OV/TV, osteoid volume to tissue volume; Tb.Th, trabecular thickness; Th.W, trabecular unit wall thickness

5. Clinical Course

The patient began treatment with the active vitamin D_3 derivative alfacalcidol at a dose of 0.5 μg/day, and ALP gradually decreased. However, after 1 year ALP increased again to 742 IU/mL; the alfacalcidol dose was increased to 1 μg/day and sodium bicarbonate was started, but ALP continued to increase. Two years later, at age 59, the patient developed generalized bone pain. At the age of 61 years, the patient was admitted to our hospital for further examination of this bone pain.

On admission, the patient was 148.4 cm tall and weighed 42.2 kg. Her blood levels were as follows (see also Table 2): calcium, 8.6 mg/dL; phosphate, 2.1 mg/dL; ALP, 742 IU/mL (reference range: 117 to 350 IU/mL); bone ALP, 88.5 μg/L (reference range: 3.8 to 22.6 μg/L); osteocalcin 13.2 ng/mL (reference range: 3.1 to 12.7 ng/mL); intact parathyroid hormone, 41 pg/mL (reference range: 25 to 117 pg/mL); 1.25-dihydroxy vitamin D_3 104 pg/mL (reference range: 20 to 60 pg/mL); and 25-hydroxyvitamin D_3, 12.1 ng/mL (normal value: > 20 ng/mL). Bone scintigraphy with ^{99m}Tc-labeled methylene diphosphonate showed characteristic findings of osteomalacia, ie, intense uptake in multifocal regions, including multiple ribs and vertebrae and both ankle and knee joints. Dual energy X-ray absorptiometry found a T-score of -3.0 in the spine. (Supplemental material).

<Bone scintigraphy >



<BMD>

	Spine		Femoral neck	
	BMD	T-score	BMD	T-score
Bone biopsy	0.708	-2,7	NM	NM
Two year After	0.707	-2.7	0.429	-3.3
On admission	0.673	-3.0	0.421	-3.4

NM: Not measured

Supplementary material

Supplementary material: Bone scintigraphy revealed multifocal regions, including multiple ribs and vertebrae and both knee and ankle joints. Dual energy X-ray absorptiometry found a T-score of -3.0 in the spine.

Table 2: Laboratory Data

	On admission	Reference range
Alkaline phosphatase (U/L)	742	38-113
Bone-specific alkaline phosphatase (U/L)	88.5	3.7-20.9
Osteocalcin (ng/mL)	13.2	3.1-12.7
25O-hydroxyvitamin D (nmol/L)	12.1	>20
1,25-dihydroxyvitamin D(pg/mL)	104	20-60
Intact PTH (pg/mL)	41	15-65
Total protein (g/dL)	6.6	6.9-8.4
Albumin (g/dL)	3.9	3.9-5.2
Calcium (mg/dL)	8.6	8.7-10.1
Phosphate (mg/dL)	2.1	2.8-4.6
Creatinine (mg/dL)	0.8	0.47〜0.79
%TRP	59.5	<80
Tmp/GFR (mg/dL)	1.3	

On the basis of the above findings, we re-examined the pathogenesis of the vitamin D-resistant osteomalacia in this patient. We noticed that tamoxifen was given as postoperative treatment after breast cancer surgery at the age of 58 years, which was when the osteomalacia started to worsen. Consequently, we suspected that this drug was an aggravating factor in the patient's osteomalacia. However, the breast oncologist wanted the patient to continue taking tamoxifen for another 2 years. Therefore, we started treatment with bisphosphonate preparation in combination with vitamin D therapy. ALP subsequently decreased from 742 IU/L to 400 IU/L but did not decrease further. The patient discontinued tamoxifen as planned, and 3 years later the severe bone pain subsided and ALP gradually returned to within the reference range. Ten years later, at the time of writing this article, the patient continues to do well.

6. Discussion

We describe a case of Fanconi syndrome-related osteomalacia that worsened after treatment with tamoxifen and improved after tamoxifen was discontinued.

Drug-induced Fanconi syndrome, which causes hypophosphatemic osteomalacia, was reported to be closely associated with adefovir dipivoxil treatment for hepatitis B [7] and with a number of other drug treatments. The characteristic feature of the disease is that it develops after initiation of drug treatment and improves when the drug is discontinued [9].

To our knowledge, this is the first report of a relationship between a SERM and osteomalacia. Many studies suggest that tamoxifen actually improves bone mineral density and thus is effective in osteoporosis. For example, Michael et al. reported that tamoxifen inhibits osteoclast formation and bone resorption [10], and Yoneda et al found that tamoxifen can increase the bone mineral density of the lumbar spine in postmenopausal breast cancer patients [11].

In conclusion, although the literature indicates that tamoxifen may be effective in patients with postmenopausal osteoporosis, our case shows that this drug may have the opposite effect in patients with Fanconi syndrome-related osteomalacia.

7. Statement of Ethics

This investigation was conducted in accordance with the Declaration of Helsinki. The patient provided signed informed consent for the publication of this case report.

8. Disclosures

Masaki Hatano, Izuru Kitajima, Masaki Nakamura, Kazuya Isawa, Tatsuya Suwabe, Junichi Hoshino, and Naoki Sawa Seizo Yamamoto, Yoshifumi Ubara declare that they have no conflict of interest.

9. Acknowledgments

We wish to thank Mrs. Akemi Ito (Ito Bone Science Institute, Niigata, Japan) for bone histomorphometric analysis.

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