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Case Report

Persistently Augmented FGF-23 Serum Values in a Surgically Resolved Oncogenic Osteomalacia Patient with No Tumor and Inflammatory Activity

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Abstract: ***Objective:*** Oncogenic osteomalacia is a paraneoplastic syndrome characterized by severe hypophosphatemia, hyperphosphaturia, and osteomalacia subordinated to renal loss of phosphate. It is caused by overproduction of phosphatonin fibroblast growth factor-23 by benign mesenchymal tumors which, when surgically eliminated, returns to basal levels. ***Methods:*** We report a case of a patient with oncogenic osteomalacia from a sacrum mesenchymal tumor whose FGF-23 levels remain elevated two years after successful surgical treatment. ***Results:*** A 53-year-old man with severe difficulty to walk and stand, severe hypophosphatemia, hyperphosphaturia, and raised levels of alkaline phosphatase and FGF-23 was diagnosed with oncogenic osteomalacia after a thorough process of elimination of causes of hyphosphatemia were excluded. Despite systemic chemotherapy, surgical removal of sacrum, primary mesenchymal tumor, phosphate and calcium supplementation, and no evidence of tumor recurrence, the serum concentration of FGF-23 remains elevated two years after discharge. ***Conclusions:*** The possible underlying mechanisms of sustained FGF-23 serum concentrations in this patient suggest the presence of molecular alterations in the FGF/FGFR signaling pathway.

Keywords: Oncogenic osteomalacia, hypophosphatemia, hypocalcemia.

INTRODUCTION

Oncogenic osteomalacia is an infrequent paraneoplastic syndrome characterized by severe hypophosphatemia, hyperphosphaturia, and osteomalacia subordinated to renal loss of phosphate [1]. It is usually caused by overproduction of fibroblast growth factor-23 (FGF23), vitamin D, and phosphate-regulating hormone [2] from benign tumors of mesenchymal origin. FGF23 decreases renal tubular phosphate reabsorption by means of the FGF receptors 1, 3, and 4 and the co-receptor Klotho, expressed in proximal renal tubules, which lead to the downregulation of type II sodium phospate co-transporters the outcome being inhibition of renal phosphate reabsorption [3]. This case of a 53 year-old male constitutes an enigma as the serum concentration of FGF23 remains markedly increased one year after proper surgical treatment and no evidence of tumor presence.

CASE PRESENTATION

A 53-year-old male presented 4 years ago with recurrent muscle weakness, fatigue, and bone pain in the hips and back that irradiated to the thoracic and lumbar columns. The pain increased progressively and one year after bilateral leg paresthesia followed by severe proximal muscular weakness forced the patient to become wheelchair-bound. The patient was treated in his local primary care unit with analgesics and anti-inflammatory drugs. He was referred to our

hospital 2.5 years ago where hepatic failure, malabsorption, leukemia, respiratory alkalosis as well as chronic infectious processes, primary neurological, or demyelinating pathologies were excluded. CT scan and MRI imaging results showed a proliferative process in the S2-S3 sacrum-coccyx region with bone deformity segments and infiltration in the natural and meningeal foramen that suggested myeloma or lymphoma but a thorough evaluation rejected those possibilities.

The patient was referred to the Internal Medicine Division where increased alkaline phosphatase (282 U/L vs 140 IU/L in healthy adults), and low calcium (9.2 mg/dl vs 10.3 mg/dl in healthy adults) and phosphorus (0.7 mg/dl vs 4.5 mg/dl in healthy adults) serum levels were detected. Severe phosphaturia (748 mg/dl vs 4.5 mg/dl in healthy adults) was also spotted. The patient had femoral osteoporosis (DMO T score -3.1) and a Tc99 bone gammagram detected multiple blast lesions in the costal arch and breastbone that advocated pathological fractures compatible with Looser Mlkman zones (Fig. 1) suggesting hypophosphatemic osteomalacia. Serum parathyroid hormone (87 pg/ml) and acid phosphatase (7.5 U/l) concentrations were elevated, whereas 25-OH vitamin D (10 ng/ml) and 1,25 dihydroxyvitamin D levels (< 8 pg/ml) were low. The above-mentioned data suggested a FGF-23 associated tumor that was confirmed by the 9-fold FGF-23 serum increase (1725 RU/ml vs <181 RU/ml in healthy adults) and a somatostatin octreoscan that confirmed the presence of neuroendocrine tumoral cells (Fig. 2). The results of the biopsy confirmed the presence of a phosphatidic mesenchymal tumor, which was surgically resected.

A nine-month post-surgery follow-up showed the persistence of phosphaturia (653 mg/dl) and increased FGF-23 serum values (303 RU/ml). A new Octreoscan found tumor activity in T11 and the MRI showed a residual lesion in S1-S2. A PET-CT F18-Fluorodeoxyglucose (FDG) study showed the presence of hypermetabolic tissue in S2 with bone remodeling (Fig. 3). A second surgery was performed to eliminate the tumor remains but serum FGF-23 values remained increased (267 RU/ml) and a new PET-CT with F18-FDG confirmed the retention of small amounts of the radio nucleotide but with no evidence of residual tumor lesions. The patient began treatment with Cinacalcet and phosphorus and vitamin D deposition. A six year follow-up showed that there is a slight persistence of metabolic activity in S3 but not tumor. The patient is completely asymptomatic and all serum biochemical parameters (phosphorus 2.5 mg/dl, PTH 24.5 pg/ml, alkaline phosphatase 89 U/L), urinary phosphorus concentration1856.4 mg/dl), and proninflammatory cytokines concentrations (IL- 1b 1.49 pg/ml, IL-6 2.15 pg/ml, TNF-a 2.2 ng/ml) are now within normal values; nevertheless, FGF- 23 serum values remain higher than normal (185 RU/ml).

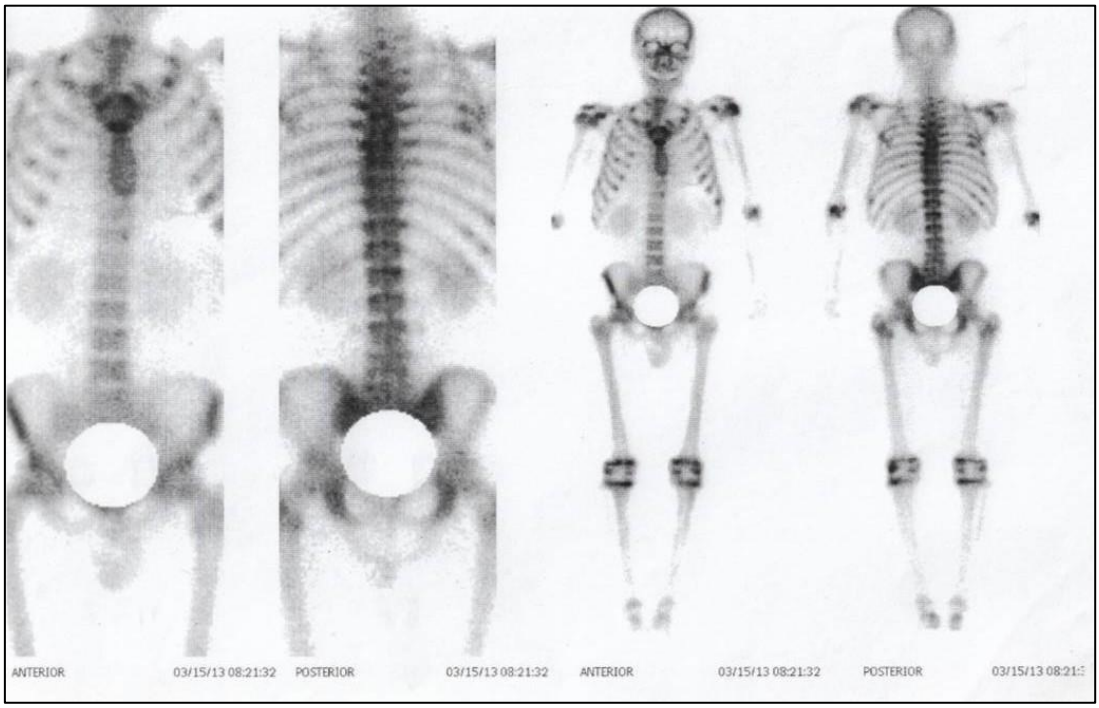

Figure 1: Initial TAC images

Figure 1 Tc 99 20 mCi bone scan showing bone tissue with increased ion exchange in multiple costal arches, proximal epiphysis of the left humerus, dorsal transverse processes, and knees and elbows suggestive of blastic lesions, inflammatory osteoarticular pathology and lytic lesion at the level of L4.

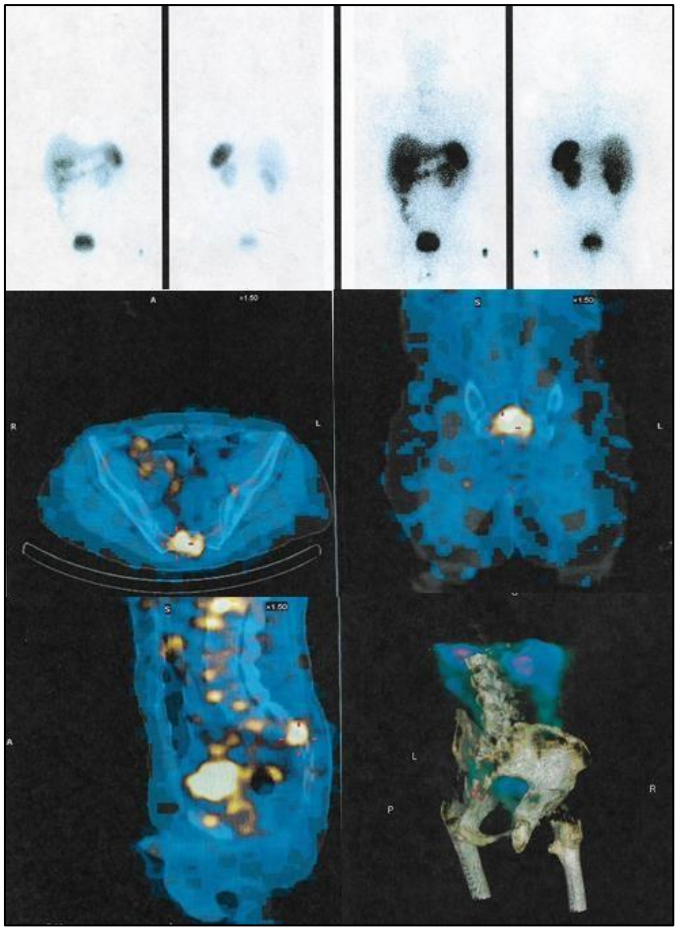

Figure 2: SPECT-CT octreotide Indium 110 images.

Figure 2 SPECT-CT octreotide Indium 110 showing heterogeneous distribution of blastic lesions with increased uptake involving S1 to S3 and in the chest with blastic lesions in the left sternal manubrium and costal arches, evidence of somatostatin analog receptor lesion at the sacral level.

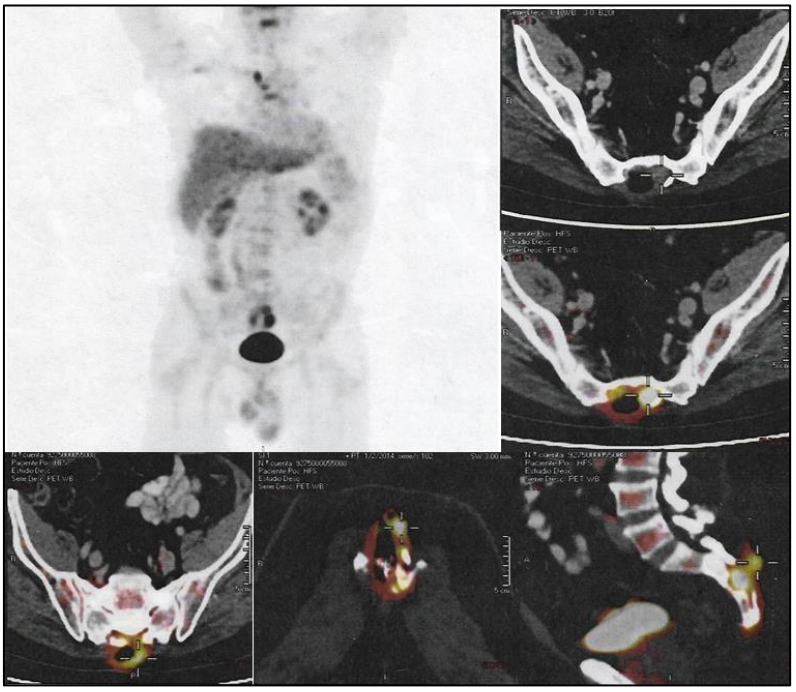

Figure 3: SPECT-CT Indian octeotide 110 images

Figure 3 SPECT-CT indian octreotide 110 shows heterogeneous distribution of blastic lesions with increased uptake involving S1 to S3 and in the chest with blastic lesions in the left sternal manubrium and costal arches, evidence of somatostatin analog receptor lesion at sacral level.

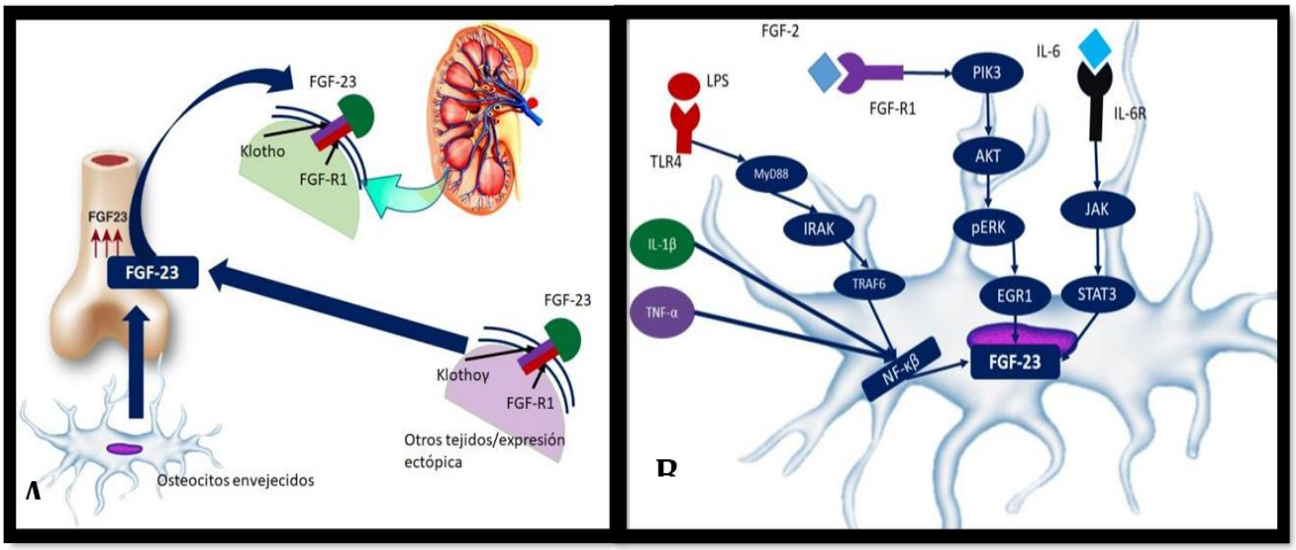

Figure 4: Mechanism involved in the persistence of FGF-23

Figure 4 Possible mechanisms involved in the persistence of FGF23 in our patient. A) Klotho converts FGFR1 into a canonical receptor for several FGFs, it shows a strong affinity for FGF-23 and enhances its biological activity, and there may be ectopic expression of Klotho detected in mesenchymal tumors that creates a local positive feedback loop for the production of FGF-23. Aged osteocytes (mature cells embedded in mineralized bone matrix) are more effective in terms of upregulating FGF23 in response to physiological and pathological changes. B) Activation of FGFR1 by other FGFs, such as FGF2, can induce Pi3K/AKT/pERK/EGR1, leading to upregulation of FGF23. Inflammatory conditions are potent inducers of FGF23; Lipopolysaccharide (LPS) can bind to osteocytes toll-like receptor 4 (TLR4) and induce MyD88/IRAK/TRAF6/NF-κB to trigger FGF23 transcription (this mechanism can also be triggered by anemia). IL-6 binding to IL-6R in osteocytes can induce JAK/STAT3 expression and subsequent FGF23 expression. The cytokines IL-1 and TNF-γ can induce NF-κβ in osteocytes leading to transcription of FGF23.

DISCUSSION

Oncogenic osteomalacia is a rare mesenchymal paraneoplasic syndrome [4, 5] affecting bone (columna, pelvis) or soft tissues (ovarian, brain, nasopharynge [6-8]. Its unspecific and slow progression delays the diagnosis [9, 10]. The major biochemical parameters that point to the disease are: elevated alkaline phosphatase due to increased osteoblastic activity, hyperphosphaturia, and hypophosphatemia due to renal loss of phosphate [1] and raised FGF-23 that decreases renal tubular phosphate reabsorption via its phosphaturic action in proximal tubule cells [3]. Phosphorus and FGF- 23 serum values return to basal levels from 2-10 days to 4 months after surgical removal of the tumor [11]. Post-surgical elevated FGF-23 values despite normal phosphorus values suggest residual disease or tumor recurrence [12, 13], although the latter is observed in less than 5% of the patients. Nevertheless, other causes of hyphosphatemia related to abnormal values of FGF-23 include iron deficiency, chronic alcohol consumption [14], and abnormal kidney function with high uremic values [15], which were discarded in our patient.

Despite the successful surgical and chemotherapy treatment that our patient received, FGF-23 values never reached normal concentration. It is well known that FGF-23 can be secreted by immune and erythroid cells from the bone marrow and liver [15]. FGF is regulated by the Klotho coreceptor and when both proteins associate, they exert suppressor activity on breast and urothelial cancer tumors, so it has been accepted that the canonical signaling of FGFR regulates tumor genesis in an independent manner [16]. Klotho converts FGFR1 into a canonical receptor for different subtypes of FGFs, although the affinity of FGFR1 is greater for FGF-23, thus enhancing the biological activity of the latter [17].

Interestingly, the transcription of Klotho is also regulated by M1 macrophages, M2 macrophages in the presence of IL-4, IL-1b, and TNFa, so the continuous presence of subluminal inflammatory processes, including diabetes, can maintain modest increases in FGF-23 thus confirming the hypothesis that FGF-23 is locally produced [18, 19] (Fig. 4-A). Our patient never had an infectious process or a chronic inflammatory state that might explain the persistent elevated FGF-23 values. *Kinoshita et al.*, have shown ectopic expression of Klotho and suggested that the FGFR signaling pathway generates local positive feedback that favors FGF-23 production [20] (Fig 4-B). It seems that osteomalacia

affects mainly the trabecula [21] and FGF-23 is primarily expressed in trabecular osteocytes [22]. We believe that old osteocytes [23] embedded in the mineralized bone matrix of our patient could explain the persistent elevation of serum FGF-23 [15, 24].

CONCLUSION

Oncogenic osteomalacia is a diagnostic challenge and the use of FGF-23 as the sole marker of this entity may not be representative of the repair/proliferation process in the affected individual. It is becoming increasingly clear that FGF-23 transcription and cleavage are independent processes and that the role of osteocytes in FGF23 production and response to regulators is far from being understood.

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CONFLICT OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

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