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Case Report

Switching to burosumab from conventional therapy in siblings with relatively well-controlled X-linked hypophosphatemia

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Highlights

- Burosumab therapy was beneficial in siblings with mild X-linked hypophosphatemia.
- No adverse events were observed other than transient popliteal pain.

Abstract. Burosumab, a fully human monoclonal antibody against fibroblast growth factor 23, is mainly administered to patients with severe X-linked hypophosphatemia (XLH). However, there have been few reports on its use in relatively mild cases. In this report, we administered burosumab to two siblings with XLH who had been effectively treated with oral phosphate and active vitamin D. Both patients showed further improvement in radiographic and laboratory findings with burosumab compared with conventional treatment. Upon switching treatment, popliteal pain was reported in case 1 until her phosphorus levels normalized. This emphasizes the importance of monitoring not only rickets and calcium/phosphate metabolism but all symptoms of XLH after initiating burosumab. Notably, in cases 1 and 2, burosumab sustained catch-up growth, especially in case 1, who had not yet reached puberty. Further clinical studies are needed to determine whether burosumab improves growth and proportional abnormalities in patients with mild XLH.

Key words: X-linked hypophosphatemia, Rickets, Burosumab, Fibroblast growth factor 23, Rickets severity score

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Introduction

X-linked hypophosphatemia (XLH) is caused by a loss-of-function variant of the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene on chromosome Xp22.11 (1). Consequently, the expression of fibroblast growth factor 23 (FGF23) in osteocytes increases; however, the detailed mechanism of FGF23 regulation by *PHEX* remains unclear (2).

FGF23 decreases the expression of sodium-dependent phosphate cotransporter proteins (NaPi-2a and NaPi-2c) in renal proximal tubules, thereby downregulating phosphate reabsorption. In addition, FGF23 suppresses 25-hydroxyvitamin D-1α-hydroxylase expression and promotes 25-hydroxyvitamin D-24-hydroxylase expression, decreasing 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels and subsequently attenuating phosphate absorption from the intestine (3).

Based on previous studies, the estimated incidence of XLH is approximately 1:20,000 in Japan and North America (4, 5). Pediatric patients with XLH demonstrate wide variability in clinical manifestations, including delayed motor development, gait abnormalities, delayed and disproportionate growth, craniosynostosis, rickets, tooth abscesses, bone and joint pain, and muscle weakness (6). Thus, XLH is a multisystemic disease, so expertise in all aspects of XLH is essential when caring for these patients (7). The conventional treatment for XLH involves the oral administration of phosphate and active vitamin D. However, safety concerns such as hypercalcemia, hypercalciuria, nephrocalcinosis, and secondary hyperparathyroidism prevent the normalization of serum phosphorus levels in these patients (8). This may partially account for incomplete rickets healing, worsening skeletal deformities, and short stature with age (9).

Burosumab, a fully human monoclonal antibody against FGF23, improved rickets in pediatric patients with XLH who were previously treated with oral phosphate and active vitamin D compared with those who continued conventional therapy (10). Since 2019, burosumab has been approved in Japan for treating FGF23-mediated hypophosphatemic rickets/osteomalacia. However, to date, there are few reports of burosumab use in pediatric patients with XLH and a rickets severity score (RSS) of < 2 (mild symptoms) (9–11).

In this case report, we describe the effects of switching to burosumab in two siblings with XLH who had well-controlled disease with conventional therapy.

Case 1

An 8-mo-old girl with a height of 63.7 cm (–2.18 SD) and weight of 6,485 g (–1.85 SD) was referred to our pediatric endocrinology outpatient clinic because of failure to thrive. She did not have genu varum, craniotabes, joint swelling, or rachitic rosaries. The patient was born at 38 wk and 1 d of gestation with a height of 43 cm (–2.4 SD) and weight of 2,781 g (–0.1 SD). Her mother had a height of 152 cm. She had been administered oral phosphate and active vitamin D for rickets since childhood. There was no family history of XLH or short stature in maternal grandparents or paternal family members (**Fig. 1**). Laboratory examinations revealed hypophosphatemia, elevated alkaline phosphatase (ALP), inappropriately normal $1,25(OH)_2D$ levels, and elevated FGF23 levels (**Table 1**). The total RSS at diagnosis was 3.0, according to the radiographs (**Fig. 2**). Based on physical examination, family history, elevated FGF23 levels, and other laboratory findings, the patient was clinically diagnosed with XLH without genetic testing. She was subsequently

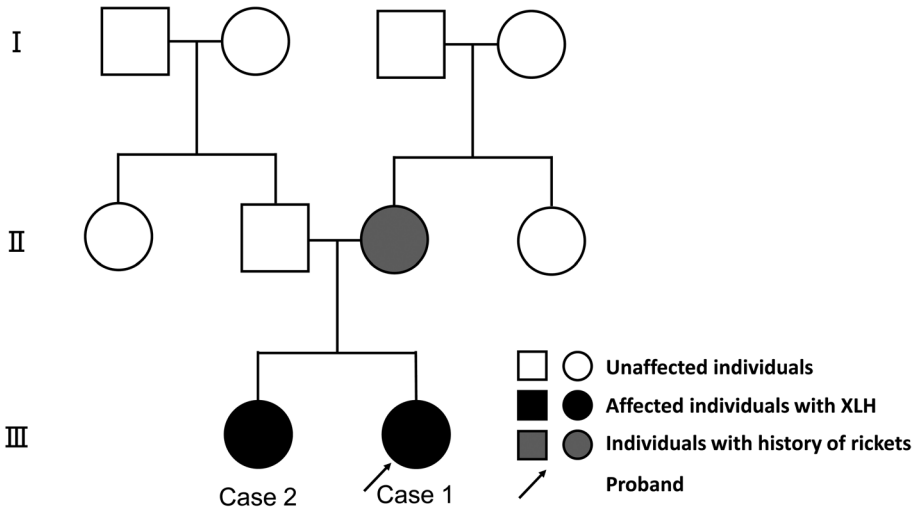

Fig. 1. Family tree of the patients included in this study. Open symbols indicate unaffected individuals and filled symbols indicate affected individuals. Black symbols represent individuals with XLH and gray symbols indicate individuals with a history of rickets. The arrow indicates the proband.

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Table 1. Laboratory data in cases 1 and 2

	Case 1						Case 2						Reference range
	At diagnosis	Under conventional therapy		Burosumab administration	post-administration		At diagnosis	Under conventional therapy		Burosumab administration	post-administration		
					2 mo	6 mo					2 mo	6 mo	
	0 yr 8 mo	1 yr 4 mo	3 yr 9 mo	5 yr 1 mo	5 yr 3 mo	5 yr 8 mo	5 yr 7 mo	6 yr 2 mo	8 yr 9 mo	9 yr 11 mo	10 yr 1 mo	10 yr 6 mo	
ALP (IFCC) (U/L)	680	625	321	382	421	418	647	532	389	390	366	403	6–10 mos old, 137–553; 4–7 yrs old, 151–455; and 10 yrs old, 165–508
Ca (mg/dL)	10	9.5	10.1	10.1	9.9	9.6	9	9.4	8.9	9.2	9.4	9.5	< 1 yr old, 9.0–11.0; 1–5 yrs old, 8.8–10.5; and 6–15 yrs old, 8.7–10.0
P (mg/dL)	2.9	4.1	3.4	3.1	3.6	4.3	2.3	3.5	4.3	2.8	4.2	4.2	1 mo to 1 yr old, 4.8-6.7; 4–5 yrs old, 4.2–5.9; and 6–15 yrs old, 3.8–5.5
U-Ca/U-Cre	0.07	NA	0.2	0.6	0.1	0.04	NA	< 0.01	0.04	0.1	0.05	0.02	< 1 yr old, 0.81; 1–6 yrs old, 0.3–0.5; and 7–17 yrs old, 0.24–0.25
TmP/GFR (mg/dL)	2.89	NA	2.74	2.83	3.27	3.7	NA	2.77	2.98	2.42	3.9	3.96	< 1 yr old, 5.6–6.5; 1–6 yrs old, 8.8–10.5; and 7–12 yrs old, 4.7–5.1
25(OH)D (ng/mL)	NA	NA	NA	26.8	NA	33	NA	NA	NA	31.5	NA	31.3	≥ 30
$1,25(OH)_2D$ (pg/mL)	48.9	NA	NA	NA	NA	NA	80.5	NA	NA	66.2	NA	NA	20–70
Intact PTH (pg/mL)	61	124	15	14	36	36	51	60	44	32	34	30	10–65
FGF23 (pg/mL)	140	NA	NA	NA	NA	NA	97	NA	NA	NA	NA	NA	< 30
Burosumab (mg)	–	–	–	10	10	20	–	–	–	20	20	20	–

NA, not available; ALP (IFCC), alkaline phosphatase (International Federation of Clinical Chemistry and Laboratory Medicine); Ca, calcium; P, phosphate; U-Ca/U-Cre, ratio of calcium to creatine; TmP/GFR, ratio of tubular maximum reabsorption rate of phosphate to glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23.

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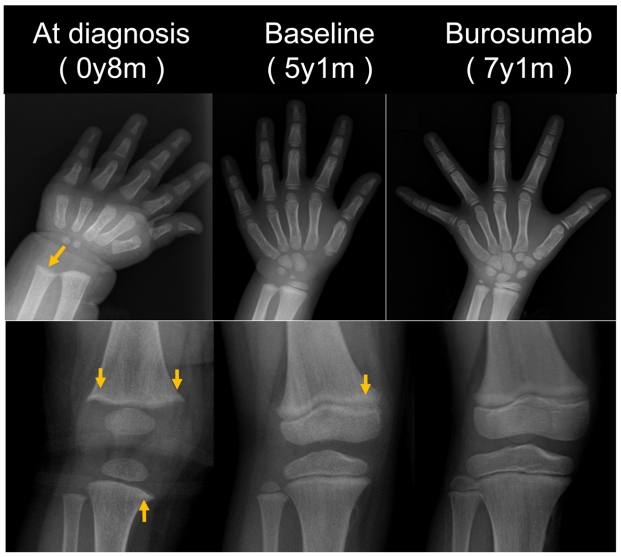

Thacher Rickets Severerity Score (mean)			
Wrist	0.5	0.25	0.25
Knee	2.5	0.75	0.25
Total	3.0	1.0	0.5
Radiographic Global Impression of Change Score (mean)			
	–	–	+2.0

Fig. 2. Radiographs and radiographical assessment for case 1. Left panels: Radiographs at the time of diagnosis show fraying at the distal metaphyses of the radius and ulna and cupping at the distal ulna. Middle panels: Fraying of the distal femoral and proximal tibial metaphyses is also observed. Radiographs taken 5 yr after the initiation of conventional therapy revealed mild hyperpermeability of the distal femoral metaphysis. Radiographs were evaluated and scored by two pediatric endocrinologists with experience in XLH, and the mean of the respective scores was noted. Burosumab treatment for 2 yr improved the rickets findings, as shown in the right panels (mean radiographic global impression of change [RGI-C] = +2.0).

administered oral phosphate and active vitamin D, and her laboratory and radiographic findings improved (**Table 1**, **Fig. 2**).

The patient received conventional oral therapy for 4 yr and 5 mo with good adherence; however, owing to the burdensome frequent oral medications, the family subsequently made a voluntary decision to switch to burosumab. To prevent hyperphosphatemia caused by burosumab, phosphate and active vitamin D were discontinued 2 wk before burosumab induction. Burosumab treatment was started at 10 mg (0.57 mg/kg) every 2 weeks at the age of 5 yr and 1 mo. The height and arm spans of the patient at the start of burosumab treatment were 101.2 cm (–1.30 SD) and 100 cm, respectively.

However, after 2 mo of treatment, serum phosphorus levels remained below the lower limit of normal (3.6 mg/dL; reference range: 4.2–5.9 mg/dL), whereas ALP levels increased to 421 U/L (IFCC) (reference range: 4–7 yr old, 151–455 U/L). The patient experienced bilateral popliteal pain. Increasing the dosage of burosumab to 20 mg (1.11 mg/kg) every 2 weeks normalized the serum phosphorus levels and phosphate reabsorption threshold (maximal tubular reabsorption of phosphate per glomerular filtration rate [TmP/GFR]) and reduced the pain (**Table 1**).

The growth rate of the patient increased from 7.49 cm/yr (+1.08 SD) to 7.91 cm/yr (+2.27 SD) after burosumab administration. Puberty started at the age of 7 yr and 7 mo when the patient's height was 121.3 cm (–0.17 SD) and arm span was 121.2 cm (**Fig. 3**). After 2 yr of treatment, the mean radiographic global impression of change (RGI-C) score improved to +2.0 (**Fig. 2**). The patient reported no adverse effects of burosumab except for popliteal pain and continued to receive 20 mg of burosumab every 2 weeks. No dental symptoms associated with XLH were observed during the follow-up.

Case 2

The older sister of the patient described in case 1 was born at 40 wk and 0 d of gestation, with a height of 50 cm (+1.0 SD) and a weight of 2,968 g (+0.7 SD). Following the diagnosis of XLH in the younger sister, the patient was brought to the pediatric endocrinology clinic at the age of 5 yr and 7 mo. At that time, the patient's height was 104.0 cm (–1.35 SD) and her weight was

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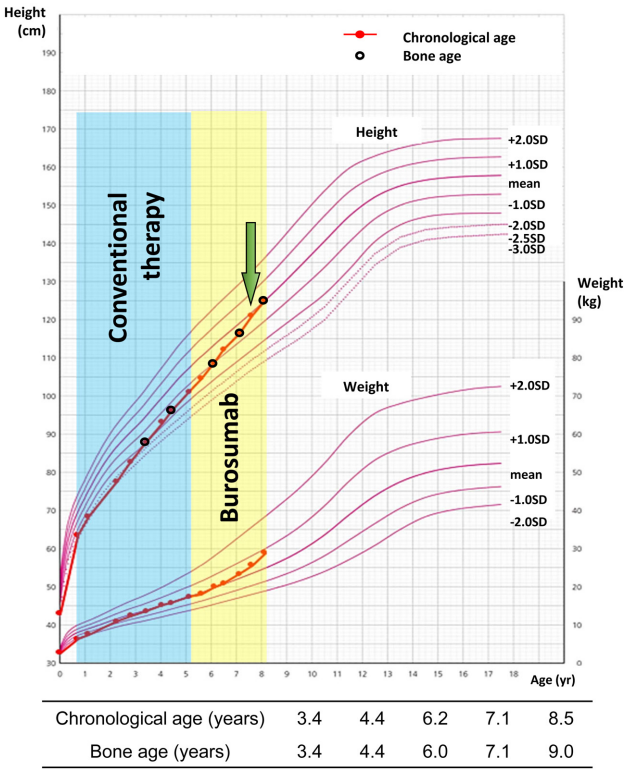

Chronological age (years)	3.4	4.4	6.2	7.1	8.5
Bone age (years)	3.4	4.4	6.0	7.1	9.0

Fig. 3. Growth chart of case 1. The growth curve of case 1 during treatment is shown. The arrow indicates the onset of puberty. Black circles indicate bone ages assessed using the Tanner-Whitehouse 2 radius-ulna-short bone (RUS) method standardized for Japanese children.

17.2 kg (–0.52 SD). Laboratory examinations revealed hypophosphatemia and elevated ALP and FGF23 levels (**Table 1**). Wrist radiographs show fraying of the distal metaphyses of the radius and ulna. Cupping was also observed in the distal ulnar region. Lower limb radiographs were not obtained. Based on these findings, XLH was clinically diagnosed without genetic testing. The patient had genu and calcaneal valgus (**Fig. 4A**), and experienced pain in the bilateral plantar and popliteal regions at 5 yr and 10 mo of age. An orthopedic team created a foot orthosis to alleviate pain in the plantar and knee regions.

The laboratory findings improved with the administration of phosphate and active vitamin D (**Table 1**). However, despite 2.5 yr of conventional therapy, genu valgum with a femorotibial angle of 168°/166° remained even at the age of 8 yr, when it should have physiologically subsided (**Fig. 4B**). Based on the radiographic findings and worsened knee pain during walking, temporary distal femoral hemiepiphysiodesis with an eight-plate system was performed in both legs. 6 mo post-operation, the genu valgum improved, and the pain disappeared; the patient underwent surgery to remove the implants.

Similar to case 1, the patient and her parents opted to switch to burosumab voluntarily because of

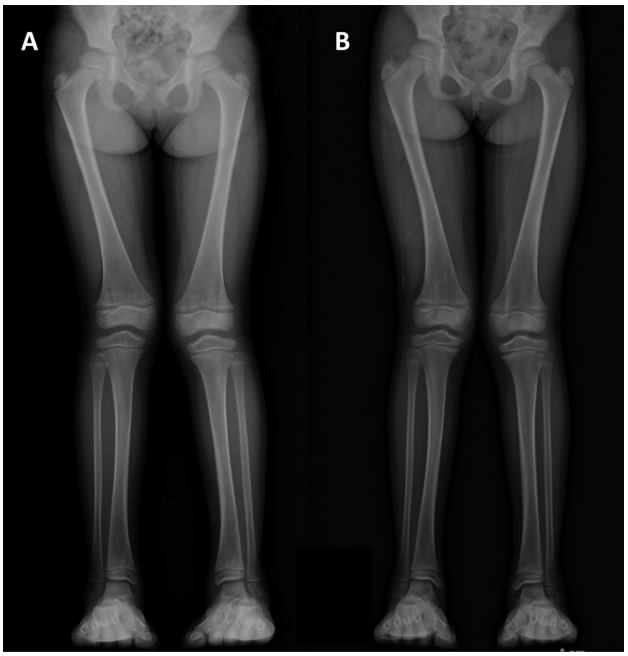

Fig. 4. Full-length standing leg radiographs for case 2. Full-length standing leg radiographs revealed abnormal lower limb alignment at 5 yr and 10 mo (A) and 8 yr and 4 mo (B).

the burdensome, frequent oral medications. After 4 yr and 5 mo, the conventional therapy was switched to burosumab 20 mg (1 mg/kg) every 2 weeks. The knee RSS at the time of burosumab therapy was 1.0 according to the radiographs (**Fig. 5**); however, no radiographs of the upper limbs were obtained. Burosumab treatment promptly improved serum phosphate levels and TmP/GFR (**Table 1**).

Following 2 yr of burosumab treatment, the patient's height increased from 130.2 cm (–1.0 SD) to 147.1 cm (–0.33 SD) and arm span expanded from 135.1 cm to 153 cm (**Fig. 6**). Because puberty occurred concurrently with burosumab initiation, the growth rate, which was 5.39 cm/yr (–0.01 SD) before burosumab administration, increased to 8.48 cm/yr (+0.57 SD). The mean RGI-C lower limb deformity score improved to +2.0 within 2 yr (**Fig. 5**). The patient reported no adverse effects due to burosumab and continued to receive 20 mg of burosumab every 2 weeks. No dental symptoms associated with XLH were observed during the follow-up.

Discussion

This report describes mild and well-controlled XLH in two siblings whose symptoms improved with burosumab treatment.

After 2 mo of burosumab therapy at an initial dose of 10 mg (0.57 mg/kg), the serum phosphorus level of case 1 remained below the lower limit of normal, and the patient experienced popliteal pain. Increasing the dose of burosumab to 1.11 mg/kg every 2 weeks normalized serum phosphorus levels and rapidly abated popliteal

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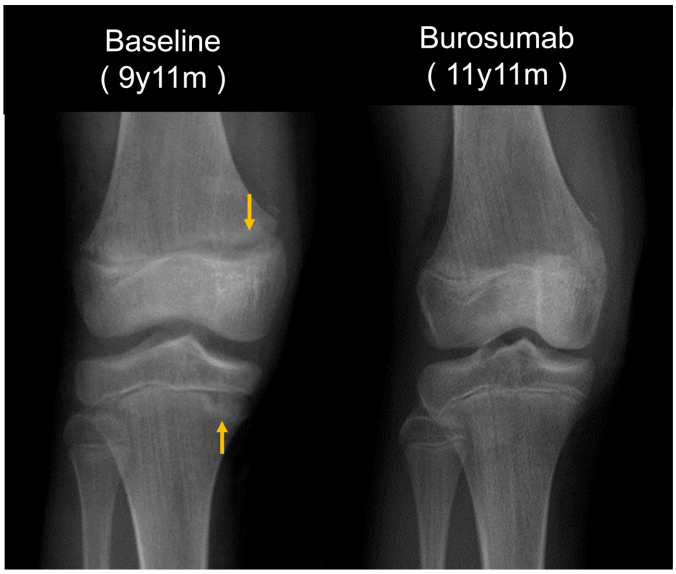

Thacher Rickets Severerity Knee Score (mean)	1.0	0
Radiographic Global Impression of Change lower limb deformity score (mean)	–	+2.0

Fig. 5. Radiographs and radiographical assessment for case 2. Left panels: Radiographs taken 5 yr after the initiation of conventional therapy showed mild hyperpermeability of the distal femoral metaphysis. Each rickets severity score or radiographic global impression of change (RGI-C) lower limb deformity was calculated as in **Fig. 2**. Burosumab treatment for 2 yr improved the rickets findings, as shown in the right panels (mean RGI-C lower limb deformity score = +2.0).

pain. As the site of pain was not consistent with the bone, we speculated that it was due to hypophosphatemia-related muscle weakness. Notably, in phase 2 and 3 trials of burosumab, pain in the extremities was reported by 30–40% of patients during the study period (9–11). Owing to the multisystemic nature of XLH, patients should be monitored carefully for such symptoms, in addition to rickets and calcium/phosphate metabolism, during the transition to burosumab treatment.

Both patients in this report had a low RSS with conventional treatment, indicating mild residual rickets; burosumab treatment further attenuated these scores. The RSS was originally developed to evaluate the severity of nutritional rickets (12), while the RGI-C score was created to assess changes in the skeletal burden of pediatric hypophosphatasia (13). Both scores help determine the therapeutic effect of burosumab on XLH (14). In a study, burosumab improved rickets and laboratory findings in pediatric patients with XLH compared to conventional therapy, with a total RSS of ≥ 2 (10). Moreover, burosumab improved rickets even in patients with a baseline RSS < 2 (15). This may be due to smaller fluctuations in serum phosphorus levels in these patients. If mild rickets persists despite conventional treatment, the radiographic findings may be further improved by switching to burosumab.

Case 1 had an obvious short stature at diagnosis; however, her height Z-score improved with conventional treatment. Starting conventional treatment in patients with XLH aged < 1 yr preserves their height Z-scores at the start of treatment and stabilizes their height Z-scores throughout childhood (16). Early diagnosis based on family history or other factors facilitates treatment before XLH symptoms become apparent and is beneficial for growth. However, this has been demonstrated with conventional therapy but not with burosumab. In case 1, changes in the height Z-score and growth rate between pre- and post-administration of burosumab exceeded previously reported values, demonstrating that some patients with mild XLH respond well to burosumab treatment. In a previous study, the height Z-score was significantly greater with burosumab than with conventional therapy in children aged 1–12 yr at week 64 (least squares mean change ± SE: 0.17 ± 0.07 with burosumab vs. 0.02 ± 0.04 with conventional therapy) (10). A subsequent phase 3/4 trial of pediatric patients with XLH with milder symptoms at baseline (total RSS [mean ± SD]: 1.3 ± 1.2) (15) showed no significant changes in growth rate at 124 wk of treatment. Further research is necessary to determine the features that characterize good responders.

Furthermore, case 1 had better body proportions at the start of burosumab administration than case 2. Case 1 started conventional treatment at 8 mo of age, considerably younger than the age at which case 2 began treatment. Patients with XLH are highly prone to developing deformities and growth impairments in the lower limbs, which carry more weight and have

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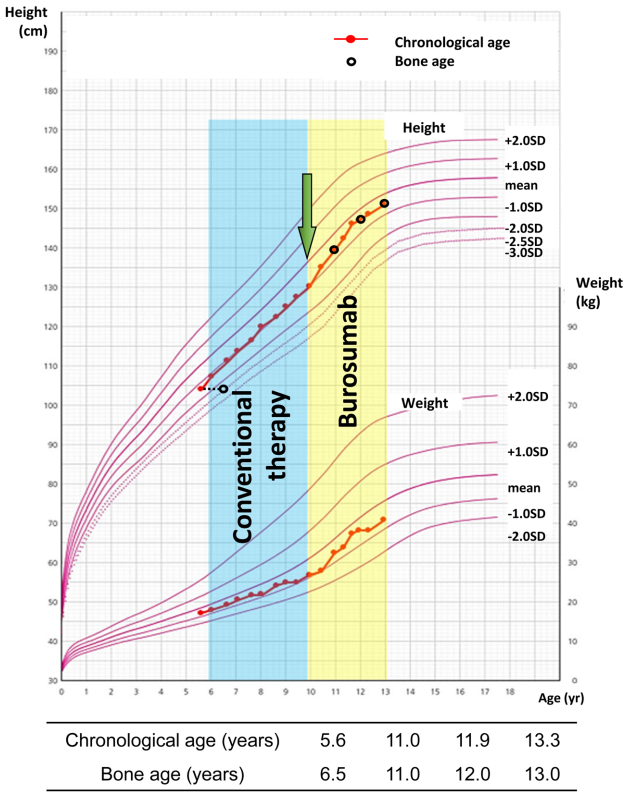

Fig. 6. Growth chart of case 2. The growth curve of case 2 during treatment is shown. The arrow indicates the onset of puberty. Black circles indicate bone ages assessed using the Tanner-Whitehouse 2 radius-ulna-short bone (RUS) method standardized for Japanese children.

more endochondral ossification than the upper limbs or trunk, resulting in a more disproportionate body size over time (17). Earlier XLH treatment may explain the proportional differences between the cases.

Conclusion

Burosumab further improved rickets even in mildly affected and adherent patients with XLH. After burosumab administration, patients should be followed up carefully not only for changes in rickets and calcium/phosphate metabolism, but also for the appearance of multisystemic symptoms due to XLH. Further clinical studies are needed to determine whether burosumab improves the growth and body proportion of patients with mild XLH.

Conflicts of interests: SS, MF, YY, MO, and KH declare no conflicts of interest. NN served as a clinical investigator for studies sponsored by Ultragenyx Pharmaceutical in partnership with Kyowa Kirin International and has received honoraria for serving as an advisory board member and for lectures from Kyowa Kirin.

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