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The Bone Phenotype and Pain Response to Pamidronate in Tyrosine Kinase Inhibitor–Treated Chronic Myelogenous Leukemia

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Tyrosine kinase inhibitors (TKIs) have been linked to bone pain and linear growth attenuation in children with TKI-treated chronic myelogenous leukemia (CML). We describe the skeletal phenotype in an 11-year-old boy with chronic bone pain due to TKI-treated CML, including his response to intravenous (IV) pamidronate. This boy was diagnosed with Philadelphia chromosome-positive CML at 4 years of age. He was treated with imatinib for 3 years, followed by dasatinib for 4 years. At age 11 years, he was seen in a bone health clinic with a 4-year history of leg pains that necessitated regular nonsteroidal anti-inflammatory drugs (NSAIDS) and downward crossing of height percentiles (from the 25th to fifth). The bone volume/tissue volume Z-score was +1.6 for a trans-iliac bone biopsy specimen, with an increase in trabecular number (Z-score, +3.1). Bone formation and resorption parameters on trabecular surfaces were within normal limits. Tibia volumetric bone mineral density (BMD) and bone geometry were normal by peripheral quantitative computed tomography, areal BMD Z-scores were average or above average at multiple skeletal sites by dual-energy x-ray absorptiometry, and tibia length Z-score was reduced (−2.3). Growth- and bone-related biochemical studies were unremarkable except a low serum alkaline phosphatase level. His bone pain resolved completely after 9 months of low-dose IV pamidronate. An increase in trans-iliac trabecular number and shortened tibia were the main skeletal features in this patient. Short-term IV pamidronate was effective for mitigating bone pain, allowing this boy to continue receiving dasatinib without the need for chronic NSAID therapy.

Freeform/Key Words: bisphosphonates, chronic myelogenous leukemia, bone histomorphometry, bone pain, growth, pamidronate, tyrosine kinase inhibitor, osteoporosis, fractures, osteomalacia

Chronic myelogenous leukemia (CML) is a rare hematological malignancy affecting between 0.6 and 1.2 million children per year, representing 2% to 3% of all pediatric hematological malignancies [1]. Greater than 90% of patients carry the Philadelphia chromosome, a genetic abnormality resulting from the fusion of the *BCR* and *ABL* genes, which expresses an active tyrosine kinase [2]. Selective inhibitors are considered standard of care for CML, blocking the

Abbreviations: BMD, bone mineral density; CML, chronic myelogenous leukemia; DXA, dual-energy x-ray absorptiometry; IGFBP-3, insulin-like growth factor-binding protein-3; NSAID, nonsteroidal anti-inflammatory drug; pQCT, peripheral quantitative computed tomography; TKI, tyrosine kinase inhibitor.

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oncogenic fusion protein BCR-ABL. These tyrosine kinase inhibitors (TKIs) have led to a 67% decrease in the risk of death from CML within a 2-year follow-up period [3]. Children receiving long-term TKI treatment are at risk for growth retardation [4] and bone pain [5] for reasons poorly understood.

The purpose of this report was to describe the skeletal phenotype in a boy with TKI-treated CML who was referred to a tertiary care bone health clinic with chronic nonsteroidal anti-inflammatory drug (NSAID) dependence due to substantial leg pain interfering with physical activities. We describe his bone health assessment in detail, including trans-iliac bone histomorphometry, three-dimensional bone and muscle imaging at the site of his bone pain (tibia), bone mineral density (BMD) at multiple sites by dual-energy x-ray absorptiometry (DXA), his linear growth trajectory plus radiographic, hormonal, and bone metabolic studies. We also describe the bone pain response to IV bisphosphonate therapy.

1. Clinical Report

We report on an 11-year-old boy diagnosed with Philadelphia chromosome-positive CML at 4 years of age. He was initially treated with imatinib and achieved all hematologic, cytogenetic, and molecular milestones. At age 7 years, he was switched to dasatinib because of renal impairment. He achieved molecular remission at 8 years of age and presented to the bone health clinic at age 11 years (after 7 years of TKI therapy) with complaints of leg pain for the past 4 years and attenuated linear growth. His leg pain interfered with physical activity and he required NSAIDS almost daily in the 2 years leading up to the bone health evaluation. He had not sustained any fractures nor did he complain of back pain.

2. Methods

Growth was assessed by serial anthropometry and hormonal studies. Bone biochemistry plus radiographs of the thoracolumbar spine, legs, and left hand were obtained by standard measures. Areal lumbar spine (L1 to L4), total body (less head), and total hip BMD were captured in the anterior-posterior direction by DXA using a Lunar Prodigy instrument (General Electric, Madison, WI). Raw BMD results were converted to age- and sex-specific Z-scores using reference data that were provided by the machine manufacturer. Muscle and bone density and geometry plus tibia strength (moment of resistance) were assessed by peripheral quantitative computed tomography (pQCT) at the left tibia using a Stratec XCT2000 device (Orthometrix, White Plains, NY), with results converted to age-, sex-, and tibia length–specific Z-scores (the latter for pQCT geometry measures). Tibia muscle and bone geometry measures are highly correlated with tibial length; therefore, tibial length was measured by physical landmarks, and Z-scores for these parameters were generated relative to tibial length [6]. A trans-iliac bone biopsy was performed after dual tetracycline labeling, with results expressed as the percentage of the healthy average [7]. Informed consent was obtained per local institutional review board standards.

3. Results

At age 11 years, skeletal deformity was absent in the patient, the gait was normal, and he was prepubertal. The height Z-score was −1.3, weight Z-score −0.6, and the upper to lower extremity ratio was 0.96. The patient's growth trajectory and midparental height are provided in Figure 1. The mother was of average height and the father was tall, giving a midparental height of 184.3 cm. Serum thyroid stimulating hormone, free thyroxine, ionized calcium, phosphate, and parathyroid hormone levels were normal. His history of calcium and vitamin D intake through diet was commensurate with Institute of Medicine guidelines for age [8], and six monthly 25-hydroxyvitamin D levels were consistently >50 nmol/L, including a level of 67 nmol/L at the time of the trans-iliac bone biopsy. In addition, insulin-like growth factor

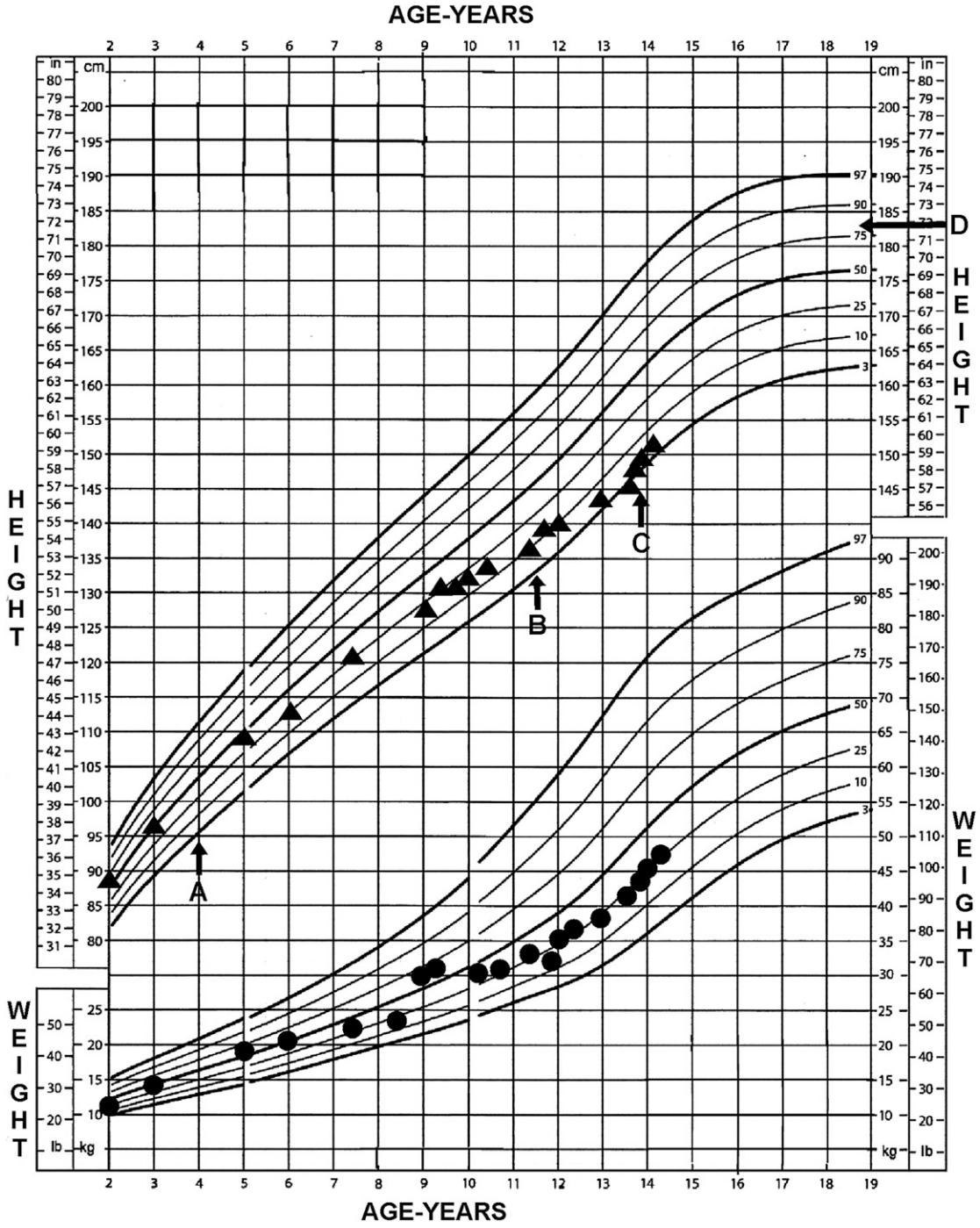

Figure 1. Growth trajectory in an 11-year-old boy with TKI-treated CML showing (A) the time at which initiation of TKI therapy was started, (B) the time pamidronate treatment was started, (C) the time of puberty onset, and (D) the midparental height.

binding protein-3 and IGF-1 levels were within normal range [IGFBP-3: 4.4 mg/L (normal range 2.7 to 9.5 mg/L); IGF-1: 128 μg/L (normal range 83 to 490 μg/L)].

The level of alkaline phosphatase (a bone formation marker) was below the reference range for age and sex (121 U/L; normal range 178 to 455 U/L) and the Z-score for c-telopeptide of type 1 collagen (CTX1; a bone resorption marker) was −1.0 [9]. Radiographs showed no evidence of rickets, skeletal dysplasia, or vertebral fractures; bone age was concordant with

chronological age [10]. On examination of the trans-iliac bone biopsy specimen, structural indices were all normal, consistent with absence of osteoporosis or osteomalacia. The bone volume/tissue volume was even above the healthy average, whereas the bone formation rate was below and the mineralization lag time was above the mean of the age-specific reference range (Table 1; Figure 2). Tibia pQCT-based muscle and bone parameters are shown in Table 2, revealing an above-average trabecular volumetric BMD, average moment of resistance, and shortened tibia. The lumbar spine, total body less head, and hip BMD Z-scores were normal to above average as follows: lumbar spine BMD −0.1; total body less head BMD +0.4; and total hip BMD +0.8.

To treat the chronic leg pain, the patient's most concerning symptom, IV bisphosphonate therapy (pamidronate 1 mg/kg) was given at 11 years of age and then repeated 4 and 9 months later. An IV bisphosphonate was chosen, given its previously reported positive effect on bone pain due to skeletal morbidity in childhood leukemia [11]. The bone pain resolved within 2 weeks of the first dose but returned in the weeks leading up to the second and third infusions. The pain has not recurred for up to 2.5 years after the third dose. At age 12 years and 9 months, he entered Tanner stage 2 pubertal development with subsequent improved growth velocity.

4. Discussion

Although TKIs for CML represent a major improvement over conventional chemotherapy, they exhibit a number of off-target effects, including bone pain and growth attenuation. We report on a child with TKI-treated CML who presented to our clinic with concern for both of these features. His in-depth skeletal assessment confirmed lack of osteoporosis or osteomalacia, given the absence of fractures, normal areal and volumetric BMD parameters at all measured sites, plus normal bone volume to tissue volume and mineralization parameters on a trans-iliac biopsy specimen. Furthermore, the bone formation rate, while below average, was nevertheless in the normal range. These are important observations, because serum biomarkers of bone turnover such as alkaline phosphatase and CTX are growth velocity–dependent and are expected to be attenuated in patients with slow linear growth, as they were in this patient. In such cases, direct measurement on trabecular surfaces after dual tetracycline labeling is required to quantify bone turnover. This study provides evidence in a

Table 1. Quantitative Trans-Iliac Histomorphometry After Dual Tetracycline Labeling in an 11-Year-Old Boy With TKI-Treated CML, Pre-Pamidronate

Parameter	Raw Result	% of the Healthy Mean	Age- and Sex-Matched Z-score
Structural parameters			
Bone volume/tissue volume, %	31.2	128	1.6
Trabecular thickness, μm	134	90	−0.6
Trabecular number per mm	2.3	141	3.1[a]
Formation parameter			
Osteoid thickness, μm	7.4	110	0.4
Osteoid surface/bone surface, %	20	91	−0.3
Osteoblast surface/osteoid surface,	8	140	0.9
Mineralizing surface/bone surface, %	8.4	72	−0.7
Mineralizing apposition rate, μm/d	0.92	106	0.6
Mineralization lag time, d	19.1	132	1.5
Bone formation rate/bone surface, $\mu m^3/\mu m^2/y$	28	76	−0.5
Resorption parameters			
Eroded surface/bone surface, %	18	121	0.6
Osteoclast surface/bone surface, %	1.2	127	0.7
Osteoclast number/bone perimeter, per mm	0.3	133	0.8

[a]Z-score substantially increased relative to normal.

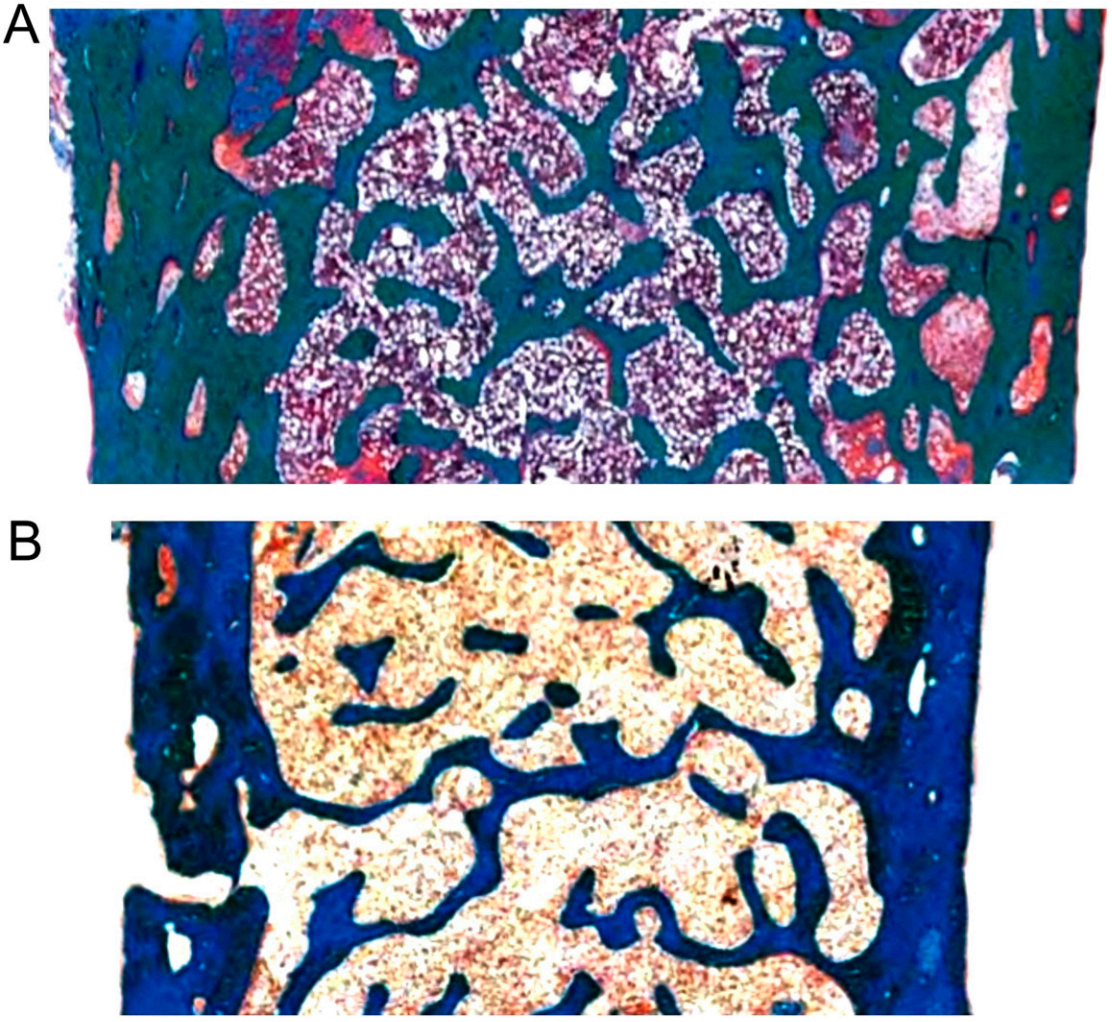

Figure 2. (A) Transiliac histomorphometry in an 11-year-old boy compared with (B) an age- and sex-matched control subject. Cortical width was determined at a ×32 magnification; all other measurements were determined at ×200 magnification.

child, that whereas serum biomarkers of bone turnover may be reduced due to attenuated linear growth, bone metabolism on trabecular surfaces may be preserved.

Although there are no other pediatric trans-iliac bone histomorphometry studies available for comparison, to our knowledge, this approach has been carried out on 11 adults with CML who received imatinib 600 mg/d but without dual tetracycline labeling; therefore, it was not possible to calculate dynamic parameters of bone metabolism in that study [12]. Again, trans-iliac bone biopsies were conducted serially by Vandyke *et al.* [12] at baseline and after 6, 12, and 24 months of imatinib treatment. Interestingly, a predominant finding was a substantial decrease in osteoclast number and osteoclast surface/bone surface after starting TKI therapy, along with increases in trabecular bone volume (due to an increase in trabecular thickness, but not number). The authors concluded that imatinib has an antiresorptive effect without dampening bone formation, and that this ultimately resulted in a higher trabecular bone volume at the iliac crest. On the other hand, the only skeletal site that showed an increase in DXA-based BMD was the distal radius, whereas changes were neutral at the spine and total body, and BMD declined at the femoral neck. Although the reasons for these site-specific differences in BMD by DXA in adults remain unclear (and furthermore, contrast with the consistently normal to above-average BMD results at all skeletal sites in the patient in our report), Vandyke *et al.* [12] proposed that the bone metabolic changes at the iliac crest were

Table 2. Tibia pQCT Muscle and Bone Parameters in an 11-Year-Old Boy With TKI-Treated CML, Pre-Pamidronate

Parameter	Raw Result	Z-score
3% site	250	0.5
Trabecular density, mg/cm^3		
Total bone mineral content, mg/cm	226	0.5
38% site	1085	0.5
Cortical density, mg/cm^3		
Periosteal circumference, mm	57.5	0.03
Endosteal circumference, mm	30.6	0.3
Cortical cross-sectional area, mm^2	189	−0.2
Cortical bone mineral content, mg/cm	205	0.0
Moment of resistance, mm^3[a]	953	0.0
Cortical thickness, mm	4.3	−0.5
66% site		
Muscle cross-sectional area, mm^2	4770	0.7
Fat cross-sectional area, mm^2	901	−0.7
Tibia length, mm	307	−2.3[b]

[a]A surrogate measure of tibia strength.
[b]Z-score substantially reduced relative to normal.

more likely the result of imatinib than CML disease remission, given a prior study showing that decreased bone marrow cellularity after interferon-α therapy for CML was not associated with a substantial change in iliac trabecular bone volume.

In contrast, osteoclast number and the percentage of bone covered by osteoclasts and eroded surfaces were not low in our patient in our report (in fact, they were all above average). We hypothesize that the disparity in observations at the bone tissue level between our patient and the adult study by Vandyke *et al.* [12] may be related to differences in TKI doses, lack of serial measurements in our patient to understand the direction of changes in bone cellular metabolism, or a difference in the bone tissue effect in a patient who is growing vs the more static adult skeleton.

DXA underestimates areal BMD in short children, which challenges the interpretation of areal BMD in this setting. In our patient, despite his short stature, all measured areal BMD parameters were normal or above average; furthermore, trans-iliac bone volume to tissue volume ratio and distal tibia volumetric BMD were above average. The lack of adverse effect of TKIs on bone volume and density are overall reassuring in this patient, given the current treatment paradigm of lifelong TKI therapy to maintain remission in pediatric CML.

Bone pain has been reported in 10% of TKI-treated children with CML [13]. In the patient we report on here, bone pain was sufficiently severe and long-standing to warrant referral to our clinic for consideration of alternative strategies to treat the leg pain. An IV bisphosphonate was chosen because of its proven analgesic effect in a variety of adult and pediatric settings, including cancer [11, 14–16]. Bisphosphonates appear to exert their analgesic effect by interfering with nociception, possibly mediated by the calcitonin gene–related peptide [17]. We observed permanent resolution of bone pain with pamidronate after three low doses spanning 9 months. This contrasts with the partial pain relief that the patient experienced with chronic NSAID therapy.

This patient's effective pain relief for up to 30 months after stopping pamidronate is similar to our experience with the long-lasting analgesic effects of IV bisphosphonate therapy in children with other painful bone conditions such as chronic recurrent multifocal myelitis and fibrous dysplasia [15, 18]. Given its overall safety profile and track record of effective use for the treatment of painful pediatric bone disorders, we propose that short-term IV pamidronate is a viable option for addressing chronic bone pain in TKI-treated children with CML.

Growth attenuation was also a concern for this patient, prompting an endocrine assessment that revealed normal thyroid function and IGFBP-3 and IGF-1 levels. The absence of thyroid dysregulation in our patient is similar to the findings in a report of six TKI-treated

children with CML [19]. On the other hand, thyroid dysfunction is a well-known adverse effect of TKI in adults, affecting 45% of patients [20]. The IGF-1 receptor is a tyrosine kinase; therefore, it is reasonable to postulate that the GH/IGF-1 axis may be impaired. Indeed, low levels of IGF-binding protein-3, IGF-1, and peak-stimulated GH levels have been observed in TKI-treated children with CML [19, 20]. GH/IGF-1 axis impairment has been further supported by low IGFBP-3 levels observed in TKI-treated juvenile rats [21]. Although the patient in this report had normal IGFBP-3 and IGF-1 levels, we recognize that normal GH studies can occur in GH-deficient patients [22], and that we cannot definitely rule out suppression of the GH/IGF-1 axis by TKI therapy.

In animal models of TKI-treated CML, shortening of long bones (*i.e.*, femurs and tibias) has been described [23]. Although the reduction in tibial length in our patient in this report (measured to carry out pQCT imaging at different sites along the length of the tibia) is consistent with these observations, in the absence of pretreatment tibial length data, it is not possible to determine whether the reduction in tibial length is directly related to TK inhibition. The growth impairment induced by TKIs has been postulated to link with impaired PDGFR-β signaling, resulting in diminished recruitment and/or activity of growth plate chondrocytes [20]. Interestingly, the increase in trabecular number in the trans-iliac biopsy specimen from our patient also calls into question growth plate function. Trabeculae are the product of secondary spongiosa, which arise directly from the growth plate through endochondral bone formation; an increase in trabecular number raises the question of whether there may be overproduction or lack of resorption of secondary spongiosa. Additional longitudinal study of bone histomorphometry in this patient, ideally following cessation of TKI therapy (if this were to arise clinically), may shed light on the relationship between TK inhibition and trabecular number.

In summary, this patient's skeletal phenotype was characterized by above-average bone volume/tissue volume ratio, an increase in trabecular number, normal bone turnover, shortened tibia, growth attenuation, and bone pain. Short-term, low-dose IV pamidronate was an effective strategy for treating the bone pain, permitting cessation of chronic NSAID therapy and a return to normal physical activities.

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References and Notes

1. de la Fuente J, Baruchel A, Biondi A, de Bont E, Dresse MF, Suttorp M, Millot F; International BFM Group (iBFM) Study Group Chronic Myeloid Leukaemia Committee. Managing children with chronic myeloid leukaemia (CML): recommendations for the management of CML in children and young people up to the age of 18 years. *Br J Haematol*. 2014;**167**(1):33–47.
2. Hochhaus A. Dasatinib for the treatment of Philadelphia chromosome-positive chronic myelogenous leukaemia after imatinib failure. *Expert Opin Pharmacother*. 2007;**8**(18):3257–3264.
3. Karalexi MA, Baka M, Ryzhov A, Zborovskaya A, Dimitrova N, Zivkovic S, Eser S, Antunes L, Sekerija M, Zagar T, Bastos J, Demetriou A, Agius D, Florea M, Coza D, Polychronopoulou S, Stiakaki E, Moschovi M, Hatzipantelis E, Kourti M, Graphakos S, Pombo-de-Oliveira MS, Adami HO, Petridou ET. Survival trends in childhood chronic myeloid leukaemia in Southern-Eastern Europe and the United States of America. *Eur J Cancer*. 2016;**67**:183–190.
4. Hijiya N, Millot F, Suttorp M. Chronic myeloid leukemia in children: clinical findings, management, and unanswered questions. *Pediatr Clin North Am*. 2015;**62**(1):107–119.

5. Suttorp M, Yaniv I, Schultz KR. Controversies in the treatment of CML in children and adolescents: TKIs versus BMT? *Biol Blood Marrow Transplant*. 2011;**17**(1, Suppl):S115–S122.
6. Dubner SE, Shults J, Baldassano RN, Zemel BS, Thayu M, Burnham JM, Herskovitz RM, Howard KM, Leonard MB. Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. *Gastroenterology*. 2009;**136**(1):123–130.
7. Glorieux FH, Travers R, Taylor A, Bowen JR, Rauch F, Norman M, Parfitt AM. Normative data for iliac bone histomorphometry in growing children. *Bone*. 2000;**26**(2):103–109.
8. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011.
9. Rauchenzauner M, Schmid A, Heinz-Erian P, Kapelari K, Falkensammer G, Griesmacher A, Finkenstedt G, Högler W. Sex- and age-specific reference curves for serum markers of bone turnover in healthy children from 2 months to 18 years. *J Clin Endocrinol Metab*. 2007;**92**(2):443–449.
10. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. 2nd ed. Redwood City, CA: Stanford University Press; 1959. https://doi.org/10.1097/00000441-195909000-00030.
11. Leblicq C, Laverdière C, Décarie JC, Delisle JF, Isler MH, Moghrabi A, Chabot G, Alos N. Effectiveness of pamidronate as treatment of symptomatic osteonecrosis occurring in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2013;**60**(5):741–747.
12. Vandyke K, Fitter S, Drew J, Fukumoto S, Schultz CG, Sims NA, Yeung DT, Hughes TP, Zannettino AC. Prospective histomorphometric and DXA evaluation of bone remodeling in imatinib-treated CML patients: evidence for site-specific skeletal effects. *J Clin Endocrinol Metab*. 2013;**98**(1):67–76.
13. Shami PJ, Deininger M. Evolving treatment strategies for patients newly diagnosed with chronic myeloid leukemia: the role of second-generation BCR-ABL inhibitors as first-line therapy. *Leukemia*. 2012;**26**(2):214–224.
14. Gralow JR. Bone density in breast cancer: when to intervene? *J Clin Oncol*. 2007;**25**(22):3194–3197.
15. Chapurlat RD, Delmas PD, Liens D, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *J Bone Miner Res*. 1997;**12**(10):1746–1752.
16. Trejo P, Rauch F. Osteogenesis imperfecta in children and adolescents-new developments in diagnosis and treatment. *Osteoporos Int*. 2016;**27**(12):3427–3437.
17. Abdulla AJ. Use of pamidronate for acute pain relief following osteoporotic vertebral fractures. *Rheumatology (Oxford)*. 2000;**39**(5):567–568.
18. TAKARA BIO Inc. Undercarboxylated Osteocalcin (Glu-OC) EIA Kit Manual. An Enzyme Immunoassay Kit for the Quantitative Determination of Undercarboxylated Osteocalcin (Glu-OC). Mountain View, CA: TAKARA BIO Inc; 2016.
19. Choeyprasert W, Yansomdet T, Natesirinilkul R, Wejaphikul K, Charoenkwan P. Adverse effects of imatinib in children with chronic myelogenous leukemia. *Pediatr Int (Roma)*. 2017;**59**(3):286–292.
20. Samis J, Lee P, Zimmerman D, Arceci RJ, Suttorp M, Hijiya N. Recognizing endocrinopathies associated with tyrosine kinase inhibitor therapy in children with chronic myelogenous leukemia. *Pediatr Blood Cancer*. 2016;**63**(8):1332–1338.
21. Ulmer A, Tabea Tauer J, Glauche I, Jung R, Suttorp M. TK inhibitor treatment disrupts growth hormone axis: clinical observations in children with CML and experimental data from a juvenile animal model. *Klin Padiatr*. 2013;**225**(3):120–126.
22. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab*. 2000;**85**(11):3990–3993.
23. Tauer JT, Hofbauer LC, Jung R, Gerdes S, Glauche I, Erben RG, Suttorp M. Impact of long-term exposure to the tyrosine kinase inhibitor imatinib on the skeleton of growing rats. *PLoS One*. 2015; **10**(6):e0131192.