

OXFORD  
UNIVERSITY PRESS

QJM: An International Journal of Medicine

**ONCOGENIC OSTEOMALACIA**

Journal:	<i>QJM: An International Journal of Medicine</i>
Manuscript ID	QJM-2017-1043
Manuscript Type:	Clinical Picture
Date Submitted by the Author:	29-Dec-2017
Complete List of Authors:	<p>Annamalai, Anand; Ashwin Speciality Hospital, Endocrinology and Diabetes Gill, Anthony; Royal North Shore Hospital, Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, University of Sydney, and NSW Health Pathology, Department of Anatomical Pathology</p> <p>Shinto, Ajit; Kovai Medical Centre Hospital, Department of Nuclear Medicine</p> <p>Sivakumar, R; Preethi Hospital, Department of Orthopaedics</p> <p>Singhi, Prahlad Kumar; Preethi Hospital, Department of Orthopaedics</p> <p>Prabhu, V A; Ashwin Speciality Hospital, Department of Orthopaedics</p> <p>Sridhar, Subbiah; Madurai Medical College, Endocrinology</p> <p>Shanthy, Radhakrishnan; Aravind Eye Care Hospitals, Department of Pathology</p> <p>Puri, Vipla; PD Hinduja National Hospital and Medical Research Centre, Department of Laboratory Medicine</p> <p>Gururaj, N; CSI College of Research and Dental Sciences, Oral Pathology</p> <p>Gopalakrishnan, Chandrasekhar ; Ashwin Speciality Hospital, Department of Surgery</p> <p>Chelian, Mathirajan; Ashwin Speciality Hospital, Department of Surgery and Anaesthesia</p> <p>Srinivasan, Kaliappan; KGS Scan Centre, Radiology</p> <p>Clifton-Bligh, Roderick ; Royal North Shore Hospital, Department of Endocrinology</p> <p>Gurnell, Mark; Institute of Metabolic Science, Addenbrooke's Hospital, Endocrinology</p>
Keywords:	Endocrinology, Biochemistry & metabolism, Musculoskeletal disease, Imaging, Medical practice

SCHOLARONE™  
Manuscripts

## ONCOGENIC OSTEOMALACIA

*Anand K Annamalai<sup>1</sup>, Anthony J Gill<sup>2</sup>, Ajit Shinto<sup>3</sup>, R Sivakumar<sup>4</sup>, Prahlad Kumar Singhi<sup>4</sup>, V.A. Prabhu<sup>5</sup>, Subbiah Sridhar<sup>6</sup>, Radhakrishnan Shanthi<sup>7</sup>, Vipla Puri<sup>8</sup>, N Gururaj<sup>9</sup>, Chandrasekhar Gopalakrishnan<sup>5</sup>, Mathirajan Chelian<sup>5</sup>, K.G. Srinivasan<sup>10</sup>, Roderick Clifton-Bligh<sup>11</sup>, Mark Gurnell<sup>12</sup>*

<sup>1</sup>Department of Endocrinology, Ashwin Speciality Hospital, Madurai, Tamil Nadu, India; <sup>2</sup>Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, University of Sydney, and NSW Health Pathology, Department of Anatomical Pathology Royal North Shore Hospital, Australia; <sup>3</sup>Department of Nuclear Medicine, Kovai Medical Centre Hospital, Coimbatore, India; <sup>4</sup>Department of Orthopaedics, Preethi Hospital, Madurai, India; <sup>5</sup>Department of Surgery and Anaesthesiology, Ashwin Speciality Hospital, Madurai, Tamil Nadu, India; <sup>6</sup>Department of Endocrinology, Madurai Medical College, Tamil Nadu, India; <sup>7</sup>Department of Pathology, Aravind Eye Care Hospitals, Madurai, India; <sup>8</sup>RIA, Department of Laboratory Medicine, Hinduja Hospital, Mumbai, India; <sup>9</sup>CSI College of Research and Dental Sciences, Madurai; <sup>10</sup>KGS Scan Centre, Madurai, India; <sup>11</sup>Department of Endocrinology, Kolling Institute, Royal North Shore Hospital, Sydney, Australia; <sup>12</sup>Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge and NIHR Cambridge Biomedical Research Centre, Addenbrooke's Hospital, Cambridge, UK;

**Key Words:** oncogenic osteomalacia, fibroblast growth factor 23

**Word Count:** 485

**Corresponding author:** Dr. Anand K Annamalai, Consultant Endocrinologist, Ashwin Speciality Hospital, Madurai, Tamil Nadu, India; Tel: +91-9442282221; E-mail: [ak\\_md2000@yahoo.com](mailto:ak_md2000@yahoo.com)

**No conflicts of interest**

1  
2  
3  
4  
5  
6 A 36-year-old male presented with a five-year history of progressive generalised body ache, severe  
7 bone pain and muscle stiffness which was markedly limiting his activities of daily living. Clinical  
8 examination revealed a soft tissue swelling in the lateral aspect of the right knee, together with  
9 multiple tender areas in the hips, forearms and legs. Radiological screening revealed bilateral multiple  
10 stress fractures involving both upper and lower limbs (Figure 1A).  
11  
12  
13  
14  
15

16 Laboratory investigation showed normal renal function and serum corrected calcium (8.9 mg/dL; RR  
17 8.5–10.6), but serum phosphorus was significantly low (1.8 mg/dL; RR 2.5–4.4). Serum parathyroid  
18 hormone (44.6 pg/mL; RR 14–72) levels were unremarkable, but 25 OH Vitamin D was elevated (107  
19 ng/mL; RR 30–100) on cholecalciferol supplements, with an inappropriately normal 1, 25 (OH)<sub>2</sub>  
20 Vitamin D (69.7 pmol/L; RR 47–190) and an inappropriately high urinary phosphorus (1476 mg/day;  
21 RR 400–1300). In view of the hypophosphatemia, phosphaturia and an inappropriately normal 1, 25  
22 (OH)<sub>2</sub> Vitamin D, a plasma C-terminal fibroblast growth factor 23 (FGF-23) level was measured  
23 which was significantly elevated (294 RU/ml; RR 0–150). Oncogenic osteomalacia was diagnosed and  
24 functional imaging with a <sup>68</sup>Ga-DOTANOC-PET revealed focal high tracer uptake (SUVmax = 9.6) in  
25 the right tibial condyle (Fig 1B). Structural correlation with CT (Fig 1C) and MRI scan revealed a  
26 small 1.8 cm intra osseous lesion in the right postero-lateral tibial condyle. Following excision of the  
27 tibial condyle lesion, FGF-23 levels fell dramatically into the low normal range (Day four post  
28 surgery: 37 RU/ml). Histopathological examination confirmed a benign phosphaturic mesenchymal  
29 cell tumour with positive expression of SSTR2A by immunohistochemistry<sup>(1)</sup> (Supplementary Figure  
30 2). After a few months the patient reported a rapid and complete resolution of the symptoms, and  
31 repeat X-rays at three months demonstrated that the previous fractures had all healed.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

48 Tumour-induced osteomalacia [(TIO) – also referred to as oncogenic osteomalacia] is an under-  
49 recognised paraneoplastic syndrome which occurs due to an over production of FGF-23 by small  
50 benign soft tissue or bone related mesenchymal tumours.<sup>(2-4)</sup> The diagnosis can be delayed by decades  
51 due to a lack of awareness of the condition.<sup>(3)</sup> TIO can present with generalised body pain,  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2 unexplained fractures, hypophosphatemia and low or inappropriately normal 1,25 (OH)<sub>2</sub> Vitamin D.  
3  
4 FGF-23 is a phosphaturic hormone that is normally secreted by the osteoblasts and osteocytes.  
5  
6 Elevated FGF-23 levels in TIO prevents phosphate reabsorption by the renal tubules and inhibits 1 $\alpha$   
7  
8 hydroxylation of 25-hydroxyvitamin D resulting in marked hypophosphatemia. Careful physical  
9  
10 examination (from “head to toe”) is essential to ensure that all seemingly insignificant soft tissue  
11  
12 swellings/lesions are not overlooked. Functional imaging with <sup>68</sup>Ga-DOTANOC-PET coupled with  
13  
14 anatomical imaging (MRI/CT) will allow identification of most lesions. Complete surgical resection  
15  
16 of the culprit lesion(s) leads to rapid normalisation of FGF-23 levels, with dramatic resolution of  
17  
18 symptoms and subsequent healing of fractures.<sup>(2)</sup> The case and images reported here highlight the  
19  
20 importance of a high clinical index of suspicion for TIO in any patient with unexplained myalgia/bone  
21  
22 pain and hypophosphatemia.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

### 33 **References**

- 34 1. Houang M, Clarkson A, Sioson L, Elston MS, Clifton-Bligh RJ, Dray M, et al. Phosphaturic  
35 mesenchymal tumors show positive staining for somatostatin receptor 2A (SSTR2A). *Hum Pathol*  
36 2013;44:2711-8.
- 37 2. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most  
38 osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32  
39 cases and a comprehensive review of the literature. *Am J Surg Pathol* 2004;28:1-30.
- 40 3. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. *Endocr*  
41 *Relat Cancer* 2011;18:R53-77.
- 42 4. Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH, et al. Tumour-induced  
43 osteomalacia. *Nat Rev Dis Primers* 2017;3:17044.
- 44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

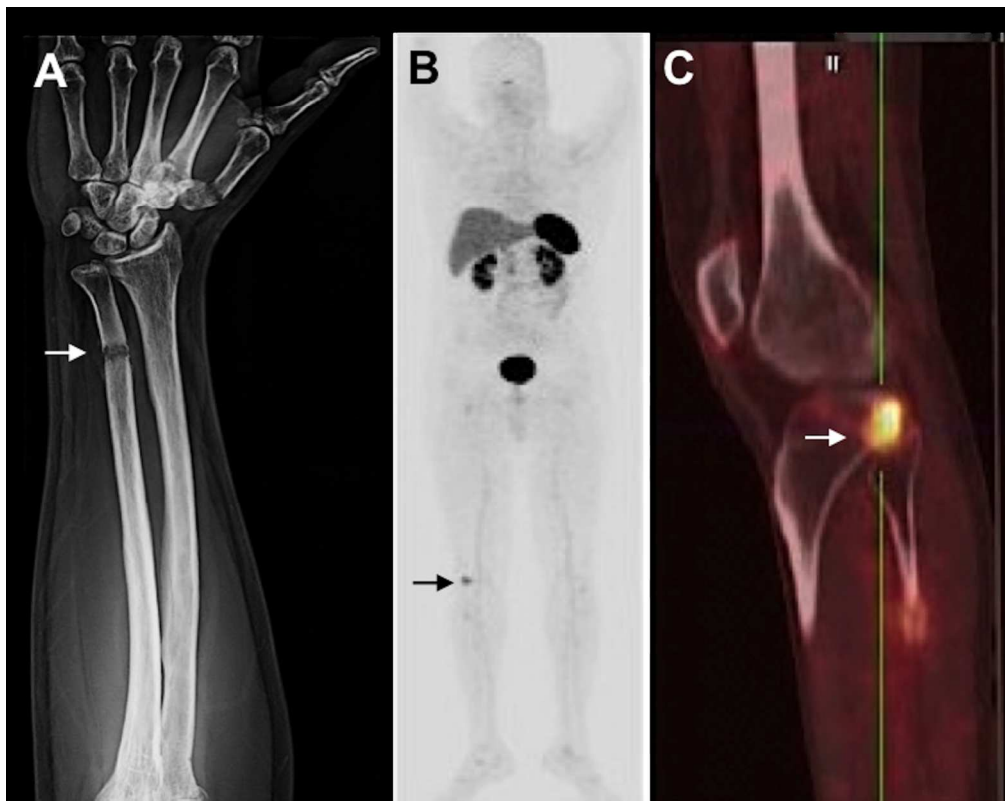
1  
2  
3  
4  
5  
6  
7  
8 **Figure legend:**  
9

10  
11 (A) X-ray of the right forearm showing an insufficiency fracture over the distal 1/3<sup>rd</sup> of the ulna; (B)  
12 Whole body Ga-68 DOTANOC PET demonstrating focal tracer uptake within the right tibial condyle  
13 (SUVmax = 9.6); (C) Fused Ga-68 DOTANOC PET CT scan of the right knee joint in the lateral  
14 plane showing a postero-lateral tibial condyle lesion.  
15  
16  
17  
18  
19  
20  
21  
22

23 **Supplementary Figure legend:**  
24

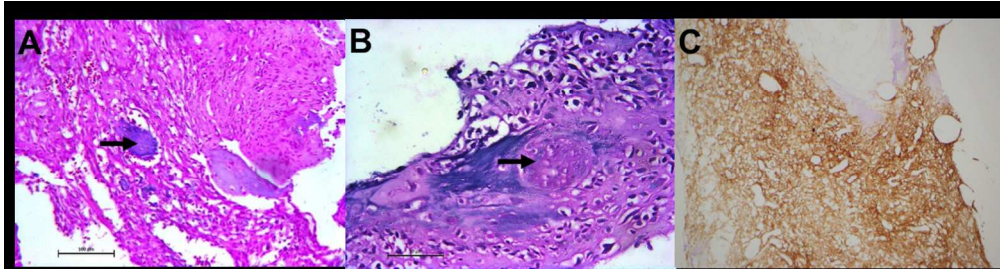
25 Histological findings of the tibial condyle lesion (A) H&E stain showing diffuse proliferation of bland  
26 tumour cells with a haemangiopericytomatous vascular pattern and smudgy matrix [arrow]; (B) area  
27 of chondroid differentiation with chondroblasts; (C) Immuno histochemistry (IHC) shows strong  
28 positive staining for somatostatin receptor subtype 2 A (SSTR2A).  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



(A) X-ray of the right forearm showing an insufficiency fracture over the distal 1/3rd of the ulna; (B) Whole body Ga-68 DOTANOC PET demonstrating focal tracer uptake within the right tibial condyle (SUVmax = 9.6); (C) Fused Ga-68 DOTANOC PET CT scan of the right knee joint in the lateral plane showing a posterolateral tibial condyle lesion.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



For Review Only