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Tumor-induced osteomalacia: nasal cavity phosphaturic mesenchymal tumor a case report and radiologic review

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Abstract

Background and aim: Phosphaturic mesenchymal tumor is a rare neoplasm composed of bone and soft tissue that is the most common cause of tumor-induced osteomalacia. Due to its nonspecific clinical presentation, rare occurrence and variable features on imaging, diagnosis is often delayed. Our aim is to review this rare disease and it's diagnostic imaging.
Case presentation: We present a case of a 44-year-old male who presented with osteomalacia-related symptoms and was found to have a nasal cavity mass expressing somatostatin receptors.
Conclusion: Functioning imaging plays a key role in localization of this rare entity with conventional imaging such as computed tomography and magnetic resonance imaging useful in pre-surgery planning.

Keywords: phosphaturic mesenchymal tumor, tumor induced osteomalacia, octreoscan, bone scan.

Abbreviations

99mTc – Technetium-99m;
CT – Computed tomography;
FGF23 – Fibroblast growth factor 23;
MDP – Methyl diphosphonate;
MRI – Magnetic resonance imaging;
NSAIDs – Non-steroidal anti-inflammatory drugs;
PET – Positron emission tomography;
PMT – Phosphaturic mesenchymal tumor;
SPECT – Single-photon emission computed tomography;
SSTR – Somatostatin receptor;
SUV – Standardised uptake value;
TIO – Tumor-induced osteomalacia.

Introduction

The most common cause of tumor-induced osteomalacia (TIO), is phosphaturic mesenchymal tumor (PMT), a rare neoplasm composed of bone and soft tissue. TIO is a rare paraneoplastic syndrome, in which the signs and symptoms of osteomalacia are due to renal phosphate wasting (1,2). The causative mechanism is increased production of fibroblast growth factor 23 (FGF23) by mesenchymal tumors (3). Patients with PMT typically present with a slow progression of generalized skeletal pain, muscular weakness, recurrent fractures, height loss, and sequential psychological distress, in addition to laboratory abnormalities such as hypophosphatemia and hyperphosphaturia (3). Because of its nonspecific clinical profile, rarity, and general lack of clinical awareness, TIO is frequently mistaken for other neurologic or musculoskeletal disorders (3). Consequently, diagnosis is frequently significantly delayed.

PMT is typically located in the soft tissues and bones and tends to be solitary, although multifocal tumors have been reported. They are difficult to detect due to their small size (4). Computed tomography (CT) and magnetic resonance imaging (MRI) are often non-contributory in detecting mesenchymal tumors (5). Bone scintigraphy or radiography only reveal osteomalacia and rarely reveal the mesenchymal tumor causing the symptoms (6). However, the feasibility of functional imaging in detecting PMT in oncogenic osteomalacia was reported (7). Successful tumor localisation and complete surgical excision usually leads to quick relief of symptoms and reversal of biochemical abnormalities (3,8,9). A timely and accurate indentification of FGF23 secreting tumors is critical in the clinical diagnosis and management of TIO (3). We report a challenging case of a nasal cavity PMT.

Case report

A 44-year-old male patient presented with a one-year history of ankle pain, which was more pronounced on the right side with radiation to the knee. He also experienced difficulty standing up in the morning. Previously he consulted with a neurologist, a traumatologist and was prescribed non-steroidal anti-inflammatory drugs (NSAIDs) for pain. Dexamethasone and methylprednisolone were also prescribed for a short while without effect.

Blood tests revealed elevated alkaline phosphatase – 719 U/l (N 40-150) and hypophosphatemia – 0,41 mmol/l (N 0,74-1,52). Serum calcium, parathyroid hormone and 1,25-dihydroxy vitamin D levels were within normal limits. Further testing for autoimmune disorders (like rheumatoid arthritis) was done and came back negative. He was also tested for tumour markers which revealed a slight elevation of chromogranin A.

A MRI of the right ankle was performed at another institution (images were not available for viewing) revealing multiple stress fractures of bones.

A whole body nuclear bone scintigraphy with Technecium-99m Methyldiphosphonate (99mTc-MDP) was performed showing heterogenous uptake and multiple fractures of ribs and vertebrae with no observable signs of metastatic bone disease (Fig.1). However, the pattern of uptake was consistent with metabolic bone disease.

Bone densitometry with dual-energy X-ray absorptiometry (DEXA) showed a T-score of -4,4 consistent with osteoporosis.

In search of a possible lesion a whole-body CT was performed, once more showing multiple axial skeleton fractures due to osteoporosis without observable tumours.

Following these findings, a whole-body scan with 99mTc-Tectrotyd was performed showing intense uptake in the paranasal sinus area (Fig 2). No other focal uptake was seen.

A repeat questioning revealed that a year ago a right paranasal sinus mass was discovered on CT and MRI. A biopsy was done and histology came back as capillary hemangioma. A full excision was planned, however, due to COVID-19 the operation was postponed.

A repeat reading of CT and MR images showed a soft tissue mass in the right nasal cavity with extension towards adjacent sinuses (Fig. 3 and Fig. 4).

A complete surgical resection of the mass was performed and after a pathologic review the tumour was confirmed as PMT.

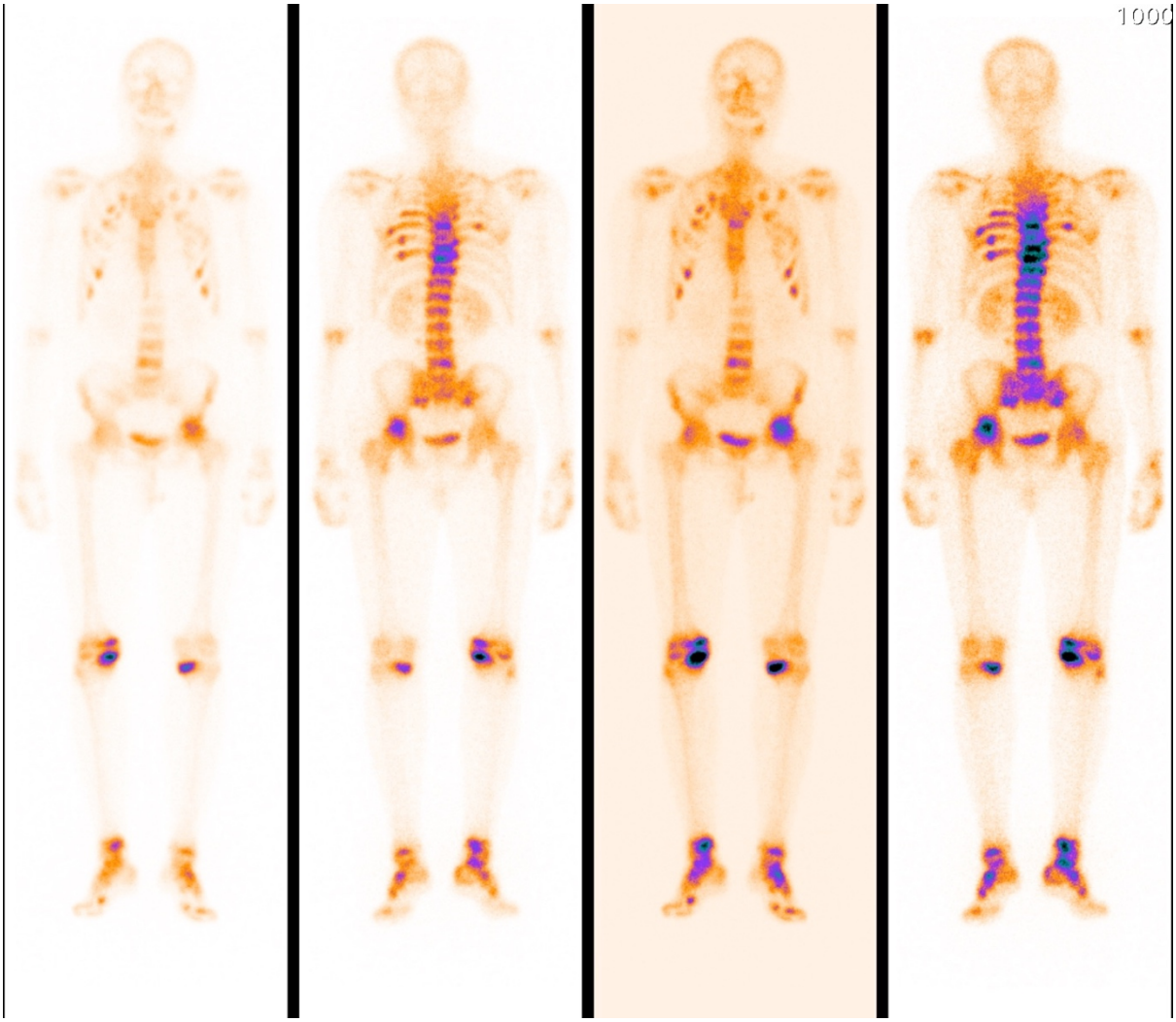

Figure 1 Fig. 1. Whole-body nuclear 99mTc-MDP bone scintigraphy. The skeletal uptake demonstrates a pattern consistent with metabolic bone disease and multiple bone fractures.

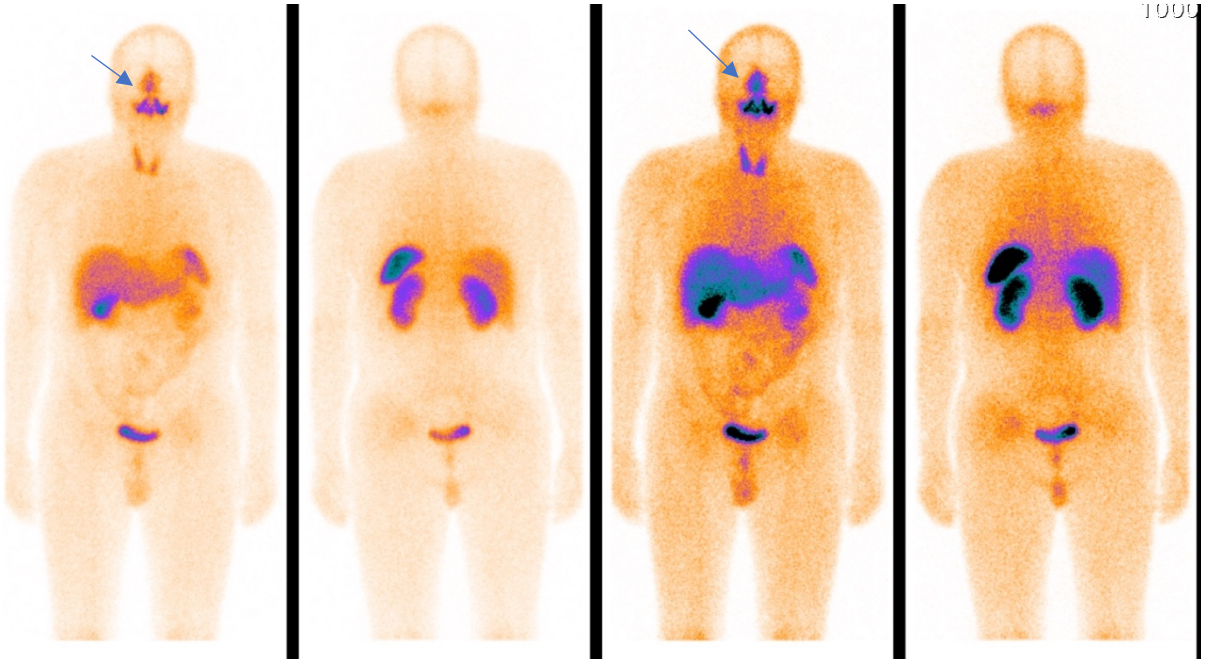

Figure 2 Fig. 2. Whole-body scan with 99mTc-Tectrotyd. (Arrows) Demonstrates increased uptake in paranasal sinus area.

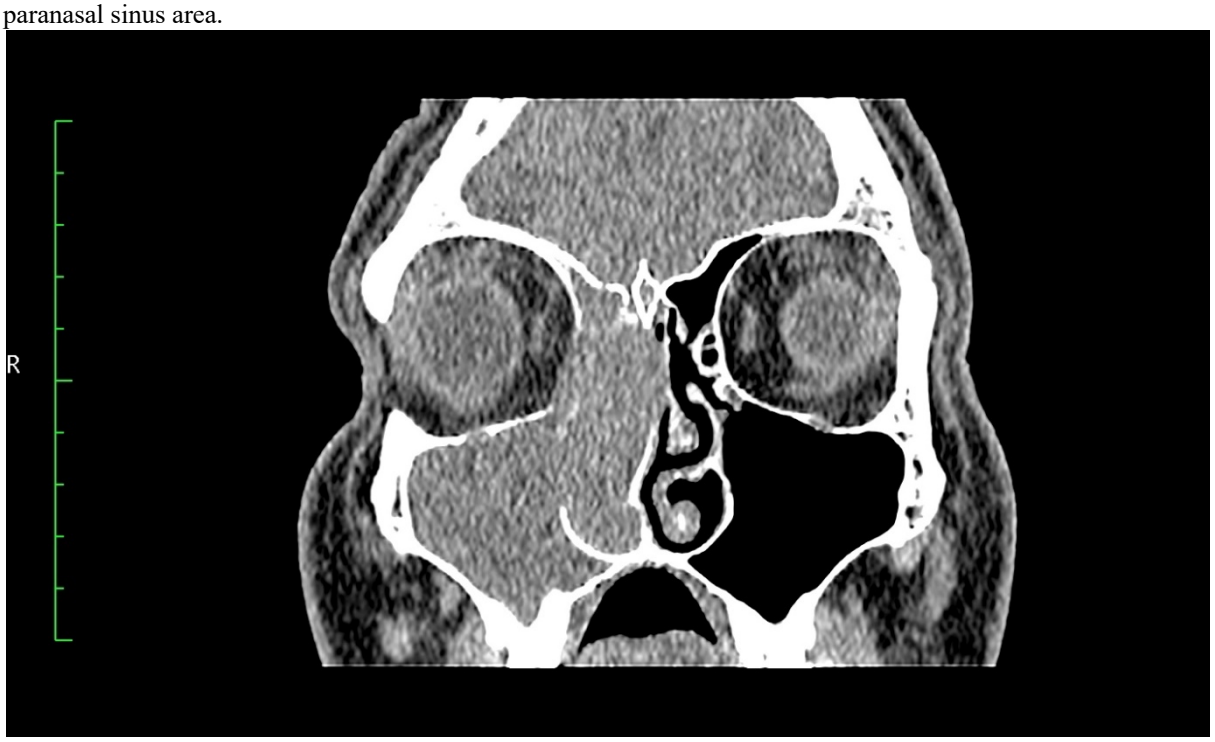

Figure 3 Fig. 3. CT sinuses (coronal view). Shows a mass filling the right nasal cavity, right maxillary and frontal sinuses and right ethmoidal cells with the destruction of conchae and the medial wall of the right maxillary sinus.

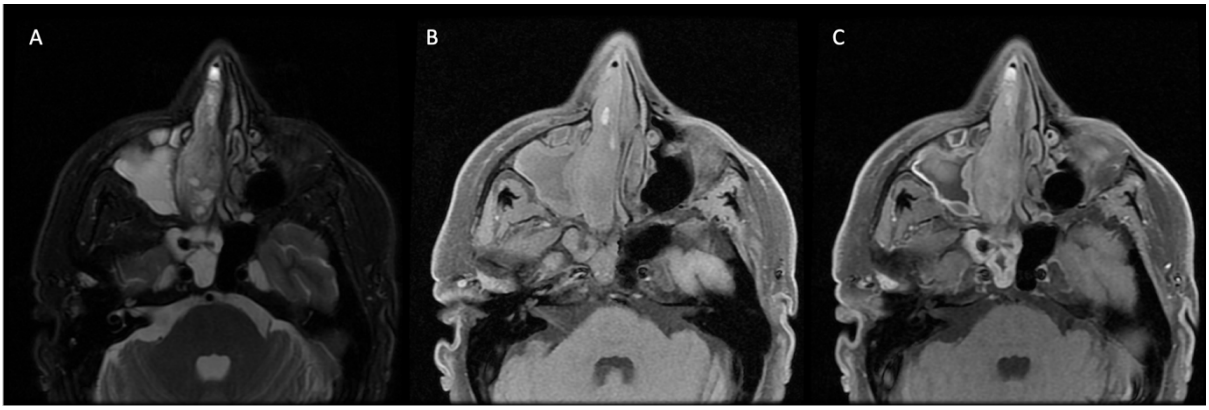

Figure 4 Fig. 4. MRI sinuses. (A) Axial T2 fat-suppressed, (B) axial T1, (C) axial T1 fat-suppressed post contrast images demonstrate a soft tissue mass hyperintense on T2, iso-/hyperintense on T1 and with faint non-homogenous enhancement post contrast.

Discussion

Clinical features

PMT is an extremely rare and diagnostically challenging neoplasm, especially when it develops in an uncommon site such as the head or neck. Most osteomalacia-inducing tumors are detected during the late fourth to early fifth decades of life (4). PMT may develope in almost any osseous location or soft tissue (10). However, they are rare in parenchymal organs or in retroperitoneum (1,11–13). PMT most often involves extremities and acral sites in soft tissues. In bones PMT commonly appears in the appendicular skeleton, cranial bones and paranasal sinuses (1,10–13). Most PMTs are solitary lesions, however, a patient with multifocal PMT has been reported (14).

The diagnosis is delayed for a long time as it is both a rare condition that is often excluded from the list of differentials by treating physicians and the patient's symptoms, such as muscle pain and progressive weakness, are of non-specific nature (15). The typical period from the onset of symptoms to the clinical diagnosis of TIO is about three years, and the average from the time of initial presentation to tumor removal is more than five years (13,16). PMT almost always manifest with biochemical abnormalities that show chronic hypophosphatemia without manifesting symptoms of the tumor itself (10). As the disease progresses bone pain and fractures occur more often and account for a large portion of the PMT related morbidity (10,13).

The overwhelming majority of PMT are benign and complete excision of the tumor usually results in rapid resolution of phosphate wasting and osteomalacia (3,13,17).

Pathologic features

PMT is a type of connective tissue tumor that is typically characterized by a specific admixture of spindle cells, microcysts, osteoclasts-like giant cells, cartilage-like matrix , prominent blood vessels, and extensive calcification (7). Hemangiopericytoma was the most frequently diagnosed PMT, seen in 70 to 80 percent of TIO cases, followed by hemangioma, granuloma, ossifying fibroma and giant cell tumor (3,12,18,19). In most cases, osteomalacia is secondary to the tumor cell production of FGF 23, but FGF 23 elevation is not specific of TIO. The differential diagnosis of TIO are x-linked hypophosphatemic, autosomal dominant and recessive hypophosphatemic rickets (3,20). Somatostatin receptor (SSTR) subtypes (1, 2A, 2B, 3, 4, 5) are expressed to a variable degree in many tumors (3,12,19,21–23). A small subset of PMTs show malignant histologic characteristic and can behave clinically malignantly (24). Consequently, in many cases PMT diagnosis is very difficult for pathologists especially if the clinical presentation of the lesion is unknown or if the pathologist is not aware of the entity at all (11).

Diagnostic imaging features

Because PMTs have a wide range of histopathological characteristics, it is more important to distinguish this malignancy from other vascular tumors before surgery. However, conventional imaging modalities such as radiography, CT and MRI also show variable characteristics on imaging (11,25,26). Some studies show, that even with a combination of 111In-pentetreotide single-photon emission computed tomography (Octreoscan-SPECT/CT), F18-fluorodeoxyglucose positron emision tomography (18F FDG-PET/CT) and anatomical localization studies (MRI and CT), only 61 percent of subjects with TIO had successful tumor localization (27).

The imaging features of PMT have only very recently been described in detail (26). Multiple pseudofractures, also known as Looser-Milkman zones, are radiolucent bands perpendicular to the cortex and are usually bilateral and symmetrical. They are most commonly located in the ribs, pubic rami, external margin of scapula, internal margin of the proximal femur, and metatarsal bones (17). They can sometimes progress to complete fractures (17).

DEXA helps to diagnose osteomalacia in patients with TIO which results from the disturbance of mineralization kinetics and increased bone resorption by osteoclasts. DEXA is useful in patient follow up to assess recovery of bone mineral density (7).

On CT scans, the tumor exhibits a round or oval, well-defined, isodense or hypodense soft tissue mass and displays a uniform enhancement, especially when the tumor is small (25). Bone lesions are typically osteolytic and characterized by a narrow transition zone and the presence of internal matrix (13). But CT has a limited role in localizing the culprit tumor (11,25,26,28,29).

PMTs are usually T1 isointense, T2 hyperintense, and markedly homogeneous enhancing on MRI, with areas of dark T2 signal indicating the presence of internal matrix (11,25,26,28–30). However, variable tumor sizes result in various MRI imaging findings (25). A large tumor can display heterogeneous signal intensity on T2W and T1W and heterogeneous enhancement on post-contrast T1W (25). Within large tumors the areas of heterogeneous low signals are consistent with vascular flow voids (25). PMTs can therefore be mistaken for other bone and soft tissue neoplasms, such as fibrous dysplasia, tenosynovial giant cell tumor, and even atypical lipomatous tumor (26). Similar to CT, the role of MRI is to anatomically define the tumor before surgery, especially in the sinonasal region, after functional imaging has identified a possible culprit tumor (7).

Bone scintigraphy is more sensitive than X-rays and often shows multiple foci of uptake at sites of insufficiency fractures or pseudofractures, however, that may misdirect the effort to localize the tumor. Increased tracer uptake by the mandible, vertebral column and the sternum creating the “tie sign” may be seen in tumor-induced osteomalacia (31). A generalized increase tracer uptake (known as superscan) may also be seen due to secondary hyperparathyroidism, especially in the cranium, chondrocostal joints, jaw (17,19). Although nonspecific scintigraphy findings can be confused with metastatic bone lesions and other metabolic causes, including vitamin D deficiency, drug abuse, malabsorption, kidney insufficiency. Increased tracer uptake in growth plates and a prominent appearance of the costochondral junction, known as the ‘rachitic rosary sign’, are thought to be more specific of TIO and should raise its suspicion if detected (7,19,31,32).

Radionuclide scans are often particularly valuable in the detection of occult PMT of the soft tissues; as metabolically active neoplasms, they may be identified with 111Indium-octreotide scintigraphy, 68Ga-DOTATATE PET/CT and 18F-FDG PET/CT (3,4,13,26,29,33–35).

Some authors advocate 18F FDG-PET/CT for localizing TIO (3,36,37). While 18F FDG-PET/CT may be very sensitive, it is non-specific and may identify areas of increased metabolic activity that are not related to the tumor (19). This is especially true in patients who have many active fracture healing regions (19). Because of the physiological uptake in brain, liver, and spleen, tumor detection in these sites may be challenging, and additional imaging modalities should be used to assess these locations (26). Also, a variable degree of FDG uptake in this group of tumors might be accountable for the unsatisfactory detection rate (26,36).

PMTs express SSTR and consistent expression of the SSTR2A subtype has been demonstrated (1,23,26). Somatostatin-analogues, such as111Indium-octreotide or Octreoscan, which has a high affinity to somatostatin receptor SSTR 2, have been

used to image these tumors (6,22,37,38). Tc-99m-HYNIC-octreotide, a Tc-99m labeled somatostatin analog has recently become more popular and successful in imaging somatostatin receptor expressing neoplasms (7). Tc-99m-HYNIC-octreotide scintigraphy has shown to be very useful to localize TIO (39,40). Multiple reports have shown clinical success of Octreoscan with combined SPECT/CT in detection of FGF23 secreting mesenchymal tumors (3). Pitfalls of these agents include tracer uptake in inflammatory conditions, which might be mistaken for bone or soft tissue malignancy (41). Nasal mucosal uptake may be seen in patients with a common cold in Octreoscan and should not be confused for sinonasal mesenchymal tumors (42). Small lesion size, poor spatial resolution of planar scintigraphy, insufficient expression of the somatostatin receptor, or adjacent location of bone fracture may be contribute to false-negative findings (3,4,6,43).

Somatostatin receptor PET/CT imaging with Ga68 labeled DOTA conjugated peptides, DOTATATE, DOTATOC, and DOTANOC, has recently emerged as a promising imaging method for localizing TIO-causing mesenchymal tumors (3–5,11). 68Ga-DOTATATE is an antagonist of the SSTR, which is internalized after binding to the receptor, leading in radioactivity accumulation in neoplasm cells (44). The higher affinity of DOTATATE for SSTR 2, the receptor subtype predominantly overexpressed, may favor its use in TIO over DOTANOC and DOTATOC (45). 68Ga-DOTATATE has shown greater spatial resolution, higher sensitivity and specificity over Octreoscan in detecting an occult tumor (4). But some studies show that it is not more sensitive than Octreoscan-SPECT/CT and 18F FDG-PET/CT combined (4,9,19,35,45,46). False positive etiologies (i.e., osteomalacia induced fractures, inflammatory conditions) also present with increased uptake and could occasionally be confusing in the localization of primary tumors (3). As with FDG PET/CT, it's critical to ensure that these imaging examinations cover the entire body from vertex to toes, including the hands and feet. Also, there is a need for careful examination of the craniofacial region which accounts for nearly 30% of the PMT (47).

Conclusion

While phosphaturic mesenchymal tumor is a rare neoplasm, it is the most common cause of tumor induced osteomalacia. The diagnosis is delayed for years due to the non-specific nature of symptoms, lack of clinical suspicion and difficulty in identifying the responsible tumor. Tumor induced osteomalacia is often a diagnostic challenge, however, advances in medical imaging have enhanced the effective localization of osteomalacia-inducing tumors. For radiologists, raising the suspicion of a phosphaturic mesenchymal tumor in any patient presenting with osteomalacia as well as localizing the tumor on imaging is crucial, as complete excision of the tumor leads to resolution of the osteomalacia and clinical symptoms.

Conflict of interest

None.

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