

Case Report

Tumour induced osteomalacia: a diagnostic challenge and its implications in orthopaedic surgery

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ABSTRACT

Tumor-induced osteomalacia (TIO) is a paraneoplastic phenomenon which encompasses a wide array of clinical features ranging from musculoskeletal pain to pathological fractures. An excess of fibroblast growth factor 23 (FGF23) is produced which is a parahormone with its target receptors in proximal convoluted tubules of glomeruli. This results in decreased blood phosphate levels and decreased hydroxylation of 25-OH vitamin-D, ultimately leading to osteomalacia. Compliance with medical treatment is unsatisfactory and tedious owing to repeated dosing schedules and overwhelming side effects. Surgical excision of the lesion is the only suitable treatment.

Keywords: TIO, FGF-23, Osteomalacia

INTRODUCTION

Tumor-induced osteomalacia (TIO) is an extremely uncommon paraneoplastic phenomenon which encompasses a wide array of clinical features ranging from musculoskeletal pain and pathological fractures.

Primary pathophysiology of clinical hypophosphatemia is augmented renal phosphate excretion secondary to elevated serum phosphatonin levels. Principal phosphatonin that has been well studied is a polypeptide, fibroblast growth factor-23 (FGF-23).¹

FGF-23 is involved in the pathophysiology of these tumors.^{2,3} FGF-23 not only causes increased renal wastage of phosphate, it inhibits activity of renal 1 α -hydroxylase also known as cytochrome p450 27B1, the enzyme that converts 25-hydroxy vitamin-D (calcifediol) to its biologically active form, 1,25-dihydroxy vitamin-D (calcitriol) at proximal convoluted tubules of glomeruli.⁴

Epidemiology

The exact prevalence of the disease is not known. Reports from the Indian subcontinent are very few.⁵ Many published case reports showing that the average age is 40 to 45 years indicating it is more common in adults and rare in young children.⁶ No sex differences or ethnic differences have been observed.

Pathogenesis

Under physiological conditions FGF-23 is secreted by bone and degraded by proteolytic enzymes. FGF-23 was first identified as the phosphaturic substance when mutations in FGF-23 were linked to autosomal dominant hypophosphatemic rickets.⁷

GF-23 is a parahormone with its target receptor, the FGF receptor present in proximal convoluted tubules of glomeruli. When secreted in excess, FGF-23 inhibits renal

phosphate reabsorption.⁸ FGF-23 acts as regulatory hormone for 1,25-vitamin D and responsible for decreased serum vitamin-D level via inhibition of renal 1-alpha-hydroxylase. This results in reduced calcitriol levels, which is mandatory for absorption of calcium and phosphate.^{9,10} FGF-23 levels secreted by these paraneoplastic tumors are alarmingly higher than normal levels causing resultant imbalanced FGF-23 degradation pathway.¹¹

The fibroblast growth factor receptor-1 (FGFR-1) binds to the ligand FGF-23, its co-receptor Klotho activates the mitogen-activated protein kinase (MAPK) pathway which ultimately regulates cell proliferation, survival, and FGF-23 secretion.¹²

Histopathology

TIO lesions are small in size and mesenchymal in origin.¹³ Most commonly these tumors are hemangiopericytomas, but phenotypically they can also be hemangiomas, sarcomas, granulomas or giant cell tumors.

They are mesenchymal tumors containing neoplastic cells which are typically incorporated within a myxoid or myxochondroid matrix with typical grungy calcification along with spindle cell component. Mitotic activity is usually absent or very low with low nuclear grade. Primary feature of these tumors is hyalinised stroma with intrinsic microvasculature and cellular area having spindle shaped cells. These cells stain positive for a variety of immunohistochemical (IHC) markers like vimentin and CD68.¹⁴ TIO tumors are generally benign although malignant presentation and metastases have been reported.^{15,16} Regardless of tumor phenotype, the sine-qua-none of diagnosis is the association of the tumor with the clinical myriad of TIO, which includes an elevation in plasma FGF-23 levels and its reduction after tumor has been surgically excised.

Clinical evaluation and diagnosis confirmation

A large number of patients with TIO present with many years of symptoms before they are diagnosed. Ranging from non-specific complaints to often progressive ones, common symptoms are muscle weakness, bone pain, reduced height, and multiple fractures, primarily in the axial skeleton, and femoral neck. Hypophosphatemia occurring because of defective renal phosphate reabsorption is the biochemical marker of the disease. In addition to decreased serum phosphate levels, parathormone (PTH) can also be increased because of secondary hyperparathyroidism, which is a normal response to low calcitriol caused by elevated FGF-23.^{17,18}

Localizing the tumours is a major diagnostic challenge and can involve whole body magnetic resonance imaging (MRI) because of ubiquitous distribution of these tumors, computed tomography (CT), scintigraphy using radiolabelled somatostatin analogue (such as ^{99m}Tc-

Tektrotyd) and positron emission tomography, with computed tomography: fluorodeoxyglucose (18FFDG) PET/CT and gallium (68Ga) Dotatate PET/CT and selective venous sampling for FGF23.¹⁹

Localizing studies

Anatomical imaging

After detection of suspicious tumors with anatomic and functional imaging studies including X-rays, CT, and/or magnetic resonance imaging (MRI) scans are done. As there are areas in brain, liver or spleen which can be missed out on both FDG-PET and octreo scan, anatomical imaging of these areas may be indicated if a tumor is not identified.

Venous sampling

A dual strategy utilising functional and anatomical imaging localizes the FGF-23 secreting tumor successfully. But, in certain circumstances where more certainty and testing are indicated, of particular utility is selective venous sampling with measurement of FGF-23.²⁰

Treatment

Treatment for TIO is resection of the tumor with wide enough margins to ensure an in-toto tumor removal. A complete resection of the tumor is often curative.

Post-removal, the recovery and improvement of the patients is fast, FGF-23 levels fall down, and serum phosphate returns to normal by end of 1st week.²¹ Most of the patients have an excellent clinical improvement following tumor excision. Bone healing although starts immediately, it may take up to an year for a more significant clinical improvement to be seen. In case of incompletely excised tumours, adjuvant radiotherapy is given to avoid relapse or metastasis. Late recurrence due to metastatic disease is rare but possible.²²

There is no any drug demonstrated efficacy in treating metastatic TIO. Radio frequency ablation has been reported as a possible treatment option.²³

Prognosis

The prognosis relies upon tumor detection and its timely removal. The tumours when detected are typically benign in most of the cases. The symptoms are allayed and the healing of the bones commences after total excision of the tumour. However, the follow-up should be continued because the delayed metastasis can occur.

CASE REPORT

45 years old man, known case of ankylosing spondylitis came to our centre for severe right hip pain and difficulty in walking, in the year 2004. Physical examination

revealed no significant abnormality except restriction of movements in all planes in right hip joint. Laboratory investigations showed elevated C-reactive protein and erythrocyte sedimentation rate. The radiology of the hip revealed advanced stage AVN of right femoral head. Following were the sequence of his multiple surgeries.



Figure 1: Patient underwent right ASR (articular surface replacement) in 2004.



Figure 2: In the year 2005, metal on metal proximal hip replacement was done on left side in an outside center.

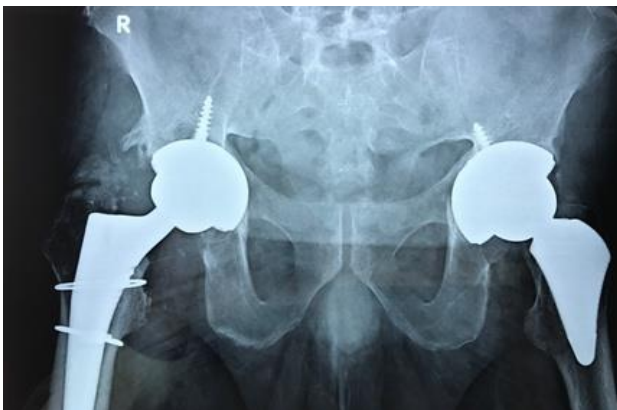


Figure 3: In the year 2017, THR (metal on poly) was done for right hip in outside center.



Figure 4: Patient had a periprosthetic fracture on the right side for which he underwent femur plating in the same year, 2017 in outside center.

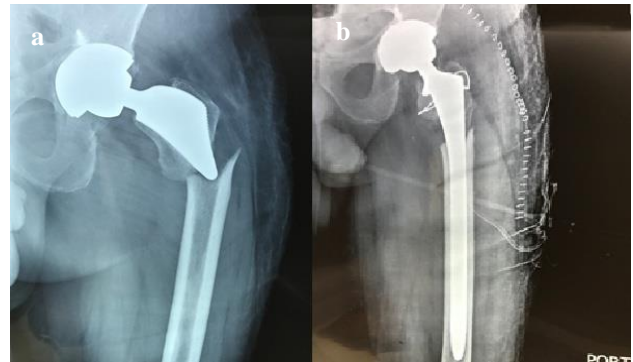


Figure 5 (a and b): In year 2017 patient underwent left hip revision surgery in our center, after the failure of previously done proximal hip replacement.

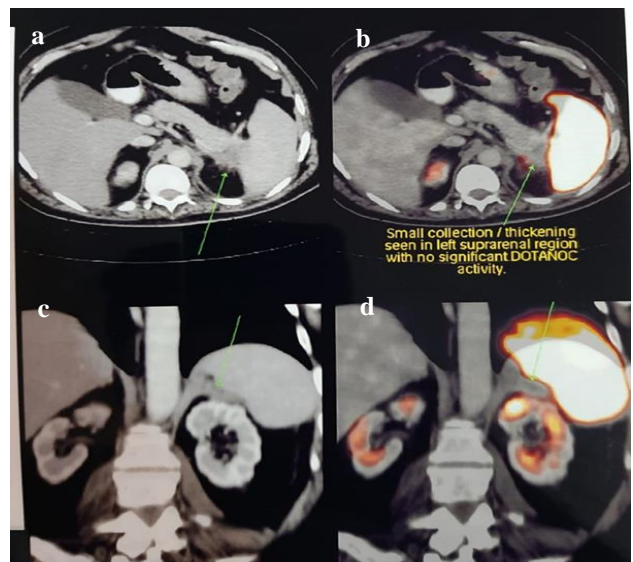


Figure 6 (a-d): In the second half of year 2017 patient started having left hypochondriac region pain for which whole body FDG-PET scan was done with increased uptake in left suprarenal region.

In this patient, FDG PET/CT revealed multiple areas of increased uptake. Octreotide based DOTANOC scan only demonstrated a single lesion. TIO partially resolved after laparoscopic excision of the lesion.

Table 1: Laboratory values at different time points before and after PMT resection.

Variables	Pre PMT resection	Post PMT resection (2019)
Serum phosphorus (2.5-4.8 mg/dl)	2.12	4.47
Serum calcium (8.5-0.5 mg/dl)	10.67	9.2
Alkaline phosphatase (37-116 U/l)	137.9	182
25-OH-vitamin D (10-100 ng/ml)	34.1	36.9
PTH (15-65 pg/ml)	102.8	113.6
FGF23 (C terminal) (0-150 RU/ml)	13940	953.3

PMT: phosphate uric mesenchymal tumor.

At present, after almost 15 years of continuous visits to multiple rheumatologists, endocrinologists, orthopaedic surgeons, GI surgeons, physiotherapists and physicians patient is still suffering from a painful right hip, periprosthetic non-union, a functionally disabling limb length discrepancy, significant loss of DALY's and a grave mental as well as physical trauma owing to this rare disease.

DISCUSSION

TIO was first recognized by Andrea Prader in 1959, when he described an adolescent girl who developed severe rickets because of a rachitogenic substance within a year.²⁴

The diagnosis of TIO is a diagnostic challenge even under the best of conditions. TIO must be included in the differential diagnosis in patients with progressive weakness, musculoskeletal pain, multiple and/or recurrent fractures. More than often, diagnosis is made years after the initial presentation due to non-specific nature of the presenting symptoms, lack of inclusion of serum phosphorus levels in routine blood chemistry testing and difficulty in identifying the culprit lesion.

Diagnostic evaluation of whole-body images, including single-photon emission tomography allows identification and better tumor contrast which can be seen within skeletal or soft tissue structures of any region of the human body.

After provisionally ascribing the diagnosis as TIO, a complete and systematic physical examination should be

performed, because the tumours causing TIO can also be found in the subcutaneous softtissues.²⁵

Due to non-specific symptoms and uncommon nature of the disorder, the period from clinical detection of osteomalacia to actually diagnosing the tumour, averages to a mean duration of 5 years.²⁶

Clinical presentation includes bone fractures, bone and muscular pains, and sometimes loss of height and even weight. Weight loss is not common but can be seen because of general debilitated state of the patient because of poor nutrient intake and loss of muscle mass.²⁷

FGF23 may be of help to understand the underlying mechanisms of TIO and a measurement to follow up the disease course. Treatment involves complete surgical removal of the tumor, open or laparoscopic depending upon the area involved. Resection of the tumor is typically followed by a sharp fall in FGF23 levels and resolution of symptoms. Anti-FGF23 antibody (KRN23) which is a recombinant human IgG1 monoclonal antibody directed at FGF23, is under investigation and in future can be used as a novel therapy for such hypophosphatemic diseases caused by FGF 23 excess.²⁸

CONCLUSION

Although very few case reports regarding this rare tumor entity were available at the time of the case's presentation, lack of awareness amongst health care providers might have been the reason for delayed diagnosis. Nevertheless, various aspects of TIO, right from pathogenesis to treatment, are yet to be understood. In the hindsight of our case report we can state that a more holistic approach, a high index of suspicion and a multifaceted line of management with involvement of a rheumatologist, endocrinologist, and GI surgeon can immensely benefit the patients of this unfamiliar disorder.

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