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Phosphaturic mesenchymal tumor demonstrated by ^{68}Ga-DOTATATE PET/CT in a patient: a case report

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Abstract

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome caused by abnormally high levels of fibroblast growth factor 23 (FGF-23), most commonly produced and secreted by small phosphaturic mesenchymal tumors (PMT). These tumors can show various anatomic locations throughout soft tissue and bone. The presence of the tumor itself rarely causes symptoms. Nonspecific symptoms such as muscle weakness and musculoskeletal pain are related to the developing hypophosphatemia and osteomalacia as a secondary effect of the increased circulating levels of FGF-23. Therefore, as the initial presentation can mimic a wide range of metabolic or inflammatory diseases, proper diagnosis is often delayed. Localization of the tumor is crucial, as its complete surgical resection is the only curative treatment. Whole-body functional imaging targeting the overexpression of somatostatin receptors (SSTR) on the surface of the PMT cells, is a highly specific and sensitive imaging method to detect the primary tumor site. Here, we discuss a case of TIO in a patient initially presenting with symptoms of inflammatory spondyloarthritis. SSTR positron emission imaging using 68Ga-DOTATATE was central in diagnosing and localizing the primary tumor.

Keywords: Tumor-induced osteomalacia, Somatostatin receptor, ^{68}Ga-DOTATATE, Positron emission tomography, Standardized uptake value

Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome characterized by abnormally high serum levels of fibroblast growth factor 23 (FGF-23). Most commonly, small phosphaturic mesenchymal tumors (PMTs) can often cause overproduction of FGF-23. No anatomical predilection for these tumors exists, as they can be found anywhere in the body: in soft tissue or bone (Crouzet et al. 1995). Furthermore, the symptomatology is nonspecific, as the main symptoms are related to the secondary effects that FGF-23 has on phosphate metabolism rather than the tumor itself. Namely, increased secretion of FGF-23 results in decreased renal tubular reabsorption of phosphorus (TRP), lowering the circulating phosphate concentration, chronically leading to osteomalacia (Erben 2018). This particular onset of symptoms, combined with the fact

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that PMTs are often small and slow-growing, renders tumor localization quite challenging, delaying, as a result, proper diagnosis for years. Even where there is high suspicion for diagnosis (mainly based on increased serum level of FGF-23), anatomic localization of the occult tumor lesion is crucial since its surgical removal is the only definitive treatment of TIO (Minisola et al. 2017). Whole-body functional imaging is the first recommended step (Minisola et al. 2017). 18F- fluorodeoxyglucose (18F-FDG) positron emission tomography with computed tomography (PET/CT) has proven to have a lower sensitivity for localizing PMTs than expected (Yu et al. 2021).

Nevertheless, it is also nonspecific and identifies areas of metabolic activity unrelated to the tumor (Chong et al. 2011). The most sensitive and specific functional imaging studies exploit that PMTs express somatostatin receptors (SSTR), mainly SSTR subtype 2A (Houang et al. 2013). Planar scintigraphy or single photon emission computed tomography (SPECT) whole-body images using the somatostatin analog pentetreotide labeled with 111In, can identify the presence of SSTR on the surface of tumor cells (Cuccurullo et al. 2017). However, 111In-pentetreotide imaging is time-consuming and needs more sensitivity due to the gamma camera's lower image resolution compared to PET.

Afterward, somatostatin analogs labeled with the positron-emitting isotope 68Ga (such as 68Ga-DOTATATE or 68Ga-DOTATOC) were found to be superior to both 111In—pentetreotide SPECT and 18F-FDG PET/CT in locating the tumor associated with TIO (El-Maouche et al. 2016).

Here, we present a case of TIO with a nonspecific initial presentation, where 68Ga-DOTATATE PET/CT detected an unusually high tumor expression of SSTR, crucial in the diagnosis as well as treatment management, leading to complete recovery and disappearance of all symptoms.

Case presentation

The Rheumatology department received a 43-year-old man who presented with a long history of lower back pain associated with morning stiffness. Previous neurological and orthopedic assessments were inconclusive. The medical history and clinical examination were compatible with the inflammatory disease – spondyloarthritis (SpA), involving the sacroiliac joints. However, the routine X-ray evaluation showed multiple vertebral fractures, and the subsequent magnetic resonance (MR) imaging of the sacroiliac joints revealed non-displaced bilateral fractures of the sacrum (Fig. 1). Further imaging included bone scintigraphy, confirming multiple bone fractures across the spine, sacrum as well as in both fibulae. Therefore, we established a differential diagnosis between metastatic or metabolic bone disease. Unfortunately, the subsequent whole-body 18F-FDG PET/CT scan failed to explain the fractures' origin (Fig. 2A). Laboratory tests included markedly elevated serum alkaline phosphatase 605 U/L (reference value (RV) 53–128) and serum phosphorus below the reference value of 0.4 mmol/L. Serum calcium (RV 2.12–2.62) and parathyroid hormone levels (RV < 37) were within the reference range.

A 24 h urine analysis showed marked phosphorus excretion, with percentage of tubular reabsorption of phosphate (%TRP) of 45% (RV 85–95%). Finally, elevated serum levels of FGF-23 of 279.8 pg/ml (RV 23.2–95.3) raised suspicion of osteomalacia induced by a mesenchymal tumor and a whole body ^{68Ga}-DOTATATE PET/CT scan was performed (Fig. 2B, C) using a General Electric GE Discovery 690 PET/CT scanner.

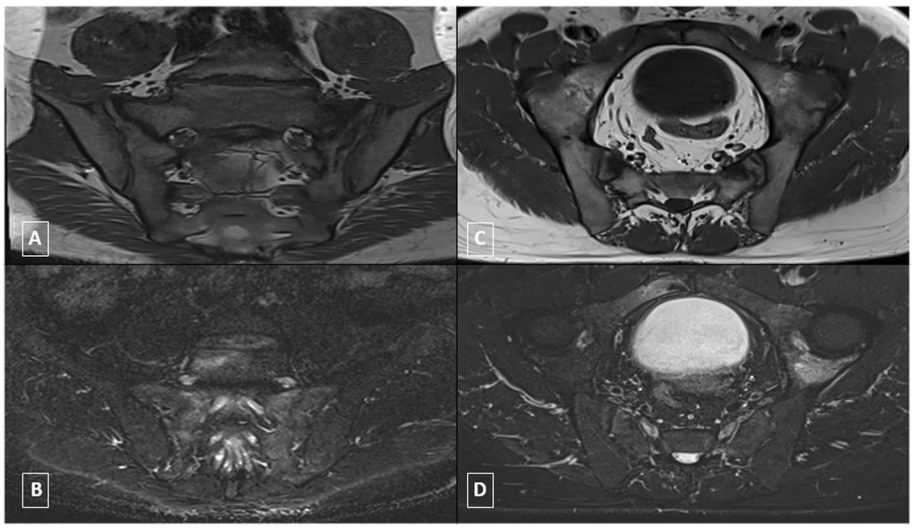

Fig. 1 MR of the sacroiliac joints revealing axial images of fractures at the sacrum in T1 (**A**) and T2 (**B**) and fractures at the right pubic branch and the left acetabulum in T1 (**C**) and T2 (**D**)

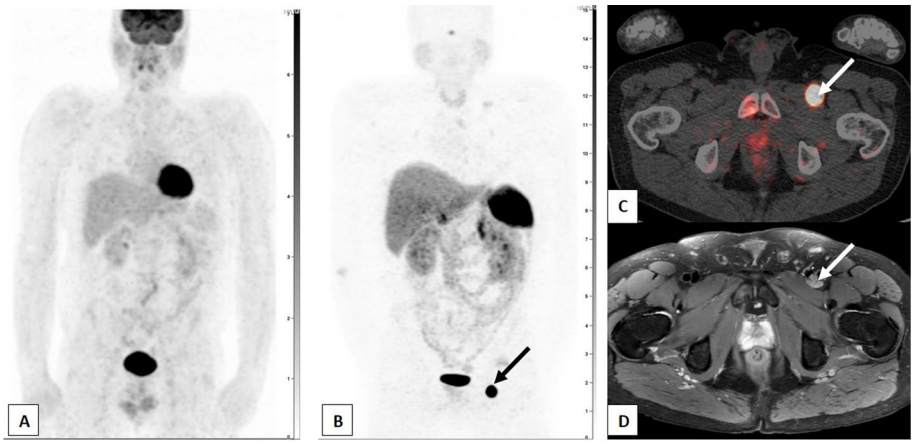

Fig. 2 Whole-body maximum intensity projection (MIP) image of an 18F-FDG PET/CT scan showing the physiological distribution of the radiotracer with no signs of abnormal hypermetabolic activity (**A**), followed by 68Ga-DOTATATE PET/CT scan revealing intense radiotracer uptake (high somatostatin receptor overexpression) in a soft tissue left inguinal nodule (arrows) as seen on whole-body MIP (**B**) and axial fusion (**C**) images. It later confirmed as a nodule with high signal intensity on T2 weighted fat saturated magnetic resonance images (**D**, arrow), consistent with a small phosphaturic mesenchymal tumor in a patient with tumor-induced osteomalacia

A soft tissue inguinal nodule showing unusually intense SSTR overexpression with a maximum standardized uptake value (SUVmax) of 130.0 was detected. After MR imaging identified a small tumor ($22 \times 16 \times 25$ mm) situated just behind and adjacent to the left femoral vein at the inguinal level (Fig. 2D), surgical resection was performed, and the histopathology report confirmed the diagnosis of PMT: spindle cell associated with osteoclasts in a non-calcified hemorrhagic mass. Serum FGF-23 level decreased to the normal range as soon as the following day. Shortly after, the serum phosphorus level normalized, and the phosphate supplement was discontinued. The bone fractures had already consolidated at a six-month follow-up, and the patient was free of symptoms.

Biochemistry analysis remained normal. 68Ga-DOTATATE PET/CT detected no signs of residual disease examination performed six months after the surgical treatment (Fig. 3). The last clinical follow-up reveals no symptoms nor new fractures.

Discussion

The clinical presentation of TIO could be more specific and, therefore, challenging. Patients mostly complain of progressive musculoskeletal pain and muscle weakness, fatigue, or even bone fractures. Occasionally, it can mimic an inflammatory back pain related to SpA, as it was initially suspected in our patient (in combination with age at symptoms' onset of less than 45 years and initial response to NSAIDs as diagnostic criteria for axial SpA). TIO should be suspected when these symptoms accompany hypophosphatemia, in which case the presence of renal phosphate wasting should be investigated. The evaluation of renal TRP is crucial for the diagnosis of TIO. %TRP is calculated from the phosphate and creatinine levels in blood and urine, and its normal range is between 85 and 95%; values are decreased in patients with TIO (Florenzano et al. 2021). Measuring blood FGF-23 levels will further narrow the diagnosis, as they are elevated or inappropriately normal in hypophosphatemia in TIO (Florenzano et al. 2021). Finally, localizing the PMT is paramount, as its surgical removal is the only established and definitive treatment of TIO. A systematic approach to tumor localization is recommended, with functional imaging as an initial step, followed by anatomical imaging (Minisola et al. 2017). 18F-FDG PET/CT has been used to localize PMTs in various reports. However, the slow-growing nature of these

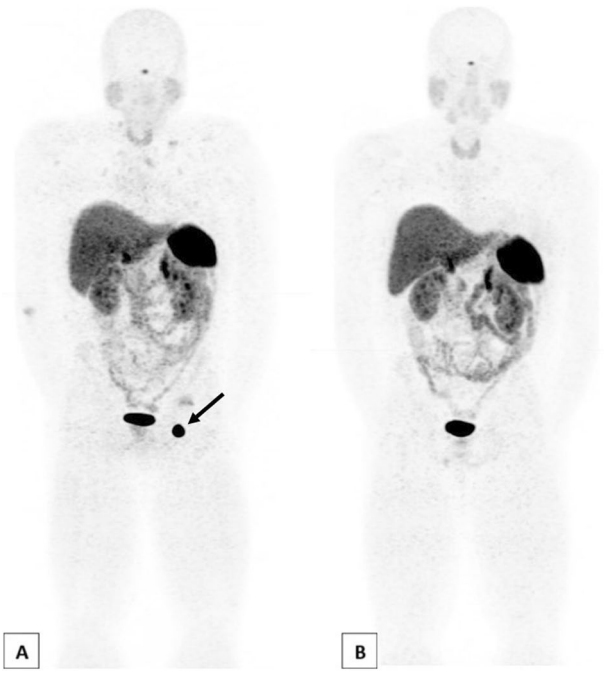

Fig. 3 Whole-body maximum intensity projection (MIP) image of an 68Ga-DOTATATE PET/CT scan revealing intense radiotracer uptake (high somatostatin receptor overexpression) in a soft tissue left inguinal nodule (arrow) prior to surgery (**A**), followed by a negative 6 months follow-up 68Ga-DOTATATE PET/CT scan after surgery (**B**)

tumors and, thus, lack of hypermetabolic activity could make them undetectable by this type of imaging (Jadhav et al. 2014). A whole body 18F-FDG PET/CT scan was performed very early in the diagnostic management of our patient; however, it could not help in detecting the primary tumor. Many reports highlight the value of SSTR PET/CT imaging early in the diagnostic workup. Clifton-Bligh et al. suggests that in a proper clinical setting of TIO, an intense focal 68Ga-DOTATATE PET/CT abnormality should be regarded as virtually diagnostic (Clifton-Bligh et al. 2013). As PMTs can be localized anywhere in the body, whole-body imaging, including the lower limbs, is essential (Woff et al. 2010). A key characteristic of PET over SPECT imaging, aside from the higher resolution and image quality, is the ability to quantify the SSTR expression level using SUV. To our knowledge, a very high SUVmax of 130.0, as observed in our patient, has not yet been described (Shi et al. 2024). This high radiotracer uptake (resulting probably from a very high density of SSTR expression on the tumor cells) might support Peptide Receptor Radionuclide Therapy (PRRT) in metastatic or unresectable tumors. A recent study, however, did not show any benefit in symptom control or tumor size reduction after four cycles of 177Lu-DOTATOC in the treatment management of a PMT localized in the sacrum (Häfliger et al. 2020). They reported an initial 68Ga-DOTATATE uptake of SUVmax 26.5, which did not change after treatment (post-treatment SUVmax 26.3). A semi-quantitative analysis of SSTR imaging using 68Ga-DOTATOC PET/CT in the diagnostic setting of TIO in 9 patients found no significant correlation between lesion SUVmax (mean 9.7, range 1.8–35) and any of the investigated biological parameters (including phosphatemia, calcemia, and FGF-23 serum levels) (Paquet et al. 2018). Further studies are needed to properly assess the value of these semi-quantitative parameters derived from SSTR PET/CT in the clinical management of patients with TIO.

Normalization of the biochemical abnormalities and patient recovery are expected following complete tumor resection. It is essential to exclude any areas of residual disease because TIO can persist even if small parts of tumor tissue remain, causing relapses to occur (Zuo et al. 2017). Lee et al. demonstrated the additional value of follow-up 68Ga-DOTATOC PET/CT to detect residual tumors in a patient where the hypophosphatemia persisted even after surgery (Lee et al. 2021). In our case, rapid post-surgical decrease of serum FGF-23 levels and complete symptomatic recovery within six months, coupled with no residual lesions detected on the follow-up 68Ga-DOTATATE PET/CT, was suggestive of complete tumor removal and disease control.

Lesion detection with 68Ga-DOTATATE PET/CT relies heavily on robust SSTR expression. Thus, integrating multiple imaging modalities ensures the best possible diagnostic accuracy and thorough assessment.

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Author contributions
Younes Abadi: nuclear physician responsible for data gathering and case report writing. Magdalena Mileva: nuclear physician that participated and supervised all the data gathering and case report writing. Marc-André Léger: nuclear physician that participated and supervised all the data gathering and case report writing. Paschalis Sidiras: rheumatologist that treated the patient in Erasme Hospital. Carlos Artigas: reviewed the manuscript. Expert opinion. Patrick Flamen: reviewed the manuscript. Expert opinion. Ioannis Karfis: reported both 68Ga-DOTATATE PET/CT scans. Reviewed the manuscript. Expert opinion.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Given the nature of the retrospective study involving a single anonymized case, need for ethics approval was waived. Consent was obtained to acquire patients outside records.

Consent for publication
The patient provided informed consent for publication in accordance to the Declaration of Helsinki.

Competing interests
All the authors declare that they have no competing interest.

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