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Original Article

Musculoskeletal oncogenic osteomalacia–An experience from a single centre in South India

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ABSTRACT

Background: Oncogenic osteomalacia is an acquired form of hypophosphatemic osteomalacia where the tumour resection may lead to cure of the disease. Tumours originating from the musculoskeletal region form an important subgroup of oncogenic osteomalacia.
Methods: This was a retrospective study conducted at a tertiary care centre in south India where we analyzed the hospital records of all the patients with musculoskeletal oncogenic osteomalacia from January 2010–April 2016.
Results: A total number of 73 patients were diagnosed to have adult onset hypophosphatemic osteomalacia out of which 13 patients (M: F = 6:7; mean age: 45.38 ± 18.23 years) with musculoskeletal oncogenic osteomalacia were included in the study. Common presenting symptoms were bony pains, proximal myopathy and fractures. Mean duration of symptoms from the initial hospital visit was 58.46 ± 64.48 months. The initial mean fibroblast growth factor (FGF) 23 levels being 828.86 ± 113.22 RU/ml (Normal range: 22–91). Imaging modalities used for localization of the tumour: DOTATATE PET/CT (8 patients), FDG PET/CT (3 patients), 1 patient (Both DOTATATE PET/CT and FDG PET/CT) and whole body Tc 99 m Red blood cell (RBC) blood pool scintigraphy (2 patients). 9 patients underwent surgery and all achieved remission. 4 patients denied surgical consent.
Conclusion: Musculoskeletal oncogenic osteomalacia is a major subgroup of oncogenic osteomalacia which need more extensive whole body imaging for the localization of the tumour. Surgical excision often leads to remission of the disease.

1. Introduction

The rare entity of “oncogenic osteomalacia” also known as “tumour induced osteomalacia”, is a paraneoplastic condition that is characterized by the development of muscle weakness, bone pains, fractures and deformities secondary to tumours secreting phosphotonins in turn causing phosphaturia and hence hypophosphatemia. Early description of the disease dates back to 1959, when it was first described as the occurrence of severe and progressive rachitic changes in an $11^1/_2$ year old girl. Further evaluation of the same had shown the presence of renal phosphate wasting in the presence of a normal renal function and a giant cell tumour in the rib. Upon removal of the tumour, there was healing of rickets.[1]

The clinical features of oncogenic osteomalacia are attributed to hypophosphatemia secondary to renal phosphate wasting usually caused by a phosphaturic factor, known as phosphatonins which have subsequently been identified as fibroblast growth factor −23 (FGF-23).[2] Other phosphatonins which have been identified to cause hypophosphatemic osteomalacia are secreted frizzled related protein-4 (sFRP-4), matrix extracellular phosphoglycoprotein and FGF-7.[3] Biochemically, oncogenic osteomalacia is characterized by hypophosphatemia, inappropriately low 1, 25 OH vitamin D and elevation in the levels of FGF-23.[2] The condition

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rather has a dramatic presentation, and upon removal of the tumour, there is remarkable improvement in the symptomatology.

The prototype of the tumours responsible is the phosphaturic mesenchymal tumours, mixed connective tissue variant (PMTMCT). Identification of these tumours is often difficult, as they are usually slow growing and indolent. Functional imaging like somatostatin based scintigraphy has recently been shown to be helpful in the detection of these small tumours that express somatostatin receptors.[4] Surgical excision of these tumours usually results in clinical recovery following a decline in the levels of FGF-23.[5] These mesenchymal tumours may occur anywhere in the body and have been reported from the extremities, head and neck region as well as from other musculoskeletal parts of the body. The tumours from musculoskeletal region form an important subgroup of oncogenic osteomalacia in terms of requiring detailed whole body imaging for the localization of these tumours.

We report our experience in the clinical features, detection, management and clinical outcomes of tumour induced osteomalacia, in the musculoskeletal region.

2. Materials and methods

2.1. Patients

It was a retrospective study conducted at the department of Endocrinology, tertiary care centre in southern India. We analysed the hospital records of all the patients with a diagnosis of adult onset hypophosphatemic osteomalacia from Centralised Hospital Information Processing Services (CHIPS) without any significant family history from January 2010 to April 2016. All the patients who were diagnosed to have hypophosphatemic osteomalacia secondary to tumours of musculoskeletal region were recruited into the study. The clinical, biochemical and radiological data of 13 patients of musculoskeletal oncogenic osteomalacia were analysed. This study was approved by institutional review board.

2.2. Methods

A detailed medical history including family history and physical examination findings of patients with adult onset hypophosphatemic osteomalacia were taken into consideration for the study. Baseline fasting serum calcium (N: 8.3–10.4 mg/dL), phosphate (N: 2.5–4.6 mg/dL), alkaline phosphatase (ALP){N: 40–125U/L}, tubular maximum of phosphate/Glomerular filtration rate (TMP/GFR) (N: ≥2.5), 25 OH vitamin D (N: 30–75 ng/ml), PTH (N: 8–74 pg/ml) and Fibroblast growth factor (FGF 23)(N: 22–91RU/ml) levels were obtained. Tubular maximum of phosphate/glomerular filtration rate (TMP/GFR) was calculated from the nomogram of Walton and Bijvoet.[6] Details regarding functional imaging (isotope scan) {FDG PET/CT or DOTATE PET/CT} or whole body Tc 99 m Red blood cell (RBC) blood pool scintigraphy were obtained. Following localization and surgical excision of the tumour, the biopsy specimens confirmed the presence of mesenchymal phosphaturic tumour. Serum calcium, phosphate, ALP and FGF 23 levels were measured in the post-operative period and during follow up for assessing the remission status.

3. Results

Of seventy three patients who presented with adult onset hypophosphatemic osteomalacia, 13 subjects (M:F = 6:7) were diagnosed to have musculoskeletal oncogenic osteomalacia with a mean age of 45.3 ± 18.2 years (Table 1).

The mean duration of symptoms prior to initial hospital visit was 51.1 ± 63.1 months (Tables 1 and 2). Mean FGF 23 level was 828.86 ± 113.22 RU/ml. All patients had functional imaging for localization [3 patients – FDG PET/CT, 8 patients- DOTATATE PET/CT and 1 patient- both modalities of imaging and whole body Tc–99 m Red blood cell (RBC) blood pool scintigraphy in 2 patients]. Nine patients underwent surgical excision of the tumour following localization, and 4 patients declined consent for surgery (Table 3). Fig. 1 shows an increased uptake in the lesion on DOTATATE PET/CT done in one of the patients (patient no. 3). All the biopsy specimens of 9 patients who underwent surgery showed the presence of phosphaturic mesenchymal tumour {Fig. 2, patient no.4} (6 had mesenchymal tumours, 2 had mixed connective tissue variant and 1 had a variant of non ossifying fibroma). All except one were in remission after the first surgery (patient no. 3 required second surgery in view of not attaining remission after first surgery). The post operative FGF-23 levels versus preoperative FGF-23 levels in patients who underwent surgery showed significant reduction ($P < 0.05$) (Table 3).

Table 1
Baseline parameters of patients with musculoskeletal oncogenic osteomalacia.

Parameters	Mean (SD) (N = 13)
Age (Years)	45.4 (18.2)
Sex (Male/Female)	6/7
Duration of symptoms (Months)	58.5 (64.5)
Serum Corrected calcium (mg/dL)	8.9 (0.6)
Serum Phosphate (mg/dL)	1.3 (0.7)
TMP GFR	0.9 (0.6)
Alkaline Phosphatase (U/L)	284.2 (189.2)
Parathyroid hormone (pg/ml)	123.1 (49.8)
25 OH vitamin D (ng/ml)	33.5 (20.4)
FGF 23 (RU/ml)	828.9 (113.2)

SD: standard deviation; TMP GFR: Tubular maximum of phosphate/glomerular filtration rate; FGF 23: Fibroblast growth factor 23.

4. Discussion

Oncogenic osteomalacia was seen in 31.5% of adult patients with hypophosphatemic osteomalacia out of which 56.5% were from the musculoskeletal region. Most prominent symptoms seen in our patients with musculoskeletal oncogenic osteomalacia were bony pains (77%), proximal muscle weakness (61.5%) and fractures (30%) (Table 2) which is concurrent with the available literature.[7] The nuclear scintigraphy imaging enabled to localise lesions in most of our patients, thus underlying the importance of functional imaging in the diagnosis of these rare tumours. The commonest location of the tumour in our series was in the lower extremities and was seen in about 85% of patients; majority of them had bony lesions (Table 3). These findings correlate with what has been observed in another study.[7]

All the patients who underwent surgery were in remission. The commonest histological subtype seen in our patients with musculoskeletal oncogenic osteomalacia was phosphaturic mesenchymal tumour/mixed connective tissue tumour. Most of these tumours are benign with low nuclear grade and poor mitotic activity.[2]

Oncogenic osteomalacia also known as “tumour induced osteomalacia”, is a rare paraneoplastic syndrome usually caused by small endocrine tumours that secrete several phosphaturic hormones like fibroblast growth factor (FGF- 23) leading to hypophosphatemia.[2,8,9] Oncogenic osteomalacia is one of the remediable causes of hypophosphatemic osteomalacia since the resection of the tumour leads to cure of this condition.[10] This is a rare condition and less than 500 cases have been reported from across the world.[2,7] They usually present with proximal muscle weakness, bony pains or pathological fractures. The commonest sites of the tumour in decreasing order were thigh and femur, head and neck, ankle and foot, pelvis, tibia and fibula followed by arms.[7]

Table 2
Details of patients with musculoskeletal oncogenic osteomalacia (presenting features and biochemical parameters).

Pt. No	Age (Years)	Sex	Presenting symptoms	Duration of symptoms (months)	Serum Corrected Calcium (mg/dL)	Serum Phosphate (mg/dL)	ALP (U/L)	TMP GFR	PTH (pg/ml)	25 OH D (ng/ml)	FGF 23 (RU/ml)
1	28	M	Proximal muscle weakness, Fracture	36	10	2.8	157	1.9	67.3	7.32	346
2	18	F	Bony pain, Fractures	48	9.02	1.1	388	0.9	151.4	27.4	202
3	34	M	Bony pain, Fractures	216	8	0.9	851	0.3	188.3	34.4	1400
4	74	F	Bony pain, Proximal muscle weakness	1	8.8	1.4	260	0.7	55.1	6	658
5	28	F	Bony pain, Proximal muscle weakness	48	8.67	0.6	97	0.6	86.7	85	945
6	62	M	Bony pain, Proximal muscle weakness	24	8.71	0.3	264	1.5	70	12.35	311
7	34	M	Bony pain, Proximal muscle weakness	72	8.6	1	311	1.2	155	29.38	NA
8	59	F	Proximal muscle weakness	5	9.19	1.2	189	1	176	39.1	509
9	55	F	Bony pain, Proximal muscle weakness	60	9	2.2	272	1.9	118.8	44.72	218
10	55	F	Bony pain, Fractures	1	8.9	2.2	130	NA	88	26.36	341
11	72	F	Bony pain	2	9.9	0.7	276	0.4	NA	38.63	231.9
12	37	M	Bony pain	168	8.7	1.5	183	NA	76	NA	416
13	34	M	Bony pains, Proximal muscle weakness	24	8.3	0.9	317	0.5	162.8	24.15	3556

ALP: Alkaline Phosphatase; TMP GFR: Tubular maximum of phosphate/glomerular filtration rate; PTH: Parathormone; FGF 23: Fibroblast growth factor 23; NA: Not available.

Thus musculoskeletal group forms a major subcategory among the oncogenic osteomalacia.

One of the most challenging aspects of oncogenic osteomalcia is to localise the tumour. Since these phosphaturic tumours are very small, various imaging techniques have been used like whole body Tc 99 m Red blood cell (RBC) blood pool scintigraphy,computed tomography (CT), whole body magentic resonance imaging (MRI), Fluorodeoxyglucose (18FFDG) positron emission tomography (PET/CT) or Gallium (68Ga) DOTATATE PET/CT.[4,11–13] The most common histological picture is phosphaturic mesenchymal tumour (PMT) with the subtypes: PMT mixed conective tissue tumour (commonest), nonossifying fibroma-like, ossifying fibroma-like and osteoblastoma-like PMT. The other histological types of oncogenic osteomalacia reported are giant cell tumour, hemangioma, hemangiopericytoma and osteosarcoma.[14,7] Identifying the precise location of these tumours is important as surgical excision leads to remission.

The treatment of this condition in the perioperative period include phosphate and active vitamin D3 supplementation. Although surgical excision is the treatment of choice, in selected

Table 3
Details of patients with musculoskeletal oncogenic osteomalacia (Localization imaging study and postoperative status).

Pt. No	Site of Tumour	Site of Tumour (Bone, Muscle)	Localization study			Biopsy proven	Type of Tumour Mesenchymal tumour/ Mixed connective tissue tumour	Remission status	Post-operative FGF 23 (RU/ml)
			Blood pool scan	FDG PET	DOTATATE PET				
1	Right proximal Femur	Bone	–	Yes	–	Yes	Mesenchymal tumour	Yes	84
2	Right proximal tibia (deep to popliteus)	Bone	–	–	Yes	Yes	Mesenchymal tumour	Yes	95.2
3	Right distal shaft of femur (superior to lateral condyle)	Bone	Negative	Yes	Yes	Yes	Mixed connective tissue tumour	Yes#	67.3
4	Right foot	Bone	–	–	Yes	Yes	Mixed connective tissue tumour	Yes	NA
5	Right distal tibia	Bone	–	Yes	–	Yes	Mesenchymal tumour	Yes	91
6	Left distal tibia	Bone	–	–	Yes	NA	NA	*	*
7	Right distal femur (lateral aspect)	Bone	Yes	–	–	Yes	Non ossifying fibroma like variant	Yes	NA
8	Medial head of right gastrocnemius	Muscle	–	–	Yes	Yes	Mesenchymal tumour	Yes	63
9	Intermuscular plane medial aspect left lower thigh	Muscle	–	–	Yes	NA	NA	*	*
10	Left Humerus (Proximal)	Bone	–	–	–	Yes	Mesenchymal tumour	Yes	68
11	Distal end of Right Femur	Bone	Yes	–	–	NA	NA	*	*
12	Distal Right femur	Bone	–	–	Yes	Yes	Mesenchymal tumour	Yes	5
13	Upper end of left ulna	Bone	–	–	Yes	NA	NA	*	NA

FDG PET: Fluorodeoxyglucose (18FFDG) positron emission tomography; FGF 23: Fibroblast growth factor 23; #: underwent second surgery; *yet to undergo surgery; NA: Not available.

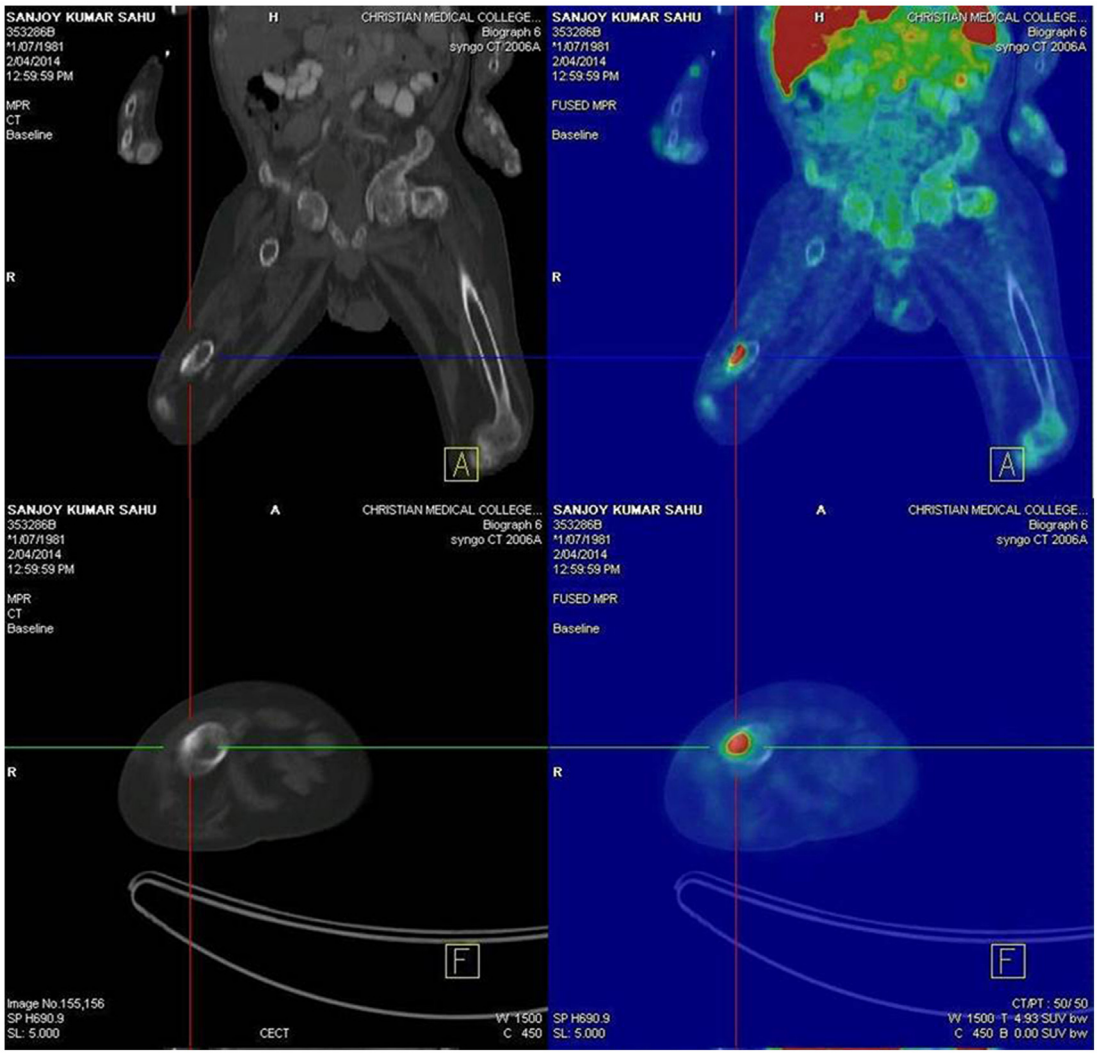

Fig. 1. Ga68 DOTA TATE PET/CT (Patient no.3) showing uptake in distal end of shaft of right femur.

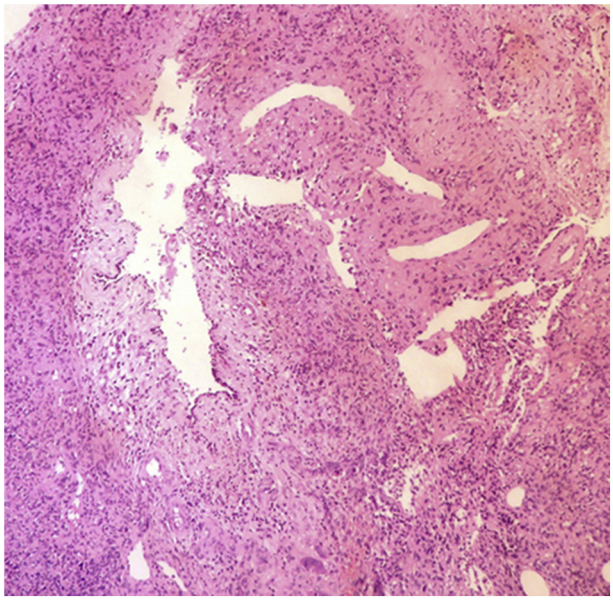

Fig. 2. Histologic picture of phosphaturic mesenchymal tumour displaying vascular pattern with thicker walled and hyalinized blood vessels (Patient no.4).

cases where surgery is not feasible, other modalities of treatment with somatostatin analogues, chemotherapeutic agents like cisplatin and doxorubicin and external beam radiotherapy may be empolyed.[2]

In conclusion, oncogenic osteomalacia is an important treatable cause for hypophosphatemic osteomalacia where surgery plays a pivotal role and excision of the tumour leads to cure of the disease. Tumours originating from the musculoskeletalregion is an important subcategory of oncogenic osteomalacia and needs more elaborate imaging modalities for precise localization and subsequent treatment.

Conflict of interest

The authors have none to declare.

References

1. McCance RA. Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Q J Med*. 1947;16(1):33–46.
2. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr Relat Cancer*. 2011;18(3):R53–R77.
3. Berndt TJ, Schiavi S, Kumar R. Phosphatonins and the regulation of phosphorus homeostasis. *Am J Physiol Renal Physiol*. 2005;289(6):F1170–1182.
4. Jan de Beur SM, Streeten EA, Civelek AC, et al. Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet*. 2002;359(9308):761–763.

5. Hu F-K, Yuan F, Jiang C-Y, et al. Tumor-induced osteomalacia with elevated fibroblast growth factor 23: a case of phosphaturic mesenchymal tumor mixed with connective tissue variants and review of the literature. *Chin J Cancer*. 2011;30(11):794–804.
6. Walton RJ, Bijvoet OL. Nomogram for derivation of renal threshold phosphate concentration. *Lancet Lond Engl*. 1975;2(7929):309–310.
7. Jiang Y, Xia W, Xing X, et al. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. *J Bone Miner Res*. 2012;27(9):1967–1975.
8. Folpe AL, Fanburg-Smith JC, Billings SD, 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 Pathol*. 2004;28(1):1–30.
9. Dadoniene J, Miglinas M, Miltiniene D, et al. Tumour-induced osteomalacia: a literature review and a case report. *World J Surg Oncol*. 2016;14(1):4.
10. White KE, Jonsson KB, Carn G, et al. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. *J Clin Endocrinol Metab*. 2001;86(2):497–500.
11. Dissanayake AM, Wilson JL, Holdaway IM, Reid IR. Oncogenic osteomalacia: culprit tumour detection whole body magnetic resonance imaging. *Intern Med J*. 2003;33(12):615–616.
12. Agrawal K, Bhadada S, Mittal BR, et al. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. *Clin Nucl Med*. 2015;40(1):e6–10.
13. Jadhav S, Kasaliwal R, Lele V, et al. Functional imaging in primary tumour-induced osteomalacia: relative performance of FDG PET/CT vs somatostatin receptor-based functional scans: a series of nine patients. *Clin Endocrinol (Oxf)*. 2014;81(1):31–37.
14. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors: a polymorphous group causing osteomalacia or rickets. *Cancer*. 1987;59(8):1442–1454.