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BRIEF REPORT

Tumor-associated FGF-23-induced hypophosphatemic rickets in children: a case report and review of the literature

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Abstract
Background Tumor-associated fibroblast growth factor 23 (FGF-23)-induced hypophosphatemic rickets is a rare but known pediatric entity first described in 1959. It results from local production of phosphatonins by benign and malignant mesenchymal tumors.
Case-Diagnosis/Treatment We report an 8-year-old boy with tumor-associated hypophosphatemic rickets due to paraneoplastic FGF-23 secretion from a benign mesenchymal pelvic-bone tumor. Excessive FGF-23 production was visualized by immunohistochemistry in the resected tumor. Phosphate wasting stopped immediately after tumor resection. We reviewed 26 reports of pediatric patients with tumor-induced hypophosphatemic rickets; paraneoplastic FGF-23 secretion was documented in only three of them. All tumors developed inside bone, were benign in 21/26 cases, and were localized in femur/tibia (13/26), radius/ulna/humerus (7/26), pelvis (4/26), rib (1/26), and craniofacial (1/26) bones. Mean interval between onset of signs and/or symptoms and diagnosis was 34 months.
Conclusions In patients with hypophosphatemic rickets acquired beyond infancy, radiologic investigations for bone tumors need to be performed rapidly. In contrast to biochemical screening for increased circulating FGF-23 levels, immunohistochemical confirmation of FGF-23 production in resected tumor tissue can be regarded as being well established.

Keywords Children · Hypophosphatemic rickets · Fibroblast growth factor 23 · Tumor-induced rickets

Abbreviations

ADHR	autosomal-dominant hypophosphatemic rickets
FGF-23	fibroblast growth factor 23
MEPE	matrix extracellular phosphoglycoprotein
MRI	magnetic resonance imaging
PET scan with ^{68}Ga-DOTA-TOC	^{68}Ga-DOTA(0)-Phe(1)-Tyr(3)-octreotide (^{68}Ga-DOTATOC) positron emission tomography computed tomography (PET-CT)
[^{18}F]-FDG	[^{18}F]-Fludeoxyglucose
sFRP4	secreted frizzled-related protein 4
SSTR	somatostatin receptor
TIO	tumor-induced osteomalacia
TIR	tumor-induced rickets
TRP	tubular reabsorption of phosphate
XLHR	X-linked hypophosphatemic rickets

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Introduction

Tumor-induced hypophosphatemic rickets (TIR) is a rare condition first described in 1959 [1]. In adults, the same pathogenetic mechanism results in tumor-induced osteomalacia (TIO), which has been reported in >250 patients [2]. In both pediatric and adult populations, the entity is characterized by hypophosphatemia caused by decreased renal phosphate reabsorption associated with local production of phosphatonins by various benign and malignant mesenchymal tumors. Only 13 years ago, in 2001, fibroblast growth factor 23 (FGF-23) was identified as a phosphaturic hormone and the disease-causing factor in TIO and TIR [3]. Other phosphatonins, such as matrix extracellular phosphoglycoprotein (MEPE) and secreted frizzled-related protein 4 (sFRP4) are also known to be involved and overexpressed in tumors causing phosphaturia, but FGF-23 remains the main disease-causing factor [4, 5].

During childhood, the clinical picture resembles features of the inherited phosphaturic disorders X-linked hypophosphatemic rickets (XLHR) and autosomal-dominant hypophosphatemic rickets (ADHR) [6]. Recommendations concerning diagnosis and treatment exist [6, 7], but diagnosis of TIO and TIR often remains extremely difficult, leading to extensive diagnostic procedures, since tumors can be too small for detection by conventional radiological methods [8].

We report an 8-year-old boy with FGF-23-induced hypophosphatemic rickets due to a mesenchymal tumor of the iliac bone with paraneoplastic FGF-23 secretion. We provide a review of the literature of published pediatric cases with TIR between 1956 and 2013 in order to emphasize the importance of accurate diagnosis, with special emphasis on immunohistochemistry.

Case report

An 8-year-old boy was investigated for a persistent abnormal gait resembling mild unilateral limping first recognized by the parents 2 years earlier. He never complained about pain. His weight continuously increased along the 25th percentile and height along the 3rd percentile. He went through multidisciplinary investigations. First, a neurologic etiology was suspected and excluded. He was then transferred to the department of pediatric orthopedic surgery and received a plain film of his pelvis, which showed a large and polylobulated cystic lesion in the left iliac bone and acetabulum. Because of suspected Langerhans cell histiocytosis, hematological/oncological investigations were initiated. At that time, typical clinical signs of rickets, such as visible epiphyseal enlargement of the wrists and ankles, were first recognized and confirmed radiologically (cupping and fraying of the metaphyseal region (Supplementary Fig. 1a). Laboratory findings, i.e., hypophosphatemia (0.5 mmol/l), renal tubular phosphate wasting (tubular reabsorption of phosphate 85.4 %) (Supplementary Fig. 2), normal parathormone, and normal levels of plasma vitamin D metabolites were not compatible with common forms of rickets in childhood, such as calcipenic rickets seen in vitamin D deficiency or XLHR. Tumor-associated rickets was therefore suspected and investigated with various methods, including a positron emission tomography (PET) scan with ^{68}Ga-DOTA(0)-Phe(1)-Tyr(3)-octreotide (^{68}Ga-DOTA-TOC) and FGF-23 plasma level assessment. A causal lesion other than the iliac tumor or a clearly abnormal FGF-23 plasma level could not be detected, though the FGF-23 plasma level was too high in relation to the low phosphate levels (FGF-23, 92 kUR/l; normal range 26–110). As the initial biopsy of the iliac lesion was not conclusive, complete curettage, high-speed burring, and stabilization with bioresorbable bone cement of the acetabular cystic lesion were performed (Supplementary Fig. 3). Histologically, the tumor consisted of monomorphic spindle cells without nuclear atypia, reactive and osteoblastoma-like osteoid deposits, and irregularly distributed and focally clustered osteoclast-like giant cells, which was consistent with a solid variant of an aneurysmal bone cyst. Intriguingly, additional immunohistochemistry using an established and commercially available antibody against FGF-23 (clone FG322-3, Enzo Life Sciences, Lausen, Switzerland) showed consistent and specific expression of the protein in the mononuclear spindle-cell component (Fig. 1). After surgery, tubular phosphate reabsorption normalized immediately (Supplementary Fig. 2), and clinical and radiological signs of rickets quickly resolved (Supplementary Fig. 1b) without any further need for substitution of phosphate or other interventions. The patient was doing well, without signs of hypophosphatemic rickets or tumor recurrence, 24 months after curettage.

Discussion and review of the pediatric literature

The patient in this report illustrates the rare entity of tumor-associated FGF-23-induced hypophosphatemic rickets in children. McCance described the first case of this entity in 1947 in a 15-year-old girl who presented with rickets and vitamin D resistance, but he did not attribute her illness to the tumor that was resected from her femur (Supplementary Table 1). Tumor-associated rickets was then first described by Prader et al. in 1959 [1]. The next cases were not described until almost 15 years later (Supplementary Table 1). In 2001, FGF-23 was identified as the disease causing phosphaturic hormone [3].

We performed a systematic MEDLINE search (1959–2013) of publications in English, French, and German. Key words were: “hypophosphatemic rickets”, “FGF-23,” and “child”. We excluded cases of McCune–Albright syndrome

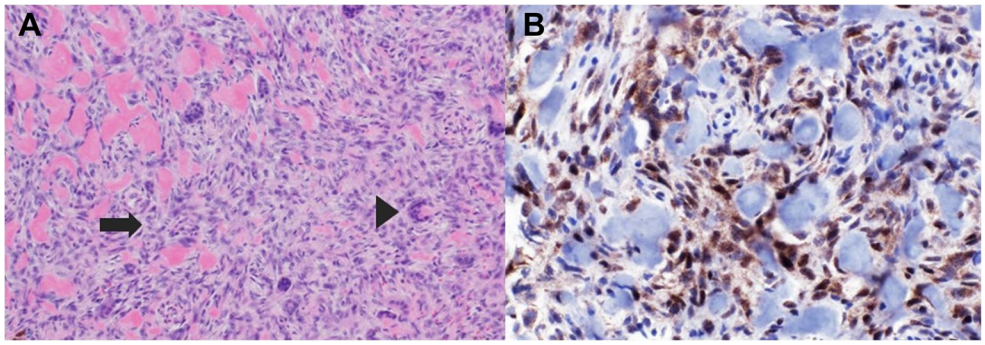

Fig. 1 Histology and immunohistochemistry of the pelvic tumor. **a** Hematoxylin and eosin (HE) staining showing mononuclear tumor-cell proliferation (*arrow*) with intermingled giant cells (*arrowhead*) and areas of reactive new bone formation, compatible with solid aneurysmal bone cyst. **b** Tumor cells show strong and consistent expression of fibroblast growth factor 23 (FGF-23) by immunohistochemistry (*brown areas*). *Blue areas* represent osteoblastoma-like osteoid deposits with intermingled inflammatory cells (no immunoreactivity)

and fibrous dysplasia, where hypophosphatemic rickets is explained by the same mechanism of FGF-23 overproduction, and cases of epidermal naevus syndrome and one report of an 8-year-old boy with pseudo-(tumor-induced) rickets, where no causative lesion was found. We identified a total of 26 patients (Supplementary Table 1), of whom 16 were boys and ten were girls, with a mean age of 12 (range 4–18) years. All tumors were localized inside bone (20 in extremities, 13 in femur/tibia, 7 in radius/ulna/humerus); four in the pelvic region; 1 in a rib and 1 in craniofacial bones. Most lesions were benign; histological signs of malignancy were described in five cases only. All patients had hypophosphatemic rickets with typical low levels of phosphate in plasma, normal calcium levels, and elevated levels of alkaline phosphatase. The mean interval between onset of clinical signs and/or symptoms and diagnosis was 34 months. Evidence of FGF-23 overproduction was illustrated in three cases only: elevated serum levels were reported in all three cases, with immunohistochemical proof of FGF-23 production in the resected tumor in two only. In all other cases, FGF-23 was not measured in blood, and local production was not visualized by immunohistochemistry, mostly because FGF-23 was not yet known as the disease-causing factor at the time of diagnosis. Details are listed in Supplementary Table 1.

The diagnosis of tumor-associated hypophosphatemic rickets is usually made in the presence of typical clinical signs, such as rickets beyond infancy, typical laboratory findings (hypophosphatemia, reduced tubular phosphate reabsorption, normal vitamin D_3 levels). In many cases, it is difficult to find the causative lesion—this often takes several months to years. Hereditary forms, such as XLHR and ADHR, should be excluded by genetic testing if the diagnosis remains unclear [9].

As our review indicates, in the pediatric population, rickets-inducing tumors are usually found inside bone, but according to the reports of TIO in adults, tumor presence in soft tissue also must be taken into consideration. The most common locations for both soft-tissue and bone tumors are the extremities and the pelvic region. Tumors are of mesenchymal origin and show various histological patterns, including: (a) phosphaturic mesenchymal tumor like; (b) osteoblastoma like; (c) nonossifying fibroma like [8]. Phosphaturic mesenchymal tumors are reported to represent ~70–80 % of tumors with TIO [10]. In the case presented here, areas of reactive new bone formation focally resembled osteoblastoma, but the largest part of the lesion showed typical features of a solid variant of an aneurysmal bone cyst.

Even with modern imaging techniques, such as high-resolution magnetic resonance imaging (MRI) and somatostatin receptor (SSTR) scintigraphy—used because osteomalacia-causing tumors often express SSTR [8]—in combination with FGF-23 sampling in plasma, tumor localization remains often difficult to determine. Recent papers confirm a good sensitivity of SSTR-based functional scans [11] and superiority to [^{18}F]-Fludeoxyglucose ([^{18}F]-FDG) and PET computed tomography (CT) scan in localizing the respective tumors [12]. Furthermore, measurement of FGF-23 plasma levels shows analytical and biological variability, complicating the interpretation of results [13]. In the diagnosis of TIR, FGF-23 measurements must be judged according to age-dependent reference ranges and may help to establish the diagnosis [14]. While preoperative demonstration of increased FGF-23 levels would be desirable, the fluctuating plasma levels and technical issues in laboratory assays have not rendered this possible as yet. In contrast, as shown in our patient, immunohistochemical demonstration of FGF-23 production on resected tumor tissue has been helpful in the small number of cases in which it has been applied so far (Supplementary Table 1). Immunohistochemical staining of other phosphatonins, such as MEPE and/or sFRP4, has not yet

been documented in TIR in the pediatric population, and only a few reports about their application in adult patients exist in the literature [4, 15].

In summary, this report illustrates a rare cause of rickets in childhood. Diagnosis is often delayed and thus requires careful investigation, comprising imaging, laboratory tests including FGF-23 plasma levels, and histopathological examination of the resected tumor with additional immunohistochemistry. Though rare, this diagnosis must be considered in pediatric patients who present with acquired hypophosphatemic rickets beyond infancy.

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Conflicts of Interest None.

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