International Orthopaedics (SICOT) (2017) 41:2597–2603
DOI 10.1007/s00264-017-3610-3

ORIGINAL PAPER

Prevalence and clinical outcomes of hip fractures and subchondral insufficiency fractures of the femoral head in patients with tumour-induced osteomalacia

Hiroshi Kobayashi[1] · Nobuaki Ito[2] · Toru Akiyama[1,3] · Tomotake Okuma[1] · Yuka Kinoshita[2] · Masachika Ikegami[1] · Yusuke Shinoda[1] · Seiji Fukumoto[2] · Sakae Tanaka[1] · Hirotaka Kawano[1,4]

Received: 18 February 2017 / Accepted: 9 August 2017 / Published online: 23 August 2017
© SICOT aisbl 2017

Abstract

Purpose Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome usually caused by phosphaturic mesenchymal tumours, leading to great distress due to bone pain and affecting quality of life (QoL). This study aimed to investigate the prevalence and clinical outcomes of hip fractures and subchondral insufficiency fractures (SIF) of the femoral head.

Methods Twelve TIO patients were treated between January 2000 and December 2016 at our hospital. All underwent surgery for the tumour causing TIO, and complete removal of the tumour was accomplished in nine of 12 cases. Plain radiographs of the hip were obtained in all cases, and magnetic resonance imaging (MRI) was obtained from 15 hips representing eight patients before tumour removal. We evaluated the prevalence of hip fractures or SIF and their clinical outcomes.

Results Hip fractures were observed in six of 12 cases, and the total number of fractures was nine, of which five were femoral neck, two were intertrochanteric and two were subtrochanteric fractures. Conservative treatment, regardless of complete remission of TIO, was successful except in one case with impending subtrochanteric fracture. SIFs were observed in 11 of 24 hips. Seven of 11 hips with SIF showed progression after surgery for tumour resection.

Conclusions Hip fractures and SIF are highly prevalent in TIO patients. Surgical and medical treatment for TIO is sufficient for treating hip fractures conservatively. However, SIF tends to show progression of femoral head collapse, serving as the main cause of pain after successful TIO treatment.

Keywords Tumour-induced osteomalacia · Hip fracture · Subchondral insufficiency fracture

Electronic supplementary material The online version of this article (doi:10.1007/s00264-017-3610-3) contains supplementary material, which is available to authorised users.

✉ Hiroshi Kobayashi
hkobayashi-tky@umin.ac.jp

[1] Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[2] Department of Nephrology and Endocrinology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[3] Department of Orthopaedic Surgery, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama 330-8503, Japan

[4] Department of Orthopaedic Surgery, Faculty of Medicine, University of Teikyo, 2-11-1, Kaga, Itabashi-ku, Tokyo 173-8606, Japan

Introduction

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome that is usually associated with phosphaturic mesenchymal tumours (PMTs) [1]. This condition is characterised by high levels of fibroblast growth factor 23 (FGF-23) secreted by the tumours, causing reduced reabsorption of phosphate in the proximal renal tubule, which results in hypophosphataemia and hyperphosphaturia [2]. Hypophosphataemia results in osteomalacia, and patients often suffer from muscular weakness and bone pain for a prolonged period before diagnosis [3, 4]. In particular, pain and disability of the hip have a significant impact on health-related quality of life (HR-QoL).

Hip fractures are common and often devastating injury in the geriatric population. Although most are due to osteoporosis, disorders affecting bone strength such as renal osteodystrophy and osteomalacia lead to insufficiency hip fractures, which are difficult to treat due to bone softness [5]. Subchondral insufficiency fracture (SIF) of the femoral head without any evidence of predisposing osteonecrosis has been proposed as a new concept regarding femoral head collapse [6]. In general, insufficiency fractures are caused by physiological stress on bones deficient in elastic resistance; therefore, SIF occurs mainly in elderly osteoporotic patients and in renal transplant recipients [7, 8]. Some SIF progress to collapse, necessitating surgery, whereas others resolve with conservative treatment [9, 10].

To our knowledge, no previous study has reported the prevalence and clinical outcomes of hip fractures and SIF in patients with TIO. Therefore, the study aimed to emphasise the importance of diagnosis and treatment of hip fractures and SIF in patients with TIO.

Materials and methods

Patients

Of 28 patients who complained of pantalgia and were diagnosed with TIO by endocrinologists, 12 were referred to the orthopaedics department at our hospital between January 2000 and December 2016, because their tumours were located in the extremities and the trunk. This study assessed these 12 patients, and they underwent surgery for the tumour causing TIO. Our hospital's institutional review board approved this study. Inclusion criteria were adult patients diagnosed with TIO and had been followed up for at least 6 months. Exclusion criteria were patients who would only receive medical treatments. All procedures described in this study were performed according to the ethical standards of the Declaration of Helsinki of 1975, revised in 2000, as well as the national law.

Imaging studies

Plain radiographs of the hip were obtained in all cases before tumour removal. Fractures were classified into intertrochanteric, subtrochanteric or femoral neck fractures. Intertrochanteric and subtrochanteric fractures were diagnosed based on the presence of the fracture line on a plain radiograph. Neck fractures were diagnosed based on the presence of varus deformity of the femoral head on plain radiographs or fracture line on magnetic resonance imaging (MRI). Examinations for hip fracture and SIF were performed in on individual hip pain. Diagnosis of bone healing was based on loss of fracture line or sclerotic changes at fracture site. MRI was performed before tumour removal in patients with hip pain. MRIs were obtained from 15 hips representing eight patients. SIF was diagnosed based on the following criteria: (1) no apparent abnormalities or sclerotic changes due to callus formation in the subchondral area and/or femoral head collapse as observed on a plain radiograph; (2) diffuse bone marrow edema pattern accompanied by a band-like low-signal-intensity lesion within the bone marrow edema pattern in the femoral head, observed on T1-weighted MRI [9]. We classified SIF hips based on the intensity of subchondral bone on fat-suppressed T2-weighted images using a previously reported method: type 1, high intensity; type 2, heterogeneous intensity; type3, low intensity [10].

Postoperative monitoring and follow-up

FGF-23 levels were measured 24, 48, and 72 hours after surgery. All patients were instructed to visit the Orthopedic and Endocrinology Department for follow-up at two to three months after surgery and every three to six months thereafter. Endocrinologists administered medical therapies to patients whose serum phosphorous levels did not return to normal. Successful treatment was defined by the presence of normal serum phosphate and FGF-23 levels at the last follow-up.

Results

Patient characteristics

Patient characteristics are presented in Table 1. The study involved three women and nine men, with a mean age of 56 years (range 37–69). Minimum follow-up period was six months (range 6–170). Tumours were located in the bone (n = 8), including femur (n = 5), ischium (n = 1), spine (n = 1), ilium (n = 1), and soft parts (n = 4), including plantar, upper arm, groin, and thigh (n = 1 each). Complete remission after tumour removal was accomplished in nine of the 12 cases (Supplementary Table 1).

Hip fractures

Hip fractures were observed in six of 12 cases, and the total number of hip fractures was nine, of which five were neck, two were intertrochanteric and two were subtrochanteric (Table 2). Hip pain was observed at a median of 7.2 years (range 2–20) prior to presentation. Patient 5, with concurrent neck, intertrochanteric and subtrochanteric fractures, suffered from hip pain for 11 years

Table 1 Characteristics of patients with tumour-induced osteomalacia and the prevalence of hip and subchondral insufficiency (SIF) fractures

Case	Age	Sex	Tumour location	Onset of hip pain prior to presentation (years)	Neck fracture	Intertrochanteric fracture	Subtrochanteric fracture	SIF	MRI	Follow-up (months)
1	51	M	Plantar	3	–	–	–	B	+	16
2	69	M	Upper arm	5	–	–	–	–*	–	56
3	37	M	Groin	3	–	R	L	–	+	170
4	67	M	Thigh	3	–	–	–	B	+	93
5	61	M	Femur	11	L	L	R	R	+	6
6	45	M	Femur	1	–	–	–	B	+	25
7	64	F	Ilium	2	L	–	–	R	+	29
8	53	M	Femur	2	L	–	–	–	–	77
9	40	F	Femur	2	–	–	–	–	–	85
10	59	M	Femur	2	–	–	–	–	+	72
11	62	M	Lumber spine	5	R	–	–	L	–	99
12	69	F	Ischium	20	L	–	–	B	+	120

B bilateral, *R* right, *L* left, *MRI* magnetic resonance imaging

(Fig. 1). Most patients had either left or right hip fracture, except in two cases with bilateral hip fractures. Among neck fractures, varus deformity of the femoral head was observed in all cases (Figs. 1 and 2), and MRI studies revealed intermittent linear hypointense signals in the femoral neck on T1-weighted images, suggesting that fractures were incomplete (Fig. 2). We allowed weight bearing for patients with hip fractures if they did not feel pain. Conservative treatment for neck, intertrochanteric and subtrochanteric fractures was successful, and they healed in about two to three months after tumour removal in cases with neck and intertrochanteric fractures (Table 2). Even incomplete remission of TIO resulted in fracture healing conservatively in one case, indicating that medical treatment with neutral phosphate and active vitamin D could be effective for fracture healing (Table 2). Prophylactic internal fixation was performed in patients with subtrochanteric fractures who had undergone tumour curettage at the femur on the ipsilateral side, and fracture healing was observed at about two months (Fig. 1).

Subchondral insufficiency fractures of the femoral head

SIF were observed in 11 of 24 hips (Table 3). Hip pain was observed at a median of 6.4 years (range 1–20) prior to presentation. In case 2, total hip arthroplasty (THA) was performed before presentation at our hospital due to collapse of the right femoral head.

Four of seven cases had bilateral SIF at the time of presentation (Fig. 3). One case (no. 5) showed flattening of the femoral head on plain radiographs\. MRI analysis detected a low-intensity band in the bone marrow edema in ten hips. Based on the intensity of subchondral bone on fat-suppressed T2-weighted images, hips were classified into three types: type 1, high intensity; type 2, heterogeneous intensity; type 3, low intensity [10]. Four hips were classified as type 1, two as type 2 and four as type 3. Weightbearing on the affected leg was not restricted. No progression of femoral head collapse was seen on plain radiographs in type 1 cases, but in all type 2 and 3 cases,

Table 2 Clinical outcomes of hip fractures

Case	Neck fracture	Intertro-chanteric fracture	Subtrochanteric fracture	Complete remission after operation	Bone union at final observation		
					Neck fracture	Intertrochanteric fracture	Subtrochanteric fracture
3	–	R	L	+		+	+
5	L	L	R	+	+	+	+
7	L	–	–	+	+		
8	L	–	–	+	+		
11	R	–	–	+	+		
12	L	–	–	–	+		

R right, *L* left

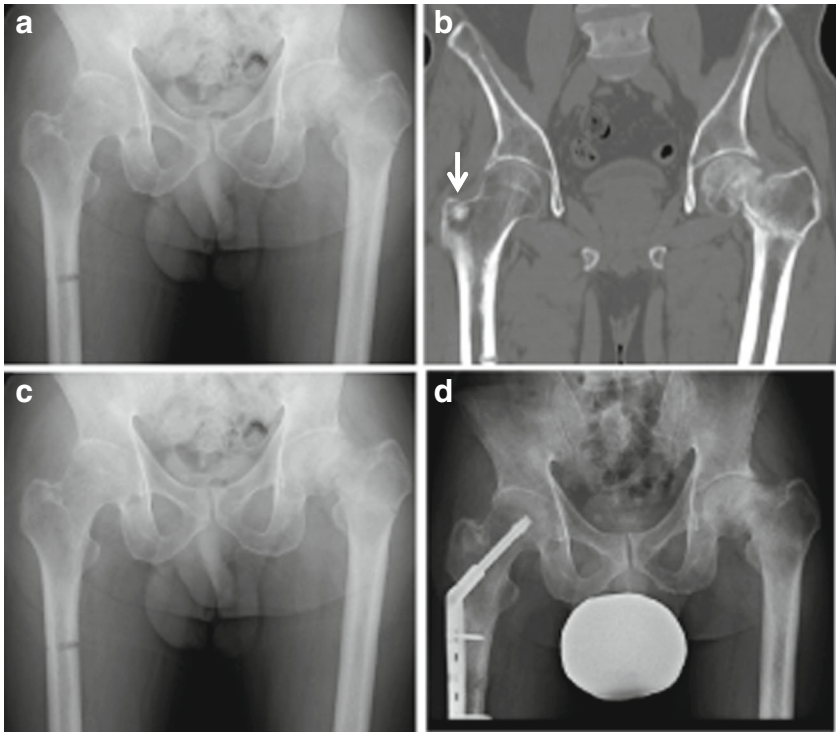

Fig. 1 Neck, inter- and subtrochanteric fractures (case 5): **a** Anteroposterior radiograph of the hip at first presentation. Varus deformity of the femoral head and intertrochanteric fracture line were observed at the left femur. Impending subtrochanteric fracture was observed at the right femur. **b** Coronal computed tomography (CT) image of the hip. Intermittent fracture line indicates incomplete neck fracture and intertrochanteric fracture. Tumour with sclerotic changes located in the greater trochanter (*arrow*). **c** Anteroposterior radiograph of the hip at one month after phosphate supplementation. Neck and intertrochanteric fracture of the left femur tended to heal conservatively, but the subtrochanteric fracture line at the right femur was obvious. **d** Anteroposterior radiograph of the hip two months after tumour resection. Femoral neck and intertrochanteric fractures were treated conservatively, and subtrochanteric fracture healed by internal fixation

femoral head collapse showed progression even if the tumour was completely removed; THA was required in one case.

Discussion

Tumour-induced osteomalacia is an extremely rare syndrome and an important cause of hypophosphataemia onset in adults [1]. TIO has been a challenging disease for clinicians for several reasons: nonspecific symptoms of osteomalacia; difficulties in finding the causative tumours; difficult anatomical location for tumour resection [1, 2, 11–13]. In particular, osteomalacia is a cause of insufficiency fractures, resulting in lower QoL of patients with TIO [1, 4]. It is important to not only remove tumours completely but also pay attention to the occurrence of insufficiency fractures, particularly hip fractures, which adversely affect QoL. To our knowledge, publications on hip fractures and SIF due to TIO include only a few

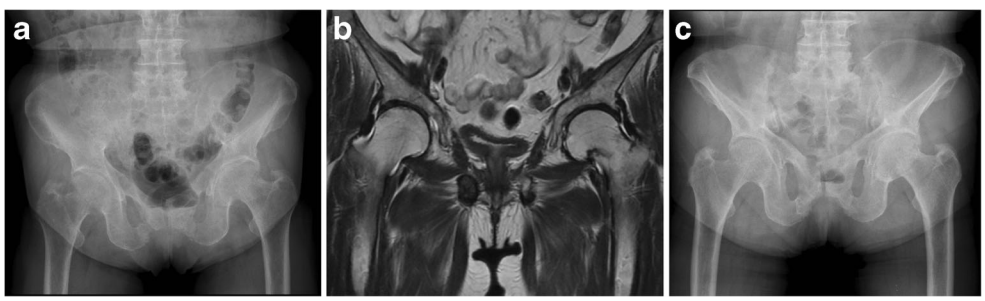

Fig. 2 Neck fracture (case 7): **a** Anteroposterior radiograph of the hip at first presentation. The cortex of the femoral neck was thin with indistinct and hazy margins. **b** T1-weighted image of hips showing intermittent linear hypointense signals in the subcapital region at the left femoral head. **c** Anteroposterior radiograph of the hip at two years and six months after tumour resection. The suspected pathologic fracture of the left femoral neck was treated conservatively; sclerotic changes at the subcapital lesion and thickening at the cortex of the femoral neck were observed

Table 3 Clinical outcomes of subchondral insufficiency fractures (SIF) and magnetic resonance imaging (MRI) findings

Case	SIF	Complete remission after operation	Plain radiograph before operation	MRI before operation		Plain radiograph at final observation
				Right	Left	
1	B	+	−	Type 2	Type 2	B. flattening
4	B	+	−	Type 3	Type 3	THA
5	R	+	−	Type 1	−	No change
6	B	+	−	Type 3	Type 3	B. flattening
7	R	+	−	Type 1	−	No change
11	L	+	L flattening	no study	no study	progression
12	B	−	−	type1	type1	no change

B bilateral, *R* right, *L* left, *THA* total hip arthroplasty

case reports [14]. In this study, we observed hip fractures in six of 12 cases and SIFs in 11 of 24 hips of patients with TIO. Although there could be selection bias because of referral to our orthopaedic surgery department, the rate of hip fractures and SIFs is considerable. These pathological situations are possibly overlooked because of their common symptoms, including whole body pain. In a few cases, SIF of the femoral head could progress to collapse, necessitating surgery. Such pathological situations are treatable conservatively by supplementation of neutral phosphate and active vitamin D or by tumour removal. Thus, our data recommend ruling out the possibility of hip fractures and SIF using diagnostic radiographsin patients with TIO.

In general, the majority of hip fractures are due to osteoporosis and falls. In all our cases, hip fractures were observed at the first presentation, and there was no history of trauma. Insufficiency hip fractures are also associated with a variety of conditions, such as vitamin D deficiency, Fanconi syndrome or renal dysfunction [4, 5, 14, 15]. Furthermore, in a few reports, the prevalence of osteomalacia among patients with hip fractures was reported to be 2.15–30% [16]. Our results indicate the importance of paying attention to insufficiency hip fractures in patients with osteomalacia, including TIO. The principal treatment of hip fractures is surgery, such as internal fixation or arthroplasty. However, in osteomalacia patients, surgical treatment alone is not successful due to softness of the bone [5]. Treating osteomalacia differs slightly depending on its cause. Osteomalacia as a result of vitamin D deficiency is curable by vitamin D supplementation. Moreover, Fanconi syndrome in adults is caused by various factors that damage the kidney, including treatment with certain drugs, kidney transplant, and multiple myeloma. Drug-induced Fanconi syndrome is curable by withdrawal of the causative drug, while other forms of the disease are cured by conservative treatment with vitamin D and phosphate supplementation. Genetic FGF-23-related hypophosphataemic disease is currently treated conservatively with vitamin D and phosphate supplementation, but in future, the anti-FGF-23 antibody could be a curative drug for this refractory disease [17]. For patients with TIO, tumour resection is a curable treatment, and medical treatment is effective in cases with unresectable or undetectable tumours [18]. In our study, most hip fractures were cured without surgical intervention by supplementation with neutral phosphate and active vitamin D or surgical resection of the tumours causing TIO. These results indicate that surgical treatment for such

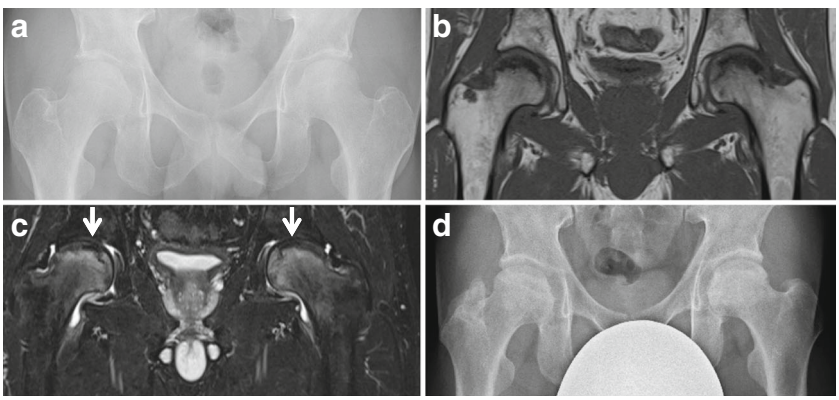

Fig. 3 Subchondral insufficiency fracture (SIF) (case 6): **a** Plain radiograph of the hip at first presentation showed no evidence of fracture or pathologic lesions. **b** A low-intensity band was observed on T1-weighted image. **c** Subchondral bone showed low intensity (*arrows*) on the fat-suppressed T2-weighted image. **d** Plain radiograph of the hip at two years after tumour resection showed collapse of both femoral heads

hip fractures is not an urgent necessity, as it can be preceded by medical treatment and resection of the tumour causing TIO.

Although SIF is generally observed in elderly women with osteoporosis [6], it is also reported in renal and liver transplant recipients receiving long-term glucocorticoid therapy [8, 19]. In our study, six of seven patients had no apparent abnormalities except osteopenia observed by plain radiographs; however, MRI revealed the presence of SIF. These results indicate that clinicians should suspect SIF in osteomalacia patients with hip pain, and MRI should be performed even if no abnormalities are observed on plain radiographs. Clinical outcomes of SIF are unclear. Some reports indicate that it could be healed conservatively, while other reports emphasise the necessity of surgery due to femoral head collapse [6–10]. Several prognostic factors, such as age, sex, degree of osteopaenia, activity, body weight and extent of fracture have been reported [20]. Furthermore, MRI findings are reported to be a predictive factor. Sonoda et al. reported that the subchondral intensity observed on fat-suppressed T2-weighted images can be classified into three types and that low-intensity subchondral bone (type 3) is a dismal prognostic factor [10]. In our cases, the four type 3 hips showed progression. However, the other four, which showed high-intensity signals on images of the subchondral bone (type 1), showed no changes. Among hips with heterogeneous subchondral intensity on fat-suppressed T2-weighted images (type 2), the healing rate in a previous report was 75%, but in our study, the two hips showed progression. These results suggest that type 2 and 3 cases tend to resolve less often with conservative treatment than type 1 cases. We believe the reason behind this poor prognosis is that we did not prohibit weight bearing, as opposed to a previously reported protocol of rest and restriction on weight bearing for 6 weeks.

Our study has some limitations. First is its retrospective design and the small number of patients. Limited clinical or imaging follow-up may have resulted in underdetection and progression estimation of SIF. Prospective studies with a larger number of patients are needed. However, to the best of our knowledge, this is the first case series on femoral neck fractures and SIF in patients with TIO.

In conclusion, hip fractures and SIF need to be considered in the differential diagnosis of hip pain in patients with TIO, and imaging examinations should be performed. Conservative treatment may be effective for most hip fractures. Furthermore, restriction of weight bearing could prevent SIF progression, findings of which are dismal on MRI. This study provides useful information for the diagnosis and treatment of TIO patients.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Fukumoto S (2014) Diagnostic modalities for FGF23-producing tumors in patients with tumor-induced osteomalacia. Endocrinol Metab 29:136–143. https://doi.org/10.3803/EnM.2014.29.2.136
2. Endo I, Fukumoto S, Ozono K et al (2015) Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment. Endocr J 62:811–816. https://doi.org/10.1507/endocrj.EJ15-0275
3. Jan de Beur SM (2005) Tumor-induced osteomalacia. JAMA 294:1260–1267
4. Chalmers J, Conacher WD, Gardner DL et al (1967) Osteomalacia–a common disease in elderly women. J Bone Joint Surg Br 49:403–423
5. Chalmers J (1970) Subtrochanteric fractures in osteomalacia. J Bone Joint Surg Br 52:509–513
6. Yamamoto T, Bullough PG (1999) Subchondral insufficiency fracture of the femoral head: a differential diagnosis in acute onset of coxarthrosis in the elderly. Arthritis Rheum 42:2719–2723
7. Yamamoto T, Iwamoto Y, Schneider R et al (2008) Histopathological prevalence of subchondral insufficiency fracture of the femoral head. Ann Rheum Dis 67:150–153
8. Vande Berg BC, Malghem J, Goffin EJ et al (1994) Transient epiphyseal lesions in renal transplant recipients: presumed insufficiency stress fractures. Radiology 191:403–407
9. Yamamoto T (2012) Subchondral insufficiency fractures of the femoral head. Clin Orthop Surg 4:173–180. https://doi.org/10.4055/cios.2012.4.3.173
10. Sonoda K, Yamamoto T, Motomura G et al (2016) Fat-suppressed T2-weighted MRI appearance of subchondral insufficiency fracture of the femoral head. Skelet Radiol 45:1515–1521. https://doi.org/10.1007/s00256-016-2462-z
11. Kobayashi H, Akiyama T, Okuma T et al (2017) Three-dimensional fluoroscopic navigation-assisted surgery for tumors in patients with tumor-induced osteomalacia in the bones. Comput Assist Surg 22:14–19. https://doi.org/10.1080/24699322.2017
12. Sun ZJ, Jin J, Qiu GX et al (2015) Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors. BMC Musculoskelet Disord 16:43. https://doi.org/10.1186/s12891-015-0496-3
13. Jiang Y, Xia WB, Xing XP et al (2012) Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. J Bone Miner Res 27:1967–1975. https://doi.org/10.1002/jbmr.1642
14. Chouhan V, Agrawal K, Vinothkumar TK et al (2010) Bilateral insufficiency fracture of the femoral head and neck in a case of oncogenic osteomalacia. J Bone Joint Surg Br 92:1028–1031. https://doi.org/10.1302/0301-620X.92B7.24526
15. Lee YS, Kim BK, Lee HJ et al (2016) Pathologic femoral neck fracture due to Fanconi syndrome induced by adefovir dipivoxil therapy for hepatitis B. Clin Orthop Surg 8:232–236. https://doi.org/10.4055/cios.2016.8.2.232
16. Riaz S, Alam M, Umer M (2006) Frequency of osteomalacia in elderly patients with hip fractures. J Pak Med Assoc 56:273–276

17. Imel EA, Zhang X, Ruppe MD et al (2015) (2015) prolonged correction of serum phosphorus in adults with X-linked Hypophosphatemia using monthly doses of KRN23. J Clin Endocrinol Metab 100(7):2565–2573. https://doi.org/10.1210/jc.2015-1551
18. Tatsumi F, Horiya M, Tanabe A et al (2016) Dramatic mitigation of bone pain after phosphorus replacement therapy in a subject with FGF23-related hypophosphatemic osteomalacia. Spring 5:1904. https://doi.org/10.1186/s40064-016-3602-6
19. Iwasaki K, Yamamoto T, Nakashima Y et al (2009) Subchondral insufficiency fracture of the femoral head after liver transplantation. Skelet Radiol 38:925–928. https://doi.org/10.1007/s00256-009-0706-x
20. Hackney LA, Lee MH, Joseph GB et al (2016) Subchondral insufficiency fractures of the femoral head: associated imaging findings and predictors of clinical progression. Eur Radiol 26:1929–1941. https://doi.org/10.1007/s00330-015-3967-x