CASE REPORT

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Tumor-induced Osteomalacia in a Boy with Maxillary Ossifying Fibroma

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What is already known on this topic?

Tumor-induced osteomalacia (TIO) is a rare syndrome characterized by severe hypophosphatemia and osteomalacia. Very few cases have been reported in children.

What this study adds?

We describe an adolescent diagnosed with TIO and we locate his tumor in the right maxilla, which is quite a rare site. We review five pediatric TIO patients with tumors in the oral/maxillary region. These findings suggest the importance of head and neck examination and suitable imaging for patients in whom TIO is suspected.

Abstract

Tumor-induced osteomalacia (TIO) is a rare, paraneoplastic disorder of hypophosphatemia associated with elevated tumor-produced fibroblast growth factor 23 (FGF23). Maxillofacial tumors are rarely involved in TIO, especially maxillary TIO in children. We present a 14-year-old boy with osteomalacia and high serum levels of FGF23, a hormone associated with decreased phosphate resorption, due to a maxillary tumor. The patient was treated with oral phosphorus and calcitriol, and surgical removal of the tumor was performed. After 21 months follow-up, he was pain free and had returned to full activity. We review the reported pediatric cases of TIO in the maxillofacial and oral region and discuss the management of these patients considering the published evidence.

Keywords: Tumor-induced osteomalacia, fibroblast growth factor-23, maxilla, children

Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome, first described in 1947 by McCance (1) but in 1959 Prader et al. (2) first highlighted the relation between the neoplasm and the disease in an 11-year-old girl who presented with rickets in association with tumor of a rib. TIO is characterized by progessive bone pain, proximal muscle weakness, gait disturbance and multiple fractures, which are a consequence of severe hypophosphatemia. The key pathogenetic mechanism of TIO involves tumor-driven secretion of phosphatonins, most frequently fibroblast growth factor 23 (FGF23). FGF23 binds to the fibroblast growth factor receptor 1-Klotho complex in the renal proximal tubule to stimulate the excretion of phosphorus from the kidney. High FGF23 levels reduce the expression of type IIa sodium phosphate contransporters leading to renal phosphorus wasting (3). FGF23 is also a regulatory hormone for 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] and

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leads to a decreased concentration of the vitamin in blood. The majority of tumors associated with TIO are located in the extremites (skin, muscles, bones) or around the head, but they may occur in almost any part of the body. Few pediatric patients with TIO have been reported; in a 2015 review of TIO in pediatrics, the authors reported 26 children in the literature (4). Pharmacotherapy is initiated with oral phosphorus and calcitriol supplementation, but surgical removal of the tumor is the definitive treatment for TIO (5).

We present a 14-year-old boy who developed hypophosphatemia and urinary phosphate wasting, muscle weakness, bone pain and he had been using a wheelchair for 18 months. This is the first adolescent with TIO reported from Vietnam.

Case Report

We report a previously healthy, 14-year-old adolescent who presented with 18 months of progressive, bilateral knee pain and ankle pain, as well as muscle weakness. He was able to walk slowly with crutches but was nearly wheelchair-bound. He had no fever and no weight loss. He was prescribed non-steroid anti-inflammatory drugs, methotrexate and physical therapy because of a misdiagnosis of juvenile idiopathic arthritis at a provincial hospital. However, his condition did not improve over the subsequent six months and he was referred to our hospital in October 2019. At the time of presentation, his weight was at the 50th percentile for age, his height was at the 7th percentile and he had no overt skeletal deformities. He had bilateral proximal weakness in upper and lower extremities. Although he was unable to walk due to pain, his joints were not swollen. The maxilla was neither painful nor enlarged. His family did not have history of hormonal, skeletal or metabolic problems.

Investigations

Laboratory test showed low serum ionized calcium [1.08 mmol/L, (reference range, 1.17-1.29 mmol/L)], hypophosphatemia [0.32 mmol/L, (reference range, 0.87-1.45 mmol/L)], elevated alkaline phosphatase [1138 U/L, (reference range, 40-129 U/L)], low $1,25(OH)_2D$ (11.4 pg/mL, [reference range 16-65 pg/mL]), nearly normal 25-hydroxyvitamin D [19.6 ng/mL, (reference range, >20 ng/mL)], and normal parathyroid hormone [59.85 ng/L, (reference range, 11-79 ng/L)]. The percent tubular reabsorption of phosphate was 85% (reference range, >90%); the maximal tubular renal phosphate reabsorption normalized for glomerular filtration rate was 0.42 mmol/L (reference range, 1.15-2.44 mmol/L). Serum FGF23 level was elevated at 159.3 pg/mL (reference range 23.2-95.4 pg/mL measured at Cerba Laboratories, Paris, France).

Radiographs of skull and bones in upper and lower of both legs demonstrated generalized demineralization with decreased bone density, cortical thinning and trabecular blurring; fatigue fracture also seen in the cortex of the right radius diaphysis accompanied by bilateral widening of the proximal humerus physis (Figure 1). A dual-energy X-ray absorptiometry (DXA) revealed a severe loss of bone mineral density (BMD) at L1-L4 (0.498 g/cm^2, Z-score, -4.0) and the femoral neck (0.448 g/cm^2; Z-score, -3.6). Positron emission tomography with ^{18}fluorodeoxyglucose (^{18}FDG-PET) demonstrated a metabolically active lesion with increased standardized uptake values in the right maxilla (Figure 2). Once the lesion was identified by ^{18}FDG-PET, magnetic resonance imaging and computed tomography (CT) scans showed a tumor measuring 23x14 mm in the right maxilla (Figure 2).

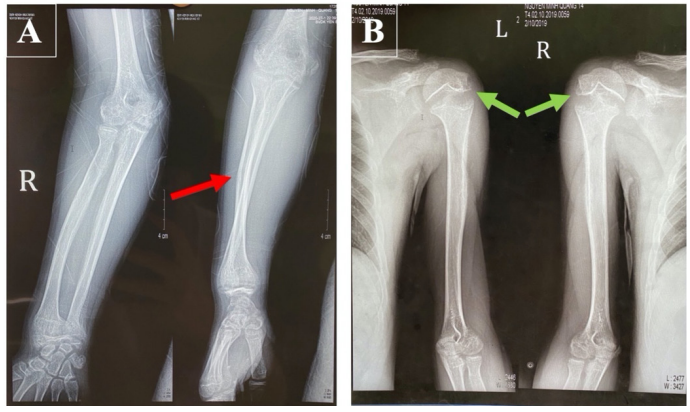

Figure 1. Radiograph of the left forearm **(A)** and arms bilateral **(B)** shows diffuse demineralization of bones, fatigue fracture (looser zones) of diaphysis in left radius (red arrow), widening of bilateral proximal humeral physics (green arrows)

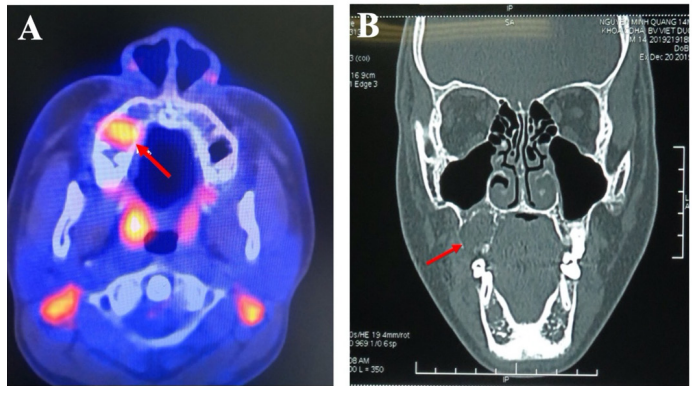

Figure 2. (A) Positron emission tomography/computed tomography (CT) with ^{18}fluorodeoxyglucose, **(B)** CT scanner, T1W images show a osteolytic lesion in the right maxilla, intense FDG uptake, hypointense on T1W and non-homogenous gadolinium enhancement (red arrows)

Differential Diagnosis

The differential diagnosis of hypophosphatemia due to urinary phosphate wasting can be divided in to genetic and acquired causes. Inherited conditions include X-linked hyphophosphatemia, autosomal dominant hypophosphatemia rickets, autosomal recessive hypophosphatemic rickets, and hereditary hypophosphatemic rickets with hypercalciuria (6). These diseases are often associated with short stature in early childhood, fractures, deformities in the legs and tooth findings. However, the presented patient had rapid onset of symptoms and a negative family history that ruled out these causes.

Acquired causes include TIO, renal tubular damage from heavy metal exposure or drugs such as aminoglycoside antibiotics, vitamin D deficiency, and primary or secondary hyperparathyroidism. In this case, the patient had a normal serum PTH level and he did not use such drugs. Besides, his parents said that he did not eat or drink something tainted with lead or mercury.

Treatment

The patient was managed medically with oral phosphorus (60-80 mg/kg/day) and calcitriol (40 ng/kg/day), which improved but did not normalize his serum phosphorus. He underwent surgical resection of the tumor three months after diagnosis. Histopathological examination indicated that the tumor was an ossifying fibroma (OF) (Figure 3). One month after removal of the tumor, the patient's serum phosphorus level was 1.57 mmol/L. Three months later, his serum FGF23 level was normal (34.3 pg/mL) and he was asymptomatic. One year later, DXA showed that his BMD in the lumbar spine had recovered with a normal Z-score of 1.58. Twenty-one months after diagnosis, he was pain free and returned to full activity. He has returned to school and at the time of writing has no evidence of tumor recurrence.

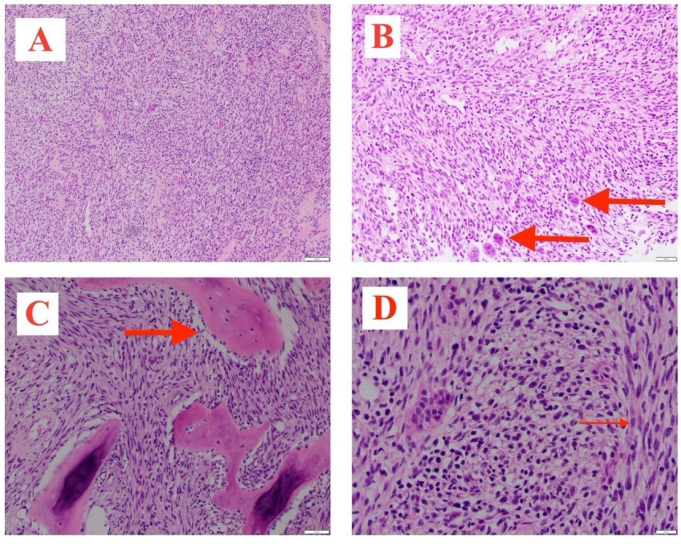

Figure 3. (A, B) Low power (x40, x100) photomicrographs showing diffuse neoplastic cells arranging in fascicular pattern infiltrates with osteoid, scattered clusters of multinucleated giant cell are noted (arrow), **(C)** low power (x100) photomicrograph showing trabecular bone with osteoblastic rimming (arrow), **(D)** intermediate power (x200) photomicrograph showing spindle tumor cells with mild to moderate nuclear pleomorphism, oval nuclei and eosinophilic cytoplasm (arrow). Mitosis is very rare

Discussion

Through this report, we aim to highlight our experience with maxillary TIO in a child and provide a review of published literature. Tumors associated with TIO may occur in the lower extremity (>40%) or craniofacial locations (>20%) (7). Generally, the maxillofacial region is rarely involved in TIO, and maxillary TIO is rare, comprising around 9% of such tumors in the neck and head (8).

We searched for all publications in English in PubMed up to August 2021 with key words "Tumor-induced osteomalacia", "Oncogenic Osteomalacia" and "Child". Only publications reporting pediatric TIO in the oral and maxillofacial area were included. Five cases were identified, of whom two were boys and three were girls, with ages from 3-18 years (Table 1). Associated tumors were found in the mandible in two cases, the maxilla in two cases and both mandible and maxilla in one case. The diagnosis of these pediatric TIO cases averaged 21.9 months and ranged from 1.5 to 72 months. The presented case took about 18 months from onset to identification of the associated tumor but it is still shorter than the average time. The delay in diagnosis may be due to several reasons. Firstly, the bone pain is just dismissed initially since this symptom may not yet be associated with radiographic abnormalities or obvious deformities. Secondly, serum phosphate is not a routine laboratory test. Lastly, TIOs tend to be quite small, hidden and clinically silent. Looking at Table 1, the managing clinicians located tumor related TIO based on physical examination for patients 3, 4 and 5 while we had to perform ^{18}FDG PET/CT to find the tumor. This difference may be explained that in our case, the tumor was not only asymptomatic but also invisible at its location. Besides, some articles reporting adult TIO showed that tumors without local symptoms were seen in over half of the patients with oral region lesions (55.9%). On admission, we did not examine the maxillary alveolus because he had no symptoms at this location. After the tumor was found by functional imaging tests (^{18}FDG-PET/CT), physical oral examinations were performed, none of which revealed any notable findings. This highlights the

role of PET/CT in diagnosis of occult tumors and it can be helpful, as seen in this case.

The presented case had uncommon microscopic findings in tumor samples, while the majority of the tumors that cause TIO are phosphaturic mesenchymal tumors (4). OF is a slow-growing, benign lesion of bone, most commonly associated with the jaws (14). The literature search performed uncovered no publications describing OF tumor as a cause of osteomalacia in children. Diagnosis of TIO was made in this case based on hypophosphatemia, hyperphosphaturia, high serum FGF23 level, and an inappropriately low $1,25(OH)_2D$. The improvement of serum phosphate level, serum FGF23 level, and clinical symptoms after tumor removal of the OF provided strong clinical evidence that this tumor was the etiology of the TIO. In the presented case, histophathological examination showed lesion-related peripheral fibroma. Mesenchymal tumors can be divided in to osteomas, chondromas, mixed connective tissue tumors and fibroma, and all may produce a phosphatonin, now termed FGF23 (15). However, a limitation in this case was not being able to obtain immunohistochemical confirmation of FGF23 production in the resected tumor tissue.

The present case was initially treated medically for around three months before surgery, due mainly to the delay in measuring serum FGF23 level for diagnosis. Moreover, this was the first TIO case from our country so there were extensive clinical consultations. After tumor removal, clinical symptoms improved remarkably and there have been no signs of tumor recurrence. The primary treatment for TIO in the literature is surgical resection but data on alternative therapies for TIO are limited, especially for children. Besides, it is necessary to clinically assess muscular strength, serum phosphate levels and alkaline phosphatase concentrations because these problems may complicate postsurgical management, for example the requirement for prolonged mechanical ventilation and delayed recovery (16). Additionally, intralesional corticosteroid injection after surgical removal has been reported in patients 3 and 5 with central giant cell tumor (Table 1). One was a 3-year-old boy with tumors in the mandible and maxilla. Surgical removal was performed but CT imaging showed growth of tumor four months later, so the patient was treated by injection of triamcinolone in maxillary and mandibular sites. This resulted in serum FGF23 and phosphorus levels normalizing two months later (13). The other patient was a 3-year-old boy and total removal of his tumor was impossible because its extension. Also, local instillation of triamcinolone resulted in disappearance of tumor 2 months after (11).

Table 1. Review of clinical, laboratory, and outcome of head and neck pediatric TIO cases

Case no.	First author (references)	Age/sex (years)	Duration of osteomalacia (months)	Symptoms at location	Serum phosphate (mmol/L)	Serum FGF23 (pg/mL)	Localization methods	Tumor region	Histopathology results	Treatment	Outcome
1	Reyes-Múgica et al. (9)	9 F	1.5	Normal	0.52	NA	MRI	Left mandible	PMT-MCT	Surgery	Recover
2	Wu et al. (10)	15 F	24	NA	NA	NA	NA	Right mandible	PMT	Surgery	Recover
3	Fernández-Cooke et al. (11)	3 M	6	Visible tumor	0.84	395.1	PE	Maxilla	CGCG	Surgery, local steroid infiltration	Recover
4	Emodi et al. (12)	18 F	72	Soft tissue	0.42	NA	PE	Left maxilla	Fibro-osseous lesions	Surgery	Recover
5	Crossen et al. (13)	3 M	6	Ulcerated lesions, thick, irregular to palpation	0.58	450	PE	Maxilla and mandible	CGCG	Surgery, local triamcinolone injection	Recover
	Present case	14 M	18	Normal	0.32	159.3	18FDG-PET	Right maxilla	OF	Surgery	Recover

F: female, M: male, MRI: magnetic resonance imaging, NA: not available, OF: ossifying fibroma, PE: physical examination, PMT-MCT: phosphaturic mesenchymal tumor mixed connective tissue type, PMT: phosphaturic mesenchymal tumor, CGCG: central giant cell granuloma,18FDG-PET: positron emission tomography with ^{18}fluorodeoxyglucose, FGF23: fibroblast growth factor 23, TIO: tumor-induced osteomalacia

Conclusion

In conclusion, we report a case with a rare cause, TIO, of osteomalacia in childhood. Diagnosis is often delayed due to the slow progression of tumor and rarity in childhood, thus physicians should perform careful investigation, extensive imaging, laboratory test, particularly serum phosphate and FGF23 plasma levels and histopathological examination of resected tissue samples. This case highlights that head and neck imaging play an important role in evaluating pediatric patients with suspected TIO.

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Ethics

Informed Consent: Written informed consent was obtained from the patient's father.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ha Nguyen Thi, Cuong Pham Manh, Linh To Tuan, Concept: Ha Nguyen Thi, Cuong Pham Manh, Linh To Tuan, Lan Anh Le Thi, Nam Nguyen Thanh, Soamarat Vilaiyuk, Design: Ha Nguyen Thi, Cuong Pham Manh, Linh To Tuan, Lan Anh Le Thi, Nam Nguyen Thanh, Soamarat Vilaiyuk, Data Collection or Processing: Ha Nguyen Thi, Cuong Pham Manh, Lan Anh Le Thi, Nam Nguyen Thanh, Analysis or Interpretation: Ha Nguyen Thi, Cuong Pham Manh, Linh To Tuan, Lan Anh Le Thi, Nam Nguyen Thanh, Soamarat Vilaiyuk, Literature Search: Ha Nguyen Thi, Cuong Pham Manh, Writing: Ha Nguyen Thi, Cuong Pham Manh, Linh To Tuan, Lan Anh Le Thi, Nam Nguyen Thanh, Soamarat Vilaiyuk.

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References

1. McCance RA. 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 1947;16:33-46.
2. Prader A, Illig R, Uehlinger E, Stalder G. [Rickets following bone tumor]. Helv Paediatr Acta 1959;14:554-565.
3. Drezner MK. [Tumor induced osteomalacia]. Rev Endocr Metab Disord 2001;2:175-186.
4. Burckhardt MA, Schifferli A, Krieg AH, Baumhoer D, Szinnai G, Rudin C. Tumor-associated FGF-23-induced hypophosphatemic rickets in children: a case report and review of the literature. Pediatr Nephrol 2015;30:179-182. Epub 2014 Oct 18
5. Chong WH, Molinolo AA, Chen CC, Collins MT. Tumor-induced osteomalacia. Endocr Relat Cancer 2011;18:53-77.
6. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. Bone Rep 2017;7:90-97.
7. Jiang Y, Xia WB, Xing XP, Silva BC, Li M, Wang O, Zhang HB, Li F, Jing HL, Zhong DR, Jin J, Gao P, Zhou L, Qi F, Yu W, Bilezikian JP, Meng XW. 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 2012;27:1967-1975.
8. Shah R, Lila AR, Jadhav RS, Patil V, Mahajan A, Sonawane S, Thadani P, Dcruz A, Pai P, Bal M, Kane S, Shah N, Bandgar T. Tumor induced osteomalacia in head and neck region: single center experience and systematic review. Endocr Connect 2019;8:1330-1353.
9. Reyes-Múgica M, Arnsmeier SL, Backeljauw PF, Persing J, Ellis B, Carpenter TO. Phosphaturic mesenchymal tumor-induced rickets. Pediatr Dev Pathol 2000;3:61-69.
10. Wu H, Bui MM, Zhou L, Li D, Zhang H, Zhong D. Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review. Mod Pathol 2019;32:189-204. Epub 2018 Sep 11
11. Fernández-Cooke E, Cruz-Rojo J, Gallego C, Romance AI, Mosqueda-Peña R, Almaden Y, Sánchez del Pozo J. Tumor-induced rickets in a child with a central giant cell granuloma: a case report. Pediatrics 2015;135:1518-1523.
12. Emodi O, Rachmiel A, Tiosano D, Nagler RM. Maxillary tumour-induced osteomalacia. Int J Oral Maxillofac Surg 2018;47:1295-1298. Epub 2018 Mar 21
13. Crossen SS, Zambrano E, Newman B, Bernstein JA, Messner AH, Bachrach LK, Twist CJ. Tumor-induced Osteomalacia in a 3-Year-Old With Unresectable Central Giant Cell Lesions. J Pediatr Hematol Oncol 2017;39:21-24.
14. Jih MK, Kim JS. Three types of ossifying fibroma: A report of 4 cases with an analysis of CBCT features. Imaging Sci Dent 2020;50:65-71. Epub 2020 Mar 17
15. Sandoval MA, Palermo MA, Carrillo R, Bundoc R, Carnate JM Jr, Galsim RJ. Successful treatment of tumour-induced osteomalacia after resection of an oral peripheral ossifying fibroma. BMJ Case Rep 2017;2017:bcr2016218637.
16. Ryhänen EM, Schalin-Jäntti C, Matikainen N. Prolonged Hypophosphatemia and Intensive Care After Curative Surgery of Tumor Induced Osteomalacia: A Case Report. Front Endocrinol (Lausanne) 2021;12:686135.