# Tumor-induced Osteomalacia: A Sherlock Holmes Approach to Diagnosis and Management

**G. V. Chanukya, Manoj Mengade[1], Jagadishwar Goud[2], I. Satish Rao[3], Anuj Jain[4]**

Department of Endocrinology, Nizam Institute of Medical Sciences, [4]Department of Nuclear Medicine, Vijaya Diagnostic Centre, Hyderabad, Departments of [1]Endocrinology, [2]Surgical Oncology and [3]Pathology, Krishna Institute of Medical Sciences, Secunderabad, Telangana, India

## Abstract

Tumor-induced osteomalacia (TIO) is a subtype of paraneoplastic syndrome associated with hypophosphatemia due to renal phosphate wasting in adults. The humoral factor responsible for clinical picture known as fibroblast growth factor 23 (FGF23) is most often secreted by benign yet elusive mesenchymal tumors, difficult to localize, access, and excise completely; rarely, they are multiple and malignant. Paradoxical inappropriately normal or low levels of 1,25-dihydroxyvitamin D in the setting of hypophosphatemia is due to suppressive effect of FGF23. The following case report describes a 31-year-old male with symptoms of multiple fractures and severe muscle weakness, hypophosphatemia with elevated tubular maximum reabsorption of phosphate/glomerular filtration rate with low active Vitamin D, prompted assay for C-terminal FGF23, which was elevated multifold. The tumor was localized with whole body 68-Gadolinium DOTANOC positron emission tomography-computed tomography fusion scan in the left nasal cavity with ipsilateral maxillary antrum. It was excised through transnasal approach and found to be mesenchymal tumor on histopathology. At 1 week of follow-up, serum phosphate became normalized without supplementation. The patient is in follow-up for further measurement of FGF23 level and signs of recurrence. Because the occurrence of such a condition is rare and most often misdiagnosed or mismanaged for years, it is important to recognize this condition in differential diagnosis as potential curative surgical option is a reality.

**Keywords:** Fibroblast growth factor 23, hypophosphatemia, tumor-induced osteomalacia

## Introduction

The spectrum of hypophosphatemic osteomalacia/rickets encompasses both hereditary and acquired bone diseases with impaired matrix mineralization. Although good number of syndromes have been described in etiopathogenesis, most common are X-linked hypophosphatemic rickets, autosomal-dominant hypophosphatemic rickets (ADHR), and tumor-induced osteomalacia (TIO). Although they have variable timing in presentation, the common denominator is reduction in the proximal renal tubular phosphate reabsorption, yet with inappropriately normal or low levels of 1,25-dihydroxyvitamin D [1,25(OH)2D] or calcitriol.[1]

Fibroblast growth factor (FGF23), a hormone secreted by osteocytes and osteoblasts, is main determinant of clinical picture either because of oversecretion or decreased catabolism. It specifically inhibits both Type IIa and IIc sodium-phosphate (NaPiT-IIa and IIc) cotransport system on the basolateral membrane and cytochrome p450 27B1 (CYP27B1) or 1-alpha-hydroxylase of proximal renal tubules.[1,2] In normal physiology, FGF23 participates in hormonal hierarchy of regulation of phosphate homeostasis with after effects on bone metabolism.[3]

TIO is a rare paraneoplastic syndrome that leads to acquired hypophosphatemic osteomalacia due to unregulated secretion of FGF23 by mesenchymal or mixed connective tissues tumors, which overwhelm catabolic pathways of specific endopeptidases.[1,3-5] Histologically, they can be of fibromas, chondrosarcomas, histiocytomas, neuroblastomas, osteosarcomas, and soft tissue tumors (angiosarcomas, prostate carcinoma, schwannoma, osteoblastoma, and mixed neuroendocrine tumors). Few syndromes have

**Address for correspondence:** Dr. G. V. Chanukya, Department of Endocrinology, Nizam Institute of Medical Sciences, Punjagutta, Hyderabad - 500 082, Telangana, India.
E-mail: chanukyagv@gmail.com

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been also associated with FGF23 overproduction, namely neurofibromatosis type 1 (NF-1), epidermal nevus syndrome, McCune–Albright syndrome, and fibrous dysplasia.[6-8] Few other proteins seem to be overexpressed by these tumors, contributing to the mineralization disturbance: matrix extracellular phosphoglycoprotein and secreted frizzled-related protein-4, but their mechanisms of action have not yet been elucidated.[5,9] Newly found another protein hypoxia-inducible factor-1α colocalizes and activates FGF23.[10]

Clinical features evolve insidiously over long period confusing the expert even leading to delayed diagnosis. Often serum phosphorus estimation is not included in routine laboratory testing, contributing to potential trap for unwary. Moreover, due to the small size and slow growth of these tumors, the condition is frequently not suspected or detected in clinical examinations. These missed opportunities contribute to severe morbidity and immobility of patient, yet potentially reversible by tumor removal, necessitating accurate localization.[2]

The authors, here, report a young man with long-standing severe muscle weakness, pain, and finally became wheelchair bound in whom diagnosis had been missed repeatedly elsewhere. The development in adult age and insignificant family history led us to suspect the existence of TIO, which was confirmed by biochemistry followed by imaging. Beyond registering this uncommon disease, the report aims discussing the diagnostic and therapeutic management of TIO.

## Case Report

A 31-year-old man referred from a surgeon had complaints of gradually progressive painless chest deformity, generalized body pains for 2 years, and difficulty in walking without support essentially because of weakness for 1 year, finally daily motion limited to wheelchair. Six months prior, he fractured both forearms after a fall from less than standing height. He was evaluated by two orthopedicians sequentially for ankylosing spondylitis, bilateral sacroiliitis, and psoriatic arthritis workup of both being normal. His basic biochemical workup including serum calcium, Vitamin D, and parathyroid hormone (PTH) was normal except with elevated alkaline phosphatase. Serum phosphate was never included in tests. There was no history of fever, rash, joint swelling, and weight loss. Past and family history was not significant with no similar complaints in his entire three generations including predecessors or current.

On examination, his vitals were normal with blood pressure 124/84 mm of Hg, weight 63 kg, supine length 156 cm. Higher cortical functions and cranial nerve examination were normal. Assessment of muscle power in all limbs showed moderate loss but with preserved tendon reflexes. Sensory system was intact.Other systemic examination related to respiratory,cardiovascular and abdominal areas was unremarkable. Biochemical parameters were performed over three days; mean serum calcium 9.8 mg/dl (normal, 8.0–10.2), mean serum phosphate 1.6 mg/dl (normal, 2.5–4.5), mean serum alkaline phosphatase 255 U/L (normal, 30–120). Serum 25-hydroxyvitamin D 34.83 ng/ml with intact PTH 47.1 pg/ml. Mean of 3 days 24 h urine estimation showed tubular maximum reabsorption of phosphate/glomerular filtration rate of 1.5 which was low (age-matched normal range - 2.5–4.5). FGF23 (C-terminal) was 1310.7 RU/ml (normal, 0–150) by ELISA technique. Serum 1,25(OH)2D was <12.0 pmol/L (normal, 47.76–190.32). Other investigations including renal parameters with electrolytes and acid-base gas analysis were normal.

Radiographs of dorsal spine showed osteopenia with coarse trabecular pattern with fracture of 9$^{th}$, 10$^{th}$, and 11$^{th}$ right thoracic rib and 9$^{th}$ and 10$^{th}$ left thoracic rib and wedge compression of D8, D9 vertebra with multiple fractures. MRI of whole spine however did not show any cord compression. Radiographs of upperlimbs were also suggestive of osteopenia. Whole body bone scan was showing multiple areas of abnormal tracer uptake in axial and appendicular skeleton most likely insufficiency/pseudofracture possibly osteomalacia.

Subsequently to detect the source of FGF23, 68-Gadolinium DOTANOC positron emission tomography-computed tomography (PET-CT) scan of whole body [Figure 1] was done which revealed a large well-defined heterogeneously enhancing mass lesion 37 × 24 × 43 (anteroposterior × transverse × craniocaudal) mm in left nasal cavity with erosion of left middle turbinate and medial wall of left maxillary antrum showing increased tracer uptake. To confirm the radiologically suggestive source of FGF23, selective venous sampling (near tumor and periphery) was planned but was not agreed by interventional radiologist as he felt it is unnecessary to do it in view of well-documented mass. The patient subsequently underwent surgery through transnasal approach and tumor was found infiltrating skull base which required neurosurgical assistance. Serum phosphate reached normal range 1 week after surgery, and he was discharged without any supplementation. Histopathology was turned out to be mesenchymal tumor with no atypical mitoses or infiltrative margins [Figures 2 and 3]. At 1 month, serum FGF23 was 109 RU/ml (normal, 0–150) and serum 1,25(OH) 2D was normalized 180 pmol/L (normal, 47.76–190.32). Third month 68-Gadolinium DOTANOC PET-CT scan did not show any anatomical or functional mass at the site implicating curative surgery [Figure 4].

## Discussion

This case report presented a young man with crippling clinical features due to a mass hidden in the nasal cavity and around essentially made of primitive mesenchymal cells and with resolution of metabolic disturbance shortly after tumor removal. The person is still restricted to wheelchair and improvement is supposed to happen gradually over months.

TIO is one of many paraneoplastic syndromes associated with neoplastic cells, presently with oversecretion of FGF23, posing challenges in suspecting and diagnosing the condition including subsequent management.[1,2] The majority of these tumors are hemangiopericytomas but can also include

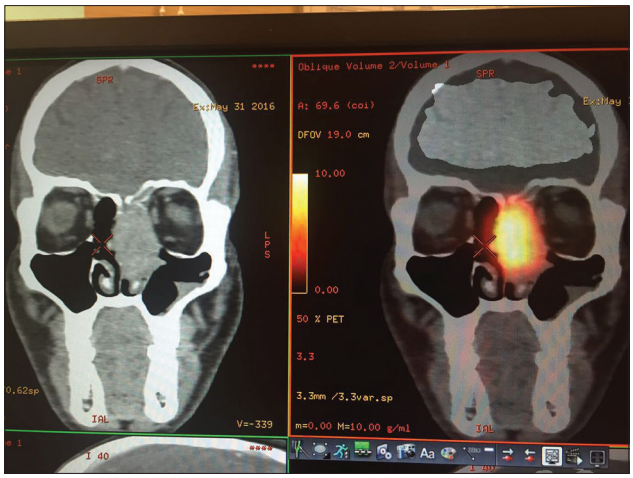


**Figure 1:** Whole body 68-Gadolinium DOTANOC positron emission tomography-computed tomography fusion scan showing mass in the left nasal cavity with ipsilateral maxillary antrum

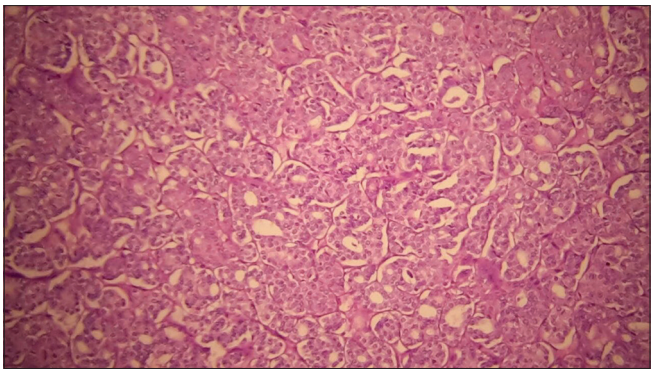

**Figure 2:** Bland spindle cells arranged with prominent intervening thin-walled capillary blood vessels in a "hemangiopericytoma" like pattern (H and E, ×400)

**Figure 3:** Intraoperative macroscopic excised tissue

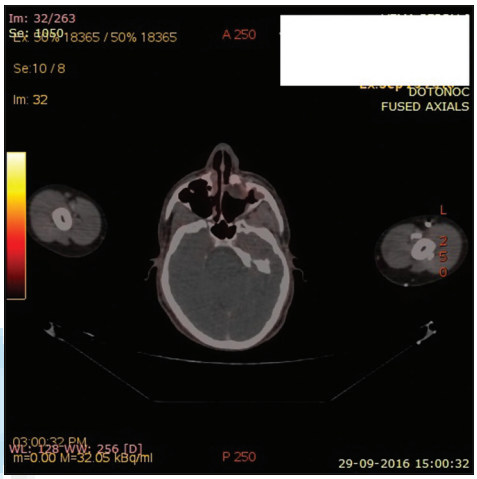


**Figure 4:** Third month postoperative 68-Gadolinium DOTANOC positron emission tomography-computed tomography fusion scan showing no active uptake and residual mass

sarcomas, ossifying fibromas, granulomas, giant cell tumors, and osteoblastomas. Based on the review until 2005, 68 cases have been reported in literature with addition of 102 reports in next decade, showing increased awareness of the condition. Its clinical and radiological features resemble other kinds of osteomalacia. Bone pains, fractures, muscle weakness, and fatigue however tend to predominate, necessitating extensive Sherlock Holmes approach to locate them.[2,11]

The main differential diagnosis is primary hyperparathyroidism in setting of hypophosphatemia,but with elevated serum calcium and PTH levels. On the other hand, phosphaturia in primary hyperparathyroidism can be explained by PTH-induced internalization of sodium-phosphate cotransporters and their subsequent lysosomal degradation.[12,13] Sometimes they coexist.[14]

Laboratory examinations, in the index case, are compatible with the usual findings described above. Evaluations before consultation elsewhere revealed a normal calcium and PTH levels, a low serum phosphate, indicating a renal phosphorus wasting. Unfortunately, neither 1,25(OH)2D levels nor tubular reabsorption of phosphate were not assessed, which could have delayed the syndrome diagnosis.

The occult nature of TIO delays its recognition, and the average time from onset of symptoms to a correct diagnosis often exceeds 3 years. Once the syndrome is recognized, inability to locate the underlying tumor further delays definitive treatment by an average of 5 years.[9] Most of TIO cases are due to currently recognized phosphaturic mesenchymal tumor (mixed connective tissue variant), an extremely rare tumor that is found mainly in soft tissues and bone in lower limbs as small and clinically unapparent lesions. Nearly 70%–80% of tumors in TIO are primitive mesenchymal tumors, mostly hemangiopericytomas.[15,16] Many of these tumors appear to have been largely unknown or overlooked by many clinicians and pathologists. Relatively, newly popular entity and their polymorphous histological appearance may account, in part, for their misdiagnoses. The defined histological features of tumor include low cellularity, myxoid changes, bland spindled cells, distinctive "grungy" calcified matrix, fat, hemangiopericytoma-like vessels, microcystis, hemorrhage,

osteoclasts, and an incomplete rim of membranous ossification. They are generally benign, but malignant variants have been described.[17] Expression of FGF23 by real-time polymerase chain reaction and by immunohistochemistry indicates the involvement of these tumors on TIO pathogenesis or resolution of clinical features by complete excision of the tumor.[18,19] Recently, it has been found that hypoxia-inducible factor-1α activates ectopic production of FGF23 in TIO. Both proteins are found to be colocalized in same cell with hypoxia-inducible factor-1α acting as direct transcriptional promoter of FGF23.[10]

Treatment of TIO involves accurate localization, confirming by differential venous sampling for FGF23 when such facility is available and complete surgical removal of tumor, which reverses its clinical and biochemical changes. Thus, tumor localization is essential and once suspected requires detailed radiologic examination with special attention to lower limbs and craniofacial areas. In past, imaging essentially was with CT, MRI, or even fluorodeoxyglucose (FDG) PET-CT.[2] However, except for FDG PET-CT in few series, they were either insensitive or nonspecific in many settings. *In vitro* studies showed that these tumors express somatostatin receptors and successful localization of causative tumors with the use of $^{111}$indio-pentetreotide or octreotide scintigraphy which has been demonstrated to be superior.[20] Recent studies have described that reliable full-length FGF23 assays have the potential to be clinically useful in the diagnosis and management of TIO and may help to establish whether tumors have been completely removed by surgery.[21] However, availability of this assay has not been widespread in the third world because of price constraints in the setting of rare entity, necessitating usage of low-cost C-terminal FGF23 assay.

In the present case, serum levels of phosphate and calcitriol as well as the tubular phosphate reabsorption become normal in 1 week after surgical removal of the tumor. However, markers of bone turnover such as the osteocalcin and alkaline phosphatase tend to take longer to normalize till fractures heal. Serum FGF23 levels fall was also detected. According to a recent study, the plasma half-life of serum full-length FGF23 is in the range of 46–58 min and biochemical cure can be predicted with normalization of FGF23 at 6 h in patients with surgically removed TIO.[2,22]

Preoperative preparation typically consists of administering elementary phosphorus at dose of 30–60 mg/kg/day, divided in 4–6 fractions and calcitriol (0.25–2 mcg/day). With adequate treatment, serum levels of alkaline phosphatase improve, reaching normal or slightly elevated levels. Doses of phosphate and calcitriol need to be followed as they increase the risk of secondary and tertiary hyperparathyroidism and nephrolithiasis, respectively.[23]

Differential diagnosis of this patient was ADHR that can exhibit a variable and delayed age at the onset. Patients with adult-onset ADHR may present severe bone pain, pseudofractures, and weakness.[2,24] The absence of family history, as well the severity and rapid progression of symptoms, made this unlikely. Moreover, identification of a facial mass, a common location of TIO, strengthened our suspicion of latter condition. The following tumor histopathology examination and the resolution of hypophosphatemia a week after surgery have further affirmed the diagnosis.

The case presented here, in contrast to the earlier cases related in literature, revealed an easily located tumor, showing us that if TIO is suspected at outset, with availability of advanced imaging techniques and differential venous sampling, diagnosis can be established quite early potentially avoiding crippling morbidity. Although TIO represents a rare disease, we need not stress on reinforcing the awareness of the condition in medical practitioners, as severe disability and even death can be avoided with the surgical removal of the causative tumor.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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