A Patient of Tumour Induced Osteomalacia Undiagnosed for 11 years

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Abstract

We report a 45 years old woman, bedridden due to severe bone pain, back pain, multiple spontaneous fractures over 10 years. She had low serum Phosphates. We detected a swelling in her right groin and suspected tumour induced osteomalacia. Resection of the tumour led to reversal of metabolic bone disease. Patient became ambulatory within 6 weeks of tumour resection.

Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome in which patients present with bone pain, fractures, and muscle weakness.[1] TIO also known as oncogenic osteomalacia results from abnormal phosphate metabolism caused by small endocrine tumours that secrete the phosphaturic hormone, fibroblast growth factor 23 (FGF23).[2] FGF23 later inhibits resorption of phosphates from proximal renal tubules, leading to renal phosphate loss and hypophosphatemia.[3] resulting in defective bone mineralization. These are generally mesenchymal tumors of extremities, sinuses, mandible, maxilla and thorax.[4] They are benign, slow growing, and predominantly of phosphaturic mesenchymal tumor of mixed connective tissue (PMTMCT).[2] The biochemical markers of oncogenic osteomalacia include hypophosphatemia, hyperphosphaturia, decreased tubular phosphate reabsorption, increased serum alkaline phosphatase in the presence of normal calcium, 25(OH) vitamin D, and normal or slightly elevated serum PTH.[5] Due to lack of knowledge of the existence of the disease, the length of time from onset of symptoms until diagnosis is often long.[1] As a result, patients frequently present with multiple fractures, height loss, and generalized debilitated status. But when the tumour is resected, there is dramatic resolution. FGF23 has a half life of approximately 45 min and disappears rapidly from the circulation[6]. A TIO-like syndrome can also be seen in association with other diseases such as prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone.[7]

Fig. 1: Swelling in right inguinal region

Case

A 45 year old female presented with history of progressive back pain, generalized body pain for 11 years and inability to walk due to which she was bedridden for 3 years. Her back pain started in 2005. She presented to us in March 2016, but had destroyed all medical records out of frustration. She underwent spinal instrumentation in 2007 for spontaneous vertebral fracture without any relief. In 2010 the implants were removed. She developed progressive painful difficulty in walking and three years prior to her present visit she was bedridden. She had to be physically lifted for bathing, toilet etc. On examination, patient was in severe distress, had scoliosis, surgical scar in the lumbar region, deformed proximal forearms, all bones were tender, she could actively raise her leg to only 5 degree and did not allow passive SLR or hip rotations due to pain. Power at shoulder was 4/5 and at hips 3/5, Deep tendon reflexes were 2+, plantars flexors and sensations preserved. On systemic examination there was 5x5 cm swelling in right groin (Figure 1) extending up to labia majora, it was soft to firm, nontender, without impulse on coughing. On inquiry she said it started as a pea size swelling in right labia majora in 2004 and progressed to its present size. Fine needle aspiration cytology of the swelling was performed and she was told it was benign, report was missing. Investigations (Table 1) revealed low serum phosphates, normal Calcium, 25-OH-D and intact PTH, raised Alkaline phosphatase. The blood pH was normal (no acidosis) and Serum Creatinine 0.5mg/dl. Twenty four hour urinary P was 102.5mg (33.107 mmol/L) and Creatinine was 297 mg (26.254 mmol/L). Calculated Fractional Tubular resorption of phosphate (TRP) 0.89 and The ratio of the renal tubular maximum resorption rate of phosphate to the glomerular filtration rate (TmP/GFR) 0.49 mmol/L

Her skeletal survey revealed severe osteopenia with multiple stress fractures (Figure 2 A, B, C) viz. bilateral femur neck, Bilateral

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ulna, L5 compression with fish mouth vertebrae and multiple ribs. Patient was started on Oral phosphate supplement 1.5gm/d, Calcium Carbonate 500mg/d and Inj Vit D3. Surgical resection of the tumour was planned.

Multislice CT scan of abdomen and pelvis revealed a large lobulated hypodense lesion in the labia majora on the right side showing predominantly marked peripheral enhancement on arterial/portovenous phase with no evidence of calcification/enhancing mural nodule- possibility of cystic neoplastic. Liver normal. No signigicant lymphadenopathy.

Table 1: Baseline investigations

	Patient's values
Hemoglobin	13.6 gm/dl
WBC	7000
ESR	50
S creatinine	0.5 mg/dl
S Ca	8.9 mg/dl
S P	1.6 mg/dl
Alkaline phosphatase	475
25-OH-D	30.6
PTH intact	46
Blood pH	7.43
Na	137
K	3.4
Cl	103
HCO3	22.5
24 hour urinary P	102.5 mg/24 hr
24 hour urinary creatinine	297 mg/ 24 hr
Creatinine phosphokinase	50 U/L
Thyroid function test	Normal
RA test & anti-CCP	Negative
SGPT	47
TRP	0.89
TmP/GFR	0.49 mmol/L

The tumour was resected with in 2 weeks, measured 5x4x3cm. On microsopy, it was composed of spindle and short oval cells in oedematous stroma in which foci of osteoclastic giant cells are scattered. The cellular portions of the tumour line pseudocystic tumour. The less cellular areas show large vascular spaces, reported as 'Phosphoturic mesenchymal tumour' (Figure 3). Six weeks post operatively she was without pain, could walk with support, actively raise legs to 90 degree. Serum Calcuim 9 mg/dl, P 4mg/dl and at 12 weeks postoperatively, she could walk without support, Serum Ca 8.6mg/dl, P 4.3 mg/dl

Discussion

TIO should be suspected in patients who present with consistent symptoms (bone pains, stress fractures and muscle weakness) and with hypophosphatemia, and approach should be as follows:

1. If hypophosphatemia is present, the presence of renal phosphate wasting should be confirmed by calculating percent tubular reabsorption of phosphate (%TRP) and tubular maximum for phosphate corrected for glomerular filtration rate (TmP/GFR).

2. Hypophosphatemia may be due to genetic or acquired cause. In a child genetic/ familial conditions like X-linked hypophospatemic rickets (XHL) or autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypophosphatemic rickets (ARHR) and hereditary hypophosphatemic rickets with hypercalciuria (HHRH), Fanconi syndrome are more likely,[8] though there are reports of TIO in paediatric age group too[9,10]. Where as in adults with symptomatic hypophosphtemia, acquired causes like TIO are more likely and a thorough search for the tumour, clinical and by PET-CT or Octreoscan should be performed. Other causes of acquired hypophaspatemic osteomalacia may be renal tubulopathy due to drugs, heavy metals, paraproteinaemias.[11] Serum FGF23 is high in TIO and low in renal tubulopathies. In patients presenting in childhood or adolescence short stature, history of bow legs in relatives, urinary loss of Ca, amino acids should be looked for, followed by genetic studies. The diagnostic approach for suspected TIO should be as depicted in Figure 4.

Calculation of Renal phosphate wasting[12]: (%TRP and TmP/GFR)

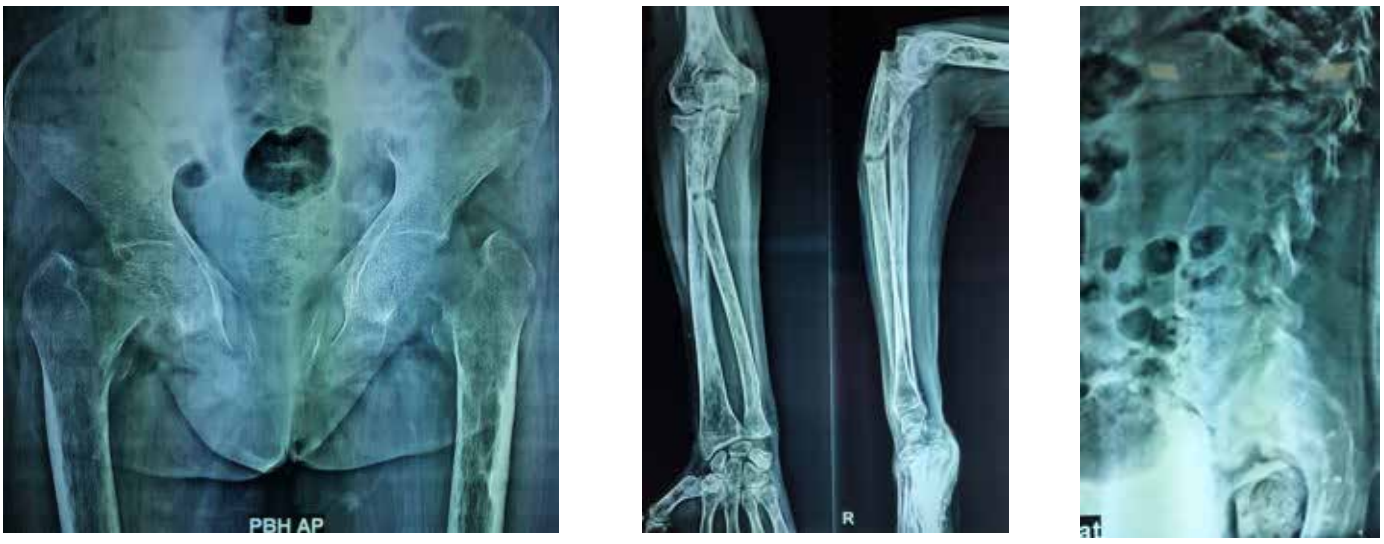
%TRP = 100 x { 1 – [(*U*p/ *P*p) x (*P*cr / *U*cr)] }

[Concentrations of urine and plasma phosphate (*U*p and *P*p), Concentrations of urine and plasma creatinine (*U*cr and *P*cr)]

When phosphates are normal tubular resorption is 85-95% [7]

TmP/GFR can be determined using a nomogram or calculated as follows : The formula used to calculate TmP/GFR is dependent on the value of TRP (< /> 0.86)

If TRP is ≤ 0.86 (86%); then



(A) (B) (C)

Fig. 2: (A) X-ray Hip, AP view, Bilateral femur neck stress fracture, (B) X-ray right forearm stress fracture ulna, (C) X-ray Lumbosacral spine : fish mouth vertebrae

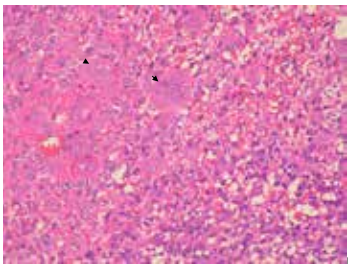


Fig. 3: Microphotograph of the tumour: spindle and short oval cells, foci of osteoclastic giant cells (black arrow)

Table 2: Normal ranges for tubular maximum for phosphate corrected for GFR

Age	Male mg/dl (mmol/l)	Female mg/dl (mmol/l)
Newborn	5.7-8.1 (1.27-2.59)	5.7-81. (1.27-2.59)
1 month-2 years	3.6-5.4 (1.15-1.73)	3.6-5.4 (1.15-1.73)
2-12 years	3.8-5.0 (1.22-1.60)	3.8-5.0 (1.22-1.60)
12-16 years	3.4-4.6 (1.09-1.47)	3.4-4.6 (1.09-1.47)
16-25 years	3.33-5.9 (1.07-1.89)	3.18-6.41 (1.02-2.05)
25-45 years	3.09-4.18 (0.99-1.34)	2.97-4.45 (0.95-1.42)
45-65 years	2.78-4.18 (0.89-1.34)	2.72-4.39 (0.87-1.40)
65-75 years	2.47-4.18 (0.79-1.34)	2.47-4.18 (0.79-1.34)

TmP/GFR = TRP x plasma phosphate (*P*p)

If TRP is >0.86 (86%); then

TmP/GFR = 0.3 x TRP/(1-0.8xTRP) x (*P*p)

One should use correct units for serum and urinary phosphat and creatinine. If there is no urinary phosphate wasting in a patient with hypophosphatemia, the values for TRP and TmP/GFR will be high. In TIO and other causes of renal phosphate wasting, these values are abnormally low.[7] Table 2 depicts normal range of TmP/GFR for various age and gender. In our patient TmP/GFR was 0.49 mmol/lit, ie very low. After confirming renal phosphate wasting as the etiology for hypophosphatemia, additional lab tests that can be helpful in making the diagnosis of TIO are 1,25- vitamin D level(low or inappropriately normal), calcium and PTH (usually normal). One can estimate serum FGF23 level in adult patients, (not performed in our patient, due to non-availability), for confirming FGF23 dependent phosphate wasting. Genetic testing (*PHEX, FGF23, DMP-1, ENPP1)* is important in paediatric and adolescent patients. In adults, after narrowing the diagnosis to TIO, ask the patient if she/he has noticed any new 'lumps', a careful physical examination including oral cavity should be performed, as the tumors that cause TIO can sometimes be found in the subcutaneous tissue or jaw.

Localizing studies : (Functional imaging followed by anatomical imaging)[7]

As tumors can arise in bone or soft tissue, occur from head to toe, and are typically very small in size, locating these tumors is often quite challenging. A step-wise approach is advocated. Functional imaging with FDG-PET/CT is very sensitive to localize, tumours of TIO, however, it is non-specific and may detect metabolic activity in a healing fracture. Another important functional imaging modality is 111Indiumoctreotide scintigraphy, ideally combined with single photon emission CT and CT. In either case emphasis should be placed on making sure these imaging tests cover the entire body, from head to toe, including the hands and feet.

Once suspicious lesions have been identified with functional imaging, one should proceed to anatomical imaging to confirm the location of the tumor, with X-rays, CT, and/or MRI. Usually functional and anatomical scan is successful in locating tumour in TIO, but in case where there is doubt, selective venous sampling or aspiration, from suspicious lesion with estimation of FGF23 can be used for confirmation, prior to surgical excision. Despite functional imaging, total body MRI, tumor localization may not be successful. If this is the case, imaging studies should be repeated, every 1-2 years, in hopes that a tumor may be more evident with time.

Treatment

Surgical excision with a wide margin is the treatment of choice after localizing the tumour.[1] Serum P normalizes within days, confirming the diagnosis of TIO. Clinical improvement depends on initial condition of the patient, but generally occurs over weeks to months, as in our patient. Recurrence of tumour is seen in <5% patients.

Medical treatment[7]

When the tumor cannot be localized or is not surgically resectable, medical therapy with phosphate supplementation(15-60mg/kg, ie 1-3gm /d, in 4-6 divided doses) and calcitriol (15-60 ng/kg, ie 1.5microgm/d, starting dose) is indicated. Goal of therapy is to achieve at least 'low-end of normal for age-appropriate normal range of phosphorus'. Phosphate supplements cause GI upset, to minimize them, give small frequent doses along with meals. A baseline ultrasound examination of kidneys and three monthly monitoring of Serum P, Ca, urinary Ca/ Creatinine, Urine for occult blood (if U Ca/Cr ration >0.2), and dose adjustment of Calcitriol to avoid hypercalciuria and nephrocalcinosis is important. If Serum P is low increase Phosphate supplement, if serum Ca is low give Ca supplement, if PTH is high increase Calcitriol. The dose at which Serum P and PTH are in target and Urine Ca/ creatinine is < 0.2 should be maintained. Other drugs used in medical treatment of TIO are Cinacalcet[2] (an agonist of Calcium sensing receptor) and Octerotide (somatostatin analog).

Robert McCance (1947) is often credited[13] with the first reported case of TIO. The first person to clearly recognize that the disease was the result of a 'rachitogenic' substance was Andrea Prader[14]. In 1959, he described an 11 1⁄2-year-old girl who developed severe rickets over the course of a year. Her investigations revealed decreased tubular phosphate reabsorption but otherwise normal kidney function. A tumor, classified as a giant cell granuloma, was identified in a rib and resected with resultant healing of her rickets. Prader highlighted the association between the resection of the tumor and the cure of the rickets and posited that the granuloma was secreting a rachitogenic substance. The first identification of FGF23 as the putative phosphatonin was when mutations in FGF23 were identified by Econs[15] in the autosomal-dominant hypophosphatemic rickets (ADHR) consortium as the cause of ADHR. Once identified as the cause of ADHR, elevations in serum FGF23 were soon found in TIO by White[16] in 2001. The discovery of FGF23 has paved the way toward a better understanding of the pathophysiology and treatment of TIO and has also provided a window

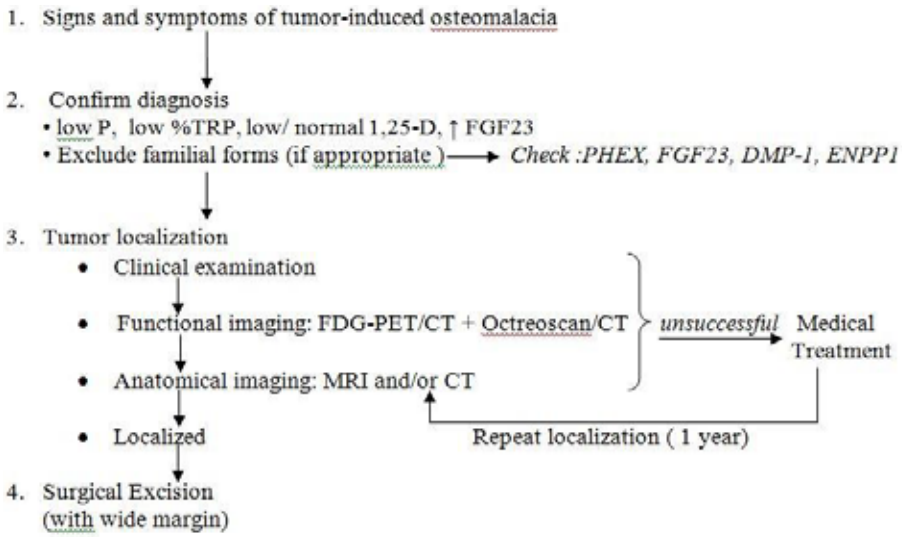


Fig. 4: Diagnostic approach to suspected TIO

into areas of mineral metabolism physiology that for years had been unexplained. Tumors associated with TIO have included a wide range of histopathological diagnoses. The prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMTMCT) contains neoplastic cells that are spindled to stellate in shape, with low nuclear or mitotic activity (ie normochromatic with small nuclei and indistinct nucleoli). Numerous osteoclast-like giant cells are a frequent finding. Weidner[17] in 1991 proposed a classification system based on the histological findings of TIO, and designated the tumors as phosphaturic mesenchymal tumors. These were then subdivided into four categories; mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non ossifying fibroma-like variant, and ossifying fibroma-like variant. The first group, PMTMCT, occurred in soft tissue, and was predominantly, benign in nature. The remaining three groups tended to occur in bone and were benign in nature. On immunohistochemistry staining, 70% tumours are FGF23 positive.[2] Metastsis is rare, though reported. While metastases are rare, infiltration of surrounding connective tissue is typically present, which has significant implications for surgical management and emphasizes the importance for wide surgical margins to avoid persistence or recurrence.

So, to sum up, patients with TIO / Phosphoturic mesenchymal tumours often present with many years of symptoms (bone pain, stress fractures and muscle weakness), or growth retardation and rickets in paediatric age, before they are diagnosed. Hypophosphatemia caused by impaired renal phosphate reabsorption is the biochemical hallmark of the disease. A systematic diagnostic approach for renal phosphate wasting and a thorough search for tumour is important in clinching the diagnosis.

Conclusion

TIO is a rare debilitating but curable condition and physicians should consider it while evaluating patients with osteomalacia and low serum phosphates. Thorough search for tumour, clinical as well as with functional and anatomical imaging is indicated considering severe disability caused by the condition and its potential reversibility.

References

1. Jan de Beur SM. Tumor-induced osteomalacia. *Journal of the American Medical Association* 2005; 294:1260–1267.
2. Folpe Al 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 Path* 2004; 28:1-30.
3. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA* 2001; 98:6500–6505.
4. Jiang Y et al. Tumor-Induced Osteomalacia: An Important Cause of Adult-Onset Hypophosphatemic Osteomalacia in China: Report of 39 Cases and Review of the Literature. *Journal of Bone and Mineral Research* 2012; 27:1967–1975.
5. Drezner MK. Tumor-induced osteomalacia. *Rev Endocr Metab Disord* 2001; 2:175–86.
6. Khosravi A, Cutler CM, Kelly MH, Chang R, Royal RE, Sherry RM, Wodajo FM, Fedarko NS & Collins MT. Determination of the elimination half-life of fibroblast growth factor-23. *Journal of Clinical Endocrinology and Metabolism* 2007; 92:2374–2377.
7. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer* 2011; 18:R53–R77.
8. Jagtap VS, Sarathi V, Lila AR, Bandgar T, Menon P, Shah NS. Hypophosphatemic rickets. *Indian J Endocr Metab* 2012; 16:177-82.
9. Reyes-Múgica M, Arnsmeier SL, Backeljauw PF, Persing J, Ellis B, Carpenter TO. Phosphaturic mesenchymal tumor-induced rickets. 2000; 3:61–69.
10. Jung GH, Kim JD, Cho Y, Chung SH, Lee JH, Sohn KR. A 9-month-old phosphaturic mesenchymal tumor mimicking the intractable rickets. *J Pediatr Orthop B* 2010; 19:127–132.
11. Amanzadeh J, Reilly Jr RF. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. *Nature Clinical Practice Nephrology* 2006; 2:136-148.
12. Barth JH, Jones RG, Payne BR. Calculation of renal tubular reabsorption of phosphate: the algorithm performs better than the nomogram. *Ann Clin Biochem* 2000; 37:79-81.
13. Mc Cance R. Osteomalaciawith loosers nodes (Milkman's syndrome) due a raised resistance to vitamin D acquired about the age of 15 years. *Quarterly J Med* 1947; 16:33-46.
14. Prader A, Illig R, Uehlinger E. Rickets following bone tumour. *Helvetica Paediatrica Acta* 1959; 14:554-565.
15. Econs MJ. Autosomal dominant hypophosphetemic risckets is associated with mutations in FGF23, ADHR consortium. *Nature Genetics* 2000; 26:345-348.
16. White KE, Jonsson KB, Carn G, Hampson G, Spector TD, Mannstadt M, The autodominant hypophosphatemic rickets ADHR gene is a secreted polypeptide overexpressed by tumours that cause phosphate wasting, *J Clin Endocrino Metab* 2001; 87:497-500.
17. Weidner N, Review and update: Oncogenic Osteomalacia Rickets, Ultrastructural Pathology 1991; 15:317-333.