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## Phosphaturic mesenchymal tumor (PMT): exceptionally rare disease, yet crucial not to miss

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### ABSTRACT

Phosphaturic mesenchymal tumors (PMTs) are very rare tumors which are frequently associated with Tumor Induced Osteomalacia (TIO), a paraneoplastic syndrome that manifests as renal phosphate wasting. The tumor cells produce a peptide hormone-like substance known as fibroblast growth factor 23 (FGF23), a physiologic regulator of phosphate levels. FGF23 decreases proximal tubule reabsorption of phosphates and inhibits 1- $\alpha$ -hydroxylase, which reduces levels of 1- $\alpha$ , 25-dihydroxyvitamin D<sub>3</sub>. Thus, overexpression of FGF23 by the tumor cells leads to increased excretion of phosphate in the urine, mobilization of calcium and phosphate from bones, and the reduction of osteoblastic activity, ultimately resulting in widespread osteomalacia. Patients typically present with gradual muscular weakness and diffuse bone pain from pathologic fractures. The diagnosis is often delayed due to the non-specific nature of the symptoms and lack of clinical suspicion. While serum phosphorus and FGF23 testing can assist in making a clinical diagnosis of PMT, the responsible tumor is often difficult to locate. The pathologic diagnosis is often missed due to the rarity of PMTs and histologic overlap with other mesenchymal neoplasms. While patients can experience severe disabilities without treatment, excision is typically curative and results in a dramatic reversal of symptoms. Histologically, PMT has a variable appearance and can resemble other low grade mesenchymal tumors. Even though very few cases of PMT have been reported in the world literature, it is very important to consider this diagnosis in all patients with hypophosphatemic osteomalacia. Here we present a patient who suffered for almost 5 years without a diagnosis. Ultimately, the PMT was located on a 68Ga-DOTA TATE PET/CT scan and subsequently confirmed by histologic and immunohistologic study. Interestingly, strong positivity for FGFR1 by IHC might be related to the recently described FN1-FGFR1 fusion. Upon surgical removal, the patient's phosphate and FGF23 levels returned to normal and the patient's symptoms resolved.

### Keywords

Neoplasm, Connective Tissue; Oncogenic Osteomalacia; Fibroblast Growth factors; Hypophosphatemia; Bone Diseases, Metabolic.

### INTRODUCTION

Phosphaturic mesenchymal tumors (PMTs) are very rare tumors which are frequently associated with Tumor Induced Osteomalacia (TIO), a paraneoplastic syndrome that manifests as renal phosphate wasting. The tumor

cells produce a peptide hormone-like substance known as fibroblast growth factor 23 (FGF23), a physiologic regulator of phosphate levels.<sup>1</sup> FGF23 decreases proximal tubule reabsorption of phosphates and

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inhibits 1- $\alpha$ -hydroxylase, which reduces levels of 1- $\alpha$ , 25-dihydroxy vitamin D3. Thus, overexpression of FGF23 by the tumor cells leads to increased clearance of phosphate in the urine, mobilization of calcium and phosphate from bones, and the reduction of osteoblastic activity, ultimately resulting in widespread osteomalacia.<sup>2</sup>

## CASE REPORT

A 48-year-old man presented with a history of long-standing progressive low back pain, which has extended to the large joints, resulting in difficulty moving. A rheumatologic workup was negative and he was treated symptomatically with NSAIDs, glucosamine, and hydrocodone. He also had a pruritic rash on his lower legs. He was also seen by his primary care provider, dermatology, endocrinology, and hematology specialists. Additional workups revealed no evidence of hyperparathyroidism, myeloma, stiff person syndrome, mixed connective tissue disease, and Paget disease.

A CT scan revealed diffuse osteopenia with insufficiency fractures. His serum alkaline phosphate level was elevated while serum phosphate was decreased. Testing for FGF23 showed an increased serum level (240 RU/ml), which has a differential of X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR), or PMT. His lack of family history argued against XLH and ADHR. Given the high clinical suspicion for a PMT, a PET scan was performed in an attempt to locate the PMT. This showed markedly PET avid right axillary adenopathy as well as a right hand mass. Biopsies of both sites were inconclusive for PMT. A repeat PET scan six months later did not show any new masses. A 68Ga-DOTA TATE PET/CT was performed and showed prominent uptake in an enlarged right inguinal lymph node, which was subsequently excised.

## SURGICAL PATHOLOGY

The right inguinal mass specimen was received as a 3.0 x 3.0 x 0.8 cm piece of pink-tan tissue. Microscopically, the tumor consisted predominantly of bland spindle to stellate cells with a well-developed capillary network, foci of hemorrhage, hemosiderin deposition, and osteoclast-like multinucleate giant cells. Scattered calcifying matrix with “grungy” material was

also identified (Figure 1A to 1D). A chromogenic in situ hybridization (CISH) study showed very strong positivity for FGF23 mRNA. FGFR1 immunohistochemistry was diffusely positive, implying the presence of the FN1-FGFR1 fusion (Figure 2A and 2B).

Laboratory test: One month after the right inguinal mass excision, the patient’s serum levels returned to normal and the patient’s symptoms decreased dramatically (Table 1)

## DISCUSSION

Phosphate plays an important role in many cell functions, including oxygen delivery, energy generation, and DNA synthesis. Acute hypophosphatemia can lead to generalized weakness, malaise, hypotension, congestive heart failure, rhabdomyolysis, respiratory failure, seizures, and altered mental status. Because these symptoms are non-specific, hypophosphatemia may not initially be suspected or recognized. Chronic hypophosphatemia results in defective bone mineralization, ultimately leading to osteomalacia in adults and rickets in children. The symptoms of osteomalacia and rickets include weakness, fractures, bone pain, and bowing of long bones.

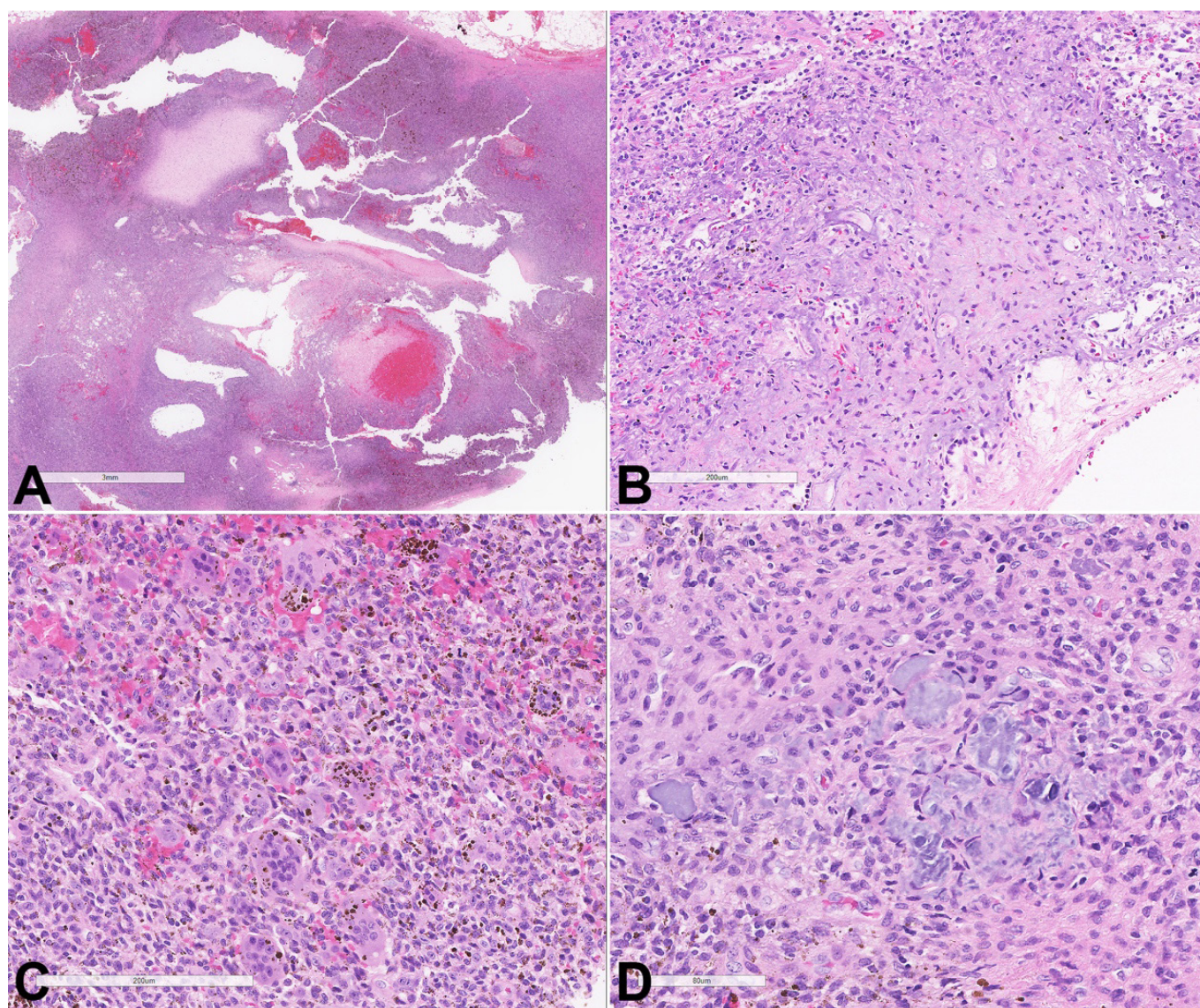
Three pathogenic mechanisms are known to cause hypophosphatemia:<sup>3</sup>

- 1 -Inadequate phosphate intake (e.g. malnutrition, malabsorption, vitamin D deficiency, and use of phosphate binding antacids)
- 2 -Phosphate shifting from extracellular to intracellular spaces (e.g. acute respiratory alkalosis, refeeding syndrome, hungry bone syndrome, and treatment of diabetic ketoacidosis with insulin)
- 3 -Increase urine excretion (e.g. hyperparathyroidism, vitamin D deficiency, Fanconi syndrome, medications (diuretics, bisphosphonates), and tumors)

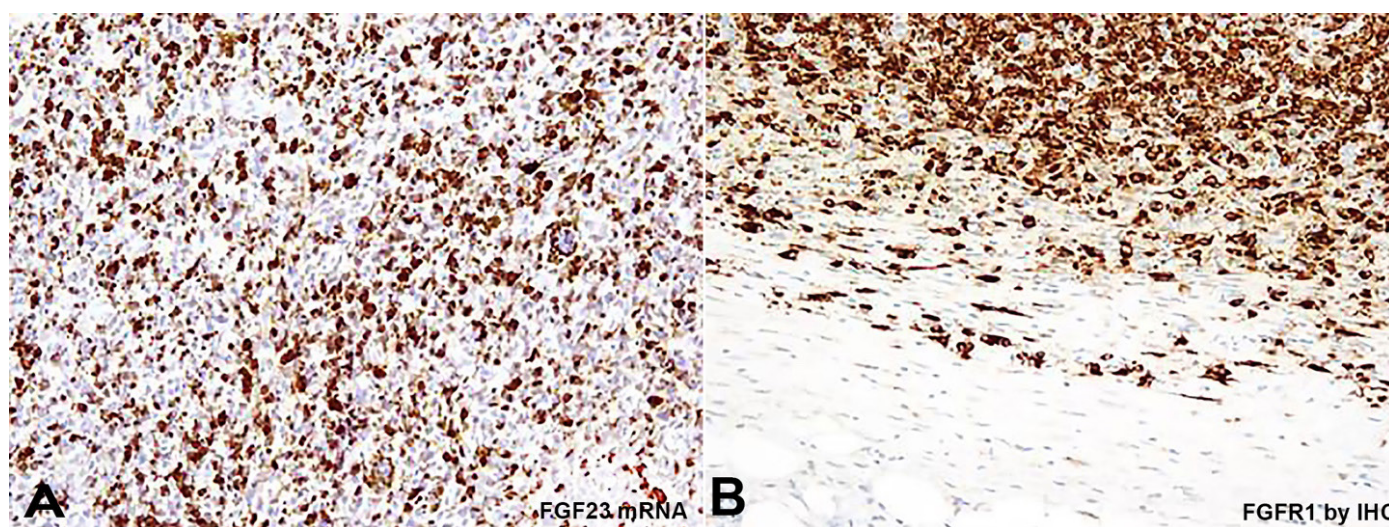
Tumor-induced osteomalacia (TIO) is a condition caused by the increased excretion of phosphate due to a tumor-secreted phosphaturic factor (so called “phosphatonins”).<sup>4</sup> It can be seen in patients with phosphaturic mesenchymal tumor as well as some other mesenchymal tumors (such as hemangiopericytoma).<sup>5</sup>

Phosphaturic mesenchymal tumors (PMTs) are rare tumors that occurs most frequently in middle aged adults and can involve essentially any bone or soft





**Figure 1.** Photomicrography of the tumor with **A** – Hypercellular and hypocellular areas, hemorrhage and vascular network; **B** – Bland spindled cells and unusual basophilic matrix a “grungy” calcification pattern; **C** – Cellular proliferation of bland spindle cells with scattered osteoblasts and hemosiderin; **D** – The neoplastic cells produce smudgy calcifications.



**Figure 2 .** Photomicrography of the tumor showing in **A** – Tumor cells are strongly positive for FGF23 mRNA by CISH; **B** – Strong positivity for FGFR1 by IHC, implying the presence of the FN1-FGFR1 fusion.



**Table 1.** Laboratory results pre- and post tumoral excision

Lab results	Calcium mg/dL	PO4 mg/dL	24 hr Urine PO4 mg/d	PTH pg/mL	FGF23 RU/mL	ALP U/L
Reference range	8.4-10.5	2.4-5.0	400-1300	12-88	≤180	35-115
Before surgery	8.4	1.6 (L)	1819 (H)	207 (H)	240 (H)	462 (H)
1 month post-surgery	9.5	4.0	426	30	98	125 (H)

ALP = alkaline phosphatase; FGF23 = Fibroblast growth factor 23; PO4 = phosphate; PTH = parathormone.

tissue location.<sup>6</sup> It typically causes osteomalacia through secreting circulating FGF23, which leads to renal wasting of phosphate and consequently causes tumor induced osteomalacia. Clinical features comprise bone pain, generalized weakness, and pathologic fractures.<sup>1</sup> Histologically, PMTs are characterized by a proliferation of bland spindle cells associated with a variable amount of 'smudgy' calcified matrix. A small subset of PMTs exhibit malignant histologic features and may behave in a clinically malignant fashion.<sup>7</sup> Because PMTs are rare, the diagnosis is often not considered by clinicians and pathologists, even in patients presenting with osteomalacia. Thus, most patients ultimately diagnosed with PMT have experienced osteomalacia for years before the tumor is identified.<sup>8</sup> Measurement of serum FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism. A high FGF23 level in a patient with normal renal function, hypophosphatemia, and with or without osteomalacia, is suggestive of PMT. FGF23 is located on chromosome 12 and is composed of three exons. Mutations in FGF23 that render the protein resistant to proteolytic cleavage lead to increased activity of FGF23 and renal phosphate loss. It was first discovered in 2000 in the autosomal dominant hypophosphatemic rickets.<sup>9</sup> The best-established receptor of FGF23 is FGFR1, which on ligand binding and activation conducts its signaling pathways to regulate cell proliferation, survival, migration, and differentiation.<sup>10</sup>

In 2015, a novel FN1-FGFR1 fusion protein was identified in nine out of fifteen PMTs by Jen-Chieh Lee et al., using RT-PCR in addition to FISH and Western blot analysis. One year later, they systematically characterized the prevalence of the FN1-FGFR1 and another novel FN1-FGF1 fusion in a larger group of well-characterized phosphaturic mesenchymal tumors, suggesting the central role of FGFR1 signaling in the

pathogenesis of phosphaturic mesenchymal tumors. As in the FN1-FGFR1 fusion gene, the FN1 gene likely provides its transcriptionally active promoter to drive the expression of FN1-FGF1 protein.<sup>11</sup> FN1 (Fibronectin 1), a protein-coding gene on chromosome 2, plays a major role in cell adhesion, growth, migration, and differentiation.<sup>12</sup> Altered fibronectin expression, degradation, and organization have been associated with a number of disorders, including cancer and fibrosis.<sup>13,14</sup> Because both fibronectin and FGF1 are secretory proteins, the FN1-FGF1 fusion protein is expected to be secreted in the form of a fusion protein which contains nearly the entirety of FGF1, and when secreted at high levels, could presumably function like normal FGF1 in excess. FGF1 protein is a crucial ligand for all FGFRs.<sup>15</sup> It acts as a potent mitogen of fibroblasts and is involved in critical biological functions including development, morphogenesis, and angiogenesis.<sup>16</sup> FN1-FGFR1 proteins could use the self-assembly and fibronectin-binding domains of the FN1 part to dimerize, perhaps with the assistance of extracellular matrix. The FGFs secreted by the tumor cells could bind the ligand-binding domains of the FGFR1 part to facilitate the dimerization and activation of the fusion protein, which would likely dimerize and bind the membranous FGFR1 in a 2:2 ternary fashion. Both pathways will converge in the activation of FGFR1 signaling, which upregulates the expression of FGF23.<sup>17</sup>  $\alpha$ -Klotho is an obligatory co-receptor for FGF23-FGFR1 binding, and its expression is mostly limited to renal tubules, choroid plexus, and parathyroid gland under normal physiologic condition.<sup>18</sup> FGF23 binds to the FGFR-klotho complex on the apical surface of the proximal renal tubule, which results in decreased phosphate reabsorption and consequent hypophosphatemia.<sup>19</sup>

The main function of FGF23 seems to be regulation of phosphate concentration in plasma. FGF23 is secreted by osteocytes in response to elevated calcitriol. It inhibits renal Pi reabsorption by reducing the apical expression and activity of NaPi-IIa in the proximal tubule epithelium.<sup>20</sup> FGF23 also reduces intestinal absorption of dietary Pi through a vitamin D receptor (VDR)-dependent decrease in NaPi-IIb activity. The latter phenomenon is most likely secondary to FGF23-mediated reduction of circulating 1,25(OH)<sub>2</sub> D<sub>3</sub> synthesis through suppression of D-1α-hydroxylase expression in the kidney.<sup>21</sup> Multiple FGF Receptors (FGFRs) can act as receptors for FGF23 when bound by the co-receptor Klotho expressed in the renal tubular epithelium.<sup>9</sup> FGFRs also regulate skeletal FGF23 secretion; ectopic FGFR activation is implicated in genetic conditions associated with FGF23 overproduction and hypophosphatemia.<sup>22</sup>

## CONCLUSION

Phosphaturic mesenchymal tumor (PMT) is a rare distinctive mesenchymal neoplasm with heterogeneous but recognizable histologic appearances. It frequently elicits a clinical paraneoplastic syndrome consisting of hypophosphatemic hyperphosphaturic osteomalacia due to increased secretion of FGF23. The patients typically present with gradual muscular weakness, bone pain, and pathologic fractures. The diagnosis is commonly delayed for years due to the non-specific nature of these symptoms, lack of clinical suspicion, failure to include serum phosphorus levels in routine blood chemistry testing, and difficulty in identifying the responsible tumor. Additionally, these tumors are often missed histologically because of their rarity and morphologic overlap with other mesenchymal neoplasms. Complete excision of the tumor is crucial as it typically result in the resolution of the osteomalacia, clinical symptoms, and laboratory abnormalities.

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## REFERENCES

1. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA*. 2001;98(11):6500-5.
2. Sundaram M, McCarthy EF. Oncogenic osteomalacia. *Skeletal Radiol*. 2000;29(3):117-24. PMID:10794548. <http://dx.doi.org/10.1007/s002560050581>.
3. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;118(10):1094-101. PMID:16194637. <http://dx.doi.org/10.1016/j.amjmed.2005.02.014>.
4. Fukumoto S, Yamashita T. Fibroblast growth factor-23 is the phosphaturic factor in tumor-induced osteomalacia and may be phosphatonin. *Curr Opin Nephrol Hypertens*. 2002;11(4):385-9. PMID:12105387. <http://dx.doi.org/10.1097/00041552-200207000-00003>.
5. Cho SI, Do NY, Yu SW, Choi JY. Nasal hemangiopericytoma causing oncogenic osteomalacia. *Clin Exp Otorhinolaryngol*. 2012;5(3):173-6. PMID:22977716. <http://dx.doi.org/10.3342/ceo.2012.5.3.173>.
6. Folpe AL. Phosphaturic mesenchymal tumour. In: Fletcher CDM, Bridge JA, Hogendoorn PCW et al. editors. *World Health Organization classification of tumours of soft tissue and bone*. Lyon: IARC Press; 2013. chap. 2.
7. Folpe AL, Fanburg-Smith JC, Billings SD, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol*. 2004;28(1):1-30. PMID:14707860. <http://dx.doi.org/10.1097/00000478-200401000-00001>.
8. Honda R, Kawabata Y, Ito S, Kikuchi F. Phosphaturic mesenchymal tumor, mixed connective tissue type, non-phosphaturic variant: report of a case and review of 32 cases from the Japanese published work. *J Dermatol*. 2014;41(9):845-9. PMID:25182295. <http://dx.doi.org/10.1111/1346-8138.12602>.
9. White KE, Evans WE, et al. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet*. 2000;26(3):345-8. PMID:11062477. <http://dx.doi.org/10.1038/81664>.
10. Tajima S, Fukayama M. Fibroblast growth factor receptor 1 (FGFR1) expression in phosphaturic mesenchymal tumors. *Int J Clin Exp Pathol*. 2015;8(8):9422-7. PMID:26464698.
11. Lee JC, Jeng YM, Su SY, et al. Identification of a novel FN1–FGFR1 genetic fusion as a frequent event in phosphaturic

- mesenchymal tumour. *J Pathol.* 2015;235(4):539-45. PMID:25319834. <http://dx.doi.org/10.1002/path.4465>.
12. Pankov R, Yamada KM. Fibronectin at a glance. *J Cell Sci.* 2002;115(Pt 20):3861-3. PMID:12244123. <http://dx.doi.org/10.1242/jcs.00059>.
  13. Puls F, Hofvander J, Magnusson L, et al. FN1-EGF gene fusions are recurrent in calcifying aponeurotic fibroma. *J Pathol.* 2016;238(4):502-7. PMID:26691015. <http://dx.doi.org/10.1002/path.4683>.
  14. Han S, Khuri FR, Roman J. Fibronectin stimulates non-small cell lung carcinoma cell growth through activation of Akt/mammalian target of rapamycin/S6 kinase and inactivation of LKB1/AMP-activated protein kinase signal pathways. *Cancer Res.* 2006;66(1):315-23. PMID:16397245. <http://dx.doi.org/10.1158/0008-5472.CAN-05-2367>.
  15. Ornitz DM, Xu J, Colvin JS, et al. Receptor specificity of the fibroblast growth factor family. *J Biol Chem.* 1996;271(25):15292-7. PMID:8663044. <http://dx.doi.org/10.1074/jbc.271.25.15292>.
  16. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. *Nat Rev Drug Discov.* 2009;8(3):235-53. PMID:19247306. <http://dx.doi.org/10.1038/nrd2792>.
  17. Lee JC, Changou CA, Yang RS et al. Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors. *Modern Pathology* 2016;29:1335-1346.
  18. Nabeshima Y. Klotho: a fundamental regulator of aging. *Ageing Res Rev.* 2002;1(4):627-38. PMID:12362891. [http://dx.doi.org/10.1016/S1568-1637\(02\)00027-2](http://dx.doi.org/10.1016/S1568-1637(02)00027-2).
  19. Quarles LD. Skeletal secretion of FGF-23 regulates phosphate and vitamin D metabolism. *Nat Rev Endocrinol.* 2012;8(5):276-86. PMID:22249518. <http://dx.doi.org/10.1038/nrendo.2011.218>.
  20. Jüppner H. Phosphate and FGF-23. *Kidney Int Suppl.* 2011;79(121):S24-7. PMID:21346724. <http://dx.doi.org/10.1038/ki.2011.27>.
  21. Perwad F, Zhang MY, Tenenhouse HS, Portale AA. Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1alpha-hydroxylase expression in vitro. *Am J Physiol Renal Physiol.* 2007;293(5):F1577-83. PMID:17699549. <http://dx.doi.org/10.1152/ajprenal.00463.2006>.
  22. Wu AL, Feng B, Chen MZ, et al. Antibody-mediated activation of FGFR1 induces FGF23 production and hypophosphatemia. *PLoS One.* 2013;8(2):e57322. PMID:23451204. <http://dx.doi.org/10.1371/journal.pone.0057322>.

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