Radiofrequency ablation, a potential cure for Tumour-Induced Osteomalacia; Case reports of short and long-term outcomes

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Abstract

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by FGF23-secreting tumours. Although typically benign, TIO may result in severe pain and disability. Surgical resection has been the traditional management however, due to tumour location, even some small lesions may require major surgery. Radiofrequency ablation (RFA) provides an alternative to surgery and offers the potential for cure of lesions not easily amenable to surgical resection. We describe the short- and long-term outcomes of three patients following RFA. CT-guided RFA has the potential to cure TIO and should be considered appropriate first-line management for suitable lesions.

Introduction

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome of phosphate wasting resulting in demineralisation of bone. TIO is caused by tumoural secretion of fibroblast growth factor 23 (FGF23) [1]. Over-secretion of FGF23 down-regulates phosphate reabsorption in the kidney and gastrointestinal phosphate absorption, leading to hypophosphataemia, muscle pain, weakness and fractures [2].

Phosphaturic Mesenchymal Tumours (PMT), rare tumours arising in bone or soft tissue, are the most common tumour types associated with TIO [3]. Lesions are typically small, solitary and historically, often difficult to locate. Due to their expression of subtype 2 somatostatin receptors, [4] locating tumours has improved in the era of functional imaging.

Removal or destruction of the tumour is required for cure. Major surgery may be required to resect small lesions. Radiofrequency ablation (RFA) offers an alternative to surgery and has been in use for other tumour types for almost twenty years [5]. Reports of RFA to manage TIO are limited and long-term outcomes have not been reported [6]–[8]. Here we describe the short- and long-term outcomes of three patients who underwent RFA to achieve cure of TIO.

Case Report

Case One.

Mrs AG, a 40-year-old Filipino woman, presented with a two-month history of musculoskeletal chest wall pain without evidence of fracture on plain film. She had no history of trauma. A persistently elevated plasma alkaline phosphatase (ALP) was noted. Increased uptake in the right seventh rib, fourth thoracic vertebrae and the tibial shafts bilaterally was seen on a technetium-99m(^{99m}Tc) bone scintiscan. It was thought that she may have sustained injuries she did not recollect and no follow-up was arranged. Symptoms progressed over 12 months and she represented with pain. Repeat whole-body ^{99m}Tc bone scintigraphy demonstrated new areas of increased uptake.

A bone biopsy demonstrated osteomalacia. Plasma phosphate was noted to be low at 0.58 mmol/L (reference range [RR] 0.7-1.5mmol/L) and had been low at symptom onset (Table 1). She had low tubular

reabsorption of phosphate (0.34mmol/L (RR 0.8 -1.35mmol/L)). TIO was suspected. Plasma FGF23 concentration was elevated at 113 RU/mL (RR 3-4RU/mL). Phosphate and calcitriol replacement were commenced.

Mrs AG underwent three MRI scans, two CT scans and an octreotide scintiscan over a six-year period before a 14mm lesion in the anterosuperior left femoral head was identified on ^{68}Ga-DOTATATE PET/CT. In retrospect this lesion, though small and not reported, could be seen on MRI at the time TIO was first suspected.

Mrs AG opted for RFA as an alternative to surgery. CT-guided biopsy was performed at the time (Fig. 1). Histology confirmed PMT with positive immunohistochemical staining for FGF23. By two months all symptoms had resolved and plasma phosphate remained normal without supplementation. Seven years following RFA, Mrs AG remained symptom-free with no biochemical evidence of relapse.

Case Two.

Mrs PJ, a 36-year-old Māori woman, presented with worsening low back pain for one year and bilateral proximal muscle weakness for four months. Spinal MRI demonstrated superior endplate insufficiency fractures of multiple vertebral bodies. With knowledge of the previous case, the reviewing radiologist noted hypophosphataemia (0.24mmol/L) and referred to an endocrinologist. Adjusted plasma calcium was 2.15mmol/L, and ALP 198U/L (Table 1). Phosphate and calcitriol replacement were commenced.

MRI demonstrated a 21mm suspicious lesion in the left acetabulum. ^{68}Ga-DOTATATE PET/CT demonstrated increased uptake in the left acetabulum corresponding to the lesion seen on MRI.

Planned RFA was deferred when Mrs PJ became pregnant. Phosphate and vitamin D supplementation were continued during pregnancy. CT-guided RFA was performed four months post-partum. Biopsy performed at the time of the RFA confirmed PMT, with FGF23 immunohistochemical staining strongly positive.

Plasma phosphate normalised for two months without supplementation, before beginning to fall. Repeat ^{68}Ga-DOTATATE PET/CT showed the original lesion had reduced uptake compared to initial imaging but was still present. RFA was repeated 21 months following the first intervention. Plasma phosphate was normal without supplementation one month following ablation (1.27mmol/L) and at five years (1.19mmol/L).

Case Three.

Mrs AY a 60-year-old Chinese woman, was referred to Endocrinology on the basis of a 12-month history of back and leg pain, and a raised ALP (407 U/L). She had a past history of treated hypertension. ^{99m}Tc bone scintigraphy showed abnormal multifocal uptake in several ribs, thoracic and lumbar vertebrae, left sacroiliac joint, left acetabulum, bilateral tibial plateau and left maxilla. Hypophosphataemia was noted (plasma phosphate 0.57 mmol/L). TIO was suspected.

A whole-body MRI turbo STIR study was performed. A solitary 18x17x38mm lesion in the intertrochanteric region of the left femur was identified. This area demonstrated increased uptake on ^{68}Ga-DOTATATE PET/CT. RFA was performed. Biopsies taken at the time of the procedure did not contain tumour elements.

One month following the procedure her plasma phosphate was elevated at 1.82 mmol/L and phosphate supplementation was stopped. Phosphate remained normal one month later (1.14mmol/L).

One year following RFA plasma phosphate had dropped to 0.61 mmol/L. Her plasma phosphate then temporarily normalised but within six months had fallen again and she had persisting symptoms. A repeat ^{68}Ga-DOTATATE PET/CT demonstrated reduced but persistent uptake in the left proximal femur (Fig. 2). Biopsy and RFA were repeated. Again, no tumour was seen on histology. Seventeen months later, and four years after the first RFA, plasma phosphate was 1.09 mmol/L off supplementation.

Discussion

We describe the short and long-term outcomes of three patients who underwent RFA for TIO. Patient characteristics are summarised in Table 1. RFA offered the chance for cure that would otherwise have required major surgery. Phosphate and calcitriol supplementation is usually not sufficient to alleviate symptoms and bone architecture remains abnormal [9]. Burosumab, an FDA-approved monoclonal antibody that binds FGF23, has an advantage over phosphate and calcitriol supplementation for improved symptom management and normalisation of bone architecture [10]. Burosumab is likely to play an important role for those patients in whom a tumour cannot be identified however, if stopped, deterioration of osteomalacia is likely to occur. In addition, cost and accessibility maybe prohibitive. A curative intervention is desirable when possible.

Surgery has traditionally been the preferred curative approach, however, not all lesions are suitable for surgical resection. The first reported case of RFA to manage TIO was more than ten years ago [6]. Subsequently, two case series have each reported three cases [7], [8]. Two additional case series report RFA in one patient in each series [11], [12]. In five of these, tumours were located in the proximal femur or acetabulum. In addition to RFA, cryoablation has been reported in one case series (n = 3) and three case reports [13]–[16]. Outcomes for patients who have undergone ablative therapy has not been described past two years [8], [13].

RFA has a number of advantages over major surgery including a shorter procedure time, little or no blood loss and a shorter hospital stay [17]. Nonetheless, not every lesion is suitable for RFA, and RFA is technically challenging and operator-dependent. Greater success has been observed when performed by experienced musculoskeletal or interventional radiologists [18]. Complications are rare, but have been reported following RFA to bone lesions of other tumour types including fracture, infection and burns to surrounding structures [19]. Due to the difficulty obtaining adequate coverage of the lesion whilst

minimising damage to adjacent normal bone or joint structures, the consent process is important, and the patient advised that a further procedure maybe required.

In our first patient, six years elapsed from the time TIO was diagnosed before the tumour was localised. Over that time many developments occurred in medical imaging. In particular, somatostatin receptor PET has been a significant advancement for localisation of tumours expressing somatostatin receptors such as PMT [4]. In a meta-analysis of somatostatin receptor PET/CT for detection of lesions causing TIO, the detection rate (sensitivity) for localising the lesion was 92.6% (95% CI 86.3–98.8%) [20].

Despite incomplete response to the first treatment, both cases two and three opted for repeat RFA over major surgery. In case three the fall in phosphate was detected 12 months after RFA. However, there had been a gap of five months between measurements. During that five-month period ALP became elevated suggesting that, had plasma phosphate been tested more frequently, recurrence could have been detected earlier. Based on our limited numbers recurrence after RFA appears to occur early after the procedure. We recommend close monitoring, for the first year, following which monitoring could be less frequent, and if symptoms suggestive of recurrence occur.

In summary, we describe the short-and-long term outcomes of three patients who underwent RFA to successfully manage TIO. Lesions difficult to access surgically should be considered for image-guided ablative therapy such as RFA. Plasma phosphate and clinical monitoring is required following the procedure and patients should be advised that in some cases a repeat procedure may be necessary. RFA is a safe and effective treatment for TIO and could be considered first line management for lesions not easily amenable to surgical resection.

Declarations

Authors have no financial conflict of interest to declare. CP, BO, ME, AD, investigated, diagnosed and followed the outcomes of the patients reported in this manuscript. PS reviewed histopathology of all cases. Imaging was reviewed by, and radiofrequency ablation performed by authors CP and DH. VB collected the patient information for case report form. All authors contributed to writing these case reports. This work was performed as part of clinical care and in accordance with the New Zealand National Health Advisory Committee's Ethical Guidelines for Observational Studies. Informed consent was obtained from all patients for publication.

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Table

Table 1. Patient characteristics, biochemistry at presentation and histology

	Case 1	Case 2	Case 3
Age at diagnosis (years)	40	36	60
Duration of symptoms (months)	14	16	12
Plasma phosphate (2.17-4.65 mg/dl) (0.7-1.5 mmol/L)	1.80 (0.58)	0.74 (0.24)	1.8 (0.57)
Plasma calcium (8.4-10.4 mg/dl) (2.1-2.6 mmol/L)	8.8 (2.2)	8.6 (2.15)	8.8 (2.2)
25-hydroxyvitamin D (50-150 nmol/L)	48	28	
1,25 dihydroxyvitamin D [a] (pmol/L 65-175)	63		
Plasma ALP (40-100 U/L)	123	198	578
Plasma FGF23 [b] (3-45RU/mL)	113		
Plasma FGF23 [c] (10-54ng/L)		410	130
Site of tumor	Left femoral head	Left acetabulum	Intertrochanteric region left femur
Histology	PMT	PMT	No histology
Time to repeat ablation (months)	Not applicable	21	26
Follow-up from second RFA (months)	Not applicable	6	18
Total follow-up time (years)	16	9	5
Plasma Phosphate at last follow-up (2.17-4.65 mg/dl) (0.7-1.5 mmol/L)	4.7 (1.50)	3.7 (1.19)	3.3 (1.09)

[a.] Chemiluminescent immunoassay, Liaison XL, DiaSorin, Saluggia, Italy

[b.] Immunotopics Human FGF-23 (C-terminal) ELISA, CA, USA

[c.] Kainos Laboratories, FGF-23 ELISA, Tokyo, Japan

Abbreviations: ALP – alkaline phosphatase, FGF23 – Fibroblast Growth Factor-23, PMT – Phosphaturic Mesenchymal Tumor, RFA – radiofrequency ablation.

Plasma calcium adjusted for albumin concentration

Figures

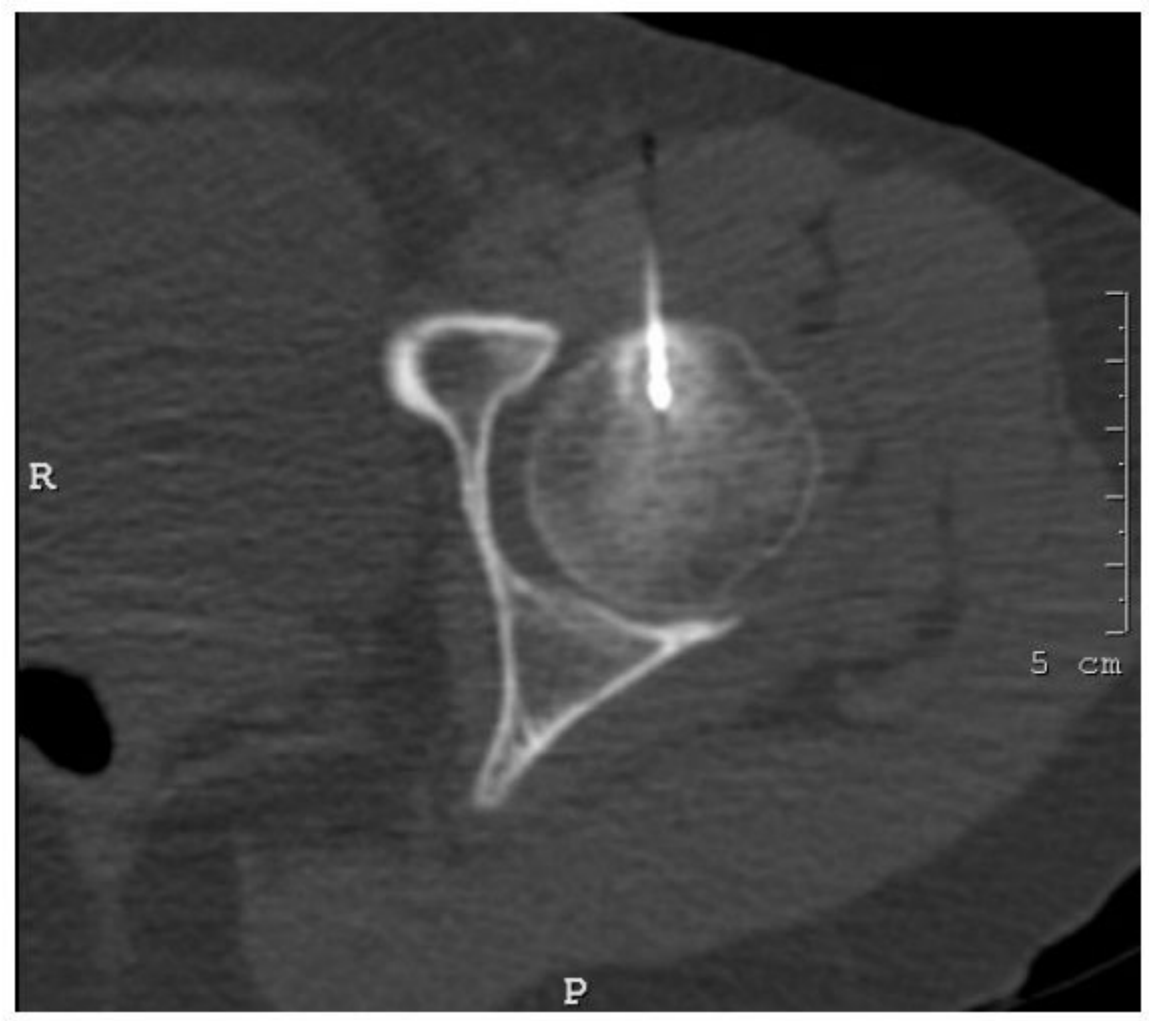

Figure 1

CT guided radiofrequency ablation, performed under general anaesthesia, of the left femoral head lesion of Case 1. Bone access was obtained using a Bonopty ® (by AprioMed AB, Uppsala, Sweden) 14-gauge cannula system. RFA was performed for six minutes in two positions using a 10mm active tip electrode by Covidien Systems, Medtronic, Minneapolis, USA achieving a temperature of 90 degrees centigrade. Biopsy was performed in the same location prior to ablation

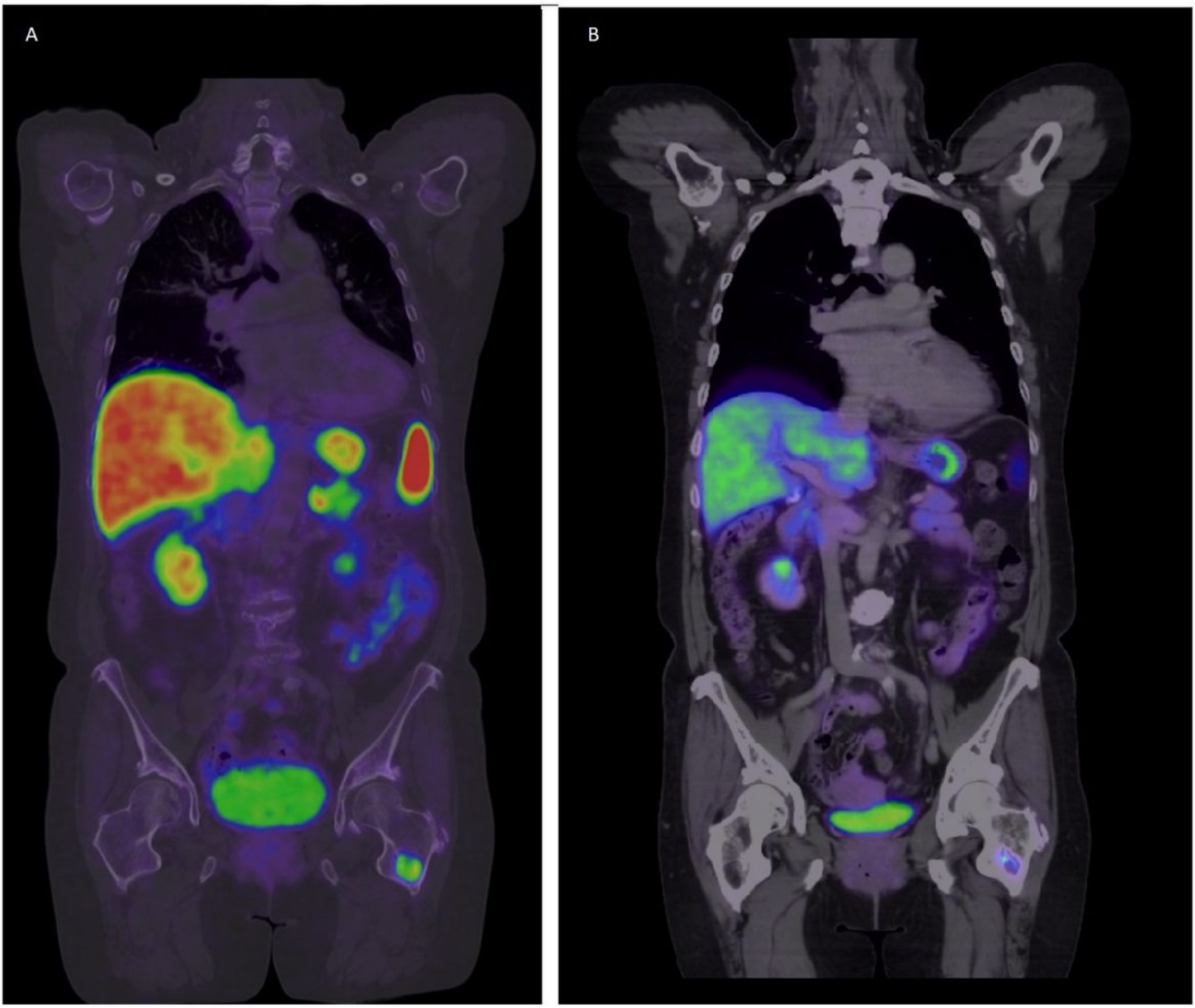

Figure 2

^{68}Ga-DOTATATE scan, from case 3, showing a left proximal femoral lesion with increased radiotracer uptake before radiofrequency ablation (Image A) and following the first radiofrequency ablation demonstrating persistent radiotracer uptake in the persisting lesion (Image B)

Supplementary Files

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