Bone Reports 21 (2024) 101772

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Tumor-induced osteomalacia: A systematic literature review

Noelia Álvarez-Rivas [a,*], Gloria Lugo-Rodríguez [b], Jose Ramón Maneiro [c], Carlota Iñiguez-Ubiaga [d], Rafael Benito Melero-Gonzalez [e], Tania Iglesias-Cabo [f], Loreto Carmona [g], Carlos García-Porrúa [h], Francisco Javier de Toro-Santos [i,j]

[a] Rheumatology Department, Hospital Público da Mariña, Servizo Galego de Saúde (SERGAS), Burela, Spain
[b] Endocrinology Department, Complexo Hospitalario Universitario de A Coruña (CHUAC), Servizo Galego de Saúde (SERGAS), A Coruña, Spain
[c] Rheumatology Department, Complexo Hospitalario Universitario de Santiago (CHUS), Servizo Galego de Saúde (SERGAS), Santiago de Compostela, Spain
[d] Rheumatology Department, Hospital Universitario del Bierzo, Servicio de Salud de Castilla y León (SACYL), Ponferrada, Spain
[e] Rheumatology Department, Complexo Hospitalario Universitario de Ourense (CHUO), Servizo Galego de Saúde (SERGAS), Orense, Spain
[f] Statistical Consulting Unit, Scientific and Technical Services, University of Oviedo, Oviedo, Spain
[g] Instituto de Salud Musculoesquelética, Madrid, Spain
[h] Rheumatology Department, Complexo Hospitalario Universitario de Lugo (CHULA), Servizo Galego de Saúde (SERGAS), Lugo, Spain
[i] Instituto de Investigación Biomédica de A Coruña (INIBIC), Universidade de A Coruña, Complexo Hospitalario Universitario de A Coruña (CHUAC), Servizo Galego de Saúde (SERGAS), A Coruña, Spain
[j] Rheumatology Department, Complexo Hospitalario Universitario de A Coruña (CHUAC), Servizo Galego de Saúde (SERGAS), A Coruña, Spain

ARTICLE INFO

Keywords:
Osteomalacia and rickets
Tumor-induced bone disease
Disorders of calcium/phosphate metabolism
PTH/Vit D/FGF23
Systematic review

ABSTRACT

Introduction: Tumor-induced osteomalacia (TIO), is a rare acquired paraneoplastic syndrome characterized by defective bone mineralization, caused by the overproduction of fibroblast growth factor 23 (FGF23) by a tumor.
Material and methods: We conducted a systematic review to identify all case reports of TIO, focusing on those associated with mesenchymal tumors. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) consensus, and we included patients with a diagnosis of TIO and histological confirmation of phosphaturic mesenchymal tumors or resolution of the condition after treatment of the tumor. Bibliographical searches were carried out until December 2023 in the Cochrane Library, Medline and Embase, as well as congress abstracts online.
Results: We identified 769 articles with 1979 cases reported. Most patients were adults, with a higher incidence on men. Disease duration before diagnosis is a mean of 4.8 years. Most tumors were histologically classified as PMT. Lower limbs were the predominant location. Hypophosphatemia was present in 99.8 % of patients. The FGF23 was elevated at diagnosis in 95.5 %. Resection of the tumor was the treatment of choice in most of patients. After resection, there was a clinical improvement in 97.6 % of cases, and serum phosphorus and FGF23 levels returned to normal ranges in 91.5 % and 81.4 % of the patients, respectively.
Conclusion: TIO is usually misdiagnosed with rheumatological or musculoskeletal disorders. The diagnosis should be suspected in patients with hypophosphatemic osteomalacia, and the measurement of serum FGF23 can be useful for diagnosis and management.

1. Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare acquired paraneoplastic syndrome, characterized by defective bone and cartilage mineralization in children, and bone mineralization in adults (Drezner, 2001).

It is caused by the tumoral overproduction of fibroblast growth factor 23 (FGF23), a physiological regulator of phosphate balance that lowers renal phosphate uptake by decreasing proximal tubule reabsorption of phosphates. FGF23 also inhibits kidney 1 α-hydroxylase, thereby decreasing vitamin D activation and implicitly reducing intestinal phosphate absorption (Chong et al., 2011; Shimada et al., 2004).

The type of tumors predominantly associated with TIO are small, benign, and slowly growing tumors of mesenchymal origin. Almost all cases are caused by a single entity, with characteristic morphological and histochemical findings, originally known as 'phosphaturic

* Corresponding author at: Hospital Público da Mariña, Rúa Rafael Vior, s/n, Burela, Lugo. Spain.
E-mail address: nalvriv@gmail.com (N. Álvarez-Rivas).

https://doi.org/10.1016/j.bonr.2024.101772
Received 15 March 2024; Received in revised form 3 May 2024; Accepted 5 May 2024
Available online 8 May 2024

mesenchymal tumors mixed connective variant' (PMT-MCT) (Weidner and Santa, 1987; Folpe et al., 2004) and now simply as 'phosphaturic mesenchymal tumors' (PMT) (Folpe, 2019). These tumors can be located anywhere in the body from the skull to the feet, involving either bone or soft tissue (Weidner and Santa, 1987; Folpe et al., 2004; Brandi et al., 2021).

Clinical features include diffuse bone pain, gradual muscle weakness, and multiple fragility fractures in adults, or rachitic deformities in children. Biochemically, TIO is characterized by hypophosphatemia due to renal phosphate wasting, low or inappropriately normal 1,25 (OH) 2D3, elevated levels of alkaline phosphatase, and normal levels of serum calcium, 25 hydroxyvitamin D and parathyroid hormone (PTH) (Drezner, 2001; Chong et al., 2011; Carpenter TO, 2003; Minisola et al., 2017).

An epidemiological study in Denmark estimated the annual incidence of TIO to be 0.13 per 100,000 and the prevalence not >0.70 per 100,000 persons (Abrahamsen et al., 2021). Nevertheless, its global prevalence and incidence remain unknown. Thus far, only approximately 1000 cases have been described in the world's literature (Florenzano et al., 2021). The diagnosis is commonly delayed by several years due to the rarity of the disease, the nonspecific nature of the symptoms, the lack of routine testing of serum phosphate levels, and the challenges to finding the tumor (Chong et al., 2011; Minisola et al., 2017; Jan de Beur et al., 2023). Furthermore, misdiagnoses or even missed diagnoses occur frequently, which delay diagnosis and the correct treatment. Patients with TIO may often be misdiagnosed with rheumatological, musculoskeletal disorders, oncological, or psychiatric disorders (Brandi et al., 2021). This can lead to long-term disability and higher morbidity with a significant impact on quality of life (QoL) (Jerkovich et al., 2021; Minisola et al., 2022).

Infrequently, a "TIO-like syndrome" can present in association with a hematologic malignancy or solid tumor such as breast carcinoma, prostate carcinoma, colon carcinoma, small cell lung cancer, ovarian cancer, or anaplastic thyroid cancer. The term cancer-associated osteomalacia (CAO) has been proposed for this condition (Florenzano et al., 2021). A recent systematic review included 1725 patients with TIO and CAO (Rendina et al., 2022), and another systematic review focused on patients where the causative tumor was localized, and treatment led to cure or marked improvement of TIO, but said revision also included solid tumors (Bosman et al., 2022).

In an effort to better understand this condition and improve the awareness of TIO in rheumatology, we performed a systemic review to summarize the most frequent misdiagnoses of rheumatic diseases, as well as the most common forms of presentation, locations, biochemical features, and diagnostic and therapeutical approaches. Purposedly, we have excluded cases with TIO-like syndrome.

2. Materials and methods

We conducted a systemic review to identify all case reports of TIO, focusing on those associated with mesenchymal tumors. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) consensus for the reporting (Liberati et al., 2009).

2.1. Search strategy

The Cochrane Library, Medline and Embase databases were searched, as well as online congress abstracts from the European Alliance of Associations for Rheumatology (EULAR), the American College of Rheumatology (ACR) and the American Society for Bone and Mineral Research (ASBMR) up to December 31, 2023. Key words and subject terms used in the search included: "osteomalacia", "rickets", "oncogenic osteomalacia", "tumor induced osteomalacia" "phosphaturic mesenchymal tumor", "connective tissue neoplasm", "hemangiopericytoma", "giant cell tumor" and "bone sarcoma". The searches were conducted with language restrictions (English, French, Italian, Portuguese, or Spanish). The full search strategy is available in supplementary file 1.

2.2. Selection criteria

We included all case-reports, case-series, and cohorts of patients with a diagnosis of TIO with tumor localization and resolution (partial or complete) of the condition after treatment of the tumor or histological confirmation of a tumor of mesenchymal origin. For each publication, we extracted: publication details, tumor location, clinical and biochemical characteristics, histological type, and treatments used. Cases reports without biochemical evidence of TIO, or cases associated with hematologic malignancies or solid tumors (CAO), as well as cases of polyostotic fibrous dysplasia of bone and neurofibromatosis were excluded. Moreover, in order to avoid inaccurate or incorrect diagnoses, cases in which the tumor was not localized were also excluded.

Two reviewers independently screened titles and abstracts and evaluated the eligibility of the identified studies, using a third reviewer for consensus when discrepancies arose. Once unrelated articles were excluded, the full report of all the selected articles was reviewed. Subsequently, articles that did not fulfill all the selection criteria were excluded. A manual search for references was also performed on publications selected for a full text review with the aim of identifying additional relevant articles.

2.3. Data extraction

One author extracted data using an ad hoc extraction data sheet in Excel. The collected information included: publication details, study design, medical or surgical department that published the cases, demographic data (age and sex), initial diagnosis (to capture misdiagnoses), clinical and biochemical features, tumor characteristics (location, histology, size, Ki-67degree according to the World Health Organization, and FGF23 expression in the tumor), bone mineral density (BMD) at the lumbar spine and femoral neck (assessed by dual-energy X-ray absorptiometry), diagnostic tools, type of treatment, and outcome (response to treatment, presence and location of recurrences, duration of follow-up, and survival).

Being that the majority of studies were case-reports, the risk of bias was difficult to assess, although given our descriptive goal and the fact that it is a rare disease, a risk of bias assessment might not reflect the true existence of biases.

2.4. Statistical analysis

A quantitative summary was carried out, calculating aggregate means (or medians) and standard deviations (or interquartile ranges) as well as absolute and relative frequencies. Difference analysis was carried out by sex, age, location of the tumor, appearance of recurrences, anatomical region affected, presentation of fragility fractures, and size of the tumor. Differences among qualitative variables were analyzed using the Pearson Chi Squared or Fisher test, depending on the expected counts. If the comparison was between a qualitative variable among two groups, Student's test or Wilcoxon test for independent samples was applied, depending on the normality hypothesis. After verifying the normality and homoscedasticity hypotheses, ANOVA or Kruskal-Wallis test was preferred for three or more groups. The level of significance utilized during analysis was 0.05. The analysis was carried out using R (R Development Core Team), version 4.1.3.

3. Results

The results for the search and selection process are shown in Fig. 1. The systematic search retrieved 3270 references and 78 meeting abstracts. After title/abstract screening, 932 articles were retrieved for full text review, 9 articles proved impossible to locate and a total of 714 articles and 11 meeting abstracts were included. In addition, 44 hand

searches were also included (Fig. 1, supplementary file 2, supplementary Table 1). In the 769 articles identified, 1979 cases were reported, mainly by endocrinology (31.7 %), pathology (14.9 %), nuclear medicine (11.8 %), orthopedics (8.7 %), otolaryngology (4.2 %) and rheumatology (4.0 %) departments.

3.1. General characteristics

The majority of patients were adults (96.1 %), with a mean age at diagnosis of 46.3 (±14.8) years (range 2–87). Of the 1705 patients with information on sex, 56.6 % were male and 43.4 % were women with a 1.3 sex ratio (male/female). Disease duration before diagnosis ranged from 1 month to 42 years, with a mean of 4.8 years (± 4.61). Compared to men, women could be older at diagnosis (47.2 ± 14.6 vs 45.7 ± 14.9 years, $p = 0.037$) and showed lower levels of alkaline phosphatase, lower serum 1,25-dihydroxyvitamin D levels and higher levels of PTH (Table 1).

For 157 patients there was information about a previous misdiagnosis of a rheumatic or musculoskeletal disease (RMD). The most frequent misdiagnosis was osteoporosis (37.2 %), followed by spondyloarthritis (26.3 %), fibromyalgia (8.8 %), rheumatoid arthritis (7.3 %), and lumbar disc hernia or lumbar canal stenosis (3.6 %). Women showed a higher frequency of misdiagnosis of osteoporosis (53.7 % vs 26.3 %, $p < 0.001$) and fibromyalgia (14.9 % vs 3.5 %, $p < 0.001$). In men, the most prevalent misdiagnoses were spondyloarthritis (35.3 % vs 7.4 %, $p < 0.001$), and osteoporosis (Fig. 2).

The most common symptoms reported were diffuse bone pain (97.2 %), muscle weakness (83 %), and insufficiency fractures (84.7 %). Fractures were frequently located in the hip or femur (289/754), ribs (236/754), and vertebral region (162/754). Pseudofractures were reported in 27.2 % of the cases. In addition, 43.1 % of the cases reported fractures in multiple locations (≥ 3). Bone densitometric values were available for only 175 cases, with severe reduction in BMD at lumbar spine or femoral neck (T score ≤ −2.5 or Z score ≤ −2.0) in 65.1 %. Cases with fractures were characterized by older age at diagnosis, large diagnostic delay, and unfavorable densitometry T scores (Table 2).

Rarely, local symptoms were related to the tumor itself ($n = 62$ patients; 3.1 %). But when symptoms where show, they were related to tumors in the following locations: head and neck ($n = 50$; 80.6 %), spine

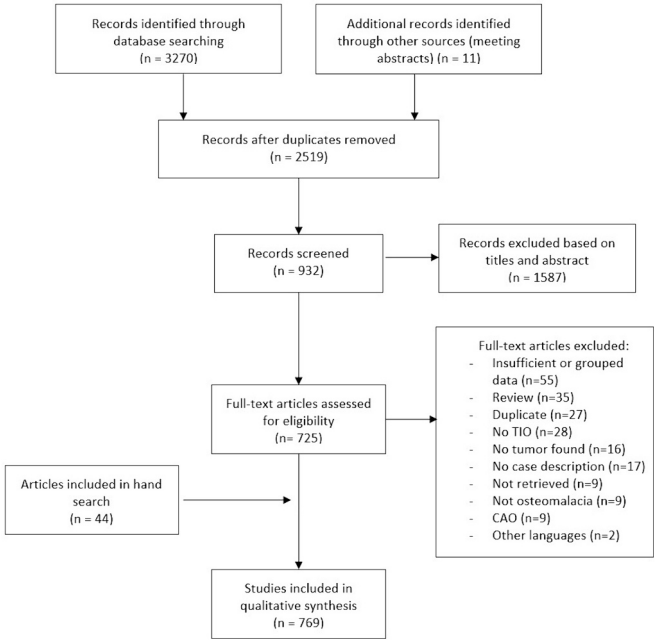

Fig. 1. Flow chart of studies selection.

(n = 6; 9.7 %) and lower extremities ($n = 4$; 6.5 %). Nasal airway obstruction or blockage was the most common symptom (19.3 %).

In pediatric TIO, the presence of features consistent with rickets was frequently reported (34 of 40 patients).

3.2. Biochemical findings

Hypophosphatemia was reported in 99.8 % of the cases, with an average value of 1.5 (±0.4) mg/dL. Serum calcium was usually normal (84.5 %), serum phosphatase alkaline was typically elevated (94.9 %), and low levels of 1,25-dihydroxyvitamin D were frequent (69.8 %). Additionally, when reported, the maximum tubular reabsorption of phosphate glomerular filtration rate ratio (TmP/GFR) was decreased in most patients (97.3 %). Twenty-eight patients had tertiary hyperparathyroidism, with a mean diagnostic delay of 12.8 ± 8.5 years.

The levels of circulating FGF23 were reported in 578 cases, either as intact FGF23 (pg/mL) or c-terminal fragment of FGF23 (RU/mL). The majority of patients (95.5 %) had elevated levels of FGF23 at diagnosis, with median serum levels of 291.0 pg/mL (interquartile range 128.9–599.2; $n = 252$) or 489.5 RU/mL (interquartile range 260.1–1005.0; $n = 326$).

3.3. Histopathology and location

Most tumors (81.2 %) were histologically classified as benign PMT or PMTMCT and only 1.7 % of patients were reported as having malignant PMT. Others histologic entities described were hemangiopericytoma (6.3 %), giant cell tumor (1.8 %), benign bone tumors (1.6 %), bone sarcoma (0.9 %), sinonasal hemangiopericytoma like-tumor or glomangiopericytoma (0.8 %) or odontogenic tumor (0.8 %). FGF23 expression by tumor was confirmed in 96.6 % of the cases (342/354). The mean Ki67 proliferation index was 5.1 % (±7.0) although it was only available in 63 patients. The mean tumor size was 3.1 ± 2.3 cm (range 0.2–14.3). Larger tumors seemed to have a longer diagnostic delay and were more likely to be detected on physical examination (Supplementary Table 2). In addition, the serum levels of FGF23 appeared to increase in parallel with the size of the tumor (c-terminal fragment of FGF23 $\rho = 0.345$ ($p < 0.001$), intact FGF23 $\rho = 0.238$ ($p = 0.043$).

Tumors were located in the bones in 44.5 % of cases, in soft tissues in 38.4 %, and in craniofacial bones, paranasal sinuses and sinonasal tracts in 17.0 %. Smaller tumors (<1.5 cm) were more common in bone and larger tumors (>5) in soft tissue ($p = 0.016$). The majority of tumors had a single location, with only 15 cases involving more than one site.

3.4. Tumor localization

Tumors were reported to have been detected by Gallium-68 DOTA based positron emission tomography/computed tomography (^{68}Ga-DOTA-based PET/CT) in 29.1 % of cases, by Tc99m labeled somatostatin analog in 17.0 %, by Indium-111 pentetreotide scans with single-photon emission and computed tomography (Octreoscan SPECT/CT) in 11.7 % of cases, and by 18-F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in 9.6 %. The detection rate was 98.9 % (462/467) for ^{68}Ga-DOTA-based PET/CT, 95.3 % (102/107) for Tc99m-HYNIC-octreotide scan, 79.4 % (189/238) for Octreoscan SPECT/CT, and 74.8 % (211/282) for ^{18}F-FDG PET/CT. The most common anatomical imaging techniques were magnetic resonance imaging (MRI) (49.6 %) and CT (34.6 %). In 106 patients, selective venous sampling (SVS) was used to confirm the diagnosis, being positive in 94 patients (88.7 %). In 98 cases (7.0 %) the tumor was reported to have been detected during a physical examination. Tumors located in soft tissues were more frequently detected in the physical examination than bone tumors (61.1 % vs 33.8 %, $p < 0.001$).

Lower limbs were the predominant location (979; 49.5 %), followed by head and neck (534; 27.0 %) and, much less frequently, upper extremities (146; 7.4 %), thorax and abdomen (66; 4.9 %) and spinal

Table 1
Analysis by sex of general and biochemical features.

	Men		Women		*P* value
	n		n		
Age at diagnosis, years	950	45.7 (±14.9)	727	47.2 (±14.6)	0.037
Diagnosis delay, years	625	4.7 (±4.1)	488	5.0 (±5.1)	0.234
Tumor size, cm	369	3.1 (±2.2)	296	3.1 (±2.3)	0.804
Biochemical findings					
• Phosphate, mg/dL	599	1.5 (±0.4)	456	1.4 (±0.4)	0.194
• Calcium, mg/dL	406	9.1 (±0.7)	295	9.0 (±0.6)	0.574
• ALP, U/L	401	466.1 (±509.4)	304	389.4 (±421.4)	0.029
• PTH, pg/mL	347	72.7 (±62.5)	256	88.4 (±97.8)	0.024
• 1,25 (OH)2D, pg/mL	244	20.6 (±16.2)	143	16.5 (±11.8)	0.004
• TmP/GFR, mg/dL	103	1.0 (±0.4)	62	1.1 (±0.6)	0.268
• C-term FGF23, RU/mL	180	1485.3 (±7327.9)	135	1078.8 (±1859.7)	0.476
• Intact FGF23, pg/mL	153	667.7 (±1101.7)	97	752.1 (±1588.3)	0.648
Clinical characteristics					
• Bone pain, n; %		672 (97.1)		520 (97.0)	0.922
• Weakness, n; %		420 (81.5)		339 (84.3)	0.270
• Bone fractures, n; %		404 (83.8)		314 (84.9)	0.677
Anatomic region					0.004
• Lower limbs, n; %		529 (56.2)		334 (46.2)	
• Upper limbs, n; %		67 (7.1)		62 (8.6)	
• Head/neck, n; %		249 (26.4)		226 (31.3)	
• Thorax/abdomen, n; %		43 (4.6)		42 (5.8)	
• Spinal, n; %		40 (4.2)		43 (5.9)	
• Others, n; %		14 (1.5)		16 (2.2)	

Continuous data are presented as mean (standard deviation) depending on the use of a parametric or non-parametric test respectively. Categorical data are presented as absolute and relative frequency distribution.
ALP total alkaline phosphatase, PTH parathyroid hormone, TmP/GFR maximum tubular reabsorption of phosphate glomerular filtration rate ratio, C-term FGF23 C terminal fibroblast growth factor 23, Intact FGF23 Intact fibroblast growth factor.

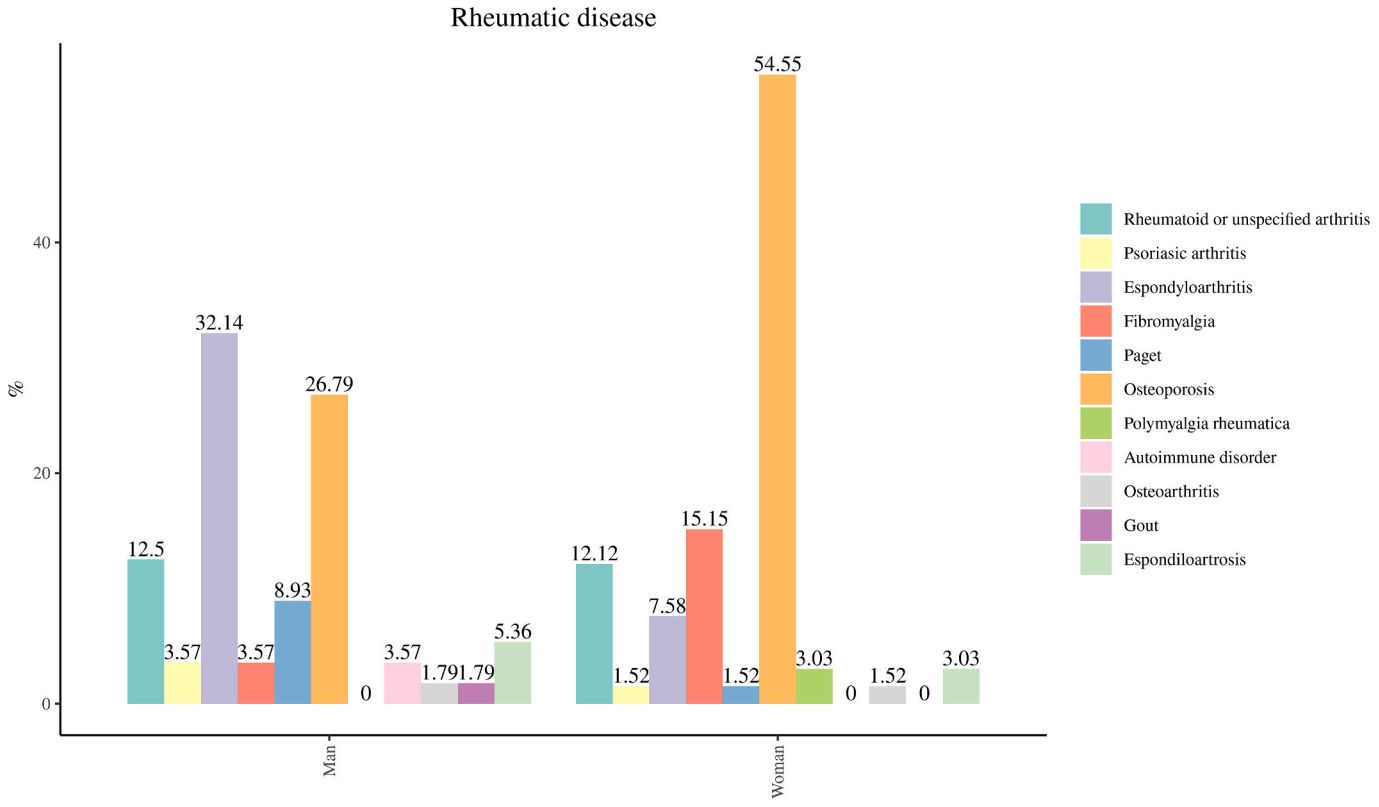

Fig. 2. Rheumatological or musculoskeletal misdiagnosis.

region (92; 4.6 %). In 4.9 % of the reports the tumor location was not reported.

3.5. *Therapy and outcome*

Surgical treatment—both exeresis (94.5 %) and curettage (4.8 %)—was the treatment of choice in 1653 patients (97.1 %). In 127 cases the

Table 2
Analysis by fragility fracture.

	Fracture		No fracture		P value
	n		n		
Age at diagnosis, years	720	47.3 (±14.9)	136	39.5 (±16.8)	<0.001
Diagnosis delay, years	598	5.1 (±4.8)	109	3.9 (±3.6)	0.004
Tumor size, cm	286	3.4 (±2.3)	58	3.4 (±2.6)	0.964
Biochemical findings					
• Phosphate, mg/dL	570	1.4 (±0.4)	112	1.5 (±0.4)	0.210
• Calcium, mg/dL	366	9.1 (±0.5)	66	9.2 (±0.70)	0.239
• ALP, U/L	380	443.8 (±535.1)	81	525.6 (±493.9)	0.207
• PTH, pg/mL	326	82.3 (±91.5)	54	76.2 (±74.6)	0.640
• 1,25 (OH)2D, pg/mL	231	17.9 (±13.2)	38	19.6 (±16.9)	0.567
• TmP/GFR, mg/dL	76	1.1 (±0.5)	17	1.2 (±0.7)	0.710
• C-term FGF23, RU/mL	187	1012.9 (±1648.6)	31	4214.8 (±17,457.4)	0.316
• Intact FGF23, pg/mL	147	625.2 (±931.3)	16	477.8 (±334.2)	0.200
Densitometry score					
• T score lumbar spine	100	−2.5 (±1.4)	6	−2.2 (±1.8)	0.721
• T score femoral neck	68	−2.8 (±1.4)	3	−2.3 (±1,9)	0.555
• Z score lumbar spine	46	−2.7 (±2.1)	4	−1.7 (±1.3)	0.341
• Z score femoral neck	38	−1.9 (±1.8)	4	−2.5 (2.2)	0.545

Continuous data are presented as mean (standard deviation) or median (interquartile range) depending on the use of a parametric or non-parametric test respectively. ALP total alkaline phosphatase, PTH parathyroid hormone, TmP/GFR maximum tubular reabsorption of phosphate glomerular filtration rate ratio, C-term FGF23 C terminal fibroblast growth factor 23, Intact FGF23 Intact fibroblast growth factor.

resection was incomplete. Some cases (4.2 %) received adjunctive therapy with radiotherapy, chemotherapy, octreotide, or embolization. Following resection of the responsible tumors, 89.9 % of cases responded to the treatment, with clinical response in 97.6 % ($n = 787$), serum phosphorus returned to normal ranges in 91.5 % patients ($n = 1252$). Likewise, FGF23 concentrations fell to within normal ranges post-surgery in 81.4 % of patients ($n = 275$).

In the cases in which the tumor was unresectable, a variety of treatments were reported, such as radiotherapy, guided ablation, or burosumab. Eighteen patients received burosumab, one prior to surgical resection, three who was not eligible for surgery, eight with persistent disease, two after recurrence and three who refused surgery. Data on outcomes are available for twelve patients, all of whom but one improved, and in whom phosphorus returned to normal. The doses varied between 0.3 and 7.7 mg/Kg per month (Table 3).

The mean follow-up time was 33.0 months (±50.5; range 0.5–732) in 679 patients. Recurrent disease was reported in 153 patients ($n = 854$) with a median of 38.2 ± 42.9 months (range 1–204), usually involving local recurrences (78.1 %). Recurrence was reported in 47.4 % tumors located at bone, 32.6 % in soft tissues, and 20.0 % in craniofacial bones, paranasal sinuses and sinonasal tracts. In patients with recurrence, normalization of serum phosphorus levels (77.5 % vs 97.9 %, $p < 0.001$) and FGF23 (50.0 % vs 91.3 %, $p < 0.001$) post treatment was not frequent, but previous incomplete surgical resection (27.8 % vs 6.2 %, $p < 0.001$) was frequently reported. A long diagnostic delay, large tumor size at diagnosis, and higher preoperative FGF23 level, were also common (Table 4). The group of tumors classified histologically as malignant (malignant PMT, bone sarcoma, soft tissue sarcoma, malignant vascular and tumors with distant metastasis) presented a higher rate of recurrences compared to benign ones (70.4 % vs 14.4 %, $p < 0.001$). Distant metastases were unusual (25/1979) and were generally found in the lung (53.12 %).

4. Discussion

The aim of this paper was to describe the clinical course of TIO patients and to analyze the misdiagnoses of RMDs. A systematic review of TIO cases was published by Rendina et al., but they also included cases with clinical suspicion of TIO without tumor confirmation (Rendina et al., 2022). Similarly, Bosman et al. systematically reviewed cases with a confirmed tumor, although they also included TIO-like paraneoplastic syndrome related to solid tumors (Bosman et al., 2022). Our review included only TIO cases associated with mesenchymal tumors, confirmed by either the resolution (partial/complete) after antitumoral treatment or histological confirmation, and so results will differ from previous reviews. Also, we wanted to focus on the most frequent misdiagnoses, clinical characteristics, imaging modalities, and treatment outcomes.

Our data show that these tumors occur usually in middle-aged individuals, with a gender predilection from men. These data are consistent with the reviews by Rendina and Bosman but differ from previously published data (Abrahamsen et al., 2021; Rendina et al., 2022; Bosman et al., 2022; Jiang et al., 2012).

A history of long-standing osteomalacia was present in most cases, with a greater delay in diagnosis, reflecting the difficultly of making a timely diagnosis. An incorrect rheumatological diagnosis was reported in 157 patients, being the most frequent misdiagnoses spondyloarthritis and osteoporosis in men, and osteoporosis and fibromyalgia in women. An initial misdiagnosis rate of up 95 % was previously reported, often with RMDs, such as osteoporosis, disc herniation or spinal canal stenosis, spondyloarthritis and fibromyalgia as the most frequent (Feng et al., 2017; Zuo et al., 2017; Hidaka et al., 2022), which can lead to incorrect treatment, a greater diagnostic delay, and an increase in long-term disability. Besides, the low BMD values can easily lead to a misdiagnosis of osteoporosis (Brandi et al., 2021). We found severe reductions in BMD at lumbar spine or femoral neck in 65.1 % of cases with reported bone densitometric values. Furthermore, in long-term hypophosphatemic osteomalacia, axial involvement and entesopathy can be seen, mimicking a spondyloarthritis (Reginato and Coquia, 2003). Feng et al. reported that serum phosphate tests were only performed in 11.1 % of patients when they were seeking medical care for the first time (Feng et al., 2017). Given that the clinical and radiological manifestations of TIO can be confused with other rheumatic diseases, a high index of suspicion is necessary for an early diagnosis. Even more, patients being evaluated for musculoskeletal symptoms should be routinely screened for serum phosphate.

The main clinical features are nonspecific and include bone pain, muscle weakness, and insufficiency fractures at diagnosis, although hypophosphatemia is present in 99.8 % of cases and renal phosphate wasting in 97.3 %, which are key indicators for clinical suspicion of TIO. A high percentage of patients presented fractures in multiple locations and the fractures were frequently located in the hip and/or femur, ribs, and vertebral regions. Similar to our findings, Colangelo et al. reported a severe reduction of BMD at lumbar and femoral sites measured by DXA

Table 3
Review of the published literature on TIO cases with burosumab and localized tumor.

Author, year	Sex/ age	Location of tumor	Serum phosphate (mg/dL)	Serum FGF23 (RU/mL)	Pathology	Burosumab indication	Clinical response	Serum phosphate N	Fracture healing	Treatment response (Mo)	Burosumab dose (mg/Kg)	Tumor growth	Adverse event	Follow-up (Mo)
Aliberti et al., 2023.	M/ 73	Rib	1,1	NA	NA	Refusal surgery	Yes	Yes	NA	15	1,7	No	No	18
Barai et al., 2022	M/ 40	Temporal bone	1,9	NA	Glomus tumor	Incomplete resection	Partial	Yes	Yes	1	0,5	No	No	8
Birkebaek et al., 2021	F/ 2,5	Neck	NA	NA	NA	No surgery	NA	No	NA	NA	NA	NA	NA	NA
Cianferotti et al., 2022	F/46	Presacra	1,2	NA	PMT	Incomplete resection	Yes	Yes	NA	NA	NA	NA	No	NA
Colazo et al., 2021	F/41	Rib	NA	1532	PMT	Prior to surgery	Partial	Yes	NA	NA	NA	NA	No	3
Crotti et al., 2021	F/46	Sacrum	1,2	NA	PMT	Recurrence	Yes	Yes	NA	2	0,8	Yes	No	24
Day et al., 2020	F/52	Intracranial	1,8	225	NA	Refusal surgery	Yes	Yes	NA	2	NA	NA	No	9
Elias et al., 2023	F/37	Humerus	1,83	170,48	PMT	Incomplete resection	NA	NA	NA	NA	0,5	NA	No	NA
Elias et al., 2019	F/52	Acetabulum	1,1	NA	PMT	Refusal surgery	NA	NA	NA	NA	0,4	NA	No	NA
Giehl et al., 2022	M/ 71	C7-T1	1,8	321	NA	No surgery	Partial	Yes	NA	NA	NA	NA	No	NA
Horinouchi et al., 2023	M/ 65	Scapula	1,58	NA	NA	No surgery	Yes	Yes	NA	2	NA	Yes	No	24
Kato et al., 2023	F/41	Maxillary sinus	NA	NA	PMT	Incomplete resection	NA	NA	NA	NA	NA	NA	NA	NA
Kato et al., 2023	M/ 66	Acetabulum	NA	NA	PMT	Incomplete resection	NA	NA	NA	NA	NA	NA	NA	NA
Kato et al., 2023	M/ 80	Ischium	NA	NA	PMT	Incomplete resection	NA	NA	NA	NA	NA	NA	NA	NA
Miyaoka et al., 2020	M/ 43	Cranial base	1,9	NA	PMT	Incomplete resection	NA	Yes	NA	1	0,3	No	No	6
Paccou et al., 2021	F/47	Intradural	1,24	777	PMT	Incomplete resection	NA	Yes	NA	2	NA	NA	No	2
Salica et al., 2020	F/51	Ischium	NA	NA	PMT	Recurrence	Yes	Yes	NA	3	NA	NA	No	NA

F, female; FGF23, fibroblast growth factor 23; M, male; Mo, month; NA, not available; N, normalization; PMT, phosphaturic mesenchymal tumor.

Table 4
Analysis by relapses.

	No relapse		Relapse		P value
	n		n		
Age at diagnosis, years	644	45.8 (±14.9)	137	46.2 (±16.1)	0.789
Diagnosis delay, years	480	4.3 (±3.9)	96	6.8 (±6.4)	<0.001
Tumor size, cm	365	3.1 (±2.1)	47	4.5 (±2.8)	0.002
Biochemical findings					
• Phosphate, mg/dL	392	1.5 (±0.4)	82	1.4 (±0.4)	0.040
• Calcium, mg/dL	250	9.1 (±0.6)	42	9.2 (±0.5)	0.597
• ALP, U/L	271	422.6 (±376.1)	41	612.8 (±820.4)	0.151
• PTH, pg/mL	220	87.2 (±103.7)	31	91.4 (±104.5)	0.837
• 1,25 (OH)2D, pg/mL	154	13.0 (9.0–20.7)	18	9.5 (6.0–19.4)	0.212
• TmP/GFR, mg/dL	53	1.1 (±0.5)	6	1.2 (±0.5)	0.457
• C-term FGF23, RU/mL	122	440.0 (254.7–693.7)	6	1555.92 (962.2–2817.2)	0.002
• Intact FGF23, pg/mL	86	225.0 (129.3–528.5)	20	482.1 (101.7–1039.0)	0.558
Tumor localization					0.607
• Bone, n; %		263 (41.3)		64 (47.4)	
• Soft tissue, n; %		238 (37.4)		44 (32.6)	
• Craniofacial bones, paranasal sinuses and sinonasal tract, n; %		136 (21.3)		27 (20.0)	
Malignant TIO, n; %		16 (29.6)		38 (70.4)	<0.001
Surgery type					0.002
• Curettage, n; %		25 (4.5)		15 (12.5)	
• Resection, n; %		521 (94.6)		102 (85.0)	
• Others, n; %		5 (0.9)		3 (2.5)	
Incomplete resection, n; %		30 (6.2)		25 (27.8)	<0.001
Normalization of phosphorus, n; %		620 (97.9)		76 (77.5)	<0.001
Normalization of FGF23, n; %		147 (91.3)		8 (50.0)	<0.001

Continuous data are presented as mean (standard deviation) or median (interquartile range) depending on the use of a parametric or non-parametric test respectively. Categorical data are presented as absolute and relative frequency distribution.
ALP total alkaline phosphatase, *PTH* parathyroid hormone, *TmP/GFR* maximum tubular reabsorption of phosphate glomerular filtration rate ratio, C-term *FGF23* C terminal fibroblast growth factor 23, *Intact FGF23* Intact fibroblast growth factor, *Malignant TIO* tumor induced osteomalacia classified as malignant on histopathology or those with distant metastases.

(Colangelo et al., 2020). In addition, previous studies have shown that bone microarchitecture and estimated bone strength are severely impaired in patients with TIO compared to healthy controls (Zanchetta et al., 2021).

In our review, the serum FGF23 level was measured in 578 cases, and it was elevated in 95.5 % of cases at the time of presentation, similar to those previously described (Jiang et al., 2012). Only 31 cases showed normal FGF23 levels. Most cases reviewed had normal levels of FGF23 after removal of the responsible tumor. Furthermore, our results suggest that tumor size is positively correlated with FGF23 levels, as well as with diagnostic delay. Therefore, FGF23 serum levels could be used both to diagnose TIO and to monitor response to treatment (Pal et al., 2019).

According to Folpe et al. (Folpe et al., 2004), most of the tumors seem to be PMT, PMT-MCT, or tumors of mesenchymal origin of which 3.3 % were classified histologically as malignant. Other histological types were hemangiopericytoma, glomangiopericytoma, or giant cell tumors. The percentage of malignant tumors is lower than that previously reported by Bosman et al., but they had also included TIO-like paraneoplastic syndrome in association with solid tumors (Bosman et al., 2022). In most tumors, FGF23 expression was detected by immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), or chromogenic in situ hybridization CISH for FGF23.

The tumors occur more frequently in the lower extremities (49.5 %) followed by head and neck (27.0 %), but they also occur less frequently in upper extremities, spinal region, and thorax and abdomen. Therefore, it is very important to scan the entire body, including head and extremities, in search of tumors (Florenzano et al., 2021). A stepwise approach to tumor localization, beginning with functional imaging and followed by anatomical imaging –to confirm the tumor and for preoperative planning— is recommended. Since PMTs express different somatostatin receptors, functional imaging based on somatostatin analogs such a 68Ga-DOTA-based PET/CT, Tc99m-HYNIC-octreotide scan and octreoscan SPECT/CT is recommended as first line diagnostics (Jan de Beur et al., 2023). In our review the most used methods for diagnosis were 68Ga-DOTA-based PET/CT, Tc99m-HYNIC-octreotide scan, Octreoscan SPECT/CT, and 18FDG PET/CT with a detection rate of 98.9, 95.3, 79.4 and 74.8 % respectively. Similar findings have been described in a recent meta-analysis, where 68Ga-DOTA-based PET/CT has been shown to be superior to Octreoscan SPECT/CT and 18F-FDG PET/CT in detecting culprit tumors, so it should be the imaging modality of choice if available (Rayamajhi et al., 2019; Jiang et al., 2020). However, SVS may be considered if additional confirmation of a suspected causative tumor is required or to differentiate between multiple possible lesions seen on functional imaging (Jerkovich et al., 2021).

Complete surgical resection with wide margins is the treatment of choice and was the first-line therapy in most patients. Radiofrequency ablation or cryoablation were effective for cases involving inoperable or partially resected tumors, but these reports included few cases and thus their long-term effectiveness cannot be evaluated. Moreover, burosumab, a fully human monoclonal antibody against FGF23, has recently been approved for the treatment of non-operable, recurrent, or non-localizable tumors. Two phase-II studies have demonstrated that burosumab improves osteomalacia, fracture healing, phosphorus homeostasis, symptoms, and physical function in patients with TIO (Jan de Beur et al., 2021; Imanishi et al., 2021).

As in a previous report (Feng et al., 2017), recurrence was observed in 17.9 % of patients, and it was usually local, and in patients with incomplete surgical resection. Patients in whom serum phosphorus and FGF23 levels did not return to normal experienced more frequently a later recurrence. Li et al. identified as risk factors high FGF23 for refractive outcomes, supported by our review (Li et al., 2020). Therefore, the preoperative FGF23 level could serve as a predictor for recurrence, but more studies are necessary to confirm this result.

Our systematic literature review had several limitations. The studies reviewed were clinical cases or case series, and the data are limited and not uniformly reported. One would have to assume that the cases reported are truly representative of TIO to draw any descriptive conclusions. Furthermore, there was significant variability with respect to FGF23 measurements as they have been performed with different assays. Unfortunately, given the absence of analytical studies, we cannot

draw conclusions regarding outcomes or the comparative effectiveness of treatments.

In summary, diagnosis of TIO is still a challenge due to its low prevalence and unspecific clinical picture that can be confused with other RMDs. Misdiagnosis at presentation is frequent, leading to incorrect treatment, and long-term disability and impaired quality of life. We would like to increase awareness of the diagnosis and consider TIO early in the differential diagnosis of unexplained persistent bone pain and muscle weakness. The diagnosis should be suspected in patients with hypophosphatemic osteomalacia with phosphate wasting and measurements of FGF23 serum levels can be useful for diagnosis, treatment management, and prognostic. Successful surgical resection can lead to a cure for most patients. Burosumab, the first treatment approved by the medical management of TIO, may represent an effective alternative to conventional treatment in those patients non-operable and with recurrent or non-localizable tumors. Periodic follow-up should be carried out to detect possible recurrences, especially in patients with incomplete resections or in whom hypophosphatemia and elevated FGF23 levels persist after surgery.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2024.101772.

CRediT authorship contribution statement

Noelia Álvarez-Rivas: Writing – original draft, Methodology, Data curation, Conceptualization. **Gloria Lugo-Rodríguez:** Writing – original draft, Methodology, Data curation, Conceptualization. **Jose Ramón Maneiro:** Writing – review & editing, Formal analysis, Conceptualization. **Carlota Iñiguez-Ubiaga:** Writing – review & editing. **Rafael Benito Melero-Gonzalez:** Writing – review & editing. **Tania Iglesias-Cabo:** Formal analysis. **Loreto Carmona:** Writing – review & editing, Formal analysis, Conceptualization. **Carlos García-Porrúa:** Writing – review & editing, Conceptualization. **Francisco Javier de Toro-Santos:** Writing – review & editing, Conceptualization.

Declaration of competing interest

None of the authors has conflicts of interest.

Data availability

Data will be made available on request.

Acknowledgements

The authors thank the Spanish Society of Rheumatology for the editing service.

References

Abrahamsen, B., Smith, C.D., Minisola, S., 2021. Epidemiology of tumor-induced osteomalacia in Denmark. Calcif. Tissue Int. 109 (2), 147–156.
Bosman, A., Palermo, A., Vanderhulst, J., De Beur, S.M.J., Fukumoto, S., Minisola, S., et al., 2022. Tumor-induced osteomalacia: a systematic clinical review of 895 cases. Calcif. Tissue Int. 111 (4), 367–379.
Brandi, M.L., Clunie, G.P.R., Houillier, P., Jan de Beur, S.M., Minisola, S., Oheim, R., Seefried, L., 2021. Challenges in the management of tumor-induced osteomalacia (TIO). Bone 152, 116064.
Carpenter TO, 2003. Oncogenic osteomalacia–a complex dance of factors. N. Engl. J. Med. 348 (17), 1705–1708.
Chong, W.H., Molinolo, A.A., Chen, C.C., Collins, M.T., 2011. Tumor-induced osteomalacia. Endocr. Relat. Cancer 18 (3), R53–R77.
Colangelo, L., Pepe, J., Nieddu, L., Sonato, C., Scillitani, A., Diacinti, D., et al., 2020. Long-term bone mineral density changes after surgical cure of patients with tumor-induced osteomalacia. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 31 (7), 1383–1387.
Drezner, M.K., 2001. Tumor-induced osteomalacia. Rev. Endocr. Metab. Disord. 2 (2), 175–186.
Feng, J., Jiang, Y., Wang, O., Li, M., Xing, X., Huo, L., et al., 2017. The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases. Endocr. J. 64 (7), 675–683.
Florenzano, P., Hartley, I.R., Jimenez, M., Roszko, K., Gafni, R.I., Collins, M.T., 2021. Tumor-induced osteomalacia. Calcif. Tissue Int. 108 (1), 128–142.
Folpe, A.L., 2019. Phosphaturic mesenchymal tumors: a review and update. Semin. Diagn. Pathol. 36 (4), 260–268.
Folpe, A.L., Fanburg-Smith, J.C., Billings, S.D., Bisceglia, M., Bertoni, F., Cho, J.Y., et al., 2004. 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 (1), 1–30.
Hidaka, N., Koga, M., Kimura, S., Hoshino, Y., Kato, H., Kinoshita, Y., et al., 2022. Clinical challenges in diagnosis, tumor localization and treatment of tumor-induced osteomalacia: outcome of a retrospective surveillance. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 37 (8), 1479–1488.
Imanishi, Y., Ito, N., Rhee, Y., Takeuchi, Y., Shin, C.S., Takahashi, Y., et al., 2021. Interim analysis of a phase 2 open-label trial assessing burosumab efficacy and safety in patients with tumor-induced osteomalacia. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 36 (2), 262–270.
Jan de Beur, S.M., Miller, P.D., Weber, T.J., Peacock, M., Insogna, K., Kumar, R., et al., 2021. Burosumab for the treatment of tumor-induced osteomalacia. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 36 (4), 627–635.
Jan de Beur, S.M., Minisola, S., Xia, W.B., Abrahamsen, B., Body, J.J., Brandi, M.L., et al., 2023. Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia. J. Intern. Med. 293 (3), 309–328.
Jerkovich, F., Nuñez, S., Mocarbel, Y., Pignatta, A., Elías, N., Cassinelli, H., et al., 2021. Burden of disease in patients with tumor-induced osteomalacia. JBMR plus 5 (2), e10436.
Jiang, Y., Xia, W.B., Xing, X.P., Silva, B.C., Li, M., Wang, O., et al., 2012. 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. Off. J. Am. Soc. Bone Miner. Res. 27 (9), 1967–1975.
Jiang, Y., Hou, G., Cheng, W., 2020. Performance of 68Ga-DOTA-SST PET/CT, octreoscan SPECT/CT and 18F-FDG PET/CT in the detection of culprit tumors causing osteomalacia: a meta-analysis. Nucl. Med. Commun. 41 (4), 370–376.
Li, X., Jiang, Y., Huo, L., Wu, H., Liu, Y., Jin, J., et al., 2020. Nonremission and recurrent tumor-induced osteomalacia: a retrospective study. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 35 (3), 469–477.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. 62 (10), e1–34.
Minisola, S., Peacock, M., Fukumoto, S., Cipriani, C., Pepe, J., Tella, S.H., Collins, M.T., 2017. Tumour-induced osteomalacia. Nat. Rev. Dis. Primers 3, 17044.
Minisola, S., Barlassina, A., Vincent, S.A., Wood, S., Williams, A., 2022. A literature review to understand the burden of disease in people living with tumour-induced osteomalacia. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 33 (9), 1845–1857.
Pal, R., Bhadada, S.K., Singhare, A., Bhansali, A., Kamalanathan, S., Chadha, M., et al., 2019. Tumor-induced osteomalacia: experience from three tertiary care centers in India. Endocr. Connect. 8 (3), 266–276.
Rayamajhi, S.J., Yeh, R., Wong, T., Dumeer, S., Mittal, B.R., Remotti, F., et al., 2019. Tumor-induced osteomalacia - current imaging modalities and a systematic approach for tumor localization. Clin. Imaging 56, 114–123.
Reginato, A.J., Coquia, J.A., 2003. Musculoskeletal manifestations of osteomalacia and rickets. Best Pract. Res. Clin. Rheumatol. 17 (6), 1063–1080.
Rendina, D., Abate, V., Cacace, G., D'Elia, L., De Filippo, G., Del Vecchio, S., et al., 2022. Tumor-induced osteomalacia: a systematic review and individual patient's data analysis. J. Clin. Endocrinol. Metab. 107 (8) e3428-e36.
Shimada, T., Hasegawa, H., Yamazaki, Y., Muto, T., Hino, R., Takeuchi, Y., et al., 2004. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 19 (3), 429–435.
Weidner, N., Santa, Cruz D., 1987. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. Cancer 59 (8), 1442–1454.
Zanchetta, M.B., Jerkovich, F., Nuñez, S., Mocarbel, Y., Pignatta, A., Elías, N., et al., 2021. Impaired bone microarchitecture and strength in patients with tumor-induced osteomalacia. J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res. 36 (8), 1502–1509.
Zuo, Q.Y., Wang, H., Li, W., Niu, X.H., Huang, Y.H., Chen, J., et al., 2017. Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients. BMC Musculoskelet. Disord. 18 (1), 403.