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# The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases

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**Abstract.** Diagnostic delay of tumor induced osteomalacia (TIO) is common in clinic practice. To investigate the diagnostic condition of TIO in China and raise clinicians' awareness of TIO, we retrospectively analyzed clinical manifestations, biochemical features, and specially evaluated missed diagnoses and misdiagnoses among 144 TIO patients from Peking Union Medical College Hospital during December 1982 to December 2014. Clinical presentations of TIO mainly included bone pain, difficulty in walking, pathological fractures, muscle weakness, and height loss. TIO patients demonstrated hypophosphatemia (0.48±0.13 mmol/L), elevated serum alkaline phosphatase (277.9±152.6 U/L), reduced tubular maximum for phosphorus/glomerular filtration rate (0.39±0.14) and markedly elevated serum fibroblast growth factor 23 (FGF23) (median level 302.9 pg/mL). The average time from onset to a correct diagnosis was 2.9±2.3 years while the mean duration from onset to tumor resection was 5.4±4.2 years. The initial misdiagnosis rate was 95.1% (137/144) and 240 case-times of misdiagnoses occurred among the 144 cases. The most frequent misdiagnoses were intervertebral disc herniation, spondyloarthritis (including ankylosing spondylitis) and osteoporosis. A total of 43.1% (62/144) cases with hypophosphatemia presented on their laboratory sheets were neglected and missed diagnosed. Our study showed that TIO was frequently misdiagnosed and missed diagnosed due to its rarity, insidious onset, nonspecific clinical manifestations and clinicians' poor recognition. It is necessary to test serum phosphorus in patients with musculoskeletal symptoms and difficulty in walking. The measurement of serum FGF23 is rather valuable. Once hypophosphatemia is discovered, TIO should be suspected and it is highly recommended to search for tumors and perform curative surgery.

*Key words*: Tumor induced osteomalacia, Hypophosphatemia, Fibroblast growth factor 23, Misdiagnosis, Missed diagnosis

**TUMOR INDUCED OSTEOMALACIA** (TIO), also known as oncogenic hypophosphatemic osteomalacia, is a rare acquired paraneoplastic syndrome with clinical manifestations including bone pain, skeletal deformities, fractures, and muscle weakness [1]. TIO is usually induced by benign mesenchymal

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Abbreviations: TIO, Tumor induced osteomalacia; FGF23, Fibroblast growth factor 23; PMT, Phosphaturic mesenchymal tumor; XLH, X-linked hypophosphatemic rickets; PDDR, Pseudo-vitamin D deficiency rickets; FS, Fanconi syndrome; ADV, Adefovir dipivoxil; PSS, Primary Sjögren's Syndrome; MGUS, Monoclonal gammopathy of undetermined significance; PMTMCT, Phosphaturic mesenchymal tumor mixed connective tissue variant; ADHR, Autosomal-dominant hypophosphatemic rickets; Ca, Calcium; TMP/GFR, Tubular maximum for phosphorus/glomerular filtration rate; P, Phosphorus; ALP, Alkaline phosphatase; PTH, Parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D.

tumors (phosphaturic mesenchymal tumor mixed connective tissue variant, PMTMCT) secreting excessive fibroblast growth factor 23 (FGF23) and FGF23 was cloned as a causative factor for TIO [2, 3]. FGF23 mainly acts on sodium-phosphate co-transporter at the renal tubule and inhibits 1α-hydroxylation of 25-hydroxyvitamin D, thus leading to renal phosphate leaking, hypophosphatemia, inappropriately normal or low 1,25-dihydroxyvitamin D level and decreased bone mineralization [1]. Serum intact FGF23 levels in healthy adults ranged from 8.2-54.3 pg/mL (mean±SE; 28.9±1.1) and an increasing number of researches have demonstrated that serum FGF23 levels are markedly elevated in TIO patients before surgery and decrease to normal range after resection of the responsible tumors [4-7]. Complete resection of the causative neoplasm is usually curative for TIO. Early disease recognition and tumor identification is essential for this management.

Nevertheless, missed diagnoses or even misdiagnoses with subsequently diagnostic and therapeutic delay (ranging from 3-19 years) are commonly seen in reported cases of TIO, accompanied by prolonged morbidity and poor prognosis [8-13]. This reflects the relatively poor recognition of the rare disease among physicians. To investigate the diagnostic situation of TIO patients in China and raise clinicians' awareness, we conducted a retrospective study analyzing clinical manifestations, biochemical features, and specially evaluating missed diagnoses and misdiagnoses among TIO patients in a large cohort from our institution.

## Patients and Methods

This is a retrospective cohort study performed in Peking Union Medical College Hospital (PUMCH), Beijing, China.

### *Patients*

We searched the PUMCH inpatient medical database for "hypophosphatemic osteomalacia" during the period from December 1982 to December 2014. A total of 252 patients with hypophosphatemic osteomalacia were hospitalized during this period. Among the above patients, we selected patients whose causative tumor was successfully localized by both the functional and anatomic imaging. The functional imaging included octreotide scanning, F-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET/CT) and Gallium (Ga)-68 DOTATATE PET/CT, while the anatomic imaging included radiography, ultrasound, CT and MRI. Then patients who met any of the following criteria were included: patients who received surgical removal of the responsible tumor and the postoperative pathology was classified as phosphaturic mesenchymal tumor (PMT) or phosphaturic mesenchymal tumor mixed connective tissue variant (PMTMCT); patients who treated with resection of causative neoplasms and serum phosphorous returned to normal range after surgery. Patients of genetic hypophosphatemia and acquired hypophosphatemia due to other causes were excluded. And we also excluded hypophosphatemic osteomalacia patients without a definitive diagnosis of TIO including those failing to locate tumors or without surgeries.

### *Methods*

#### Data collection

Detailed information regarding general characteristics (age of onset, gender, height, course of disease, tumor pathology and prognosis), clinical manifestations (bone pain, difficulty in walking, muscle weakness/fatigue, pathological fractures, height loss, skeletal deformities, tooth loss or loose tooth, local lumps), laboratory examinations [serum calcium, serum phosphorus, serum 25-hydroxyvitaminD, serum 1,25-dihydroxyvitaminD, serum parathyroid hormone, tubular maximum for phosphorus/glomerular filtration rate (TMP/GFR)], and the situation of missed diagnoses and misdiagnoses were obtained through medical records.

#### Measurement of serum full-length FGF23

Preoperative serum samples preserved at -80°C in our center were found in 82 TIO patients. Serum full-length FGF23 levels were measured by a two-site enzyme-linked immunosorbent assay using the FGF23 ELISA Kit from Kainos Laboratories (Tokyo, Japan). If serum FGF23 concentration in the sample exceeded the measurable range (3-800 pg/mL), the sample was diluted 10 times. In our laboratory, the normal range of FGF23 in healthy persons is 10.0 to 50.0 pg/mL [14-16].

#### Definition of misdiagnosis and missed diagnosis

Any diagnosis except "tumor induced osteomalacia", "hypophosphatemic osteomalacia" or "vitamin D resistant hypophosphatemic osteomalacia" was considered as a misdiagnosis. And we also calculated

the misdiagnosed case-times for each misdiagnosis of every patient. In addition, when hypophosphatemia presented on patients' laboratory sheets was neglected by clinicians, it was considered as a missed diagnosis.

**Statistical analysis**

The data distribution was assessed by the Kolmogorov-Smirnov test. Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range), according to the normality of the data distribution. Categorical variables are denoted as number (percentage). All statistic analyses were performed with SPSS 19.0 software (IBM SPSS Statistics 19). Figures were made by GraphPad Prism 5.

## Results

Among the 252 hospitalized hypophosphatemic osteomalacia patients, 144 cases of TIO were included in the study. Forty-eight patients with genetic disorders or other acquired causes were excluded (Fig. 1). And 58 adult-onset hypophosphatemic osteomalacia patients without a definitive diagnosis of TIO were also excluded, including those failing to locate tumors or without surgeries. In addition, two postoperative patients remaining hypophosphatemia and without the pathology classified as PMT or PMTMCT were not included.

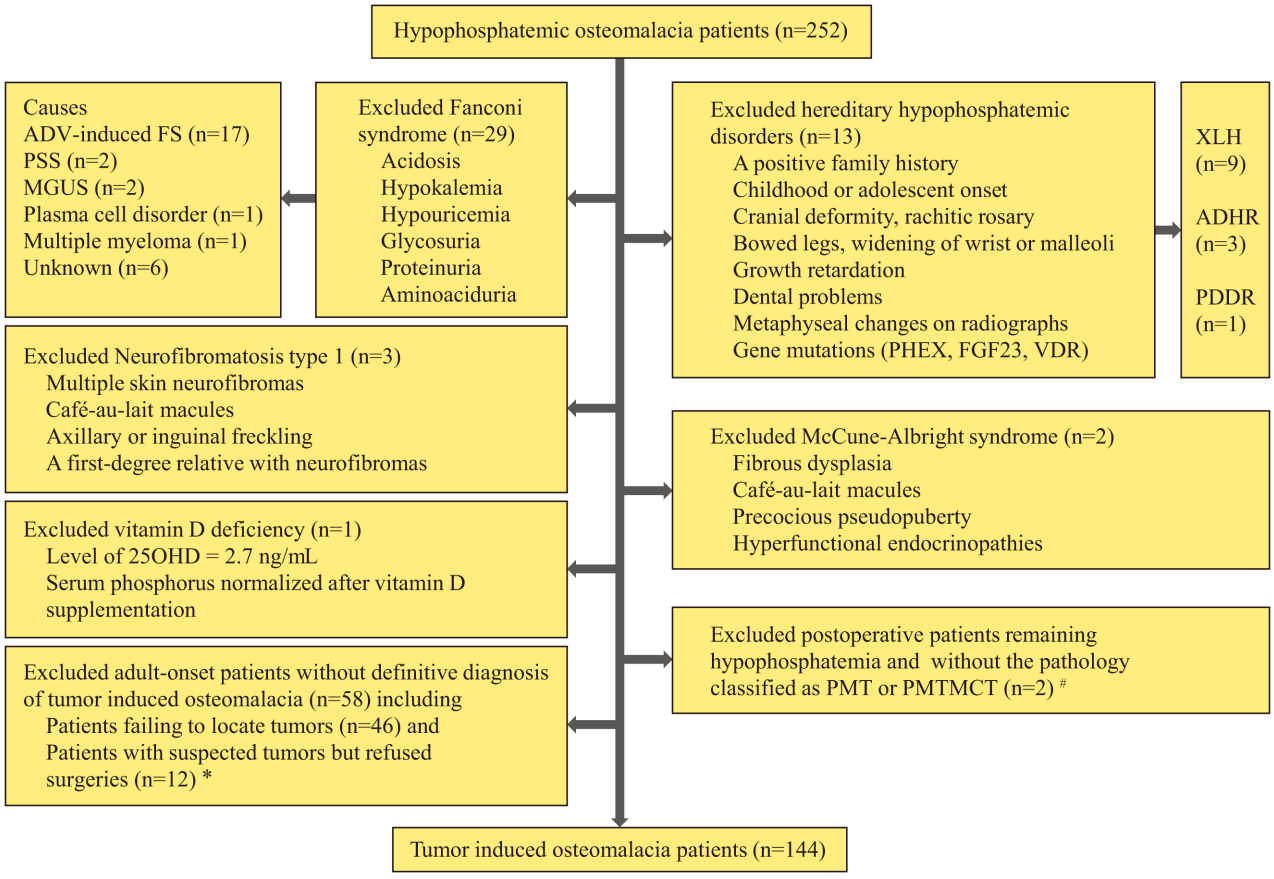


**Fig. 1** The inclusion and exclusion of our study among 252 hospitalized hypophosphatemic osteomalacia patients

N in parentheses presents the number of patients. The characteristics of the excluded patients in the study are listed below their diagnoses. * Patients refused surgeries were due to concerns about surgical risks, postoperative recovery of related joints function and walking function, multiple metastasis, economic reasons, and other relative contraindications of surgeries. # The pathology of the 2 patients was glandular cystitis and thymic carcinoid respectively. Abbreviations: FS, Fanconi syndrome; ADV, Adefovir dipivoxil; PSS, Primary Sjögren's Syndrome; MGUS, Monoclonal gammopathy of undetermined significance; XLH, X-linked hypophosphatemic rickets; ADHR, Autosomal-dominant hypophosphatemic rickets; PDDR, Pseudo-vitamin D deficiency rickets; 25(OH)D, 25-hydroxyvitamin D; PMT, Phosphaturic mesenchymal tumor; PMTMCT, Phosphaturic mesenchymal tumor mixed connective tissue variant.

### *General characteristics of the study participants*

There was no obvious gender predilection for TIO (M:F=1.25:1). The average age of onset was 38±11 years (13-63 years). The discovery of hypophosphatemia and effective surgery was delayed for years (Table 1). Except forty-three cases without related information documented in their medical records, the clinical departments TIO patients visited mainly distributed in department of Endocrinology, Orthopaedics, Rheumatology and Immunology, Neurology, followed by department of Nephrology, Hematology, Otolaryngology, Psychology, Neurosurgery. The causative tumors located in various soft tissues and skeletal sites (67.4% *vs* 32.6%). After resection of the responsible tumors, serum phosphorus of 118 cases returned to normal range, while 26 cases were still with persistent hypophosphatemia. A majority of the tumors (135/144, 93.8%) were classified as PMT or PMTMCT.

### *Clinical manifestations of TIO patients*

The clinical presentations of TIO are displayed in Fig. 2. Bone pain was the most common symptom and might be the initial symptom (132/144, 91.7%). It often started from lower limbs (78/144, 54.2%), with ankles and feet being the most common sites. Patients also suffered from lumbar and back pain (37/144, 25.7%), sternocostal pain (19/144, 13.2%), diffuse bone pain (4/144, 2.8%), omarthralgia (3/144, 2.1%) and neck ache (2/144, 1.4%). Pathological fractures commonly occurred in TIO patients. They frequently occurred at vertebrae (83/144, 57.6%), ribs (62/144, 43.1%), femurs (34/144, 23.6%) and the pelvic (29/144, 20.1%). A total of 99 patients had height loss and the average height reduction was 7.8±4.7 cm (1.0-24.0 cm). Several patients (21/144, 14.6%) had local lumps which were proved to be pathogenic tumors after surgery. In addition, there were three cases whose tumors were in the nasal sinus presenting symptoms of nasal obstruction and epistaxis.

**Table 1** General characteristics of TIO patients

| | Male | Female | Total |
|---|---|---|---|
| Number of cases (%) | 80 (55.6%) | 64 (44.4%) | 144 |
| Age of onset (years) | 37 ± 12 | 39 ± 11 | 38 ± 11 |
| Mean height (cm) | 163.1 ± 7.2 | 154.1 ± 7.8 | |
| Duration from onset to discovery of hypophosphatemia (years) | 3.0 ± 2.4 | 2.8 ± 2.2 | 2.9 ± 2.3 |
| Duration from onset to surgery (years) | 5.0 ± 3.3 | 5.9 ± 5.0 | 5.4 ± 4.2 |

Data are reported as mean ± SD or number (percentage).

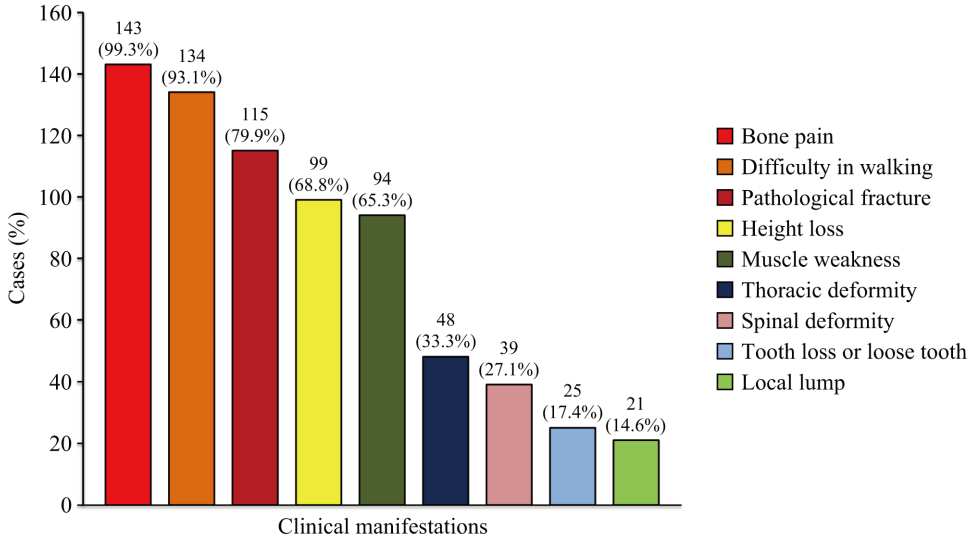


**Fig. 2** The clinical manifestations of TIO patients
Data are presented as number (percentage).

### *Biochemical patterns of TIO patients*

Patients demonstrated low serum phosphorus, reduced TMP/GFR, elevated serum alkaline phosphatase and inappropriately normal or reduced concentration of 1,25-dihydroxyvitamin D (Table 2).

### *Serum full-length FGF23 levels in TIO patients*

In the 82 TIO patients, preoperative serum intact FGF23 ranged from 20.1 to 6,498.7 pg/mL and the median serum FGF23 level was 302.9 pg/mL (interquartile range 142.4-706.5 pg/mL).

### *The condition of misdiagnoses and missed diagnoses among TIO patients*

Among the 144 TIO patients, 137 cases had once been misdiagnosed and the initial misdiagnosis rate was 95.1% (137/144). There were 240 case-times of misdiagnoses occurred among these patients. As is shown in Fig. 3, TIO patients were often misdiagnosed as intervertebral disc herniation, spondyloarthritis (including ankylosing spondylitis), and osteoporosis, followed by femoral head necrosis, hyperparathyroidism, rheumatoid arthritis, arthritis, bone

**Table 2** Biochemical features of TIO patients

| Biochemical markers | Mean ± SD | Range of patients | Reference range |
|---|---|---|---|
| P (mmol/L) | 0.48 ± 0.13 (n=144) | 0.17-0.80 | 0.81-1.45 |
| Ca (mmol/L) | 2.28 ± 0.12 (n=144) | 1.99-2.61 | 2.13-2.70 |
| ALP (U/L) | 277.9 ± 152.6 (n=144) | 69-1101 | Male 45-125<br>Female 35-100 |
| PTH (pg/mL) | 66.4 ± 39.1 (n=144) | 4.8-277 | 12.0-65.0 |
| TMP/GFR | 0.39 ± 0.14 (n=117) | 0.12-0.70 | 0.80-1.35 |
| 25(OH)D (ng/mL) | 15.6 ± 6.8 (n=99) | 2.9-37.1 | 8.0-50 |
| $1,25(OH)_2D$ (pg/mL) | 9.1 ± 6.2 (n=77) | 0.01-23.00 | 19.6-54.3 |

Abbreviations: P, phosphorus; Ca, calcium; ALP, alkaline phosphatase; PTH, parathyroid hormone; TMP/GFR, tubular maximum for phosphorus/glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D. The number of cases involved is presented in parentheses.

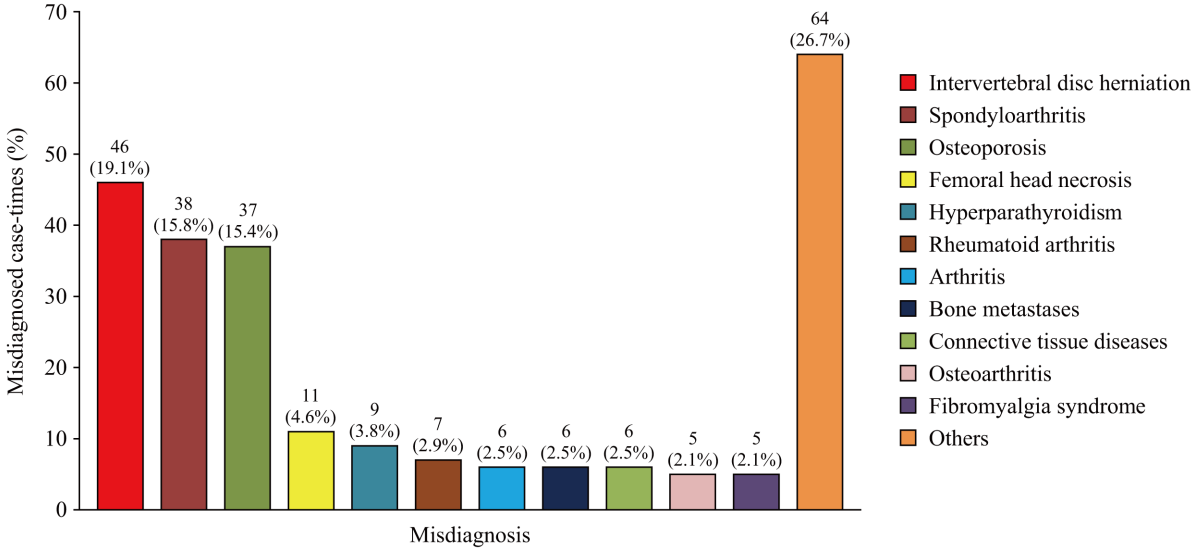


**Fig. 3** The misdiagnosis condition in TIO patients

A total of 240 case-times of misdiagnoses occurred in the 144 TIO patients. Data are expressed as number (percentage). Others covered misdiagnoses less than five case-times for each, mainly including spinal stenosis, synovitis, waist muscle strain, rib cartilage inflammation, multiple myeloma, neuropathic pain, polymyalgia rheumatica, rheumatic arthritis, paget's disease, motor neuron disease, intercostal neuralgia, renal tubular acidosis, chronic renal failure, multiple myositis, myodystrophia, stroke, hysterical paralysis, somatization disorder.

metastases, connective tissue diseases, osteoarthritis, fibromyalgia syndrome.

### *Analysis of major misdiagnoses and improper treatments among TIO patients*

**Misdiagnosed as lumbar disc herniation**

Lumbar disc herniation was the most frequent misdiagnosis among TIO patients. The mean onset age of these misdiagnosed patients was 40±10 years. Patients mainly presented with symptoms of lumbar and back pain (31 case-times, 67.4%) and lower limbs pain (14 case-times, 30.4%). The majority of visited clinical departments included department of Orthopaedics, department of Rheumatology and Immunology and department of Neurology. Among these patients, there were 26 case-times (56.5%) with radiographic signs of protrusion of intervertebral disc. Subsequently, some patients were improperly treated with physiotherapy, acupuncture, anti-inflammatory drugs and glucocorticoids. A small percentage of patients even received surgery of intervertebral disc.

**Misdiagnosed as spondyloarthritis**

Spondyloarthritis was the second most common misdiagnosis. The average onset age of patients misdiagnosed as spondyloarthritis was 30±9 years. Mostly, these patients were referred to department of Rheumatology and Immunology (21 case-times, 55.3%) and the most common symptom was lumbar and back pain or lumbosacral pain (33 case-times, 86.8%). Imaging examination (X-ray/CT/MRI) showed signs of sacroiliac joint changes (12 case-times, including fuzzy sacroiliac joint, joint space stenosis, joint fusion, and coarse joint surface), fractures of ilium bone (2 case-times), ilium sclerosis (1 case-times) or even normal sacroiliac joint (3 case-times). The human leukocyte antigen B27 (HLA-B27) was negative in most cases with only 1 cases being positive. Unfortunately, some patients received non-steroidal anti-inflammatory drugs, sulfasalazine, methotrexate and glucocorticoids while some were mistakenly treated with thalidomide, tripterygium wilfordii, etanercept, infliximab, leflunomide, physiotherapy, and acupuncture.

**Misdiagnosed as osteoporosis**

There were 37 case-times of misdiagnoses as osteoporosis. The mean onset age of patients misdiagnosed as osteoporosis was 43±10 years. These patients mainly exhibited symptoms of bone pain (37 case-times, 100%), fractures (32 case-times, 86.5%), and height loss (26 case-times, 70.3%). They sought medical care mainly in department of Endocrinology (22 case-times, 59.5%). There were 25 case-times (67.6%) of low bone mineral density as revealed by dual-energy X-ray absorptiometry (DXA). Consequently, they were only treated with calcium plus vitamin D, calcitonin, or bisphosphonates.

### *The situation of missed diagnoses in TIO patients*

A total of 43.1% (62/144) cases with hypophosphatemia presented on their laboratory sheets were neglected and missed diagnosed. Moreover, only a small proportion (17/144, 11.8%) of patients received laboratory test of serum phosphorus when they sought medical care for the first time.

In addition, even though hypophosphatemia was once noticed, there were still several patients without treatment of oral phosphorus or being improperly treated with bisphosphonates and calcitonin.

## Discussion

This study retrospectively reviewed clinical and laboratory features of 144 TIO patients, and analyzed the condition of missed diagnoses and misdiagnoses. TIO should be differentiated with hereditary disorders or other acquired causes mainly including XLH, ADHR, McCune-Albright syndrome and Fanconi syndrome caused by hematological diseases or drugs. Findings of clinical manifestations and biochemical abnormalities in our series are in common with previous studies from Jiang, Y [14]. We confirmed that FGF23 levels increased significantly in TIO patients and the median intact serum FGF23 level in Chinese TIO patients was 302.9 pg/mL. It was similar to the result of a recent research from Yu, W J [4]. But we also discovered a female patient with normal FGF23 level (20.1 pg/mL). TIO with normal systemic FGF23 level has been reported, and it is noteworthy that in case of hypophosphatemic condition, the "normal" FGF23 level might be inappropriately normal [17]. Notably, we found that TIO was severely misdiagnosed or missed diagnosed. Patients suffered from improper medical treatments or even unnecessary surgery related to the misdiagnoses. Moreover, our data revealed that the definite diagnosis and effective treatment of TIO was significantly delayed for years. Our data are consistent with repeated reports of delays in diagnosis, improper treatment and prolonged morbidity of TIO patients [8-13, 18]. A typical example

is a case report from E. Michael Lewiecki and his colleague, describing an unusual TIO case presented with musculoskeletal symptoms and fragility fractures [13]. Despite consultations of a number of physicians and specialists, the patient was unsuccessfully treated for piriformis syndrome, seronegative polyarthritis, severe osteoporosis, and polyostotic Paget's disease of bone. In comparison, our study showed that intervertebral disc herniation, spondyloarthritis (including ankylosing spondylitis) and osteoporosis ranked top three among the misdiagnosis spectrum. Our results confirm but also extend the misdiagnosis spectrum from several previous retrospective studies analyzing the misdiagnosed situation of hypophosphatemic osteomalacia with limited sample size ranging from 5-13 cases [19, 20].

Additionally, it is essential to deeply explore and analyze the possible related factors for frequently seen misdiagnoses of TIO. Firstly, it is possible that the insidious onset and nonspecific nature of clinical symptoms results in misdiagnoses. As Anke H. Hautmann concluded in his review, "Nonspecific symptoms including fatigue, bone pain, and musculoskeletal weakness make the diagnosis elusive and often lead to a delay in treatment" [21]. Patients were incorrectly attributed to intervertebral disc herniation, spondyloarthritis, osteoporosis, femoral head necrosis, and hyperparathyroidism. These diseases may show one or more symptoms similar to TIO, thus making it challenge to find a specific symptom of TIO. It coincides with Jin's research in which he summarized that hypophosphatemic osteomalacia was misdiagnosed as spondyloarthritis, a different kind of disease, mainly due to the similar clinical symptom of low back pain [22]. Moreover, our results concur with previous findings that the typical time from onset of symptoms to a tentative diagnosis of TIO often exceeds 2.5 years and the average duration from the presumptive diagnosis to the identification of the underlying responsible tumor is 5 years [13, 23]. The nonspecific symptoms of TIO delay its recognition. Secondly, the coincidence that several radiographic changes caused by osteomalacia may resemble many other diseases could be another potential factor. We discovered that radiographic signs of protrusion of intervertebral disc were common among patients misdiagnosed as lumbar disc herniation. Spine and vertebral deformation or vertebral fractures due to osteomalacia might affect intervertebral discs, and several patients were just diagnosed as lumbar disc herniation following the radiographic signs. Similarly, TIO patients having sacrum or ilium changes due to osteomalacia might be misdiagnosed as spondyloarthritis. Both our study and a retrospective research by Jin and his colleague confirmed the above mentioned condition. The main radiographic difference between TIO and spondyloarthritis is that, the skeletal lesions of TIO are mostly on sacrum or ilium bone itself while spondyloarthritis involves inflammation or destruction of joints and adjacent tissues [22]. In addition, we found that more than half of the cases misdiagnosed as osteoporosis had low bone mineral density assessed by DXA. TIO is characterized by decreased bone mineralization, thus patients may be frequently misdiagnosed as osteoporosis due to reduced bone mineral density detected by DXA. As early as 2009, the New England Journal of Medicine published a monograph emphasizing that these two diseases could be quite confusing [24]. Bone mineral density measured by DXA often cannot distinguish osteomalacia from osteoporosis. Thirdly, this study discovered that cases misdiagnosed as lumbar disc herniation, spondyloarthritis and osteoporosis were mainly referred to department of Orthopedic, department of Rheumatology and Immunology, and department of Endocrinology respectively. It is possible that a misdiagnosis is somewhat influenced by the department that a patient visited, involving commonly encountered diseases of each medical department. Lastly, the presence of hypophosphatemia on laboratory sheets was generally neglected in our study, and only 11.8% of patients received laboratory test of serum phosphorus during their first visit. However, hypophosphatemia is a vital clinical clue to the diagnosis of TIO. Chang holds that TIO was much more misdiagnosed than rare and his study also concludes that discovery of hypophosphatemia might be the key to avoid misdiagnosis [25]. Furthermore, we also found that even if hypophosphatemia was once noticed, clinicians sometimes failed to give a proper prescription with oral phosphorus. The lack of formally approved clinically used phosphate supplements in China might contribute to the situation.

Although the diagnosis of TIO is frequently challenging, there are several important key points that can help to avoid misdiagnoses and missed diagnoses. Bone pain was the initial symptom of most TIO patients. Thus, when encountering a patient with complaints of bone pain, it is necessary to make a detailed inquiry about the onset of age, family history,

medication history, accompanying symptoms such as fatigue or muscle weakness, pathological fractures, height loss, difficulty in walking. At the same time, pay attention to check whether there were skeletal deformities, dental problems, and local bumps. These data are vital in the differential diagnosis with hereditary hypophosphatemia and other acquired causes. TIO should be suspected in patients with progressive weakness, bone pain, multiple fractures, skeletal deformities, and difficulty in walking. Laboratory tests of calcium, phosphorus and alkaline phosphatase should be routinely performed in case of suspected TIO [8, 21]. Hypophosphatemia and elevated alkaline phosphatase can be the key diagnostic clues for TIO. The measurement of serum FGF23 is quite valuable. Another diagnostic challenge is to locate the responsible tumors as these tumors are usually small in size, slowly growing and locating at variable elusive sites. Currently, it is advocated performing a step-wise approach including functional imaging (octreotide scanning, 18F-FDG PET/CT and Ga-68 DOTATATE PET/CT), followed by anatomic imaging (radiography, ultrasound, CT and MRI). And if needed, selective venous sampling for FGF23 is usually successful in locating the tumors [8, 26, 27]. Chong WH and his colleague reported a series of 31 TIO subjects regarding tumor localization and proposed a systematic approach to localizing tumors in tumor induced osteomalacia [26]. But he failed to include 68Ga DOTATATE PET/CT in localizing these tumors. However, an increasing number of researches have demonstrated that 68Ga DOTATATE PET/CT is an accurate imaging modality (overall accuracy 97.7%) and can be used as the first imaging modality in the detection of obscure TIO tumors [28-30]. Once the neoplasm is located, complete resection of the neoplasm with wide margins will be the most appropriate treatment.

There are several limitations of our study. The study was a single center study, thus the diagnostic condition of TIO might not represent all. In addition, as a retrospective study, information regarding misdiagnoses or missed diagnoses was acquired through medical records, which largely depended on the patient's subjective statements. Thus, there might be recall bias, and we could not distinguish whether patients had coexistence of TIO and some of the given misdiagnoses.

In summary, TIO is frequently misdiagnosed or missed diagnosed due to its rarity, insidious onset, nonspecific nature of clinical manifestations, and clinicians' poor recognition. Many doctors often fail to include laboratory assay of serum phosphorus or neglect hypophosphatemia presented on the laboratory sheets. Thus, definitive diagnosis and curative surgery is often delayed, and consequently the life quality of TIO patients is profoundly affected. Clinicians should enhance their understanding and recognition of the disease. The diagnosis of TIO should be suspected in patients who present with symptoms of fatigue, muscle weakness, bone pain, pathological fractures, height loss, skeletal deformities, and difficulty in walking. Besides taking detailed medical history and cautious physical examination, it is critical to test serum phosphorus. The measurement of serum FGF23 might have critical role in improving diagnosis and management of TIO. Once hypophosphatemia is discovered, TIO should be considered and it is highly recommended to search for tumor lesions and perform curative surgery.

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## Disclosure

None of the authors have any potential conflicts of interest associated with this research.

## References

1. Chong WH, Molinolo AA, Chen CC, Collins MT (2011) Tumor-induced osteomalacia. *Endocr Relat Cancer* 18: R53-77.

2. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, *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: 1-30.
3. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, *et al*. (2001) Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci U S A* 98: 6500-6505.
4. Yu WJ, He JW, Fu WZ, Wang C, Zhang ZL (2017) Reports of 17 Chinese patients with tumor-induced osteomalacia. *J Bone Miner Metab* 35: 298-307.
5. Hu FK, Yuan F, Jiang CY, Lv DW, Mao BB, *et al*. (2011) Tumor-induced osteomalacia with elevated fibroblast growth factor 23: a case of phosphaturic mesenchymal tumor mixed with connective tissue variants and review of the literature. *Chin J Cancer* 30: 794-804.
6. Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, *et al*. (2003) Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. *N Engl J Med* 348: 1656-1663.
7. Yamazaki Y, Okazaki R, Shibata M, Hasegawa Y, Satoh K, *et al*. (2002) Increased circulatory level of biologically active full-length FGF-23 in patients with hypophosphatemic rickets/osteomalacia. *J Clin Endocrinol Metab* 87: 4957-4960.
8. Dadoniene J, Miglinas M, Miltiniene D, Vajauskas D, Seinin D, *et al*. (2016) Tumour-induced osteomalacia: a literature review and a case report. *World J Surg Oncol* 14: 4.
9. Slot-Steenks MM, Hamdy NA, van de Sande MA, Vriens D, Cleven AH, *et al*. (2016) Identifying the culprit lesion in tumor induced hypophosphatemia, the solution of a clinical enigma. *Endocrine* 54: 642-647.
10. Meng T, Zhou W, Li B, Yin H, Li Z, *et al*. (2015) En bloc resection for treatment of tumor-induced osteomalacia: a case presentation and a systematic review. *World J Surg Oncol* 13: 176.
11. Ledford CK, Zelenski NA, Cardona DM, Brigman BE, Eward WC (2013) The phosphaturic mesenchymal tumor: why is definitive diagnosis and curative surgery often delayed? *Clin Orthop Relat Res* 471: 3618-3625.
12. Xian-Ling W, Jian-Ming B, Wen-Wen Z, Zhao-Hui L, Jing-Tao D, *et al*. (2012) Osteomalacia caused by tumors in facies cranii mimicking rheumatoid arthritis. *Rheumatol Int* 32: 2573-2576.
13. Lewiecki EM, Urig EJ Jr, Williams RC Jr (2008) Tumor-induced osteomalacia: lessons learned. *Arthritis Rheum* 58: 773-777.
14. Jiang Y, Xia WB, Xing XP, Silva BC, Li M, *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* 27: 1967-1975.
15. Xia WB, Jiang Y, Li M, Xing XP, Wang O, *et al*. (2010) Levels and dynamic changes of serum fibroblast growth factor 23 in hypophosphatemic rickets/osteomalacia. *Chin Med J (Engl)* 123: 1158-1162.
16. Xia W, Meng X, Jiang Y, Li M, Xing X, *et al*. (2007) Three novel mutations of the PHEX gene in three Chinese families with X-linked dominant hypophosphatemic rickets. *Calcif Tissue Int* 81: 415-420.
17. Amblee A, Uy J, Senseng C, Hart P (2014) Tumor-induced osteomalacia with normal systemic fibroblast growth factor-23 level. *Clin Kidney J* 7: 186-189.
18. Clunie GP, Fox PE, Stamp TC (2000) Four cases of acquired hypophosphataemic ('oncogenic') osteomalacia. Problems of diagnosis, treatment and long-term management. *Rheumatology (Oxford)* 39: 1415-1421.
19. YE Jin (2013) AnaIysis of 9-case misdiagnosis of osteomalacia. *Chin J Osteoporos* (08): 816-819 (In Chinese).
20. WU Youwei, KE yaohua, ZhANG zhenlin (2010) Clinical analysis of 5 misdiagnosed cases of sporadic hypophosphatemic osteomalacia. *Chin J Osteoporos* (10): 758-760+785 (In Chinese).
21. Hautmann AH, Hautmann MG, Kolbl O, Herr W, Fleck M (2015) Tumor-Induced Osteomalacia: an Up-to-Date Review. *Curr Rheumatol Rep* 17: 512.
22. Jin J, Sun F, Wang G, Yang J, Luo G, *et al*. (2014) The clinical characteristics of 26 cases of hypophosphatemia osteomalacia misdiagnosed as spondyloarthritis. *Zhonghua Nei Ke Za Zhi* 53: 847-851 (In Chinese).
23. Jan de Beur SM, Streeten EA, Civelek AC, McCarthy EF, Uribe L, *et al*. (2002) Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet* 359: 761-763.
24. Reilly BM, Hart PD, Mascarell S, Chatrath H (2009) Clinical problem-solving. A question well put. *N Engl J Med* 360: 1446-1451.
25. Chang CV, Conde SJ, Luvizotto RA, Nunes VS, Bonates MC, *et al*. (2012) Oncogenic osteomalacia: loss of hypophosphatemia might be the key to avoid misdiagnosis. *Arq Bras Endocrinol Metabol* 56: 570-573.
26. Chong WH, Andreopoulou P, Chen CC, Reynolds J, Guthrie L, *et al*. (2013) Tumor localization and biochemical response to cure in tumor-induced osteomalacia. *J Bone Miner Res* 28: 1386-1398.
27. Andreopoulou P, Dumitrescu CE, Kelly MH, Brillante BA, Cutler PC, *et al*. (2011) Selective venous catheterization for the localization of phosphaturic mesenchymal tumors. *J Bone Miner Res* 26: 1295-1302.
28. Bhavani N, Reena AA, Kallur K, Menon AS, Pavithran PV, *et al*. (2016) Utility of Gallium-68 DOTANOC PET/CT in the localization of Tumour-induced osteomalacia. *Clin Endocrinol (Oxf)* 84: 134-140.
29. El-Maouche D, Sadowski SM, Papadakis GZ, Guthrie L, Cottle-Delisle C, *et al*. (2016) 68Ga-DOTATATE for Tumor Localization in Tumor-Induced Osteomalacia. *J Clin Endocrinol Metab* 101: 3575-3581.
30. Agrawal K, Bhadada S, Mittal BR, Shukla J, Sood A, *et al*. (2015) Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. *Clin Nucl Med* 40: e6-e10.