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CASE REPORT

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FGF23-related hypophosphatemic rickets preceding the onset of systemic lupus erythematosus: A juvenile case

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Key Clinical Message

This case report describes the clinical course of a juvenile female with FGF23-related hypophosphatemic rickets preceding the onset of SLE. Our study demonstrates the possibility of hypophosphatemic rickets as an early symptom of SLE.

Abstract

Fibroblast growth factor 23 (FGF23)-related hypophosphatemic rickets is observed in both genetic and acquired disorders. Various reports describe FGF23-related hypophosphatemia with systemic lupus erythematosus (SLE), although FGF23-related hypophosphatemia preceding the onset of SLE has never been described. Here, we report the case of a 9-year-old female with FGF23-related hypophosphatemic rickets preceding the onset of SLE. The patient presented to us with arthralgia in the lower extremities and abnormality of gait lasting for 8 months. She was diagnosed with FGF23 hypophosphatemic rickets due to the presence of hypophosphatemic rickets symptoms and high serum levels of FGF23. Additional examination excluded hereditary diseases and tumor-induced osteomalacia. Three months after diagnosis of FGF23-related hypophosphatemic rickets, she developed nephritis and was diagnosed with SLE. She was treated with prednisolone, hemodialysis, and disease-modifying drugs, as well as oral sodium phosphate to improve hypophosphatemia. Serum anti-double-stranded DNA antibody (dsDNAab) and plasma tumor necrosis factor-α (TNF-α) were elevated at FGF23-related hypophosphatemic rickets diagnosis. During the clinical course, serum FGF23 correlated with dsDNAab and TNF-α serum levels, which are involved in SLE disease activity. In this case, FGF23-related hypophosphatemic rickets without hereditary diseases or tumor-induced osteomalacia occurred before the appearance of juvenile SLE symptoms, and serum FGF23 represented disease activity in SLE.

KEYWORDS

childhood, fibroblast growth factor-23, hypophosphatemia, rickets, systemic lupus erythematosus

1 | INTRODUCTION

Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that is essential for regulating extracellular phosphate concentration. Excess production of FGF23 is the hormonal basis for several musculoskeletal syndromes characterized by hypophosphatemia due to renal phosphate wasting. FGF23-related hypophosphatemia is observed in both genetic diseases and acquired disorders. Inflammatory diseases elevate serum FGF23 concentration.[1–4] FGF23 is elevated in patients with primary lupus nephritis,[5] and hypophosphatemia occurs at diagnosis and during the course of systemic lupus erythematosus (SLE).[6] However, there have been no reports of FGF23-related hypophosphatemic rickets preceding SLE, and the correlation between serum FGF23 level and disease activity of SLE is not clearly understood. We report a juvenile case of FGF23-related hypophosphatemic rickets preceding the onset of SLE.

2 | CASE PRESENTATION

A 9-year-old female was referred to our clinic due to an 8-month history of arthralgia in the knee and hip joints and abnormality of gait. Simple radiographs revealed X-leg and opened epiphyseal lines. Serum calcium and serum phosphorous were 9.4 mg/dL and 2.3 mg/dL, respectively. Peripheral blood counts showed hemoglobin of 12.4 g/dL and white blood cell count of 5300/μL. Erythrocyte sedimentation rate was 12 mm/h. Serum 1,25-dihydroxyvitamin D_3 and serum intact-parathyroid hormone (i-PTH) were 33 μg/L and 45.3 pg/mL, respectively. Urinary protein and urinary occult blood were negative. Estimated glomerular filtration rate was 166.8 mL/min/m^2. The level of phosphate tubular maximum per volume of filtrate (Tmp/GFR) was low (2.37 mg/dL). She was diagnosed with FGF23-related hypophosphatemic rickets due to an elevation in the level of serum FGF23 (106 pg/mL, See Appendix S1 for the kit utilized to measure FGF23). Additional simple radiographs revealed a periosteal reaction at the distal end of the right femur, and partial lucency of the zone of provisional calcification at both femoral condyles and both tibial plateaus of bilateral knees (Figure 1A). Radiograph of wrist demonstrated fraying and concavity of the metaphyseal margins of both the radius and ulna (Figure 1B). A score of two points each was given for both the femur and the tibia, and a score of two points each was given for the radius and ulna giving the rickets-severity scale of eight points.[7] We suspected tumor-induced osteomalacia, but bone scintigraphy and somatostatin receptor scintigraphy findings ruled this out. The periosteal reaction was the obsolete fracture by the

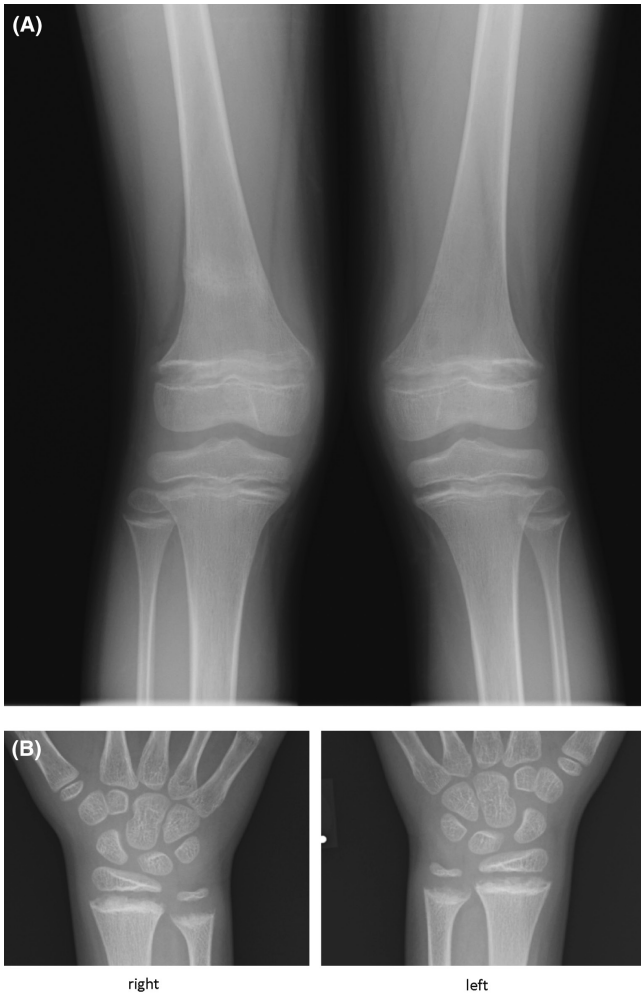

FIGURE 1 (A) Simple radiographs at diagnosis of FGF23-related hypophosphatemic rickets revealed a periosteal reaction at the distal end of the right femur, and partial lucency of the zone of provisional calcification at both femoral condyles and both tibial plateaus of bilateral knees. (B) Simple radiographs of wrist at diagnosis of FGF23-related hypophosphatemic rickets revealed fraying and concavity of the metaphyseal margins of both the radius and ulna.

bone fragility. Analysis of the protein coding region of the *PHEX*, *FGF23*, *DMP1*, *ENPP1*, *FAM20C*, *FGFR1*, *PTH1R*, *SLC34A3*, *SLC9A3R1*, *CLCN5*, *OCRL*, *CYP2R1*, *HNRNPC*, *CYP3A4*, *NF1*, *SLC34A1*, and the splice site region at both ends of these genes by next-generation sequencing showed no mutations. Although arthralgia subsided over a few months, hypophosphatemia persisted, and symptoms of rickets worsened.

Three months after the diagnosis of FGF23-related hypophosphatemic rickets, she developed urinary occult blood (80/HPF) and overt proteinuria (>0.5 g/day) which caused hypoalbuminemia. She was diagnosed with SLE based on the results of autoantibodies (antinuclear antibody titer 1:640 and anti-ds-DNA IgG antibody (dsDNAab) 2650 IU/mL) and serum complement levels (C3 43.0 mg/

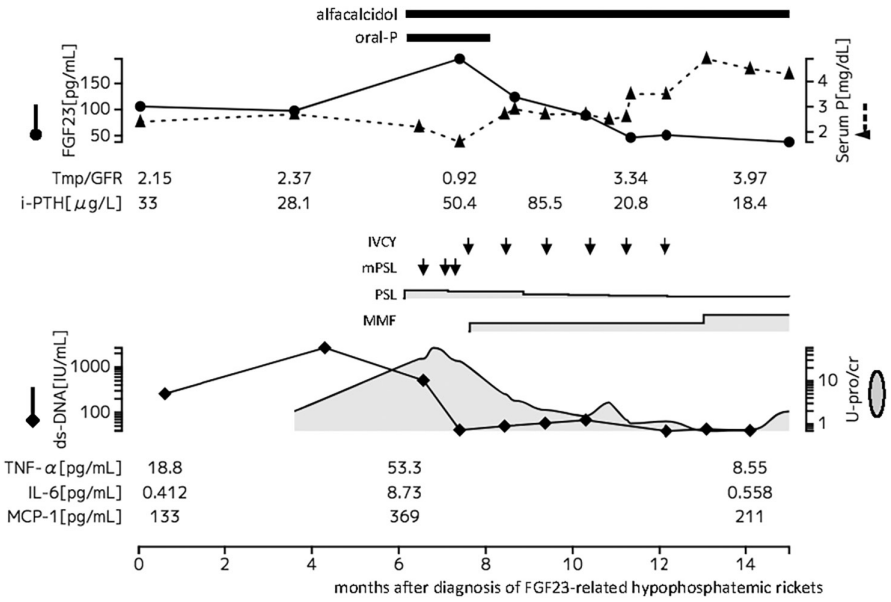

FIGURE 2 After initiation of treatment for SLE, FGF23 decreased along with a decrease in urinary protein and dsDNAab, and hypophosphatemia also improved. TmP/GFR: excretion reabsorption of phosphate/glomerular filtration rate, Serum P: serum phosphorus, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone pulse, PSL: prednisolone, MMF: Mycophenolate mofetil, U-pro/cr: urinary protein-creatinine ratio.

dL, C4 5.0 mg/dL, CH50 < 14.0 IU/mL). Five months after the diagnosis of FGF23-related hypophosphatemic rickets, we initiated treatment with oral sodium phosphate and alfacalcidol for hypophosphatemia (1.6 mg/dL). At the same time, we also started treatment with prednisolone and methylprednisolone pulse therapy for SLE; however, the proteinuria did not improve. Temporary extracorporeal ultrafiltration and hemodialysis were required for the management of progressive edema. Additional treatment with mycophenolate mofetil and intravenous cyclophosphamide gradually decreased her urinary protein and serum dsDNAab levels (Figure 2). After 5 months of SLE treatment, serum FGF23 level decreased to 46.5 pg/mL from the pretreatment level of 197 pg/mL (peak value) and serum i-PTH level increased. After 8 months of SLE treatment, rickets healed and the periosteal reaction of the distal end of the right femur disappeared (Figure 3). Simple radiographs showed normal wrists and normal knees (Figure 3B), resulting in a score of zero point on the rickets-severity scale. Serum phosphorus level and i-PTH level remained within the normal range after discontinuing the phosphorus preparation. Serum dsDNAab and plasma tumor necrosis factor-α (TNF-α) were elevated at the time of diagnosis of FGF23 hypophosphatemic rickets (See Appendix S1 for the kits utilized to measure TNF-α, interleukin 6 and monocyte chemotactic protein-1.). During the clinical course, serum FGF23 correlated with dsDNAab and TNF-α, which have been shown to be involved in SLE disease activity.

3 | DISCUSSION

It has been reported that serum FGF23 is elevated in patients with newly diagnosed lupus nephritis[5] and that hypophosphatemia occurs at the time of diagnosis and during the course of SLE.[6] In addition to SLE, elevated serum FGF23 has been reported in other pro-inflammatory diseases.[8] However there have been no reports of hypophosphatemic rickets preceding the onset of pro-inflammatory diseases. The patient in our case had no symptoms of SLE, except for arthralgia in the knee and hip joints, when she was diagnosed with FGF23-related hypophosphatemic rickets. Therefore, FGF23-related hypophosphatemic rickets may be noted as a very early symptom of SLE.

The role of cytokines in the diagnosis and treatment of SLE has been studied extensively.[9] Pro-inflammatory cytokines such as plasma TNF-α and interleukin 6 (IL-6) have been reported to correlate with the severity of SLE.[9-12] Further, Fujiwara et al. reported that elevated levels of plasma TNF-α and IL-6 are associated with hypophosphatemia.[6] Urine monocyte chemotactic protein-1 (MCP-1) has been identified as a biomarker of lupus nephritis.[13] Yung et al. also reported increased expression of IL-6 and TNF-α in renal tissues of lupus nephritis patients.[14] Regarding the relationship between serum FGF23 and pro-inflammatory cytokines, Resende et al. reported that serum FGF23 was elevated in patients with newly diagnosed lupus nephritis, and serum FGF23 correlated with urine MCP-1.[5] Furthermore, the authors stated that serum FGF23 may be a new marker for lupus nephritis. However, the correlation between serum FGF23 and disease activity in SLE is not clear. In this case, serum FGF23 was decreased in correlation with decrease in urinary protein, serum dsDNAab, and pro-inflammatory cytokines such as serum plasma TNF-α, IL-6, and MCP-1. In addition, at the time of diagnosis of FGF23-related hypophosphatemic rickets, serum FGF23 was increased before plasma IL-6 and MCP-1 was elevated.

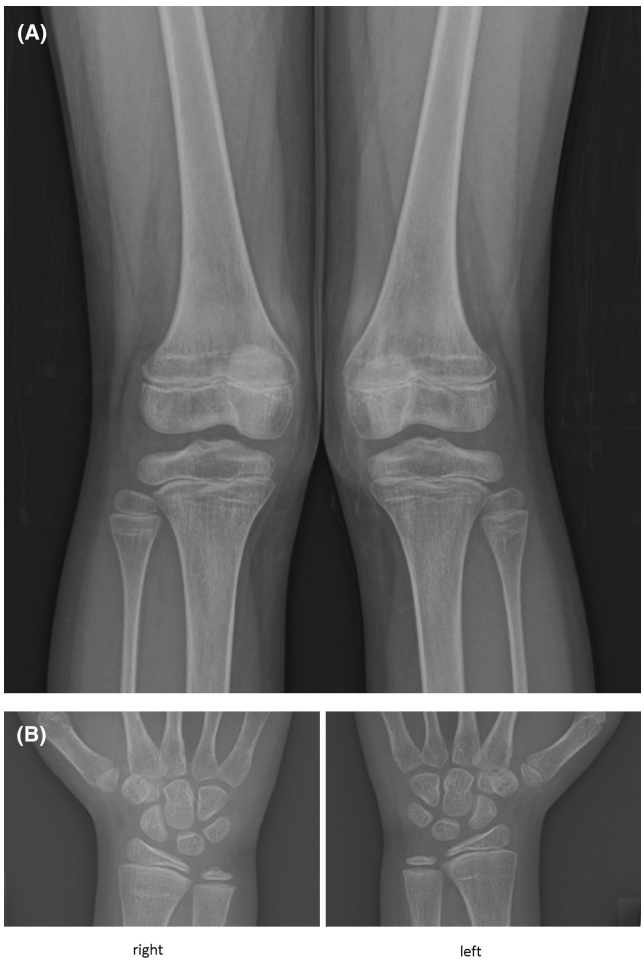

FIGURE 3 (A) Simple radiographs of knee after 8 months of SLE treatment did not reveal a periosteal reaction at the distal end of the right femur. Simple radiographs showed normal knees. (B) Simple radiographs after 8 months of SLE treatment showed normal wrists.

In this case, FGF23-related hypophosphatemic rickets occurred before the appearance of SLE symptoms, and serum FGF23 decreased in correlation with decreased SLE disease activity. Further case accumulation and investigation are required to reveal the association between serum FGF23 level and disease activity in SLE.

AUTHOR CONTRIBUTIONS

Yoko Tabei: Data curation; formal analysis; investigation; methodology; project administration; writing – original draft; writing – review and editing. **Yoshiaki Ohtsu:** Conceptualization; data curation; investigation; project administration; writing – review and editing. **Masaharu Shimada:** Writing – review and editing. **Aya Wada:** Writing – review and editing. **Emi Hamajima:** Writing – original draft. **Yoshimitsu Osawa:** Writing – review and editing. **Takumi Takizawa:** Supervision; writing – review and editing.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

This study protocol was reviewed and approved by Ethics Committee of Gunma University Hospital.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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REFERENCES

1. Fukumoto S. Physiological regulation and disorders of phosphate metabolism—pivotal role of fibroblast growth factor 23. *Intern Med*. 2008;47(5):337-343.
2. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest*. 2004;113(4):561-568.
3. Gulati S, Wells JM, Urdaneta GP, et al. Fibroblast growth factor 23 is associated with a frequent exacerbator phenotype in COPD: a cross-sectional pilot study. *Int J Mol Sci*. 2019;20(9):2292.
4. Lang F, Leibrock C, Pandyra AA, Stournaras C, Wagner CA, et al. Phosphate homeostasis, inflammation and the regulation of FGF-23. *Kidney Blood Press Res*. 2018;43(6):1742-1748.
5. Resende AL, Elias RM, Wolf M, et al. Serum levels of fibroblast growth factor 23 are elevated in patients with active Lupus nephritis. *Cytokine*. 2017;91:124-127.
6. Fujiwara I, Ogawa E, Kondo Y, Ohura T, Iinuma K. Hypophosphatemia in juvenile patients with systemic lupus erythematosus. *Pediatr Int*. 2003;45(1):23-30.
7. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. *J Trop Pediatr*. 2000;46(3):132-139.
8. Yamazawa K, Kodo K, Maeda J, et al. Hyponatremia, hypophosphatemia, and hypouricemia in a girl with macrophage activation syndrome. *Pediatrics*. 2006;118(6):2557-2560.
9. Park J, Jang W, Park HS, et al. Cytokine clusters as potential diagnostic markers of disease activity and renal

involvement in systemic lupus erythematosus. *J Int Med Res*. 2020;48(6):300060520926882.
10. Sabry A, Elbasyouni SR, Sheashaa HA, et al. Correlation between levels of TNF-alpha and IL-6 and hematological involvement in SLE Egyptian patients with lupus nephritis. *Int Urol Nephrol*. 2006;38(3–4):731-737.
11. Aringer M, Smolen JS. The role of tumor necrosis factor-alpha in systemic lupus erythematosus. *Arthritis Res Ther*. 2008;10(1):202.
12. Idborg H, Eketjäll S, Pettersson S, et al. TNF-α and plasma albumin as biomarkers of disease activity in systemic lupus erythematosus. *Lupus Sci Med*. 2018;5(1):e000260.
13. Rovin BH, Zhang X. Biomarkers for lupus nephritis: the quest continues. *Clin J Am Soc Nephrol*. 2009;4(11):1858-1865.
14. Yung S, Cheung KF, Zhang Q, Chan TM. Mediators of inflammation and their effect on resident renal cells: implications in lupus nephritis. *Clin Dev Immunol*. 2013;2013:317682.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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