Tumor-Induced Rickets in a Child With a Central Giant Cell Granuloma: A Case Report

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abstract

Tumor-induced osteomalacia/rickets is a rare paraneoplastic disorder associated with a tumor-producing fibroblast growth factor 23 (FGF23). We present a child with symptoms of rickets as the first clinical sign of a central giant cell granuloma (CGCG) with high serum levels of FGF23, a hormone associated with decreased phosphate resorption. A 3-year-old boy presented with a limp and 6 months later with painless growth of the jaw. On examination gingival hypertrophy and genu varum were observed. Investigations revealed hypophosphatemia, normal 1,25 and 25 (OH) vitamin D, and high alkaline phosphatase. An MRI showed an osteolytic lesion of the maxilla. Radiographs revealed typical rachitic findings. Incisional biopsy of the tumor revealed a CGCG with mesenchymal matrix. The CGCG was initially treated with calcitonin, but the lesions continued to grow, making it necessary to perform tracheostomy and gastrostomy. One year after onset the hyperphosphaturia worsened, necessitating increasing oral phosphate supplements up to 100 mg/kg per day of elemental phosphorus. FGF23 levels were extremely high. Total removal of the tumor was impossible, and partial reduction was achieved after percutaneous computed tomography–guided radiofrequency, local instillation of triamcinolone, and oral propranolol. Compassionate use of cinacalcet was unsuccessful in preventing phosphaturia. The tumor slowly regressed after the third year of disease; phosphaturia improved, allowing the tapering of phosphate supplements, and FGF23 levels normalized. Tumor-induced osteomalacia/rickets is uncommon in children and is challenging for physicians to diagnose. It should be suspected in patients with intractable osteomalacia or rickets. A tumor should be ruled out if FGF23 levels are high.

Tumor-induced osteomalacia/rickets (TIO) is a rare paraneoplastic disorder caused by overproduction of fibroblast growth factor 23 (FGF23) from the responsible tumors.1,2 FGF23 is a hormone associated with decreased resorption of phosphate that causes hyperphosphaturia, leading to osteomalacia or rickets.3-5 Tumors are typically benign, small, and with mesenchymal origin.6-8 We report the first pediatric case of TIO in association with a central giant cell granuloma (CGCG).9 Our case is unique because the child presented with clinical signs of rickets as the first sign of CGCG with high FGF23 serum levels.

PATIENT PRESENTATION

A previously healthy 3-year-old boy with no history of trauma or other joint problems presented with an increasing limp. Initial radiographs and basic laboratory studies, including calcium and phosphate, were normal. He initially received a diagnosis of...
transient synovitis. His family history was negative.

Six months later he presented with insidious and painless growth of the jaw. On examination, gingival hypertrophy and mobile teeth were observed (Fig 1), and he presented with genu varum, with a waddling gait. Laboratory tests revealed serum phosphate level 2.6 mg/dL (reference range 3.7–5.3 mg/dL), 1,25-(OH)₂-vitamin-D 35.2 pg/mL (reference range 15–65 pg/mL), 25-(OH)-vitamin D 15.1 ng/mL (reference range 15–55 ng/mL), and parathyroid hormone (PTH) 7.5 pg/mL (reference range 15–60 pg/mL). Serum bone formation markers were high: osteocalcin 52 ng/mL (reference range 4–12 ng/mL), alkaline phosphatase 23 µg/L (reference range 7.5–17 µg/L), and bone-specific alkaline phosphatase 36.5 µg/L (reference range 7.5–17 g/L). Tubular reabsorption of phosphate measured by ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was normal initially (Fig 3). MRI showed an osteolytic lesion measuring 28 × 19 mm at the maxilla. Skeletal radiographs revealed typical rachitic findings (Fig 2), and bone mineral density scans showed a Z score of −2.92 SD at the lumbar spine. Incisional biopsy of the tumor revealed a CGCG with mesenchymal matrix. Cherubism mutations were negative.

The CGCG was treated initially with calcitonin and phosphate supplements, and calcitriol were started for the rickets (Fig 3 summarizes treatment timeline aligned with laboratory tests and phosphate supplement requirements). Despite treatment, the maxillary bone lesions continued to grow, measuring 45 × 70 × 100 mm in the maxilla and 80 × 40 × 70 mm in the jaw by MRI (Fig 1 and 2C). Although the lesions were benign, they led to obstructive sleep apnea and malnutrition. These complications made it necessary to perform a tracheostomy and gastrostomy. Multiple pathologic fractures made the patient wheelchair-bound, and weakness of the thoracic cage was reflected in a reduction in lung volume parameters (Fig 2A and 2B).

Additional studies 1 year after the onset of the disease revealed significant hyperphosphaturia, with TmP/GFR of 0.44 mg/dL at the lowest, necessitating increasing oral phosphate supplements starting at 8 mg/kg per day (of elemental phosphorus; 500 mg = 16.1 mmol) at the onset of the disease and up to 100 mg/kg per day during follow-up. Osteocalcin was >300 ng/mL (the upper limit of detection of the laboratory), and alkaline phosphatase was 246 µg/L (7.5–17) (Fig 3). Two years into follow-up, bone mineral density worsened to a Z score of −4.4 SD at the lumbar spine.

The challenge was to find the link between the tumor and rickets in an otherwise healthy child. After a literature search, TIO induced by FGF23 was our main suspected diagnosis despite being rare in children.

FGF23 levels were extremely high: intact FGF23 395.1 pg/mL (N < 40) and C-terminal peptides 1267.2 RU/mL (N < 60), as measured by ELISA Kit (Kainos Laboratories, Tokyo, Japan). CGCG producing FGF23 was thought to be the primary cause of his rickets but was not confirmed by messenger RNA on the surgery samples because this was not available technique in our hospital.

Total removal of the tumor was impossible because of its extension, and the CGCG did not respond to conventional treatment with calcitonin. An octreotide scan was
performed but was negative for somatostatin receptors. Conservative treatment of the CGCG including bisphosphonates and simple curettage was tried to reduce the volume, with poor response. Partial reduction was achieved after percutaneous CT-guided radiofrequency sessions, with a Cool Tip 15-10 (Tyco-Radionics-Covidie, Minneapolis, MN) and an umbrella-type electrode (Leeving 4 cm; Boston Scientific, Marlborough, MA), with an overall decrease in size of 5 mm at all axes. Also, local instillation of triamcinolone resulted in disappearance of 2 40-mm cysts 2 months after therapy. Finally, propranolol was given for 6 months in an attempt to reduce the tumor’s vascularization and therefore its growth. Two months later an MRI scan showed tumor reduction (40 × 62 × 77 mm in the maxilla and 57 × 38 × 70 mm in the jaw).

Together with the local control of the tumor, the main problem was to control phosphate renal wasting and more pathologic fractures. Compassionate use of cinacalcet, a calcimimetic drug that suppresses PTH secretion and by reducing PTH-induced phosphate excretion may raise serum phosphate, was tried. This treatment was unsuccessful and was discontinued after a month because of hypocalcemia. The tumor was then stable for more than a year, with no specific treatment, and phosphate wasting was managed with phosphorus supplements and calcitriol. The tumor spontaneously and slowly regressed the third year after onset. Bone mass, bone reabsorption parameters, and FGF23 levels normalized. Because the samples had to be sent away, we measured FGF23 only twice, at diagnosis and after improvement, to prove normalization. Phosphate supplements were tapered and gastrostomy and tracheostomy tubes removed. The patient started to walk again and is now back in school 4 years after the onset of the disease.

**DISCUSSION**

To the best of our knowledge, this is the first pediatric case of severe FGF23 tumor-induced rickets.
secondary to a CGCG of the maxillary bones. Retrospectively, we think the initial limp was the first sign of weakness associated with rickets. We assumed that the tumor was the source of production of FGF23 because rickets started with the onset of the CGCG, coinciding with an extremely high FGF23 serum level. Also, the rickets and the need for phosphorus supplementation improved as the tumor’s size gradually decreased. The limitation of our case is that we could not provide the final proof of concept, because we did not perform tests looking for FGF23 production in the surgical samples.

TIO is a rare condition first described by McCance in 1947 as a paraneoplastic disorder characterized by phosphaturia, hypophosphatemia, low serum levels of 1,25-dihydroxy-vitamin D, and rickets or osteomalacia.7,10 Tumors responsible for this condition usually affect patients >30 years old and are typically benign, small, and of mesenchymal origin.2,6–8 Very few children with TIO have been reported; the youngest was a 9-month-old boy with a soft tissue tumor on his right thigh.6,11

In our case the tumor was a benign CGCG with a collagen fibroblast matrix, located in the maxillary bones. In an extensive literature review on CGCG of the jaw by de Lange,9 none of the patients presented with osteomalacia, suggesting that the tumors did not produce FGF23, unlike that of our patient.

In 2000 FGF23 was implicated in the development of hypophosphatemic diseases.12 FGF23 is a bone-derived hormone that regulates and is regulated by blood levels of phosphate and active vitamin D. FGF23 acts at renal tubule cells by binding to an FGF receptor (probably FGFR1) and its coreceptor Klotho to decrease the overall activity of the enzyme (1α-hydroxylase), which converts inactive vitamin D to active 1,25-D, and increasing the activity of the 24(OH)ase, which catalyzes the degradation of 1,25-D. FGF23 also increases phosphate transport into
the urine via the sodium-dependent phosphate transporters 2a and c. On the other hand, FGF23 production is stimulated in response to elevations in phosphorus and 1,25-D.13

MRI has been shown to be the best tool for searching for the primary tumor.14 Tumor localization is improved by somatostatin receptor imaging, such as octreotide scintigraphy and octreotide single-photon emission CT/CT.8,15 Imaging methods such as gallium-68 (68Ga) DOTA-NOC, 68Ga DOTA-TOC, and 68Ga DOTA-TATE positron emission tomography/CT show promising first results in patients with TIO and negative octreotide scans.16

Our challenge was on one hand the rapidly growing CGCG and on the other hand the consequences of FGF23 overproduction. The most common treatment of CGCG has been surgical curettage, with high recurrence rates. The most successful pharmacologic agents have been intralesional corticosteroid injections and systemic treatment with calcitonin or interferon-α2.9 Other agents such as imatinib17 or denosumab,18 a monoclonal antibody with antiresorptive effects developed for osteoporosis, could be useful in treating CGCG. Radiofrequency thermal ablation is less invasive, and in our experience it had a mild effect in reducing the tumor’s volume; therefore, we think it should be offered when complete surgical resection cannot be performed.19 Propranolol was our last treatment attempt, intended to reduce vascularization of the tumor and therefore its growth.20 In our experience there was mild improvement, with a reduction in tumor size 2 months after we initiated treatment.

The treatment of choice for TIO is total removal of the tumor. When the tumor is completely removed, clinical improvement and resolution of the laboratory abnormalities can be seen.2,6,7,10 There are reported cases of TIO that improved with octreotide therapy when scans were positive for somatostatin receptors. Geller et al21 treated patients successfully with cinacalcet, a calcimimetic agent. They hypothesized that medically induced hypoparathyroidism with cinacalcet increases renal phosphate reabsorption and decreases phosphate supplementation, showing evidence of bone healing. In our case this treatment did not work and led to hypocalcemia, although other studies have shown its effectiveness.21–23 A phase 1 clinical trial of an anti-FGF23 antibody has shown that it increases serum phosphate in patients with X-linked hypophosphatemic rickets and may open the door to treat other FGF23-related hypophosphatemic diseases.24

In conclusion, TIO is uncommon in children. The diagnosis is challenging for physicians, and it should be suspected in patients with intractable osteomalacia or rickets. If FGF23 levels are high, a tumor should be looked for. FGF23 levels in serum and histologic samples are useful for diagnosis and follow-up. Curative treatment of TIO involves surgical removal of the tumor when possible. Propranolol is a treatment option if the primary tumor is well vascularized and cannot be totally removed. When the tumor expresses somatostatin receptors, treatment with somatostatin analogs should be tried. Cinacalcet may be useful for improving phosphate wasting. CGCG that does not respond to standard treatment could be candidate for denosumab or imatinib. In our experience, CGCG producing FGF23 is an aggressive disease that if not completely removed causes severe osteomalacia or rickets, with few effective treatment options but with an encouraging natural history toward regression.

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