

**Case Report**

# The Difficult Diagnosis of Hypophosphatemic Rickets-A Review of 8 Clinical Cases

Anna-Maria Borissova<sup>1,2</sup>, Yordan Vlahov<sup>1,2</sup>, Seiji Fukumoto<sup>3</sup>, Yuichiro Shimizu<sup>4</sup>, Todor Zahariev<sup>5,6</sup>, Valentin Govedarski<sup>5,6</sup>, Svetoslav Dimitrov<sup>5,6</sup>, Radina Ivanova<sup>6,7</sup>, Milena Nikolova<sup>6,8</sup>, Boyana Trifonova<sup>1,2,\*</sup>

<sup>1</sup>Clinic of Endocrinology, University Hospital Sofamed, Sofia, Bulgaria

<sup>2</sup>Medical Faculty, Sofia University "Saint Kliment Ohridsky", Sofia, Bulgaria

<sup>3</sup>Department of Molecular Endocrinology, Fujii Memorial Institute of Medical Sciences, Tokushima University, Tokushima, Japan

<sup>4</sup>Shimizu Clinic Akasaka, Minato-ku, Tokyo, Japan

<sup>5</sup>Clinic of Vascular and Endovascular Surgery, University Hospital "Saint Ekaterina", Sofia, Bulgaria

<sup>6</sup>Medical Faculty, Medical University, Sofia, Bulgaria

<sup>7</sup>Pathological Department, University Hospital Alexandrovska, Sofia, Bulgaria

<sup>8</sup>Clinic of Nephrology, University Hospital "Saint Ivan Rilski", Sofia, Bulgaria

**Email address:**

boianatri@abv.bg (B. Trifonova)

\*Corresponding author

**To cite this article:**

Anna-Maria Borissova, Yordan Vlahov, Seiji Fukumoto, Yuichiro Shimizu, Todor Zahariev, Valentin Govedarski, Svetoslav Dimitrov, Radina Ivanova, Milena Nikolova, Boyana Trifonova. The Difficult Diagnosis of Hypophosphatemic Rickets-A Review of 8 Clinical Cases. *Clinical Medicine Research*. Vol. 9, No. 5, 2020, pp. 97-102. doi: 10.11648/j.cm.20200905.11

**Received:** August 3, 2020; **Accepted:** August 18, 2020; **Published:** September 14, 2020

---

**Abstract:** Hypophosphatemic rickets is a rare, usually genetic disease associated with decreased phosphate reabsorption in the proximal renal tubule and vitamin D resistance. Several genetic mutations have been discovered, the most common being the X-linked PHEX mutation with high fibroblast growth factor 23 (FGF23) circulating levels. The hypophosphatemic type osteomalacia is usually hereditary or tumour-induced (TIO). In the past 20 years, we have discovered, treated and followed up overall 8 cases of the disease-3 women and 5 men, aged 18 to 52 years. In all patients the diagnostic process was long (a mean of 2-3 years) and involved multiple clinical consults, laboratory evaluations: Biochemical Standard Research, Hormonal Tests [PTH, 25 (OH) D, 1,25 (OH) 2D], Specialized Research (FGF23), Instrumental Research (Ultrasonography of whole body; Computed tomography; Magnetic resonance imaging; DXA examination with an assessment of T-score and Z-score of spine/hip). All of these studies aimed at ruling out different neurological, hematological, oncological, rheumatic, gastroenterological, urological, nephrological diseases and conditions. One of the patients had Fanconi syndrome, five had X-linked hypophosphatemia (XLH) and two had TIO. In the last two patients, we found a high level of FGF23 secreting a small lung neoplasm in the first case and a mesenchymal tumor in the median upper part of the right thigh in the second case. The surgical removal of the tumor mass lead to a fast decrease in FGF23 levels and correction of metabolic disturbances. We present clinical cases with hypophosphatemic rickets/osteomalacia and discuss the etiopathogenesis and treatment of this rare disease. Historically until now phosphate supplementation and therapy using analogs of highly active vitamin D (calcitriol, alfacalcidol, paricalcitol) have been used to manage conditions involving hypophosphatemia. In recent years there has been a progression of clinical trials for monoclonal anti-FGF23 antibodies for the treatment of XLH. These monoclonal anti-FGF23 antibodies may have potential for treating other conditions associated with FGF23 overactivity. However, clinical trials to support that possibility are not available at present.

**Keywords:** Hypophosphatemic Rickets, FGF23, Hereditary Forms, Mesenchymal Tumour, Treatment

---

## 1. Introduction

Rickets is one of the common disturbances in calcium-phosphate metabolism. According to the underlying pathogenic mechanism, it can be classified as hypocalcemic or hypophosphatemic. The more common form is the hypocalcemic type that is related to the lifestyle. The hypophosphatemic type osteomalacia is usually hereditary or tumor-induced and is associated with decreased phosphate reabsorption in the proximal renal tubuli with resistance to the effect of vitamin D. The discovery of the fibroblast growth factor 23 (FGF23) brought light to the obscure underlying mechanisms of this phosphate metabolism disturbance [1]. This chronic hypophosphatemia causes rickets and osteomalacia. FGF23 gene was identified using position cloning in 2000 year [2]. It was found later that several types of hypophosphatemic rickets are characterized by high circulating levels of FGF23 [3]. The most common type of inborn rickets and osteomalacia (approximately 1:20 000 individuals) is due to X-linked hypophosphatemia (XLH) mutation of PHEX (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), that causes increase in FGF23 levels [4]. X-linked hypophosphatemia and tumor-induced osteomalacia (TIO) are the most common causes of hypophosphatemic vitamin D-resistant rickets/osteomalacia [5].

## 2. Material

Eight patients with hypophosphatemic rickets for a period of 20 years, aged 18 to 52 years, 3 women and 5 men, were studied and followed up.

## 3. Methods

The diagnosis of this rare disease of hypophosphatemic rickets/osteomalacia is very difficult and usually takes years, going through many specialists.

### 3.1. Biochemical Standard Research

Calcium (normal range 2.12-2.62 mmol/L), Phosphate (normal range 0.81-1.45 mmol/L), ALP (normal range 35-110 mU/L), total protein; *Urine parameters*: uCa (normal range < 7.5 mmol/24 h), uP (normal range < 40 mmol/24 h), eGFR (ml/min/1.73 m<sup>2</sup>).

### 3.2. Hormonal Tests

PTH (normal range 10-65 pg/mL), 25 (OH) D (normal range > 30 ng/mL), 1,25 (OH) 2D (normal range 35-80 ng/L).

### 3.3. Specialized Research

FGF23 (normal range 26-110 kRU/L); Histological examination;

Most of the tumors (induced osteomalacia) are solitary and small and their localization is very difficult [6].

### 3.4. Instrumental Research

Ultrasonography of whole body; Computed tomography (CT); Magnetic resonance imaging (MRI); DXA examination with an assessment of T-score and Z-score of spine/hip.

## 4. Results

### 4.1. Case Presentation of First Six Patients with XLH Resp. Fanconi Syndrome

For the past two decades we have diagnosed and treated overall 8 cases of hypophosphatemic rickets. In all patients the diagnostic process was long (a mean of 2-3 years) and involved multiple clinical consults, laboratory evaluations and imaging studies aimed at ruling out different neurological, hematological, oncological, rheumatic, gastroenterological and urological/nephrological diseases and conditions. In the first 6 cases the diagnosis was based on the characteristic disturbances in calcium and phosphate metabolism, parathormone (PTH) and vitamin D [25 (OH) D and 1,25 (OH) 2D] disturbances with presumed hypophosphatemic rickets with probable increase in FGF23 levels. Subsequently, in 5 of these 6 patients the diagnosis was confirmed by investigation of FGF23 levels in the Medical University of Tokyo, and we assumed that the patients had the most common form of hypophosphatemic rickets/osteomalacia-XLH or tumor-induced osteomalacia (TIO) [7, 8]. The sixth patient was confirmed to have Fanconi syndrome with low FGF23 levels [9].

### 4.2. Case Presentation of Two Patients with TIO

As the time passed, we diagnosed two more patients with severe hypophosphatemia and extremely high FGF23 levels (detected in the Germany laboratory), suggesting the presence of TIO [8]. Both patients had marked fatigue, muscle weakness and locomotion was impossible (the first patient was in a wheel chair and the second had to be carried by his relatives). In these two patients the detection of the underlying tumor appeared to be a long and exhausting process.

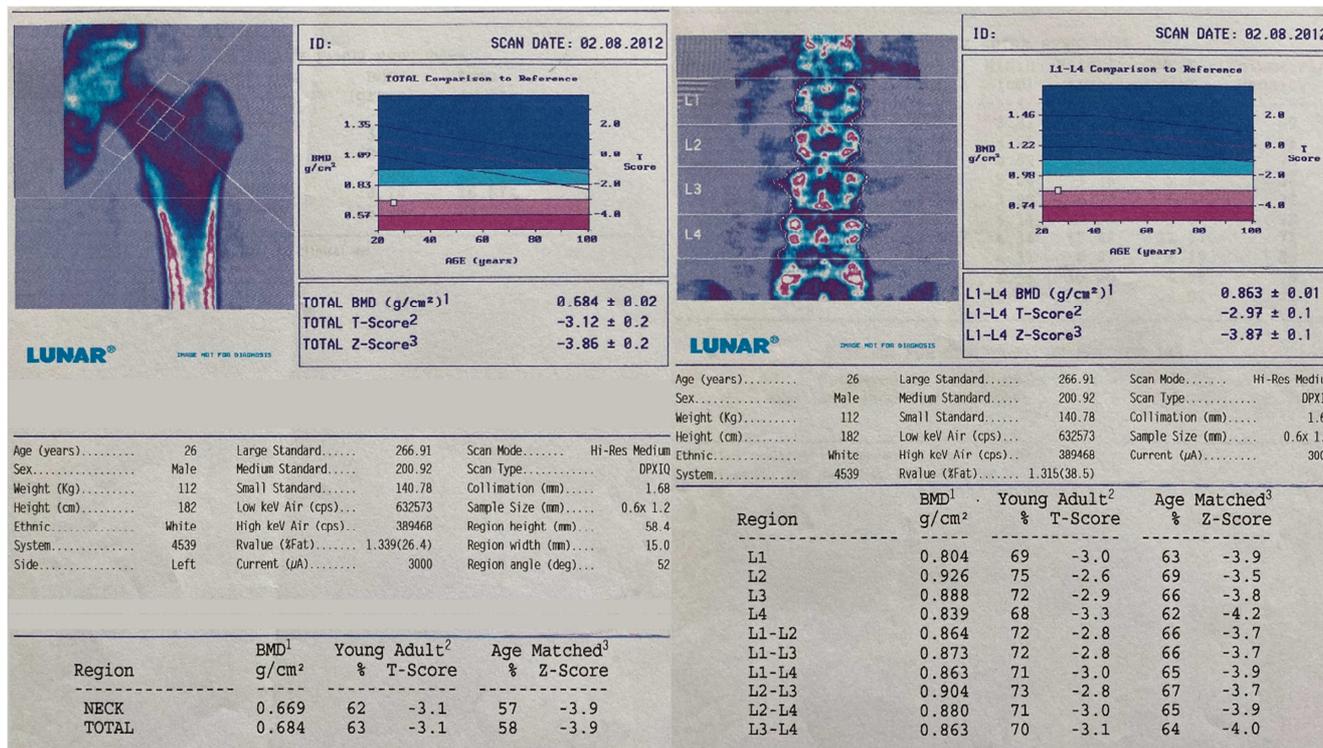
#### 4.2.1. First Patient with Confirmed TIO

The first patient was a 60-years-old male (patient number 7-AVN), a ranger and active sportsman, who had past history of chronic lymphatic leukemia, in remission, and after long search for other tumors, a small lung neoplasm was detected. After the surgical removal of the tumor, we observed marked improvement-the patient was able to stand up from the wheel chair and walk on his own and go back to active sports-swimming and boxing. The phosphate levels increased from 0,37 mmol/L before to 0,79 mmol/L after the operation, but the patient continued to take phosphates (2 g/d) after the operation. Due to the constantly increased FGF23 levels after the operation (1219 kRU/L (26-110) before vs. 3466 kRU/L (26-110) after the operation, respectively) we are still looking for recurrence of the lung neoplasm or for another neoplasm.

The patient is in good clinical condition. The opportunity to treat him with anti-FGF23 monoclonal antibodies could give us time to find the probable tumor source of FGF23 that we have been searching for two years now. The first FDA approved drug for the treatment of XLH is Burosumab. This is human IgG1 monoclonal antibody binding the excess FGF23 and blocking its biologic activity [10]. This medication could postpone the progression of hypophosphatemia and give us time to find the underlying neoplasm.

**4.2.2. Second Patient with Confirmed TIO**

The second patient (patient number 8-NAJ) was a 26-years-old active male in whom muscle weakness were detected in March 2011. Hypophosphatemic rickets/osteomalacia was diagnosed in July 2012 (i.e., 18 months later) based on increased FGF23 three times above the upper limit of the normal range-355 kRU/L (26-110), hypophosphatemic rickets and very low bone mass on osteodensitometric evaluation (Table 1 and Figure 1).



**Figure 1.** DXA examination of patient number 8 from August 2012-severe secondary osteoporosis (T-score L<sub>1-4</sub>-3.0 SD, Z score L<sub>1-4</sub>-3.9SD; T score hip-3.1SD, Z score hip-3.9SD).

**Table 1.** Biochemical and hormonal changes of patient number 8 (NAJ) with detected and surgically removed FGF23-producing mesenchymal tumor.

Parameters	At diagnosis, June 2012	On treatment with phosphates 2 g/d and Rocaltrol 1µg/d [1,25 (OH) 2D]	Before surgery-December 10, 2018	One month post-surgery January 2019	Three months post-surgery March 2019
Ca (normal range 2.12-2.62 mmol/L)	2.42	2.35	2.51	2.72	2.63
P (normal range 0.81-1.45 mmol/L)	0.51	0.52	0.61	1.7	1.27
ALP (normal range 35-110 mU/L)	191	123	120	107	101
uCa (normal range <7.5 mmol/24 h)	2.76 mmol/24 h	2.2 mmol/24 h	5.2 mmol/24 h	9.2 mmol/24 h	7.9 mmol/24 h
uP (normal range <40 mmol/24h)	100 mmol/24 h	86 mmol/24 h	83.3 mmol/24 h	65.5 mmol/24 h	60.4 mmol/24 h
GFR (ml/min)	193 ml/min	173 ml/min	206 ml/min	124 ml/min	156 ml/min
FGF23 (normal range 26-110 kRU/L)	355 kRU/L		6380 kRU/L	277 kRU/L	206 kRU/L
PTH (normal range 10-65 pg/mL)	24.1 pg/mL	7.5 pmol/L (1.9-6.9)	57 pg/mL (10-65)	79.4 pg/mL (10-65)	72.8 pg/mL (10-65)
25 (OH) D (normal range->30ng/mL)	13.3 ng/mL-Jul	14.4 ng/ml-Sep	15.9 ng/ml-Dec	18.84 ng/ml-Jan	13.4 ng/ml-Mar
1,25 (OH) 2D (35-80 ng/L)	<12				

Ca=serum calcium; P=serum phosphates; ALP=serum alkaline phosphatase; uCa=urine calcium; uP=urine phosphates; GFR=glomerular filtration rate; FGF23=fibroblast growth factor 23; PTH=parathormone; 25 (OH) 2D=dihydroxyvitamin D.

The patient started taking Phosphate 2 g/d plus Calcitriol 1.0 µg/d and marked clinical improvement was observed-the patient could stand up from bed on his own, locomotion was restored and he started swimming again. But phosphate levels remained around the baseline values (Table 1). During the next six years

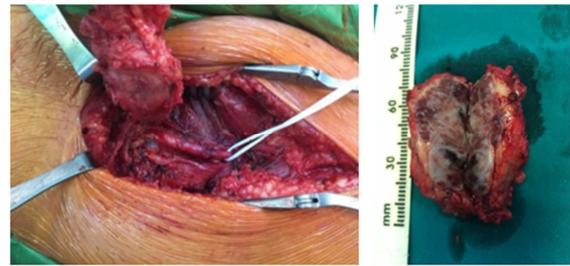
regular biochemical and hormonal evaluations were performed along with instrumental investigations aimed at finding an underlying neoplasm. In 2012 the patient noted slight asymmetry in both thighs, but the imaging and other instrumental studies found no underlying pathology. The asymmetry progressed and

in 2018 the control ultrasound and MRI studies revealed the presence of solid and well-vascularized formation in the median upper part of the right thigh, between the sartorius and the long adductor muscles. The formation was situated before the femoral vessels and the artery and vein were slightly dislocated dorsally. No regional lymphadenopathy was present. The tumor was surgically removed in the Clinic of Vascular and Endovascular Surgery, University Hospital "Saint Ekaterina", Medical University-Sofia. The surgical protocol (N1031/Dec 13, 2018): Through a typical femoral access the tumor formation was reached in the proximal third of the thigh, located between adductor longus and sartorius muscles. Approximate size of the formation was 40/40/60 mm, without disturbing tumor capsule. The tumor capsule was dissected. Communication between the tumor, arterial branch of the right superficial femoral artery and venous branch was detected and after that ligated. The tumor was extirpated and sent for histological examination. Figure 2 reveals the macroscopic appearance of the formation. The preoperative FGF23 levels reached 6380 kRU/L (normal range 26-110). Table 1 shows the dramatic improvement in laboratory results after the operation.

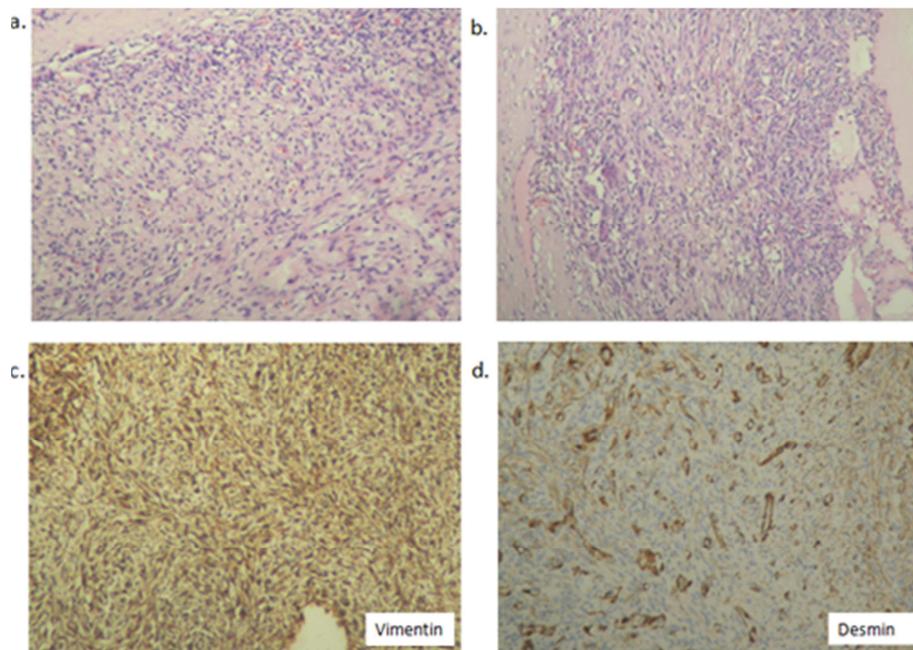
The histopathological study (Figure 3) revealed: Macroscopic evaluation: well-defined by fibrous capsule

tumor 6.5/3.5/5 cm.

Histological examination: moderately cellular mesenchymal tumor, containing pleomorphic oval shaped cells with no significant nuclear atypia or mitotic activity, with nested or fascicle growth pattern (Figure 3a and 3b). In some areas the presence of vessels with varying shape and size, and also some cystic spaces was evident. Immunohistochemical stainings showed strong immunoreaction for *vimentin* in the tumor cells and focal positive reaction for *desmin* (Figure 3c and 3d). Based on the morphological, immunohisto-chemical and patient's clinical data, the tumor was classified as phosphaturic mesenchymal tumor, mixed connective tissue variant.



**Figure 2.** Mesenchymal tumor of the right inguinal area of patient number 8 (NAJ).



**Figure 3.** Histopathological features of phosphaturic mesenchymal tumor, mixed connective tissue variant. (a) A moderately cellular mesenchymal tumor of oval shaped cells, with no signs of nuclear atypia (HE). (b) A tumor area with numerous vessels and some cystic spaces (HE). (c) Strong positive reaction of tumor cells with vimentin (IHH). (d) Focal positive reaction of neoplastic cells with desmin (IHH).

Phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT) causes tumor-induced osteomalacia (TIO) and in most cases follows a benign clinical course, with rare occurrences of malignant transformation [11].

## 5. Discussion

The phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT), diagnosed in our case with TIO

has been reported as the most common type among the mesenchymal tumors associated with TIO (up to 70-80% of all reported cases) [5, 12, 13]. It usually occurs in the soft tissues or bones and is characterized by slow growth and benign behavior, although several cases of malignant variants, including metastatic dissemination, have been described. Various histological features of PMT-MCT have been described, but the most frequently encountered are spindle-shaped immature mesenchymal cells, with small

normochromatic nuclei, prominent vessels, osteoclast-like giant cells and cartilage-like matrix. According to the literature, the immunohisto-chemical stainings with various markers for cellular differentiation give controversial results. In our case the strong positive reaction of tumor cells for *vimentin* proved mesenchymal origin of the tumor and the focal positive reaction for *desmin* defined its partly myogenic phenotype. Therefore, despite being morphologically heterogeneous, probably PMT-MCT constitute a single, histopathological entity [5]. Regardless of tumor morphology, the hallmark for the diagnosis of PMT-MCT is the association of the tumor with the clinical syndrome of TIO, including elevation in plasma FGF23, and its disappearance after tumor extirpation. The precise mechanism of FGF23 hypersecretion outside the bones in patients with mesenchymal tumors remains unclear.

Our patient number 8 once again shows the difficult path to the diagnosis of hypophosphatemic rickets/osteomalacia and the long way the clinicians and patient walk to the finding of the underlying tumor mass after FGF23 hypersecretion is detected. In the majority of patients with FGF23 hypersecretion the patient has a slow growing mesenchymal tumor with rich expression of FGF23 with the latter entering the systemic circulation. In our patient FGF23 levels were 580 times above the upper limit of the normal range before the operation, and after the intervention dropped 23 times within two months! Therefore, we assumed that the extirpated tumor mass was the source of FGF23 secretion. Usually, TIO subsides after the removal of the tumor mass. In our patient, phosphate and vitamin D [1,25 (OH) 2D] treatment ceased after the surgical intervention and on month three post-operation biochemical remission was detected and only moderate hyperphosphaturia persisted. The physical and emotional status of the patient showed marked improvement. Bone density will be measured again on month 18 post-operation and we expect an improvement of BMD at both lumbar and femoral sites similar to the results reported by Colangelo L. et al. This is the consequence of huge mineralization of a large amount of osteoid tissue after resolution of the disease [14]. The patient will be followed up closely in the upcoming years concerning serum and urine calcium, phosphate and FGF23 levels, which will be monitored.

## 6. Conclusion

We observed 8 patients with hypophosphatemic rickets/osteomalacia. One of them was detected Fanconi syndrome, two had TIO and five had XLH. X-linked hypophosphatemia and TIO are the most common causes of hypophosphatemic vitamin D-resistant rickets/osteomalacia. These patients pose a serious problem of maintaining pathogenic treatment. Historically until now phosphate supplementation and therapy using analogs of highly active vitamin D (calcitriol, alfalcidol, paricalcitol) have been used to manage conditions involving hypophosphatemia. The cutting-edge medical technologies offer us treatment in the face of monoclonal

anti-FGF23 antibodies [10]. The progression of clinical trials with burosumab (monoclonal anti-FGF23 antibodies) for the treatment of XLH and its recent availability for clinical use may have potential for treating other conditions associated with FGF23 overactivity. Clinical trials to support that possibility are not available at present [15, 16]. Novel therapeutic approaches include image-guided tumor ablation and the pan-FGFR tyrosine kinase inhibitor (BGJ398/infgratinib), which is great progress in the treatment of TIO [17].

## Conflicts of Interests

The authors declare that they have no competing interests.

## References

- [1] Xianglan H. (2013). FGF23 and Phosphate Wasting Disorders, *Bone Research*. 2, 120-132.
- [2] ADHR Consortium. (2000). Autosomal dominant hypophosphatemic rickets is associated with mutations in FGF23. *Nat Genet*. 26: 345-348.
- [3] Pettifor JM, Thandrayen K. (2012). Hypophosphatemic rickets: unraveling the role of FGF23. *Calcif Tissue Int*. 91: 297-306.
- [4] Carpenter T. O, Imel E. A, Ruppe M. D, Webber T. J, Klausner M. A, Wooddell M. M, Kawakami T, Ito T, Zhang X, Humphrey J, Insogna K. L, Peacock M. (2014). Randomized trial of the anti-FGF23 antibody KRN23 in X-linked hypophosphatemia. *The Journal of Clinical Investigation*. 24; 1587-1597.
- [5] Rayamajhi SJ, Yeh R, Wong T, Dumeer S, Mittal BR, Remotti F, Chikeka I, Reddy AK. (2019). Tumor-induced osteomalacia-Current imaging modalities and a systematic approach for tumor localization. *Clin Imaging*. Jul-Aug; 56: 114-123. doi: 10.1016/j.clinimag.2019.04.007. Epub 2019 Apr 17.
- [6] Bianchini JW, Stambler AA, Harrison HE. (1971). Familial Hypophosphatemia rickets showing autosomal dominant inheritance. *Birth Defects Orig Artic Ser*. 7: 287-295.
- [7] Farrow EG, White KE. (2009). Tumor-induced osteomalacia. *Expert Rev Endocrinol Metab*. 4: 435-442.
- [8] Karatzas A, Paridis D, Kozyrakis D, Tzortzis V, Samarinas, Dailiana Z, Karachalios T. (2017). Fanconi syndrome in the adulthood. The role of early diagnosis and treatment. *J Musculoskelet Neuronal Interact*. 17 (4): 303-306.
- [9] Portale A. A, Carpenter T. O, Brandi M. L, Briot K, Cheong H. II, Cohen-Solal M, Crowley R, De Beur S. J, Eastell R, Imanishi Y, Imel E. A, Ing S, Ito N. et al. (2019). Continued Beneficial Effects of Burosumab in Adults with X-Linked Hypophosphatemia: Results from a 24-Week Treatment Continuation Period After a 24-Week Double-Blind Placebo-Controlled Period. *Calcified Tissue International*. 105: 271-284.
- [10] Noriko Oyama, Kanako Kojima-Ishii, Naoko Toda, Terumichi Matsuo, Vlad Tocan, Kazuhiro Ohkubo, Utako Oba, Yuhki Koga, Nokitaka Setsu, Yuichi Yamada, Kenichi Kohashi, Yasuharu Nakashima, Yoshinao Oda, Kenji Ihara, and Shouichi Ohga. (2020). Malignant transformation of phosphaturic mesenchymal tumor: a case report and literature review.

- [11] Weidner N, Santa CD. (1987). Phosphaturic mesenchymal tumors. *Cancer*. 59: 1442-1454.
- [12] Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho J. Y, Econs M. J. et al. (2004). Most osteomalacia associated mesenchymal tumors are a single histopathological entity. *Am J Surg Pathol*. 28: 1-30.
- [13] Chong WH, Molinolo AA, Chen CC, Collins MT. (2011). Tumor-induced osteomalacia. *Endocr Relat Cancer*. 18 (3): R53–R77. doi: 10.1530/ERC-11-0006.
- [14] Colangelo L, Pepe J, Nieddu L, Sonato C, Scillitani A, Diacinti D, Angelozzi M, Cipriani C, Minisola S. (2020). Long-term bone mineral density changes after surgical cure of patients with tumor-induced osteomalacia. *Osteoporos Int*. 31 (7): 1383-1387. doi: 10.1007/s00198-020-05369-1. Epub 2020 Mar 17.
- [15] Imel E. A, Biggin A, Schindeler A, Munns C. F. (2019). FGF23, Hypophosphatemia, and Emerging Treatments. *JBMR1 Plus (WOA)*, 3, 8, e10190.
- [16] Athonvarangkul D, Insogna KL. (2020). New Therapies for Hypophosphatemia-Related to FGF23 Excess. *Calcif Tissue Int*. Jun 5. doi: 10.1007/s00223-020-00705-3.
- [17] Florenzano P, Hartley IR, Jimenez M, Roszko K, Gafni RI, Collins MT. (2020). Tumor-Induced Osteomalacia. *Calcif Tissue Int*. Jun 5. doi: 10.1007/s00223-020-00691-6.