

## ONCOGENIC OSTEOMALACIA

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ONCOGENIC OSTEOMALACIA

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**No conflicts of interest**

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

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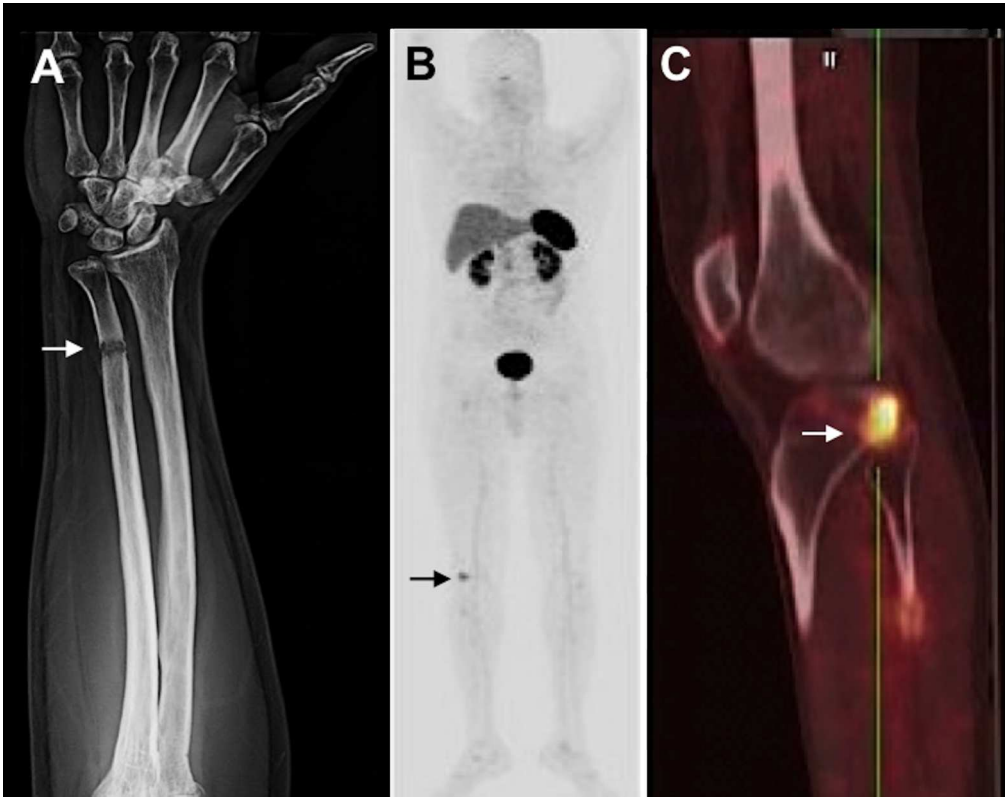
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**Figure legend:**

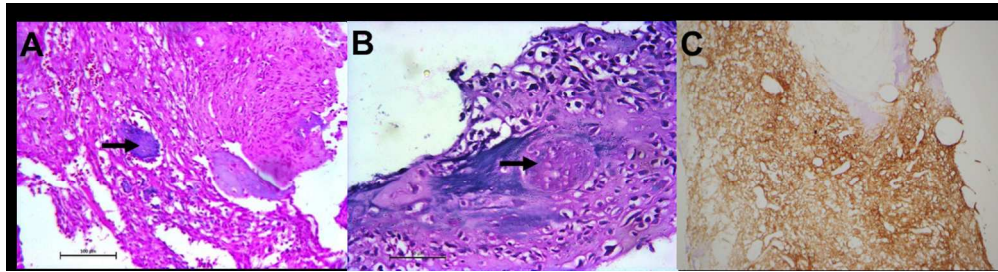
(A) X-ray of the right forearm showing an insufficiency fracture over the distal 1/3<sup>rd</sup> of the ulna; (B) Whole body Ga-68 DOTANOC PET demonstrating focal tracer uptake within the right tibial condyle (SUVmax = 9.6); (C) Fused Ga-68 DOTANOC PET CT scan of the right knee joint in the lateral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

**Supplementary Figure legend:**

Histological findings of the tibial condyle lesion (A) H&E stain showing diffuse proliferation of bland tumour cells with a haemangiopericytomatous vascular pattern and smudgy matrix [arrow]; (B) area of chondroid differentiation with chondroblasts; (C) Immuno histochemistry (IHC) shows strong positive staining for somatostatin receptor subtype 2 A (SSTR2A).



(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 postero-lateral tibial condyle lesion.



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