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ORIGINAL ARTICLE

Latent metabolic bone disease, skeletal dysplasia and other conditions related to low bone formation among 38 patients with subtrochanteric femoral fractures: a retrospective observational study

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Abstract

Summary Subtrochanteric femoral fracture is rare and intractable due to the possible association with low bone formation. Retrospective analysis of 38 patients with subtrochanteric femoral fractures revealed that four patients suffered from disorders related to low bone formation and there were specific treatments for two of them.

Purpose The main aim of this study was to detect latent metabolic bone diseases and skeletal dysplasia associated with low bone formation among patients with morphologic atypical femoral fracture (AFF). A second aim was to evaluate the frequency of recognized risk factors, such as antiresorptive agents, glucocorticoids, and age.

Methods Clinical information was retrospectively analyzed among 38 Japanese patients who were admitted to the Department of Orthopedic Surgery and Spinal Surgery and the Division of Emergency and Critical Care Medicine at the University of Tokyo Hospital with diagnoses of subtrochanteric fractures between February 2012 and March 2022.

Results Among 38 patients (including 30 females), 21 patients were aged 75 and over. Ten patients had past oral glucocorticoid use, and 18 had past antiresorptive agent use. Two patients were diagnosed with hypophosphatemic osteomalacia after the development of fractures. One patient was suspected to be a carrier of a loss-of-function variant of *alkaline phosphatase*, *biomineralization associated* (*ALPL*), and one other patient had previously been genetically diagnosed with pycnodysostosis. Among four patients with a diagnosis or suspicion of these metabolic bone diseases and skeletal dysplasia, four had past clinical fractures, two had past subtrochanteric femoral fractures, and two had subtrochanteric femoral fractures on both sides.

Conclusion If clinicians encounter patients with morphologic AFF, latent diseases related to low bone formation should be carefully differentiated because appropriate treatment may prevent delayed union and recurrent fractures. Additionally, it may be desirable to exclude these bone diseases in advance before initiating long-term use of antiresorptive agents in osteoporotic patients by screening with serum alkaline phosphatase levels to reduce the risk of morphologic AFF.

Keywords Atypical femoral fracture · Antiresorptive · Glucocorticoid · FGF23-related hypophosphatemic osteomalacia · Fanconi syndrome · Pycnodysostosis · Hypophosphatasia

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Introduction

AtypicalPlease femoral fracture (AFF) is a type of fracture that develops with weak external forces or without trauma in the subtrochanteric area or shaft of the femur [1]. More than three cases per 1000 patient-years of treatment involve AFF in osteoporotic women who have taken antiresorptive agents continuously for more than 8 years. The risk of AFF among antiresorptive agent users with osteoporosis is approximately eightfold greater in Asian women than in Caucasian women [2–4]. Bisphosphonate use is a historically well-recognized risk factor for AFF, and there are now multiple recent case reports regarding AFF after denosumab in bisphosphonate-naive patients [5–9]. Glucocorticoids are also a candidate risk factor for AFF in osteoporotic women who take antiresorptives [10, 11]. There are reports of the development of AFF after romosozumab treatment, although it is still unclear whether this treatment is associated with the development of AFF [12]. The incidence of AFF in people who have taken antiresorptive agents for skeletal metastasis for more than 1 year is more than 2%, perhaps because the cumulative annual absorbed dose of an antiresorptive agent in patients with cancer is about ten times greater than the cumulative annual absorbed osteoporosis dose [13–15].

More than one-third of patients with one AFF eventually develop contralateral AFF. The union of the AFF is often delayed, which places patients in adverse situations and suggests a slow healing response due to antiresorptive-based inhibition of Haversian remodeling, an underlying bone disease, or perhaps even a combination of the two [10, 16].

Several metabolic bone diseases, such as hypophosphatemic osteomalacia, including X-linked hypophosphatemic rickets/osteomalacia (XLH), tumor-induced osteomalacia (TIO), Fanconi syndrome, and vitamin D-dependent rickets (VDDR), and several skeletal dysplasias, including hypophosphatasia (HPP) and osteopetrosis, are recognized to cause fractures that are morphologically identical to the AFF [17–21]. Several reports indicating that morphologic AFF is sometimes associated with monogenic bone diseases have been reported, and several genes, including *ALPL*, *GGPS1*, *COL1A2*, and *CYP1A1*, have been identified as disease susceptibility genes by candidate-gene association studies and *genome-wide association* studies (GWASs) [17–32].

The updated epidemiology of AFF and the high frequency of bilateral fracture and delayed union in AFF suggest the possible existence of conditions and unidentified bone disorders that are associated with low bone formation, including the disorders mentioned above. Thus far, few studies have explored latent metabolic bone disease and skeletal dysplasia comprehensively in patients with atypical femoral fractures in a single cohort. In the current study, we retrospectively collected and analyzed the clinical characteristics of 38 patients with subtrochanteric fractures to reveal the presence of known risk factors such as bisphosphonate and glucocorticoid use, along with latent bone metabolic disorders and skeletal dysplasia associated with low bone formation.

Methods

Participants

Data on the clinical characteristics, recognized risk factors for AFF, and disorders associated with low bone formation were collected retrospectively from the clinical records of all 38 patients aged 15 or older admitted to the Department of Orthopedic Surgery and Spinal Surgery and Division of Emergency and Critical Care Medicine at the University of Tokyo Hospital between February 2012 and March 2022, with a diagnosis of subtrochanteric femoral fractures which are identical to the 2nd definition of AFF by ASBMR except for the inclusion of fractures among patients with already-recognized bone diseases [1].

Data collection

The following data were collected from each patient: age, date of diagnosis, height, weight, body mass index (BMI), laterality of subtrochanteric femoral fracture, past medical history, all past clinical fractures, past subtrochanteric femoral fractures, alcohol consumption, smoking, medication (specifically including bone modifying medications, such as antiresorptive agents, and glucocorticoids), plasma, serum, and urine laboratory data related to bone metabolism, and serum albumin (Alb), albumin adjusted calcium (cCa), inorganic phosphate (Pi), alkaline phosphatase (ALP), creatinine (Cre), γ-glutamyl transpeptidase (γGTP).

Biochemical measurements, including Alb, Ca, Pi, ALP, Cre, and γGTP, were assayed by JCA-BM8040 (JEOL, Tokyo, Japan) before May 2013 and LABOSPECT008 (Hitachi High-Tech, Tokyo, Japan), thereafter using the manufacturer's standard reagents.

Statistical analysis

Continuous data are presented as medians (interquartile ranges), and categorical data are summarized as numerical values (%). Chi-square tests to identify risk factors other than age were performed in two patient groups divided by several cutoff ages to evaluate the influence of age as a risk

factor for morphologic AFF. All the statistical analyses were performed with JMP Pro 16 (SAS Institute Japan, Tokyo, Japan).

Study approval

All procedures were performed following the ethical standards of the Declaration of Helsinki and were approved by the institutional ethical board of the University of Tokyo Hospital [Ref. 3820].

Results

Characteristics of 38 patients

Clinical characteristics of 38 patients are presented in Table 1. Among the 38 patients, 30 patients (79%) were female, 18 patients (47%) had past clinical fractures, six patients (16%) (patients #7, 12, 25, 26, 32, and 38) had past subtrochanteric fractures, and five patients (13%) (patients #7, 12, 25, 34, and 38) had subtrochanteric fractures on both sides (Table 2). Among the five patients who experienced subtrochanteric fractures on both sides, four patients (patients #7, 12, 25, and 38) had previous subtrochanteric fractures and developed new subtrochanteric fractures on the other side this time, while one patient (patient #34) developed incomplete bilateral subtrochanteric fractures simultaneously this time.

Laboratory data

The median serum Alb concentration was 3.4 g/dL, which was below the reference range (4.1–5.1 g/dL). The median serum Pi, cCa, Cre, and γGTP levels were within the reference ranges (Table 3). Among the 37 patients whose ALP could be obtained, ALP levels were within the reference interval in 30 patients and were lower and higher than the reference range in two and five patients, respectively. Among the two patients with low ALP, a 56-year-old male (patient #19) was suspected of being a carrier of a heterozygous *ALPL* variant due to mildly and continuously low serum ALP and a history of tibial fracture. There was another patient with low serum ALP levels (patient #13; the left endmost patient in Supplementary Fig. 1). He was treated with alendronate for 4 years, which was likely responsible for the low ALP level. Low ALP was observed only once on admission, so he was not suspected to be a carrier with a heterozygous loss-of-function variant for *ALPL*. Regarding the patients with high ALP levels, a 48-year-old female (patient #34) was diagnosed with TIO. One of the patients with high serum ALP levels (patient #8), who was in a wheelchair for 11 years due to complete paraplegia below Th10, was a 15-year-old male, and the ALP level was within the reference range for that age. Two patients (patients #28 and 35) showed high ALP levels, and at the same time, serum γGTP levels were also elevated; hence, liver dysfunction was probably the cause of high ALP levels. The other patient with persistently high ALP levels (patient #2) was retrospectively considered to have hypophosphatemic osteomalacia, but detailed differential diagnosis was difficult due to the lack of measurements for serum Pi.

Potential risk factors

The most frequent risk factors were age ≥ 75 years, antiresorptive agents, and glucocorticoids when combined with antiresorptive agents (Table 2). Among the 18 patients with antiresorptive agents, 15 (83%) were treated with osteoporosis doses of bisphosphonates, one changed alendronate to denosumab (60 mg/6 months), and two were treated with denosumab (120 mg/month) for bone metastasis of breast cancer (Supplementary Table 1). All patients in the glucocorticoid category were treated with prednisolone, and no patient was administered intravenous glucocorticoid (Supplementary Table 2). Four patients were treated with anticancer drugs; three patients (patients #28, 35, and 37) had breast cancer and the other patient (patient #20) suffered from lung cancer (Supplementary Table 3). As shown in the Venn diagram created to evaluate the overlap trend of major risk factors, 12 out of 21 patients who are 75 years or older did not have any other risk factor. According to the chi-square test, in the group of 17 patients aged < 75 years and the group of 21 patients aged ≥ 75 years, the number of patients without any of the eight risk factors in Table 2, except for age, were one (6%) and ten (48%), respectively ($p = 0.0048$). Similarly,

Table 1 Clinical characteristics of 38 patients with subtrochanteric femoral fractures

	All ($n = 38$)	Female ($n = 30$)	Male ($n = 8$)
Age, years: median (range)	82 (15–94)	82 (48–94)	77 (15–91)
Height, cm: median (range)	151 (138–172)	150 (138–172)	162 (140–169)
Body weight, kg: median (range)	48.7 (28.0–74.5)	48.7(28.0–74.5)	55.1(42.0–74.5)
Body mass index: median (range)	20.9 (14.7–29.8)	20.9 (14.7–29.8)	20.7 (16.0–26.1)
Smoking (%)	9 (24)	5 (17)	4 (50)
Drinking (%)	11 (29)	7 (23)	4 (50)

Table 2 List of whole patients with subtrochanteric femoral fractures

Patient number	Year	Month	Age	Sex	Antiresorptive agent	Glucocorticoid	Anticancer drug	Bone metabolic disease and skeletal dysplasia associated with low bone formation	Past clinical fracture	Past subtrochanteric femoral fracture	Subtrochanteric femoral fracture on both sides	Other risk factors
1	2012	Feb	91	F	No	No	No	No	**Yes**	No	No	
2		Apr	86	F	No	No	No	No	No	No	No	
3		Jul	84	F	No	No	No	No	No	No	No	
4		Sep	81	F	No	No	No	No	No	No	No	
5	2013	Jul	72	F	**Yes**	**Yes** (aortitis syndrome)	No	No	No	No	No	
6		Jul	64	F	**Yes**	**Yes** (linear IgA bullous dermatosis)	No	No	**Yes**	No	No	
7	2014	Jan	74	F	No	**Yes** (*Myasthenia gravis*)	No	**Fanconi syndrome**	**Yes**	**Yes**	**Yes**	
8		Jul	15	M	No	No	No	No	No	No	No	In a wheelchair for 11 years
9		Dec	85	M	No	No	No	No	**Yes**	No	No	
10	2015	May	79	F	**Yes**	No	No	No	**Yes**	No	No	
11	2016	Jan	91	M	No	No	No	No	No	No	No	
12		Jun	67	F	**Yes**	**Yes** (rheumatoid arthritis)	No	No	**Yes**	**Yes**	**Yes**	
13		Dec	83	M	**Yes**	No	No	No	No	No	No	
14	2017	Jan	88	F	No	No	No	No	No	No	No	
15		Jan	84	F	**Yes**	**Yes** (sarcoidosis)	No	No	**Yes**	No	No	
16		May	70	M	**Yes**	**Yes** (Castleman's disease)	No	No	No	No	No	
17		Nov	94	F	No	No	No	No	No	No	No	
18	2018	Apr	58	M	No	No	No	No	No	No	No	
19		May	56	M	No	No	No	**Suspected *ALPL* variant**	**Yes**	No	No	
20		May	61	F	No	No	**Yes** (lung cancer)	No	**Yes**	No	No	
21		Jun	82	F	No	No	No	No	No	No	No	
22		Jun	88	F	**Yes**	No	No	No	No	No	No	
23		Sep	93	F	No	No	No	No	No	No	No	
24		Nov	88	F	**Yes**	No	No	No	**Yes**	No	No	

Table 2 (continued)

Patient number	Year	Month	Age	Sex	Antiresorptive agent	Glucocorticoid	Anticancer drug	Bone metabolic disease and skeletal dysplasia associated with low bone formation	Past clinical fracture	Past subtrochanteric femoral fracture	Subtrochanteric femoral fracture on both sides	Other risk factors
25	2019	Apr	58	F	**Yes**	**Yes** (chronic eosinophilic pneumonia)	No	No	**Yes**	**Yes**	**Yes**	
26		May	68	F	**Yes**	**Yes** (systemic lupus erythematosus)	No	No	**Yes**	**Yes**	No	
27		May	86	F	**Yes**	No	No	No	**Yes**	No	No	
28		Jun	65	F	**Yes**	No	**Yes** (Breast cancer)	No	No	No	No	
29		Jun	83	F	No	No	No	No	No	No	No	
30	2020	Jul	84	F	No	No	No	No	No	No	No	
31	2021	Mar	89	F	**Yes**	No	No	No	**Yes**	No	No	
32		Apr	53	F	No	No	No	**Pycnodysostosis**	**Yes**	**Yes**	No	
33		Apr	85	M	**Yes**	**Yes** (Behçet's disease)	No	No	No	No	No	
34		Jul	48	F	No	No	No	**Tumor-induced osteomalacia**	**Yes**	No	**Yes** (on both sides simultaneously)	
35		Nov	63	F	No	No	**Yes** (breast cancer)	No	No	No	No	
36		Dec	88	F	**Yes**	No	No	No	**Yes**	No	No	
37		Dec	61	F	**Yes**	No	**Yes** (breast cancer)	No	No	No	No	
38	2022	Mar	62	F	**Yes**	**Yes** (*Myasthenia gravis*)	No	No	**Yes**	**Yes**	**Yes**	
n (%)					18 (47%)	10 (26%)	4 (11%)	4 (11%)	18 (47%)	6 (16%)	5 (13%)	

Table 3 Laboratory data

	Reference interval	Median (interquartile range)
Albumin ($n=36$) (g/dL)	4.1–5.1	3.4 (2.9–3.8)
Albumin adjusted calcium ($n=35$) (mg/dL)	8.8–10.1	9.2 (9.0–9.5)
Inorganic phosphate ($n=29$) (mg/dL)	2.7–4.6	2.9 (2.6–3.6)
Alkaline phosphatase ($n=37$) (U/L)	38–113 (20 years old and above) 95–420 (15 years old male, #8)	69 (59–94)
Creatinine ($n=37$) (mg/dL)	0.65–1.07	0.69 (0.62–0.98)
γ-glutamyl transpeptidase ($n=36$) (U/L)	Male: < 70 Female: < 30	17 (13–44)

Samples were collected on the day of admission for surgery

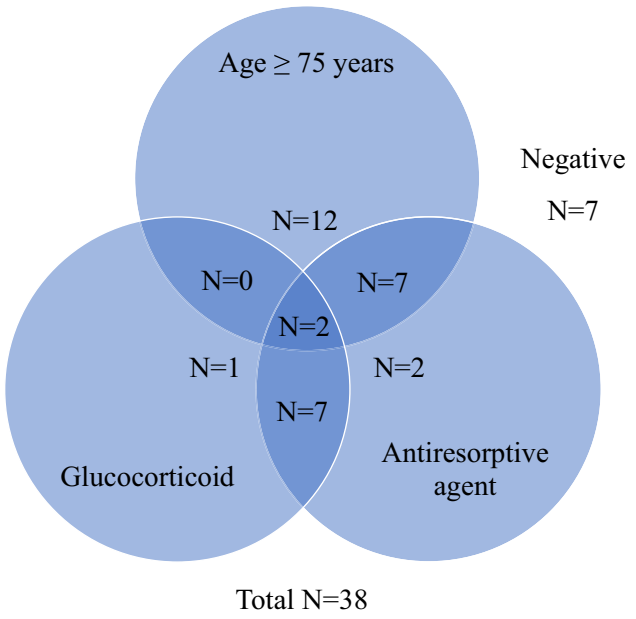

Fig. 1 The Venn diagram describes the number of age ≥ 75 years, antiresorptive agents (bisphosphonate or denosumab) users, and glucocorticoid users and their overlap in 38 patients who were diagnosed with subtrochanteric femoral fractures. Three out of 7 patients without these three risk factors were diagnosed with suspected carrier of heterozygous *ALPL* variant (patient #19), pycnodysostosis (patient #32), and TIO (patient #34), and the other two patients (patients #20 and 35) were treated with anticancer drugs

there were one (6%) and ten (50%) patients in the respective groups with the cutoff age of 80 years was used ($p=0.0026$) (Supplementary Table 5). The area under the curve (AUC) for the receiver operating characteristic (ROC) curve for predicting whether a patient had any risk factors other than age was 0.74, and the cutoff age with the maximum Youden's index was 79 years (Supplementary Fig. 2). In contrast, 16 out of the 18 patients treated with antiresorptive agents had additional risk factors; likewise, nine of ten patients who used glucocorticoids also received antiresorptive agents for osteoporosis (eight: bisphosphonates, one: denosumab) (Fig. 1).

Bone metabolic disorders and skeletal dysplasia associated with low bone formation were diagnosed or suspected in four participants (patients #7, 19, 32, and 34). Three of these were among seven patients without the aforementioned major risk factors (patients #7, 18, 19, 20, 32, 34, and 35); two were diagnosed with pycnodysostosis (patient #32) and TIO (patient #34), and one was suspected to be a carrier of a heterozygous *ALPL* variant characterized by consistently low serum ALP (patient #19). Patient #32 had already been diagnosed with pycnodysostosis with a genetic test before the fracture. Pycnodysostosis is characterized by a low rate of bone remodeling and osteosclerosis. This low rate of bone remodeling is associated with a low bone formation rate, much like that found in patients who take antiresorptives [33]. It was noteworthy that three (patients #7, 19, and 34) of the four patients had not been diagnosed with or suspected of these disorders until the time they developed AFF. Clinical data of those four patients are presented in Supplementary Table 4, and brief case reports are described in Supplementary Text 1 [34].

The associations of each risk factor with past clinical fractures, past subtrochanteric fractures and subtrochanteric fractures on both sides were investigated. The findings revealed that among four patients with diseases associated with low bone formation (hypophosphatemic osteomalacia and carriers of *ALPL* variants are associated with low bone mineralization), all four (patients #7, 19, 32, 34) had past clinical fractures, two (patients #7 and 32) had previous subtrochanteric femoral fractures, and two (patients #7 and 34) experienced subtrochanteric femoral fractures on both sides (Table 2).

Discussion

AFF is a fracture that occurs on the subtrochanteric femur or shaft of the femur with minor external force or without trauma, and the detailed 2nd definition of AFF was

introduced by ASBMR in 2013 [1]. A systematic review of 14 studies reported that the incidence of AFF was as low as 3.0 to 9.8 cases per 100,000 person-years [35], although the incidence of AFF in osteoporotic women who are treated with antiresorptive agents continuously for more than 8 years is more than three cases per 1000 patient-years of treatment [3, 4].

Similar to the purpose of our current study, Nguyen et al. [17] conducted a literature review to determine the presence of monogenic disorders among patients with AFF. In this article, 2566 relevant citations were searched, and reports of 23 individuals with seven monogenic bone disorders (osteogenesis imperfecta, pycnodysostosis, HPP, X-linked osteoporosis, osteopetrosis, XLH, and osteoporosis pseudoglioma syndrome) were identified. In eight patients, monogenic disorders were uncovered after the development of morphologic AFF [17]. Similarly, in a literature review by Zhou et al., AFF was reported in 57 patients with monogenic bone diseases; 17.5% of those patients were diagnosed after the development of AFF and 56.1% had no history of antiresorptive treatment [36]. These studies not only point out that both antiresorptive agent and particular metabolic bone diseases/skeletal dysplasia are independently associated with morphologic AFF, but also raise the possibility that when both antiresorptive treatment and monogenetic bone diseases exist simultaneously in the same individual, their effects on AFF may be additive. In one report, 14 of 16 untreated osteoporosis patients with persistently low serum ALP levels had loss-of-function mutations in the *ALPL* gene [37]. The serum ALP level is a serological marker of overt osteomalacia, especially when it is persistently elevated; therefore, clinicians should consider serum ALP levels to help exclude typical metabolic bone disease/skeletal dysplasia before initiating antiresorptive agents for osteoporotic patients [37, 38]. Based on serum ALP levels, two patients with metabolic bone disease/skeletal dysplasia were identified among four patients in the current cohort. However, in addition to serum ALP levels, detailed clinical examinations such as bone mineral density (BMD), past medical history, and medication history are necessary to thoroughly identify metabolic bone disease/skeletal dysplasia. The current study revealed that four out of 38 of the patients with morphologic AFF were suffering from definite and suspected bone diseases, and, notably, bone diseases were diagnosed or suspected only after the first morphologic AFF in three of them.

In this study, 16 out of 38 patients (42%) had a history of past bisphosphonate treatment. Bisphosphonate use is the most recognized risk factor for the development of AFF and the occurrence of AFF in osteoporotic women who have used antiresorptive drugs for more than 8 years is not uncommon [3, 4]. The development of AFF has also been reported in patients treated with denosumab [5–9, 39]. Although there is no definite evidence that anticancer drugs increase AFF, it has been reported that cyclophosphamide decreases osteoblasts and osteoclasts in mice, suggesting that particular anticancer drugs may suppress bone turnover in humans [40]. All 38 patients included in the current study were Japanese. Regarding racial differences, it has long been suggested that Asian race is a risk factor for AFF, and recently, Lo et al. reported that Asians were eight times more likely to develop AFF than non-Asians in a cohort in the USA, Nguyen et al. reported that Asians were 3.4 times more likely to develop AFF than non-Asians in a cohort in an Australian hospital, and Dhanekula et al. reported that Asian ethnicity increased the risk of developing AFF by sevenfold in an Australian multicenter cohort [2, 41, 42]. AFF risk is significantly greater in patients over age 65 than in those younger than age 65. In previous reports, the incidence rates were higher in the 65–74 and 75–84 age groups than in the 50–64 age group (2.24, 2.35, and 0.83 per 10,000 person-years, respectively) [11].

Patients younger than 79 years with morphologic AFF are more likely to have any risk factor other than age, such as bone metabolic disorders and skeletal dysplasia, should be excluded, especially when a patient is not treated with antiresorptive agents or glucocorticoids. In contrast, only one of the ten patients who used glucocorticoids had no other risk factors, thereby providing no evidence concerning the relationship between glucocorticoid use alone and AFF. Previously, Takahashi et al. reported that "antiresorptive treatment (> 3.5 years)" and "prior zoledronic acid treatment" were risk factors for developing AFF among bone metastatic patients with antiresorptive treatment [13]. The two denosumab cases with antiresorptive treatment in the current study suffered from breast cancer, and the durations of treatment (5 and 2 years) were shorter compared to the previous report (Supplementary Table 1).

Antiresorptive agents increase BMD by inhibiting bone resorption; nevertheless, long-term use increases the risk of AFF. It has been proposed that in the bones of antiresorptive agent users who develop AFF, the natural mechanism of dissipating energy and slowing crack propagation is impaired [43]. The main cause of AFF could be that microdamage in the lateral femoral cortex of the subtrochanteric region is not repaired in a timely fashion, due to the suppression of cortical bone remodeling by antiresorptive agents or the low rate of cortical bone remodeling in patients with metabolic bone diseases/skeletal dysplasia. Although the characteristic lateral periosteal callus forms normally, the gradual accumulation of unrepaired microdamage in the lateral femoral cortex leads first to unicortical fracture of the lateral femoral cortex and often thereafter to complete fracture through the medial cortex, at that point comprising a complete AFF. AFF occurs in patients with long-term antiresorptive agent use, pycnodysostosis, HPP, heterozygous loss-of-function variant with *ALPL*, and hypophosphatemic osteomalacia. On

the other hand, although osteoblastic function could largely be low in patients with long-term antiresorptive agent use and pycnodysostosis, compensatory activation of osteoblasts with an increase in osteoid is seen in HPP, heterozygous loss-of-function variants with *ALPL*, and hypophosphatemic osteomalacia, and also seen is an elevated ALP in hypophosphatemic osteomalacia. Therefore, although remodeling of bone hard tissue is low, remodeling of bone matrix protein is activated in these disorders [19, 44, 45].

Usually, serum ALP level is low among the disorders and conditions with low bone turnover, such as the patients using glucocorticoid and antiresorptive drugs, HPP, and patients with heterozygous loss-of-function variants in *ALPL*, while high serum ALP levels are typically observed in the patients with hypophosphatemic osteomalacia due to compensatory activation of osteoblasts. Therefore, paying attention to serum ALP levels might facilitate the detection of latent causative bone metabolic disorders and skeletal dysplasia among some patients with morphologic AFF, although ALP is not a perfect indicator because its level varies depending on several other factors. A recent study by Ng et al. reported that among 1839 patients visiting an osteoporosis clinic, seven (0.4%) had persistently low serum ALP levels. Five patients were genetically diagnosed with HPP, including four patients with persistently low ALP levels [46]. Similarly, Alonso et al. reported that out of 3285 patients in the osteoporotic clinic, 16 had low serum ALP and 14 of the 16 had *ALPL* gene variants [37]. HPP is a skeletal dysplasia caused by heterozygous, compound heterozygous, or homozygous variants in *ALPL* encoding ALP. Symptoms of HPP show a wide range and mild cases only present low serum ALP, arthrosis, and musculoskeletal pain. Such cases are mainly associated with loss of heterozygous function of *ALPL*, which has been shown to be dominantly inherited and relatively frequent (one in 187) [47–50]. In 2012, Sutton et al. reported a case of bilateral subtrochanteric fracture after 4 years of bisphosphonate use for osteoporosis with mildly low serum ALP and later demonstrated a heterozygous variant in the *ALPL* gene (c.212G > A, p. Arg71His). Based on this result, it was suggested that administration of antiresorptive agents to osteoporotic patients with even heterozygous loss-of-function variants of *ALPL* should be carefully considered to avoid the development of subtrochanteric fractures [51]. In the present case with low serum ALP (patient #19), a heterozygous variant of *ALPL* is suspected, given the previous tibial fracture. However, even if serum ALP was decreased by other causes, low ALP itself could be associated with the risk of morphologic AFF. In 30 patients with ALP within the reference range, 19 (63%) had lower levels of ALP than the middle of the reference range, where elevation of ALP levels was expected due to active fractures. Given that ALP is usually supposed to elevate after a fracture due to enhanced bone remodeling at the fracture site, which may reflect low bone remodeling in all bone areas except the fracture site due to antiresorptive therapy [52].

The median serum Alb concentration in this cohort was relatively low (3.4 g/dL) compared with the reference value. Decreased food intake or absorption, decreased muscle mass, proinflammatory cytokines, acute illness, and comorbidities are common causes of hypoalbuminemia [53]. Considering that more than half of the patients in this study were older than 75 years, it is possible that low muscle mass and a greater complication rate of chronic inflammatory diseases contributed to low albumin levels.

To our knowledge, this is the first attempt to evaluate latent bone metabolic diseases and skeletal dysplasia associated with low bone formation comprehensively among patients with morphologic AFF in a single-center cohort. However, the sample size of this study was too small to predict the actual frequency of these bone diseases in morphologic AFF. Moreover, the genuine number of patients with these disorders in the current cohort was uncertain because it was a retrospective study, and some participants lacked pivotal data to conduct the differential diagnosis. For example, three, nine, and one patients were missing serum cCa, Pi, and ALP data, respectively.

Because of the retrospective nature of the current study, there were several analytical limitations. One of the limitations is a lack of information about the laboratory data relating to bone metabolism. For example, lack of measurement of 25-hydroxyvitamin D, which meant we could not evaluate the involvement of vitamin D deficiency in the development of AFF, which was reported elsewhere [54]. Inappropriately low BMD for age and sex without derangement of the bone metabolism-related laboratory measurements might suggest the possibility of mild osteogenesis imperfecta and related skeletal dysplasia [55]. Thus, in combination with genetic tests, screening for BMD might help evaluate the involvement of other skeletal dysplasia, including mild cases of osteogenesis imperfecta, in the development of morphologic AFF. In addition, since data collection was conducted on the electronic medical record in our hospital, past medical history, including past fractures, might be inaccurate. In the future, to clarify the genuine prevalence of bone disorders among patients with morphologic AFF, the execution of a comprehensive study with a large number of patients with morphologic AFF equipped with a completed laboratory dataset for all participants, and genetic testing if needed, is warranted.

When clinicians encounter patients with AFF, the careful exclusion of bone metabolic diseases and skeletal dysplasia associated with low bone formation should be conducted, since, in the cases of these disorders, appropriate treatment or elimination of the causative factor will reduce the risk of delayed union and recurrent fracture as those were observed in cases 1 and 2 in the current study. Furthermore,

given that two out of the six patients with recurrent subtrochanteric fractures and two out of the five patients with subtrochanteric fractures on both sides had underlying bone metabolic disorders or skeletal dysplasia, in cases with these conditions, metabolic bone disease/skeletal dysplasia should be carefully differentiated. In addition, it is also desirable to exclude these bone diseases in advance before initiating long-term use of antiresorptive agents in osteoporotic patients to reduce the risk of the development of morphologic AFF. To determine the subjects who require a screening for metabolic bone disease/skeletal dysplasia, it might be adequate to select subsets of patients with high or low fasting, antiresorptive-free, measurement of serum ALP [37]. It is also important to confirm that the change in ALP levels is persistent and not transient because only the long-term suppression of bone formation serves as a risk factor for developing morphologic AFF.

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Data availability All data generated or used during the study are available from the corresponding author and first author upon reasonable request.

Declarations

Ethics approval All procedures were performed following the ethical standards of the Declaration of Helsinki and were approved by the institutional ethical board of the University of Tokyo Hospital [Ref. 3820].

Conflicts of interest None.

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