Endocrinology, Diabetes & Metabolism CASE REPORTS

Z Adnan and others | Phosphaturic mesenchymal tumors among elderly

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Phosphaturic mesenchymal tumors among elderly patients: a case report and review of literature

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Summary

Phosphaturic mesenchymal tumor (PMT) represents a rare cause of osteomalacia. The clinical signs and symptoms are vague and these lead to diagnosis delay. In the presence of hypophosphatemia and relatively high urine phosphate excretion, this entity should be taken into consideration in the deferential diagnosis of osteomalacia. In the present article, we report 81-year-old man presented to our clinic for evaluation due to osteopenia. His laboratory results disclosed hypophosphatemia, relatively increased urine phosphate excretion and increased level of intact fibroblast growth factor 23 (FGF23). A ^{68}Gallium DOTATATE PET/CT revealed pathological uptake in the upper aspect of the left shoulder adjacent to the coracoid process. For suspected PMT a wide resection of the tumor was performed and pathological findings were consistent for PMT. Laboratory tests were normalized postoperatively. Reviewing the literature, we had identified 33 reported cases of PMTs among elderly patients age ≥70 years. Unlike previously reported data, where tumors predominantly localized in the lower extremities and pelvis, our search disclosed a high rate of tumor localization (10 cases – 33.3%) in the head with equal number of tumors (14 cases – 42.4%) localized in the head and upper extremity as well as in pelvis and lower extremity. The present case describes unique tumor localization in an elderly patient and our literature search demonstrated for the first time a high rate of tumor localization in the head among this group of patients.

Learning points:

- PMTs represent a rare entity that should be considered in the differential diagnosis of elderly patients presented with persistent hypophosphatemia.
- Unlike previously reported data, head and neck tumor localization is frequent among elderly patients.
- ^{68}Gallium-conjugated somatostatin peptide analogs, such as ^{68}Ga-DOTATATE PET/CT demonstrated the greatest sensitivity and specificity for tumor localization in patients with phosphaturic mesenchymal tumors (PMTs).
- Wide tumor resection using intraoperative ultrasound is of major importance in order to ensure long-term cure.

Background

Osteomalacia (OM) represents a metabolic disorder characterized by decreased mineralization of mature bone. Multiple causes underline this abnormality including inborn errors, chronic kidney disease and insufficient levels of vitamin D or calcium (1). Phosphaturic mesenchymal tumor (PMT) is an uncommon cause of osteomalacia, usually manifests as a solitary benign neoplasm. Most of the tumors are located either in bone or soft tissue (2). The tumors are common in middle age individuals, although the age range may vary considerably with male to female ratio of 1.2:1 (3, 4).

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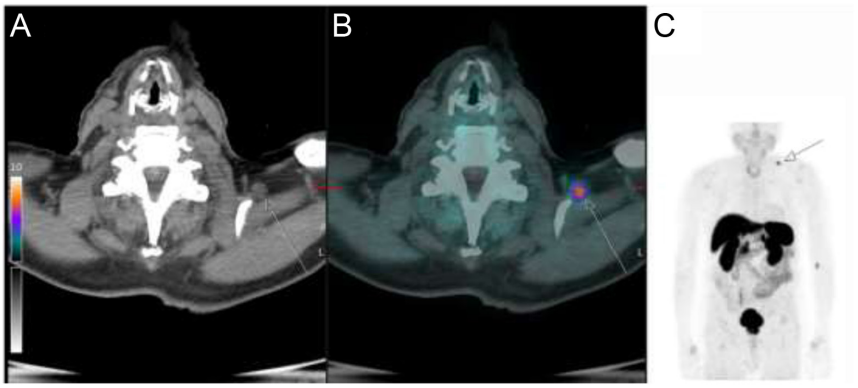

Figure 1
68GA-DOTATATE PET/CT shows normal biodistribution in the PET 3D maximal intensity projection (C) with physiological uptake in the spleen, liver, kidneys and urinary bladder and pathological uptake in the left supraclavicular region (arrow). An axial slice at this level demonstrates a soft tissue nodule (arrow) on the CT portion of the study (A) that is located deep in the soft tissues, near the scapula, at the junction between the serratus anterior and supraspinatus muscles. The fusion axial image at this level (B) of the PET slice in color, and the CT slice beneath it in grayscale, demonstrates the high uptake in orange-purple in the nodule (arrow).

The clinical symptoms are vague. Therefore, diagnosis may last for up to 10 years. Weidner and Santa Cruz coined the term PMT in 1987. One of the clinical features of PMT is tumor-induced osteomalacia (TIO) characterized by bone pain, muscle weakness and pathological fractures; others may be without symptoms and only laboratory tests may disclose hypophosphatemia and hyperphosphaturia (5). Increased levels of fibroblast growth factor 23 (FGF23) and relative hyperphosphaturia in the presence of hypophosphatemia are important clues for suspecting PMT (6). Different imaging modalities are essential for tumor localizations. Surgery is curative and a wide resection with negative margins is of major importance for preventing recurrence (7).

PMT among elderly patients is relatively rare. The aim of this article is to report a case of PMT with extremely rare localization in a patient 81 years old and to review the literature focusing on published data regarding this entity among elderly patients.

Case presentation

An 81-year-old man was referred in 2014 to our clinic due to osteopenia with T score of −1.5 in the spine and −1.2 in the femur. He was treated previously by his family physician for 5 years with alendronate, vitamin D and calcium. In 2011, he was referred to orthopedic consultation for left hip pain. His physical examination and pelvic CT were normal. Medical history did not disclose any chronic diseases or hereditary bone disease apart from old bullet fragments in different body sites.

Investigation

Laboratory results since 2004 disclosed normal calcium levels 9.9 mg/dL (normal range: 8.8–10.20 mg/dl), low blood phosphorus 2.10 mg/dL (normal range: 2.5–5 mg/dL), mild elevated alkaline phosphatase 144 U/L (normal range: 30–120 U/L), normal level of 25 hydroxyvitamin D 121 nmol/l. Quantitative determination of 1,25 dihydroxyvitamin D (1,25(OH)2D) in serum revealed a normal level 99 pmol/L (normal range: 39–160 pmol/L) using DiaSorin LIAISON XL *in vitro* chemiluminescent immunoassay (CLIA) performed on the LIAISON XL Analyzer. Intact FGF-23 was elevated 150.8 pg/mL (normal range: 23.2–95.4 pg/mL) using the same method. Repeated 24-h urine phosphate collection disclosed relatively high phosphate excretion 959 mg/24 h (normal range: 400–1300 mg/24 h). For suspected PMT, ^{68}Gallium DOTATATE PET/CT was performed and a pathological uptake in the upper aspect of the left shoulder adjacent to the coracoid process was observed. No mediastinal and axillary lymphadenopathy were observed (Fig. 1).

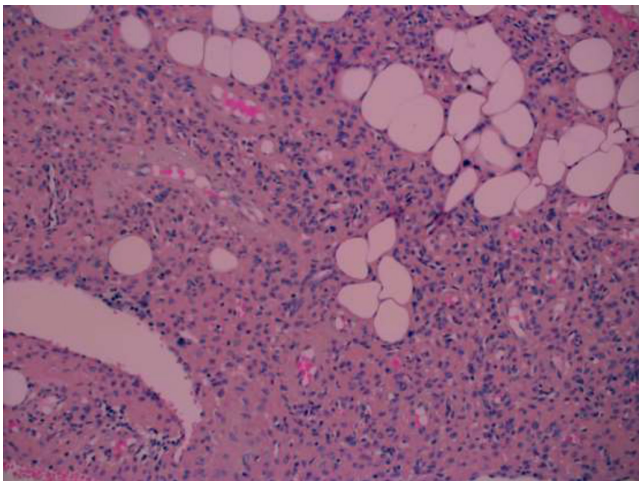

Figure 2
Fat tissue with proliferation of bland spindle cells, numerous blood vessels with amorphous matrix deposition and few calcifications without atypia and mitosis. The findings are consistent with benign phosphaturic mesenchymal tumor (stain, hematoxylin and eosin; original magnification, ×200).

Table 1 Elderly patient characteristics with phosphaturic mesenchymal tumor.

Authors and year of publication	No. of cases	Age	Sex	Site of tumor	Signs and symptoms
Park *et al*. (13)	1	76	F	Humerus	NA
Baronofsky *et al*. (14)	1	72	F	Acetabulum	Rt. Hip pain
Folpe *et al*. (4)	4	73	M	Hip	NA
		71	F	Forearm	
		77	F	Abdominal wall	
		80	M	Ischium	
Dupond *et al*. (15)	1	71	M	Mandible left	Bone pain and muscle weakness
Vollbrecht *et al*. (16)	1	87	M	Third metacarpal	Myalgia
Kenealy *et al*. (17)	3	79	F	Ethmoid sinus lt	Hip fracture
		70	M	Extradural lt	Hip fracture
		70	F	Ischium	Skeletal pain
Yun *et al*. (18)	1	71	F	Mandible lower with neck extension	Itching sensation, kyphosis and distorted arms and legs
Savage and Zimmer (19)	1	73	F	Pterygopalatine fossa	Leg pain, walking difficulties, fracture of ribs and foot
Shelekhova *et al*. (20)	1	70	F	Sinonasal cavity	NA
Bauer *et al*. (21)	2	71	F	First toe of the left foot	Fractures multiple sites and osteoarthritis of the hip
		77	M	Parotid gland left	Back pain and hip fracture left
Fok *et al*. (22)	1	74	M	Soft tissue mass plantar surface adjacent to left second metatarsal head	Limb pain left lower, proximal myopathy
Wémeau *et al*. (23)	1	86	F	sub maxillary	Rib and vertebral fracture
Westerberg *et al*. (24)	1	73	F	Sole of the right for foot	Multiple site fractures and muscle weakness
Syed *et al*. (25)	1	71	F	Temporal bone (middle ear and mastoid)	Hearing loss, facial nerve palsy
Fatani *et al*. (26)	3	81	M	Femoral neck	Bone pain and fractures
		76	F	Great toe	
		87	F	C2	
Ledford *et al*. (27)	1	74	M	Calcaneus	Bone pain, muscle weakness, fractures (lumbar, vertebral and pelvis)
Honda *et al*. (28)	1	73	M	Neck	Femur metastasis Bon pain, proximal muscle weakness
Aizawa *et al*. (29)	1	72	M	C5	Weakness
Jerkovich *et al*. (30)	1	70	F	3rd metacarpal bone left hand	Diffuse bone pain Myalgia
Tajima *et al*. (31)	1	77	M	Left parotid gland	NA
Lee *et al*. (32)	1	73	M	Femur	Refractory bone pain and muscle weakness
Paul *et al*. (33)	2	74	F	Right foot	Bone pain, proximal muscle weakness
		72	F	Distal end of right femur	Bone pain
Gambhir (34)	1	70	M	Superior mediastinum at D1/D2 levels	NA
Chazal *et al*. (35)	1	70	F	Second phalanges right foot	Multiple fractures and diffuse pain

Treatment

During his evaluation, the patient was treated ineffectively with potassium phosphate monobasic (Calciless) eight tablets daily and vitamin D 1000 IU. His blood phosphorus levels remained consistently low despite this treatment modality. According to above investigation, the patient was referred to the orthopedic surgical department and a guided ultrasound wide resection of the tumor was performed. Histopathological examination disclosed fat tissue with proliferation of bland spindle cells with numerous blood vessels, amorphous matrix deposition and few calcifications without atypia and mitosis. The margins were free of tumor. These findings were consistent with benign PMT (Fig. 2).

Follow-up and outcome

Three months after surgery, his blood phosphorus levels and 24-h phosphorus urine collection were normalized without any treatment.

Table 2 Tumor localization according to different regions.

Localization of primary tumor	Total number	Sex F/M
Head and neck	10	6/4
Upper limb	4	2/2
Lower limb and pelvis	14	7/7
Others (mediastinum, abdomen and spine)	5	2/3
Total number of patients	33	17/16

Discussion

PMT represents a rare entity especially among elderly patients. The diagnosis is usually delayed due to multiple factors including vague signs and symptoms, difficulty in tumor localization and histological identification.

PMTs secrete proteins such as FGF-23, FGF-7, frizzeled-related protein 4 and matrix extracellular phosphoglycoprotein (8). FGF-23 represents the only clinically relevant protein among them, its main action is by inhibiting the sodium phosphate renal co-transporters and the suppression of 1α hydroxylase activity, causing decreased renal reabsorption and increased urinary phosphate excretion. As a result, in addition to hypophosphatemia, relative hyperphosphaturia, a decrease in 1,25 dihydroxyvitamin D are observed (2). It is noteworthy that recent identification of a fusion fibronectin and fibroblast growth factor receptor 1 (FN/FGF-1) as a molecular abnormality in some tumors enhanced our knowledge in understanding not only the pathophysiological mechanisms underlying this entity, but also the transcriptional, translocational and posttranscriptional modifications, suggesting future approaches to target therapies (9).

Tumor localization represents another obstacle during patient's evaluation. PMTs are slow-growing tumors and their localization is difficult. Octreotide scintigraphy, whole-body Tc-99m sestamibi scanning, 18F-flurodexyglucose positron emission tomography (FDG-PET), ^{68}Gallium-conjugated somatostatin peptide analogs, such as ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTANOC PET/CT, whole-body MRI and CT are used for tumor localization. It is worthy of mention that ^{68}Ga-DOTATATE PET/CT demonstrated the greatest sensitivity and specificity in comparison to Octreoscan SPECT/CT, FDG-PET and ^{18}F FDG-PET for tumor localization in patients with TIO (10, 11). ^{68}Ga-DOTATATE PET/CT was chosen for tumor localization in this case. The scan revealed pathological uptake measuring 1.3 cm in the upper aspect of left shoulder subcutaneously adjacent to the coracoid process. This very rare localization was challenging for orthopedic surgeons expert in this field using intraoperative ultrasonography for precise localization and wide excision.

About 404 cases of oncogenic osteomalacia have been reported of which PMTs are the most frequent. Both genders are equally affected and most patients are between the ages of 30 and 40 years. The most common localization of PTM involves the extremities (95%) followed by head and neck sites (5%). Most of PMTs are localized in the lower extremities (12).

A PubMed search between the years 1990 and 2018 has been conducted using the terms 'phosphaturic mesenchymal tumor', 'tumor-induced osteomalacia' and 'oncogenic osteomalacia'. Our search focused on reported cases among elderly patients age ≥70 years, tumor localization, the presence or absence of signs and symptoms such as bone pain, muscle weakness and pathological fractures as well.

We had identified 33 cases with PMTs among elderly patients age ≥70 years old with mean age (mean age 77.2 years), the female-to-male ratio was 1.35:1. Of these, 14 cases (42.4 %) with tumor localization in the pelvis and lower extremity, 14 cases (42.4%) in the head, neck and upper limb, of which ten cases (33.3%) with tumor localized in the head and neck, the remaining four cases (16.2%), the tumor was localized in other sites such as mediastinum, abdominal wall and spine. Unlike previously reported data – where tumor localization was predominantly in the lower extremities – our search demonstrated that PMTs among elderly patients are present at a higher rate in the head and neck and with equal number of cases in the pelvis and lower extremities as well as in the head, neck and upper limb (Tables 1 and 2).

In the case presented in this manuscript, the tumor was located in the upper aspect of the left shoulder adjacent to the coracoid process. To the best of our knowledge, this tumor localization was unique and the first to be reported in the literature. Furthermore, surgical resection was challenging for the surgeon and guided intraoperative ultrasonography was used in order to perform a successful wide resection.

Conclusions

The diagnosis of PMTs should be considered among elderly patients presented with osteomalacia. Reviewing the literature, head and neck tumor localization is frequent among this group of patients and should be taken into account. Performing wide resection of the tumor represents an important matter for cure and preventing recurrence.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of clinical details and clinical images was obtained from the patient.

Author contribution statement

Zaina A is the main endocrinologist physician who followed the patient and reviewed and edited the manuscript. Nikomarov D performed the surgery. Weiler-Sagie M was responsible for imaging-related aspect of the case. Roguin Maor N was responsible for literature reviewing and preparing the manuscript. All authors approved the final draft of the report.

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