CASE REPORT

Tumor producing fibroblast growth factor 23 localized by two-staged venous sampling

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Abstract

Background: Tumor-induced osteomalacia is a rare paraneoplastic syndrome characterized by hypophosphatemia, renal phosphate wasting, suppressed 1,25-dihydroxyvitamin D production, and osteomalacia. It is caused by a usually benign mesenchymal tumor producing fibroblast growth factor 23 (FGF-23). Surgical excision of the tumor is the first choice of treatment because complete resection is curative. Unfortunately, localization often fails due to the small size of these neoplasms. According to the current standards, supportive care with oral phosphate and calcitriol is the only feasible option in such cases.

Case: In this report, we describe the diagnostic value of two-staged venous sampling to localize the FGF-23 secreting tumor in a case where conventional imaging failed. In addition, we examined the effect of dipyridamole on renal phosphate excretion, explored the efficacy of octreotide and calcitonin to suppress the FGF-23 production, and closely evaluated the hormonal changes following successful removal of the tumor. The latter observations indicate that calcitonin may be useful to suppress tumor-FGF-23 production and that FGF-23 may be a clinically relevant inhibitor of parathyroid hormone secretion in man.

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Introduction

Severe hypophosphatemia is a well-known cause of proximal leg muscle weakness. Usually, symptoms occur only if serum phosphate concentration is less than 0.3 mmol/l (1). The most frequent underlying abnormality is severe 25-OH vitamin D (25-D) deficiency with secondary hyperparathyroidism and parathyroid hormone (PTH)-dependent renal phosphate loss (2).

In this report, we describe a patient with severe muscle weakness, acquired hypophosphatemia, PTH-independent renal phosphate loss, and unexplained 1,25-dihydroxyvitamin D (1,25-D) deficiency. This combination of findings is highly suggestive of tumor-induced osteomalacia (TIO), a rare paraneoplastic syndrome caused by tumors secreting phosphaturic factors known as phosphatonins (3–5). The most important and clinically relevant phosphatonin is fibroblast growth factor 23 (FGF-23) (5). This factor inhibits renal tubular phosphate reabsorption and suppresses 1 α -hydroxylase activity. FGF-23 producing tumors are predominantly of benign mesenchymal origin (6, 7). Surgical removal is the treatment of choice because complete resection results in a prompt resolution of all biochemical defects. However, tumor localization is usually very problematic because of the

small size of these neoplasms. In most cases, the tumor is not found with conventional imaging techniques. In these patients, symptomatic treatment with oral phosphate and 1 α -calcidiol or calcitriol is started. Many patients will develop severe gastrointestinal side effects on high-dose oral phosphate treatment (8).

In this paper, we describe how repeated, zooming, venous sampling may provide a clue about the localization of the tumor, and we report our experience with new approaches to reduce renal phosphate excretion or to suppress FGF-23 production.

Case

A 69-year-old woman was referred because of progressive muscle weakness, painful ribs, an elevated serum alkaline phosphatase and a bone scan revealing multiple hot spots. Leg muscle weakness had developed gradually over 1 year, and for the past 4 months she had been unable to rise from a chair without assistance. Her medical history included mild chronic obstructive pulmonary disease and type 2 diabetes mellitus. Both were well controlled. Medication consisted of salmeterol and beclomethasone inhalers, gliclazide, metformin and insulin lispro. There was no family history of metabolic

bone disease or muscle disorders. Physical examination revealed severe, symmetrical, proximal leg muscle weakness without neurological deficits. Several ribs were painful on palpation. Initial laboratory results showed a normal serum creatinine, a total calcium of 2.29 mmol/l (normal range (NR): 2.10–2.55 mmol/l), an albumin level of 38 g/l (NR: 35–50 g/l), a reduced serum phosphate (0.25–0.51 mmol/l, NR: 0.87–1.45 mmol/l), a mild elevation of serum alkaline phosphatase (278 U/l, NR: <120 U/l) with a high normal γ GT (36 U/l, NR: 1–35 U/l), a suboptimal 25-hydroxyvitamin D 26 nmol/l (25-D, NR: 23–94 pmol/l), and a PTH within the normal range (2.6–5.4 pmol/l, NR: 1.6–6.9 pmol/l). In a sample obtained four years previously serum phosphate levels had been normal (1.08–1.21 mmol/l). A technetium diphosphate bone scan showed multiple and symmetrical hot spots in the ribs at the costochondral junctions, and increased uptake in the left medial tibia plateau and in the right ankle. X-rays of the ribs, the left knee and right ankle did not reveal any bone lesions. Bone density of the lumbar spine and hips measured by dual energy X-ray absorptiometry was within the normal range. The accumulated findings did not support a diagnosis of secondary hyperparathyroidism caused by 25-D deficiency. Therefore, it was decided to extend the diagnostic evaluation. Renal phosphate reabsorption, assessed by the method of Bijvoet *et al.* was severely reduced (TmP/gfr 0.3 mmol/l, NR: 0.7–1.4 mmol/l), PTH-related peptide was normal (<0.3 pmol/l, NR: <0.6 pmol/l) (9). It was concluded that renal phosphate wasting was not PTH-dependent. Further evaluation of vitamin D status revealed a severe reduction of 1,25-D (11 pmol/l, NR: 48–161 pmol/l), indicating impaired 1α -hydroxylation. The combination of acquired hypophosphatemia, PTH-independent phosphaturia, and inappropriately low serum 1,25-D levels suggested a diagnosis of TIO. This was confirmed by a markedly elevated serum FGF-23 level (426 kRU/l, NR: 5–210 kRU/l). The muscle weakness and bone pain were attributed to a combination of phosphate depletion and severe 1,25-D deficiency. The absence of signs indicative of osteomalacia was attributed to the relatively recent onset of FGF-23 overproduction. The patient was started on 1α -caldiol 1 μ g a day, later increased to a maximum of 3 μ g/day, based on the monitoring of serum calcium, phosphate, and creatinine. This raised the 1,25-OHD levels to 54–89 pmol/l and increased serum phosphate to 0.63–0.73 mmol/l. Serum total calcium rose to mildly elevated levels (2.66–2.80 mmol/l) and serum PTH decreased to 0.9 pmol/l (NR: 1.6–6.9 pmol/l). The initially elevated bone resorption marker carboxy-terminal cross-linked telopeptide of type I collagen (ICTP) decreased from 12.4 to 3.2 μ g/l (NR: 1.8–5.0 μ g/l), and the bone formation marker carboxy-terminal propeptide of type I procollagen (PINP) decreased from 84 to 45 μ g/l (NR: 19–84 μ g/l). Muscle strength and mobility improved, bone pain

decreased and previous bone scan abnormalities diminished. Unfortunately, 1α -caldiol treatment frequently required dose adjustment because of hypercalcemia and worsening of renal function. It was therefore decided to look for alternative modes of treatment, one aiming at suppression of FGF-23 secretion and one aiming at inhibition of renal phosphate wasting. In addition, an extensive search was started to localize the tumor.

FGF-23 suppression

FGF-23 producing tumors may express somatostatin receptors, and some respond to octreotide whereas others do not (10). We hypothesized that, because of their osteogenic nature, FGF-23 producing tumors might also be responsive to calcitonin and decided to examine the FGF-23 suppressive effects of a s.c. injection of NaCl 0.9%, octreotide, and calcitonin on three consecutive days, separated by 24-h drug-free intervals (11). At 0830 h, a venous catheter was inserted in a forearm vein to permit frequent blood sampling. Basal blood samples were taken at 0845 and 0900 h. At 0900 h, the patient received a s.c. injection of 1 ml NaCl 0.9% on day 1 (control), 200 μ g octreotide on day 3, and 200 IU calcitonin on day 5. Subsequently, blood samples were taken after 1, 3, 5, 7, 9, and 12 h. FGF-23 was measured by a C-terminal FGF-23 ELISA kit (Immunotopics, San Clemente, CA, USA; NR: 5–210 kRU/l). This assay recognizes the full length 32 kDa FGF-23 protein as well as the 12 kDa C-terminal FGF-23 fragments (5). The results of the FGF-23 suppression tests are shown in Fig. 1. Octreotide had no effect on serum FGF-23 levels, whereas calcitonin suppressed serum FGF-23 from 1343 to a nadir of 744 kRU/l at 9 h. Subsequent long-term calcitonin treatment was not considered at that time because tumor localization was given first priority.

Stimulation of renal phosphate absorption

It has been observed that PTH-independent renal phosphate wasting can be reduced by dipyrindamole

Figure 1 Changes in serum FGF-23 levels in response to a single s.c. injection of NaCl 0.9%, octreotide 200 μ g and calcitonin 200 IU, at 0900 h.

300 mg/day orally for at least 3 weeks (12, 13). As the efficacy of this approach has never been examined in patients with FGF-23 producing tumors, it was decided to evaluate the effect of slow-release dipyridamole 200 mg twice a day for a period of 3 weeks. During this test period, 1α -calcidiol was continued at a dose of 1 μ g/day. Serum PTH and 1,25-OHD remained stable at a level of 1.5 pmol/l and 35 nmol/l respectively. Serum phosphate and urinary phosphate excretion did not change significantly (data not shown).

Two-staged venous sampling

An extensive search to localize the FGF-23 producing tumor with octreotide scanning, PET scanning, and total body computed tomography failed to reveal any abnormalities. Ultrasonography of the ovaries was classified as normal. Magnetic resonance imaging (MRI) of the left knee revealed only normal structures. As all available imaging techniques failed to provide a clue, it was decided to perform a total body venous sampling for FGF-23 (14). During the first sampling

procedure, a flexible catheter was inserted in the right femoral vein, and subsequently moved to all first-order (superior and inferior caval veins) and second-order veins (first branches of the caval veins) in neck, chest, abdomen, and both legs. As shown in Fig. 2A, a diagnostic rise in FGF-23 at a single spot in a first- or second-order vein was not observed. However, when the mean FGF-23 concentration from samples obtained in the chest, abdomen, and legs were calculated, the mean intra-abdominal value of 1565 kRU/l was found to be higher than that in the chest (1355 kRU/l) or in the legs (1330 kRU/l). Although the differences in FGF-23 levels were small, it was decided to perform a second, more detailed venous sampling in the abdominal compartment by extending the search to third-order veins. As shown in Fig. 2B, high FGF-23 levels were found in the right ovarian vein and in the right distal internal iliac vein, with values of 2060 and 3750 kRU/l, against a background value of 1365 kRU/l measured in a right forearm vein. This suggested that the tumor was most likely located in the right pelvic compartment. However, a detailed pelvic MRI showed a slightly enlarged ovary

Figure 2 FGF-23 sampling. (A) Total body sampling, mean FGF-23 levels are highest in the abdominal compartment, and (B) detailed sampling of the abdominal veins. High FGF-23 levels were observed in the right ovarian vein, and in the distal part of the internal iliac vein. VJI, vena jugularis interna; VS, vena subclavia; VCS, vena cava superior; RA, right atrium; VCI, vena cava inferior; VR, vena renalis; V. Ov, vena ovarica; VI, vena iliaca; VIC, vena iliaca communis; VIE, vena iliaca externa; VII, vena iliaca interna; VF, vena femoralis.

on the left (maximal diameter 30 mm). The right ovary appeared to be normal. As left to right shunts are not unusual in the venous system, and some ovarian tumors may produce FGF-23, it was concluded that the FGF-23 producing tumor might be in the left ovary. Both ovaries and fallopian tubes were removed by laparoscopy. Unfortunately, postoperative serum phosphate levels remained low, FGF-23 did not decrease, and microscopic examination of both ovaries proved to be normal. A repeat abdominal MRI several weeks later showed a small mass in the subserosal region of the right anterior uterine wall. Compared with the preoperative MRI, this tumor, initially diagnosed as a myoma, had grown from 24 to 30 mm. As myomas are unlikely to grow in postmenopausal women, it was concluded that this structure might be the FGF-23 producing tumor we were looking for, and a second surgical procedure was planned.

Changes after tumor resection

Three days prior to the second surgical procedure, 1α -caldiol treatment was discontinued. Abdominal hysterectomy was performed by Pfannenstiel laparotomy. Pathological examination revealed a leiomyoma located in the right anterior uterine wall, with a diameter of 2.5 cm, and with the characteristics of a phosphaturic mesenchymal tumour, mixed connective tissue variant (PMT-MCT) (6, 7). Within the first 24 h after surgery, serum FGF-23 decreased rapidly from 8050 to 242 kRU/l and remained around this level during the following days (Fig. 3). PTH increased from a preoperative level of 1.9 to 5.3 pmol/l at 24 h postoperatively, and peaked on the third postoperative day at 7.3 pmol/l. Subsequently, PTH gradually decreased to the low normal range. Serum 1,25-D did not change during the first 24 h after surgery (preoperative level 24 pmol/l, 24 h postoperatively 12 pmol/l). However, on the third postoperative day 1,25-D had increased to 68 pmol/l and after 7 days it peaked at 98 pmol/l. Serum calcium corrected for albumin (Ca_{corr}) and phosphate level rose very gradually. The serum Ca_{corr} increased from 2.31 mmol/l preoperatively to 2.48 mmol/l 7 days after surgery, and peaked at day 14 with a value of 2.61 mmol/l. Serum phosphate slowly rose from a preoperative value of 0.56–0.86 mmol/l after 1 week, and continued to rise very gradually thereafter. Six weeks after surgery serum phosphate reached its maximum of 1.57 mmol/l. The TmP/gfr assessed 4 and 6 weeks postoperatively had increased to the high normal range (1.2 and 1.4 mmol/l respectively).

Discussion

The clinical picture of TIO was first described by McCance in 1947, but it was Prader *et al.* in 1959, who recognized that a tumor producing an as yet

Figure 3 Serum calcium corrected for albumin (Ca_{corr} , mmol/l), phosphate (mmol/l), 25-OH vitamin D ($\circ$, nmol/l), 1,25-OH vitamin D ($\bullet$, pmol/l) and FGF-23 ($\text{kRU/l} \times 10^3$) levels before and after surgery (dashed line).

unknown substance was the likely cause of the disease (15, 16). In 1977, Drezner & Feinglos recognized impaired 1α -hydroxylation as a characteristic biochemical abnormality of the syndrome, which was later confirmed by Sweet *et al.* (17, 18). In 2001,

Shimada *et al.* identified FGF-23 as the causative humoral factor of TIO (19). Their finding started extensive research activities to define the physiological importance of FGF-23 in phosphate homeostasis in health and disease (20). This advanced the understanding of disorders in phosphate metabolism enormously.

FGF-23 decreases renal phosphate reabsorption by inhibiting the expression of the type 2 sodium phosphate (NaP-2a) transporters in the proximal renal tubule brush border (21). In addition, it inhibits the expression of renal 1- α hydroxylase, the enzyme that is necessary to convert 25-D to its active metabolite 1,25-D. In healthy subjects, FGF-23 increases in response to phosphate loading and produces phosphaturia and inhibition of renal 1 α -hydroxylase (22, 23). FGF-23 levels are increased in chronic kidney disease and its suppressive effects on 1,25-D production may play an important role in the pathogenesis of secondary hyperparathyroidism (24). FGF-23 is also involved in several genetic disorders of phosphate metabolism, such as X-linked hypophosphatemia and autosomal dominant hypophosphatemic rickets (3–5).

Tumors associated with FGF-23 production are characteristically slow-growing, polymorphous, benign, mesenchymal neoplasms (6). They are described as PMT-MCT and are characterized by an admixture of spindled cells, distinctive calcified matrix, osteoclast-like giant cells, prominent blood vessels, cartilage-like matrix, and metaplastic bone (7). Occasionally, malignant tumors have been reported (6). The tumors are usually very small and difficult to find. They are most commonly found within the bones of the upper and lower extremities, but may also present as a palpable soft tissue tumor mass in the arm, leg, or neck. Nasal cavities are also relatively common locations.

A correct diagnosis of TIO is often delayed by several years, and the inability to locate the tumor often delays cure by about 5 years (5). Some reports suggest that radiolabeled octreotide scintigraphy is useful to reveal the tumor involved in TIO (25). However, in our patient as well as in several other reports, this technique did not provide a localization. The PET-CT, although successful in one report, was not conclusive in our patient (26). In fact, all imaging techniques that have been recommended previously failed in our patient.

Venous sampling has been used to confirm local FGF-23 production in a tumor located in the groin that was palpable on physical examination (20). So far, there are no reports describing a key role of venous sampling in the localization of a FGF-23 producing tumor. Apparently, it is difficult to find a gradient and our case supports that. When sampling was restricted to the first- and second-order veins, no gradient was detected. The mean compartment concentrations provided a clue of where to look in more detail. When sampling was extended to the third-order veins, we were able to find the gradient.

If the tumor cannot be found, patients are generally treated with oral phosphorus 1–4 g/day, in combination with calcitriol 1–3 μ g/day (8, 27). This mode of treatment is far from ideal. High-dose oral phosphate treatment is frequently associated with intolerable gastrointestinal side effects. Calcitriol treatment may induce hypercalciuria and cause nephrocalcinosis, urolithiasis, and renal insufficiency. Hydrochlorothiazide has been used successfully to reduce renal calcium excretion in some cases. Recently, it was reported that patients may benefit from treatment with the calcimimetic cinacalcet (28). Both subjects had high normal serum PTH levels, probably as a result of a calcium deficit due to the severely reduced 1,25-D levels. Cinacalcet reduced serum PTH by about 70%, raised tubular phosphate reabsorption from 50% to about 70–80%, which permitted a dose reduction of 67–75% of the oral phosphorus dose needed to maintain normophosphatemia. Both PTH and FGF-23 act by decreasing the expression of the NaP-2a cotransporter; however, the mechanisms by which they regulate NaP-2a levels are different (21). Not all patients with TIO present with high normal or elevated PTH levels. In our patient, PTH levels were relatively low, probably at least partly as a result of 1 α -calcidiol treatment. In such cases, cinacalcet is unlikely to improve renal phosphate reabsorption.

We also examined the efficacy of dipyridamole as an agent to reduce renal phosphate excretion. Although this has been effective in subjects with renal phosphate leak of various etiologies, dipyridamole was not effective in our case (12, 13). We have no obvious explanation for this lack of effect. The dose was sufficiently high to expect an effect but the treatment period may have been too short. A 3-week treatment period with 300 mg/day has been shown to reduce renal phosphate wasting; however, one study indicates that the maximal effects on renal phosphate reabsorption are observed after 3–6 months (12, 13).

Treatment of TIO patients has also been directed at suppression of FGF-23 production. Octreotide 100 μ g thrice a day normalized serum phosphate in one case but failed in other patients, despite dose increments up to 200 μ g thrice daily (29). Our patient also did not respond to octreotide. We chose to evaluate the efficacy of calcitonin, reasoning that TIO tumors are derived from osteogenic cells and thus might carry calcitonin receptors. A single dose of calcitonin produced a profound reduction of the serum FGF-23 level. Thus, calcitonin may be an alternative in patients not responding to octreotide. However, its long-term efficacy remains to be demonstrated.

Calcium and phosphate metabolism was closely monitored during both surgical procedures. The observations during the second procedure that led to successful removal of the FGF-23 producing tumor were most informative. In agreement with reported half lives of FGF-23 of 20–60 min, normalization of the elevated

FGF-23 levels occurred rapidly, within 24 h (14, 30). The serum PTH levels were the first to respond to this dramatic decrease in FGF-23, and rose considerably within the first 24 h. This suggests that FGF-23 may be a physiologically important inhibitor of PTH secretion in humans, an observation that is supported by the *in vitro* findings of Krajisnik *et al.* showing that FGF-23 potently and dose-dependently decreased PTH mRNA levels within 12 h in a culture of bovine parathyroid cells (31). In rats, the FGF-23 was shown to suppress PTH gene expression and PTH secretion (32). This FGF-23-mediated PTH suppressive effect may explain why PTH levels were within the normal range before surgery. Normally, suboptimal 25-D and severely reduced 1,25-D levels would have led to secondary hyperparathyroidism, but this was not the case in our patient. The next change after the increase in PTH was a rise in 1,25-D on day 3 after surgery. The latter probably reflects the loss of FGF-23 inhibition on renal 1 α -hydroxylase in combination with PTH-mediated stimulation of the enzyme. The rapidity of the rise in serum phosphorus level lagged behind the rise in 1,25-D by several days, which suggests that it was a consequence of enhanced 1,25-D-stimulated intestinal phosphorus absorption, now effective because the renal phosphate leak was no longer present.

In conclusion, tumor localization in TIO patients is very difficult and time consuming. Two-staged, zooming venous sampling may be helpful, and sampling of the smaller veins will usually be necessary to detect a gradient. If localization fails, suppression of FGF-23 production by octreotide or calcitonin might be considered. Furthermore, postoperative observations in this patient suggest that FGF-23 may act as an inhibitor of PTH secretion in man.

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