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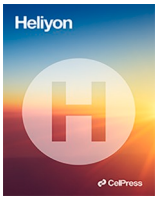

Case report

Challenges in the diagnosis and management of tumor-induced osteomalacia: A case report

Anna Maria Bochicchio [a], Aldo Cammarota [b], Giovanni Storto [c], Luciana Possidente [d], Antonio Villonio [b], Ludmila Carmen Omer [a], Geppino Falco [e], Simona Laurino [f,*], Sabino Russi [f]

[a] *Experimental Oncology Unit, IRCCS CROB Centro di Riferimento Oncologico Della Basilicata, Rionero in Vulture (PZ), Italy*
[b] *Diagnostic and Imaging Department, IRCCS CROB Centro di Riferimento Oncologico Della Basilicata, Rionero in Vulture (PZ), Italy*
[c] *Nuclear Medicine Unit, IRCCS CROB Referral Cancer Center of Basilicata, Rionero in Vulture, Italy*
[d] *Pathology Unit, IRCCS CROB Centro di Riferimento Oncologico Della Basilicata, Rionero in Vulture (PZ), Italy*
[e] *Department of Biology, University of Naples Federico II, Naples, Italy*
[f] *Laboratory of Preclinical and Translational Research, IRCCS CROB Centro di Riferimento Oncologico Della Basilicata, Rionero in Vulture (PZ), Italy*

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ABSTRACT

The present case report is aimed to highlight the difficulty and the reason for the delayed diagnosis of phosphaturic mesenchymal tumors, emphasizing the need of standardized protocols for diagnosis, surgery and follow-up in high-volume hospitals. The clinical signs and symptoms, diagnostic and therapeutic procedures, immunohistological features were analyzed. Delayed diagnosis of phosphaturic mesenchymal tumor was primarily due to non-specific clinical symptoms such as fatigue, muscular and bone pain, and multiple fractures. This cryptic clinical picture made the diagnosis tricky that led to treatment of patient for non-specific pain and stress fractures before to consider the tumor-induced osteomalacia syndrome. Some well-documented studies were found in the literature in which the history of trauma is a critical trigger of glomus tumors. Extra-subungual tumors most frequently occur in the knee and ankle regions, particularly among young adults, and the diagnosis is typically made approximately 7.2 years after initial symptom onset. The difficult tumor localization represented an additional obstacle to the prompt treatment, leading to delayed curative surgery.

1. Introduction

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by renal phosphate wasting and reduced mineralization of bones [1,2]. TIO is usually triggered by mesenchymal, small and slow growing tumors (Phosphaturic Mesenchymal Tumor Mixed Connective Tissue variant [PMTMCT]) [3,4]. Fatigue, bone pain, and musculoskeletal weakness represent the non-specific symptoms that often lead to delayed or even miss diagnosis with a consequent deferring of appropriate medical and surgical treatments [5,6]. Complete resection of the tumor mass determine symptoms regression and an excellent prognosis of TIO patients [7,8].

* Corresponding author. Laboratory of Preclinical and Translational Research, IRCCS CROB Centro di Riferimento Oncologico della Basilicata, via Padre Pio 1, 85028, Rionero in Vulture (PZ), Italy.
E-mail address: simona.laurino@crob.it (S. Laurino).

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We report a case of a young man that received a diagnosis of TIO after 4 years from the initial onset of symptoms who underwent many needless treatments.

2. Case presentation

A 29 years old man presented with inability to walk without support, unexplained bone fractures, widespread and persistent pain. Patient denied growth delay and family history was negative for metabolic bone disease. His medical history started on February 2015, after a trauma of the right hip during a football match; he performed an X-ray exam that excluded bone fractures. To mitigate paroxysm of pain radiating away from the trauma area, he took drugs for symptomatic pain control for several months. On January 2016, due to persistence of a right cruralgia and the development of lameness, he underwent to magnetic resonance imaging (MRI) of the pelvis, which resulted negative. Whole-body bone scintigraphy with 99mTc-MDP 550 MBq exhibited an increased radiotracer asymmetrical uptake in the proximal right femur and chondral-costal joints, not diagnostic for a specific disease.

Subsequently, due to worsening of limping gait and development of right ankle pain, he underwent to a second MRI showing diffuse bone edema. A pelvis computed tomography (CT) revealed multiple occult fractures and osteonecrosis of the right femoral head. On June 2016, when patient self-referred to a high-specialized orthopedic Center and subsequently to IRCCSCROB for imaging study, he complained about severe coxalgia and inability to walk without support. The patient underwent treatment with regenerative micro perforations of the femoral head and neridronate for complex regional pain syndrome (CRPS) of the right foot.

On November 2016, for the persistence of coxalgia, it was hypothesized a lumbar involvement and highlighted L3-L4 instability with foraminal stenosis. Hence, he underwent to L3-L4 laminectomy with bone graft. The patient was followed-up with imaging studies (MRI, X-ray and CT) that found biconcave lens dysmorphism of all vertebral bodies distinctive of osteomalacia. Imaging also showed signs of disk-somatic distress between L3-L4 peculiar of chronic spondylodiscitis. The patient underwent surgery of vertebral deformities with positioning of interapophyseal stabilizers but without substantial relief of severe back pain, also following parenteral administration of methylprednisolone (8 mg) once a day.

On March 2017, due to non-responsive painful bone marrow edema syndrome of the right hip, patient was treated with adductor tenotomy. On November 2017, patient underwent osteosynthesis with metal screws for a spontaneous subcapital and basicervical right femoral neck fractures. Nevertheless, patient had no benefit or resolution of the right coxalgia, which later extended to the contralateral hip. After that, he became wheelchair dependent.

One year later, a left ankle MRI highlighted an extended bone edema with multiple stress fractures to the distal tibia and calcaneus; similar pathological alterations were evident on the left knee. The laboratory investigations showed no inflammation; among metabolic blood markers, levels of total alkaline phosphatase (622 U/l) and serum phosphate (2.2 mg/dL) were out of normal range.

On October 2018, due to persistence of bilateral hip and knee pain, a whole-body bone scintigraphy with 99mTc-MDP 550 MBq was repeated, showing an increase of radiotracer focal absorption at multiple sites (wrists, shoulder blades, humeral joints, sternum, clavicles, ribs, sacroiliac joint, right distal tibia, femoral heads and bilateral knees; Fig. 1). The rheumatologist hypothesized polyostotic Paget's disease and therefore a new therapy cycle with neridronate was administered.

On December 2018, patient was admitted to rheumatology department that expanded the biochemical profile evaluation and suspected a TIO. Laboratory tests showed low phosphate level (1.4 mg/dL), elevated alkaline phosphatase (275 U/L), normal calcium

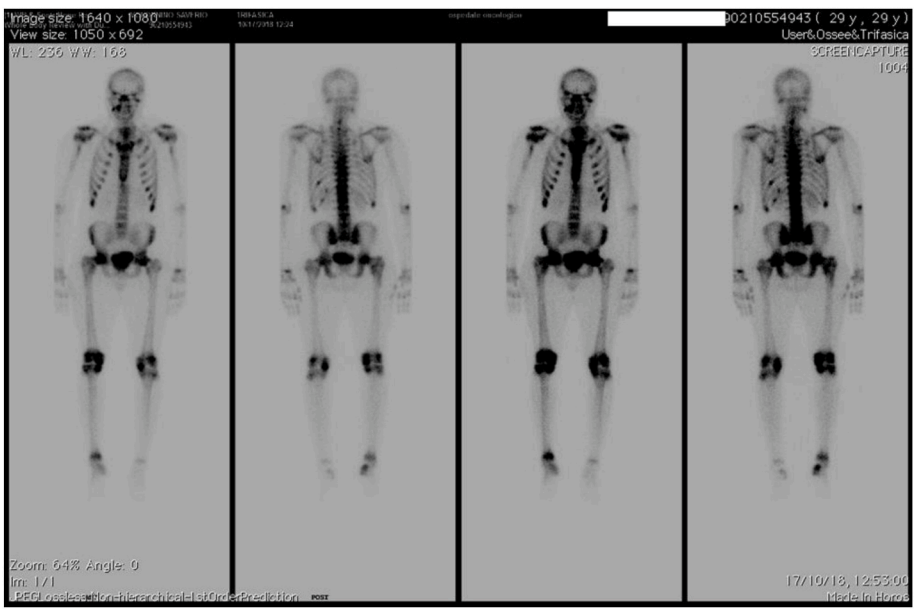

Fig. 1. Whole-body scintigraphy showing absorption of radiotracer at multiple sites.

and parathyroid hormone levels, an insufficient 25-hydroxyvitamin D and a very low 1,25-dihydroxyvitamin D (calcitriol) level (5.5 ng/L). Conversely, complete blood count, hepatic and renal function indices, creatine phosphokinase, serum protein electrophoresis, thyroid-stimulating hormone, antinuclear antibodies, aldolase and rheumatoid factor were in the physiological range. A 24-h urine sample revealed normal phosphate level (499 mg/24 hours), although the tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR) ratio confirmed a reduced phosphate tubular reabsorption rate (TRP). Furthermore, the level of circulating intact fibroblast growth factor-23 (FGF23) was high as reported in Table 1. Bone mineral density showed a reduced score with a total hip of −3.6 (normal value −1) and a lumbar spine T of −2.9 (normal value −2.5). The standard X-ray of the spine showed compressive fractures in T11 and T12, confirmed by the subsequent CT scan and MRI imaging.

On January 2019, he was subjected to a 68Ga PET/CT scan, showing increased uptake in soft tissues in front of the right distal tibia epiphysis with standardized uptake value (SUV) of 40.9 (Fig. 2A–B). Only on February 2019, MRI examination finally showed a mass of 25 x 7 × 47 mm between inferior articular surface of the right tibia and the extensor digitorum longus muscle, which was compatible with a glomus tumor (GT). Moreover, the presence of lower third of tibia stress fracture was recorded (Fig. 2C). This nodular formation, attached to the medial side of periosteum, was characterized by regular margins. This nodule produced signal hypointense in T1 and T2 STIR sequences. Immunohistological findings on fine needle aspirate were compatible with a glomangioma, characterized by round cells with hypercellularity and eosinophilyc cytoplasm (Fig. 3A). Ki67 expression (2 %) indicated a low cells proliferative rate (Fig. 3B). Vimentin and actin smooth muscle were positive to immunohistochemistry (Fig. 3C–D). On the contrary, CD34, S-100, and desmin were negative (Fig. 4A–D). The ECOG (Eastern Cooperative Oncology Group) performance status scale at this phase was 2. Further confirmation of the ectopic hormone production was obtained through venous sampling of the arm and leg, measuring very high FGF23 levels next to the causal lesion.

On March 2019, patient underwent surgery and tumor was entirely removed. The surgical specimen included soft tissues of right ankle, tibial cancellous bone and periosteum. Examination detected a circumscribed tumor with a diameter of about 2.5 cm. Brownish, compact, elastic, macroscopically undamaged by tumor was the bone tissue. Under articular surface, it was characterized by a broad band of cartilage, and was coated in depth by periosteum and superficially by continuous pseudocapsule. Histologic evaluation of the radically resected specimen identified a phosphaturic mesenchymal tumor. The very low mitotic index was defined as negligible. Irregular sized and shaped surrounding bone trabeculae with wide osteoid coagulative necrotic areas was recorded. The tumor cells were focally positive to FGF23 but no reactivity to calponin, caldesmon, collagen IV, actins (1A4, HHF35), desmin, S-100, CD34, Ki67/Mib1:< 5 % was reported. Soon after surgery, serum phosphate reached normal value and circulating FGF23 was observed with a concomitant slight reduction of alkaline phosphatase levels; no further treatments were administered. After 3 months from surgery, at physical examination patient had no pain, and gained partial autonomy for daily activities. After 6 months of follow-up, blood alkaline phosphatase was still out of range.

On the last follow-up (March 2022), two years after surgery, patient's mobility for basic daily activities markedly improved. Spinal X-rays showed no alterations except for the post-surgical dysmorphia of the vertebral bodies and the presence of metal lumbar spacers.

3. Discussion

Tumor-induced osteomalacia is a rare condition with less than 1000 cases described [5]. Data on real prevalence and incidence are not consistent. Current knowledge suggest that FGF23-mediated hypophosphatemia is commonly due to TIO [7,9,10], affecting equally both genders with an average onset age of 40–45 years.

Glomus tumor is a mesenchymal tumor characterized by alteration of smooth muscle cells that arise from the glomus body. It represents about 1.6 % of soft tissue tumors and it commonly arise in the upper extremity (62 % of cases, 27 % in the fingers), while the lower extremity represents about 9 % of all body sites. As essential features, we noticed the benign character of tumor with very rare malignant variants and the immunohistochemistry examination positive for SMA (smooth muscular actin), MSA (multiple system atrophy), calponin, h-caldesmon, collagen type IV; negative for cytokeratin and S-100 [11]. Clinically, those tumors are manifest for

Table 1
Main laboratory findings before and after surgery.

LABORATORY FINDINGS **(REFERENCE VALUES)**	TUMOR EXCISION	
	BEFORE	AFTER
SERUM PHOSPHATE **(2.5–4,6 MG/DL)**	1.4	4.2[a]
URINARY PHOSPHATE **(400–1000 MG/24H)**	499	820[b]
TRP **(>85 %)**	77	88[b]
SERUM ALKALINE PHOSPHATASE **(30–130 U/L)**	641	250[c]
SERUM INTACT PTH **(15–65 PG/ML)**	44	50[c]
SERUM CALCIUM **(8.4–10.2 MG/DL)**	9	9[a]
SERUM 25-HYDROXYVITAMIN D **(>30 NG/ML)**	14	33[c]
SERUM 1,25-DIHYDROXYVITAMIN D **(25–86 NG/L)**	5.5	N/A
INTACT FGF23 **(25–45 PG/ML)**	397	4.3[a]

N/A = NOT AVAILABLE.
[a] = THREE DAYS FOLLOW-UP.
[b] = TWENTY DAYS FOLLOW-UP.
[c] = SIX MONTHS FOLLOW-UP.

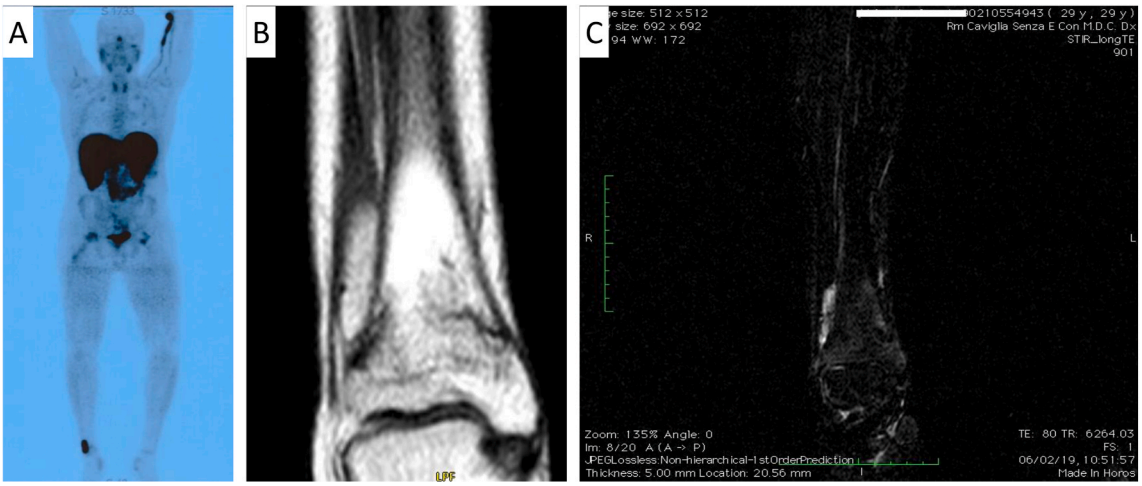

Fig. 2. PET/CT scan showing increased uptake at tibia distal epiphysis (A). MRI imaging showing a mass at the articular surface of right tibia (B). MRI examination confirming a mass at inferior articular surface of the right tibia and the presence of lower third of tibia stress fracture (C).

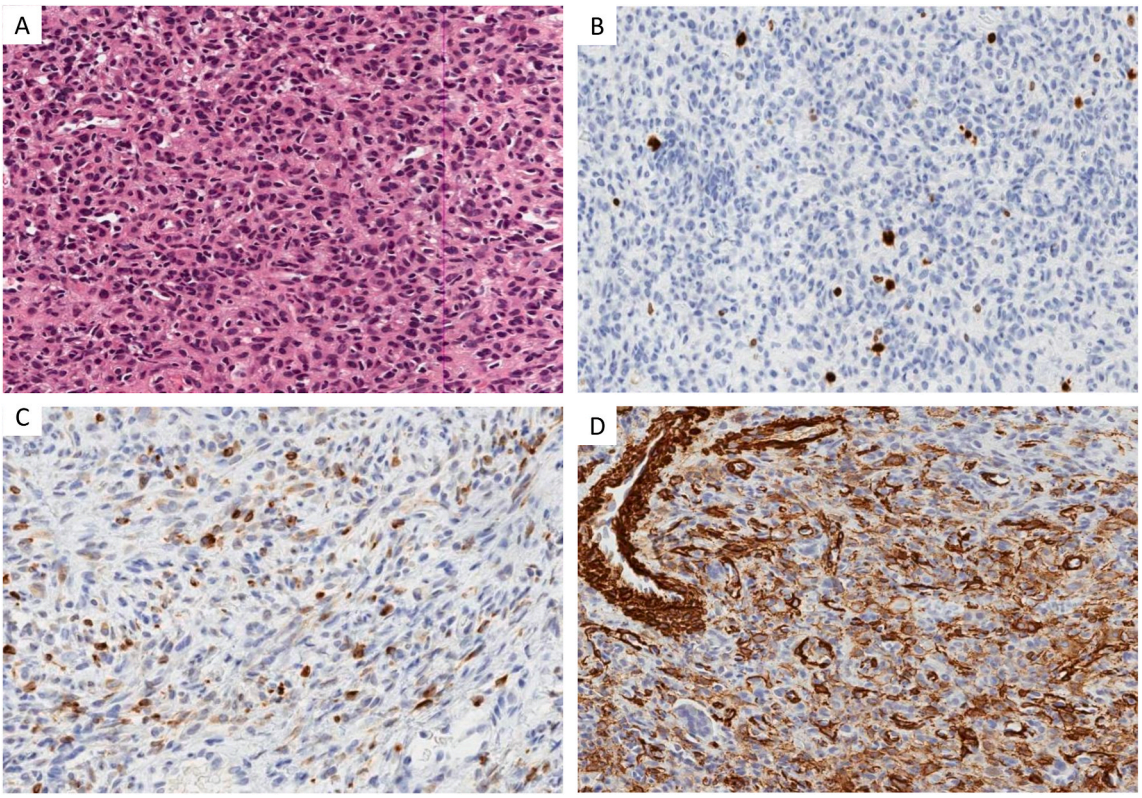

Fig. 3. Microscopically, phosphaturic mesenchymal tumors consist of a hypercellular tumor composed of round cells and eosinophilyc cytoplasm at hematoxylin eosin staining (A). Low Ki67 positivity (B). Vimentin immunostaining showed focal positivity (C). Diffuse positive marking for Smooth muscle actin (D). Magnification: 20×.

paroxysm of pain radiating from lesion, hypoesthesia, muscle atrophy and osteoporosis [6]. Interestingly, a Chinese review of 91 cases underlines that GTs are often caused by a trauma. Indeed, the most common site of GTs in young adults is the knee [8] and the mean age at diagnosis is 7.2 years (range 2–12 years) [12]. Although several hundred cases have been described since the first TIO case reported by McCance et al., in 1947 [13], to date most physicians are still not familiar with this rare disease. Indeed, only a small number of cases with tumor-induced osteomalacia consequential to glomus tumor are reported in recent literature [14–16]. TIO patients often refer a long history of symptoms, usually non-specific and often progressive, before they receive an appropriate

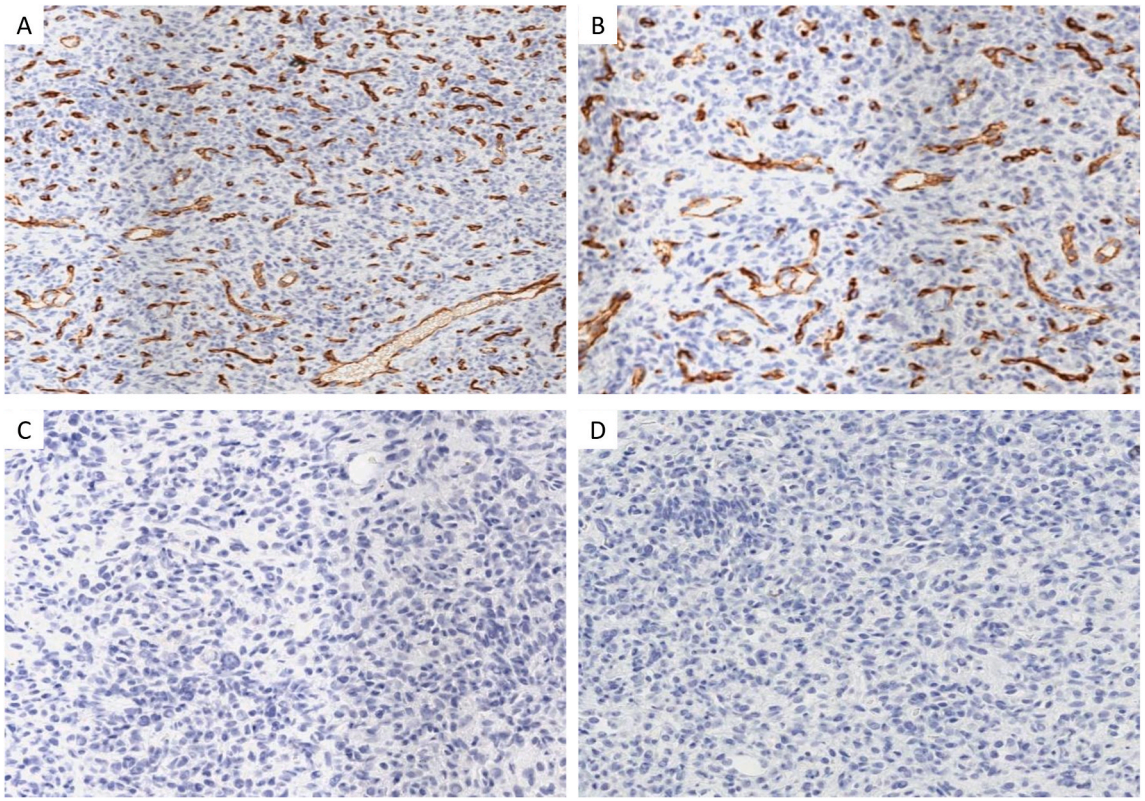

Fig. 4. CD34 immunostaining highlighting the vessels present in the lesion at 10x and 20x (A and B). Negative staining for S-100 (C) and desmin (D) markers. Magnification: 20×.

diagnosis. Common symptoms are bone pain, muscular feebleness, decreased stature, and multiple fractures commonly affecting the ribs, vertebral bodies, and femur's neck.

In this case report, normal development in adulthood and negative family history has led us to exclude genetically determined forms of hypophosphatemic osteomalacia [2] (such as Xlinked hypophosphatemic rickets - XHR or autosomal dominant hypophosphatemic rickets - ADHR) and to suspect the existence of TIO, which was confirmed by clinical biochemistry and diagnostic imaging evaluation. Low serum phosphate, increased urinary phosphate excretion and elevated alkaline phosphatase were the main laboratory findings suggesting more specific investigations (TmP/GFR [17]; 1,25-dihydroxyvitamin D serum level and circulating FGF23 dosage) that led to appropriate diagnosis. Indeed, mesenchymal tumor itself may overexpress FGF23, which lead to hypophosphatemia via inappropriate urinary phosphate wasting and 1α-hydroxylase activity inhibition [18]. In this case, a TRP below 85 % was indicative of renal salt wasting, although the level of urinary phosphate was normal; moreover, calcitriol levels were inappropriately normal or low during TIO, due to reduced function of the 1-alpha-hydroxylase enzyme.

Identifying the primary tumor represents a critical diagnostic challenge and may require a stepwise method including both functional and anatomical imaging. Commonly, the total body functional exams using radiolabeled somatostatin analogues should be conducted first [19]; especially 68Ga DOTATATE PET/CT have demonstrated the highest accuracy in identifying the tumor and therefore has gradually replaced the 111In-octreoctide SPECT becoming the first option for PMT localization [20,21]. The high specificity of these investigations in locating causal tumors lies in their somatostatin receptors (SSTR1-5) expression; through their targeting with radiolabeled somatostatin analogue [22]. Once functional imaging recognizes lesions, the stepwise approach foresees that anatomical imaging tests ought to be done to confirm them. This complex process of TIO suspicion and diagnosis extends the time elapsed between the onset of symptoms and the tumor identification, with an average delay of 6 years (ranging from 9 months to 20 years) [7].

Accordingly, our young patient first performed the 68Ga DOTATATE PET/CT, and then the MRI allowed us to confirm the presence of the tumor and determine its relationship with the surrounding tissues, guiding surgical resection. The patient, despite the complete resolution of metabolic alterations and the good recovery of autonomy, has persistent dorsum lumbar pain due to the vertebral deformities and a heterometry of the lower limbs, following the multiple interventions he suffered.

Skeletal fragility and the occurrence of multiple fractures, that afflicts these patients due to chronic hypophosphatemia, can be further complicated by the diagnostic delay. When this happens in young patients, it is not only responsible for the net reduction in the quality of life, compromising family and professional life, but sometimes it can be responsible for permanent physical damage. The resolutive treatment of PMTs is early surgical resection [23]. This is followed by serum phosphate normalization, FGF23 and 1,

25-dihydroxyvitamin D levels within few weeks. Once the phosphate homeostasis is restored, the clinical manifestations are remarkably improved [24], as recorded during our patient's follow-up. Radiotherapy or guided ablation can represent adjuvant treatments in partially resected tumors or for those with difficult and risky surgery [25,26]. In case of unresectable or unrecognized tumors, phosphate supplements and active vitamin D should be orally administered [27].

4. Conclusion

At present, research data on TIO are still scarce and its diagnosis is a great clinical challenge [28], as confirmed by this case report. Progressive weakness, bone and muscle pain, especially in the presence of fragility fractures not otherwise explained and associated with hypophosphatemia are the main signs that made a suspect of oncogenic osteomalacia.

The undeniable aspect of our case is the long diagnostic delay. In particular, a proper diagnosis was made after 46 months from the onset of symptoms, which led to worsening of general condition and a consequent severe disability. Moreover, missing the appropriate diagnosis impacted treatments administration, since the patient underwent three surgical procedures for fractures and two medical treatments (corticosteroids and neridronate) before the final resolutive surgical resection of tumor. Although commonly described in literature, the diagnostic delay is impressive. Therefore, we foster a mandatory multidisciplinary discussion for the differential diagnosis of fragility fractures, from the general practitioner to the endocrinologist and orthopedic specialist. The correct diagnostic approach to this disease lies in the careful interpretation of laboratory tests, explaining the values of urinary phosphorus and 1,25-dihydroxyvitamin D for the value of circulating phosphate. In addition, some PMT's are molecular driven by FN1-FGFR translocation, this had encouraged interest in the tailored targeting of FGFR1 with the aim to inhibit FGF23 secretion and tumor growth [29].

Our observations aimed to remark that the clinicians involved in the diagnostic setting of osteomalacia have to take a critical attitude for all cases of rapid, unexpected and so-called "sine *materia*" bone pain. We also suggest adhering to Cancer Registry for rare tumors/diseases, an information system useful to define appropriate health programs and improve disease-specific guidelines.

Ethics statement

Written informed consent was obtained from the patient for the publication of this case report.

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Data availability statement

All data were included in article.

CRediT authorship contribution statement

Anna Maria Bochicchio: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Aldo Cammarota:** Writing – review & editing, Formal analysis, Data curation. **Giovanni Storto:** Formal analysis, Data curation. **Luciana Possidente:** Formal analysis, Data curation. **Antonio Villonio:** Formal analysis, Data curation. **Ludmila Carmen Omer:** Writing – original draft, Formal analysis, Data curation. **Geppino Falco:** Writing – review & editing. **Simona Laurino:** Writing – original draft, Formal analysis, Conceptualization. **Sabino Russi:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.K. Drezner, Tumor-induced osteomalacia, Rev. Endocr. Metab. Disord. 2 (2001) 175–186, https://doi.org/10.1023/a:1010006811394.
[2] S.M. Jan de Beur, Tumor-induced osteomalacia, JAMA 294 (2005) 1260–1267, https://doi.org/10.1001/jama.294.10.1260.
[3] A.L. Folpe, Phosphaturic mesenchymal tumors: a review and update, Semin. Diagn. Pathol. 36 (2019) 260–268, https://doi.org/10.1053/j.semdp.2019.07.002.
[4] D.J. Evans, J.G. Azzopardi, Distinctive tumours of bone and soft tissue causing acquired vitamin-D-resistant osteomalacia, Lancet 1 (1972) 353–354, https://doi.org/10.1016/s0140-6736(72)92844-9.
[5] J. Feng, Y. Jiang, O. Wang, M. Li, X. Xing, L. Huo, F. Li, W. Yu, D.-R. Zhong, J. Jin, Y. Liu, F. Qi, W. Lv, L. Zhou, X.-W. Meng, W.-B. Xia, The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases, Endocr. J. 64 (2017) 675–683, https://doi.org/10.1507/endocrj.EJ16-0587.

[6] P. Florenzano, I.R. Hartley, M. Jimenez, K. Roszko, R.I. Gafni, M.T. Collins, Tumor-induced osteomalacia, Calcif. Tissue Int. 108 (2021) 128–142, https://doi.org/10.1007/s00223-020-00691-6.

[7] A.L. Folpe, J.C. Fanburg-Smith, S.D. Billings, M. Bisceglia, F. Bertoni, J.Y. Cho, M.J. Econs, C.Y. Inwards, S.M. Jan de Beur, T. Mentzel, E. Montgomery, M. Michal, M. Miettinen, S.E. Mills, J.D. Reith, J.X. O'Connell, A.E. Rosenberg, B.P. Rubin, D.E. Sweet, T.N. Vinh, L.E. Wold, B.M. Wehrli, K.E. White, R.J. Zaino, S.W. Weiss, Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature, Am. J. Surg. Pathol. 28 (2004) 1–30, https://doi.org/10.1097/00000478-200401000-00001.

[8] Y. Wang, Y. Xiang, Y. Bian, B. Feng, Y. Liu, X. Zhou, L. Zhou, X. Weng, Glomus tumors associated with the bone and joints: a review of 91 cases, Ann. Transl. Med. 8 (2020) 1460, https://doi.org/10.21037/atm-20-6998.

[9] Y. Jiang, W. Xia, X. Xing, B.C. Silva, M. Li, O. Wang, H. Zhang, F. Li, H. Jing, D. Zhong, J. Jin, P. Gao, L. Zhou, F. Qi, W. Yu, J.P. Bilezikian, X. Meng, Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature, J. Bone Miner. Res. 27 (2012) 1967–1975, https://doi.org/10.1002/jbmr.1642.

[10] W.H. Chong, A.A. Molinolo, C.C. Chen, M.T. Collins, Tumor-induced osteomalacia, Endocr. Relat. Cancer 18 (2011) R53–R77, https://doi.org/10.1530/ERC-11-0006.

[11] F. Obeidin, B.A. Alexiev, Glomus tumor, PathologyOutlines.Com. http://www.pathologyoutlines.com/topic/softtissueglomus.htm, 2022. (Accessed 28 October 2022).

[12] C.K. Ledford, N.A. Zelenski, D.M. Cardona, B.E. Brigman, W.C. Eward, The phosphaturic mesenchymal tumor: why is definitive diagnosis and curative surgery often delayed? Clin. Orthop. Relat. Res. 471 (2013) 3618–3625, https://doi.org/10.1007/s11999-013-3178-1.

[13] R.A. McCANCE, Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years, Q. J. Med. 16 (1947) 33–46.

[14] R. Raj, S. Hasanzadeh, M. Dashtizadeh, M. Kalantarhormozi, K. Vahdat, M.H. Dabbaghmanesh, I. Nabipour, M. Ravanbod, M. Assadi, B. Hashemi, K. Asadipooya, Oncogenic osteomalacia secondary to glomus tumor, Endocrinol. Diabetes Metab. Case Rep. 2021 (2021), https://doi.org/10.1530/EDM-20-0202.

[15] M. Dehghani, M.H. Dabbaghmanesh, A. Khalafi-Nezhad, N. Riazmontazer, A. Dehghanian, R. Vojdani, M. Sasani, Glomus tumor as a cause of oncogenic osteomalacia, Clin. Cases Miner. Bone Metab. 14 (2017) 359–362, https://doi.org/10.11138/ccmbm/2017.14.3.359.

[16] R. Barai, T. Tsang, L. Cespedes, Tumour-induced osteomalacia due to residual benign glomangioma, BMJ Case Rep. 15 (2022), https://doi.org/10.1136/bcr-2022-250237.

[17] P. Manghat, R. Sodi, R. Swaminathan, Phosphate homeostasis and disorders, Ann. Clin. Biochem. 51 (2014) 631–656, https://doi.org/10.1177/0004563214521399.

[18] T. Shimada, H. Hasegawa, Y. Yamazaki, T. Muto, R. Hino, Y. Takeuchi, T. Fujita, K. Nakahara, S. Fukumoto, T. Yamashita, FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis, J. Bone Miner. Res. 19 (2004) 429–435, https://doi.org/10.1359/JBMR.0301264.

[19] W.H. Chong, S. Yavuz, S.M. Patel, C.C. Chen, M.T. Collins, The importance of whole body imaging in tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 96 (2011) 3599–3600, https://doi.org/10.1210/jc.2011-1757.

[20] J. Zhang, Z. Zhu, D. Zhong, Y. Dang, H. Xing, Y. Du, H. Jing, Z. Qiao, X. Xing, H. Zhuang, F. Li, 68ga DOTATATE PET/CT is an accurate imaging modality in the detection of culprit tumors causing osteomalacia, Clin. Nucl. Med. 40 (2015) 642–646, https://doi.org/10.1097/RLU.0000000000000854.

[21] D. El-Maouche, S.M. Sadowski, G.Z. Papadakis, L. Guthrie, C. Cottle-Delisle, R. Merkel, C. Millo, C.C. Chen, E. Kebebew, M.T. Collins, 68Ga-DOTATATE for tumor localization in tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 101 (2016) 3575–3581, https://doi.org/10.1210/jc.2016–2052.

[22] M. Houang, A. Clarkson, L. Sioson, M.S. Elston, R.J. Clifton-Bligh, M. Dray, D. Ranchere-Vince, A.-V. Decouvelaere, A. de la Fouchardiere, A.J. Gill, Phosphaturic mesenchymal tumors show positive staining for somatostatin receptor 2A (SSTR2A), Hum. Pathol. 44 (2013) 2711–2718, https://doi.org/10.1016/j.humpath.2013.07.016.

[23] Z. Yin, J. Du, F. Yu, W. Xia, Tumor-induced osteomalacia, Osteoporos. Sarcopenia. 4 (2018) 119–127, https://doi.org/10.1016/j.afos.2018.12.001.

[24] M.L. Brandi, G.P.R. Clunie, P. Houillier, S.M. Jan de Beur, S. Minisola, R. Oheim, L. Seefried, Challenges in the management of tumor-induced osteomalacia (TIO), Bone 152 (2021) 116064, https://doi.org/10.1016/j.bone.2021.116064.

[25] E. Hesse, H. Rosenthal, L. Bastian, Radiofrequency ablation of a tumor causing oncogenic osteomalacia, N. Engl. J. Med. 357 (2007) 422–424, https://doi.org/10.1056/NEJMc070347.

[26] A.H. Hautmann, M.G. Hautmann, O. Kölbl, W. Herr, M. Fleck, Tumor-induced osteomalacia: an up-to-date review, Curr. Rheumatol. Rep. 17 (2015) 512, https://doi.org/10.1007/s11926-015-0512-5.

[27] M. Peacock, J.E. Aaron, P.J. Heyburn, B.E. Nordin, The action of 1alphahydroxy vitamin D3 and phosphate supplements in hypophosphataemic osteomalacia, Adv. Exp. Med. Biol. 81 (1977) 431–440, https://doi.org/10.1007/978-1-4613-4217-5_44.

[28] L. Filipová, V. Zikán, M. Krsek, D. Netuka, M. Michal, I. Lazúrová, Tumor induced osteomalacia - a long way toward correct diagnosis and management, Bone Rep 16 (2022) 101180, https://doi.org/10.1016/j.bonr.2022.101180.

[29] J.-C. Lee, S.-Y. Su, C.A. Changou, R.-S. Yang, K.-S. Tsai, M.T. Collins, E.S. Orwoll, C.-Y. Lin, S.-H. Chen, S.-R. Shih, C.-H. Lee, Y. Oda, S.D. Billings, C.-F. Li, G. P. Nielsen, E. Konishi, F. Petersson, T.O. Carpenter, K. Sittampalam, H.-Y. Huang, A.L. Folpe, Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors, Mod. Pathol. 29 (2016) 1335–1346, https://doi.org/10.1038/modpathol.2016.137.