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Tumour Induced Osteomalacia: Rapid Clinical and Biochemical Control Using Octreotide

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OE and NW designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript managed the analyses of the study. Managed the literature searches Author AAM made the diagnosis and referred the patient to us for management. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To assess the effects of short acting octreotide on the Fibroblast Growth Factor-23 levels and the clinical outcome in a bedridden patient with Tumour Induced Osteomalacia.
Presentation of the Case: A 40-year old female, presented with a 16-year history of progressive weakness and bone pains. Severe hypophosphatemia had been documented throughout and she had been treated intermittently with oral phosphate and various preparation of vitamin D. Hypercalcaemia due to parathyroid hyperplasia was diagnosed 4 years previously. In the last 2 years she had undergone bilateral hip prostheses and removal of 2 hyperplastic parathyroid glands. When seen by us she was bedbound with severe restriction of all joint movements, there was a palpable left buttock mass 4x4 cm. Tumour induced osteomalacia was suspected and confirmed by finding grossly elevated levels of Fibroblast growth factor (FGF-23) 3400 Ru/ml (44-140).The serum calcium 2.5 mmol/L (n 2.1-2.5), phosphate 0.3 mmol/L (n 0.8-1.45).Alkaline phosphatase (ALP) 400 U/L (n 35-104), Parathyroid hormone (PTH) 27 pmol/L (n 1.6-9.3) , and creatinine 70 umol/L (n 45-84). Octreotide scanning revealed focal uptake in the buttock corresponding to the MRI findings. Treatment with octreotide 100 mcg 8 hourly was given for 10

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days before surgery. By day 3 the FGF-23 had fallen to 400 and on the day of surgery was 210 Ru/ml. A benign mesenchymal tumour was completely resected and 8 weeks following surgery the FGF-23 was normal, serum calcium 2.7 mmol/L, serum phosphorus 0.63 mmol/L, ALP 690 U/L, PTH 22 pmol/L . The patient was then able to walk in a Zimmer frame after 2 months. Since then she recovered completely, she is able to walk without assistance for the last 2 years.

Conclusion: This case provides an example of successful use of short acting octreotide in controlling the disease and demonstrated a rapid normalisation of elevated FGF-23 levels achieved during treatment with octreotide. It describes a rare association between tumour induced osteomalacia (TIO) and parathyroid hyperplasia, the value of octreotide scanning in tumour localisation and the potential for using LA octreotide therapy in patients with responsive tumours that cannot be localised or removed for any reason.

Keywords: Tumour induced osteomalacia; hypophosphatemia; octreotide; fibroblast growth factor.

1. INTRODUCTION

Tumour induced osteomalacia (TIO) is a rare disorder first described in 1947 [1]. These tumours are usually benign and mesenchymal in origin although a patient with a colonic carcinoma has recently been reported [2]. They secrete Fibroblast growth factor 23 (FGF-23) which decreases tubular reabsorption of phosphate (TRP) and inhibits 1 alpha hydroxylation of 25(OH) D3. This results in increased urinary phosphate excretion and reduced intestinal phosphate absorption leading to hypophosphataemia [3,4,5,6].

Tumor-induced osteomalacia (also known as oncogenic osteomalacia) [7] is a rare disorder characterized by phosphaturia, hypophosphatemia, and osteomalacia mimicking the clinical phenotype of either X-linked or autosomal dominant hereditary hypophosphatemic rickets. Tumor-induced osteomalacia develops because of tumors that are predominantly of benign mesenchymal origin but that may occasionally be malignant, as was recently reported. Surgical removal of the tumor relieves all symptoms. Hemangiopericytoma is the most dominant histologic entity in tumor-induced osteomalacia. Paraneoplastic secretion by the tumor of an unknown factor or factors — termed “phosphatonins” — causing renal tubular phosphate wasting has been proposed as the pathogenic mechanism.

We describe a young woman who had hypophosphatemic osteomalacia for several years before. An octreotide scan revealed a mesenchymal tumor in her buttock. In addition, subcutaneous administration of octreotide, a synthetic somatostatin analogue, abolished renal tubular phosphate wasting, normalized FGF-23 before subsequent surgical removal of the tumor.

2. CASE REPORT

A 40-year old female, presented with a 16-year history of progressive weakness and bone pains. Severe hypophosphatemia had been documented throughout and she had been treated intermittently with oral phosphate and various preparation of vitamin D. Hypercalcaemia due to parathyroid hyperplasia was diagnosed 4 years ago. In the last 2 years she had undergone bilateral hip prostheses and removal of 2 hyperplastic parathyroid glands. When seen by us she was bedbound with severe restriction of all joint movements, there was a palpable left buttock mass 4x4 cm. Tumour induced osteomalacia was suspected and confirmed by finding grossly elevated levels of Fibroblast growth factor (FGF-23) 3400 Ru/ml (44-140).

Investigations: The serum calcium 2.5 mmol/L (n 2.1-2.5), phosphate 0.3 mmol/L (n 0.8-1.45).Alkaline phosphatase (ALP) 400 U/L (n 35-104),, 1,25(OH)2 vitamin D level 19 pg/ml (n 20 – 80), Vitamin D (25-OH) 46 nmol/l (deficiency < 50) and creatinine 70 umol/L (n 45-84). Fibroblast growth factor (FGF-23) 3400 Ru/ml (44-140). Octreotide scanning revealed focal uptake in the buttock (Fig. 1) corresponding to the MRI findings (Fig. 2). A parathyroid scan revealed positive uptake in the two remaining glands. Bone mineral density revealed severe osteoporosis with a lumbar spine Z-score -4.7.

Treatment with octreotide 100 mcg 8 hourly was given for 10 days before surgery. By day 3 the FGF-23 had fallen to 400 Ru/ml., and one the day of surgery was 210 Ru/ml. The mesenchymal tumour completely resected (Fig. 3) and 8 weeks following surgery the FGF-23 was further reduced to 200 Ru/ml (Fig. 4),

Her serum calcium 2.7 mmol/L, serum phosphorus 0.63 mmol/L, ALP 690 U/L, PTH 22 pmol/L. The histopathology is consistent with benign mesenchymal tumour (Fig. 5).

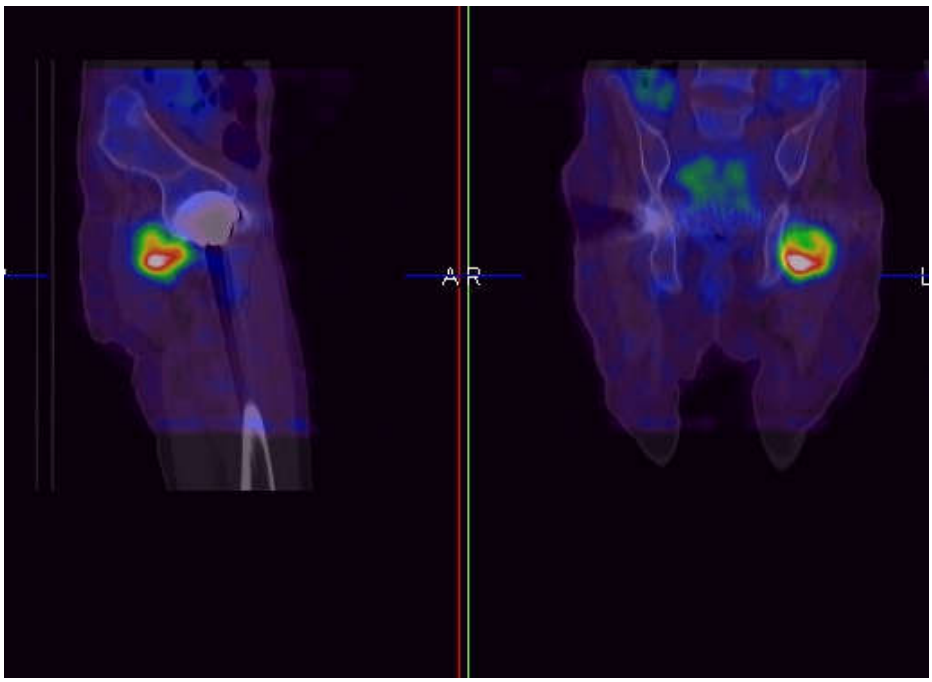

Fig. 1. Octreotide scanning showing a positive focal uptake in the area of pelvis, increased tracer uptake in the left gluteal

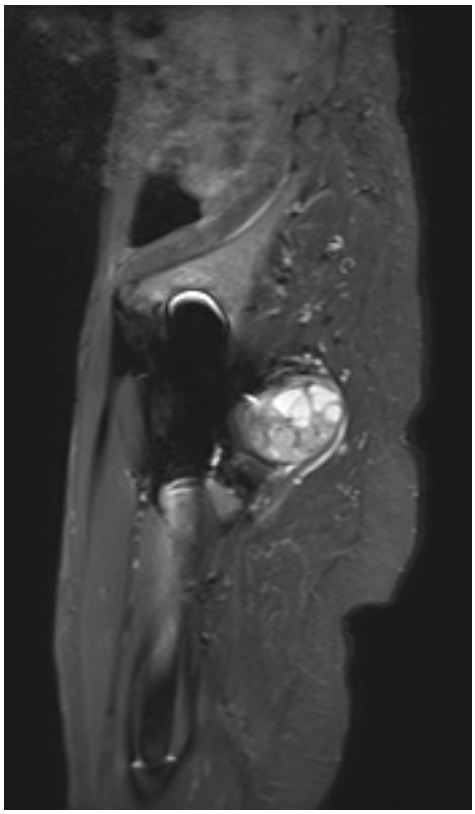

Fig. 2. MRI showing a 4x4 cm left gluteal soft tissue mass

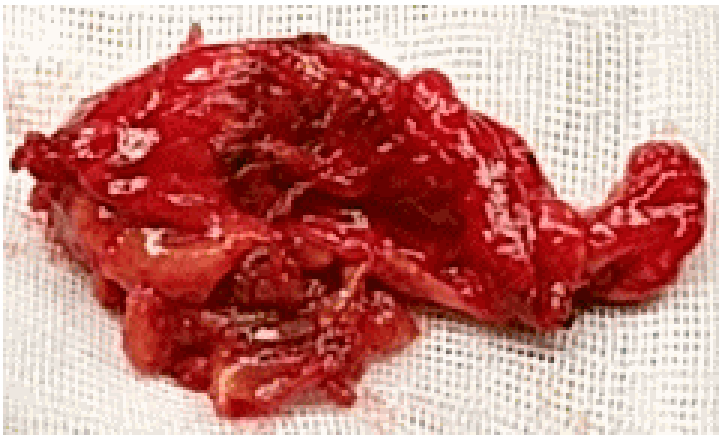

Fig. 3. The mesenchymal tumour completely resected (4x4 cm)

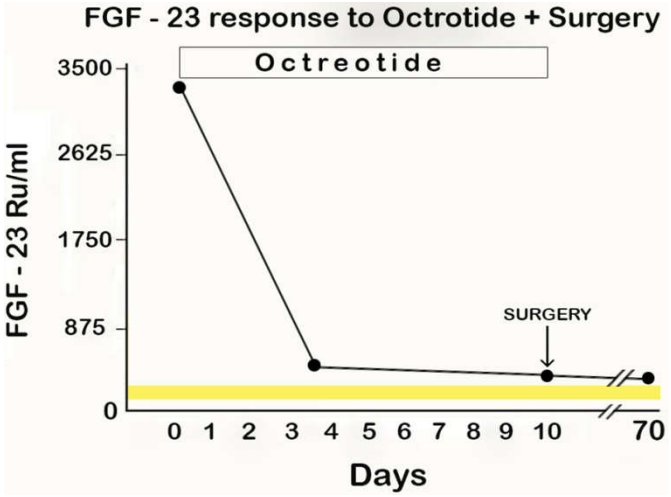

Fig. 4. Showing FGF-23 level and serum phosphate response to octreotide and surgery

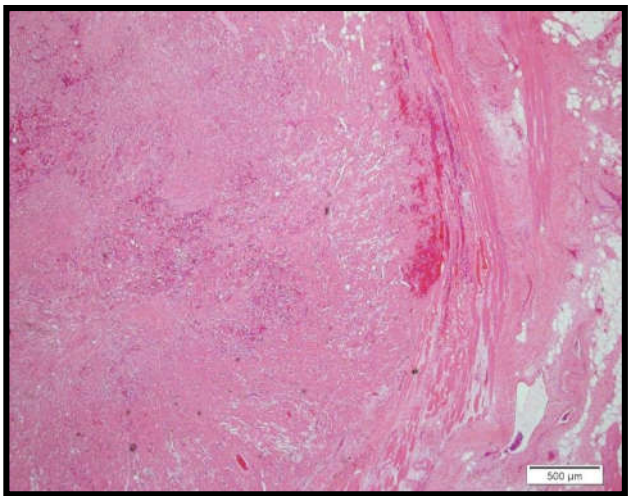

Fig. 5a. The lesion was well circumscribed surrounded by skeletal muscle bundles (asterisk), A (H&E X4)

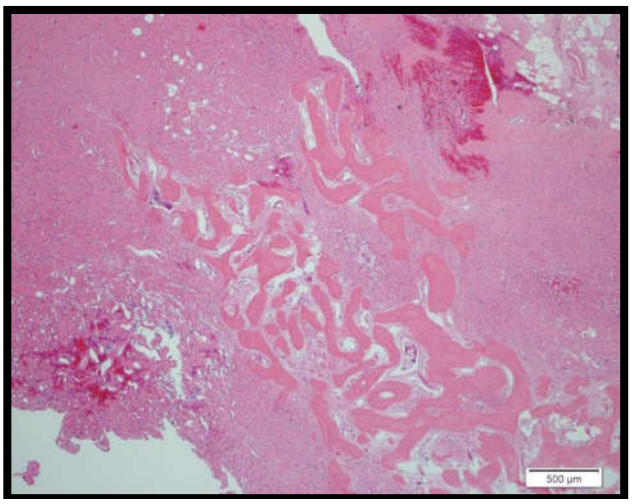

Fig. 5b. There were trabeculae of woven bone in its center, B (H&E, X4) and a rich vascular network, C (H&E, X10)

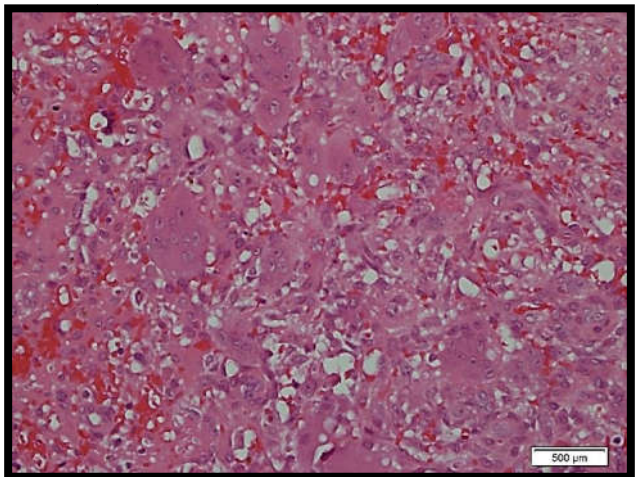

Fig. 5c. The cells were uniform spindle cells, D (H&E, X20) with aggregates of osteoclast giant cells, E (H&E, X 40)

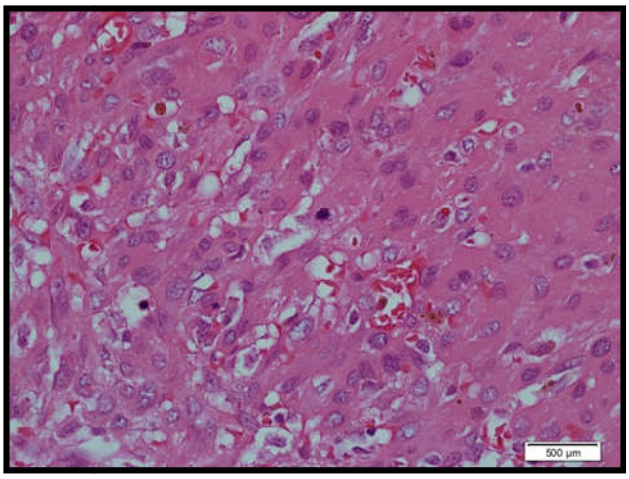

Fig. 5d. In some places, the cells were more epithelioid and a rare mitosis consistent with a benign mesenchymal tumour

Two months' post-surgery most of her symptoms have disappeared, the patient was then able to walk in a Zimmer frame. Since then she recovered completely, she is able to walk without assistance for the last 2 years.

3. DISCUSSION

Although our patient had a typical history of progressive bone pains, muscle weakness and multiple fractures, the diagnosis of the tumour was delayed for 16 years until seen in our institution. As in this case patients with TIO often present with symptoms for many years before they are diagnosed [8].

The diagnosis was confirmed by finding grossly elevated FGF-23 levels and the tumour localized by octreotide scanning. Fortunately most of these tumours express the SS receptor subtype 2 [9,10,11] which provides the molecular basis for the positive octreotide scan and acute response to octreotide therapy with a rapid reduction of FGF-23 levels before surgery. The surgery was successful as 2 months later the FGF-23 level was near normal, However mild hyperparathyroidism persist. This is unsual as most patients TIO's have normal calcium and PTH levels [12]. There are 2 possible explanations for the hyperparathyroidism in this patient; either is was due to parathyroid hyperplasia as a result of long term phosphate therapy which is known to stimulate PTH secretion in man [13] or to the coexistance of primary hyperparathyroidism. The latter is unlikely however as hyperplasia was confirmed histologically and the parathyroid scan revealed increased activity in both remaining parathyroid glands. This aspect will be further investigated when we have achived maximum bone healing following surgery.

The treatment of choice for patients with TIO is surgical removal of the tumour. If surgery is not possible for any reason most will respond to oral phosphate and 1,25 (OH) 2 D3 supplementation. Recently total parathyroidectomy has been advocated following which serum phosphate levels return to normal inspite of persisantly elevated FGF-23 levels [12]; This indicates that FGF-23 requires the presense of PTH for its action on the renal tubule. An alternative approach not previously advocated might be the use of long term octreotide [14]. As seen here normal FGF-23 levels can be achieved short term. We have used LA octreotide successfully for more than 30 years in several different types of neuroendocrine tumours (NETs) without any significant complications.

4. CONCLUSION

This case provides an example of successful use of short acting octreotide in controlling the disease and demonstrated a rapid normalisation of elevated FGF-23 levels achieved during treatment with octreotide.

It describes a rare association between tumour induced osteomalacia (TIO) and parathyroid hyperplasia, the value of octreotide scanning in tumour localisation and the potential for using LA octreotide therapy in patients with responsive tumours that cannot be localised or removed for any reason.

CONSENT

Written informed consent was obtained for publication of the submitted article and accompanying images from the patient and her family.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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