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Olgu Sunumu / Case Report

Hypophosphatemia Associated with Tumor-Induced Osteomalacia Caused by A Third Primary Tumor: A Case Report.

Üçüncü Primer Tümör Nedeniyle Gelişen, Tümör İlişkili Osteomalaziye Bağlı Bir Hipofosfatemi Olgusu.

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Abstract

Tumor-induced osteomalacia (TIO) is a paraneoplastic condition in which a tumor, usually of mesenchymal origin, causes osteomalacia often by producing Fibroblast Growth Factor-23 (FGF-23). FGF-23 induces hypophosphatemia through its phosphaturic action. Case Presentation: A 65-year-old male patient presented with complaints of muscle weakness, difficulty walking and severe bone pain. His medical history included distal gastrectomy for a moderate-risk gastrointestinal stromal tumor (GIST) of 4 cm in diameter, Billroth II antecholic gastroenterostomy and subsequently total thyroidectomy for Stage 1 multicentric micropapillary carcinoma (CA). Widespread lesions detected on bone scintigraphy were considered as bone metastases of GIST. Laboratory investigations revealed the following results: calcium (Ca): 8.3 mg/dL; phosphate (P): 1.5 mg/dL; Parathormone (PTH): 75 pg/mL; 25-OH vit D3: 31 ng/mL; 1-25-(OH)2 vit D3: 36 pg/mL; creatinine: 0.75 mg/dL; ALP: 109 IU/L, urine phosphate: 2.54 g/day. His hypophosphatemia was considered to be most probably due to TIO induced by bone metastases of GIST. Since it was not possible to remove the metastases, the patient was started on oral phosphate and calcitriol therapy. However, despite an improvement in Ca levels after the initiation of the treatment, P levels persisted around 2 mg/dL. After one year of treatment, an ulcer developed on his right first toe, which was excised and identified as "extraskeletal myxoid chondrosarcoma" on pathological examination. Following excision of the tumor, the patient's Ca and P values returned to normal range. The development of TIO in the presence of a GIST and thyroid CA is an unusual occurrence. As a matter of fact, the cause of hypophosphatemia was TIO which induced by a third primary tumor in this patient. To the best of our knowledge, TIO due to a third primary tumor is the first and only case in the literature. Another primary tumor focus should be suspected and carefully investigated if the patient already has a primary tumor and that tumor is not among those frequently inducing TIO.
Keywords: Third primary tumor, tumor-induced osteomalacia, hypophosphatemia, hypophosphatemic osteomalacia

Özet

Tümörle ilişkili osteomalazi (TİO), genellikle mezenkimal kaynaklı bir tümörün sıklıkla Fibroblast Büyüme Faktörü- 23 (FGF-23) üreterek osteomalaziye neden olduğu paraneoplastik bir durumdur. FGF-23, fosfatürik etki ile hipofosfatemiye neden olur.Olgu: Altmışbeş yaşında erkek hasta, kas güçsüzlüğü, zor yürüme ve şiddetli kemik ağrıları şikayetleri ile başvurdu. Tıbbi öyküsünde: 4 cm çapta orta riskli gastrointestinal sistem stromal tümör (GİST) sebebiyle distal gastrektomi, Billroth 2 antekolik gastroenterostomi ve sonrasında Evre 1 multisentrik mikropapiller karsinom (CA) sebebiyle total tiroidektomi operasyonları mevcuttu. Kemik sintigrafisindeki yaygın lezyonları GİST'in kemik metastazı olarak kabul edilmişti.Laboratuvar tetkiklerinde: Kalsiyum (Ca):8.3 mg/dL, fosfor (P): 1.5 mg/dL, parathormon (PTH): 75 pg/mL, 25-OH vit D3: 31 ng/mL, 1-25-(OH)2 vit D3: 36 pg/mL, kreatinin: 0.75 mg/dL ALP: 109 IU/L, idrar fosforu: 2.54 gr/gün idi. Hastanın hipofosfatemisinin olası sebebi GIST kemik metastazlarına bağlı olarak gelişmiş TİO'ye bağlı olduğu düşünüldü. Metastazların cerrahi olarak çıkartılması mümkün olmadığından, hastaya oral fosfat ve kalsitriol tedavisi başlandı. Ancak tedavi başlandıktan sonra Ca düzeyleri düzelmesine rağmen, P düzeyleri yaklaşık 2 mg/dl düzeylerinde seyretti. Tedavi başlandıktan bir yıl sonra sağ ayak birinci parmağında ülser gelişmesi üzerine, bu lezyon eksize edildi ve patoloji sonucu "ekstraskeletal miksoid kondrosarkom" olarak raporlandı. Tümörün eksizyonu sonrasında Ca ve P değerleri tamamen normale geldi. GIST ve tiroid CA ile TİO gözlenmesi genellikle beklenilen bir durum değildir. Nitekim hipofosfatemi sebebi olarak, hastamızda üçüncü primer tümöre bağlı olarak gelişmiş bir TİO tespit edildi. Üçüncü primer tümöre bağlı olarak gelişen TİO bildiğimiz kadarıyla literatürde ilk ve tek olgudur. Eğer hastada halihazırda primer bir tümör var ve bu tümör TİO'ye sık neden olan tümörlerden değilse, başka bir primer tümör odağının olup olmadığı dikkatle araştırılmalıdır.
Anahtar Kelimeler: Üçüncü primer tümör, tümör ilişkili osteomalazi, hipofosfatemi, hipofosfatemik osteomalazi

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1. Introduction

Oncogenic osteomalacia, also known as tumor-induced osteomalacia (TIO), is a paraneoplastic disorder often caused by a bone or soft tissue tumor that secretes fibroblast growth factor-23 (FGF-23), a phosphaturic protein, leading to the signs and symptoms of osteomalacia (or rickets)1. The mean age of onset is 40 to 45 years. Phosphaturic mesenchymal tumor, mixed connective type (PMT-MCT) is a rare mesenchymal tumor which is most frequently associated with TIO. The majority of PMT-MCTs are benign, slowly growing polymorphic neoplasms and the time from onset of symptoms to definitive diagnosis usually is longer than 2.5 years1,2. It has been reported that about 56% of these tumors are located in the lower extremities and 31% in the head region3. Colon, prostate, ovarian, lung cancers, osteosarcoma and spindle cell sarcoma are other tumors that can rarely cause TIO4,5.

Hypophosphatemia, phosphaturia, and low or inappropriately normal serum calcitriol levels are observed in TIO2,6. FGF-23 reduces reabsorption of phosphate from renal tubules and production of 1,25-dihydroxyvitamin D3 in the kidney via FGF receptor-1 (FGFR-1) signaling7. The resulting hypophosphatemia leads to bone pain, muscle weakness, rickets/osteomalacia and fractures. Pathological fractures have been reported to occur most commonly in vertebrae, ribs, femur and pelvis8.

As patients with X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR) and autosomal recessive hypophosphatemic rickets (ARHR) also have increased serum FGF-23 levels, these diseases need to be differentiated from TIO9,10. Compared to patients with XLH, clinical manifestations of patients with TIO are usually more severe, which may be related to more severe drops in serum phosphate and calcitriol levels. The presence of a previously normal serum phosphate level in an affected patient often supports the diagnosis of TIO11. If the diagnosis remains uncertain, genetic testing may be done for XLH, ARHR and ADHR. Until the underlying tumor is identified, other disorders causing renal phosphate wasting should also be considered in the differential diagnosis12.

The only definitive treatment of TIO is the resection of the tumor. Since the tumors are typically small in size and can be anywhere in the body, locating them on X-ray images is challenging. Therefore, whole body magnetic resonance imaging (MRI), 111indium-pentetreotide scintigraphy, 18F-Fluoro-2-deoxy-glucose positron emission tomography/computed tomography (FDG-PET/CT) and Gallium-68 (Ga68)-DOTA-TATE PET/CT may be used when necessary1,3,8. Despite the availability of various diagnostic tools, localization of the culprit tumor can only be achieved in 65-80% of patients. In general, serum levels of FGF-23 decrease to normal, biochemical abnormalities improve rapidly and bone disease resolves within a period of 6 to 12 weeks following tumor resection2,6,13.

However, pharmacological therapy is required when the tumor cannot be localized. The goals of treatment are to try to achieve normal serum phosphate, alkaline phosphatase (ALP) and parathormone (PTH), manage bone pain, address mobility limitations and treat fractures. Oral calcitriol and oral phosphate have been traditionally used for the treatment of TIO. Calcitriol is usually administered as 0.5 to 1 mcg/day (15–60 ng/kg/day) in two divided doses and phosphate is given as 1 to 2 g daily (15–60 mg/kg/day) elemental phosphate in three to four divided doses. Since abdominal pain and diarrhea commonly occur with phosphate treatment, doses should be increased by up-titration. Serum phosphate, calcium, creatinine, bone-specific ALP, 24-hour urinary calcium, and PTH levels should be assessed at least every six months in patients receiving treatment with phosphate and calcitriol. Patients should be followed on a regular basis since toxicity manifested by hypercalcemia and hyperphosphatemia may occur suddenly in a patient who has been stable for many years11.

If the tumor cannot be identified or removed, medical therapy is continued indefinitely. It

would be appropriate to repeat tumor localization investigations at different intervals after starting drug therapy.

The best of our knowledge, this case is that it was the first TIO case developed due to the third primary tumor in the literature. For this reason, we wanted to publish this case to draw attention to this rare condition.

2. Case Presentation

A 65-year-old patient was referred to our clinic from the oncology department in 2015 because of hypophosphatemia. His complaints were muscle weakness, difficulty walking and bone pain. The patient was taking Levothyroxine 150 mcg/day for hypothyroidism due to thyroidectomy and alendronate 70 mg weekly orally for osteoporosis. He had a history of distal gastrectomy and Billroth II antecholic gastroenterostomy in 2011, with a pathology report of a moderate-risk gastrointestinal stromal tumor (GIST) of 4 cm in diameter. He also had a history of total thyroidectomy in 2013 due to FDG uptake by the thyroid gland on PET-CT scan which was requested by the oncology department for staging and follow-up purposes, and Stage 1 multicentric micropapillary carcinoma (CA) was reported by the pathologist. The patient has been experiencing bone pain since 2013 when extensive lesions were detected on bone scintigraphy, which were considered by the oncology department to be consistent with metastasis. During that period, he was followed by oncologists for metastatic GIST and started on alendronate therapy because of established osteoporosis. A PET-CT scan in 2015 showed diffuse FDG uptake in the middle portion of the right clavicle and on the right side of the ribs and a mass (16x12 mm) showing increased FDG uptake in the right adrenal gland was also considered as metastasis by the oncologists. On bone scintigraphy from 2015, minimally increased activity was observed as multiple foci in the left frontoorbital, occipital and parietal bones in the cranium; the medial segment of the right clavicle; in both hemithorax ribs; left lateral segment of the sacrum, the tarsal bones of the right foot and first metatarsophalangeal joint. These findings were first considered to be consistent with bone metastasis and despite the disappearance of some foci compared to bone scintigraphy from 2014, they were identified as progression due to the presence of new foci in both hemithoraxes.

At the time of his initial presentation in January 2015, physical examination showed that his general condition was fair, his blood pressure was 110/70 mmHg, pulse was 80 beats/minute and rhythmic and lung sounds were normal, and he was walking with assistance. An incision scar over the abdomen and a thyroidectomy scar on the neck were observed. Biochemistry results were as follows: Ca: 8.3 mg/dL (ref. range: 8.5-10.5 mg/dL), P: 1.5 mg/dL (ref. range: 2.5-4.5 mg/dL), PTH: 75 pg/mL (ref. range: 15-65 pg/mL), 25-OH vit D3: 31 ng/mL (ref. range: 20-50 ng/mL) 1-25 (OH)2- vit D3: 36 pg/mL (ref. range: 18-64 pg/mL), urea: 32 mg/dL (20-40 mg/dL), creatinine: 0.75 mg/dL (ref. range: 0.6-1.2 mg/dL), sodium: 145 mmol/L (ref. range: 135-145 mmol/L), potassium: 4.3 mmol/L (ref. range: 3.5-5 mmol/L), AST: 14 IU/L (ref. range: 5-34 IU/L), ALT: 10 IU/L (ref. range: 3-42 IU/L), ALP: 109 IU/L (ref. range: 40-129 IU/L), TSH: 0.71 mIU/mL (ref. range: 0.27-4.2 mIU/mL), free T4: 1.22 ng/dL (ref. range: 0.93-1.7ng/dL), Thyroglobulin: <0.2 ng/mL (ref. range: 0.2-0.3 ng/mL), Anti-Tg:<10 ng/mL (ref. range: :<10 ng/mL) .

While the 24-hour urinary phosphate excretion measured in 2018 and 2019 was low, tubular phosphate reabsorption was found to be high (Table 1).

Serum metanephrine and normetanephrine and basal cortisol levels and aldosterone/renin ratio were in normal range. His adrenal mass was classified as a non-functioning incidentaloma. Celiac tests (tissue transglutaminase IgA, IgG, anti-endomysial antibodies IgA and IgG) were negative. A L1-L4 T-score of -2.3 (consistent with osteopenia) was found on a DXA scan obtained while he was receiving alendronate therapy, which was initiated by an external center. The patient was started on treatment with oral phosphate, calcium and 25-OH vit D3. Bisphosphonate therapy was discontinued and the patient was asked to return for follow--up every month. His symptoms started to

improve with this treatment. At 6 months after starting treatment, he had virtually no complaints with improvement of clinical symptoms and he was able to walk without help. However, his phosphate levels did not exhibit a significant improvement. At 12 months of treatment, 25-OH vitamin D3 was stopped and calcitriol was started on 30.03.2016 due to persistently low phosphate levels despite oral phosphate and 25-OH vitamin D3 treatment. In 2019, the patient presented to the orthopedics clinic for an ulcer on his right toe. An MRI scan showed an iso-hyperintense well-defined lesion area (approximately 2.5x4 cm in size) on the T2A sequence at the sole of the right foot, located under the first metatarsal bone (Figures a, b, c).

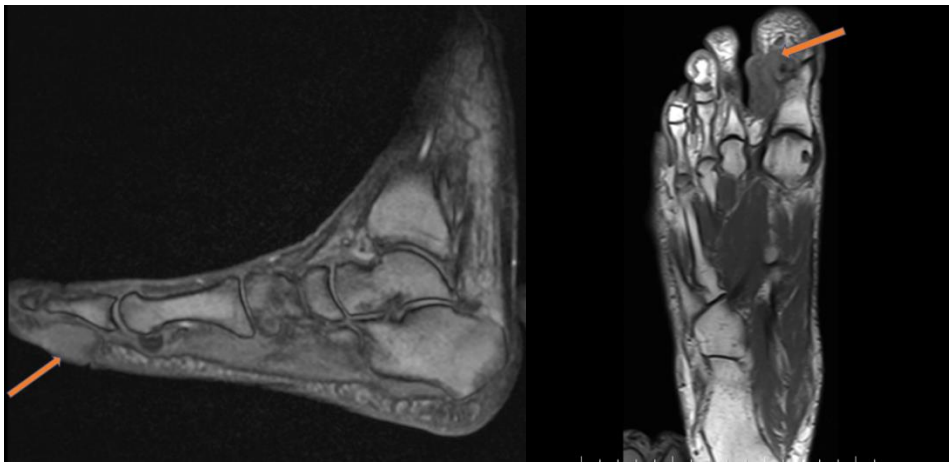

Figure 1a **Figure 1b**

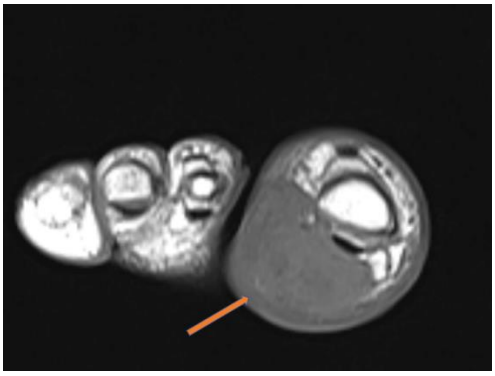

Figure 1c

An iso-hyperintense well-defined lesion on MRI T2A sequence at the sole of the right foot, located under the first metatarsal bone area (approximately 2.5x4 cm in size).

Table 1. Follow-up laboratory investigations for Ca and P metabolism

Parameter Reference range	Ca (mg/dL)* (8.5-10.5 mg/dL)	P (mg/dL) (2.5-4.5mg/dl)	25-OH-Vit D3 (ng/L) (20-50 ng/mL)	PTH (pg/mL) (15-65 pg/mL)	24-h urinary Ca (mg/day) (100-320 mg/day)	24-h urinary P (g/day) (0.4-1.30 g/day)	Tubular P reabsorption (%) (% 82-95)
23.06.2015	6.6	2.8	56.1	113	198	0.71	
01.06.2016	7.3	2.4	3.7	70			
14.02.2017	8.2	2.1	27.5		164		
01.11.2018	9	2	34.6	92.6		2.54	% 17
31.10.2019	8.6	2.15	45.5	114	242	2.23	% 26.5
28.11.2019		Tumor resection					
19.08.2020	8.9	3.05	34				
22.01.2021	9	2.6				1.11	% 82.5
06.09.2021	9.3	2.67		67			

*Abbreviations: *Ca: Serum calcium levels adjusted for serum albumin levels, P: Serum phosphate levels, PTH: Serum intact parathormone, 24-h urinary Ca: 24-hour urinary calcium excretion, 24-h urinary P: 24-hour urinary phosphate excretion, tubular P reabsorption: Renal tubular phosphate reabsorption.*

On 26.11.2019, PET scans showed increased FDG uptake (max. SUV: 3.8) in a soft tissue lesion adjacent to the proximal phalangeal and metotarsophalangeal joint of the right first toe, FDG-negative lesions in the liver and a FDG-positive (max. SUV: 5.3) lesion in the right adrenal gland. Preliminary diagnoses of acral metastasis and osteomyelitis were considered by the orthopedists. This lesion in the right toe which also showed activity on 2014 bone scans was not excised because it was evaluated as metastasis. However, the patient was operated on 28.11.2019 with the decision of the hospital council since osteomyelitis and GIST tumor metastasis were deemed unlikely based on his laboratory and clinical findings and the mass lesion located in his right toe was excised. Pathological examination revealed extraskeletal myxoid carcinoma with a tumor size of 3x1.7x4 cm.

A postoperative whole body bone scan showed increased osteoblastic activity in the cranium, which was focal and most prominent in the left occipital region as well as focal, moderately increased activity in the superolateral segment of the left orbit and slightly increased, diffuse osteoblastic activity in the upper neighborhood of the right orbit, slightly increased osteoblastic activity in all costae, increased osteoblastic activity in the sacroiliac joint bilaterally, increased osteoblastic activity in the thoracic (T)11, L1 and L3 vertebrae, increased osteoblastic activity in the lateral portion of the right scapular spine, inferior segment of the left humeral head, superior segment of the left trochanter minor and right femoral neck, slight-to-moderate increase in osteoblastic activity in the maxillary region, and moderately increased osteoblastic activity in the lateral segment of the anterior tubercle of the right tibia. These findings were evaluated by the radiologist as bone metastases of the primary disease most probably and changes secondary to oncogenic osteomalacia were considered less likely (Figures-2a and 2b).

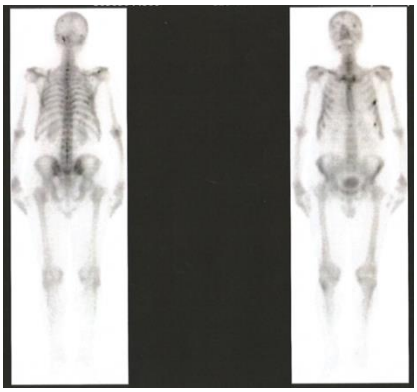

Figure 2a

Increased osteoblastic activity in the T11, L1 and L3 vertebrae; lateral portion of the right scapular bone; inferior segment of the left humeral head; superior segment of the left trochanter minor and right femoral neck; slight-to-moderate increase in osteoblastic activity in the maxillary region and moderately increased osteoblastic activity in the lateral segment of the anterior tubercle of the right tibia.

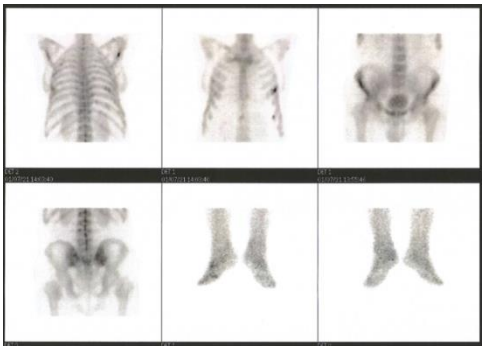

Figure 2b

Multiple foci of increased osteoblastic activity uptake: in the left frontoorbital, occipital and parietal bones in the skull; medial segment of the right clavicle; on both hemithorax ribs; left lateral part of the sacrum; in the tarsal bones of the right foot and the first metatarsophalangeal joints.

During postoperative follow-up, oral phosphate therapy was discontinued since the patient's serum phosphate level was increased up to 3.9 mg/dL two months after the surgery. Treatment with oral calcium and calcitriol was stopped due to elevation of calcium level up to 10.2 mg/dL eight months after the operation. Currently, the patient is followed routinely free of medication and his calcium and phosphate levels are normal.

3. Discussion

At the time of our patient's first presentation to our clinic with severe signs of osteomalacia, he had a history of two primary tumors including a differentiated thyroid tumor and a GIST. Assuming the risk of bone metastasis was very low due to the fact that thyroid CA was a stage 1 tumor with low risk, the appearances in the bone were considered to be consistent with bone metastasis of GIST. Initially, TIO was considered in this patient since he had clinical manifestations of new-onset hypophosphatemia and osteomalacia without prior history and clinical symptoms thereof. TIO associated with thyroid CA and GIST has not been previously reported in the literature. However, the patient was kept under observation due to the presence of these two tumors and failure to locate any other tumor keeping in mind the clinical suspicion of another possible tumor.

Elevated FGF-23 is detected in XLH, ADHR, ARHR, McCune-Albright Syndrome, Epidermal Nevus Syndrome and Type 1 Neurofibromatosis Syndrome, all associated with hypophosphatemia. All of these conditions are included in the differential diagnosis of TIO but further investigations for these disorders were not deemed necessary for two reasons: firstly, because of recent development of hypophosphatemia with no previous laboratory data indicating hypophosphatemia and secondly, other clinical components suggestive of McCune-Albright Syndrome, Epidermal Nevus Syndrome and Type 1 Neurofibromatosis Syndrome were absent. Ultimately, improvement of his signs and symptoms and laboratory tests following tumor excision led us to exclude these hereditary conditions in the differential diagnosis.

Fanconi syndrome is a condition that should be considered in the differential diagnosis of TIO because it can cause chronic phosphaturia. Isolated hypophosphatemia is uncommon and other electrolytes are also lost in Fanconi syndrome. This diagnosis was ruled out due to the absence of phosphaturia and other electrolyte disturbances in our patient.

FGF-23 testing is unavailable in our hospital. As a matter of fact, TIO was considered right from the start in our patient but no tumor focus could be identified which could then be removed. Since FGF-23 testing would not help tumor localization except for confirming the diagnosis of TIO and would provide no additional benefit for the follow-up of the patient, no attempt has been made to send for FGF-23 testing at an external center.

At the initial presentation, our patient had intolerable bone pain and was unable to walk without assistance. Shortly after starting conventional osteomalacia treatment (oral phosphate and calcitriol), his clinical symptoms improved dramatically but his phosphate levels did not improve completely and persisted around 2 mg/dL.

Our patient has been started on oral bisphosphonate (alendronate) treatment before presenting to our clinic. It was thought that this treatment was prescribed because of osteoporosis detected on DXA (dual-energy X-ray absorptiometry) scan. Bisphosphonates are the first-line agents for the treatment of male osteoporosis and among them, alendronate is the most commonly used bisphosphonate14. At our hospital, osteopenia was detected on DXA scan. Bisphosphonates are frequently used for bone pain associated with metastatic tumors. However, parenteral bisphosphonates such as pamidronate and zoledronate are mostly used for this indication15,16. Bisphosphonates can also be used to reduce bone pain from metastatic GIST but zoledronic acid is the recommended bisphosphonate for this condition16,17.

Bisphosphonate therapy has no place in the treatment osteomalacia. Upon the diagnosis of TIO, no progression of bone loss was detected during follow-up bone densitometry after discontinuation of alendronate therapy and initiation of conventional osteolamacia.

A new treatment option for TIO is burosumab, an anti-FGF-23 monoclonal antibody, which has been to be used as monotherapy in this indication. As of June 2020, burosumab has been approved by the US Food and Drug Administration (FDA) for use in patients diagnosed with TIO induced by curatively unresectable tumors18. Burosumab is not associated with potential side effects that occur with oral phosphate and calcitriol use which were previously first-line treatment10,19. Since burosumab is a newly approved agent with no sufficient experience in this indication and it is currently not readily accessible, we still need to follow traditional treatment methods for the management of TIO.

When a non-healing ulcer newly developed on our patient's foot, the mass in that area was excised and identified as extraskeletal myxoid chondrosarcoma. As in our patient, tumors causing TIO are usually of mesenchymal origin and almost all of them are benign, slowly growing tumors with an indolent course1,2.

In this patient, the cause of hypophosphatemia was identified as TIO that developed as a result of a third primary tumor. He also had two other primary tumors which were not demonstrated to be associated with TIO. After removal of the last detected tumor, his clinical symptoms improved which was reflected by an improvement in quality of life, as observed by reduced bone pain and walking without help. At the same time, he no longer needed to continue treatment with oral phosphate and calcitriol he has been receiving, further improving his quality of life. This highlights the importance of investigating a newly developed tumor focus even when there are two primary tumors at hand. Our patient has become able to live his remaining years more comfortably.

This case underscores the challenging and often difficult diagnosis of TIO. In our opinion, the take home message from this case is that in a patient with TIO, another primary tumor focus tumor should be carefully investigated in the presence of a primary tumor that is not the associated with TIO.

Note

This case was presented as a poster (Poster No: 27) by Hünkar AĞGÜL, MD at the Postgraduate Training Course (Endokurs-5) held in Antalya/Turkey between November 10 and 14, 2021.

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Written informed consent was obtained from the patient for the use of his medical data, laboratory tests and imaging details to publish his case anonymously. We thank him for his contribution

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