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Treating 'osteoporosis': a near miss in an unusual case of FGF-23-mediated hypophosphataemic osteomalacia

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Summary

We present the case of a 60-year-old female who developed repeated atraumatic stress fractures. She was initially diagnosed with osteoporosis based on her dual-energy X-ray absorptiometry (DXA) scan bone mineral density (BMD) T-scores and started on denosumab therapy. Secondary osteoporosis screen revealed abnormal myeloma screen and low serum phosphate levels. It was thought that the patient had multiple myeloma with associated Fanconi-related tubular dysfunction. However, fibroblast growth factor-23 (FGF-23) levels were grossly elevated, making Fanconi syndrome unlikely. The patient was subsequently diagnosed with two separate conditions, namely cardiac amyloid light-chain (AL) amyloidosis and FGF-23-related hypophosphataemia, likely due to tumour-induced osteomalacia. This case highlights the importance of excluding osteomalacia as a cause of low BMD and checking FGF-23 levels in the workup for hypophosphataemia.

Learning Points

- Tumour-induced osteomalacia is a difficult diagnosis as the tumour is often small and slow growing. Imaging may fail to identify a tumour, and treatment therefore consists of calcitriol and phosphate replacement.
- Tumour-induced osteomalacia should be suspected in the adult presenting with new-onset hypophosphataemia, elevated FGF-23 levels and isolated renal phosphate wasting.
- Serum phosphate is not part of the routine chemistry panels. Routinely checking phosphate levels prior to initiating antiresorptive therapy is warranted.
- DXA cannot distinguish low bone mineral density due to osteoporosis from osteomalacia. Antiresorptive therapy should be avoided in osteomalacia due to the risk of clinical and radiographic deterioration.

Background

Osteoporosis is a condition of low bone mass, leading to an increased risk of fragility fractures. Despite low bone mass, mineralisation of bone is normal in osteoporosis. Osteomalacia can also result in a low bone mineral density (BMD) on dual-energy X-ray absorptiometry (DXA) scan; however, it is characterised by demineralised bone rather than low bone mass. We report a patient misdiagnosed with osteoporosis and initiated in denosumab therapy but was later found to have FGF-23-related hypophosphataemia.

We believe our case is unique due to the following reasons:

1. This is the first case report of simultaneous diagnosis of cardiac AL amyloidosis and FGF-23-related hypophosphataemia.

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2. Unlike previous case reports, we were unable to localise the tumour in our patient on functional and structural imaging. However, our patient has responded well to medical therapy of calcitriol and phosphate replacement, which is usually poorly tolerated due to gastrointestinal side effects.
3. Our patient inadvertently received antiresorptive therapy for her osteomalacia, which could have led to clinical or radiographic deterioration. This case highlights the importance of excluding osteomalacia as a cause of low BMD on DXA scan prior to diagnosing osteoporosis.

Case presentation

A 60-year-old female of Middle Eastern background living in Australia presented to her general practitioner with left-sided rib pain following self-massage with a rubber massage ball. This was on a background of hypertension, hyperlipidaemia, chronic sinusitis and cervical spondylosis. Her regular medications include telmisartan 80 mg daily, amlodipine 5 mg daily and rosuvastatin 10 mg nocte.

Left-sided rib x-ray did not show any fractures, and she was presumed to have clinical rib fracture. DXA scan revealed T-scores in the osteoporotic range at the lumbar spine and osteopaenic range in the hips (Table 1). Z-score of the lumbar spine was –2.3 S.D., which raises suspicion for a secondary cause (1). Nonetheless, the patient was commenced on denosumab 60 mg subcutaneous six monthly, calcium carbonate 600 mg once daily and vitamin D 1000 IU daily by her general practitioner.

The patient had no previous fragility fractures or family history of metabolic bone disease. Her gynaecological history was unremarkable, with menarche at the age of 13 and menopause at the age of 48 years. There was no history of hyperthyroidism or malabsorptive syndromes. She did have two steroid injections for her cervical spondylosis in the past but denied any long-term prednisone use. Dietary calcium and sunlight exposure was adequate.

Table 1 DXA scan performed in March 2021 showing low bone density in the lumbar spine and hips.

	Bone density	T-score (S.D.)	Z-score (S.D.)
L1–L4	0.86 g/cm^2	–2.8	–2.3
Left femoral neck	0.77 g/cm^2	–1.9	–1.0
Right femoral neck	0.76 g/cm^2	–2.0	–1.1

One month later, the patient presented with lower back and right groin pain as well as proximal leg weakness. On examination, she was tender in the sacral region and had pain with flexion and internal rotation of the right hip. She was unsteady with single-leg standing and squatting, implying weak gluteal muscles. CT of her lumbar spine showed mild spondylotic changes with no vertebral fractures.

She was referred to a neurosurgeon who performed a bone scan (Fig. 1) demonstrating stress reaction around the sacroilliac joints and right acetabulum. There was no increased uptake in the axial skeleton to suggest metabolic bone disorders like osteomalacia. She was then referred to a rheumatologist who organised sacroiliac MRI confirming bilateral sacral stress fractures. Results of her secondary osteoporosis screen is shown in Table 2.

The abnormal kappa light chain ratio raised concern for possible multiple myeloma. The patient was referred to haematology who organised bone marrow aspirate which demonstrated only 5% clonal plasma cells. There was positive apple-green birefringence on Congo Red stain characteristic of amyloidosis. CT skeletal survey was negative for lytic lesions while cardiac MRI showed amyloid involving the ventricles. The patient was subsequently diagnosed with cardiac AL amyloidosis and started on daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone therapy (CyBorD). Expected median overall survival was 35 months.

The patient was simultaneously referred to endocrinology for review of her elevated parathyroid hormone (PTH). This was thought to be secondary hyperparathyroidism related to denosumab therapy. Reassuringly, repeated calcium on bloods was normal. Of greater interest was the abnormally low phosphate of 0.52 mmol/L [reference range (RR): 0.8–1.5 mmol/L) on the secondary osteoporosis screen with a normal phosphate of 1.06 mmol/L 4 years earlier.

Investigation

To further investigate the cause of this patient's hypophosphataemia, we performed several urine investigations. Fractional excretion of phosphate was elevated (32%, RR: < 5%) while tubular maximal reabsorption of phosphate to estimated glomerular filtration rate (eGFR) was reduced (0.174 mmol/L, RR: 1.00–1.35 mmol/L), reflecting renal phosphate wasting. In light of the amyloidosis diagnosis, it was thought that this renal phosphate wasting could represent acquired

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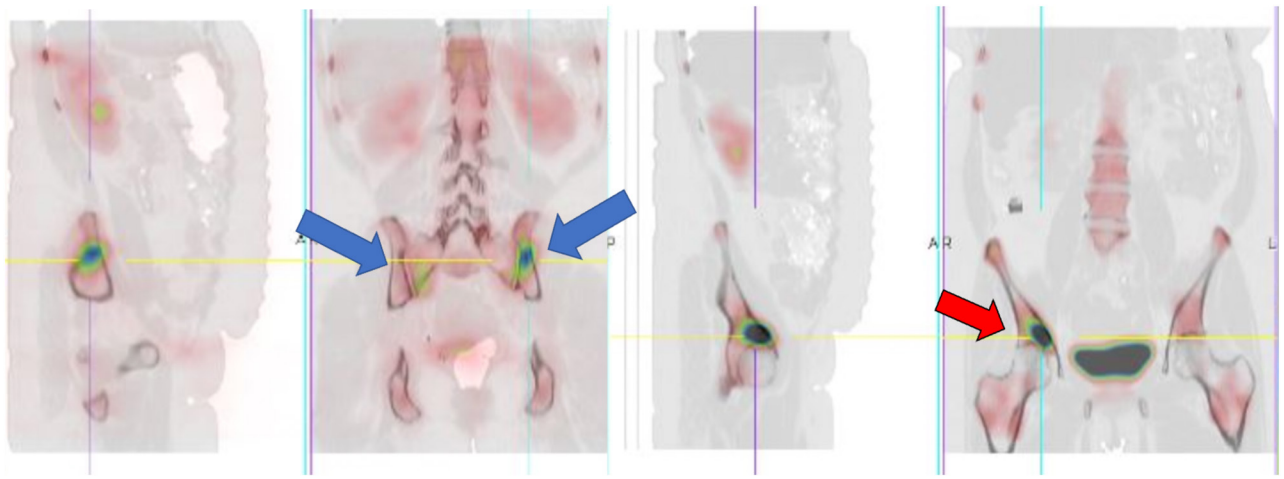

Figure 1
Bone scan with single-photon emission computed tomography (SPECT)/CT. Blue arrows indicate patchy activity around the sacroiliac joints which reflect combination of degeneration and stress reaction. The red arrow shows prominent activity in the right acetabulum suspicious for stress reaction.

Fanconi syndrome. However 24-h urine studies were not consistent with this diagnosis (Table 3).

Further tests included 1,25 vitamin D level which was inappropriately normal (83 pmol/L, RR: 60–208 pmol/L) given the degree of hypophosphataemia. FGF-23 levels were markedly elevated at 174 ng/L (RR: 23.2–95.4 ng/L), which was not consistent with amyloid causing tubular damage. Possible causes of this FGF-23-dependent osteomalacia include hereditary causes such as X-linked hypophosphataemic rickets; however, this was deemed unlikely given the patient's previous normal phosphate level, the onset of symptoms during adulthood and lack of family history. There was also no previous history of iron infusions to suggest an acquired cause.

Suspecting an FGF-23-secreting tumour, the patient underwent whole-body 68Ga Dotatate PET-CT which did not show any focal areas of avidity (Fig. 2). Given the history of chronic sinusitis, MRI of the brain, paranasal sinuses and neck was performed, which did not identify any mesenchymal tumours. The likely diagnosis at this stage was tumour-induced osteomalacia (TIO) that could not be localised on imaging. Given the pressing problem

Table 2 Results of our patient's secondary osteoporosis screen. Note the elevated PTH with low calcium suggestive of secondary hyperparathyroidism. Also note the abnormal kappa lambda ratio with elevated lambda-free light chain.

	Result	Reference range
Calcium, mmol/L	2.10	2.15–2.55
25-hydroxyvitamin D, nmol/L	69	50–140
Magnesium, mmol/L	0.88	0.7–1.10
Phosphate, mmol/L	0.52	0.8–1.50
PTH (Roche), pmol/L	17.7	1.6–6.9
Thyroid-stimulating hormone, mIU/L	3.26	0.4–4.0
eGFR, mL/min/1.73m^2	>90	>59
AST, U/L	23	10–35
ALT, U/L	32	5–30
ALP, U/L	79	30–115
Coeliac serology	Negative	
Kappa-free light chain, mg/L	7.8	3.3–19.4
Lambda-free light chain, mg/L	493	5.7–26.3
K/L ratio	0.02	0.26–1.65
EPG	Moderate reduction in gamma globulin	
IEPG	Monoclonal free lambda light chains overlying beta region	

AST, aspartate transaminase; ALT, alanine transaminase; K/L, kappa/lambda ratio; EPG, serum protein electrophoresis; IEPG, serum immunoelectrophoresis.

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Table 3 Twenty-four-hour urine analysis in our patient did not demonstrate the glycosuria, phosphaturia and amino aciduria expected with Fanconi syndrome.

	Result	Reference range
Volume, L	1.78	
pH	5.0	
Phosphate, mmol/day	18	13–42
Protein, g/day	0.28	<0.14
Glucose, mmol/day	<0.2	0–2.7
Creatinine, mmol/day	5.7	7.1–15.9
Potassium, mmol/day	1.6	2.5–7.5
Calcium, mmol/day	69	25–125
Amino acid	Normal	N/A
Urate, mmol/day	2.1	1.6–4.5

of the cardiac AL amyloidosis with a poor prognosis, the patient wished to pursue medical therapy for her hypophosphataemia.

Treatment

The patient was commenced on calcitriol 0.25 µg twice daily and phosphate supplementation 500 mg twice daily. Serum phosphate levels were monitored serially with blood taken prior to the morning phosphate dose with a 12 h interval to minimise fluctuations in phosphate levels. Phosphate levels increased to 1.11 mmol/L and were maintained in the normal range, whilst the patient underwent treatment of her cardiac AL amyloidosis. The patient reported no further fractures, as well as rapid resolution of her bone pain and proximal lower limb weakness.

Outcome and follow-up

Following 3 months of daratumumab and CyBorD treatment, her serum-free light chains had normalised, indicating an excellent response to haematological therapy. To assess whether treatment of the amyloidosis may have supressed the secretion of FGF-23, serum phosphate was performed 3 days after cessation of calcitriol and phosphate. Her serum phosphate level dropped significantly to 0.59 mmol/L, prompting resumption of supplementation (Fig. 3). This strengthened our suspicion that our patient had an FGF-23-secreting tumour that was separate from her amyloidosis.

The patient had a progress DXA scan 12 months after the previous one, which showed modest improvement in her bone density (Table 4). We plan to continue medical therapy and repeat localisation imaging in 12 months'

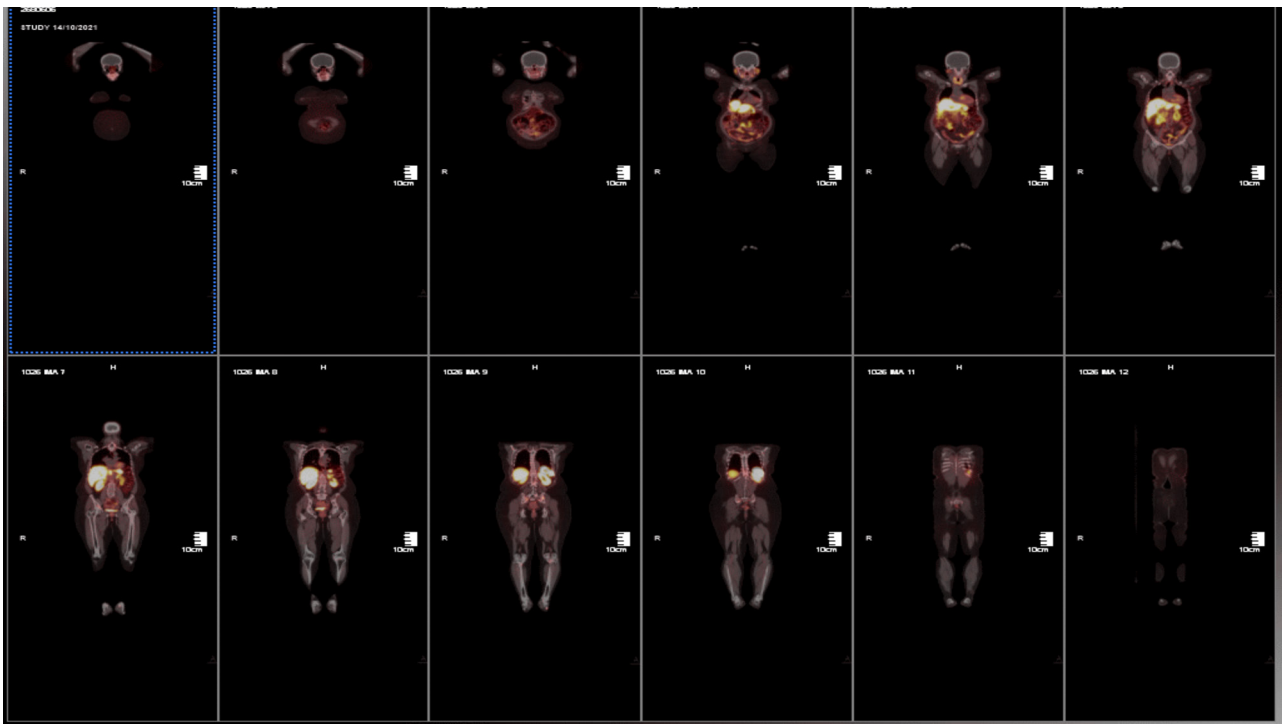

Figure 2
Whole-body Ga68 DOTATATE PET-CT did not find any definite focal regions of increased tracer uptake to indicate an underlying tumour in our patient.

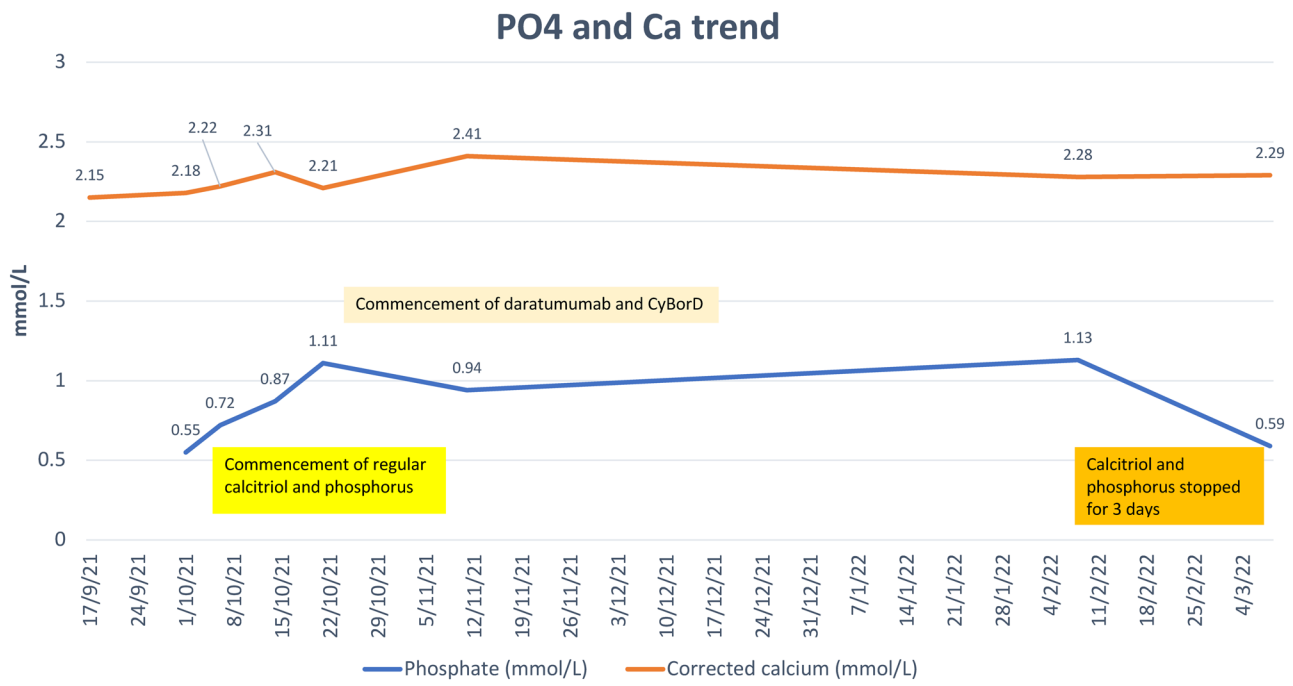

Figure 3
Trend in phosphate and calcium levels over time. Note the fall in phosphate levels to 0.59 mmol/L at the right side of the diagram after a 3-day trial of calcitriol and phosphorus cessation.

time in the hope that the FGF-23-secreting tumour declares itself.

Discussion

TIO is a challenging diagnosis, and our case like many previous highlights how patients cycle through multiple medical specialties before reaching a correct diagnosis. The mean time to diagnosis is 2.9 years and to resection of tumour is 5.3 years (2).

TIO should be suspected in the adult patient presenting with new-onset hypophosphataemia, elevated FGF-23 levels and isolated renal phosphate wasting. Other differential diagnoses for this triad include acquired causes such as parental iron infusions and hereditary causes such as X-linked hypophosphataemic rickets, autosomal dominant hypophosphataemic rickets or autosomal recessive hypophosphataemic rickets (2, 3). These differential diagnoses were deemed unlikely in our patient, given her previous normal phosphate levels, adulthood onset of symptoms, lack of family history and absence of previous iron infusions.

Table 4 DXA scan performed 12 months after previous showing improvement in bone density.

	Bone density	T score (S.D.)	Change from previous
L1–L4			
March 2021	0.86 g/cm²	−2.8	
March 2022	0.89 g/cm²	−2.7	+2.7%
Left femoral neck			
March 2021	0.77 g/cm²	−1.9	
March 2022	0.79 g/cm²	−1.8	+5.9%
Right femoral neck			
March 2021	0.76 g/cm²	−2.0	
March 2022	0.76 g/cm²	−2.0	+0.4%

TIO is a form of paraneoplastic syndrome caused by an FGF-23-secreting tumour. Approximately 1000 cases have been reported worldwide, with 90% of cases being phosphaturic mesenchymal tumour of mixed connective tissue. The peak age of onset is 40–45 years with equal gender distribution. Clinical features include bone pain, muscle weakness, fatigue and multiple stress fractures (3).

To localise the tumour, a combination of structural and functional imaging is required. Common tumour sites include the extremities and craniofacial region. Structural imaging in the form of MRI or CT requires correlation with functional imaging such as whole-body 68Ga-DOTATATE PET/CT, Octreoscan SPECT/CT or FDG-PET/CT (2, 3). A meta-analysis of 14 studies and 346 patients showed 68Ga-DOTATATE PET/CT had the highest sensitivity with a pooled detection rate of

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90%. This is due to TIO often expressing somatostatin receptors (SSTRs), particularly SSTR type 2 (4). In cases where multiple lesions are found on imaging, it is recommended to proceed to systemic FGF-23 venous sampling to identify the likely culprit (5).

Our case is unique from previous published case reports in that alkaline phosphatase level was not elevated and bone scan did not show multifocal lesions of increased activity typically seen in patients with osteomalacia (6). We hypothesise that the denosumab medication given several months earlier had suppressed her bone turnover markers and limited radiotracer uptake on bone scan.

Our case is also unique in that the tumour was not successfully localised on imaging. Had the tumour been identified, prognosis would have been excellent as surgical resection is often curative with rapid resolution of phosphate homeostasis and large gains in bone density (3). The options for those with non-localised tumours or who are poor surgical candidates include medical therapy with calcitriol and phosphate replacement. Recommended dosing is 0.5–3 µg of calcitriol per day and 1–3 g of phosphorus per day. Therapy is often poorly tolerated due to gastrointestinal side effects; however, split dosing may improve tolerance. However, compliance can be difficult due to the frequent dosing regimen. Complications of therapy include secondary hyperparathyroidism, hypercalciuria and nephrocalcinosis, necessitating regular blood and urine monitoring. Treatment goals are for phosphate levels in the low-normal range with avoidance of hypercalciuria (5).

Burosumab is a monoclonal antibody against FGF-23 which was US FDA approved in 2020 for treatment of TIO. In an ongoing phase 2 open-label single-arm trial of 14 patients, burosumab was demonstrated to improve symptoms, physical function, phosphorus homeostasis, fracture healing and osteomalacia on bone biopsy (7). Burosumab was not considered in our patient as she responded well to conventional medical therapy. It is also not TGA approved in Australia for this indication at this stage.

Paraproteinaemias are associated with excess FGF-23 levels. In a 2006 study by Stewart *et al.,* patients with multiple myeloma and monoclonal gammopathy of unknown significance had elevated FGF-23 levels and plasma cells showing cytoplasmic expression of FGF-23. However, there was a weak positive correlation between FGF-23 and phosphate levels, with no patients observed to have hypophosphataemia. It is thought that the FGF-23 produced by the clonal B cells lacks systemic bioactivity or that other factors contributed to maintain serum phosphate (8). Indeed, our patient trialled cessation of calcitriol and phosphate supplementation after several months of amyloidosis treatment and was unable to conserve her phosphate levels. This indicates that our patient's excess FGF-23 is independent of her amyloidosis.

It is possible that our patient may have sustained harm with the denosumab therapy inadvertently given for the presumed osteoporosis diagnosis. Antiresorptive therapy should be avoided in osteomalacia due to risk of radiological and clinical deterioration. Bone biopsies on osteomalacic patients incorrectly given bisphosphonates showed frozen cellular activity and severely impaired bone self-repair precipitating increased fracture risk. Biochemical changes in these patients include reductions in calcium and phosphate levels and increases in PTH level, as demonstrated in our patient's secondary osteoporosis screen (9).

In terms of future directions, our patient will continue with her calcitriol and phosphorus replacement for her imaging negative TIO. We plan to repeat functional and structural imaging in 12 months' time in the hope that the tumour declares herself. We note with great interest that systemic FGF-23 venous sampling may have a role in detecting blind lesions, as first reported by Takeuchi *et al.* (2004) and confirmed in further case reports (10, 11, 12, 13), but this avenue was not pursued due to patient preference for conservative management. Lee *et al.* (2017) describe one patient who had elevated FGF-23 levels in the right profunda femoris vein on systemic venous sampling. The same patient had previous negative Octreoscan SPECT/CT and whole-body MRI scans. Subsequent dedicated MRI of the right leg revealed a mass in the gluteus maximus muscle, leading to surgical cure (11).

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of their clinical details was obtained from the patient.

Author contribution statement
M Lin was responsible for first draft of the manuscript and literature review. K Ganda was the consultant endocrinologist responsible for care of patient and review of and preparation of final draft of manuscript.

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