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CASE REPORT

Extended Whole-body Ga-68 DOTATATE PET-CT in evaluating Tumour-Induced Osteomalacia: Case report and review of literature

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Abstract

Tumour-induced osteomalacia is a rare paraneoplastic syndrome that manifests as chronic hypophosphataemia, non-specific bone pain and muscle weakness. It is generally caused by phosphaturic mesenchymal tumour (PMT), which is uncommonly associated with synchronous tumours. However, diagnosis is often delayed for several years due to the rarity, indolent growing nature and non-specific symptoms of the disease, often resulting in an overlook by clinicians during assessments. The patient initially presented with hypophosphataemia and generalised skeletal pain with multiple atraumatic fractures. Blood tests revealed serum calcium levels at the upper limit and extremely low inorganic phosphate levels. Herein, we report a case where two synchronous PMTs from two different sites were detected by 'extended' whole-body Ga-68 DOTATATE PET-CT, leading to remission of the disease after complete surgical removal. Early detection and diagnosis of PMT neoplasm is crucial, as complete surgical resection of this tumour is the only definitive treatment currently known. Upon excision, this curable disease will result in complete resolution of symptoms and blood parameters, leading to remission of the disease which significantly improves the patient's quality of life. PMT often over-expresses somatostatin receptors (SSTR), predominantly subtype 2A, and Ga-68 DOTATATE PET-CT is a selective SSTR imaging that targets this characteristic over-expression in these tumours. The high diagnostic accuracy of Ga-68 DOTATATE PET-CT should be the primary imaging modality for full evaluation of this disease.

Keywords Tumour-induced osteomalacia · Phosphaturic mesenchymal tumour · Ga-68 DOTATATE PET-CT · Hypophosphataemia

Introduction

Tumour-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is an extremely rare paraneoplastic syndrome characterized by severe hypophosphataemia and osteomalacia, resulting in severe generalised skeletal pain [1]. The earliest known case of TIO was first reported by Robert McCance in 1947, where he described a hypophosphataemic tumour in an adolescent girl causing crippling osteomalacia [2]. It is commonly associated with a distinct

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tumour called PMT [3]. Diagnosis of PMT neoplasm is crucial as complete excision of this tumour often results in complete resolution of symptoms and blood parameters. Here, we reported a case where two synchronous PMTs were detected by 'extended' whole-body Ga-68 DOTATATE PET-CT, leading to remission of the disease after complete surgical removal.

Case Report

A 70-year-old female presented with chronic hypophosphatemia and generalised bone pain for 7 years. She had a history of multiple atraumatic fractures, involving ribs, pubic rami and bilateral hip, that led to bilateral hip replacement. Initial Fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography (F-18 FDG PET-CT) performed 5 years ago, was unremarkable. Subsequently, she was then treated with teriparatide and oral phosphate. Despite medical therapy, she continued to develop increasing bone pain and muscle weakness.

On presentation, she was wheelchair-bound due to the pain. Blood tests revealed serum calcium at 2.5 mmol/L (2.2 – 2.6) and inorganic phosphate at 0.3 mmol/L (0.74 – 1.52). In view of this, a re-evaluation with Gallium-68-DOTA-Tyr3-octreotate (Ga-68 DOTATATE) PET-CT was performed to locate PMT. Ga-68 DOTATATE PET-CT demonstrated intense uptake at a soft tissue nodule at the right pelvic cavity (Fig. 1, b-d). Furthermore, by extending the imaging view to knee, an unexpected bone lesion at the medial condyle of the right femur was detected (Fig. 1, e–g). Retrospective review of previous F-18 FDG PET-CT showed the faint uptake at the right pelvic nodule, which was smaller at that time of examination (Fig. 2, b-d).

Based on the 'extended' whole-body 68-Ga DOTATATE PET-CT findings, both soft tissue and bone lesions were resected. Histopathological examination of both resected samples showed stellate-to-spindle-shaped cells dispersed in myxochondroid and chondroid matrix, with irregular calcification and large prominent vessels in the stroma, which were typical features of PMT.

One month after surgery, her serum phosphate levels returned to normal 1.2 mmol/L. The symptoms of bone pain and muscle weakness gradually improved and resolved completely at 3-months follow-up.

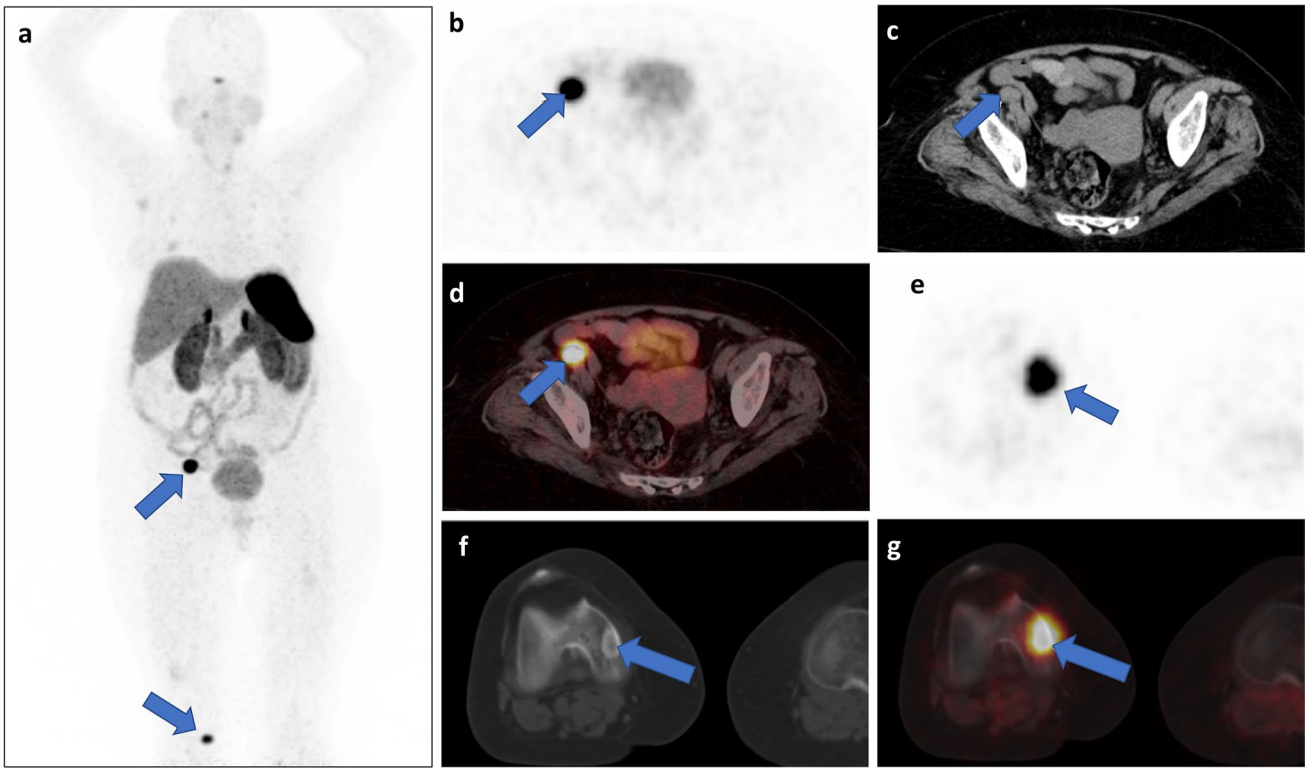

Fig. 1 Extended whole-body Ga-68 DOTATATE PET-CT demonstrating two occult synchronous PMTs (blue arrows). Maximum intensity projections (MIP) images (**a**, **b**, **e**), followed by corresponding non-contrast-enhanced fused PET/CT images in axial slices in soft tissue and bone windows (**c**, **d**, **f**, **g**) showing both PMTs at the soft tissue nodule in the right pelvic cavity (**b**, **c**, **d**), and a bone lesion on the medial condyle of the right femur (**e**, **f**, **g**)

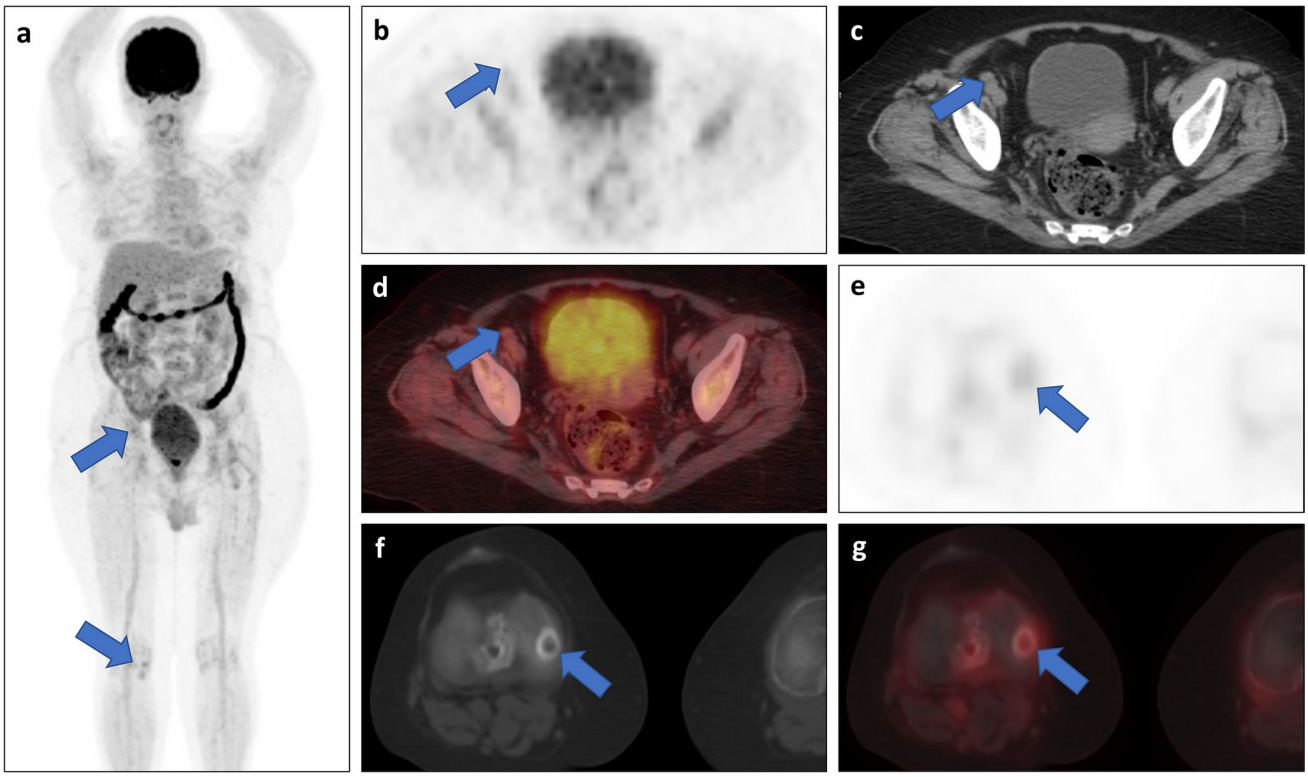

Fig. 2 Whole body F-18 FDG PET-CT demonstrating insignificant F-18 FDG uptake when correlated with exact locations on Ga-68 DOTATATE PET-CT images (see Fig. 1). MIP images (**a**, **b**, **e**), followed by corresponding non-contrast-enhanced fused PET/CT images in axial slices as in Fig. 1 (**c**, **d**, **f**, **g**) showing a faint uptake in both the right pelvic nodule (**b**, **c**, **d**), and the right femoral condyle lesion (**e**, **f**, **g**)

Discussion

This case demonstrates the typical chronological event of TIO, where the diagnosis and tumour localization pose a challenge to clinicians and radiologists.

TIO is a rare paraneoplastic disorder caused by distinct tumour entity, PMT, that overproduces fibroblast growth factor 23 (FGF23) [4, 5]. Due to the disease rarity, it is usually missed by an initial assessment. Furthermore, the epidemiology is not known. It is generally observed that PMTs are more frequently diagnosed in middle-aged adults, regardless of gender [6]. A nationwide survey in Japan estimated that the annual incidence of FGF23 related hypophosphataemic disease was 177 per year [7].

PMT is an indolent tumour that can be found in any location in the bone or soft tissue, more commonly at extremities, head and neck regions [8, 9]. PMT is a variant of mixed connective tissue, characterized by high vasculatures with a proliferation of spindle-shaped to stellate-shaped cells. These cells produce 'smudgy' matrix, which resembles primitive cartilage or chondroid [10, 11]. Over-secretion of FGF23 by PMT impairs phosphate reabsorption, leading to renal wasting, hypophosphatemia and low levels of vitamin D [12], which eventually results in osteomalacia [10, 11, 13].

As shown in case presentations, the symptoms reported by patients with TIO varies. Nonetheless, symptoms can be caused by either the tumour itself or the consequence of chronic hypophosphataemia. As PMT is a small and slow-growing tumour, symptoms that relate to the tumour itself are unusual. Bone pain is a common symptom if the tumour is located within the bone.

Phosphate plays an important role in bone modelling and mineralisation, cell signaling for protein, carbohydrate metabolism and energy phosphorylation. Chronic hypophosphataemia frequently results in progressive musculoskeletal pain, muscle weakness and disability with multiple fragility fractures [14]. These symptoms are non-specific and may mimic other diseases, such as hyperparathyroidism, myeloma, mixed connective tissue disease or Paget's disease [4, 15].

When TIO is suspected, serum inorganic phosphate should be tested to establish the diagnosis of hypophosphatasemia. Percentage of tubular reabsorption of phosphate (% TRP) should be performed to demonstrate decrease reabsorption and increase excretion of phosphate,

Table 1 Detection rate of phosphaturic mesenchymal tumour by Ga-68 DOTATATE PET-CT

Authors	Study Design	Number of patients	Lesions detected	Detection Rate
Jadhav et al. (2014) [26]	Retrospective	9	7	7/7 (100%)
Zhang et al. (2015) [29]	Retrospective	54	32	32/32 (100%)
El-Maouche et al. (2016) [24]	Prospective	11	6	6/6 (100%)
Singh et al. (2017) [20]	Retrospective	17	9	9/17 (52.9%)
Zhang et al. (2018) [30]	Retrospective	37	37	37/37 (100%)
Ding et al. (2018) [23]	Retrospective	54	53	53/54 (98.1%)
Paquet et al. (2018) [28]	Retrospective	15	8	8/11 (72.7%)
John et al. (2019) [27]	Retrospective	27	13	13/16 (81.3%)

which is the biochemical hallmark of TIO [16]. Other methods such as measuring maximum rate of tubular phosphate reabsorption (TmP) or TmP per unit of glomerular filtration rate (TmP/ GFR), can be used to measure renal phosphate transport more accurately but are more cumbersome to perform and may not be readily available [5]. Due to the speed and ease of testing, direct measurement of parathyroid hormone (PTH) levels has widely replaced this, but TmP/GFR tests may still be of use in the assessment of renal phosphate excretion levels in hypophosphataemia-related pathological diseases [17], as described in this study. As serum levels of FGF23 are commonly elevated in these patients, measurement of FGF23 thereby plays a key role in diagnosis of TIO, but it is costly and not widely available [18].

Once the diagnosis of TIO is established, locating PMT is crucial as surgical excision of the tumour is the only definitive curative treatment. In view of the small and indolent tumour, medical history and physical examination seldom reveal any 'lump 'or 'bump'. Additionally, approximately 2% of patients may have a multifocal disease at initial presentation [3].

Therefore, imaging plays an important role to locate the tumour(s). As morphological features of PMT often mimic other more common bone or soft tissue neoplasms, such as fibrous dysplasia or giant cell tumour, conventional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI), are generally inconclusive [19]. Furthermore, synchronous small PMTs, especially occurring at distal extremities, may be missed by CT or MRI [3, 20].

Increasing evidence in literature as shown in Table 1 suggests the recommendation of molecular imaging as the initial imaging tool in the detection and localisation of PMT. PMT is a highly vascularized tumour and often over-expresses somatostatin receptor (SSTR), predominantly subtype 2A [21, 22]. Ga-68 DOTATATE PET-CT, a selective SSTR imaging, has been established as a preferred primary imaging modality. Ga-68 DOTATATE PET-CT has not only shown high sensitivity and specificity in localizing PMT, the whole-body acquisition of PET-CT enables it to identify synchronous lesions, which is shown in this case scenario. Table 1 demonstrates high detection rate of Ga-68 DOTATATE PET-CT in locating PMT [4, 19, 20, 23–30]. Recent meta-analysis by Meyer et al. [31] has shown pooled detection rates of PMT using Ga-68 DOTATATE to be 92.6% (95% CI: 86.3–98.8%). In this meta-analysis, the authors have raised concerns of limited data for analysis, which is justified by the rarity of the disease [31], thus demonstrating the need for this somatostatin receptor-based functional imaging for patients presenting with such symptoms. When performing whole-body Ga-68 DOTATATE PET-CT, it is crucial to 'extend' imaging to include distal extremities to prevent missing distal lesions [32].

Apart from Ga-68 DOTATATE PET-CT, F-18 FDG PET-CT can be used as an alternative imaging tool despite having lower sensitivity compared to the former radioisotope [24, 26, 33]. In this case, we found that Ga-68 DOTATATE PET-CT performed better than F-18 FDG PET-CT in localizing PMT tumours. Furthermore, F-18 FDG PET-CT lacks specificity in the differentiation between types of tumour and other unrelated conditions such as other solid tumours, enlarged lymph nodes, healing fractures or inflammation, especially if the patient coincidentally presents with two primary neoplasms [34].

As presented in this case, once all the tumours have been located, complete excision of tumours will lead to the reversal of biochemical markers, recovery of clinical symptoms and improvement in quality of life. However, interval biochemical follow-up is necessary because the disease may recur, particularly in incomplete surgical removal [35]. Although rare, the possibility of nodal metastasis recurrence is < 10%, with the percentage increasing with nodal or pulmonary metastases at the baseline scan; thus, local radiotherapy should be considered an adjuvant option [1].

Clinicians need to consider the possibility of TIO when dealing with patients presenting with non-specific symptoms such as chronic bone pain and muscle weakness, along with severe hypophosphatasemia. Synchronous PMT tumours should be radiologically screened to identify all tumours

for complete excision. This report reveals the usefulness of Ga-68 DOTATATE PET-CT in the case of TIO with two synchronous PMTs. Despite limited data due to rarity of disease, Ga-68 DOTATATE PET-CT has demonstrated high diagnostic accuracy in detecting and mapping of PMT. Furthermore, this report highlights the benefits of 'extendable' PET-CT, enabling the detection of two lesions simultaneously (soft tissue and bone), resulting in curative surgical treatment. Hence, this 'extended' whole-body Ga-68 DOTATATE PET-CT should be recommended as the primary imaging modality for full evaluation of TIO.

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Authors' Contribution **Teik Hin Tan:** Conceptualization and design; funding acquisition; analysis and interpretation of data; writing – review and revision; final approval of version for publication.

Ew-Jun Chen: Investigation; data acquisition and analysis; data curation; writing – original draft, review and editing.

Ming Tsuey Chew: Funding acquisition; investigation; writing – article draft, review and editing; final approval of version for publication.

Ping Ching Chye: Acquisition and interpretation of data; review of writing.

Ming Wong: Acquisition, interpretation and analysis of data; review of writing; final approval.

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Declarations

Conflict of Interest Teik Hin Tan, Ew-Jun Chen, Ming Tsuey Chew, Ping Ching Chye and Ming Wong declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration as revised in 2013 and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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